ORGANIC LETTERS

2010
Vol. 12, No. 7
1520−1523

Cyclopropylmethylation of Benzylic and Allylic Chlorides with Cyclopropylmethylstannane Catalyzed by Gallium or Indium Halide

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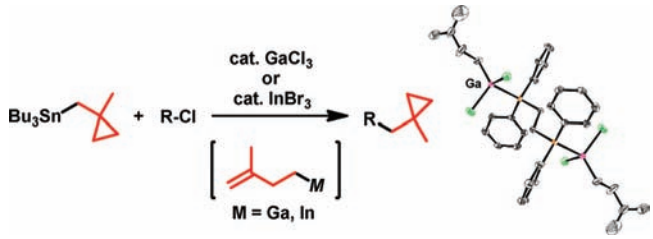
Received January 30, 2010

ABSTRACT



Benzylic and allylic chlorides easily coupled with cyclopropylmethylstannane in the presence of $GaCl_3$ or $InBr_3$ catalyst, in which an intermediate of an active butenylgallium or -indium species was confirmed by NMR spectroscopy and X-ray analysis. An ionic reaction process is plausible for this coupling.

Cyclopropane functional compounds are versatile synthetic intermediates because of their unique reactivity.[1] Moreover, cyclopropyl rings also exist in many natural compounds that show biological activity.[2] For their preparation, the Simmons−Smith reaction[3] and transition-metal-catalyzed cyclopropanation with diazo compounds[4] have been widely used.[5] Although butenyl metal species are useful reagents for construction of cyclopropyl ring systems, their low nucleophilicity has limited their synthetic applications.[6] Only a few examples have been reported. For example, an equimolar amount of $TiCl_4$ promoted the coupling of butenyltrimethylsilane and acid chlorides.[7] Similar types of reactions have been achieved using butenyltributylstannanes in the presence of Lewis acids.[8] In addition, *in situ* generated butenylgallium, -indium, and -aluminum species from butenyl Grignard reagents have been coupled with α-halocarbonyl compounds[9] in a radical manner.[10] Recently, we confirmed the generation of active indium species by

(1) (a) Paquette, L. A. *Chem. Rev.* **1986**, *86*, 733–750. (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C. W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198. (c) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196.

(2) (a) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589–8627. (b) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603–1623. (c) Wessjohann, L. A.; Brandt, W. *Chem. Rev.* **2003**, *103*, 1625–1647.

(3) (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323–5324. (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53–58.

(4) Brookhart, M.; Studabaker, W. B. *Chem. Rev.* **1987**, *87*, 411–432.

(5) For stereoselective cyclopropanation reaction, see: (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.

(6) Reactions of butenylstannane with inorganic electrophiles have been reported, see: (a) Peterson, D. J.; Robbins, D.; Hansen, J. R. *J. Organomet. Chem.* **1974**, *73*, 237–250. (b) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704–3706. (c) Ueno, Y.; Ohta, M.; Okawara, M. *Tetrahedron Lett.* **1982**, *23*, 2577–2580. (d) Herndon, J. W.; Harp, J. J. *Tetrahedron Lett.* **1992**, *33*, 6243–6246.

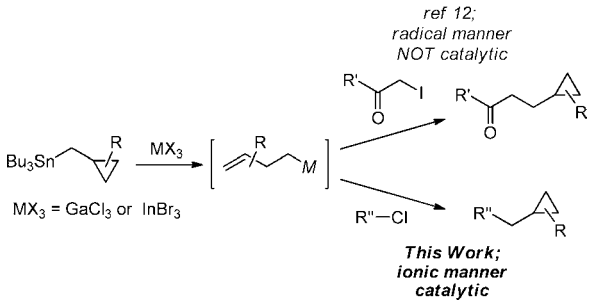
(7) (a) Sakurai, H.; Imai, T.; Hosomi, A. *Tetrahedron Lett.* **1977**, *18*, 4045–4048. (b) Hatanaka, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 719–722.

(8) (a) Sugawara, M.; Yoshida, J. *Chem. Commun.* **1999**, 505–506. (b) Sugawara, M.; Yoshida, J. *Tetrahedron* **2000**, *56*, 4683–4689.

10.1021/ol100240b
Published on Web 03/10/2010

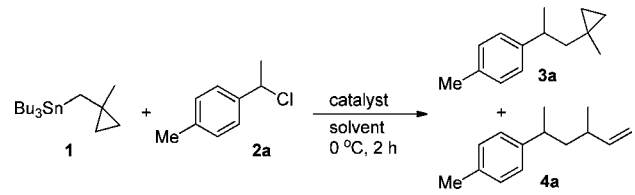
transmetalation between cyclopropylmethylstannane[11] and indium halide and its radical coupling reaction with α-iodocarbonyl compounds, although a catalytic trial failed.[12] In this communication, we report the $GaCl_3$- or $InBr_3$-catalyzed cyclopropylmethylation of alkyl chlorides, which are readily available but less reactive than iodides or bromides, with cyclopropylmethylstannane (Scheme 1). Contrary to our previous report, this reaction proceeded by an ionic mechanism, which apparently enabled the catalytic coupling. In addition, the generated butenylgallium intermediate was isolated and confirmed by its complexation with a phosphine ligand.

Scheme 1. Reactivity of Butenylgallium or Butenylindium Species



First, we chose the reaction of 1-chloro-1-(4-methylphenyl)ethane (**2a**) with cyclopropylmethylstannane **1** for the investigation of the catalysts (Table 1).[13] No reaction took place without catalyst loading (entry 1). Use of 5 mol % of $InBr_3$ in CH_2Cl_2 effectively promoted the coupling reaction to afford the cyclopropylmethylated product **3a** in 81% yield along with 19% yield of the ring-opening product **4a** (entry 2). Other indium halides, $InCl_3$ or InI_3, gave yields lower than that of $InBr_3$ (entries 3 and 4). Hydrocarbon solvents such as hexane and toluene were also effective (entries 5 and 6), whereas no reaction was observed in MeCN, perhaps because the interaction between the indium catalyst and the substrates was disturbed by its strong coordination ability

Table 1. Reaction of 1-Chloro-1-(4-methylphenyl)ethane (**2a**) with Cyclopropylmethylstannane **1**[a]



			yield (%)[b]	
entry	catalyst	solvent	**3a**	**4a**
1	none	CH_2Cl_2	0	0
2	$InBr_3$	CH_2Cl_2	81	19
3	$InCl_3$	CH_2Cl_2	69	18
4	InI_3	CH_2Cl_2	58	19
5	$InBr_3$	hexane	59	26
6	$InBr_3$	toluene	52	19
7	$InBr_3$	MeCN	0	0
8	$GaCl_3$	CH_2Cl_2	57	14
9	$GaBr_3$	CH_2Cl_2	55	14
10[c]	$InBr_3$	CH_2Cl_2	55	15
11[d]	$InBr_3$	CH_2Cl_2	73	20
12[c]	$GaCl_3$	CH_2Cl_2	45	13
13[d]	$GaCl_3$	CH_2Cl_2	71	21

[a] All entries were carried out at 0 °C for 2 h using 1.0 mmol of **1**, 1.0 mmol of **2a**, and 0.05 mmol of catalyst. [b] Determined by ^{1}H NMR. [c] TEMPO (0.05 mmol) was added. [d] Galvinoxyl (0.05 mmol) was added.

(entry 7). In addition, it was found that gallium halide was also an efficient catalyst (entries 8 and 9). The reactions were not affected by the addition of a radical inhibitor, such as TEMPO or galvinoxyl, which had completely disturbed the reactions with α-haloesters, as previously reported[12] (entries 10−13). These data strongly indicated that the reaction proceeded in an ionic manner. All previous reactions of organic halides with organoindium species proceed via a radical mechanism. For example, the reduction by indium hydride[14] and the coupling between α-halocarbonyl compounds with vinyl-, allyl-, or alkynylindium species[15] are both known to be radical reactions.[16] Organogallium species[9,15,17] also reacted with organic halides in a radical manner. An ionic reaction with organic halides has never been reported for either the organoindium or the organogallium species, as far as we know.

We next explored the scope of this system using either $InBr_3$ or $GaCl_3$ catalyst (Table 2). Various secondary benzylic chlorides furnished cyclopropylmethylated products in moderate to high yields (entries 1−12).[18] In the case of **2c** and **2e**, which bear two types of chlorine atoms, selective coupling was achieved at benzylic positions. 3-Chlorocy-

(9) Usugi, S.; Tsuritani, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 841–845.

(10) (a) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547–2549. (b) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041–11047. (c) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415–3434. (d) Yorimitsu, H.; Oshima, K. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, Chapter 1.2.

(11) (a) Brown, R. S.; Eaton, D. F.; Hosomi, A.; Traylor, T. G.; Wright, J. M. *J. Organomet. Chem.* **1974**, *66*, 249–254. (b) San Filippo, J., Jr.; Silbermann, J. *J. Am. Chem. Soc.* **1982**, *104*, 2831–2836. (c) Alnajjar, M. S.; Smith, G. F.; Kuivila, H. G. *J. Org. Chem.* **1984**, *49*, 1271–1276. (d) Lucke, A. J.; Young, D. J. *Tetrahedron Lett.* **1991**, *32*, 807–810. (e) Lucke, A. J.; Young, D. J. *J. Org. Chem.* **2005**, *70*, 3579–3583.

(12) Yasuda, M.; Kiyokawa, K.; Osaki, K.; Baba, A. *Organometallics* **2009**, *28*, 132–139.

(13) The reaction using unmethylated cyclopropylmethylstannane failed. An equimolar use of indium halide was required. The reaction of unmethylated cyclopropylmethylstannane (2 mmol) with benzhydryl chloride (1 mmol) in the presence of $InBr_3$ (1 mmol) in dichloromethane gave cyclopropylmethylated product in 58% yield (ring-opening product, 28% yield).

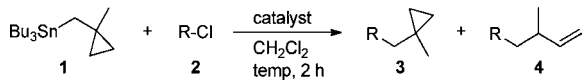
(14) Baba, A.; Shibata, I. *Chem. Rec.* **2005**, *5*, 323–335.

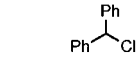
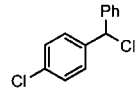
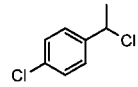
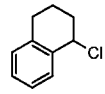
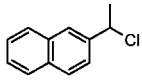
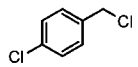
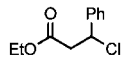
(15) Takami, K.; Usugi, S.; Yorimitsu, H.; Oshima, K. *Synthesis* **2005**, 824–839.

(16) A halogen substitution reaction using alkylindium species toward haloalkenes was reported, see: Nomura, R.; Miyazaki, S.-i.; Matsuda, H. *J. Am. Chem. Soc.* **1992**, *114*, 2738–2740.

(17) A gallium hydride also reacts with organic halides in a radical manner, see: Mikami, S.; Fujita, K.; Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1853–1855.

Table 2. $GaCl_3$ or $InBr_3$−Catalyzed Cyclopropylmethylation of Various Alkyl Chlorides **2**[a]



entry	2		temp (°C)	product	catalyst	yield (%)[b] 3	4
1		**2b**	0	**3b**	$GaCl_3$	72	16
2					$InBr_3$	79	20
3		**2c**	0	**3c**	$GaCl_3$	82	14
4					$InBr_3$	78	19
5		**2d**	rt	**3d**	$GaCl_3$	59	21
6					$InBr_3$	trace	trace
7		**2e**	80	**3e**	$GaCl_3$	56	22
8					$InBr_3$	trace	trace
9		**2f**	0	**3f**	$GaCl_3$	63	15
10					$InBr_3$	73	17
11		**2g**	0	**3g**	$GaCl_3$	73	20
12					$InBr_3$	80	19
13		**2h**	rt	**3h**	$GaCl_3$	45	12
14					$InBr_3$	15	5
15[c]		**2i**	80	**3i**	$GaCl_3$	36	46
16[c]					$InBr_3$	70	14
17[d]		**2j**	0	**3j**	$GaCl_3$	40	22
18[d]					$InBr_3$	0	0

[a] All entries were carried out with 1.0 mmol of **1**, 1.0 mmol of **2a**, and 0.05 mmol of catalyst. [b] Determined by ^1H NMR. [c] 1.5 mmol of **1** and 0.75 mmol of catalyst were used. [d] 0.5 mmol of catalyst was used.

clohexene (**2h**) was also transformed to the corresponding product **3h** (entries 13 and 14). Primary benzylic chloride, *p*-chlorobenzyl chloride (**2i**), gave the product when an equimolar amount of metal halide was used (entries 15 and 16). $GaCl_3$ catalyzed the reaction with *β*-chloro ester **2j** to afford the ester **3j**, while the starting ester was recoverd in the case of $InBr_3$ (entries 17 and 18).

To confirm the active gallium species, a mixture of an equimolar amount of $GaCl_3$ and **1** was monitored by ^1H NMR. Similar signals were observed with two doublets for the vinylic protons (*a*), two triplets for the allylic protons (*c*), and two singlets for the methyl protons (*b*) (Figure 1ii). On the basis of the reported facts,[12] they were assigned the designations of mono- and dibutenylgallium species **5a** and **6a**. The integration ratio of the peaks was ∼2.5:1, and the

(18) Benzylic bromides were also applicable in a similar range to the chlorides. For example, the reaction of 1-bromo-1-phenylethane (1 mmol) with **1** (1 mmol) in the presence of $GaCl_3$ (0.05 mmol) in dichloromethane gave **3d** (62%) and **4d** (22%).

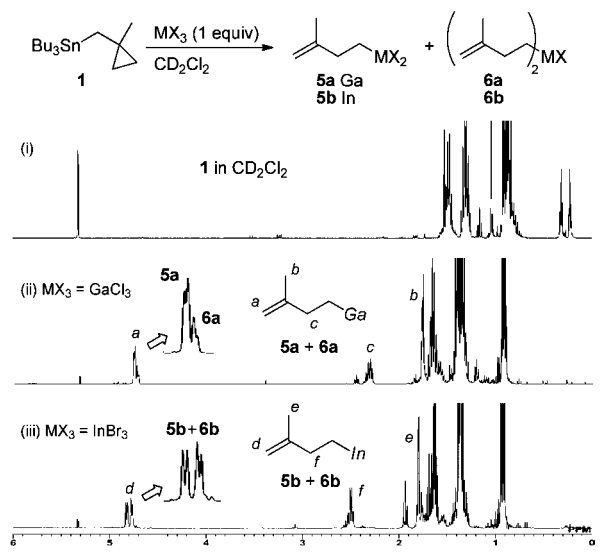
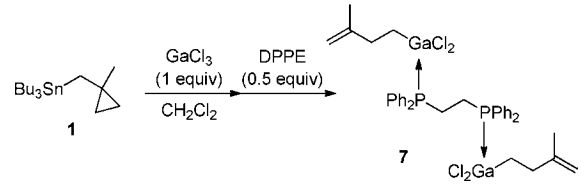


Figure 1. ^1H NMR spectra of (i) **1**, (ii) the mixture of $GaCl_3$ and **1**, and (iii) the mixture of $InBr_3$ and **1** in CD_2Cl_2.

product ratio of **5a**/**6a** was ∼5:1. On the other hand, a 1:2 mixture of $GaCl_3$/**1** preferentially gave **6a** (integration ratio of **5a**/**6a** ≈ 1:10) with no other highly substituted species (see Supporting Information). The integration ratio was somewhat different in the case of $InBr_3$ (**5b**/**6b** ≈ 1:1) (Figure 1iii). The addition of benzhydryl chloride (**2b**) to the stirred mixture of **1** and $GaCl_3$ (**1**/$GaCl_3$ = 1:1) for 30 min in dichloromethane-d_2 gave the coupling product in 86% yield ($InBr_3$, 71% yield). These results demonstrated that the active species in the reaction was a mono- and dibutenyl metal species.[12]

Scheme 2. Complexation and Isolation of the Butenylgallium Species



Furthermore, we attempted to isolate the butenylgallium species by complexation using external ligands. The addition of DPPE to a 1:1 mixture of $GaCl_3$/**1** in CH_2Cl_2 gave a crystal, which was determined by X-ray crystal structural analysis to be butenylgallium complex **7** (Scheme 2). The structure is shown in Figure 2. The four-coordinated gallium center had a butenyl group, a phosphorus in DPPE, and two chlorines. Each phosphine moiety in DPPE coordinated to the other molecule's gallium centers. The angles for Cl1−Ga−Cl2 (107.02°) and C−Ga−Cl (115.58° and 113.48°) indicated that the gallium center exhibited a distorted tetrahedral structure. This stable structure was different from that of TBP of the indium species.[12]

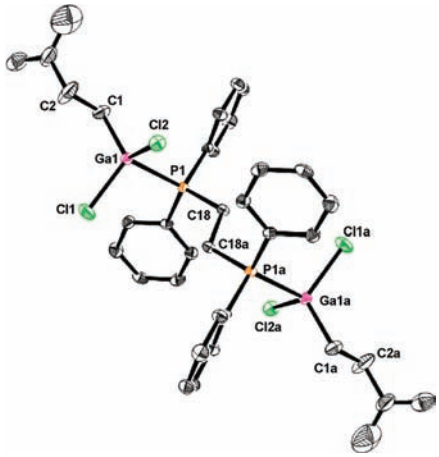
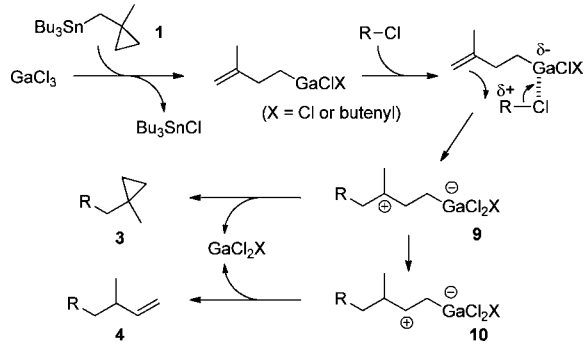


Figure 2. X-ray structure of **7** (all hydrogens are omitted for clarity).

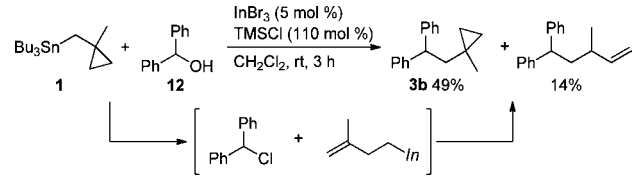
A plausible reaction mechanism is shown in Scheme 3. Transmetalation between **1** and $GaCl_3$ gives butenylgallium species. Then the resulting gallium species activates alkyl chloride by formation of an intermediate **9**, perhaps via the alkyl cation species. Finally, cyclization takes place with the release of gallium chloride to form a cyclopropyl ring. When the isomerization from **9** to **10** via a hydride shift occurs, the ring-opening product is formed.[7a,8b,19] The interaction of the butenylgallium species and alkyl chloride may be a key step in this ionic mechanism to complete the catalytic cycle. The reaction using $InBr_3$ as a catalyst proceeds in a similar manner.

Scheme 3. Plausible Reaction Mechanism



Finally, this reaction system was applied to the direct use of alcohol instead of chloride, as shown in Scheme 4. Using alcohols as substrates would be ideal for synthetic organic chemistry because alcohols are plentiful and readily available. The reaction of **1** with benzhydrol (**12**) in the presence of $InBr_3$ and trimethylsilyl chloride furnished corresponding cyclopropylmethylated product **3b** in 49% yield. It is assumed that a reaction using trimethylsilyl chloride chlorinated alcohol in the presence of $InBr_3$,[20,21] followed by coupling with cyclopropylmethylstannane, would proceed in the manner discussed above.

Scheme 4. Cyclopropylmethylation of Alcohol



In conclusion, we have developed $GaCl_3$- or $InBr_3$-catalyzed cyclopropylmethylation of benzylic and allylic chlorides with cyclopropylmethylstannane. NMR spectroscopy and X-ray crystal structural analysis revealed the generation of butenylgallium and -indium species. Further investigation of the mechanism and synthetic application of this transformation is now underway.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas [No. 18065015 ("Chemistry of Concerto Catalysis") and No. 20036036 ("Synergistic Effects for Creation of Functional Molecules")] and for Scientific Research (No. 21350074) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank Dr. Nobuko Kanehisa (Osaka University) for the valuable advice regarding X-ray crystallography. K.K. thanks the Global COE Program "Global Education and Research Center for Bio-Environmental Chemistry" of Osaka University.

Supporting Information Available: Experimental details, characterization data and CIF of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100240B

(19) Ogasawara, M.; Okada, A.; Murakami, H.; Watanabe, S.; Ge, Y.; Takahashi, T. *Org. Lett.* **2009**, *11*, 4240–4243.

(20) We have reported indium-catalyzed direct chlorination of alcohols using chlorodimethylsilane-benzil system, see: Yasuda, M.; Yamasaki, S.; Onishi, Y.; Baba, A. *J. Am. Chem. Soc.* **2004**, *126*, 7186–7187.

(21) Chlorination of alcohols using trimethylsilyl chloride catalyzed by $BiCl_3$ has been reported, see: Labrouillère, M.; Roux, C. L.; Gaspard-Iloughmane, H.; Dubac, J. *Synlett* **1994**, 723–724.