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Syntheses of 2,5-Disubstituted Dihydrofurans from γ-Substituted Chiral Allenamides

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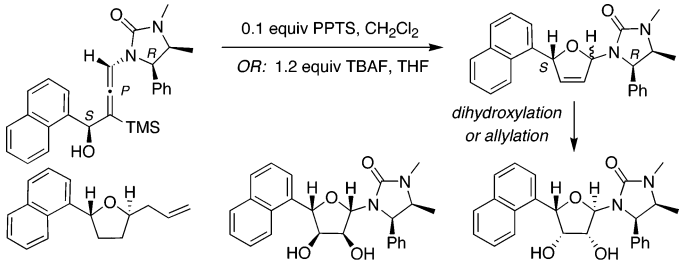

Details of a synthesis of dihydrofurans using γ-substituted chiral allenamides are described here. Some transformations of these dihydrofurans are also examined including a highly stereoselective dihydroxylation and a rare account of a Lewis acid-mediated removal of an *N*-acyl substituent at the anomeric carbon of a tetrahydrofuran ring system. These studies provide further support for the synthetic utility of allenamides.

Introduction

Allenamides have emerged as a useful functional group in organic synthesis.[1−9] In our own work,[4−8] we encountered the need for accessing γ-substituted chiral allenamides that can be used in stereoselective intramolecular [4 + 3] cycloaddition reactions.[5] However, our past work had only allowed for selective deprotonation at the α-position of allenamide **1** followed by addition of electrophiles such as MeI to produce α-substituted allenamide **2** (Scheme 1).[8] With only the α-position being blocked, subsequent deprotonation of **2** at the γ-position was successful, but after a D_2O quench only provided a modest diastereomeric ratio (2:1) for **3** in 60% yield. A more practical, efficient, and selective access to these compounds was desired.

In 2002, Seebach[9] reported a very elegant method to synthesize γ-substituted allenamides (Scheme 1). Treatment of TMS-protected *N*-propargyloxazolidinone **4** with

(1) For a review on allenamides, see: Hsung, R. P.; Wei, L.-L.; Xiong, H. *Acc. Chem. Res.* **2003**, *36*, 773.

(2) For reviews on allenes, see: (a) Saalfrank, R. W.; Lurz, C. J. Heterosubstituierte Allene and Polyallene. In *Methoden Der Organischen Chemie (Houben-Weyl);* Kropf, H., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1993; pp 3093−3102. (b) Schuster, H. E.; Coppola, G. M. *Allenes in Organic Synthesis*; John Wiley and Sons: New York, 1984.

(3) For recent allenamide chemistry, see: (a) Añorbe, L.; Poblador, A.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* **2004**, *45*, 4441. (b) Achmatowicz, M.; Hegedus, L. S. *J. Org. Chem.* **2004**, *69*, 2229. (c) Ranslow, P. D. B.; Hegedus, L. S.; de los Rios, C., *J. Org. Chem.* **2004**, *69*, 105. (d) Bacci, J. P.; Greenman, K. L.; Van Vranken, D. L. *J. Org. Chem.* **2003**, *68*, 4955. (e) Armstrong, A.; Cooke, R. S.; Shanahan, S. E. *Org. Biomol. Chem.* **2003**, *1*, 3142. (f) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 1499. (g) Nair, V.; Sethumadhavan, D.; Nair, S. M.; Shanmugam, P.; Treesa, P. M.; Eigendorf, G. K. *Synthesis* **2002**, 1655. (h) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2001**, *42*, 4869. (i) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. T. *Org. Lett.* **2001**, *3*, 2045. (j) van Boxtel, L. J.; Korbe, S.; Noltemeyer, M.; de Meijere, A. *Eur. J. Org. Chem.* **2001**, 2283. (k) Grigg, R.; Köppen, I.; Rasparini, M.; Sridharan, V. *Chem. Commun.* **2001**, 964 and key references therein. (l) For other papers during or before 2001, see ref 1.

(4) For syntheses of allenamides, see: (a) Xiong, H.; Tracey, M. R.; Grebe, T. P.; Mulder, J. A.; Hsung, R. P.; Wipf, P.; Smotryski, J. *Org. Synth.* **2004**, *81*, 147. (b) Tracey, M. R.; Grebe, T. P.; Brennessel, W. W.; Hsung, R. P. *Acta Crystallogr.* **2004**, C**60**, o830. (c) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459.

(5) For our efforts in [4 + 3] cycloadditions using allenamides, see: (a) Huang, J.; Hsung. R. P. *J. Am. Chem. Soc.* **2005**, *125*, 50. (b) Rameshkumar, C.; Hsung, R. P. *Angew Chem., Int. Ed.* **2004**, *43*, 615. (c) Xiong, H.; Huang, J.; Ghosh, S.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694. (d) Xiong, H.; Hsung. R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174. (e) Rameshkumar, C.; Xiong, H.; Tracey, M. R.; Berry, C. R.; Yao, L. J.; Hsung, R. P. *J. Org. Chem.* **2002**, *67*, 1339.

(6) For radical cyclization using allenamides, see: Shen, L.; Hsung, R. P. *Org. Lett.* **2005**, *7*, 775.

(7) For Diels−Alder cycloadditions using allenamides, see: (a) Berry, C. R.; Hsung, R. P. *Tetrahedron* **2004**, *60*, 7629. (b) Rameshkumar, C.; Hsung, R. P. *Synlett* **2003**, 1241. (c) Berry, C. R.; Rameshkumar, C.; Tracey, M. R.; Wei, L.-L.; Hsung, R. P. *Synlett* **2003**, 791. (d) Wei, L.-L.; Hsung, R. P.; Xiong, H.; Mulder, J. A.; Nkansah, N. T. *Org. Lett.* **1999**, *1*, 2145. (e) Wei, L.-L.; Xiong, H.; Douglas, C. J.; Hsung, R. P. *Tetrahedron Lett.* **1999**, *40*, 6903.

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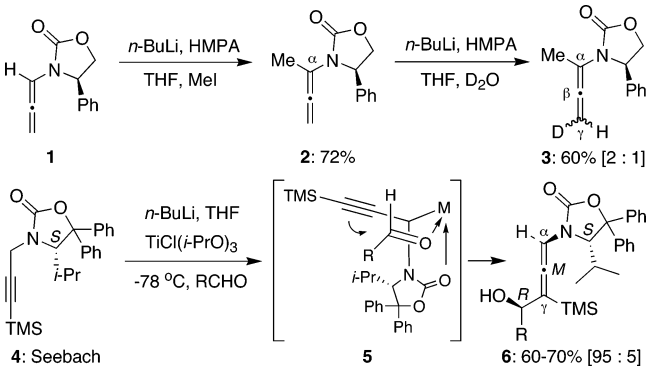
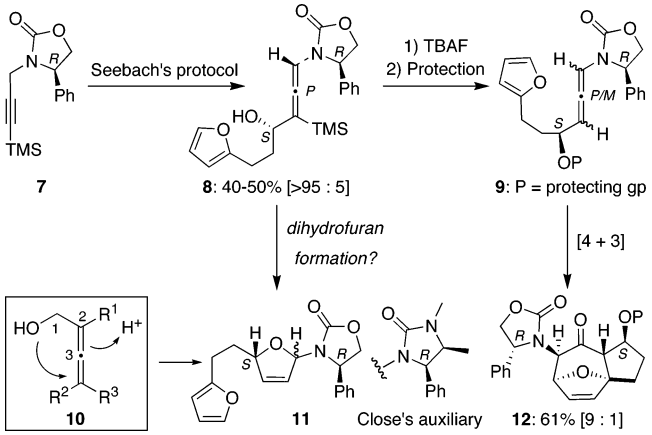
SCHEME 1



SCHEME 2



n-BuLi and TiCl(*i*-PrO)$_3$ followed by the addition of a range of different aldehydes led to the isolation of allenyl alcohols **6** with excellent diastereoselectivities (≥95:5) and good yields. The proposed mechanistic model (see **5**) involves coordination by the Ti metal to form a six-membered chairlike transition state where the aldehyde adds at the π-facial away from the *i*-Pr group on the auxiliary.

Utilizing Seebach's protocol,[9] *N*-propargyloxazolidinone **7** was used to give allenyl alcohol **8** in slightly lower yields (40−50%) but the same high degree of stereochemical integrity (≥95:5) (Scheme 2).[5b] While this γ-substituted chiral allenamide **8** itself did not undergo the desired intramolecular [4 + 3] cycloaddition, allenamide **9**, after desilylation using TBAF followed by protection of the hydroxyl group, did undergo a highly stereoselective [4 + 3] cycloaddition involving a rare example of a nitrogen-stabilized oxyallyl cation to form cycloadduct **12** in 61% yield and a 9:1 ratio of diastereomers favoring the one shown.[5b] However, this was where we became intrigued because it is well documented that 2,3-allenyl alcohols such as **10** can readily undergo cyclization to form dihydrofurans **11**[10] under acidic or basic conditions. Since neither **8** nor **9**, two more reactive allenyl alcohols, cyclized under TBAF conditions, we further investigated this unusual stability.

It turns out that this stability is auxiliary dependent. The chiral auxiliary in γ-substituted allenamides, either prepared in our work or those reported in Seebach's paper,[9] is oxazolidinone based. When we prepared γ-substituted allenamides containing an imidazolidinone based auxiliary, such as the Close auxiliary,[11] we encountered facile dihydrofuran formation under both basic and acidic conditions. Dihydrofurans have been shown to be versatile intermediates in methodological studies and key components of many natural products.[12,13] We report here syntheses of 2,5-disubstituted dihydrofurans via a stereodivergent intramolecular cyclizations of γ-substituted chiral allenamides.

Results and Discussion

Our initial encounter in the dihydrofuran formation was with allenyl alcohol **14** that was prepared in comparable yields and diastereoselectivity from TMS-protected *N*-propargylimidazolidinone **13** utilizing conditions described by Seebach.[9] However, we were unable to achieve a successful [4 + 3] cycloaddition using **14** because we never got beyond the desilylation step. Upon exposure to TBAF to remove the TMS group, dihydrofuran **16** was obtained in 38% yield as a mixture of two diastereomers, 2,5-*syn* and 2,5-*anti*, with a ratio of 1:1 (Scheme 3). We then proceeded to synthesize a series of allenyl alcohol **17a**−**j** employing *N*-propargylimidazolidinone derivative **13** (Table 1).

The overall yields of allenyl alcohols **17a**−**j** were less as compared with Seebach's report, but diastereoselectivities were all comparable (≥95:5). Allenyl alcohols **17a**−**h** (entries 1−8) derived from aromatic aldehydes appeared to be less prone to decomposition than their nonaromatic counterparts **17i** and **17j** (entries 9 and 10) during purification using silica gel column chromatography. Notably, allenyl alcohol **17j** (entry 10) was found to partially cyclize to its respective dihydrofuran during the purification. In addition, it is noteworthy that a TBS protected *N*-propargylimidazolidinone (entry 2) gave the expected allenyl alcohol (**17b**) in comparable yields and diastereoselectivity.

The initial cyclization experiment was repeated, and allenyl alcohol **17a** was subjected to 1.2 equiv of TBAF

(8) Xiong, H.; Hsung, R. P.; Wei, L.-L.; Berry, C. R.; Mulder, J. A.; Stockwell, B. *Organic Lett.* **2000**, *2*, 2869.

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(10) (a) For a review on cyclizations of allenyl alcohols, see: (a) Olseon, L.; Claesson, A. *Synthesis* **1979**, 743. For some examples, see: (b) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1371. (c) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180. (c) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1991**, *56*, 4913. (d) Pravia, K.; White, R.; Fodda, R. Maynard, D. F. *J. Org. Chem.* **1996**, *61*, 6031. (e) Ma, S.; Li, L. *Org. Lett.* **2000**, *2*, 941 and references therein

(11) Close, W. J. *J. Org. Chem.* **1950**, *15*, 1131.

(12) For some recent examples of syntheses of substituted dihydrofuran derivatives, see: (a) Antonioletti, R.; Malancona, S.; Bovicelli, P. *Tetrahedron* **2002**, *58*, 8825. (b) Jiang, Y.; Ma, D. *Tetrahedron: Asymmetry* **2002**, *13*, 1033. (c) Ma, S.; Gao, W. *Synlett* **2002**, 65 and references therein. (d) Hagiwara, H.; Sato, K.; Nishino, D.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2946. (e) Wang, Y. L.; Zhu, S. Z. *Tetrahedron* **2001**, *57*, 3383. (f) Carrido, J. L.; Alonso, I.; Carretero, J. C. *J. Org. Chem.* **1998**, *63*, 9406. (g) Melikyan, G. G.; Vostrowsky, O.; Bauer, W.; Bestmann, H. J.; Khan, M.; Nicholas, K. M. *J. Org. Chem*. **1994**, *59*, 222.

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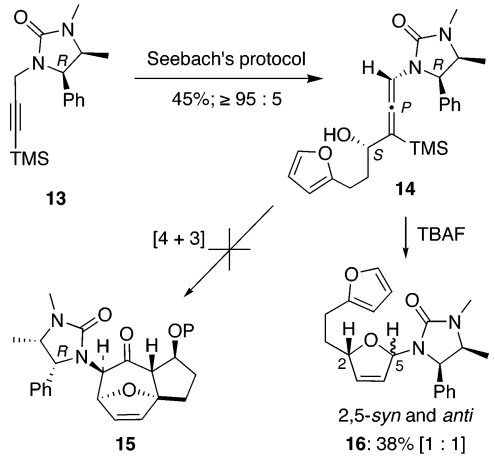
SCHEME 3



SCHEME 4

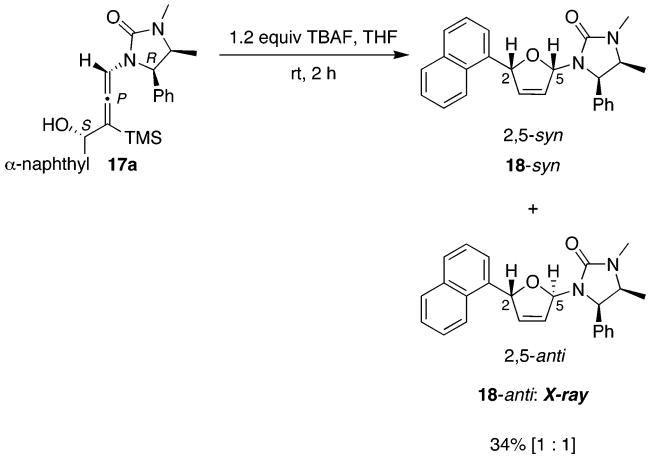
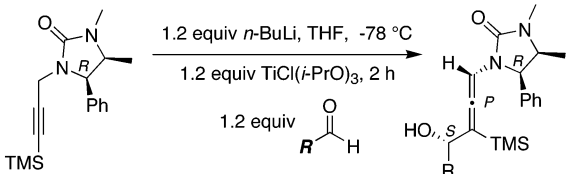


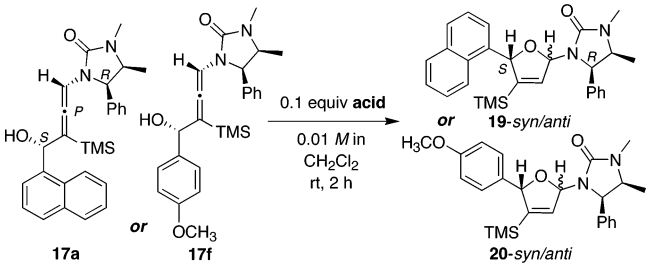
TABLE 1



entry	aldehydes: *R* =	allenamide	yield (%)[a]
1		**17a**	44
2		**17b**[b]	34
3	R^1 = F	**17c**	38
4	R^1 = Cl	**17d**	40
5	R^1 = H	**17e**	38
6	R^1 = OCH_3	**17f**	36
7	R^1 = CH_3	**17g**	31
8	R^1 = OCH_3	**17h**	34
9		**17i**	29
10		**17j**	25

[a] Isolated yields, and ratios are >95:5 as determined by ^{1}H NMR. [b] TBS substituted *N*-propargylallenamide was used instead of TMS.

TABLE 2



entry	acid	allenamide	product	yield (%)[a]	*syn/anti* ratio[b]
1	PNMSA[c]	**17a**	**19**	nd	nd[d]
2	CSA	**17a**	**19**	trace	nd
3	*p*-TsOH	**17a**	**19**	nd	nd
4	silica gel	**17a**	**19**	trace	nd
5	**PPTS**	**17a**	**19**	**82**	**1:1**
6	CSA	**17f**	**20**	trace	nd
7	*p*-TsOH	**17f**	**20**	nd	nd
8	$HNTf_2$	**17f**	**20**	nd	nd
9	silica gel	**17f**	**20**	trace	nd
10	**PPTS**	**17f**	**20**	**80**	**1:1**

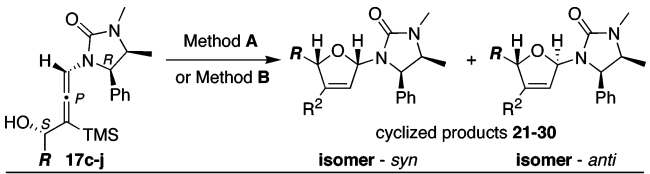
[a] Isolated yields. [b] Determined by ^{1}NMR. [c] PNBSA = *p*-nitrobenzenesulfonic acid. [d] nd: not determined.

(Scheme 4). Dihydrofurans **18**-*syn* and **18**-*anti*, as indicated by ^{1}H NMR analysis, were isolated and showed a 1:1 ratio being diastereomeric at C-5. The X-ray crystal structure (see Supporting Information for an ORTEP drawing) of **18**-*anti* does confirm that the chiral auxiliary at C-5 and the naphthalene ring at C-2 are *trans*. Acidic conditions for this cyclization were then examined using allenyl alcohols **17a** and **17f** (Table 2). After screening a variety of acids that either gave decomposition or a trace amount of product, addition of a catalytic amount of pyridinium *para*-toluenesulfonate (PPTS) (0.1 equiv) to **17a** or **17f** gave a 1:1 mixture of **19**-*syn/anti* and **20**-*syn/anti*, respectively, in excellent yields. The yield for dihydrofuran **19** is vastly improved from the TBAF conditions that led to **18** (Scheme 4). This protocol provides practical synthetic access to both 2,5-*syn*- and 2,5-*anti*-dihydrofurans. In addition, PPTS effected the transformation with the trimethylsilyl group still intact at C-3. It is noteworthy that the vinylsilane is in itself a viable functional group for further synthetic transformations.[14]

We then examined cyclizations of remaining allenyl alcohols **17a**−**j** using either 1.2 equiv of TBAF or catalytic PPTS and compared these results in Table 3. In general, method A (TBAF) provided lower yields, while method B (0.1 equiv PPTS) provided the desired products **21**−**30** in improved yields [except those with alkyl substituents (entries 8−10)], although *syn* to *anti* diastereomeric ratios mostly remained low. In contrast, the respective allenyl alcohols, prepared from *N*-propargyloxazolidinone **7**, led to no observable cyclization using either TBAF or PPTS.

(14) For recent examples, see: (a) Taguchi, H.; Tsubouchi, A.; Takeda, T. *Tetrahedron Lett*. **2003**, *44*, 5205. (b) Zhao, H.; Ming-Zhong, C. *Synth. Commun*. **2003**, *33*, 1643. (c) Taguchi, H.; Ghoroku, K.; Makoto, T.; Tsubouchi, A.; Takeda, T. *J. Org. Chem*. **2002**, *67*, 8450. (d) Taguchi, H.; Miyashita, H.; Tsubouchi, A.; Takeda, T. *Chem. Commun*. **2002**, *19*, 2218. (e) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Org. Lett*. **2001**, *3*, 3811.

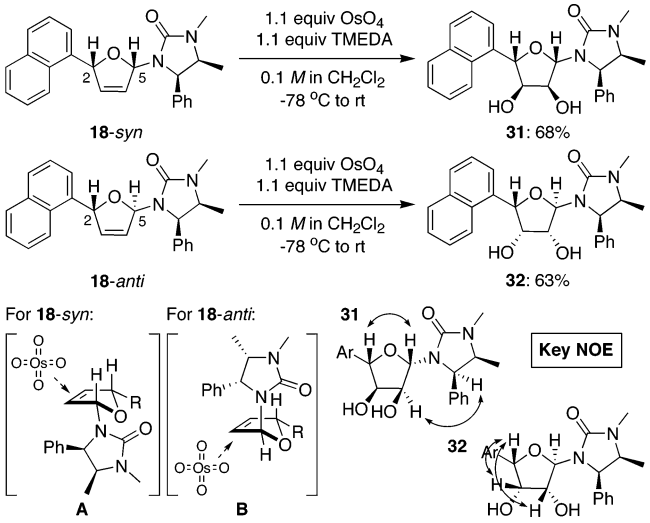
TABLE 3



entry	allenamides: R =		method	R^2	products	yield[a]	syn : anti[b]
1	R^1 = F	17c	B[c]	TMS	21	58%	2.5 : 1
2	R^1 = Cl	17d	B	TMS	22	50	1 : 1
3	R^1 = H	17e	A[c]	H	23	28	2 : 1
4	R^1 = H	17e	B	TMS	24	60	2.2 : 1
5	R^1 = OCH_3	17f	A	H	25	37	1 : 1
6	R^1 = CH_3	17g	B	TMS	26	38%	2.3 : 1
7	R^1 = OCH_3	17h	B	TMS	27	58	1 : 1
8		17i	A	H	28	27%	1 : 1
9		17i	B	TMS	29	trace	1 : 1
10		17j	A	H	30	24%	1 : 1

[a] Isolated yields. [b] Determined by ^{1}H NMR. [c] Method A: 1.2 equiv of TBAF, THF, rt, 2 h. Method B: 0.1 equiv of PPTS CH_2Cl_2, rt, 2 h.

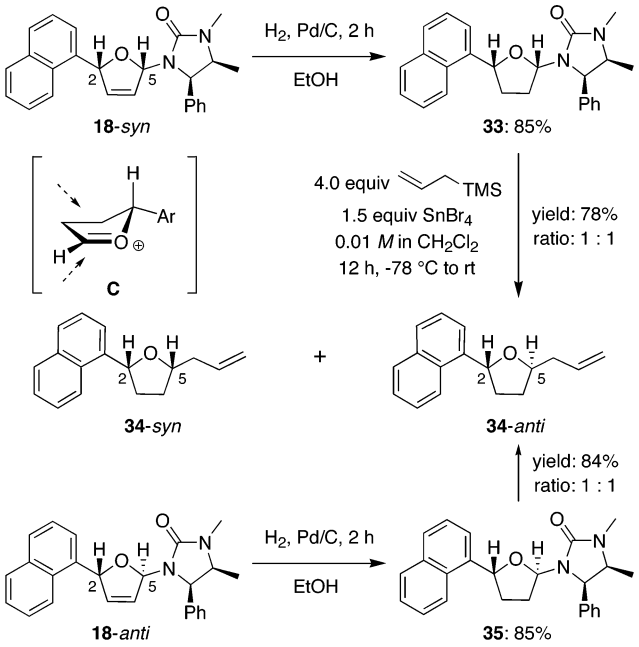
SCHEME 5



Because a significant amount of both **18**-*syn* and **18**-*anti* could be attained, it allowed for the demonstration of the synthetic utility of both of these 2,5-disubstituted dihydrofurans. To this end, dihydroxylation of the endocyclic olefin in **18**-*syn* was carried out using 1.1 equiv of OsO_4 in the presence of TMEDA and provided diol **31** as a single diastereomer in 58% yield (Scheme 5). Employing identical conditions, **18**-*anti* was dihydroxylated to produce diol **32** also as one diastereomer (Scheme 5).

NOE experiments confirmed that the addition took place from the more sterically accessible bottom face in both cases (see A and B). These two dihydroxylation reactions, especially the latter, support that the chiral auxiliary, and not the large aromatic substituent, is dictating the approach of osmium in these systems. It is also noteworthy that dihydrofurans **18**-*syn* and **18**-*anti* led to different, but complimentary, stereochemical outcome depending upon if it is 2,5-*syn* or 2,5-*anti* in the relative diastereomeric configuration.

SCHEME 6



We next tested our allylation protocol to remove the anomeric imidazolidinone substituent and elected to employ a simpler tetrahydrofuran ring system.[3c] Stereoselective removal of an *N*-acyl substituent at the anomeric carbon was unprecedented[15−17] until our recent studies of a Lewis acid promoted allylation of related pyranyl[7b,c] and piperidinyl[7a] heterocyclic systems. To the best of our knowledge, stereoselective removal of an *N*-acyl substituent at the anomeric carbon of a tetrahydrofuran ring system is not known.[20]

Toward this goal, simple hydrogenation of compound **18**-*syn* with Pd/C led to tetrahydrofuran **33** in excellent yield (Scheme 6). Allylation of **33** took place using 4.0 equiv of allyltrimethylsilane and 1.5 equiv of $SnBr_4$[18,19] and gave the allylation product **34** in 78% yield as an inseparable 1:1 isomeric mixture of 2,5-*syn* and 2,5-*anti* isomers. Similarly, **18**-*anti* was subjected to identical allylation conditions after the hydrogenation and gave the same allylation product **34** in 84% yield (from **35**) also in 1:1 ratio.

This result is significant because it represents the first example of removal of an anomeric *N*-acyl substituent in a tetrahydrofuran ring system in high yields, despite the fact that it was not selective.[20] Attempts using other Lewis Acids, such as $SnCl_4$, afforded similar results, while $BF_3{\cdot}OEt_2$ resulted in decomposition of **18**-*syn*. Mechanistically, it has been suggested previously that this reaction likely proceeds through an oxocarbenium

(15) (a) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545. (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*, 1st ed.; Pergamon Press: New York, 1995; Vol. 13.

(16) Parker, K. A. *Pure Appl. Chem.* **1994**, *66*, 2135.

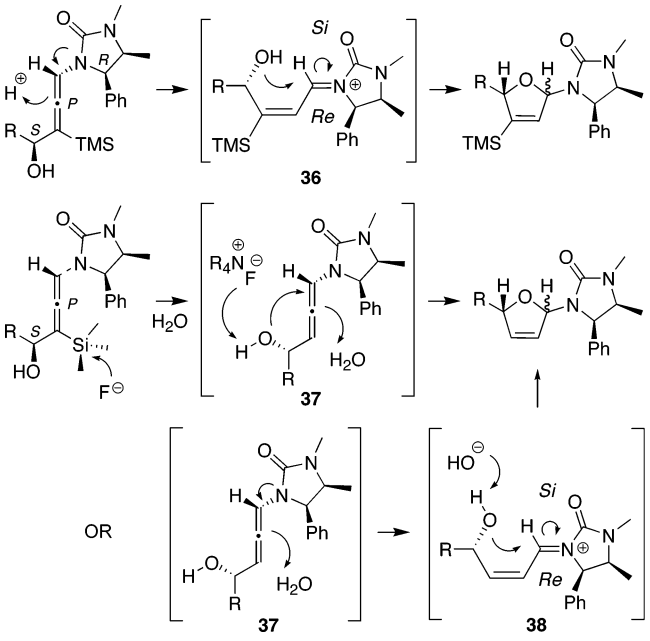
(17) For an example, see: Petó, C.; Batta, G.; Györgydeák, Z.; Sztaricskai, F. *J. Carbohydr. Chem.* **1996**, *15*, 465.

(18) Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063.

(19) (a) Larsen, C. H.; Ridgeway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208. (b) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168.

(20) For reviews on tetrahydrofuran synthesis, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Harmange, J.-C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711 (c) Koert, U. *Synthesis* **1995**, 115.

SCHEME 7

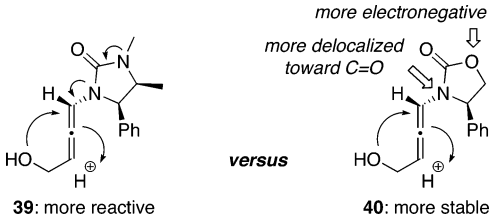


ion intermediate where the incoming allyltrimethylsilane, and in this case, the nucleophilic attack occurred indiscriminately from either face of the same oxocarbenium intermediate **C** for both **18**-*syn* and **18**-*anti*.

Mechanistically, the dihydrofuran formation under acidic conditions should proceed through vinyl iminium ion **36** after an initial protonation of allenyl alcohols by PPTS (Scheme 7). Cyclization would then proceed through a 5-*exo*-trig mode leading to both 2,5-*syn* and 2,5-*anti* dihydrofurans through addition at either the *Re* or the *Si* face. It is surprising that there are no facial discriminations at all here exerted either by Close's auxiliary or the allylic stereocenter.

The exact pathway for the dihydrofuran formation under the TBAF addition is not clear except perhaps that a facile desilylation occurs to give a neutral allenamide intermediate **37**. Thus, the ensuing cyclization should be slower, for it is likely activated only by the presence of H_2O in TBAF and perhaps in part assisted by TBAF or hydroxide anion serving as a base (Scheme 7). A more retarded cyclization using TBAF in part justifies a lower yielding process than that obtained from employing PPTS conditions.

SCHEME 8



Last, the difference between oxazolidinone-substituted allenamides used in our previous work (and in Seebach's work) and these imidazolidinone-substituted allenamides in the current work deserves some comments. This contrast originates from the electronegativity difference between the nitrogen and oxygen atoms. In oxazolidinone-substituted allenamides (see **40** in Scheme 8), the oxygen being more electronegative allows the allenamide nitrogen to delocalize its lone pair into the carbonyl group in a greater extent than that in **39**. This leads to a diminished reactivity in **40**, and thus, the dihydrofuran formation occurred with imidazolidinone-substituted allenamides **39** and not **40**. It is noteworthy that a rather small electronic perturbation actually plays a significant role in dictating the overall reactivities and, thus, stabilities of different allenamides.

Conclusions

We have provided here details of syntheses of 2,5-disubstituted dihydrofurans using γ-substituted allenamides. We have demonstrated the first example of removal of an *N*-acyl substituent at the anomeric carbon of a tetrahydrofuran ring system. Stereoselective dihydroxylations of these dihydrofurans are also examined to illustrate their viability as useful organic building blocks.

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Supporting Information Available: Experimental procedures, characterizations, and ^{1}H NMR spectra for all new compounds as well as X-ray structural data. This material is available free of charge via the Internet at http://pubs.acs.org.

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