

Enantioselective Imidazole-Directed
Allylation of Aldimines and Ketimines

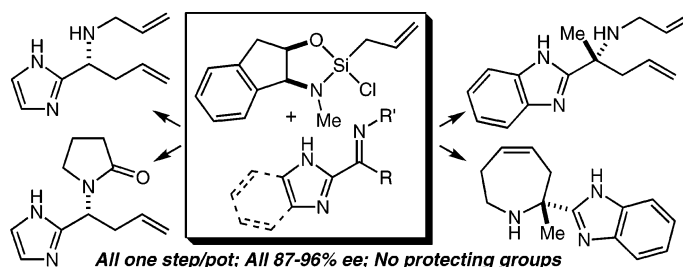
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ABSTRACT

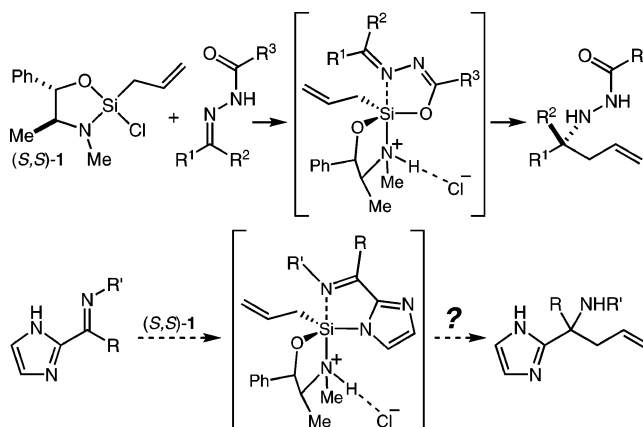


A new chiral allylchlorosilane has been developed that allows the highly enantioselective allylation and crotylation of a range of 2-imidazolylaldimines and ketimines. The method may be exploited for the protecting group-free synthesis of a diverse array of imidazole-bearing chiral carbinamines and, when coupled with ring-closing metathesis reactions, allows the one-pot synthesis of unusual heterocyclic motifs with potential relevance in medicinal chemistry.

Given the importance of imidazoles/benzimidazoles and of chiral carbinamines in medicinal chemistry,¹ general, reliable, and user-friendly methods for the synthesis of structurally and stereochemically complex imidazole-bearing chiral carbinamines might be expected to enjoy significant utility. If in addition such methods were compatible with unprotected imidazoles, they might enjoy significant advantages relative to other methods. This line of reasoning was inspired by our recent demonstration that a variety of aldehyde- and ketone-derived acylhydrazones may be allylated enantioselectively using chiral allylsilane reagent **1** (Scheme 1).^{2,3} Mechanistic investigations revealed that the hydrazones attach themselves to the silane by chloride displacement, thus generating an equivalent of HCl which protonates the amino group of the pseudoephedrine, thereby greatly increasing the activity of

the silane Lewis acid. This mechanism inspired the question of what other nucleophilic functionalities could effectively play the same role,⁴ and among the groups considered was the NH group of imidazoles and other related heterocycles. In this case, however, the directing group would be a part of the substrate, and not an auxiliary attached to the nitrogen

Scheme 1



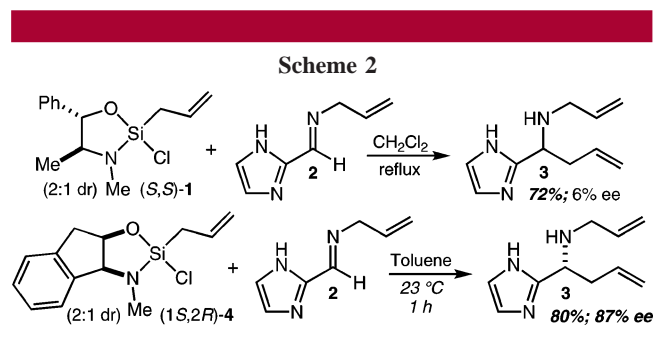
(1) For some recent examples, see: (a) Breslin, H. J.; Cai, C.; Miskowski, T. A.; Coutinho, S. V.; Zhang, S.-P.; Hornby, P.; He, W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2505. (b) Combs, A. P. et al. *J. Med. Chem.* **2006**, *49*, 3774. (c) Balboni, G.; Onnis, V.; Congiu, C.; Zotti, M.; Sasaki, Y.; Ambo, A.; Bryant, S. D.; Jinsmaa, Y.; Lazarus, L. H.; Trapella, C.; Salvadori, S. *J. Med. Chem.* **2006**, *49*, 5610.

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

(3) For a recent and comprehensive review of asymmetric imine allylation methods, see: Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815.

of the imine that would need to be cleaved in an efficiency-reducing additional step. While this approach would limit the substrate scope by definition, it would also allow unprecedented flexibility in the selection of the imine substituent (R'), flexibility that, as will be demonstrated, may be exploited for efficient access to unusual and interesting structures. Herein we demonstrate that imidazoles (and benzimidazoles) are effective activators of strained allylchlorosilane reagents and that this may be exploited for the highly enantioselective, efficient, and *protecting group-free* synthesis of a variety of functionally and stereochemically complex imidazole-bearing chiral carbinamine structures.

Our investigations began with imine **2**, derived from 2-formylimidazole and allylamine. Treatment of **2** with allylsilane **1** did indeed lead to smooth conversion to amine **3**, but with negligible (<10% ee) enantioselectivity (Scheme 2). A survey of other allylsilanes derived from chiral



aminoalcohols that are available inexpensively and in bulk led to the discovery that *cis*-1-amino-2-indanol-derived allylsilane (1*S*,2*R*)-**4**⁵ was effective in inducing good levels of enantioselectivity. Upon optimization, it was found that treating imine **2** with (1*S*,2*R*)-**4** in toluene for 1 h at room temperature provided amine **3** in 80% yield and 87% ee.

With a readily available and effective allylsilane identified, a survey of the scope of the reaction was carried out (Table 1). As alluded to above, a variety of imine N -substituents (R') are well tolerated, as demonstrated by the synthesis of amines **3**, **5**, and **6** (entries 1, 2, and 3), with the latter entry demonstrating some functional group tolerance as well. From the standpoint of medicinal chemistry and structural diversity this is an especially useful feature, and one not possible with a chiral auxiliary-based approach (R' = chiral auxiliary), wherein the auxiliary must be removed and the resulting primary amine functionalized in additional steps. Ketimines may also be allylated under surprisingly mild and practical reaction conditions (toluene, room temperature, 1 h) as demonstrated by the enantioselective synthesis of tertiary

(4) We have recently shown in two different contexts that phenols are effective activators of our allylchlorosilane family of reagents: (a) Burns, N. Z.; Hackman, B. M.; Ng, P. Y.; Powelson, I. A.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3811. (b) Rabbat, P. M. A.; Valdez, S. C.; Leighton, J. L. *Org. Lett.* **2006**, *8*, 6119.

(5) As is the case with allylsilane **1**, **4** is produced, isolated, and employed as a ~2:1 mixture of diastereomers. See the Supporting Information.

Table 1. Enantioselective Imidazole-Directed Allylation

Entry	Imine	Product	yield (%)	ee (%)
1			80	87
2			85	95
3 ^a			71	88
4 ^b			85	91
5			86	91
6 ^c			69	70

^a After 1 h, this reaction was heated to 45 °C for 1 h to effect lactamization. ^b The enantiomeric reagent (1*R*,2*S*)-**4** was employed in this experiment. ^c This reaction was conducted at 10 °C for 38 h.

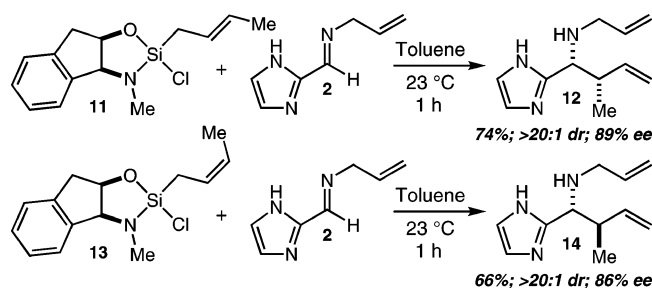
carbinamines **7** and **8** (entries 4 and 5),⁶ and these reactions also demonstrate that imidazole and benzimidazole may be used interchangeably. Remarkably, phenylketimine **9** may be smoothly allylated as well to provide tertiary carbinamine **10** in 69% yield and 70% ee (entry 6). Despite the moderate enantioselectivity, we contend that this is a useful reaction as alternate methods to access enantioenriched structures of this type are not readily apparent.⁷

One of the more powerful features of allylation reactions of this type is the potential for the establishment of a second stereocenter at the allylic position of the products by substitution of the terminal carbon of the allylsilane. Most often this takes the form of crotylation reactions, and we have established that crotylation is viable in the present context (Scheme 3). Thus, treatment of aldimine **2** with *trans*-

(6) For other recent advances in asymmetric ketimine allylation, see: (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. (e) Canales, E.; Hernandez, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 8712.

(7) Structurally related tertiary carbinamines have been accessed with, in some cases, very good diastereoselectivity employing the Ellman *tert*-butanesulfinimine methodology. See: Shaw, A. W.; deSolms, S. J. *Tetrahedron Lett.* **2001**, *42*, 7173.

Scheme 3

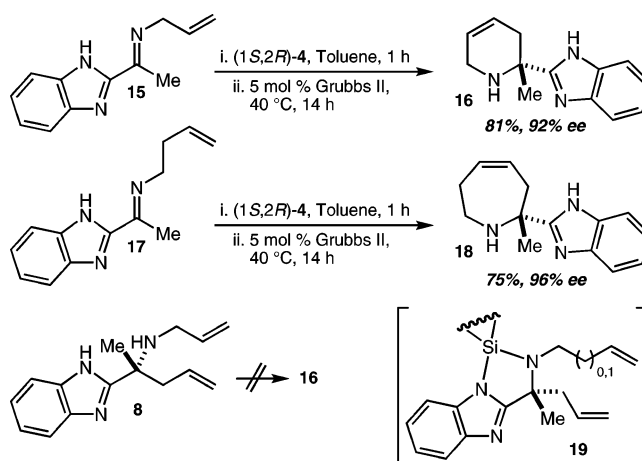


crotylsilane **11** leads to the syn diastereomer **12** in 74% yield with excellent stereoselectivity (>20:1 dr, 89% ee), and *cis*-crotylsilane **13** leads to the anti product **14** in 66% yield (>20:1 dr, 86% ee). As above, these reactions are notable for the practical and experimentally trivial reaction conditions under which they are conducted.

As described above (amines **3**, **5**, and **6**, Table 1), the method is tolerant of a range of imine *N*-substituents, a feature that allows the rapid generation of diversely functionalized amine products. While this is useful in its own right, we also saw a further opportunity to view the imine *N*-substituent as part of the carbon framework of a given target. Thus, reaction of ketimine **15** with **4**, followed *prior to workup* by the addition of 5 mol % of the second-generation Grubbs catalyst⁸ led to piperidine derivative **16** in 81% yield and 92% ee (Scheme 4). By using the homologue **17**, azepine derivative **18** was accessed in 75% yield and 96% ee. It is important to note that attempts to perform the ring-closing metathesis reactions on the isolated products of the allylation reactions (e.g., **8**) were unsuccessful. Thus, while the allylation reactions require the use of unprotected imidazoles, the *in situ* silylation thereof (as in intermediate **19**) may be exploited for reactions that do require imidazole protection, without actually requiring a separate protection step.

We expect that this methodology may find utility in medicinal chemistry applications, due to its ability to provide rapid access to a diverse collection of functionally and stereochemically complex products while requiring only

Scheme 4



remarkably simple experimental procedures. The importance of the imidazole group and of chiral carbinamines in medicinal chemistry may hardly be exaggerated, and the chemistry reported here provides ready access to a variety of unusual imidazole-bearing chiral carbinamines. Efforts to extend this methodology to other medicinally important NH-containing heterocycles (indoles, pyrazoles, etc.) are underway.

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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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(8) (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.