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Tetrahedron Letters 49 (2008) 3492–3495

Tetrahedron Letters

(*Z*)-Selective Wittig and Corey–Chaykovsky reactions of propargyl ylides using trialkylgallium bases

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Received 21 February 2008; revised 12 March 2008; accepted 17 March 2008
Available online 24 March 2008

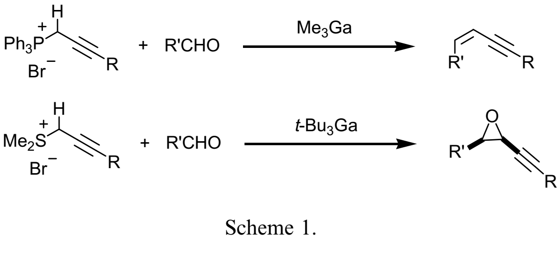
Abstract

Trialkylgalliums deprotonated propargylphosphonium salts and propargylsulfonium salts to form propargyl ylides. The resulted organogallium intermediates underwent the Wittig reaction and the Corey–Chaykovsky reaction with aldehydes giving (*Z*)-enynes and (*Z*)-epoxides predominantly. The use of an appropriate trialkylgallium is essential for the stereoselectivity.

Phosphorous and sulfur ylides, which are conveniently generated by the treatment of onium salts with bases, are a group of compounds used in organic synthesis. Their reactions with aldehydes or ketones give olefins and epoxides, respectively, the Wittig[1] and the Corey–Chaykovsky reaction.[2] Strong alkali metal bases such as butyllithium, sodium amides, or potassium hydride have been used for the generation of ylides, and these ylides exhibited different reactivity and the selectivity depending on the base. The base effect in the *E*/*Z* selectivity of the Wittig reaction is a well-documented example. Whereas lithium bases gave mixtures of (*E*)- and (*Z*)-isomers, sodium or potassium bases showed high (*Z*)-selectivity.[3] The observations were explained by the presence or absence of the interactions of the alkali metal cations and ylides.[4] It can therefore be expected that the use of other metal bases will exhibit still different reactivity and selectivity. However, such method has been unexplored, because the organometallic reagents other than alkali metal derivatives were considered not basic enough to deprotonate the α-position of the onium groups.

Previously, we reported a method to use trialkylgalliums for the deprotonation of ketones.[5] The reagent exhibited notable regioselectivity in the enolization of unsymmetrical ketones, which the conventional alkali metal bases did not. It was therefore considered interesting to extend the methodology to the deprotonation of other organic compounds, and described here is the ylide formation reactions of phosphonium and sulfonium salts. Relatively high (*Z*)-selectivity was observed for the Wittig and the Corey–Chaykovsky reaction using an appropriate trialkylgallium base (Scheme 1).

When (3-triethylsilyl-2-propynyl)triphenylphosphonium bromide **1** (2.0 equiv), trimethylgallium (2.0 equiv), and benzaldehyde **2** were treated in THF at room temperature for 1 h, 1-triethylsilyl-4-phenyl-3-buten-1-yne **3** was obtained in 93% yield in a ratio Z:$E = 74$:26 (Table 1, entry 1). The reactions with triethyl-, triisopropyl-, and tri(*t*-butyl)gallium gave (*E*)-**3** with lower selectivities (entries



Scheme 1.

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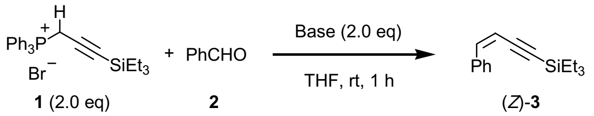
doi:10.1016/j.tetlet.2008.03.086

Table 1
Effect of trialkylgalliums on the Wittig reaction



Entry	Base	Yield (%) **3**	*Z*:*E*
1	Me_3Ga	93	74:26
2[a]		92	80:20
3[b]	$NaN(SiMe_3)_2/Me_3Ga$	71	76:24
4	$NaN(SiMe_3)_2$	66	11:89
5[b]	$BuLi/Me_3Ga$	71	67:33
6[c]	BuLi	91	28:72
7	Et_3Ga	87	39:61
8	*i*-Pr_3Ga	43	17:83
9	*t*-Bu_3Ga	22	32:68

[a] The reaction was conducted at 0 °C.

[b] **1** was treated with alkali metal bases at 0 °C for 1 h, and then Me_3Ga and **2** were added.

[c] **1** was treated with butyllithium at 0 °C for 1 h, and then **2** was added.

7–9). In order to know the effect of the gallium reagent, an ylide was prepared from **1** beforehand by sodium bis(trimethylsilyl)amide or butyllithium (1.0 equiv), and was reacted with benzaldehyde (1.0 equiv) in the presence of trimethylgallium (entries 3 and 5). The reaction proceeded with (*Z*)-selectivity in ratios similar to the reaction using trimethylgallium (entry 1). The results confirmed the importance of trimethylgallium for (*Z*)-selectivity. It was later found that the reaction at 0 °C enhanced the selectivity to 80:20 (entry 2).

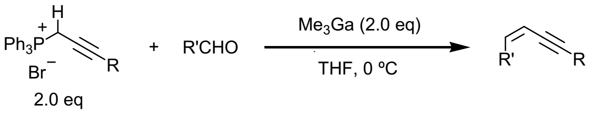
The reaction was applied to various propargylphosphonium salts and aldehydes, and (*Z*)-enynes were obtained in good stereoselectivity (Table 2). The electron-withdrawing group at the *p*-position of benzaldehyde enhanced the (*Z*)-selectivity (entry 3). A bulky aliphatic aldehyde showed higher (*Z*)-selectivity than less α-substituted aldehydes (entries 4–6). Propargylphosphonium salts with alkyl groups at the terminal carbon also underwent the (*Z*)-selective reactions in moderate yields at 60 °C (entries 12–15), which may be due to relatively low acidity of the propargyl protons of these substrates compared to the silyl derivatives.

The synthesis of (*Z*)-enynes by the olefination of aldehydes has attracted a considerable interest, and Yamamoto developed the (*Z*)-selective Peterson reaction using disilylated propargyl Grignard or titanium reagents derived from 1,3-bis(trialkylsilyl)propynes.[6] In general, the Wittig reaction of propargylphosphonium salts gives (*E*)-enynes as the major product,[7] and (*Z*)-selective reaction is rare restricted to the reaction of aldehydes possessing five-membered cyclic ether ring.[8] The present method can be useful for the synthesis of (*Z*)-enynes using phosphonium salts, which is more convenient to prepare than the propargylsilanes.

The ylide formation of propargylsulfonium salts using trialkylgalliums was next examined in order to compare the reactivity with the propargylphosphonium salts. The reaction of sulfonium ylides with aldehydes, the Corey–Chaykovsky reaction, generally gave (*E*)-epoxides, and an exception was reported using propargyltelluride.[9,10] Trialkylgallium method turned out to be effective for the (*Z*)-selective Corey–Chaykovsky reaction of propargylsulfonium ylide, which is generally easier to prepare than the corresponding tellurides.

(3-Triethylsilyl-2-propynyl)dimethylsulfonium bromide **4** (3.0 equiv), tri(*t*-butyl)gallium (2.5 equiv), and cyclohexanecarboxaldehyde **5** were treated in chlorobenzene at room temperature for 3 h, and (*Z*)-1-triethylsilyl-4-cyclohexyl-1-buten-3-yne epoxide **6** (*Z*:*E* = 93:7) was obtained in 70% yield (Table 3, entry 4). The use of trimethylgallium, triethylgallium, and triisopropylgallium showed lower (*Z*)-selectivity (entries 1–3).[11] The effect of bulkiness in the trialkylgalliums for the (*Z*)-stereoselectivity is reverse in the Corey–Chaykovsky and the Wittig reaction.

Table 2
The Wittig reaction of propargyl ylide using trimethylgallium



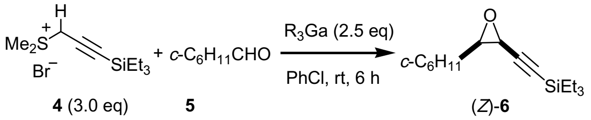
Entry	R	R′	Time (h)	Yield (%)	*Z*:*E*
1	$SiEt_3$	Ph	7	92	80:20
2		*p*-$CH_3C_6H_4$	10	86	78:22
3		*p*-ClC_6H_4	24	94	85:15
4		*n*-C_6H_{13}	10	82	85:15
5		*c*-C_6H_{11}	11	89	81:19
6[a]		*t*-Bu	24	71	88:12
7		*t*-$BuMe_2SiO(CH_2)_5$	10	87	81:19
8		$PhCO_2(CH_2)_5$	13	84	81:19
9	$SiBu_3$	*n*-C_6H_{13}	20	83	84:16
10	Si*i*-Pr_3	*n*-C_6H_{13}	20	94	84:16
11[b]	$SiMe_3$	*n*-C_6H_{13}	8	62	78:22
12[c]	*n*-C_6H_{13}	*n*-C_6H_{13}	4	63	77:23
13[c]		*c*-C_6H_{11}	4	45	78:22
14[c]	*c*-C_6H_{11}	*n*-C_6H_{13}	4	72	76:24
15[c]		*c*-C_6H_{11}	4	53	85:15

[a] The reaction was conducted using 3.0 equiv of phosphonium salt and 10.0 equiv of Me_3Ga.

[b] The reaction was conducted using 3.0 equiv of phosphonium salt and 3.0 equiv of Me_3Ga.

[c] The reaction was conducted using 4.0 equiv of Me_3Ga at 60 °C.

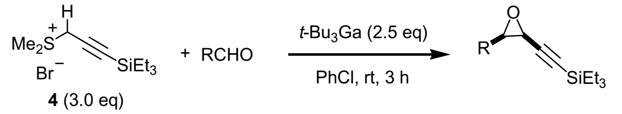
Table 3
Effect of trialkylgalliums on the Corey–Chaykovsky reaction



Entry	R_3Ga	Yield (%) **6**	*Z*:*E*
1	Me_3Ga	87	48:52
2	Et_3Ga	62	56:44
3	*i*-Pr_3Ga	30	75:25
4[a]	*t*-Bu_3Ga	70	93:7

[a] The reaction was conducted for 3 h.

Table 4
The Corey–Chaykovsky reaction of a propargylsulfonium salt using tri(t-butyl)gallium



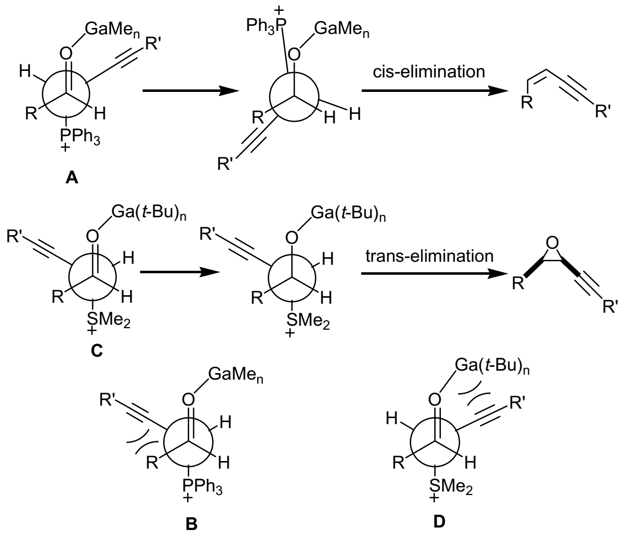
Entry	R	Yield (%)	Z:E
1	Ph	70	90:10
2	p-ClC$_6$H$_4$	75	92:8
3	p-BrC$_6$H$_4$	68	93:7
4	o-MeC$_6$H$_4$	68	92:8
5	c-C$_6$H$_{11}$	70	93:7
6[a]	n-C$_6$H$_{13}$	79	93:7
7[a]	PhCH$_2$CH$_2$	66	94:6

[a] The reaction was conducted using 4.0 equiv of sulfonium salt and 3.0 equiv of t-Bu$_3$Ga.

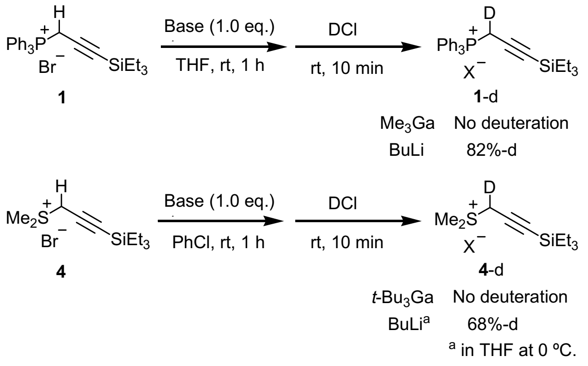
The reaction was applied to several aldehydes, and both aliphatic and aromatic aldehydes gave (Z)-epoxides predominantly (Table 4).

Both the ylides formed from phosphonium salts and sulfonium salts using trialkylgallium bases exhibited (Z)-selectivity. It is interesting to consider the stereoselectivity of these two reactions and the effect of the alkyl groups in the gallium-derived bases.[4] A hypothesis is presented in Scheme 2. Thus, ylide addition to aldehydes can be considered to take place with the anti-configuration of carbonyl oxygen coordinated with trialkylgallium and the onium group. In case of phosphonium ylide reaction, the lack of the gauche interactions between aldehyde R and ethynyl group would favor the transition state **A** rather than **B**. Then, the cis-elimination provided (Z)-enynes. In case of sulfonium ylides, the gauche interactions between the gallium t-butyl group and the ethynyl group became serious at the addition step, and the transition state **C** was favored over **D**. The trans-elimination provided (Z)-epoxides.

The interaction of carbonyl oxygen and trialkylgallium affected not only the addition process as noted above but also the deprotonation process. When **1** was reacted with trimethylgallium (1.0 equiv) at room temperature for 1 h followed by quenching with 10 M deuterium chloride in D$_2$O (5.0 equiv) at the same temperature for 10 min, no deuteration occurred in the recovered **1**. It was confirmed that the use of butyllithium gave **1**-d in a quantitative yield with 82%-d (Scheme 3). The results indicated that trimethylgallium deprotonated **1** only in the presence of an aldehyde, which may be due to the enhanced basicity of trimethylgallium by the coordination to aldehyde. A similar observation was obtained with a sulfonium salt.



Scheme 2.



Scheme 3.

In summary, (Z)-selective Wittig reaction and Corey–Chaykovsky reaction of propargyl ylides were developed using trialkylgallium base. The ligand effect on the gallium metal played an important role in the stereoselectivity.

Acknowledgment

Y.N. thanks JSPS for financial support (No. 18850004).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.086.

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11. A referee suggested to conduct the reaction using other bases. Use of $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$, *t*-BuOK, NaH, KOH, K_2CO_3, and Cs_2CO_3 did not give epoxide **6** by reacting at rt, and formed decomposed products derived from **4**. In contrast, butyllithium and LDA gave **6** in 43% ($Z{:}E = 98{:}2$) and 47% ($Z{:}E = 97{:}3$) yields, respectively. The origin of the metal effect on the stereochemistry is a subject of interest in future.