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Annulations of Enantioenriched Allenylsilanes with in Situ Generated Iminium Ions: Stereoselective Synthesis of Diverse Heterocycles

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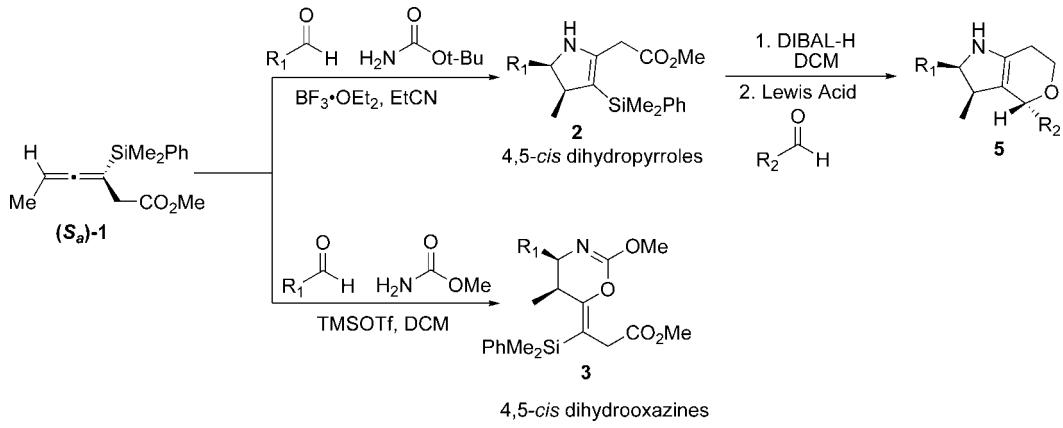
ABSTRACT



Highly enantioenriched allenylsilanes participate in Lewis acid mediated annulations with in situ generated iminium ions derived from *tert*-butyl carbamate and methyl carbamate to selectively form functionalized 4,5-dihydropyrroles and 4,5-dihyrooxazines, respectively. The dihydropyrrole products were further elaborated in a stereocontrolled vinylsilane terminated cyclization with in situ generated oxonium ions, resulting in pyranopyrroles.

Recently allenes have emerged as an important functional group for a variety of organic transformations.[1] In particular, allenylsilanes have proven useful as carbon nucleophiles in addition to carbon−oxygen π-bonds producing homopropargylic alcohols,[2] homopropargylic ethers,[3] furans,[4] and dihydrofurans.[5] Many of these reactions occur with excellent diasetereo- and enantioselectivity.

Whereas the additions of allenylsilanes to carbonyl groups have been well developed, there are fewer examples of similar reactivity with activated carbon−nitrogen π-bonds. The addition of crotylsilanes to in situ generated iminium ions for the formation of homoallylic amines and pyrrolidines has been well developed and generally proceeds with high

(1) For recent reviews on allene chemistry see: (a) Hassam, H. H. A. M. *Curr. Org. Synth.* **2007**, *4*, 413–439. (b) Ma, S. *Chem. Rev.* **2005**, *105*, 2829–2872. (c) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067–3125.

(2) (a) Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870–3878. (b) Marshall, J. A.; Maxson, K *J. Org. Chem.* **2000**, *65*, 630–633.

(3) Brawn, R. A.; Panek, J. S. *Org. Lett.* **2007**, *9*, 2689–2692.

(4) Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407–4413.

(5) Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1985**, *107*, 7233–7235.

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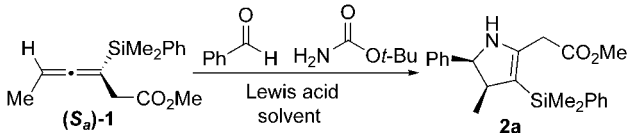
Table 1. Optimization of the Annulation of (S_a)-**1** with Benzaldehyde and *tert*-Butyl Carbamate



entry	Lewis acid	time (h)	solvent	yield (%) of **2a**[a]	dr[c]
1	TMSOTf	48	DCM	9	>20:1
2	TMSOTf	48	EtCN	41	>20:1
3	$TiCl_4$	48	DCM	<5	>20:1
4	$TiCl_4$	48	EtCN	33	>20:1
5	TfOH	48	DCM	44	>20:1
6	TfOH	48	EtCN	47	>20:1
7	BF_3•OEt_2	72	DCM	14	>20:1
8	BF_3•OEt_2	72	MeCN	56	>20:1
9	BF_3•OEt_2	72	EtCN	67	>20:1

[a] Isolated yields after purification over silica gel. All reactions run with 1.2 equiv of Lewis acid at −78 to −40 °C except for entry 8, which was run at −40 °C. [c] Diastereomeric ratios were determined by ^{1}H NMR analysis on crude material.

yield and selectivity.[6] Racemic allenes have been used in a variety of additions to imines, resulting in [3 + 2] and [4 + 2] annulation products, many with high diastereoselectivity and enantiomeric excess due to the use of chiral catalysts.[7] In addition, a few reports containing examples of allenylsilanes being used in [3 + 2] annulations with iminium ions are available, but they show a limited substrate scope and selectivity. In interest of complete transparency, Danheiser was the first to demonstrate a [3 + 2] annulation of racemic allenylsilanes with β-alkoxylactams, affording pyrrolizinones as the major products.[5] More recently, Akiyama reported a Cu(I)-catalyzed cycloaddition to afford dihydroproline derivatives.[8] The purpose of this communication is to report our initial studies on the use of chiral allenylsilanes in annulations with *N*-acyl iminuim ions generated in situ from carbamates and aldehydes.

We have recently reported an efficient synthesis of highly enantioenriched allenylsilane (S_a)-**1** and its enantiomer. That sequence, from the corresponding propargylic alcohol, utilized a lipase resolution followed by a Johnson orthoester Claisen rearrangement. These reagents can be accessed on a multigram scale (>15 g) with >95% ee.[3]

Several conditions were explored for the addition of these allenylsilanes to iminium ions, which were formed in situ

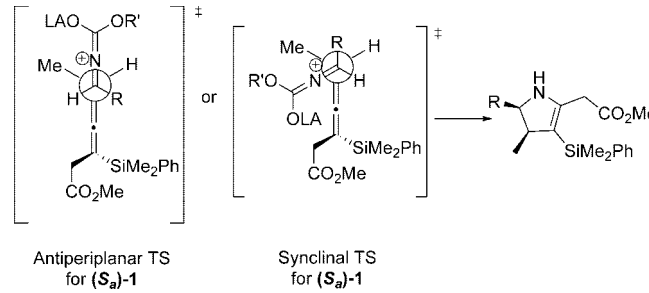


Figure 1. Open transition state model. For detailed analysis on the proposed transition states, see Supporting Information.

by activating an aldehyde in the presence of an amine with a Lewis acid. After screening a number of amines, benzyl amines, hydrazones, and acetamides were found to be unreactive under a variety of conditions, and the use of sulfonamides resulted in a complex mixture of products. Carbamates proved to be the most effective amine source for iminium ion formation. When allenylsilane (S_a)-**1** was exposed to benzaldehyde in the presence of *tert*-butyl carbamate and a Lewis acid activator, the major product obtained was dihydropyrrole **2a**.

The optimal Lewis acid for iminium ion formation was found to be BF_3•OEt_2. Attempts to catalyze the reaction with $Sc(OTf)_3$ resulted in the recovery of the starting materials, while $TiCl_4$, TfOH, and TMSOTf provided lower yields (see Table 1). Use of an excess of Lewis acid led to decomposition of the products, and using substoichiometric amounts of Lewis acid resulted in incomplete reactions. No protodesilylation product was isolated under any of the reaction conditions, suggesting that the vinylsilane product is robust. Polar nitrile solvents (MeCN, EtCN) were found to give the highest yields for the [3 + 2] annulation reactions.[9] In all cases a single diastereomer was observed as determined by NMR analysis. The best yields were obtained when the iminium ion was formed in situ, by treatment of a solution of aldehyde and carbamate with Lewis acid at −78 °C. The allenylsilane was then added dropwise, and the resulting solution was warmed to −40 °C.

The stereochemical course of the [3 + 2] annulation can be described by either an antiperiplanar or synclinal transition state, where the axial chirality of the allenylsilane (S_a)-**1** is transferred to the *si* face of the iminium ion (see Figure 1). The antiperiplanar transition state limits the gauche interactions, while the synclinal transition state places the R group of the iminium ion furthest from the incoming allenylsilane. The absolute sterechemistry of the products is based on the addition to the allene being *anti* to the carbon−silicon bond.[10]

The [3 + 2] annulations were successful for a variety of aldehydes (see Table 2). Aromatic aldehydes typically

(6) (a) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1994**, *59*, 2674–2675. (b) Schaus, J. V.; Jain, N. F.; Panek, J. S. *Tetrahedron* **2000**, *56*, 10263–10274. (c) Lipomi, D. J.; Panek, J. S. *Org. Lett.* **2005**, *7*, 4701–4704. (d) Restorp, P.; Fischer, A.; Somfai, P. *J. Am. Chem. Soc.* **2006**, *128*, 12646–12647.

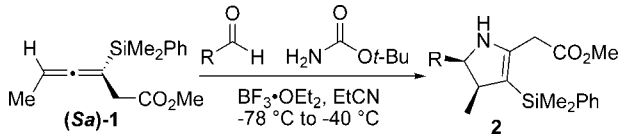
(7) (a) Depature, M.; Grimaldi, J.; Hatem, J. *Eur. J. Org. Chem.* **2001**, 941–946. (b) Ma, S.; Gao, W. *Org. Lett.* **2002**, *4*, 2989–2992. (c) Kaden, S.; Brockmann, M.; Reissig, H.-U. *Helv. Chim. Acta* **2005**, *88*, 1826–1838. (d) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234–12235. (e) Castellano, S.; Fiji, H. D. G.; Kinderman, S. S.; Watanabe, M.; de Leon, P.; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 5843–5845. (f) Fuchibe, K.; Hatemata, R.; Akiyama, T. *Tetrahedron Lett.* **2005**, *46*, 8563–8566. (g) Fang, Y.-Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660–5661.

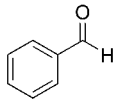
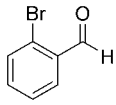
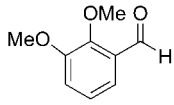
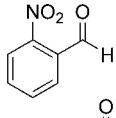
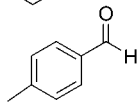
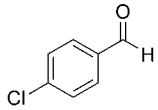
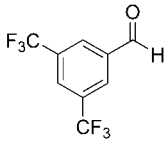
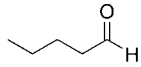
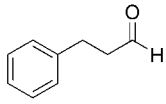
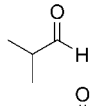
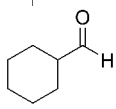
(8) Daidouji, K.; Fuchibe, K.; Akiyama, T. *Org. Lett.* **2005**, *7*, 1051–1053.

(9) All reactions were run until the allene was consumed, as determined by TLC analysis. Reactions run in a variety of other solvent systems, including THF, diethyl ether, toluene, and hexanes, produced little or no desired product.

(10) Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630–633.

Table 2. [3 + 2] Annulations with *tert*-Butyl Carbamate

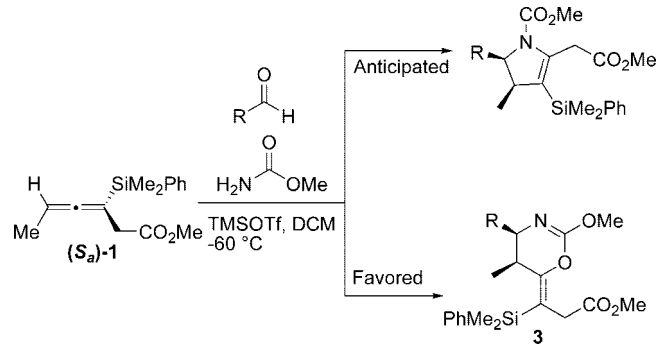


entry	aldehyde	yield[a]	dr[b]	product **2**
1		67%	>20:1	**2a**
2		82%	>20:1	**2b**
3		60%	>20:1	**2c**
4		50%	>20:1	**2d**
5		67%	>20:1	**2e**
6		69%	>20:1	**2f**
7		58%	>20:1	**2g**
8		57%	>20:1	**2h**
9		48%	>20:1	**2i**
10		33%	>20:1	**2j**
11		37%	>20:1	**2k**

[a] Isolated yields after purification over silica gel. [b] Diastereomeric ratios determined by ^{1}H NMR analysis on crude material.

provided the highest yields, whereas straight chain aliphatic substrates provided moderate yields and branched aliphatic aldehydes provided slightly lower yields. For the cases examined, the annulation products were formed as a single diastereomer. Stereochemical assignment of the annulation products was confirmed with the aid of NOE measurements and clearly indicated a *cis* relationship between the C-4 and C-5 stereocenters.[11]

Table 3. Annulations with Methyl Carbamate: Dihydrooxazines



entry	aldehyde	yield (%)[a]	dr[b]	product **3**
1	benzaldehyde	63	>20:1	**3a**
2	2-bromobenzaldehyde	81	>20:1	**3b**
3	2,3-dimethoxybenzaldehyde	54	>20:1	**3c**
4	2-nitrobenzaldehyde	58	>20:1	**3d**
5	4-chlorobenzaldehyde	59	>20:1	**3e**
6	valeraldehyde	61	>20:1	**3f**
7	hydrocinnamaldehyde	38	>20:1	**3g**
8	isobutyraldehyde	47	>20:1	**3h**
9	cyclohexanecarboxaldehyde	48	>20:1	**3i**

[a] Isolated yields after purification over silica gel. [b] Diastereomeric ratios determined by ^{1}H NMR analysis on crude material.

In reactions with *tert*-butyl carbamate, the only observed product was the dihydropyrrole bearing a free secondary amine; no BOC-protected product was isolated. Presumably, the combination of Lewis acidic conditions and/or the equivalent of water produced in the formation of the iminium ion promoted decomposition of the acid-labile BOC protecting group.

Additional carbamate sources were explored in an effort to expand the scope of the annulation and allow for the formation of *N*-acylated dihydropyrroles. However, when the amine source was changed to methyl carbamate, the major product was determined to be the dihydrooxazine. The optimal conditions for the specific formation of 4,5-*cis*-dihydrooxazines were found when TMSOTf was employed as the Lewis acid and DCM as the solvent (**3a**−**3g**, table 3). These products are similar to a byproduct observed by Danheiser.[5] 2D NMR studies have confirmed that the major product is the oxazine bearing an *E*-vinyl silane and not the anticipated methyl carbamate protected pyrrole.[11]

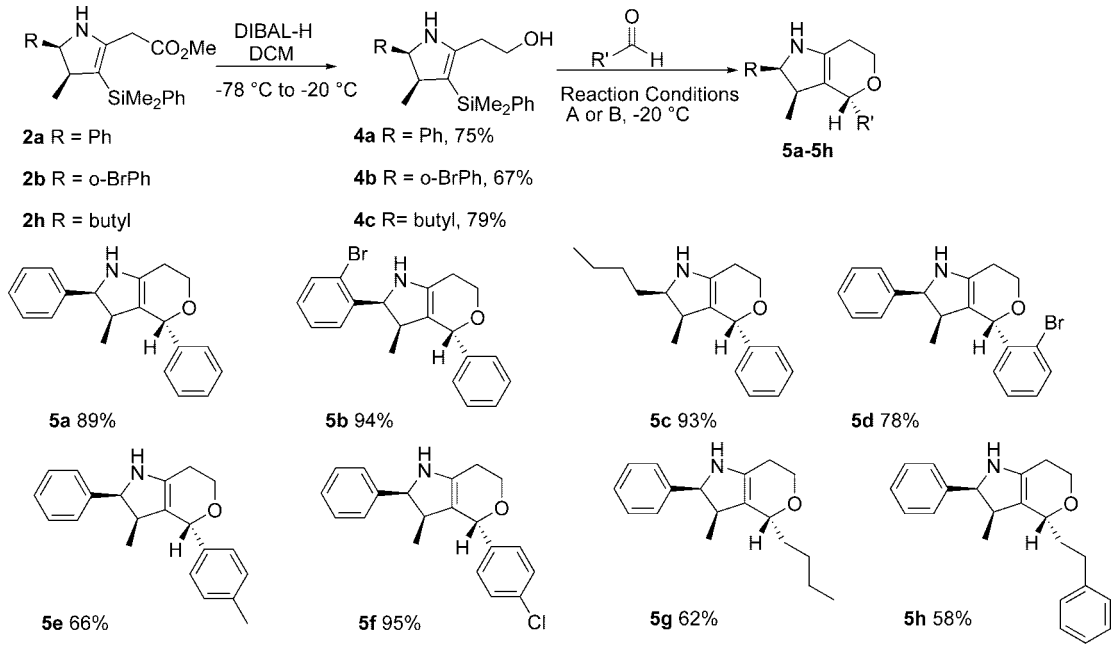
HPLC traces of select examples show that the axial chirality of the allenylsilane is fully transferred into central chirality in the dihydropyrroles and dihydrooxazines, which are obtained in >99% ee when the (S_a) allene is used.[12]

The combined activating effects of the enamine and vinylsilane functional groups of the dihydropyrrole products were exploited as illustrated in Scheme 1. Reduction of the methyl ester in **2** to alcohol **4** proceeds well with DIBAL-H

(11) See Supporting Information for details of NOE and 2D NMR experiments. The authors are grateful to a referee for suggesting the possibility of dihydrooxazine formation.

(12) See Supporting Information for HPLC traces and ee analysis.

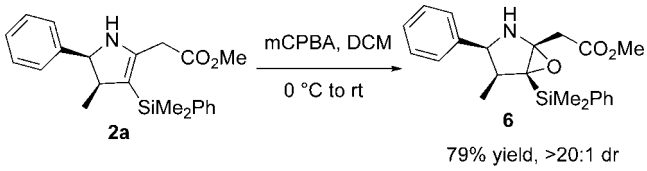
Scheme 1. Formation of Pyranopyrroles[a]



[a] Reaction conditions A (1.2 equiv of TMSOTf, DCM) used for **5a**−**5e** and B (1.2 equiv of BF_3·OEt_2, MeCN) used for **5g** and **5h.** Isolated yields after purification over silica gel. All products were obtained in >20:1 dr, as determined by ^{1}H NMR analysis on crude material.

in DCM. Primary alcohols **4a**−**4c** can then form hemiacetals using a series of aldehydes, mediated by TMSOTf or BF_3·OEt_2. The resulting oxonium ion undergoes vinylsilane terminated cyclization,[13] resulting in the formation of pyranopyrrole products **5a**−**5h**, in high yields as a single diastereomer. The relative stereochemistry of the pyranopyrrole products has been assigned by NOE studies.[10]

Scheme 2. Epoxidation of Dihydropyrrole **2a**



Exposure of dihydropyrrole **2a** to *m*-CPBA in DCM results in the formation of epoxide **6** as a single diastereomer. The stereochemistry of this product has not been confirmed but is tentatively assigned as the α-epoxide, as epoxidation likely takes place from opposite the sterically hindered face containing the aromatic ring and methyl group.

In closing, we have documented the use of chiral allenylsilanes in enantioselective annulations that assemble vinylsilane substituted 4,5-*cis*-dihydropyrrole and 4,5-*cis*-dihydrooxazine building blocks. We have illustrated that these dihydropyrroles can be used in vinylsilane terminated cyclizations, generating pyranopyrroles with good functional group variation. Ongoing experiments seek to apply this annulation strategy in complex molecule and natural product synthesis.

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

OL802618P

(13) (a) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857–873. (b) Zhang, X.; Li, X.; Lanter, J. C.; Sui, Z. *Org. Lett.* **2005**, *7*, 2043–2046.