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Highly Selective α-Acylvinyl Anion Additions to Imines

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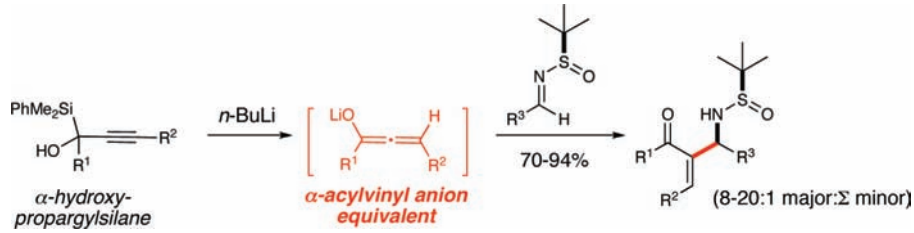
ABSTRACT



α-Hydroxypropargylsilanes undergo rearrangement to form reactive lithium allenolates. The resulting α-acylvinyl anion equivalents undergo highly selective additions to *N-tert*-butanesulfinyl imines generating *β*-substituted *aza*-MBH-type products. High yields are achieved for a wide range of α-hydroxypropargylsilanes as well as for a diverse selection of imines. The reactions proceed with good to excellent diastereoselectivity and regioselectivity (8−20:1 major/∑ minor) favoring the *Z*-isomer of the alkene.

Optically active, chiral amines are valuable and ubiquitous compounds found abundantly in many biologically active natural products and pharmaceutical agents.[1] Consequently, synthetic methods that access these useful amines in a modular and stereocontrolled manner are exceedingly important. One such approach is the *aza*-Morita−Baylis−Hillman (*aza*-MBH) reaction, which involves the Lewis base-catalyzed addition of an electron-deficient alkene and an activated imine (Scheme 1).[2] This formal α-acylvinyl anion addition generates highly functionalized, allylic amines efficiently and in an atom-economical fashion.[3−5] Recently, the *aza*-MBH reaction has been the subject of many synthetic advances. Particularly, the development of enantioselective variants has allowed for the rapid generation of optically active amines in a highly convergent manner.[6] Unfortunately, this reaction remains limited in many aspects. Useful asymmetric *aza*-MBH reactions are reported *only* for aromatic-substituted imines, and the electron deficient olefin (e.g., vinyl ketone or acrylate) is typically unsubstituted at the *β*-position of the alkene, thus further restricting the substrate scope. Due to these problematic restrictions and the substantial value of the chiral amine products, alternative methods that access allylic amines with similar substitution patterns as the *aza* -MBH reaction with far greater substrate scope are essential.[7]

Our research group has focused on the development of new reactions utilizing nontraditional nucleophiles for the construction of unconventional carbon−carbon bonds.[8] One particular area of current interest is the addition of α-acylvi-

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(6) For examples of enantioselective *aza*-MBH reactions, see: (a) Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *47*, 4507. (b) Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103. (c) Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2003**, *44*, 2521. (d) Shi, M.; Chen, L. H. *Chem. Comm.* **2003**, 1310. (e) Shi, M.; Xu, Y. M.; Shi, Y. L. *Chem.−Eur. J.* **2005**, *11*, 1794. (f) Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701. (g) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680. (h) Shi, M.; Chen, L. H.; Li, C. Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790. (i) Liu, Y. H.; Chen, L. H.; Shi, M. *Adv. Synth. Catal.* **2006**, *348*, 973. (j) Vesely, J.; Dziedzic, P.; Cordova, A. *Tetrahedron Lett.* **2007**, *48*, 6900. Also, see ref 2d.

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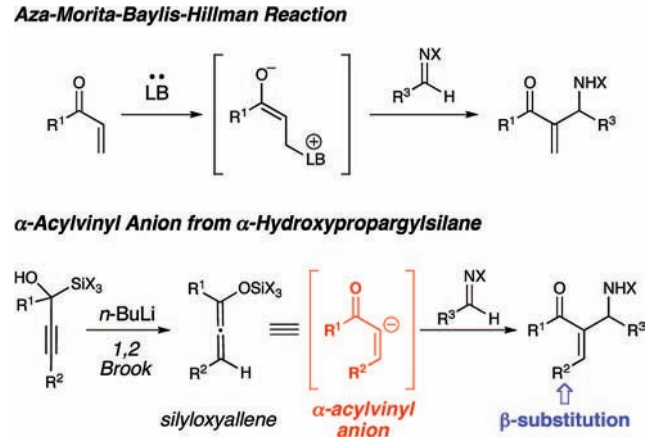
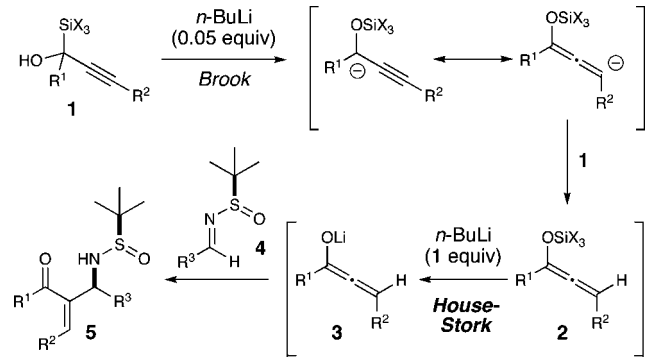
nyl anion equivalents from easily accessible precursors. We have demonstrated that silyloxyallenes, which can be prepared directly from α-hydroxypropargylsilanes via a base-initiated rearrangement, serve as latent allenolates and valuable α-acylvinyl anion equivalents. In the presence of catalytic Lewis acid or base, silyloxyallenes undergo additions to aldehydes in excellent yields for a wide range of substrates.[9,10] These reactions are highly selective forming *Z*-substituted α,*β*-unsaturated carbinol products exclusively. Excellent enantioselectivities can be achieved as well using a Cr(III)-catalyst.[11] Herein, we address the limitations of the *aza*-MBH reaction by adding silyloxyallene-derived α-acylvinyl anion equivalents to imines to afford allylic amines with excellent levels of selectivity and yield (Scheme 1, bottom).

Our synthetic strategy explored the diastereoselective α-acylvinyl anion additions to *N-tert*-butanesulfinyl imines. Elegant work by Davis and Ellman has previously demonstrated that metal reagents (e.g., Grignard and organolithium reagents, metal enolates) undergo 1,2-additions to optically active sulfinyl imines with excellent stereocontrol.[12] Due to the mild nucleophilicity of silyloxyallenes, we postulated that more reactive lithium allenolates, which can be prepared readily from the silyloxyallene via the House−Stork desilylation method, should undergo addition to the *N-tert*-butanesulfinyl imine.[13] More desirably, we sought to begin directly from α-hydroxypropargylsilane **1**, conducting the rearrangement to silyloxyallene **2**, desilylation to lithium allenolate **3**, and addition to imine **4** in a single-flask operation (Scheme 2). If successful, this method would generate *β*-substituted *aza*-MBH-type products rapidly with exquisite stereocontrol in a single flask.

Scheme 1. α-Acylvinyl Anion Additions to Imines



Scheme 2. Addition of α-Hydroxypropargylsilanes to *N-tert*-Butane Sulfinylimines



Starting with α-hydroxypropargylsilane **1a**, we examined the reaction with *tert*-butanesulfinyl imine **4a**. Lithium allenolate **3a** was prepared *in situ* using *n*-BuLi in THF at 0 °C followed by addition of imine **4a**. Gratifyingly, the *β*-substituted *aza*-MBH-type product was obtained in 70% yield (Table 1, entry 1). Unfortunately, the stereoselectivity of the addition is low (2:1 major/sum of minor). The selectivity of the addition can be improved by lowering the temperature prior to the addition of the imine (entries 2−3). However, the stereoselectivity is still only 5:1 at −78 °C (entry 3). A variety of additives were examined to enhance the selectivity. While forming different metal allenolates via transmetallation led to low yields and selectivities, the addition of hexamethylphosphoramide (HMPA) to the reaction mixture improves the stereolectivity of the addition (entry 4−6). In fact, increasing the amount of HMPA (5:1 HMPA/*n*-BuLi, entry 6) gives the optimal results. The product was obtained exclusively as the *Z*-isomer in 75% yield and 20:1 dr.

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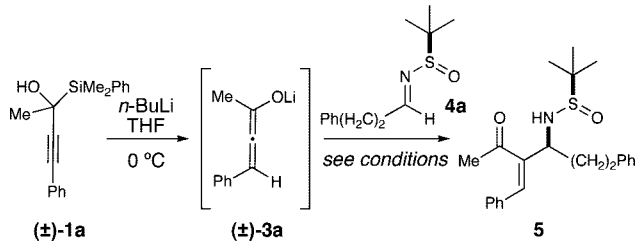
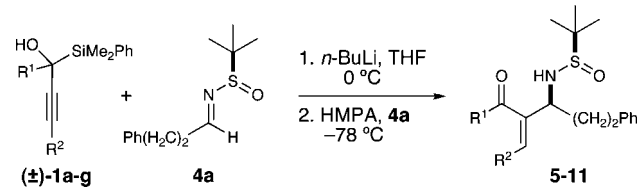
Table 1. Optimization of Reaction[a]



entry	conditions	yield (%)[b]	major/Σ minor[c]
1	0 °C	70	2:1
2	−40 °C	61	3:1
3	−78 °C	64	5:1
4	−78 °C, 2.5 equiv HMPA	64	6:1
5	−78 °C, 5.0 equiv HMPA	73	7:1
6	−78 °C, 12.5 equiv HMPA	75	20:1

[a] Two equivalents of **1a**, 2.5 equiv of *n*-BuLi, 1 equiv of **4a**. [b] Yield of isolated product after column chromatography. [c] Determined by ^{1}H NMR spectroscopy (500 MHz).

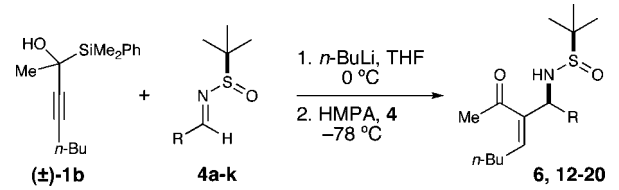
Table 2. α-Hydroxypropargylsilane Scope[a]



entry	R^1	R^2	yield (%)[b]	major/Σ minor[c]
1	Me	Ph (**1a**)	75	20:1 (**5**)
2	Me	*n*-Bu (**1b**)	77	17:1 (**6**)
3	Me	*t*-Bu (**1c**)	83	20:1 (**7**)
4	Me	$(CH_2)_3$OTBS (**1d**)	85	13:1 (**8**)
5	Et	Ph (**1e**)	70	20:1 (**9**)
6	*i*-Pr	Ph (**1f**)	70	20:1 (**10**)
7[d]	*t*-Bu	Ph (**2g**)	86	20:1 (**11**)

[a] Two equivalents of α-hydroxypropargylsilane, 2.5 equiv of *n*-BuLi, 12.5 equiv of HMPA, 1 equiv of **4a**. [b] Yield of isolated product after column chromatography. [c] Determined by ^{1}H NMR spectroscopy (500 MHz). [d] Reaction was conducted starting from the silyloxyallene, see Supporting Information for details.

Table 3. *tert*-Butane Sulfinylimine Scope[a]



entry	R	yield (%)[b]	major/Σ minor[c]
1	Ph (**4b**)	84	13:1 (**12**)
2	4-Cl-Ph (**4c**)	85	14:1 (**13**)
3	4-Br-Ph (**4d**)	77	11:1 (**14**)
4	4-OMe-Ph (**4e**)	81	20:1 (**15**)
5	2-Cl-Ph (**4f**)	83	13:1 (**16**)
6	PhCH=CH (**4g**)	71	20:1 (**17**)
7	$PhCH_2CH_2$ (**4a**)	77	17:1 (**6**)
8	*i*-Pr (**4h**)	94	10:1 (**18**)
9	CyHex (**4i**)	84	8:1 (**19**)
10	*t*-Bu (**4j**)	74	8:1 (**20**)

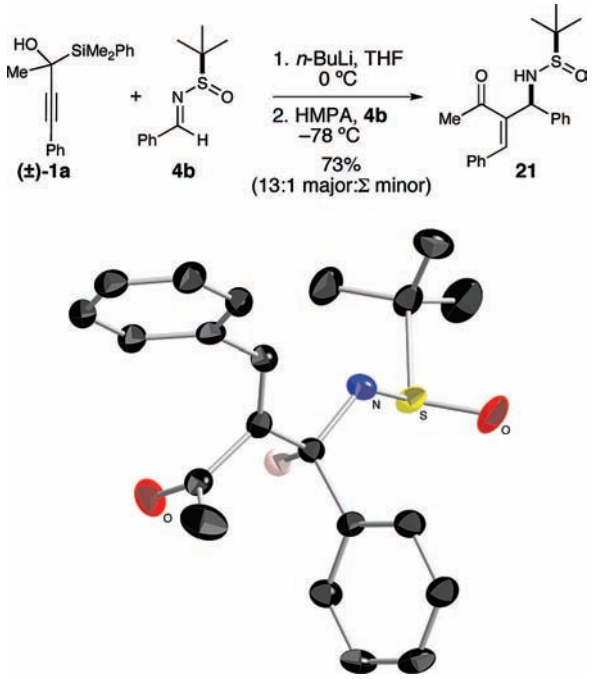
[a] Two equivalents of **1b**, 2.5 equiv of *n*-BuLi, 12.5 equiv of HMPA, 1 equiv of imine. [b] Yield of isolated product after column chromatography. [c] Determined by ^{1}H NMR spectroscopy (500 MHz).

With the optimized bond-forming conditions in hand, the scope of the α-acylvinyl anion addition was investigated. First, various α-hydroxypropargylsilanes were studied (Table 2). The reaction was discovered to be general for the propargylsilane component. A wide range of β-substituents (R^2) is accommodated. Aryl and alkyl substituted propargylsilanes give good yields and selectivities (entries 1 and 2). A bulky *tert*-butyl group can be incorporated as well as a TBS-protected alcohol (entries 3 and 4). Substitution at R^1 was also explored. Ethyl, *iso*-propyl, and *tert*-butyl substituted lithium allenolates are all quality substrates (entries 5−7). Each of the β-substituted products is formed in high yields with good to excellent stereoselectivity (13−20:1). The effect of the imine on the reaction was investigated as well (Table 3). Various electron-rich and electron-poor aromatic imines react with α-hydroxypropargylsilane **1b** (entries 1−5). Excellent yields are achieved as well as regio- and diastereoselectivities. Selective 1,2-addition is observed with cinnamyl imine **4g** in 71% yield, 20:1 Z/E, and 20:1 dr (entry 6). Aliphatic imines are also tolerated (entries 7−10). Notably, α-substituted imines are reactive partners. Both *iso*-propyl and cyclohexyl imines undergo additions in good yields and stereoselectivity (entries 8 and 9). α-Hydroxypropargylsilane **1b** even reacts with *tert*-butyl imine **4j** with good results (entry 10). Upon examining the scope of the transformation, we explored the stereochemical aspects of the α-acylvinyl anion addition. First, the absolute stereochemistry of the addition product **21** was determined to be *S* after single crystal X-ray crystallography (Scheme 3).

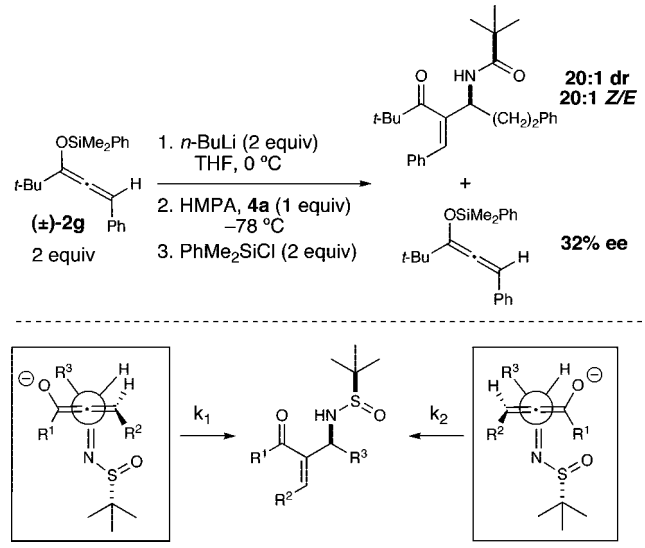
Since the reaction involves two chiral reagents (racemic lithium allenolate and optically active imine), a kinetic resolution of the allene during the reaction is possible.[14] To explore this potential reaction pathway, two equivalents of the lithium allenolate, prepared from silyloxyallene **2g**, and a single equivalent of imine **4a** were combined under the optimized conditions. After full consumption of the imine (as measured by thin layer chromatography), chlorodimethylphenylsilane (2 equiv) was added and the reaction mixture was allowed to warm to 0 °C to silylate the unreacted allenolate (Scheme 4, top). The reaction was quenched with pH = 7 phosphate buffer and, after an extraction with ethyl acetate, the unreacted silyloxyallene was purified by flash chromatography on silica gel. Analysis of the remaining silyloxyallene (as determined by HPLC with a Chiralcel-

(14) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1.

Scheme 3. Absolute Stereochemistry and ORTEP of **21**



Scheme 4. Mechanistic Studies



OD column) indicated that **2g** was optically enriched at 32% ee. From this result, one enantiomer of the allene appears to undergo preferential reaction with the chiral imine.

To explain the high stereoselectivity exhibited in this reaction, we propose the α-acylvinyl anion addition to go through two diastereoconvergant transition states exhibiting slightly different rates (Scheme 4, bottom). In the presence of HMPA, we postulate that a noncoordinated allenolate is formed which will then proceed through open transition states via synclinal disposition minimizing dipole−dipole interactions.[15,16] The high diastereoselectivity of the addition is achieved since the "naked" allenolate will most likely attack the imine opposite the bulky *tert*-butyl group. The high regioselectivity favoring the *Z*-alkene product is then due to the electrophiles preferential approach away from the R^2 substituent. Interactions with the R^1 substituent lead to the difference in rates of addition of each enantiomer of allene.

In conclusion, α-hydroxypropargylsilanes undergo facile rearrangement to form reactive lithium allenolates in situ. The resulting α-acylvinyl anion equivalent undergoes highly selective additions to *N*-*tert*-butanesulfinyl imines generating *β*-substituted *aza*-MBH-type products. High yields are achieved for a wide range of α-hydroxypropargylsilanes as well as for a diverse selection of imines. The reactions proceed with good to excellent stereoselectivity (8−20:1) favoring the *Z*-isomer of the alkene. Further studies of α-hydroxypropargylsilanes and silyloxyallenes as α-acylvinyl anion equivalents and applications of these *β*-substituted *aza*-MBH-type products are currently ongoing.

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

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