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Gallium-Mediated Allyl Transfer from Bulky Homoallylic Alcohol to Aldehydes via Retro-allylation: Stereoselective Synthesis of Both *erythro*- and *threo*-Homoallylic Alcohols[1]

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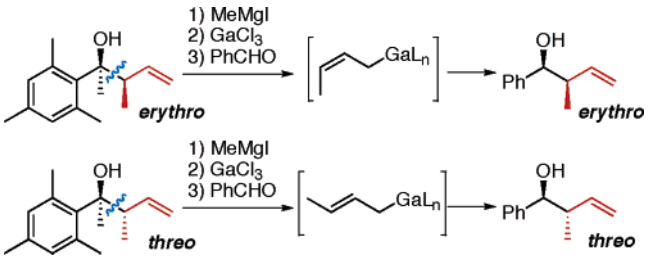
ABSTRACT



Retro-allylation of bulky gallium homoallylic alkoxides occurs to generate (*Z*)- and (*E*)-crotylgallium reagents stereospecifically, starting from *erythro*- and *threo*-homoallylic alcohols, respectively. The (*Z*)- and (*E*)-crotylgallium reagents immediately reacted with aromatic aldehydes to afford the corresponding *erythro*- and *threo*-homoallylic alcohols, respectively.

Allylation of carbonyl compounds is among the most important reactions in organic synthesis.[2] Thus, preparation of allylic metals has been well investigated, including reductive metalation of allylic halide (or pseudohalide) by low-valent metal, transmetalation of highly reactive allylic metal to another metal, and direct allylic deprotonation by a strong base. Recently, we have developed a novel and mild method for the preparation of allylic zirconium reagents by allylic C−H bond activation of alkene and applied it to carbonyl allylation.[3] Here we report a new method for the generation of allylic gallium reagents[4] by gallium-mediated retro-allylation reaction of bulky homoallylic alcohols.[5]

Treatment of bulky homoallylic alcohol (**1a**, 1.2 mmol) with methylmagnesium iodide (1.2 mmol) in dioxane afforded the magnesium alkoxide of **1a**. Gallium trichloride (1.2 mmol) and benzaldehyde (1.0 mmol) were sequentially added at 25 °C. After the mixture was stirred for 0.5 h, extractive workup followed by silica gel column purification provided homoallylic alcohol **2a** in excellent yield. Unfortunately, no *erythro*/*threo* selectivity was observed. A substoichiometric amount of gallium trichloride also effected the crotylation[6] reaction, affording **2a** in 79% yield. On the

(1) Throughout this manuscript, we have adopted the unambiguous *erythro*/*threo* nomenclature proposed by Noyori: Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106−2108.

(2) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2793.

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(4) (a) Yamaguchi, M. In *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1., Chapter 7. (b) Araki, S.; Ito, H.; Butsugan, Y. *Appl. Organomet. Chem.* **1988**, *2*, 475−478. (c) Tsuji, T.; Usugi, S.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Chem. Lett.* **2002**, 2−3. (d) Takai, K.; Ikawa, Y. *Org. Lett.* **2002**, *4*, 1727−1729.

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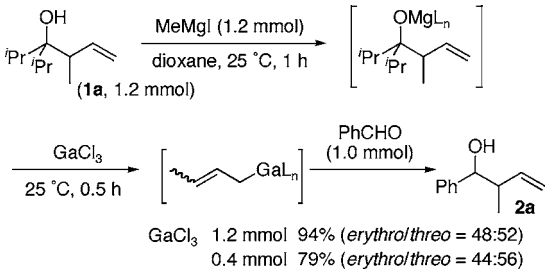
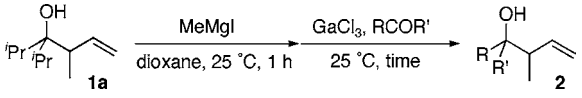
Scheme 1



basis of the regioselectivity of the reaction, the reaction mostly proceeded via a mechanism completely different from the Lewis acid-mediated allyl transfer reactions reported by Nokami and Loh.[7] Formation of crotylgallium species by retro-crotylation is most probable.

A variety of aldehydes underwent the crotylation reaction (Table 1). Not only aromatic aldehydes but also aliphatic

Table 1. Crotylation of Various Carbonyl Compounds via Retro-crotylation[a]



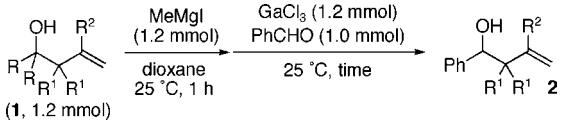
entry	RCOR′	time	2	yield	*erythro*/*threo*
1	*p*-$CH_3C_6H_4CHO$	1.5 h	**2b**	88%	48:52
2	$PhCH_2CH_2CHO$	1 h	**2c**	72%	55:45
3	*c*-$C_6H_{11}CHO$	0.5 h	**2d**	99%	12:88
4	(*E*)-PhCH=CHCHO	3 h	**2e**	70%[b]	54:46
5	*p*-$MeOCOC_6H_4CHO$	2.5 h	**2f**	85%	42:58
6	cyclohexanone	0.5 h	**2g**	59%	

[a] Performed as described in the second paragraph by using 1.2 equiv of $GaCl_3$. [b] Performed in ether at 0 °C. Conversion of cinnamaldehyde under the standard conditions resulted in a lower yield because of the concomitant formation of 4-methyl-1-phenyl-1,3,5-hexatriene.

ones participated in the crotylation reaction. Crotylation of cyclohexanecarbaldehyde proceeded with high *threo* selectivity (entry 3). Selective 1,2-addition took place in the reaction of cinnamaldehyde (entry 4). The allylation of an aldehyde moiety predominated over that of ester (entry 5). The reaction with ketone gave the corresponding tertiary alcohol **2g** in modest yield (entry 6).

Other allylic gallium reagents were readily prepared (Table 2). Completion of unsubstituted allyl transfer took more time

Table 2. Allylation, Methallylation, and Prenylation of Benzaldehyde

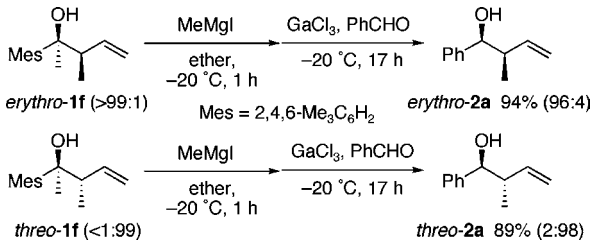


entry	1	R	R^1	R^2	time	2	yield
1	**1b**	*i*Pr	H	H	13 h	**2h**	68%
2	**1c**	*i*Pr	H	Me	0.5 h	**2i**	94%
3	**1d**	*i*Pr	Me	H	11 h	**2j**	32%
4	**1e**	Me	Me	H	1 h	**2j**	78%

yet provided the anticipated product **2h** in good yield (entry 1). Methallylation proceeded as smoothly as the crotylation to furnish **2i** in excellent yield (entry 2). Intriguingly, prenylation was not efficient starting from diisopropyl-substituted **1d**. However, dimethyl substitution at the oxygenated carbon dramatically enhanced the prenylation (entry 4). Delicate steric factors around the hydroxy groups play a key role in these allyl transfer reactions.

Having noticed the delicate steric effect, we further examined the crotylation reaction by using other crotyl sources. Fortunately, we found that homoallylic alcohol **1f**, which bears mesityl and methyl groups at its oxygenated carbon, effected crotyl transfer reaction in ether at −20 °C. Gratifyingly, the reaction exhibited stereospecificity when diastereomerically pure **1f** was used; the reactions of *erythro*-**1f**[8] and *threo*-**1f** with benzaldehyde afforded *erythro*- and *threo*-**2a**, respectively (Scheme 2). Both isomers of **1f** were

Scheme 2

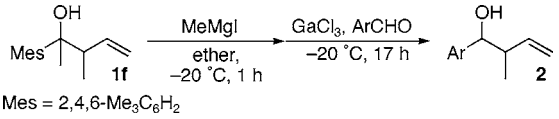


prepared by treatment of mesityl methyl ketone with crotyl Grignard reagent and readily separated from each other by column purification on silica gel. Other aromatic aldehydes underwent the stereospecific crotylation reaction (Table 3). The reactions with dihydrocinnamaldehyde and cinnamaldehyde resulted in lower stereoselectivity (See Supporting Information).

(5) Retro-allylations from lithium, magnesium, and zinc alkoxides were observed. Among them, Knochel reported *threo* selectivity. (a) Benkeser, R. A.; Siklosi, M. P.; Mozdzen, E. C. *J. Am. Chem. Soc.* **1978**, *100*, 2134−2139. (b) Gerard F.; Miginiac, P. *Bull. Chim. Soc. Fr.* **1974**, 2527−2533. (c) Jones, P.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 186−195. We have serendipitously found similar behavior of zirconium homoallylic alkoxides. See ref 3c. Under harsh conditions, retro-allylation took place by the action of tin: (d) Peruzzo, V.; Tagliavini, G. *J. Organomet. Chem.* **1978**, *162*, 37−44. (e) Giesen, V. Dissertation, University Marburg, Germany, 1989. Ruthenium-catalyzed deallylation was reported: (f) Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587−5588.

(6) For convenience, throughout the manuscript, crotylation, methallylation, and prenylation are defined as introductions of 1-methyl-2-propenyl, 2-methyl-2-propenyl, and 1,1-dimethyl-2-propenyl groups, respectively, into a carbonyl group. On the other hand, crotyl, methallyl, and prenyl groups denote herein 2-butenyl, 2-methyl-2-propenyl, and 3-methyl-2-butenyl groups, respectively.

Table 3. Selective Synthesis of *erythro*- and *threo*-Homoallylic Alcohols



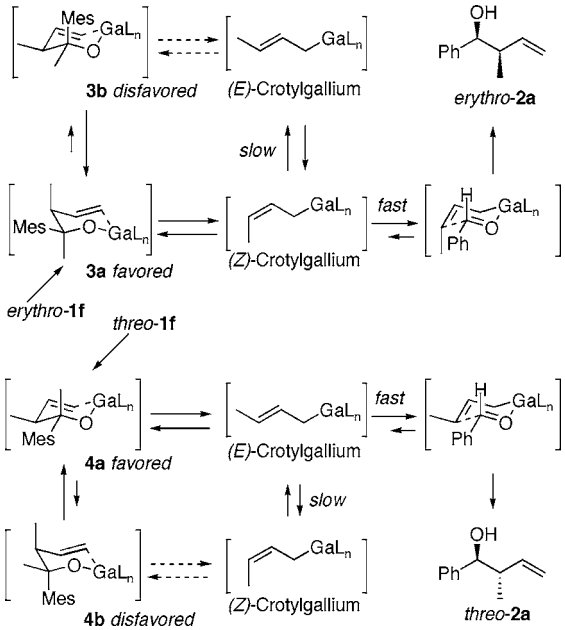
entry	**1f**	Ar	**2**	yield	*erythro*/*threo* of **2**
1	*erythro*	*p*-$CF_3C_6H_4$	**2k**	84%	96:4
2	*threo*	*p*-$CF_3C_6H_4$	**2k**	92%	2:98
3	*erythro*	*o*-ClC_6H_4	**2l**	87%	99:1
4	*threo*	*o*-ClC_6H_4	**2l**	83%	3:97
5	*erythro*	*p*-$CH_3C_6H_4$	**2b**	95%[a]	98:2
6	*threo*	*p*-$CH_3C_6H_4$	**2b**	64%[a]	2:98

[a] Reaction time was 30 h.

We are tempted to assume the reaction mechanism as follows (Scheme 3). Upon the retro-crotylation reaction of *erythro*-**1f**, a chair transition state **3a** would be the most stable, because of steric reasons, in comparison to other possible transition states, including another chair transition state **3b** and twist-boat transition states. Formation of a (*Z*)-crotylgallium reagent is thus favored. The (*Z*)-crotylgallium reagent probably reacts so rapidly with benzaldehyde in the same pot that its isomerization into the (*E*)-form is negligible. The crotylation would proceed via a cyclic transition state, which selectively provides *erythro*-**2a**. Starting from *threo*-**1f**, an (*E*)-crotylgallium reagent would be predominantly generated via **4a** and led to *threo*-**2a**.

Stereoselective preparations of crotylmetals represent an important challenge. Stereochemically defined crotylmetals should always be prepared in advance of the crotylation reaction.[2] Our new method utilizes stable and easy-to-handle homoallylic alcohols as the precursors. Selective generations of (*E*)- and (*Z*)-crotylgallium were established in situ via the gallium-mediated retro-allylation and can be applied to other allylation reactions.

Scheme 3



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Supporting Information Available: Experimental details, additional examples for Table 3, an ORTEP diagram of a derivative of *erythro*-**1f**, and ^{1}H NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Representative examples: (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609−6610. (b) Nokami, J.; Anthony, L.; Sumida, S. *Chem. Eur. J.* **2000**, *6*, 2909−2913. (c) Nokami, J. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 992−1001. (d) Tan, K.-T.; Chng, S.-S.; Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 2958−2963. (e) Lee, C.-L. K.; Lee, C.-H. A.; Tan, K.-T.; Loh, T.-P. *Org. Lett.* **2004**, *6*, 1281−1283. Also see: (f) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815−3818. (g) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577−580. (h) Samoshin, V. V.; Smoliakova, I. P.; Hank, M. M.; Gross, P. H. *Mendeleev Commun.* **1999**, 219−221. (i) Horiuchi, Y.; Taniguchi, M.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1994**, *35*, 7977−7980.

(8) Relative configuration of *erythro*-**1f** was determined by X-ray crystallographic analysis after derivatization. See Supporting Information.