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COMMUNICATIONS

Published on Web 11/10/2006

Stereoselective Lewis Acid-Catalyzed α-Acylvinyl Additions

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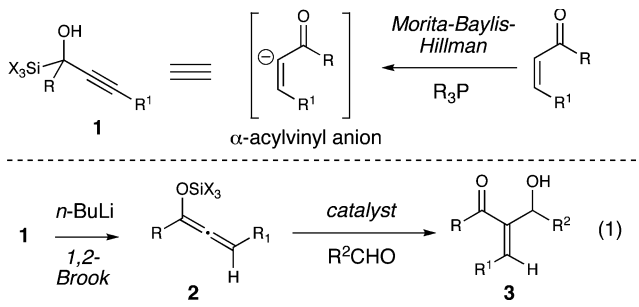
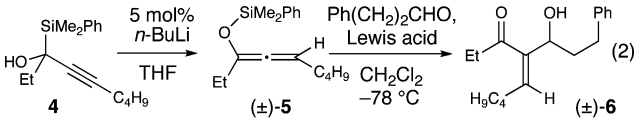
The development of atypical nucleophilic reagents provides unconventional access to valuable molecules.[1] A well-established catalytic method to access unusual α-acylvinyl anion reactivity is the Morita−Baylis−Hillman (MBH) reaction.[2,3] Advances to render this reaction enantioselective[4] and intramolecular[5] have been recently reported, but the MBH process continues to be restricted in scope and selectivity. Since the reaction involves a conjugate addition of a catalytic nucleophile, the *β*-substituent (R^1) is typically a hydrogen atom. A potential alternative strategy to generate α-acylvinyl anion reactivity is the use of silyloxyallenes prepared from α-hydroxypropargylsilanes **1**.[6] Herein we report a stereoselective process for the addition of silyloxyallene **2** derived from **1** to carbonyl compounds catalyzed by Lewis acids (eq 1). This sequence efficiently generates α,*β*-unsaturated carbonyl compounds **3** with control over alkene geometry and the stereochemistry of the newly formed carbinol.



The conversions of α-hydroxypropargylsilanes into silyloxyallenes were pioneered independently by Kuwajima[7] and Reich.[8] Kuwajima demonstrated that racemic α-hydroxypropargylsilanes undergo a base-catalyzed rearrangement to form silyloxyallenes **2**. In a related process, Reich converted acylsilanes into allenyl metal reagents via a [1,2]-Brook rearrangement[9] initiated by the addition of alkynyl lithium reagents. The allenyl anions generated in situ using Reich's method have been used in alkylations, protonations, and formylations. However, employing related *neutral* silyloxyallenes as nucleophiles has been limited to date, and the few examples require harsh conditions or are limited to *β*-halo substitution.[10] With our interest in acylsilanes and unusual nucleophiles,[11] we recognized that an efficient method to access α-acylvinyl anions under mild conditions would significantly enhance the utility of these unconventional reagents.[12]

Our strategy initially focused on the use of Lewis acids with silyloxyallene **5** (Table 1). The controlled addition of alkynyl Grignard reagents to acylsilanes furnishes the racemic propargylsilanes in high yields.[13] The corresponding allene is obtained by exposure of **4** to 5 mol % of *n*-BuLi and removal of THF in vacuo.[14] Stoichiometric quantities of strong Lewis acids (BF_3, entry 1) deliver **6** in good yield, favoring the *Z* alkene. In searching for a catalytic variant, scandium(III) triflate emerged as the most efficient catalyst for additions of silyloxyallene **5**. Surprisingly, numerous other metal triflate salts surveyed did not promote the reaction.[15] In the optimal process, 10 mol % of $Sc(OTf)_3$ generates the desired α-acylvinyl addition product **6** at low temperature with excellent selectivity for the *Z* alkene isomer (1:20, *E*:*Z*).

Table 1. Optimization of α-Acylvinyl Anion Additions



4 (±)-**5** (±)-**6**

entry	Lewis acid	*E*:*Z*[a]	yield (%)[b]
1	1 equiv of $Et_2O{\cdot}BF_3$	1:6	80
2	10 mol % of TMS−OTf	1:4	52
3	10 mol % of $Cu(OTf)_2$		0
4	10 mol % of $Zn(OTf)_3$		0
5	10 mol % of $Sc(OTf)_3$	1:20	78

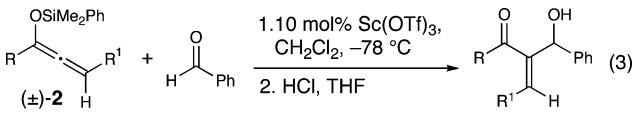
[a] Determined by 500 MHz ^{1}H NMR spectroscopy. [b] Isolated yield.

In contrast to the MBH reaction, this process accommodates a wide variety of *β*-substitution of the α-acylvinyl nucleophile and also provides the products in greater than 90% yield (Table 2). Aryl-, alkyl- (entries 1, 2, and 4), and trimethylsilyl (entry 3)-substituted silyloxyallenes are excellent substrates for this Lewis acid-catalyzed reaction. A silyl-protected alcohol (entry 5) and a *tert*-butyl group (entry 6) can also be incorporated into the products without complications. Notably, the product alkene geometry for these reactions is 20:1 favoring the *Z* isomer (except for R^1 = Me).

Racemic silyloxyallene **5** also adds to a variety of aromatic and unbranched aliphatic aldehydes with excellent yields and alkene selectivity (Table 3). Enolizable α-branched aldehydes afford complex reaction mixtures, and further work with these substrates is necessary. With 20 mol % of Sc(III), allene **5** smoothly adds to pivaldehyde (entry 6), resulting in a 95% yield. A highly reactive ketone does provide low yields under the current reaction conditions (entry 8).

With this selective bond-forming sequence in hand, we wished to control the stereochemistry of the product through chirality transfer from the propargylsilane (reagent control). Accordingly, we have developed a catalytic asymmetric alkyne addition to acylsilane **20** using tridentate Schiff base ligand **21** to access an

Table 2. Addition of Silyloxyallenes **2** to Benzaldehyde



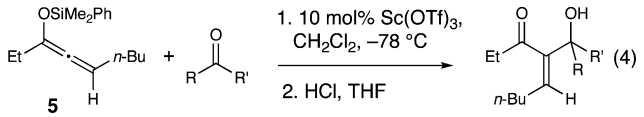
(±)-**2**

entry	R	R^1	*E*:*Z*[a]	yield (%)[b]
1	Et	Me	1:4	99 (**7**)
2	Et	Ph	1:20	98 (**8**)
3	Et	$SiMe_3$	1:20	98 (**9**)
4	Et	*n*-Bu	1:20	91 (**10**)
5	Et	$CH_2OTBDPS$	1:20	97 (**11**)
6	Et	*t*-Bu	1:20	98 (**12**)
7	C_3H_5	*n*-Bu	1:20	95 (**13**)

[a] Determined by 500 MHz ^{1}H NMR spectroscopy. [b] Isolated yield.

10.1021/ja0653674 CCC: $33.50

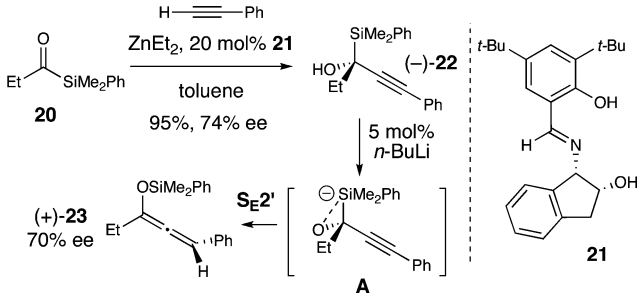
Table 3. Additions of Allene **5** to Aldehydes



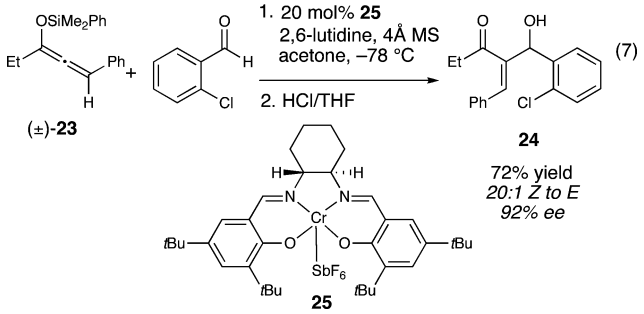
entry	R	R′	*E*:*Z*[a]	yield (%)[b]
1	Ph	H	1:20	91 (**10**)
2	4-Cl-Ph	H	1:20	96 (**14**)
3	4-MeO-Ph	H	1:20	97 (**15**)
4	2-Nap	H	1:20	98 (**16**)
5	$PhCH_2CH_2$	H	1:20	78 (**6**)
6	*t*-Bu	H	1:20	95 (**17**)[c]
7	C_3H_5	H	1:20	56 (**18**)
8	Ph	COMe	1:20	18 (**19**)[c]

[a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield. [c] 20 mol % of $Sc(OTf)_3$.

enantioenriched propargylsilane (**22**) in 74% ee.[16] The exposure of (−)-**22** to 5 mol % of *n*-BuLi at −78 °C provided chiral allene (+)-**23** with minimal erosion of stereochemical information. This process is presumably controlled by a [1,2]-Brook rearrangement-initiated S_E2' pathway from an intermediate such as **A**, and studies to explore this rearrangement further are underway.[17] Initial results employing (+)-**23** and $Sc(OTf)_3$ proved unpromising for chirality transfer.[18] While the geometry of (+)-**23** enforces a strong preference for the electrophile to approach away from the phenyl substituent (*E* vs *Z* selectivity), there is not sufficient bias to control the facial selectivity of the aldehyde (enantioselectivity).



With substrate control proving unlikely, we examined chiral catalysts for the addition of racemic silyloxyallenes (e.g., **23**). Gratifyingly, the use of (−)-(salen)Cr(III)−SbF_6 with racemic silyloxyallene **23** (1 equiv) and 2-chlorobenzaldehyde (1 equiv) affords carbinol **24** in 92% ee, demonstrating that a chiral catalyst can modulate the facial selectivity of both reagents with a high level of control.[19]



In summary, silyloxyallenes generated from acylsilanes undergo scandium(III)-catalyzed α-acylvinyl additions to a variety of aldehydes. A wide range of *β*-substitution on the allene is accommodated with excellent yields and a high degree of control over the new alkene geometry. The carbinol stereocenter of the resulting unsaturated ketone products can be controlled by a chiral catalyst. Full development of the asymmetric addition of alkynes to acylsilanes as well as the enantioselective Cr(III)-catalyzed reactions with silyloxyallenes are underway and will be reported in due course.

Acknowledgment. Financial support for this work has been provided by Northwestern University, the NSF, and the PRF. K.A.S. thanks Abbott, Amgen, 3M, and Boehringer Ingelheim for generous research support. Wacker Chemical, FMCLithium, and BASF have provided reagents for this work. We thank Dr. Jacob Janey (Merck) for the kind gift of (−)-1,2-*cis*-aminoindanol.

Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0653674