

# Transition-Metal-Free Formylation of Allylzinc Reagents Leading to $\alpha$ -Quaternary Aldehydes

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**Supporting Information** 

**ABSTRACT:** The first example of formylation of allylzinc reagents using *S*-phenyl thioformate is presented. The reaction proceeded under mild conditions without any transition-metal catalyst, forming quaternary carbon centers with reactive



functionalities, such as formyl and vinyl groups. Moreover, Barbier-type formylation of an allylic bromide with a sterically demanding thioformate was achieved. As a preliminary result, asymmetric formylation was conducted using a menthol-derived chiral thioformate.

C arbon-carbon bond formation reactions are still of central importance in organic synthesis. They are especially needed in the construction of quaternary carbon centers, which has been recognized as one of the most challenging tasks in synthetic chemistry because of the difficulties associated with the repulsion of four carbon substituents.<sup>1</sup> However, quaternary carbon centers are indispensable units found in many natural products and pharmaceuticals.<sup>2</sup> Therefore, the development of novel reagents and catalysts for the construction of quaternary carbon centers is a highly demanding but necessary synthetic task.

Aldehydes with quaternary carbons at the  $\alpha$ -position are useful building blocks of these centers because formyl groups can be utilized for various C–C, C–N, and C–S bond formation reactions.<sup>3</sup> The most established approach to the synthesis of  $\alpha$ -quaternary aldehydes is the reaction of  $\alpha,\alpha$ disubstituted aldehydes with C-electrophiles (Scheme 1, eq 1).<sup>4,5</sup> Other strategies employ carbon migration (Scheme 1, eq 2) or [3,3]-sigmatropic rearrangement (Scheme 1, eq 3) as an efficient process for the preparation of these aldehydes.<sup>6,7</sup>

Most recently, two research groups presented an elegant methodology for the preparation of  $\alpha$ -quaternary aldehydes by





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introducing formyl or imidoyl groups (Scheme 1, eq 4).<sup>8,9</sup> Fujihara and Tsuji developed a method for the formylation of allylcopper(I) species that were generated by borylcupration of allenes (Scheme 2, eq 1).<sup>9a</sup> Moreover, Ohmiya and Sawamura

# Scheme 2. Formylation and Imidoylation for the Construction of Quaternary Carbon Centers

Previous Work

Copper-Catalyzed Formylation (Fujihara and Tsuji)



Copper-Catalyzed Imidoylation (Ohmiya and Sawamura)



This Work

Transition-Metal-Free Formylation



reported the catalytic asymmetric synthesis of  $\alpha$ -quaternary aldehydes through the reaction of in situ-generated formimidoylcopper(I) species and allylic phosphates followed by hydrolysis (Scheme 2, eq 2).<sup>9b</sup> In most of these strategies (Scheme 1, eqs 1–4), catalysts play an important role in the construction of quaternary carbon centers by lowering the activation energy. Herein we describe the first example of



Α

intermediate

#### **Organic Letters**

formylation of allylzinc species with the use of S-phenyl thioformate (Scheme 2, eq 3). The reaction proceeded without any transition-metal catalyst under mild conditions, eventually forming quaternary carbon centers. A variety of allylzinc reagents were successfully employed in the formylation to afford  $\alpha$ -quaternary aldehydes bearing a terminal olefin. Moreover, a Barbier-type formylation reaction of an allylic bromide with a sterically demanding thioformate was achieved.

During the course of our research concerning catalytic formylation of organozinc reagents,<sup>10</sup> we focused on the formylation of  $\gamma$ , $\gamma$ -disubstituted allylzinc reagents. First, the palladium-catalyzed formylation of allylzinc reagent **1a** with **2a** was attempted under the optimized reaction conditions previously employed for the formylation of arylzinc reagents,<sup>10</sup> affording the formylated product **3a** in 75% yield (see the Supporting Information for details).

After extensive screening of different reaction conditions, it was found that the reaction proceeded at -78 °C for 30 min without any transition-metal catalyst, providing the desired product 3a in 94% yield (Table 1, entry 1). The effects of the



Me 1a (X = Br·	∼ZnX + PhS H THF -78 °C, 30 min 2a	Me 3a
entry	variation from the "standard" conditions $^{\!\scriptscriptstyle c}$	yield (%) <sup>b</sup>
1	none	94
2	HCOOEt instead of 2a	trace
3	HCOOPh instead of 2a	16
4	DMF instead of 2a	0
5	2b instead of 2a	93
6	2c instead of 2a	94
7	2d instead of 2a	94
8	at -40 °C	61
9	at 0 °C	60
10	at 25 °C	35

<sup>a</sup>Standard conditions: 1a (0.22 mmol) and 2a (0.20 mmol) in THF (2.0 mL) at -78 °C for 30 min. <sup>b</sup>Determined by <sup>1</sup>H NMR analysis of the crude mixture using dibromomethane as the internal standard. <sup>c</sup>Structures of 2b-d:



reaction parameters on the formylation are shown in Table 1. The use of ethyl or phenyl formate as the formylating reagent gave 3a in lower yield (Table 1, entries 2 and 3). Moreover, when dimethylformamide (DMF) was employed instead of 2a, no formation of the product was observed (Table 1, entry 4).<sup>11</sup> In contrast, the use of thioformates 2b-d instead of 2a allowed formation of the product in high yields (Table 1, entries 5–7). However, increasing the reaction temperature led to a gradual reduction in the reaction yield (Table 1, entries 8–10). From thioformates 2a-d used in the screening study, 2a was selected as an optimal formylating reagent because of its easy availability.

With the optimized reaction conditions in hand, the scope of allylzinc reagents in the formylation reaction was examined next (Table 2). Various allylzinc reagents with aryl and alkyl





<sup>*a*</sup>Standard conditions: 1 (0.22 mmol) and 2a (0.20 mmol) in THF (2.0 mL) at -78 °C for 30 min. <sup>*b*</sup>Br·LiCl is represented as X for clarity. <sup>*c*</sup>Isolated yields. <sup>*d*</sup>At -40 °C for 30 min. <sup>*e*</sup>At 0 °C for 10 min. <sup>*f*</sup>At -85 °C for 30 min. <sup>*g*</sup>At -100 °C for 1 h. <sup>*h*</sup>Isolated yield as an alcohol after reduction with NaBH<sub>4</sub>. <sup>*i*</sup>Determined by <sup>1</sup>H NMR analysis of the crude mixture using dibromomethane as the internal standard.

substituents at the  $\gamma$ -position (Table 2, entries 1–12) were utilized in this reaction to provide the corresponding  $\alpha$ -

quaternary aldehydes.<sup>12</sup> Both the presence of electron-donating and electron-withdrawing groups at the para position of the phenyl groups had little effect on the efficiency of the reaction (Table 2, entries 2–4). However, when sterically demanding allylzinc reagents were employed, the reaction temperature had to be increased for thioformate 2a to be completely consumed (Table 2, entries 5, 6, and 9). In contrast, in the case of 1k and 1l, which are not sterically demanding, the reaction temperature was decreased to -85 or -100 °C in order to suppress the decomposition of the products. Because of a problem associated with instability toward silica gel column chromatography, alcohol 3k' was obtained as a product after reduction with sodium borohydride (Table 2, entry 11).

In order to enhance the practicality of this formylation method, the Barbier-type formylation of allylic bromide 4 with 2a was investigated. In the reaction, zinc dust and lithium chloride converted allylic bromide 4 to allylzinc reagent 1a, which then reacted with 2a to afford the formylated product 3a. However, product 3a was obtained in only 30% yield when compound 4 was reacted with an equimolar amount of 2a at room temperature for 1 h (Table 3, entry 1). This

Table 3. Barbier-Type Formylation of Allylic Bromide 4 with Thioformate  $2^a$ 

Me Br 4 (1.0 equiv)	+	RS H LiCl (1.0 zinc duct (1 THF, rt	equiv) .5 equiv) , 1 h Me 3a
entry	2	yield of 5 $(\%)^b$	yield of 3 $(\%)^b$
1	2a	16	30
2	2b	34	0
3	2c	17	26
4	2d	9	46
5 <sup>c</sup>	2d	35	73

<sup>a</sup>Standard conditions: 4 (0.20 mmol) and 2 (0.20 mmol) in THF (2.0 mL) at room temperature for 1 h. <sup>b</sup>Determined by <sup>1</sup>H NMR analysis of the crude mixture using dibromomethane as the internal standard. <sup>c</sup>The amounts of 4 and zinc dust were increased to 0.40 and 0.60 mmol, respectively.

disappointing result was a consequence of the formation of allylic sulfide 5, which was caused by the reaction of 4 and in situ-generated zinc thiolate 6 (Scheme 3). We envisioned that



the appropriate choice of S substituent on thioformate 2 could suppress this side reaction to some extent. Therefore, the effects of changing thioformate 2 were investigated (Table 3). Among the reagents employed, mesityl-substituted thioformate 2d with a sterically demanding substituent gave the best result (Table 3, entry 4). Nitro-substituted 2b was decomposed by zinc dust and lithium chloride, resulting in no formation of the desired product 3a (Table 3, entry 2). Finally, the use of 2 equiv of allylic bromide 4 with 2d afforded product 3a in 73% yield. As a preliminary result, we carried out the asymmetric formylation of allylzinc reagents using chiral thioformate 2e, which was prepared from menthol in three steps. The synthetic route to 2e and the respective procedure are shown in the Supporting Information. Thioformate 2e was reacted with allylzinc reagent 1a under the optimized reaction conditions, affording (-)-3a in 44% yield with 34% ee (Scheme 4). In spite of the low enantioselectivity, this result indicated the potential to expand this formylation method to the asymmetric version.





In summary, we have developed the first example of formylation of allylzinc reagents with S-phenyl thioformate. This protocol enabled the construction of quaternary carbon centers with a formyl group and a terminal olefin. Moreover, studies showed that various allylzinc reagents could be successfully utilized in this reaction. In addition, Barbier-type formylation of an allylic bromide with a sterically demanding thioformate was achieved. Finally, preliminary investigations of the asymmetric formylation were conducted using a mentholderived chiral thioformate. Future work will be devoted to the design of effective chiral thioformates to improve the enantioselectivity of the asymmetric formylation.

#### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b00360.

Detailed experimental procedures and compound characterization data (PDF)

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## Notes

The authors declare no competing financial interest.

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(12) The reaction of a monosubstituted allylzinc reagent with 2a was also attempted, leading to the formation of a double-allylated secondary alcohol as the sole product (see the Supporting Information for details).