

# N-Heterocyclic Carbene-Initiated $\alpha$ -Acylvinyl Anion Reactivity: Additions of $\alpha$ -Hydroxypropargylsilanes to Aldehydes

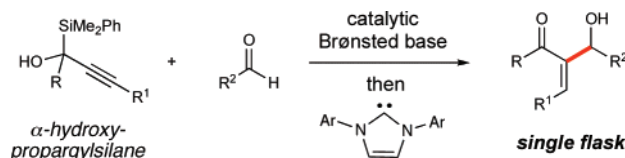
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## ABSTRACT



Highly substituted  $\alpha,\beta$ -unsaturated ketones are prepared by the N-heterocyclic carbene-initiated addition of  $\alpha$ -hydroxypropargylsilanes to aldehydes. This strategy serves as a highly efficient alternative to the standard Morita–Baylis–Hillman (MBH) approaches for these types of compounds. In contrast to the MBH reaction, different substitution in the  $\beta$ -position of the product (R<sup>1</sup>) can be accommodated in moderate to excellent yields with a high degree of control over the resulting alkene.

The Morita–Baylis–Hillman (MBH) reaction is an efficient reaction that generates highly functionalized compounds by employing  $\alpha$ -acylvinyl anion reactivity.<sup>1</sup> Significant advances in the MBH reaction have been made recently, including mechanistic studies as well as asymmetric and intramolecular variants.<sup>2,3</sup> Despite this progress, the intermolecular MBH reaction has intrinsic limitations. In particular, the  $\beta$ -substituents of the activated alkene starting materials (e.g., ethyl acrylate, vinyl ketones) are almost always hydrogen atoms. Recently, we reported the scandium(III)-catalyzed addition

of silyloxyallenes to aldehydes as a valuable alternative to the MBH and other  $\alpha$ -acylvinyl anion processes (Option I, Figure 1).<sup>4–6</sup> These reactions proceed under very mild conditions (10 mol % Sc(OTf)<sub>3</sub>) and accommodate a wide scope of  $\beta$ -substitution with excellent yields and a high degree of control over the resulting alkene geometry. Also, enantioenriched products could be synthesized by the (–)-

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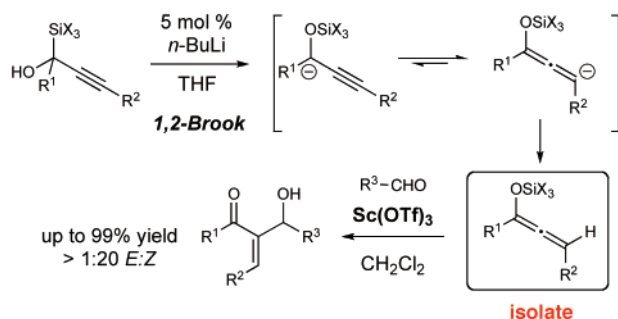
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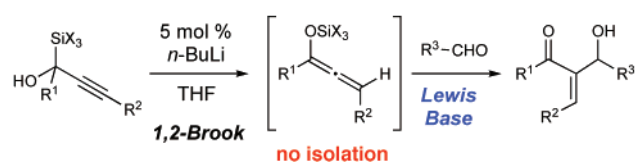
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### Option I: Lewis Acid-Catalyzed Addition (Step-wise)



### Option II: Lewis Base-Catalyzed Addition (Single Flask Operation)



**Figure 1.** Silyoxyallene addition strategies.

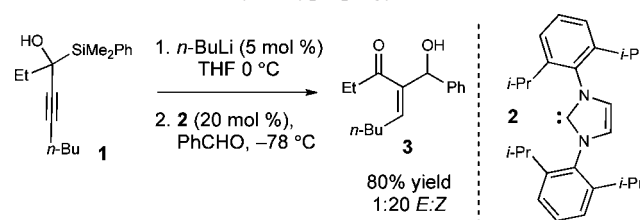
(salen)Cr(III)-catalyzed addition of racemic silyoxyallenes.<sup>4</sup> One aspect of the transformation is the prerequisite of preparing the silyoxyallenes in a separate step through the Kuwajima–Reich rearrangement of the  $\alpha$ -hydroxypropargylsilane precursors.<sup>7</sup> Herein, we present an alternative single-flask approach starting directly from the propargylsilanes, thus further enhancing the applicability of this unconventional  $\alpha$ -acylvinyl addition reaction (Option II, Figure 1).

Our current interests include the development of reactions employing Lewis base activation to efficiently access unconventional reactivity. Several transformations from our laboratory, including acyl anion additions, homoenolate reactions, alkyne additions, disilylations of activated alkenes, and hydroacylations of ketones have been facilitated by the use of Lewis bases.<sup>8</sup> Given our strong interest in the combination of Lewis basic promoters/catalysts, we reasoned that Lewis bases may activate silyoxyallenes toward addition. In particular, they should be more compatible with the rearrangement conditions (substoichiometric *n*-BuLi, THF) of the  $\alpha$ -hydroxypropargylsilanes to the allenes and facilitate a single flask procedure.

Starting with  $\alpha$ -hydroxypropargylsilane **1** in THF at 0 °C, the allene was formed with use of 5 mol % of *n*-BuLi. The

resulting solution was then cooled to –78 °C and followed by addition of benzaldehyde and a substoichiometric amount of Lewis base. At the onset of these studies, we performed a limited survey of nucleophilic species. For example, fluoride sources (20 mol % tetrabutylammonium difluorotriphenylsilicate, 27% yield) and potassium *tert*-butoxide (20 mol %, 20% yield) generated the desired product, but both these classes of anions afforded poor yields with virtually no catalyst turnover.<sup>9</sup> While a potential solution to increase the yields of this reaction was simply to add more fluoride or potassium alkoxide, we were compelled to identify a promoter that could be effective in amounts less than 1 equiv. We reasoned that the cations associated with the fluoride or alkoxides might be complicating the desired transformation and looked to find zwitterionic nucleophilic molecules that would avoid these possibilities. Gratifyingly, 20 mol % of *N*-heterocyclic carbene (NHC) **2** catalyzes the addition to benzaldehyde in an 80% yield and 1:20 *E*:*Z* ratio for the new alkene (Scheme 1).<sup>10,11</sup>

**Scheme 1.** NHC-Initiated Addition of  $\alpha$ -Hydroxypropargylsilane



*N*-Heterocyclic carbenes have become increasingly powerful in synthesis not only as ligands but also as reagents and catalysts for several bond-forming transformations, including benzoin condensations, Stetter reactions, homoenolate additions, transesterifications, and acylations.<sup>12,13</sup> The use of an NHC to activate silicon reagents has only been observed recently.<sup>14</sup> Song and co-workers were the first to demonstrate that *N*-heterocyclic carbenes effectively catalyze the addition of TMSCF<sub>3</sub> as well as TMSCN to carbonyl compounds in high yields and with very low catalyst loadings.<sup>15</sup> This reactivity has also been reported with the NHC-catalyzed ring-opening of aziridines with silylated nucleophiles.<sup>16</sup> Most

(7) (a) Kuwajima, I.; Kato, M. *Tetrahedron Lett.* **1980**, 21, 623–626. (b) Reich, H. J.; Olson, R. E.; Clark, M. C. *J. Am. Chem. Soc.* **1980**, 102, 1423–1424.

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(10) Arduengo, A. J., III; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, 55, 14523–14534.

(11) Attempts at using a single base to catalyze both the rearrangement as well as the addition provided low yields of desired product.

(12) For reviews of *N*-heterocyclic carbenes as ligands, see: (a) Herrmann, W. A.; Ofele, K.; Von Preysing, D.; Schneider, S. K. *J. Organomet. Chem.* **2003**, 687, 229–248. (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, 41, 1291.

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(14) (a) Song, J. J.; Tan, Z. L.; Reeves, J. T.; Gallou, F.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2005**, 7, 2193–2196. (b) Song, J. J.; Gallou, F.; Reeves, J. T.; Tan, Z. L.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.* **2006**, 71, 1273–1276.

recently, Song and his colleagues have extended their research to include carbene-catalyzed additions of silyl enol ethers in Mukaiyama aldol reactions.<sup>17</sup>

With the optimized bond-forming conditions in hand for this process, we set out to investigate the scope of the reaction using **1** as the nucleophilic precursor (Table 1). Addition

**Table 1.** Addition of  $\alpha$ -Hydroxypropargylsilane **1** to Aldehydes

entry	aldehyde	product	<i>E:Z</i> <sup>a</sup>	yield (%) <sup>b</sup>
1		<b>3</b>	1:20	80
2		<b>4</b>	1:20	70
3		<b>5</b>	1:20	73
4		<b>6</b>	1:20	70
5		<b>7</b>	1:20	38
6		<b>8</b>	1:20	45

<sup>a</sup> Determined by 500 MHz <sup>1</sup>H NMR spectroscopy. <sup>b</sup> Isolated yields.

occurred readily to aromatic aldehydes (entries 1–4) in good yields. The  $\alpha$ -hydroxypropargylsilane **1** also added to aliphatic aldehydes (entries 5 and 6) albeit in lower yields. For all of the aldehydes, the *E/Z* selectivity of the reaction was greater than 1:20 favoring the *Z* isomer.

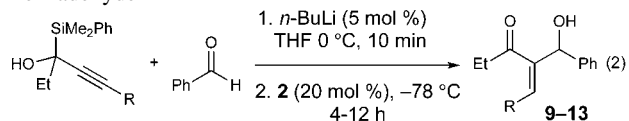
An advantage of this reaction over the standard MBH approaches is the tolerance of  $\beta$ -substitution of the alkene on the product (Table 2). A wide range of  $\alpha$ -hydroxypropargylsilanes are tolerated including both alkyl (entry 1) and aromatic (entry 2) substituted substrates. A trimethylsilyl (entry 3), silyl protected alcohol (entry 4), and *tert*-butyl (entry 5) group can also be accommodated. Moderate to excellent yields were achieved as well as excellent *E:Z* regiocontrol.

(15) Other NHC-catalyzed cyanation reactions: (a) Fukuda, Y.; Maeda, Y.; Ishii, S.; Kondo, K.; Aoyama, T. *Synthesis* **2006**, 589–590. (b) Fukuda, Y.; Maeda, Y.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, 54, 397–398. (c) Fukuda, Y.; Maeda, Y.; Kondo, K.; Aoyama, T. *Synthesis* **2006**, 1937–1939. (d) Fukuda, Y.; Kondo, K.; Aoyama, T. *Synthesis* **2006**, 2649–2652. (e) Suzuki, Y.; Abu Bakar, M. D.; Muramatsu, K.; Sato, M. *Tetrahedron* **2006**, 62, 4227–4231. (f) Kano, T.; Sasaki, K.; Konishi, T.; Mii, H.; Maruoka, K. *Tetrahedron Lett.* **2006**, 47, 4615–4618.

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(17) Song, J. J.; Tan, Z. L.; Reeves, J. T.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2007**, 9, 1013–1016.

**Table 2.** Addition of  $\alpha$ -Hydroxypropargylsilanes to Benzaldehyde



entry	silyoxyallene	product	<i>E:Z</i> <sup>a</sup>	yield (%) <sup>b</sup>
1		<b>9</b>	1:10	78
2		<b>10</b>	1:20	94
3		<b>11</b>	1:20	61
4		<b>12</b>	1:20	72
5		<b>13</b>	1:20	88

<sup>a</sup> Determined by 500 MHz <sup>1</sup>H NMR spectroscopy. <sup>b</sup> Isolated yields.

The role of the *N*-heterocyclic carbene in this reaction is currently under investigation: two reaction pathways can be envisaged (Scheme 2). The first possibility is that the *N*-heterocyclic carbene acts in a catalytic capacity. In their recent report, Song and co-workers invoke initial NHC addition to the TMS enol ether, which subsequently activates the silyloxy species to form a pentavalent silicon complex analogous to other Lewis base-catalyzed Mukaiyama aldol reactions.<sup>18</sup> Support for this pathway includes the known interaction of TMSI as well as polychlorosilanes with *N*-heterocyclic carbenes to form stable adducts.<sup>19</sup> However, these experiments by Kuhn involved less sterically encumbered carbenes than **2**.

A second possible mode of reactivity is an NHC-initiated reaction in which the *N*-heterocyclic carbene interacts with the aldehyde and not the silyloxy compound. A clear possibility based on the known interactions of *N*-heterocyclic carbenes with aldehydes<sup>13</sup> is the initial addition of the nucleophilic NHC **2** to the aldehyde to form an alkoxide intermediate **14** devoid of an external cation, which can then proceed to desilylate the silyloxyallene **1** via silyl transfer.<sup>20</sup> This highly reactive “naked” allenolate would react readily with a second equivalent of aldehyde to form the desired

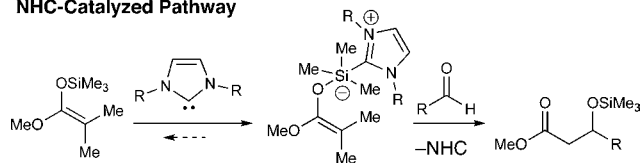
(18) See ref 17. For a recent review of the Mukaiyama aldol reaction see: Mukaiyama, T. *Angew. Chem., Int. Ed.* **2004**, 43, 5590.

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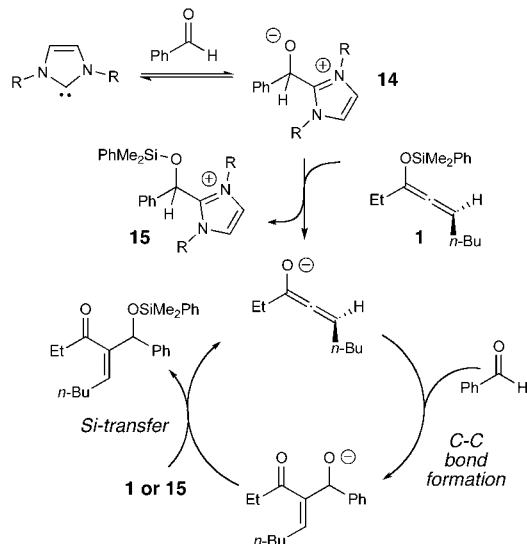
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## Scheme 2. Proposed Mechanisms

### NHC-Catalyzed Pathway



### NHC-Initiated Pathway



carbinol product (Figure 1). A similar model has been proposed previously by both Aoyama et al. and Suzuki et al. with cyanosilylations of carbonyl compounds.<sup>15</sup>

We lend support for the latter NHC-initiated mechanism with the isolation and X-ray structure of the *N*-heterocyclic carbene–aldehyde adduct (Figure 2). In an effort to elucidate

and recrystallization of the resulting solid produced the NHC–aldehyde adduct as a single product with chloride as the counterion to the positively charged heterocycle (**H14·Cl**, Figure 2). The NHC–Si adduct was not detected or recovered under the reaction conditions. This ORTEP provides for the first time definitive, structural evidence for the widely invoked addition of carbenes to aldehydes. Initial experiments to determine if this adduct is a catalyst in the reaction were inconclusive most likely due to the potential reversibility of the addition. We believe this adduct to be the more likely intermediate in the addition of silyloxyallenes and aldehydes “catalyzed” by *N*-heterocyclic carbenes. We reason that the aldehyde carbonyl carbon is significantly more accessible to the NHC **2** than the silicon atom of the silyloxyallene. An examination of space-filling depictions of tetrasubstituted silyl species and a large, sterically encumbered *N*-heterocyclic carbene such as **2** make a direct interaction between the C2 carbon of the carbene and the silicon atom highly tenuous.

In summary, we have developed a highly efficient single-flask procedure for the addition of α-hydroxypropargylsilanes to aldehydes. The reaction generates β-substituted unsaturated ketone products in moderate to excellent yields with exquisite control of the alkene geometry. The reaction pathway of this process currently invokes the initial formation of a nucleophilic alkoxide resulting from the addition of a free *N*-heterocyclic carbene to an aldehyde. This alkoxide promotes a silyl group transfer to generate a reactive allenolate. Structural evidence supporting the NHC–aldehyde adduct as the initiator of the reaction has been reported. Further investigations of the synthetic utility of silyloxyallenes and this unique mode of silicon activation reported herein are currently underway.

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**Supporting Information Available:** Experimental procedures and spectral data for all new compounds, and a CIF file for **H14·Cl**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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**Figure 2.** ORTEP of NHC–aldehyde Adduct **H14·Cl**.<sup>21</sup>

the role of the *N*-heterocyclic carbene in our reaction, benzaldehyde (1 equiv), chlorodimethylphenylsilane (1 equiv), and **2** (1 equiv) were combined in THF at  $-78^{\circ}\text{C}$ . After warming, the removal of the solvent under reduced pressure

(21) Solvent, hydrogen atoms (including OH) were removed from ORTEP for clarity. X-ray data for **14**:  $\text{C}_{36}\text{H}_{45}\text{Cl}_5\text{N}_2\text{O}$ , MW = 698.99,  $T = 153(2)\text{ K}$ ,  $\lambda = 0.71073\text{ Å}$ , monoclinic space group,  $P2(1)/c$ ,  $a = 10.0917(8)\text{ Å}$ ,  $b = 15.981(12)\text{ Å}$ ,  $c = 23.623(18)\text{ Å}$ ,  $\beta = 95.076(1)^{\circ}$ ,  $V = 3794.8(5)\text{ Å}^3$ ,  $Z = 4$ ,  $D_c = 1.223\text{ g/cm}^3$ ,  $\mu = 0.411\text{ mm}^{-1}$ ,  $F(000) = 415$ , crystal size  $0.30 \times 0.29 \times 0.28\text{ mm}^3$ , independent reflections 9255 [ $R(\text{int}) = 0.0930$ ], reflections collected 35196, refinement method was full-matrix least-squares on  $F^2$ , goodness-of-fit on  $F^2$  was 0.976, final  $R$  indices [ $I > 2\sigma(I)$ ]  $R_1 = 0.0906$ ,  $wR_2 = 0.2519$ ,  $R$  indices (all data)  $R_1 = 0.1274$ ,  $wR_2 = 0.2519$ , largest diff. peak and hole 2.047 and  $-1.193\text{ e Å}^{-3}$ . See the Supporting Information for additional details.