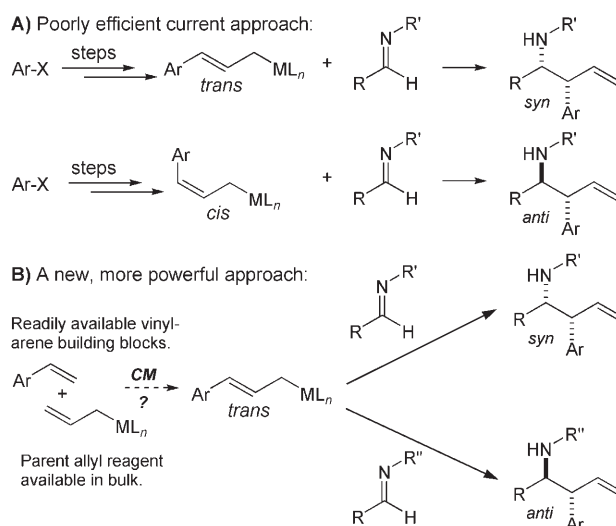


# Allylsilane–Vinylarene Cross-Metathesis Enables a Powerful Approach to Enantioselective Imine Allylation\*\*

John D. Huber, Nicholas R. Perl, and James L. Leighton\*

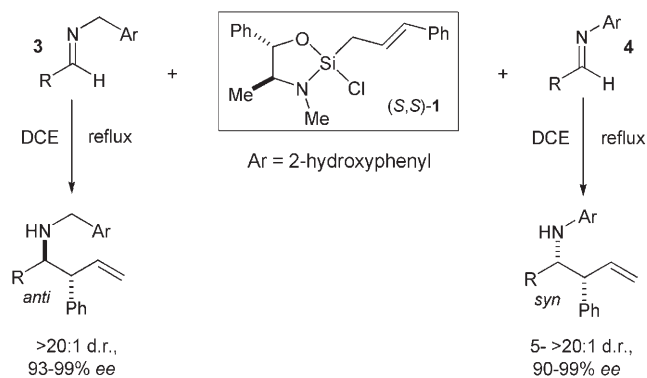
The development of methods for the asymmetric addition of allyl metal reagents to imines has received a significant amount of attention in recent years,<sup>[1]</sup> as the homoallylic amine products are useful in natural products synthesis and medicinal chemistry. Importantly, a second stereocenter may be established in the allylic position of the homoallyl amine products by substitution at the terminal carbon atom of the allyl fragment. In practice, however, the majority of published work in this regard,<sup>[1]</sup> including our own,<sup>[2]</sup> has described only the incorporation of simple methyl groups, and many of these methods allow access to only one of the two possible diastereomeric products. Furthermore, the methods that do allow access to both diastereomers uniformly require the synthesis of both the *trans*- and the *cis*-substituted allyl fragments. When one seeks to go beyond methyl substitution and toward the use of aryl-substituted allyl fragments, the limitations of this paradigm becomes starkly apparent: each different aryl fragment to be incorporated, and each diastereomeric product would require a separate, multistep, and otherwise nontrivial synthesis of the requisite *trans*- or *cis*-cinnamyl metal reagent (Scheme 1 A). If one were to design the “ideal” way to carry out imine cinnamylation, we contend it would resemble the process outlined in Scheme 1 B, wherein the parent allyl-metal reagent is combined with vinylarenes in a cross-metathesis (CM) reaction,<sup>[3]</sup> and the resulting *trans*-cinnamyl metal reagent may be used in situ for the synthesis of either diastereomer, based only upon the choice of imine. Such an approach would dramatically increase the power of the method to assemble stereochemically and functionally complex carbinamine products from extraordinarily simple starting materials. As a step towards testing this design proposal, we have reported that cinnamylsilane **1** is effective for highly enantioselective imine cinnamylation reactions,<sup>[4]</sup> and further reported that either product diastereomer may be accessed from the same *trans*-cinnamylsilane **1** based upon a subtle change to the structure of the



**Scheme 1.** A) Current approach requires the multistep synthesis of a separate *trans*- or *cis*-cinnamyl metal reagent for every different (hetero)aryl group to be incorporated and for each diastereomer. B) A new paradigm for imine cinnamylation with vastly improved efficiency and flexibility.

imine, resulting in a “diastereochemical switch” (Scheme 2).<sup>[5]</sup> Herein, we describe the use of cross-metathesis to facilitate the incorporation of a diverse collection of arenes and heteroarenes at the allylic position of the homoallylamine products, as well as preliminary examples of how the methodology may be employed for the rapid construction of complex heterocyclic structures.

The investigation began with examination of the CM reaction between allylsilane **2**<sup>[6,7]</sup> and styrene (Scheme 3). This process could be monitored by <sup>1</sup>H NMR spectroscopy,

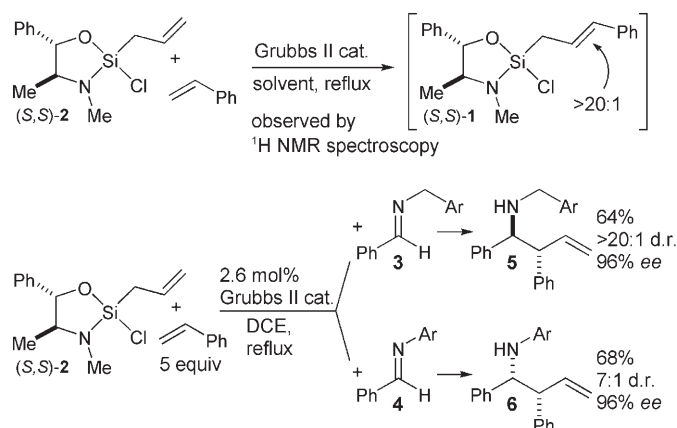


**Scheme 2.** Enantioselective imine cinnamylation with a “diastereochemical switch.”

[\*] J. D. Huber, N. R. Perl, Prof. Dr. J. L. Leighton  
 Department of Chemistry  
 Columbia University  
 New York, NY 10027 (USA)  
 Fax: (+1) 212-932-1289  
 E-mail: leighton@chem.columbia.edu

[\*\*] This work was supported by a grant from the NSF (CHE-04-53853) and a Focused Funding Award from Johnson & Johnson. We thank Merck Research Laboratories and Amgen for unrestricted support. J.D.H. was the recipient of an NDSEG Fellowship from the Department of Defense, and N.R.P. was supported by a fellowship provided by Boehringer-Ingelheim.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

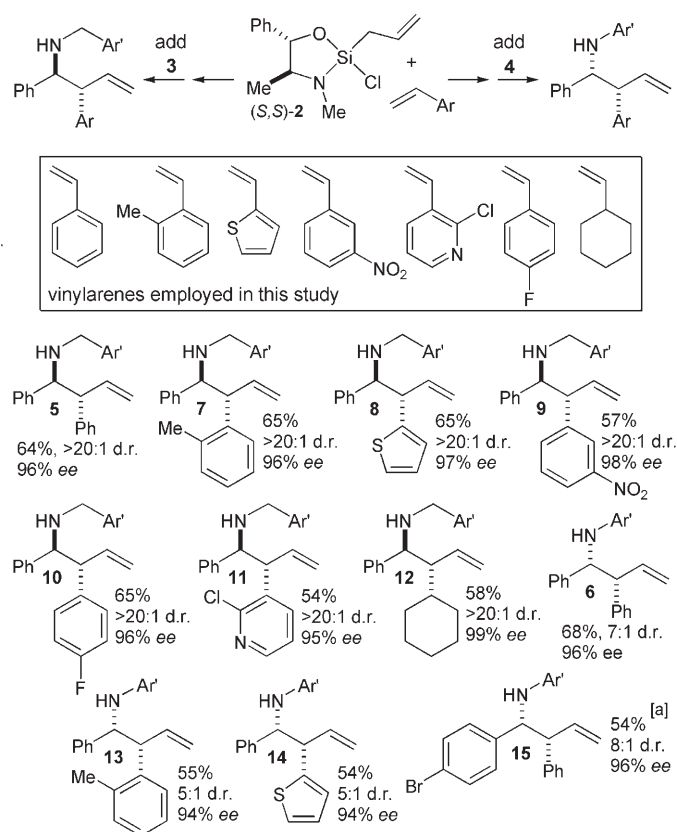


**Scheme 3.** Successful and selective cross-metathesis reactions with styrene and allylsilane **2**. Ar = 2-hydroxyphenyl, DCE = 1,2-dichloroethane.

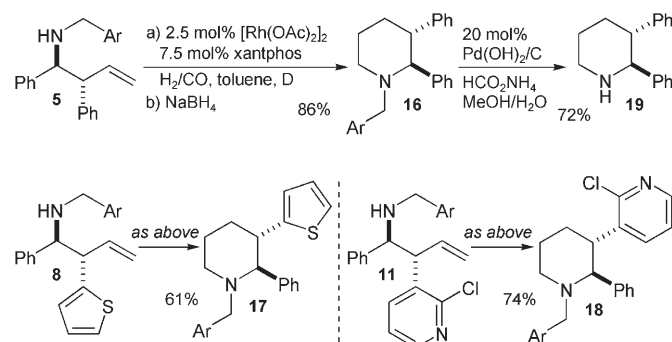
and it was observed that the second-generation Grubbs catalyst<sup>[8]</sup> was effective for this reaction and that the *trans* isomer (**1**) was produced with excellent selectivity (>20:1). Allylsilane **2** did dimerize during the reaction, but over time, in the presence of styrene, the dimer was converted into cinnamylsilane **1**, albeit accompanied by some decomposition. The use of an excess of styrene (5 equiv) thus became standard procedure, and the optimized reaction conditions (2.6 mol% catalyst in refluxing DCE) were applied to the reaction with imines **3** and **4**. Consequently, amines **5** and **6** were isolated in 64% and 68% yield, respectively, and the diastereoselectivities were identical to those of the reactions described in Scheme 2 and enantioselectivities were marginally lower.

An examination of the scope of the process, with respect to the vinylarene, was carried out and the results (**5–15**) are compiled in Scheme 4. A selection of substituted styrenes and vinylheteroarenes was employed and all participated in the CM/cinnamylation process successfully. Although the focus of this study is cinnamylation, we have demonstrated in one example that vinylalkanes may be employed (vinylcyclohexane to give **12**) with good efficiency and excellent diastereo- and enantioselectivity. Finally, although the yields for these reactions are moderate (54–68%), this is offset by the concise nature of the reaction; a traditional approach would require independent multistep syntheses of seven different cinnamylsilane reagents.

The products described in Scheme 4 may be rapidly transformed into potentially useful heterocyclic structures. For example, hydroformylation of **5** with xantphos<sup>[9]</sup> as the ligand, followed by a reductive workup provided piperidine **16** in 86% yield (Scheme 5). Two additional examples of this process are shown, and it is a testament to the flexibility of the methodology that piperidines **16**, **17**, and **18** may be assembled in two steps from allylsilane **2**, the vinylarene, and imine **3**. Armed only with a diverse supply of vinylarenes and imines, one may rapidly install various arenes onto these piperidine structures, a feature that may facilitate application of methods such as this in medicinal chemistry. Finally, we have demonstrated that our method for the removal of the 2-



**Scheme 4.** Tandem cross-metathesis imine cinnamylation. Standard reaction conditions: 2.6 mol% Grubbs II cat., DCE, CHCl<sub>3</sub> or CH<sub>2</sub>Cl<sub>2</sub>, reflux. [a] The imine derived from *p*-bromobenzaldehyde and 2-amino-phenol was employed in this reaction. Ar' = 2-hydroxyphenyl.

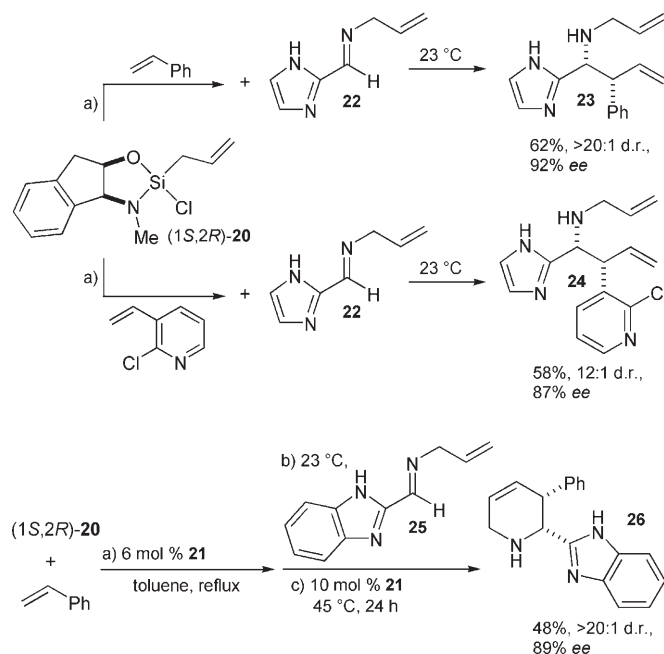


**Scheme 5.** One-pot conversion of the cinnamylation products into an important heterocyclic motif (piperidines), with the flexibility to rapidly incorporate, in principle, any arene or heteroarene at the 2- and 3-positions. Ar = 2-hydroxyphenyl, xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

hydroxybenzyl group<sup>[5]</sup> is applicable in this context. Thus, transfer hydrogenation of **16** gave piperidine **19** in 72% yield.

We have recently described how the aminoindanol-derived allylsilane **20** may be employed in the enantioselective allylation of 2-iminoimidazoles,<sup>[2c]</sup> and it seemed desirable to demonstrate that the CM process is also effective in

this context. Thus, CM with **20** and styrene catalyzed by the Hoveyda–Grubbs II catalyst (**21**),<sup>[10,11]</sup> followed by addition of imine **22** led to **23** in 62% yield as a single diastereomer and 92% *ee* (Scheme 6). When the process was repeated with 2-chloro-3-vinylpyridine, **24** was isolated in 58% yield as a 12:1 mixture of diastereomers and 87% *ee*. While ring-closing



**Scheme 6.** Tandem cross-metathesis imidazole-directed cinnamylation, and one-pot synthesis of complex heterocyclic structures without the use of protecting groups.

metathesis (RCM) was unsuccessful with **23**, it proved possible to develop a triple tandem process, taking advantage of the in situ silylation of the imidazole to allow the RCM process to proceed. In this fashion, **26** could be isolated in 48% yield and 89% *ee*. The one-pot synthesis of **26** from **20**, styrene, and **25** without the use of protecting groups, further illustrates the practical utility of the CM/cinnamylation methodology.

A new and powerful approach to imine cinnamylation has been established. Cross-metathesis with allylsilane **2** and a variety of vinylarenes allows the rapid generation of a variety of stereochemically and functionally complex homoallylic amines. In addition, methods to exploit this chemistry for the synthesis of heterocyclic structures have been developed. Future efforts will focus on expanding the scope of the

method and on other ways of exploiting the products of the methodology.

Received: December 8, 2007

Published online: March 12, 2008

**Keywords:** allylsilanes · asymmetric synthesis · cinnamylation · cross-coupling · homoallylic amines

- [1] For a recent review, see: a) H. Ding, G. K. Friestad, *Synthesis* **2005**, 2815; for reports since publication of this review, see: b) D. J. Lipomi, J. S. Panek, *Org. Lett.* **2005**, 7, 4701; c) P. V. Ramachandran, T. E. Burghardt, *Chem. Eur. J.* **2005**, 11, 4387; d) R. Wada, T. Shibuguchi, S. Makino, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, 128, 7687; e) E. Canales, E. Hernandez, J. A. Soderquist, *J. Am. Chem. Soc.* **2006**, 128, 8712; f) T. R. Wu, J. M. Chong, *J. Am. Chem. Soc.* **2006**, 128, 9646; g) K. L. Tan, E. N. Jacobsen, *Angew. Chem.* **2007**, 119, 1337; *Angew. Chem. Int. Ed.* **2007**, 46, 1315; h) R. Kargbo, Y. Takahashi, S. Bhor, G. R. Cook, G. C. Lloyd-Jones, I. R. Shepperson, *J. Am. Chem. Soc.* **2007**, 129, 3846; i) S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2007**, 129, 15398.
- [2] a) R. Berger, P. M. A. Rabbat, J. L. Leighton, *J. Am. Chem. Soc.* **2003**, 125, 9596; b) P. M. A. Rabbat, S. C. Valdez, J. L. Leighton, *Org. Lett.* **2006**, 8, 6119; c) N. R. Perl, J. L. Leighton, *Org. Lett.* **2007**, 9, 3699.
- [3] For cross-metathesis reactions between allylboranes and various alkenes in the context of aldehyde allylboration reactions, see: a) S. D. Goldberg, R. H. Grubbs, *Angew. Chem.* **2002**, 114, 835; *Chem. Int. Ed.* **2002**, 41, 807; b) Y. Yamamoto, M. Takahashi, N. Miyaoura, *Synlett* **2002**, 128.
- [4] For other reports of enantioselective imine cinnamylation reactions, see: a) Y. Gao, F. Sato, *J. Org. Chem.* **1995**, 60, 8136; b) M. Nakamura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.* **1996**, 118, 8489; c) S. Hanessian, R.-Y. Yang, *Tetrahedron Lett.* **1996**, 37, 5273; d) R. Yanada, A. Kaieda, Y. Takemoto, *J. Org. Chem.* **2001**, 66, 7516; e) C.-L. K. Lee, H. Y. Ling, T.-P. Loh, *J. Org. Chem.* **2004**, 69, 7787.
- [5] J. D. Huber, J. L. Leighton, *J. Am. Chem. Soc.* **2007**, 129, 14552.
- [6] J. W. A. Kinnaird, P. Y. Ng, K. Kubota, X. Wang, J. L. Leighton, *J. Am. Chem. Soc.* **2002**, 124, 7920.
- [7] Allylsilane **2** has been prepared on a multikilogram scale by Gelest, Inc., Morrisville, PA, USA.
- [8] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, 1, 953.
- [9] M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, *Organometallics* **1995**, 14, 3081.
- [10] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, 122, 8168.
- [11] Use of the Hoveyda–Grubbs catalyst for this reaction gave slightly higher yields. For the most part, however, the catalysts may be used interchangeably.