ORGANIC LETTERS

2011
Vol. 13, No. 15
4056–4059

A New Synthesis of Pyrrolidines by Way of an Enantioselective Mannich/ Diastereoselective Hydroamination Reaction Sequence

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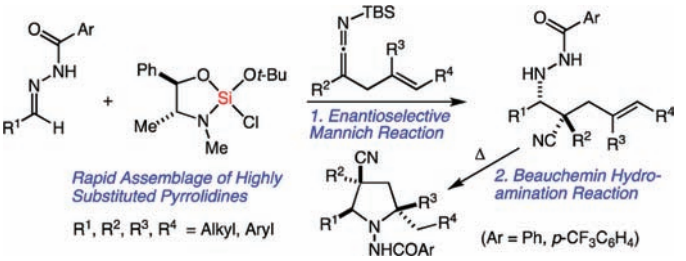
Received June 10, 2011

ABSTRACT



A new two-step synthesis of highly substituted pyrrolidines has been developed. Chiral silane Lewis acid promoted enantioselective Mannich reactions of silyl ketene imines with acylhydrazones may be used to access bishomoallylic benzoic hydrazides that in turn may be cyclized to pyrrolidines by way of the thermal hydroamination reaction reported recently by Beauchemin. Importantly, excellent diastereoselectivity may be realized in the hydroamination reactions.

The development of experimentally simple, efficient, and highly enantioselective methods to synthesize chiral pyrrolidines is an important goal for chemical synthesis. While great strides have recently been made in the development of enantioselective azomethine ylide cycloaddition reactions,[1] this approach has significant limitations in scope, and there is a continuing need for new methods to access a greater range of pyrrolidine structures, especially those with a high degree of substitution. Beauchemin and co-workers recently reported that bishomoallylic benzoic hydrazides may be converted to pyrrolidines by way of a thermal hydroamination reaction,[2] and because our acylhydrazone-silane Lewis acid platform provides access to a structurally diverse array of benzoic hydrazides,[3] the coupling of these two processes seemed a worthwhile pursuit (Scheme 1A). Realization of this idea would require (1) an enantioselective hydrazone addition reaction that would lend itself to the synthesis of highly substituted bishomoallylic benzoic hydrazides and (2) the development of diastereoselective variants of the hydroamination reaction,

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(3) (a) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686. (b) Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2858. (c) Shirakawa, S.; Lombardi, P. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 9974. (d) Notte, G. T.; Leighton, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 6676. (e) Valdez, S. C.; Leighton, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 14638. (f) Lee, S. K.; Tambar, U. K.; Perl, N. R.; Leighton, J. L. *Tetrahedron* **2010**, *66*, 4769. (g) Notte, G. T.; Baxter Vu, J. M.; Leighton, J. L. *Org. Lett.* **2011**, *13*, 816.

(4) For early studies on the generation of silyl ketene imines and their use in reactions with electrophiles, see: (a) Gornowicz, G. A.; West, R. *J. Am. Chem. Soc.* **1971**, *93*, 1714. (b) Watt, D. S. *Synth. Commun.* **1974**, *4*, 127. (c) Cazeau, P.; Llonch, J.-P.; Simonin-Dabescat, F.; Frainnet, E. *J. Organomet. Chem.* **1976**, *105*, 145. (d) Cazeau, P.; Llonch, J.-P.; Simonin-Dabescat, F.; Frainnet, E. *J. Organomet. Chem.* **1976**, *105*, 157. (e) Meier, S.; Würthwein, E.-U. *Chem. Ber* **1990**, *123*, 2339.

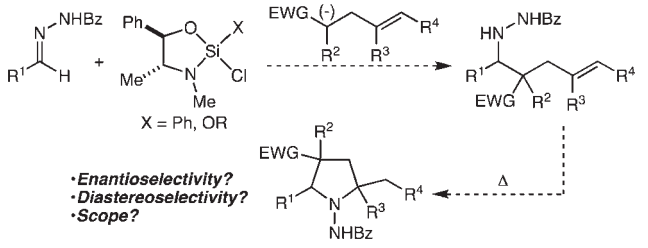
(5) For two recent examples of the use of silyl ketene imines in asymmetric reactions, see: (a) Mermerian, A. H.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 949. (b) Denmark, S. E.; Wilson, T. W.; Burk, M. T.; Heemstra, J. R., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 14864.

10.1021/ol201566u
Published on Web 07/12/2011

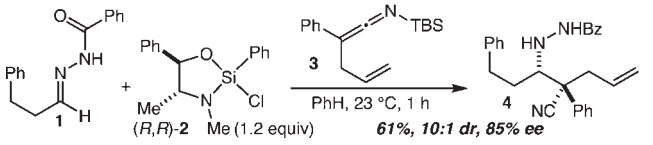
as this question was largely unaddressed in the Beauchemin report. With regard to the first point, we recently reported a few examples of the addition of silyl ketene imines[4,5] (SKI) to chiral silane Lewis acid activated acylhydrazones,[3g,6] and one of those reactions involved treatment of the complex derived from hydrazone **1** and phenylsilane **2** with SKI **3** to give bishomoallylic benzoic hydrazide **4** in good yield and moderately high enantioselectivity (Scheme 1B).[7] The further development of this reaction seemed an excellent starting point for the present study, and we detail herein our efforts to do exactly that and the results of an investigation into the behavior of such hydrazides in Beauchemin-type hydroamination reactions.

Scheme 1

(A) Proposal for a two-step synthesis of pyrrolidines by way of enantioselective nucleophilic additions to chiral silane Lewis acid activated acylhydrazones, followed by a Beauchemin-type hydroamination reaction:

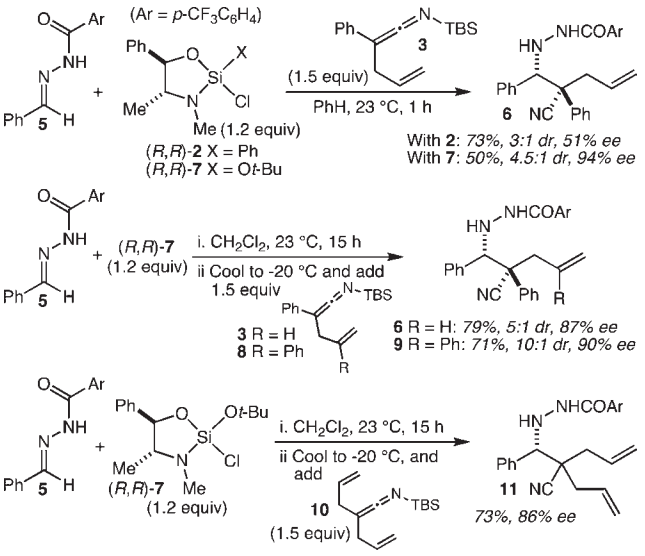


(B) A chiral silane Lewis acid promoted enantioselective Mannich reaction with a silyl ketene imine to give a bishomoallylic benzoic hydrazide (ref. 3g):



At the outset we were optimistic that the result described in Scheme 1B would prove general for a range of both hydrazones and substituted allyl-bearing SKIs. Unfortunately, this was not the case as, for example, benzaldehyde-derived hydrazone **5** performed poorly under otherwise identical reaction conditions (Scheme 2). Prior experience alerted us to the fact that these hydrazone addition reactions can often be optimized simply by varying the spectator group (Ph in the case of **2**) on the silane Lewis acid.[3d,f,g] Indeed, when the reaction of hydrazone **5** with SKI **3** was repeated with previously reported *tert*-butoxysilane **7**,[3d] **6** was produced in 94% ee, albeit with only moderate diastereoselectivity and efficiency. Extensive optimization studies eventually revealed that when the reaction of **5** was conducted in CH_2Cl_2 at −20 °C,[8] the product **6** was obtained in 79% yield (5:1 dr) and 87% ee. Under otherwise identical conditions substituted SKI **8** gave **9** in 71% yield (10:1 dr) and 90% ee. Diallyl SKI **10** was also effective under these optimized conditions leading to **11** in 73% yield and 86% ee.

Scheme 2



Unfortunately, these conditions were significantly less effective for aliphatic aldehyde-derived hydrazone **1**. Re-optimization of the reaction between hydrazone **1** and SKI **3** promoted by **7** eventually led to the discovery that this reaction was best conducted in trifluorotoluene at −20 °C, conditions which resulted in the isolation of **4** in 59% yield (9:1 dr) and 85% ee (Scheme 3). While these results are essentially identical to those described in Scheme 1B, these optimized conditions proved to be far more general with respect to the SKI. Thus, reaction of the complex derived from **1** and **7** with substituted SKIs **12**–**15** gave products **16**–**19**, respectively, in the yields and stereoselectivities shown. Hydrazones **20** and **21** were also treated with SKI **3** under the same conditions leading to products **22** and **23** in improved yields (relative to the reactions of hydrazone **1**) albeit with reduced enantioselectivity. The mechanistic origin of the consistently lower yields observed with hydrazone **1** remains unexplained, but the reactions of **20** and **21** (as well as the reactions in Scheme 2) seem to indicate that **1** is an outlier in this regard. There does seem to be a

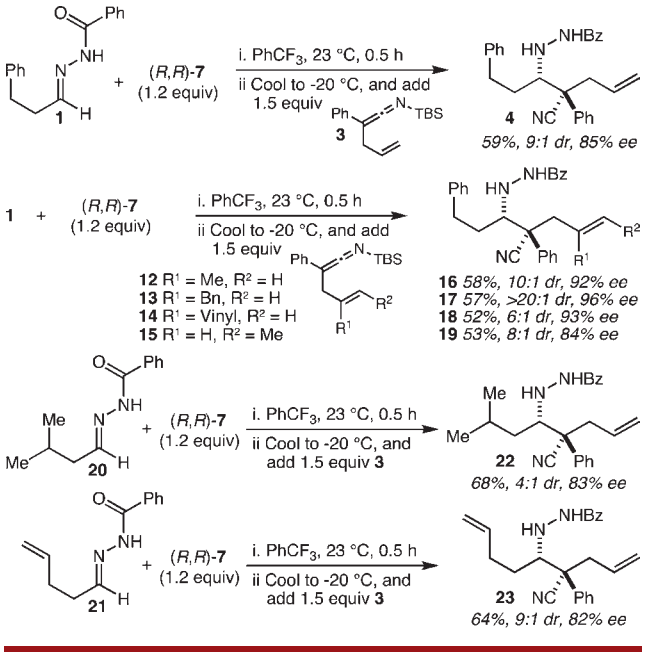
(6) For other examples of Mannich-type reactions with acylhydrazones, see: Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5176.

(7) The effective use of disubstituted enolates or enolate equivalents in enantioselective Mannich reactions for the generation of all-carbon quaternary stereocenters is extremely rare (and, with hydrazones as the electrophile, nonexistent). See: (a) Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2896. (b) Tian, X.; Jiang, K.; Peng, J.; Du, W.; Chen, Y.-C. *Org. Lett.* **2008**, *10*, 3583. (c) Cheng, L.; Liu, L.; Jia, H.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2009**, *74*, 4650. (d) Yin, L.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9610.

(8) As is the case with all of the pseudoephedrine-derived silanes, **7** is prepared, isolated, and employed as a mixture (in this case 2.5:1) of diastereomers. We have provided evidence that this is of no consequence as the mixture converges on a single complex when reacted with acylhydrazones (see refs 3a,3d). In the case of complexation reactions of **7** with acylhydrazones carried out in CH_2Cl_2, we have found that the complexation and convergence onto a single complex takes considerably longer (details are provided in the Supporting Information), and this is the reason for the significant "ageing" time in the first part of these reactions.

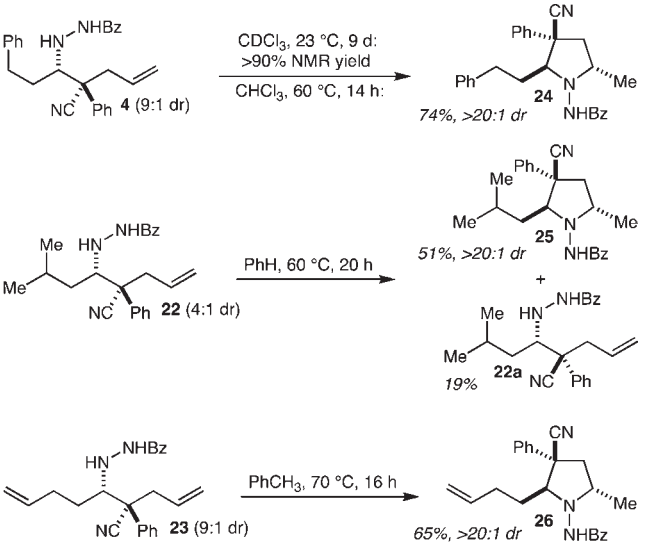
trend in the data presented in Schemes 2 and 3 that more hindered SKIs (**8** and **12**–**14**) consistently lead to higher levels of enantioselectivity (90–96% ee) than do SKIs **3**, **10**, and **15** (82–87% ee), while no trends at all are discernible that might explain the fairly dramatic variations in diastereoselectivity. Nevertheless, the use of *tert*-butoxysilane **7** under the optimized conditions as outlined in Schemes 2 and 3 does allow for the synthesis of a reasonably diverse array of bishomoallylic benzoic hydrazides.

Scheme 3



With access to a range of bishomoallylic benzoic hydrazides secured, we turned our attention to an examination of the Beauchemin hydroamination reaction. Indeed, even before we formally initiated this study we unwittingly performed our first hydroamination when a solution of **4** in $CDCl_3$ was allowed to stand at ambient temperature overnight. Reacquisition of the ^1H NMR spectrum of this solution revealed the presence of a new compound, and after 9 days the conversion to this new species was complete and quite clean. This new compound was subsequently identified as **24**, and it was found that if a solution of **4** (produced, isolated, and employed as a 9:1 mixture of diastereomers) in $CHCl_3$ was heated at 60 °C for 14 h, **24** could be isolated in 74% yield as a single diastereomer (Scheme 4). Among the notable features of this transformation are the especially mild conditions necessary to effect it, and the diastereoselectivity: not only did the major diastereomer of **4** undergo hydroamination with excellent diastereoselectivity, but the minor diastereomer of **4** apparently undergoes hydroamination much more slowly, if at all. A potentially difficult separation of the diastereomers of **4** in order to obtain diastereomerically pure pyrrolidine product **24** was thereby obviated. That this interesting resolution was due to the minor diastereomer simply not reacting (as opposed to decomposing by an alternate pathway) was corroborated by the hydroamination (benzene, 60 °C) of **22**, which was produced, isolated, and employed as a 4:1 mixture of diastereomers (see Scheme 3). A single pyrrolidine product (**25**) was isolated in 51% yield, along with the unreacted minor diastereomer (**22a**) of the starting material in 19% yield. Hydroamination of **23** (9:1 dr) in toluene at 70 °C led to the isolation of **26** as the sole pyrrolidine product both providing another example of this resolution and establishing that complete regioselectivity for two alkenes can be realized based solely on the *gem*-disubstituent effect.[9,10]

Scheme 4



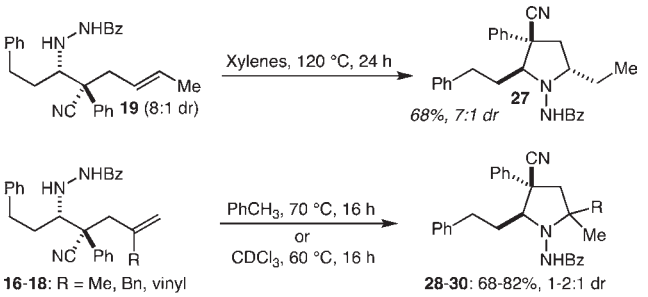
The impact of alkene substitution on the reactivity and diastereoselectivity was examined next, and although (*E*)-alkene **19** underwent hydroamination to give **27** in 68% yield (isolated yield of pure major diastereomer), more forcing conditions (xylenes, 120 °C, 24 h) were required (Beauchemin and co-workers made similar observations) which in turn caused a drop in the diastereoselectivity (7:1 dr) of the hydroamination event (Scheme 5). Remarkably, even at this elevated temperature the resolution was operative as the minor diastereomer present in the starting material did not react. Despite the more forcing conditions and reduced diastereoselectivity, this result nevertheless establishes that groups other than methyl (i.e., CH_2R) can be installed at C(5) of the pyrrolidine with useful levels of efficiency and diastereoselectivity. We turned next to an examination of the impact of substitution on the internal carbon of the alkene using substrates **16**–**18**. In every case

(9) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. (b) Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305. (c) Ingold, C. K.; Sako, S.; Thorpe, J. F. *J. Chem. Soc.* **1922**, *120*, 1117.

(10) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

the reaction proceeded with reasonable efficiency to give **28**–**30** in good yields establishing that substitution at this position is well-tolerated. Unfortunately, in the reactions of **17** and **18**, whose hydroamination creates a fully substituted carbon stereocenter, little to no diastereoselectivity was observed.

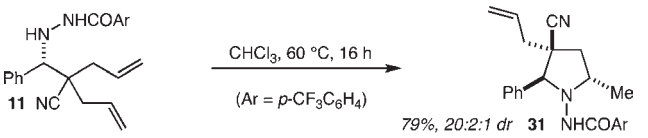
Scheme 5



Finally, the dramatic difference in rates at which the diastereomers of the bishomoallylic hydrazides undergo the hydroamination reaction suggested the intriguing possibility that the diastereotopic allyl groups of **11** might be effectively differentiated in a reaction that would create the C(5) stereocenter *and* a quaternary carbon stereocenter at C(3) of the pyrrolidine product. Indeed, heating a $CHCl_3$ solution of **11** at 60 °C for 16 h led to the selective production of **31** with 20:2:1 diastereoselectivity (measured by ^1H NMR spectroscopic analysis of the unpurified reaction mixture). Pyrrolidine **31** was isolated as a ≥10:1 mixture of diastereomers in 79% yield (Scheme 6).

The present study has established a method for the synthesis of bishomoallylic benzoic hydrazides by way of an enantioselective Mannich-type reaction with silyl ketene imines, and we have documented a reasonable scope

Scheme 6



and generality for this reaction. In addition, we have documented that very high levels of diastereoselectivity may be realized in the Beauchemin hydroamination reaction. Coupled together, these reactions expand the pool of complex pyrrolidine structures that may be easily accessed by asymmetric chemical synthesis. Of course, the Mannich chemistry described here is just one of many possible ways to generate bishomoallylic benzoic hydrazides. We anticipate that the broader principle established here—that the pairing of our chiral silane-benzoylhydrazone methodology with the diastereoselective Beauchemin hydroamination reaction adds up to a powerful new pyrrolidine synthesis—will facilitate access to a much broader range of valuable nitrogen-containing heterocycles.

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE-08-09659). We thank Novartis for a Graduate Fellowship to J.M.B. We thank Prof. Ged Parkin and Mr. Wesley Sattler (Columbia University) for an X-ray structure analysis (see Supporting Information), and the National Science Foundation (CHE-0619638) is thanked for acquisition of an X-ray diffractometer.

Supporting Information Available. Experimental procedures, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.