Asymmetric Catalysis

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# Catalytic Enantioselective α-Acylvinyl Anion Reactions of Silyloxyallenes**

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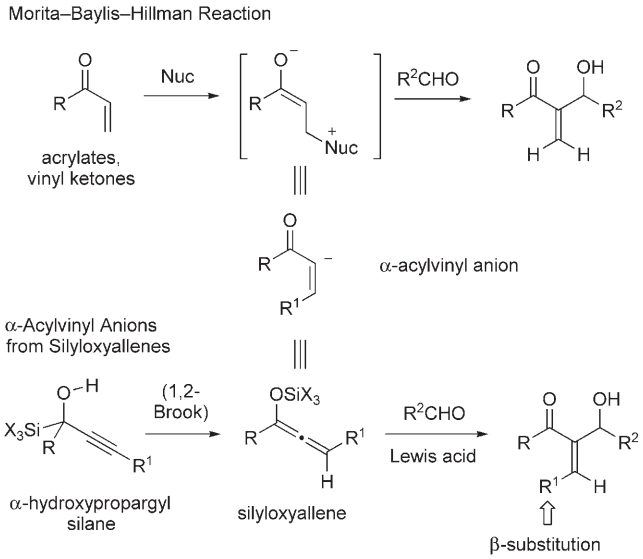
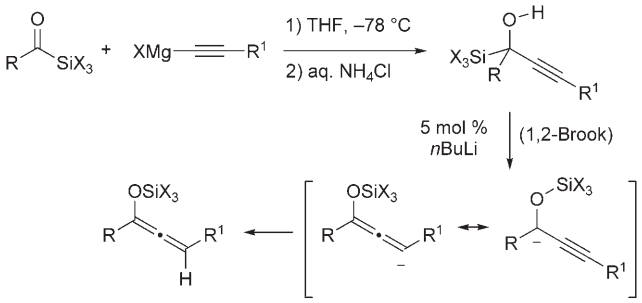
The asymmetric and catalytic construction of carbon–carbon bonds remains a considerable challenge and important goal in organic chemistry.[1] This aim is especially relevant for the synthesis of pharmaceutical agents and biologically active natural products. A significant focus of our research program is the development of new methods to facilitate nonobvious and unconventional C–C bond disconnections.[2,3] Recently, we have expanded our interests in these unusual strategies to include the development of useful α-acylvinyl anion equivalents. These anions are nontraditional nucleophiles that provide access to highly valuable α,β-unsaturated carbonyl compounds in a convergent fashion.[4] The Morita–Baylis–Hillman (MBH, Scheme 1) reaction is the classic method to access this type of reactivity.[5] Even with recent advances in this area, intermolecular MBH reactions are typically restricted to acrylates and unsubstituted vinyl ketones, because the generation of the necessary enolate involves the initial conjugate addition of a nucleophilic catalyst. Use of other α-acylvinyl anion equivalents primarily involves the trapping of allenolate intermediates accessed in situ, which limits the control of stereoselection and reactivity.[6,7]




*Scheme 1.*

The value of this unusual bond construction and limitations of existing approaches are compelling reasons to investigate alternatives with potentially much broader utility. In this vein, we recently reported the addition of silyloxyallenes to aldehydes under scandium(III)-catalyzed conditions, giving a wide range of β-substituted α,β-unsaturated carbinols in excellent yields with control over alkene geometry.[8,9] The synthesis of silyloxyallenes from the corresponding acylsilanes is based on the straightforward Kuwajima–Reich rearrangement of hydoxypropargysilanes (Scheme 2).[10] Herein, we describe the catalytic enantioselective development of this unconventional α-acylvinyl anion reaction.




*Scheme 2.* Silyloxyallenes from acylsilanes.

Given the synthetic potential of silyloxyallenes as α-acylvinyl anions, we initiated work to develop asymmetric processes using these unique nucleophiles. Initial studies using enantioenriched silyloxyallenes as the chiral components in combination with achiral Lewis acids were discontinued owing to the lack of efficient transfer of stereochemical information. However, after an extensive survey of potential chiral Lewis acids and reaction conditions with racemic silyloxyallene **1** and 2-chlorobenzaldehyde, we determined that [(salen)Cr($SbF_6$)] (**2**, salen = N,N′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexandiamine) was an efficient catalyst with excellent control over the alkene geometry and the new stereogenic center ($Z{:}E > 20{:}1$, 94% *ee*).[11]

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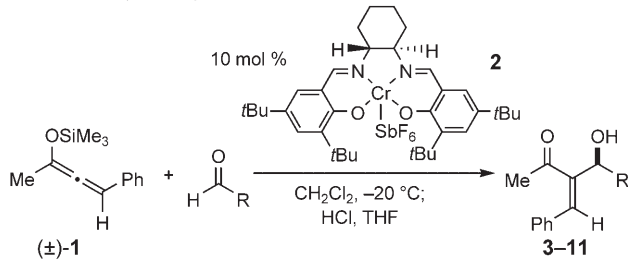
On the basis of these optimized conditions, the scope of this asymmetric α-acylvinyl anion addition was explored by combining silyloxyallene **1** in $CH_2Cl_2$ at −20 °C with 10 mol % **2** and various aldehydes (Table 1). Aromatic aldehydes as

***Table 1:*** Aldehyde scope.[a]



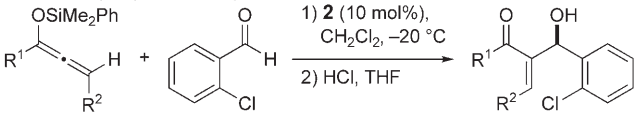

| Entry | R | Yield [%][b] | *Z*:*E*[c] | *ee* [%][d,e] |
|---|---|---|---|---|
| 1 | Ph | 88 | 20:1 | 85 (**3**) |
| 2 | 1-naphthyl | 84 | 20:1 | 91 (**4**) |
| 3 | 2-Cl($C_6H_4$) | 99 | 20:1 | 94 (**5**) |
| 4 | 2-Br($C_6H_4$) | 98 | 20:1 | 91 (**6**) |
| 5 | 2-OTBS($C_6H_4$) | 79 | 20:1 | 86 (**7**)[f] |
| 6 | 4-Cl($C_6H_4$) | 94 | 20:1 | 88 (**8**) |
| 7 | 4-Me($C_6H_4$) | 74 | 20:1 | 84 (**9**) |
| 8 | $PhCH_2CH_2$ | 95 | 20:1 | 61 (**10**) |
| 9 | cyclohexyl | 57 | 20:1 | 34 (**11**) |

[a] 1.5 equiv **1**, 1 equiv aldehyde. [b] Yield of isolated product after column chromatography. [c] Determined by $^1$H NMR spectroscopy (500 MHz). [d] Determined by chiral HPLC, Chiracel OD column. [e] The absolute configuration of **8** was determined by single crystal X-ray diffraction and the configuration of the other compounds were assigned by analogy; see the Supporting Information. [f] *tert*-butyl methyl ether used as solvent; TBS = *tert*-butyldimethylsilyl.

substrates provide excellent yields and enantioselectivities of the carbinol products (Table 1, entries 1–7). Aliphatic aldehydes are competent electrophiles for the addition reaction, but the current optimal $Cr^{III}$ Lewis acid affords secondary alcohols with lower enantioselectivity (Table 1, entries 8 and 9). The reaction with cyclohexanecarboxaldehyde proceeds at the slowest rate of all substrates examined to date and provides a poor yield of the desired product.

In addition to the electrophilic component of this reaction, various silyloxyallenes were also examined for their nucleophilic abilities in the presence of the chiral chromium(III) catalyst.[12] The achiral work with $Sc(OTf)_3$ (OTf = $O_3SCF_3$) as the Lewis acid had demonstrated that an advantage of this methodology was the capacity of the silyloxyallene to incorporate a broad range of substituents at the β-position of the α,β-unsaturated ketone product. Gratifyingly, this aspect of the reaction remains true for the new $Cr^{III}$-catalyzed transformation. The alkyl-, trimethylsilyl-, and *tert*-butyl-substituted silyloxyallenes add to 2-chlorobenzaldehyde in very high yields and selectivities (Table 2, entries 1, 2, and 3). A protected alcohol can also be used, giving excellent results as well (Table 2, entry 4). The use of 1-ethyl silyloxyallene (Table 2, entry 5) also works well, with 88 % *ee*, thereby indicating that the *n*-alkyl substitution in this position is not problematic. The methyl and ethyl substituents at the 1-position of these nucleophiles are significant for

***Table 2:*** Silyloxyallene Scope.[a]




| Entry | $R^1$ | $R^2$ | Yield [%][b] | *Z*:*E*[c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1 | Me | *n*Bu | 98 | 15:1 | 80 (**12**) |
| 2 | Me | $SiMe_3$ | 90 | 20:1 | 90 (**13**) |
| 3 | Me | *t*Bu | 99 | 20:1 | 90 (**14**) |
| 4 | Me | $(CH_2)_3$OTBS | 92 | 20:1 | 87 (**15**) |
| 5 | Et | Ph | 96 | 20:1 | 88 (**16**) |

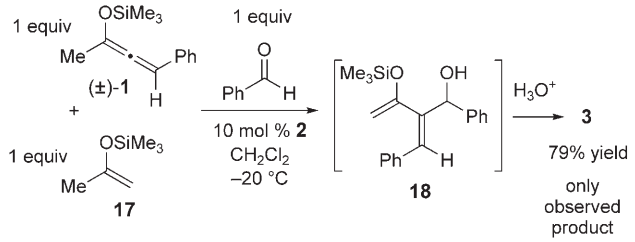
[a] 1.5 equiv silyloxyallene, 1 equiv aldehyde. [b] Yield of isolated product after column chromatography. [c] Determined by $^1$H NMR spectroscopy (500 MHz). [d] Determined by chiral HPLC, Chiralcel OD column.

applications in total synthesis; further exploration of additional silyloxyallene structures are ongoing.

After initially examining the scope of the transformation, we explored the stereochemical aspects of the α-acylvinyl anion addition. Since the reaction involves two chiral reagents (racemic silyloxyallene and optically active catalyst **2**), kinetic resolution of the racemic allene during the reaction is a distinct possibility. To explore this potential situation, two equivalents of **1** and a single equivalent of 2-chlorobenzaldehyde were combined in the presence of chromium(III) Lewis acid **2**. After full consumption of the aldehyde (as determined by thin layer chromatography), the reaction mixture was filtered through a pad of silica and concentrated in vacuo. At 100 % conversion to product, the analysis of the remaining silyloxyallene (as determined by HPLC with a Chiralcel OD column) indicated that there was no optical enrichment—the allene starting material remains racemic during the course of the reaction. From this result, one enantiomer of allene does not appear to undergo preferential reaction with the chiral aldehyde–Lewis acid complex. However, subjecting enantioenriched silyloxyallene to $Cr^{III}$ catalyst **2** in $CH_2Cl_2$ at −20 °C for 12 h results in racemization of the allene.[13] While we currently cannot make conclusive statements regarding the reaction rates of addition of each antipode of the silyloxyallenes, this interesting observation provides future opportunities to use racemic silyloxyallenes in enantioselective processes.

Given the limited number of examples of silyloxyallenes in Lewis acid promoted reactions, we probed their relative reactivity.[14] For example, reaction of silyloxyallene **1** (1 equiv) and enolsilane **17** (1 equiv) in the presence of one equivalent of benzaldehyde and 10 mol % **2** affords only **3** after desilylation (Scheme 3).[15] In a second experiment, 10 mol % $Sc(OTf)_3$ as the Lewis acid with the same reactants provides a 1.5:1 ratio of the aldol product (from addition of **17**) and **3**. Since related $Cr^{III}$ Lewis acids are known to catalyze carbonyl ene reactions between enolsilanes and aldehydes,[11] we currently favor this mechanistic pathway via **18**.[16] In support of this contention, we can observe the sensitive hetero-ene intermediate analogous to **18** from 2-chlorobenzaldehyde and silyloxyallene **1** using a modified procedure. These silyloxydienes are instable towards various

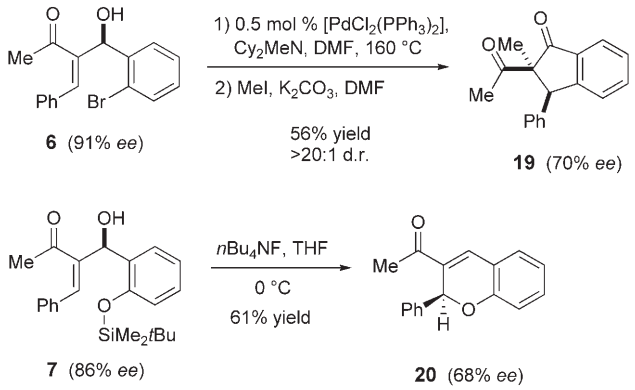
  




***Scheme 3.*** Competition experiment.

purification techniques, but after rapid chromatography, the intermediate diene from entry 3 of Table 1 can be isolated in 18% yield along with the hydrolyzed product **5** in 69% yield. Aryl-substituted silyloxyallenes ($R^1 = Ph$) do not afford products, which also supports an ene-type mechanism. Lastly, the above comparison of the two Lewis acid experiments indicates that these allenes are similar in reactivity to enolsilanes in a Mukaiyama reaction[17] but more reactive in a carbonyl ene pathway.

Our preliminary studies on the synthetic utility of the products from this reaction have produced two new cyclization reactions of the 2-substituted aryl compounds. The aryl bromide addition product (91% *ee*, **6**) can be converted to a disubstituted indanone in 10 min with 0.5 mol% palladium(II) in DMF with microwave heating. The subsequent exposure of this diketone to methyl iodide in the presence of potassium carbonate delivers indanone **19**, which possess a new quaternary center, in 70% *ee* and greater than 20:1 d.r. (Scheme 4).[18] In a second approach, the exposure of 2-




***Scheme 4.*** Indanone and chromene synthesis.

silyloxyaryl carbinol (86% *ee*) **7** to $n$Bu$_4$NF in THF at low temperature delivers the 2,3-disubstituted chromene **20** in 61% yield and 68% *ee*.[19] While there is a modest erosion of optical activity in these cyclizations, the promising transfer of chirality, even at high temperatures in the case of **19**, bodes well for additional transformations utilizing these α-acylvinyl equivalent addition products.

In summary, the first general, enantioselective addition of silyloxyallenes to aldehydes catalyzed by a {(salen)Cr$^{III}$} complex has been developed. This α-acylvinyl anion transformation provides efficient access to highly functionalized β-hydroxy unsaturated ketones with a high degree of control over both the resulting alkene and the secondary alcohol stereocenter. In the presence of the Cr$^{III}$ catalyst, silyloxyallenes undergo selective additions to aldehydes in the presence of a standard enolsilane. The isolation of silyloxydienes from the reaction before a hydrolysis step supports a Lewis acid catalyzed carbonyl ene-type mechanism. Lastly, the products from the reaction can be converted easily into substituted indanones and chromenes with good transfer of chirality. The development and applications of new reactions involving these latent allenolates derived easily from acylsilanes are in progress.[20]

## Experimental Section

2-Chlorobenzaldeyde (26 μL, 0.23 mmol) was added to a 2-dram vial equipped with a magnetic stir bar and **2** (19 mg, 0.023 mmol). The vial was cooled to −20 °C and silyloxyallene **1** (75 mg, 0.34 mmol) in $CH_2Cl_2$ (250 mL) was added via syringe in one portion. Upon consumption of aldehyde (24 h) as determined by TLC, the solution was concentrated in vacuo. The resulting residue was dissolved in THF (5 mL) and treated with 1M HCl (1 mL). After 30 min, the solution was diluted with water (10 mL) and ether (20 mL). The aqueous layer was discarded, and the ether layer was washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL). The resulting ether layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated to provide the unpurified carbinol. The residue was purified by flash chromatography (15% EtOAc/hexanes) to afford 65 mg (99%) of **5** as yellow oil. IR (film): $\tilde{\nu} = 3423, 3061, 2920, 1681, 1431, 1354, 1196, 1028, 755, 700\ cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 7.64$ (d, $J = 7.7$ Hz, 1H), 7.39–7.27 (m, 6H), 7.20 (m, 2H), 6.79 (s, 1H), 5.88 (d, $J = 5.1$ Hz, 1H), 3.54 (d, $J = 5.3$ Hz, 1H), 1.89 ppm (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta = 208.4, 142.9, 138.3, 135.6, 134.5, 132.7, 129.8, 129.3, 129.0, 128.9, 128.8, 127.4, 72.9, 31.4$ ppm; LRMS (electrospray): Exact mass calcd for $C_{17}H_{15}O_2Cl$ $[M]^+$ 286.08. Found $[M-H]$ 285.4. $[\alpha]_D = +22.2\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($CH_2Cl_2$, $c = 1.0\ g\,cm^{-3}$, *ee* = 94%). Enantiomeric ratio was measured by chiral HPLC (Chiralcel OD-H, 5% IPA/Hexanes, $R_{t1} = 11.86$, $R_{t2} = 12.41$).

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[20] Detailed experimental procedures and full characterization of new compounds are contained in the Supporting Information. CCDC-631929 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

  