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Synthetic Methods

Gallium Tribromide Catalyzed Coupling Reaction of Alkenyl Ethers with Ketene Silyl Acetals**

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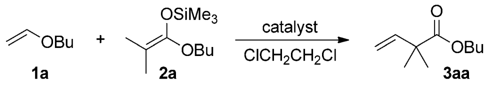
The coupling reaction of alkenyl electrophiles with organometallics has been strenuously developed because it is a powerful tool for the construction of π-conjugated carbon frameworks, which are very valuable as functional materials.[1] In general, alkenyl halides and pseudohalides are used as electrophilic coupling partners in the presence of a transition-metal catalyst. The use of these electrophiles, however, has some drawbacks in terms of high cost, storage instability, and the production of metal halide wastes. To overcome these drawbacks, significant effort has gone into replacing alkenyl halides with alkenyl alcohol derivatives such as alkenyl ethers,[2] acetates,[3] carbonates,[4] carbamates,[5] phosphates,[6] and silyl enol ethers.[7] Therefore, some success using alkyl- and arylmetals have been reported. However, to the best of our knowledge, the cross-coupling between alkenyl alcohol derivatives and metal enolates has never before been achieved[8] in spite of the vital importance of α-alkenyl carbonyls.[9]

Recently, we developed carbometalations of alkenes and alkynes using ketene silyl acetals and metal halides such as $InBr_3$,[10] $GaBr_3$,[11] and $BiBr_3$[12] to conveniently produce the corresponding organometallics, wherein the independent *anti* addition of metal species and nucleophiles took place without the preliminarily generation of an organometallic intermediate. Herein, we wish to extend this carbometalation to a new type of catalytic coupling between alkenyl ethers and ketene silyl acetals.

At first, we focused on the carbometalation of butyl vinyl ether (**1a**) using dimethylketene butyl trimethylsilyl acetal (**2a**) and an equimolar amount of $InBr_3$ (Table 1, entry 1), in which the effective interaction between the double bond of **1a** and $InBr_3$ was expected because the electron density of **1a** is higher than that of the alkenes employed in our reported system.[10b] Although a vigorous reaction took place, even at low temperature as expected, the coupling product **3aa** was obtained quantitatively instead of the expected alkylindium derivative. This result indicated that **1a** acted as a vinylation reagent through the removal of the butoxy group. Gratifyingly, the coupling reaction was promoted at 80 °C by a catalytic amount of $InBr_3$ (10 mol%) to give the product **3aa** in 86% yield (Table 1, entry 2). $GaBr_3$ was found to be more effective, thus affording **3aa** in 95% yield (Table 1, entry 3),[11] and these conditions were determined to be optimal. In contrast, $BiBr_3$ showed quite a low catalytic effect (Table 1, entry 5) although it reportedly promoted the effective carbometalation of alkynes.[12] No coupling, of course, took place without a catalyst (Table 1, entry 6), and representative Lewis acids such as $BF_3{\cdot}OEt_2$, $AlCl_3$, and $TiCl_4$ were not effective (Table 1, entries 7–9).

Table 1: Effect of catalysts in coupling of alkenyl ether with ketene silyl acetal.[a]



Entry	Catalyst (equiv)	*T* [°C]	Yield [%][b]
1	$InBr_3$ (1)	−20	quant
2	$InBr_3$ (0.1)	80	86
3	$GaBr_3$ (0.1)	80	95
4	$GaBr_3$ (0.1)	RT	19
5	$BiBr_3$ (0.1)	80	6
6	–	80	0
7	$BF_3{\cdot}OEt_2$ (0.1)	80	4
8	$AlCl_3$ (0.1)	80	0
9	$TiCl_4$ (0.1)	80	trace

[a] **1a** (1 mmol), **2a** (1.5 mmol), $ClCH_2CH_2Cl$ (2 mL), 2 h. [b] Determined by ^1H NMR spectroscopy.

With the optimum reaction conditions in hand, the scope of with respect to the ketene silyl acetals **2** was investigated as shown in Scheme 1. Dialkylketene silyl acetals gave the corresponding α-vinyl esters in high yields (**3ab**, **3ac**, and **3ad**). The alkylarylketene silyl acetal also showed good reactivity, thus furnishing **3ae**. In the case of monosubstituted ketene silyl acetals, alkylketene and arylketene substrates gave the desired products **3af** and **3ag** in 90 and 83% yields, respectively. The phenoxy-substituted ketene silyl acetal furnished the α-phenoxy α-vinyl ester **3ah** in 44% yield, and the reaction using an unsubstituted ketene silyl acetal also took place, although the yield was only 20% (**3ai**). Heteroaryl-substituted ketene silyl acetals were found to be facile nucleophiles (**3aj** and **3ak**).

Furthermore, the applicable alkenyl ethers are shown in Table 2. The isopropyl vinyl ether (**1b**) gave the desired product in 50% yield, which was lower than that of **1a** as

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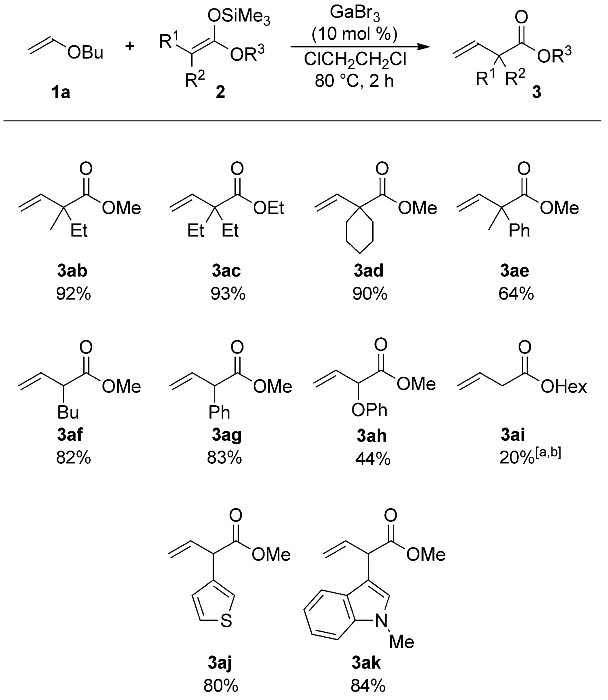
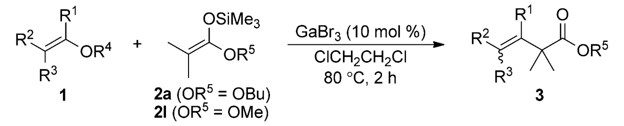
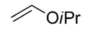
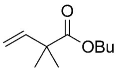
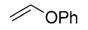
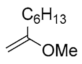
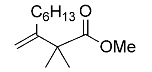
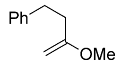
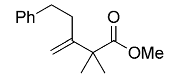
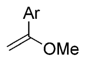
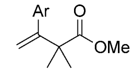
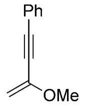
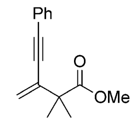
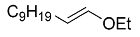
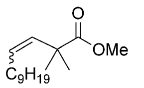
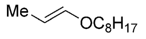
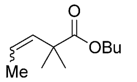
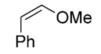
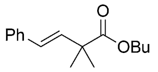


Scheme 1. Scope of reaction with respect to the ketene silyl acetal. Reaction conditions: **1a** (1 equiv), **2** (1.5 equiv), $GaBr_3$ (0.1 equiv), $ClCH_2CH_2Cl$, 80 °C, 2 h. Yields of isolated products are noted. [a] Determined by ^1H NMR spectroscopy. [b] **2** (3 equiv), $GaBr_3$ (0.2 equiv).

Table 2: Reaction scope: alkenyl ethers.[a]

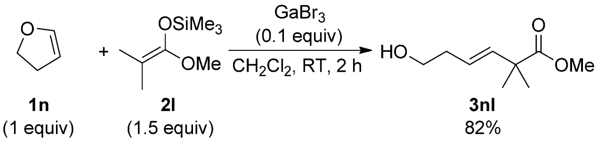


Entry	1		Product		Yield [%][b]
1		**1b**		**3aa**	50[c]
2		**1c**			98[c]
3[d]		**1d**		**3dl**	77
4[d]		**1e**		**3el**	69
					
5[d,e]	Ar = C_6H_5	**1f**		**3fl**	43
6[e]	2-naphthyl	**1g**		**3gl**	59
7[e]	4-ClC_6H_4	**1h**		**3hl**	61
8[e]	4-MeC_6H_4	**1i**		**3il**	43
9[d]		**1j**		**3jl**	73
10		**1k**		(*Z*/*E*)-**3kl**	91 (54:46)
11		**1l**		(*Z*/*E*)-**3la**	quant. (63:37)
12[f]		**1m**		**3ma**	58

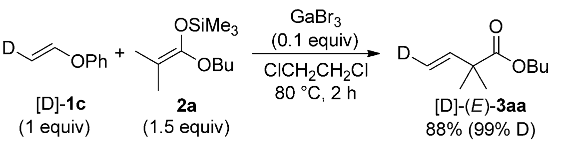
[a] **1** (1 equiv), **2** (1.5 equiv), $GaBr_3$ (0.1 equiv), $ClCH_2CH_2Cl$, 80 °C, 2 h. [b] Yields of isolated products are shown. [c] Determined by ^1H NMR spectroscopy. [d] 24 h. [e] **2** (3 equiv), $GaBr_3$ (0.2 equiv). [f] $GaBr_3$ (0.2 equiv), 70 °C.

a result of bulk (Table 2, entry 1). The reaction of phenyl vinyl ether (**1c**) afforded a 98% product yield (Table 2, entry 2). The 1-alkylated 1-methoxyethenes **1d** and **1e** were found to be facile substrates which gave the corresponding α-alkenylated esters in moderate yields (Table 2, entries 3 and 4). 1-Phenyl- and 1-naphtyl-1-methoxyethenes smoothly gave the desired products in 43 and 59% yields, respectively (Table 2, entries 5 and 6). 1-Aryl-1-methoxyethenes possessing electron-withdrawing and electron-donating groups on phenyl rings were suitable coupling partners (Table 2, entries 7 and 8). Enyne ether **1j** effectively reacted with ketene silyl acetal **2l** to produce ester **3jl** in 73% yield (Table 2, entry 9). The 2-substituted 1-alkoxyethenes also showed good reactivity. The reaction of (*E*)-1-nonyl-2-ethoxyethene (**1k**) with the ketene silyl acetal **2l** afforded methyl-2,2-dimethyltridec-3-enoate **3kl** in 91% yield with an *E*/*Z* ratio of 54:46 (Table 2, entry 10). (*Z*)-1-Methyl-2-octoxyethene (**1l**) also gave a mixture of *E*- and *Z*-**3la** in a quantitative yield (Table 2, entry 11). Interestingly, the corresponding (*E*)-β,γ-unsaturated ester **3ma** was exclusively obtained from the reaction of (*Z*)-1-phenyl-2-phenoxyethene (**1m**; Table 2, entry 12). Unfortunately, more substituted alkenyl ethers such as 1,1-disubstituted and 1,2-disubstituted enol ethers, were not applicable.

To reveal more of the stereochemistry, the reaction of dihydrofuran (**1n**) with **2l** was performed to produce the *E*-alkene **3nl** exclusively, through cleavage of the cyclic ether ring, with complete inversion of the stereochemistry [Eq. (1)]. In contrast, (*E*)-2-deuterated-1-phenoxyethene ([D]-**1c**) was treated with **2a** to furnish the (*E*)-β,γ-unsaturated ester selectively [Eq. (2)]. The stereochemical configuration of the starting alkene [D]-**1c** was completely retained in the course of the coupling reaction.

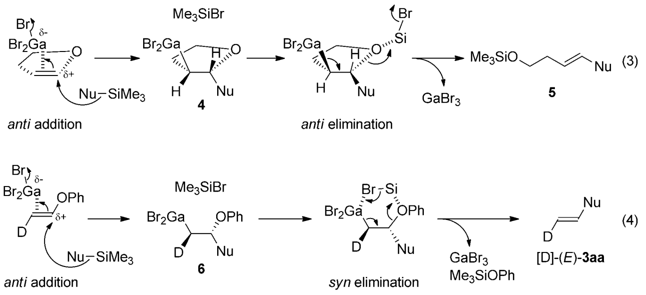


(1)



(2)

Possible mechanisms for these stereochemical phenomena are illustrated in Scheme 2 and are proposed on the basis



Scheme 2. Plausible mechanisms.

of our previously reported carboindation system.[10b] The reaction using dihydrofuran (**1n**) occurs through the mechanism shown in Equation (3). $GaBr_3$ effectively interacts with the alkene moiety of **1n** to increase the positive charge on the carbon atom, α to the oxygen atom, because $GaBr_3$ moves to the electron-dense β-carbon atom. The nucleophilic attack of the ketene silyl acetal (Nu-$SiMe_3$) from the opposite side of $GaBr_3$ occurs regio- and stereoselectively,[10b] and then the β-oxyalkylgallium intermediate **4** and Me_3SiBr are generated. Finally, the *anti* elimination of Br_2Ga and the alkoxide moieties occurs to give the *E*-alkene product **5**.[13] The generated Me_3SiBr plausibly assists the *anti* elimination as illustrated because of the low leaving-group ability of an alkoxy group and the high oxophilicity of silicone. In the reaction of (*E*)-2-deuterated-1-phenoxyethene ([D]-**1c**) [Eq. (4)], the *anti* addition of $GaBr_3$ and ketene silyl acetal to [D]-**1c** also occurs to afford the β-phenoxyalkylgallium intermediate **6** and Me_3SiBr. The *syn* elimination of $GaBr_2$ and OPh groups takes place in succession via a six-membered transition state consisting of the alkylgallium **6** and Me_3SiBr to give the α-vinyl ester [D]-(*E*)-**3aa** and Me_3SiOPh and to regenerate $GaBr_3$.[14,15] Although no direct experimental evidence exists, the assistance of Me_3SiBr on both *syn* and *anti* eliminations to compensate for the low oxophilicity of $GaBr_3$ is plausible. In addition, the sterics of the substituents of alkenyl ethers effectively determines the elimination mode that changes the *E*/*Z* ratio of the product olefins, as exemplified in entries 10–12 in Table 2.

In conclusion, we have accomplished the $GaBr_3$-catalyzed coupling reaction of alkenyl ether with ketene silyl acetals. The developed coupling reaction allows expedient access to β,γ-unsaturated esters. Various types of alkenyl ethers and ketene silyl acetals were applicable. Additional mechanistic studies are in progress.

Experimental Section

Butyl vinyl ether (**1a**, 1 equiv) was added to a solution of $GaBr_3$ (0.1 equiv, 0.05 M in dichloroethane) and ethylmethylketene methyl trimethylsilyl acetal (**2b**; 1.5 equiv). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HCl. The mixture was extracted with diethyl ether. The collected organic layer was dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm) to give the product **3ab** (92 %).

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Keywords: alkenes · homogenous catalysis · indium · silicon · synthetic methods

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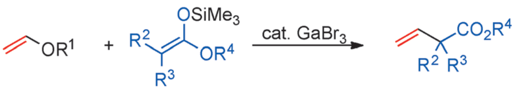
[13] In Equation (1), we observed the exclusive production of the silyl ether **5** in situ by ^{1}H NMR spectroscopy. And, we isolated silyl ether **5** without the quench with 1N HCl in another examination. See the Supporting Information.

[14] For the addition/elimination mechanism in $GaCl_3$-catalyzed reactions, see: a) R. Amemiya, A. Fujii, M. Arisawa, M. Yamaguchi, *J. Organomet. Chem.* **2003**, *686*, 94; b) R. Amemiya, K. Suwa, J. Toriyama, Y. Nishimura, M. Yamaguchi, *J. Am. Chem. Soc.* **2005**, *127*, 8252; c) R. Amemiya, Y. Miyake, M. Yamaguchi, *Tetrahedron Lett.* **2006**, *47*, 1797; d) Y. Nishimura, R. Amemiya, M. Yamaguchi, *Tetrahedron Lett.* **2006**, *47*, 1839.

[15] β Eliminations from β-oxyalkylmetals. Reviews for Peterson olefinations: a) D. J. Ager, *Synthesis* **1984**, 384; b) A. G. M. Barrett, J. M. Hill, E. M. Wallace, J. A. Flygare, *Synlett* **1991**, 764; c) L. F. van Staden, D. Gravestock, D. J. Ager, *Chem. Soc. Rev.* **2002**, *31*, 195; β Eliminations from β-oxyalkylmetals. Peterson olefinations using β-hydroxymetals other than β-hydroxysilanes: D. J. Ager, *Org. React.* **1990**, *38*, 1.

Communications



A 'Ga'llant couple: The α-alkenylation of esters was accomplished by $GaBr_3$-catalyzed coupling between alkenyl ethers and ketene silyl acetals. In this reaction system, various alkenyl ethers, including those with vinyl and substituted alkenyl groups, were applicable, and the scope of applicable ketene silyl acetals was sufficiently broad. The mechanism is also discussed.