

Phenol-Directed Enantioselective
Allylation of Aldimines and Ketimines

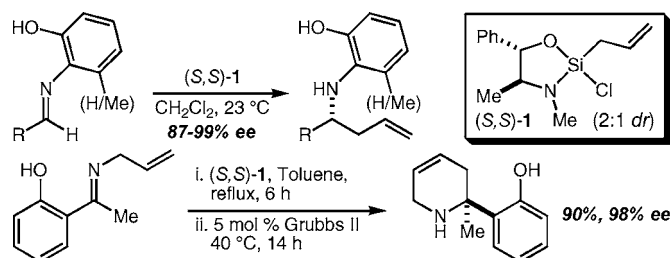
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ABSTRACT



Phenols are effective directing and activating groups for our allylchlorosilane reagents, allowing the highly enantioselective allylation of a range of 2-aminophenol-derived aldimines. When the phenol is incorporated into the substrate ketimines may be allylated highly enantioselectively, leading to the experimentally simple synthesis of a range of tertiary carbinamine structures.

Chiral carbinamines represent an important target for the development of asymmetric reaction methodology, due to their importance in a range of disciplines including medicinal chemistry and natural product synthesis. Especially for the former purpose, it is essential that such methodology be general, reliable, and user-friendly. To this end, we have reported a new class of allyl- and crotylsilane reagents for the enantioselective allylation and crotylation of aldehyde- and ketone-derived acylhydrazones.^{1,2} This chemistry suffers from an important limitation, however, in that the use of aliphatic aldehyde-derived acylhydrazones typically results in poor levels of enantioselectivity.^{1a} Herein, we report a solution to the problem of aliphatic aldehyde-derived imines and an expansion in the scope of effective ketimine substrates leading to the protecting group free synthesis of interesting heterocycle motifs.

Mechanistic studies^{1b} have revealed that the acylhydrazone reactions operate by nucleophilic displacement of the chloride on the silane reagent **1** by the oxygen of the acylhydrazone

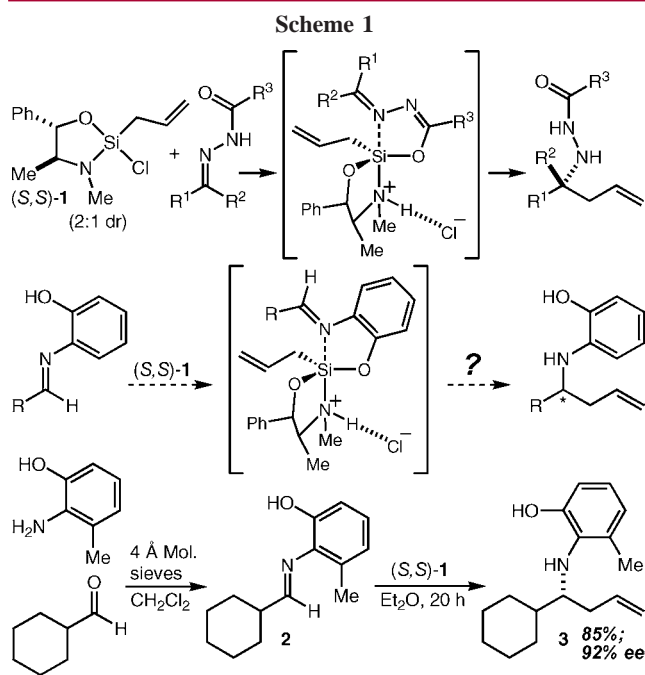
(Scheme 1). This reaction generates an equivalent of HCl which protonates the amino group of the pseudoephedrine chiral controller, resulting in a significant increase in the Lewis acidity of the silicon center. It was therefore straightforward to design new imine derivatives for use with this family of silane reagents, the only requirement being that they carry an appropriately configured nucleophile for chloride displacement and concomitant HCl generation. 2-Aminophenol-derived imines^{3–5} seemed well suited for this purpose and their oxidative cleavage from the product amines has been extensively documented as well,^{4,5b,e,g,6} and we therefore prepared cyclohexanecarboxaldimine **2**. The selection of the 2-amino-3-methylphenol in this case was guided by observations made by Kobayashi that with aliphatic aldehydes the added methyl group significantly improves imine stability.^{5c,7} Reaction of **2** with silanes **1** did indeed result in the desired allylation product, and after optimization it was found that the reaction was best performed in Et₂O at

(1) (a) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596. (b) Berger, Duff, R.; K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686.

(2) Methods for the asymmetric addition of allylic nucleophiles to various imine derivatives have recently been reviewed: Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815.

(3) We have recently demonstrated that a related phenol-based strategy may be employed for asymmetric ketone allylation reactions. See: Burns, N. Z.; Hackman, B. M.; Ng, P. Y.; Powelson, I. A.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3811.

(4) Kobayashi has previously made a similar analogy between acylhydrazones and 2-aminophenol-derived imines for imine allylation with allyltrichlorosilane: Sugiura, M.; Robvieux, F.; Kobayashi, S. *Synlett* **2003**, 1749.



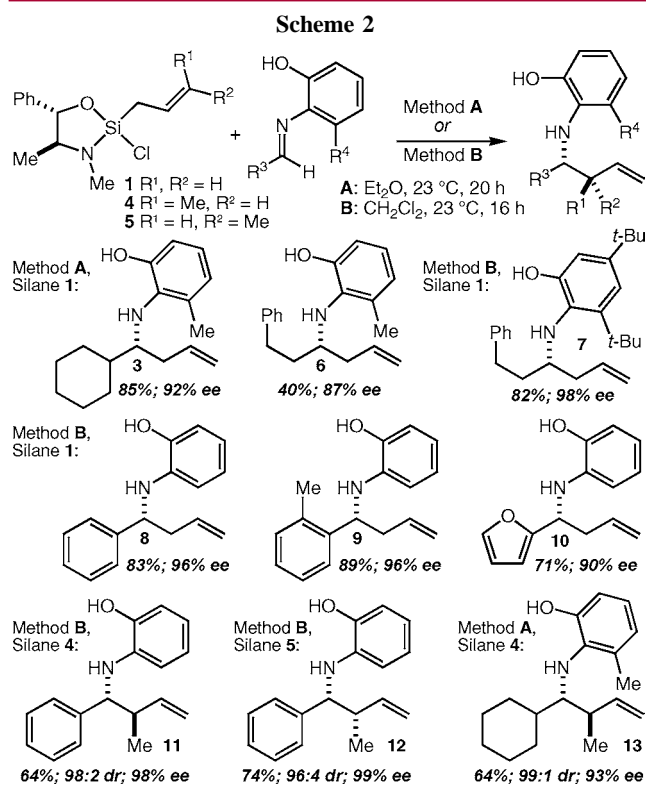
ambient temperature. Under these conditions, **3** was isolated in 85% overall yield (from cyclohexanecarboxaldehyde) and 92% ee. Consistent with our mechanistic analysis, the corresponding methyl ether of phenol **2** does not react at all with silanes **1**. This result thus validated the underlying mechanistic hypothesis and represented a solution to the problem of aliphatic aldimines.

A survey of substrate scope was carried out with allylsilane **1** and *cis*- and *trans*-crotylsilanes **4** and **5**, and the results are outlined in Scheme 2. In an effort to address the generality of the initial success with aliphatic aldimine **2**, it was quickly discovered that while sterically less hindered aliphatic aldimines did indeed lead to good levels of enantioselectivity, the efficiency was poor (**6**, 40% yield, 87% ee). Pursuing the theory that this inefficiency was due to imine instability, we prepared the corresponding aldimine derived from 2-amino-3,5-di-*tert*-butylphenol, and indeed, this imine provided superior results in the allylation reaction with allylsilane **1** (**7**, 82% yield, 98% ee). Aromatic aldehyde-

(5) For other examples of the use of 2-aminophenol-derived imines in asymmetric nucleophilic addition reactions, see: (a) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 979. (b) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762. (c) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180. (d) Ueno, M.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 3395. (e) Kobayashi, S.; Kobayashi, J.; Ishitani, H.; Ueno, M. *Chem. Eur. J.* **2002**, *8*, 4185. (f) Kobayashi, S.; Ueno, M.; Saito, S.; Mizuki, Y.; Ishitani, H.; Yamashita, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5476. (g) Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2271. (h) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (i) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141. (j) Jagtap, S. B.; Tsogoeva, S. B. *Chem. Commun.* **2006**, 4747.

(6) (a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409. (b) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734.

(7) (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (b) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431.

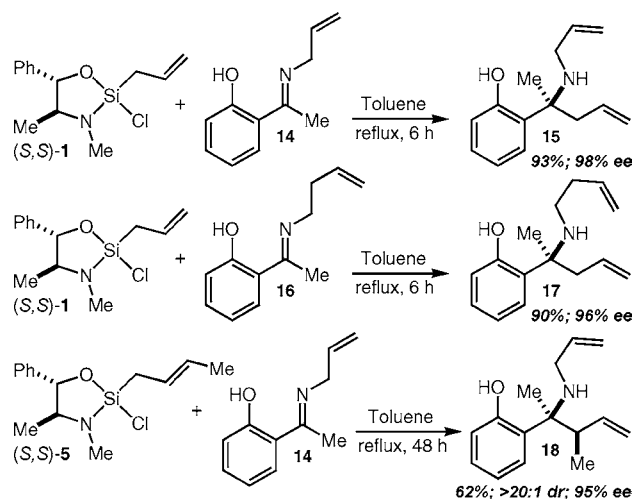


derived imines were excellent substrates for the allylation reaction with **1** as well, although in these cases CH₂Cl₂ proved to be a better solvent in terms of both efficiency and enantioselectivity (**8–10**). As expected, it was found that both the aromatic and aliphatic aldehyde-derived imines could be crotylated with excellent diastereo- and enantioselectivity (**11–13**). In all cases, it is noteworthy that the reaction conditions involve simply mixing the imine and silane in the appropriate solvent at ambient temperature. With a supply of the requisite silane (150 g batches of allylsilane **1** are prepared routinely) in hand, and given the commercial availability of both 2-aminophenol and 2-amino-3-methylphenol, these reactions are thus experimentally trivial to perform.

Seeking to expand the scope of useful transformations based on this concept, we decided to examine the possibility that the phenol activating/directing group might be a part of the substrate rather than an auxiliary attached to the imine nitrogen. A potential advantage of this strategy would be that, in principle, there would be significant flexibility in the choice of the *N*-substituent of the imine, and we were also interested in the possibility that this strategy would allow success with ketimines.⁸ Thus, the simple *N*-allyl ketimine **14** was prepared and treated with allylsilane reagent **1** (Scheme 3). Remarkably, although the reaction only proceeded at a reasonable rate in refluxing toluene, amine **15**

(8) For other reports of enantioselective allylation of ketimines and related derivatives, see ref 1b and: (a) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4. (b) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (d) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.

Scheme 3

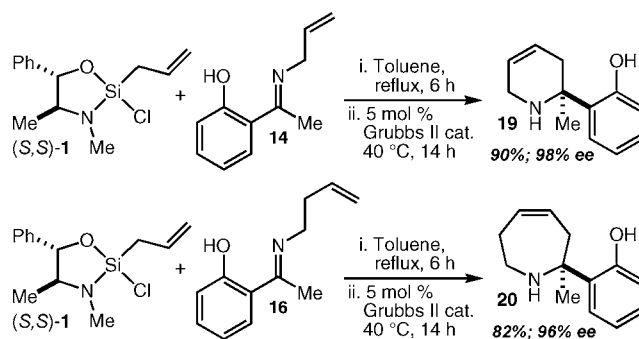


was isolated in excellent yield (93%) and with superior enantioselectivity (98% ee). Ketimine **16** performed similarly, providing access to amine **17** in 90% yield and 96% ee. Ketimine **14** could also be successfully crotylated with *trans*-crotylsilane **5** to provide amine **18** as a single diastereomer in 62% yield and 95% ee, attesting to the robustness of the silane reagents to prolonged and significant heating.

That there is some flexibility in the choice of imine *N*-substituents allows the possibility that they might be chosen so as to be useful for the synthesis of a given target, rather than being viewed as a group to be removed after the allylation reaction. For example, simply by adding the second-generation Grubbs catalyst⁹ to the allylation reactions of ketimines **14** and **16** prior to workup, the efficient one-pot synthesis of piperidine and azepine (ring systems of potential medicinal relevance) derivatives **19** and **20** could be readily achieved in excellent overall yield and with superior enantioselectivity (Scheme 4). It is important to note that in the case of **20**, attempts to subject isolated amine **17**

(9) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

Scheme 4



to the metathesis reaction were met with complete failure. The one-pot procedure described here is therefore not only convenient but also necessary at least in this case. It is further noteworthy that this methodology proceeds without recourse to any protecting groups and produces these nitrogen-containing heterocycles in their free NH state.

We have described how the phenol functionality may be employed in different contexts for the highly enantioselective allylation and crotylation of a variety of aldimines and ketimines using our previously reported family of allylsilane reagents. The reactions may reasonably lay claim to high degree of practicality and allow ready access not only to a range of homoallylamine derivatives but also to tertiary carbinamine-containing heterocycles such as **19** and **20**. Further exploitation of these allylsilane reagents and of the mechanistic paradigm described herein for access to more unusual structures may be anticipated.

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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>.

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