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## Highly Enantioselective Imine Cinnamylation with a Remarkable Diastereochemical Switch

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For almost 30 years, methods devoted to the diastereo- and enantioselective addition of allylic nucleophiles to aldehydes and, more recently, aldimines<sup>1</sup> have comprised a broad reaction class that occupies a privileged place in asymmetric synthesis. The enduring appeal of this reaction type is in part due to the fact that substitution of the allyl reagent allows the establishment of a second stereocenter, as in the familiar and powerful aldehyde crotylation reactions for polyketide natural product synthesis.<sup>2</sup> Most studies addressing the addition of substituted allyl reagents to aldimines (including our own<sup>3</sup>) have focused on crotylation reactions as well,<sup>4</sup> but is this focus merited? Chiral carbinamines are important in several areas of chemistry, but perhaps in none more so than medicinal chemistry, and in this context, it would surely be more useful to develop an asymmetric *cinnamylation* reaction for the incorporation of aryl groups to give products with vicinal carbinamine and benzylic stereocenters (Figure 1). While a few sporadic examples of asymmetric imine cinnamylation reactions have been reported,<sup>5</sup> no general method that can provide either product diastereomer has been developed. Herein we report the development of such a method and an unprecedented imine-dependent diastereochemical switch that allows the synthesis of either diastereomer from the same cinnamylsilane reagent, a discovery with important practical consequences.



**Figure 1.** Two examples of medicinally active compounds (ABT-341<sup>6</sup> and Focalin) with vicinal carbinamine and benzylic stereocenters, and a proposed imine cinnamylation reaction.

On the basis of our discovery that the corresponding unsubstituted allylsilane is effective for the highly enantioselective allylation of acylhydrazones<sup>3a,7</sup> and 2-aminophenol-derived imines, <sup>3b</sup> *trans*- and *cis*-cinnamylsilanes **1** and **2** were prepared (Scheme 1).<sup>8</sup> While the reactions of reagents **1** and **2** with acylhydrazones proceeded with poor efficiency and selectivity, 2-aminophenol-derived aldimines gave more promising results, although elevated temperatures (relative to the allylation reactions) were necessary. Indeed, it was found that conducting the reaction of **1** and **3** in refluxing 1,2-dichloroethane (DCE) led to the best results, and under these conditions, the *syn* product **4** was isolated in 87% yield (7:1 dr, 99% ee). As expected, when *cis*-cinnamylsilane **2** was employed, *anti*-diastereomer **5** was obtained in 81% yield (7:1 dr, 98% ee).

Our excitement over these extraordinarily enantioselective reactions was tempered by the recognition that the classical Type I





paradigm<sup>9</sup> is inherently inefficient in requiring the separate synthesis of both **1** and **2**. Further, while the large-scale synthesis of **1** is trivial, the same cannot truthfully be said for  $2^{.10}$  This led us to wonder whether we might find a way to skirt the limitations of the Type I reagent paradigm and discover a simple—and unprecedented<sup>11</sup>—way to access either product diastereomer from the same *trans*-cinnamylsilane **1**. This would not only be conceptually interesting and challenging but also would have clear and important practical advantages, not least of all that of obviating the less straightforward synthesis of **2**.

On the basis of our observations in the hydrazone allylation chemistry,<sup>7</sup> a mechanistic model for the cinnamylation reactions described in Scheme 1 may be advanced with the following features: (1) the phenol displaces the chloride from the silane; (2) the liberated HCl protonates the amino group of the pseudoephedrine, thereby activating the silane; and (3) the imine nitrogen and protonated pseudoephedrine nitrogen occupy the apical positions on the resulting trigonal bipyramidal complex. Applied to the reaction of 1 and 3, these assumptions result in complex 1-3-trans (where trans refers to the imine geometry), which correctly rationalizes the syn product 4 (Scheme 2). Although we have previously observed imine trans-cis isomerization in related systems7 (presumably effected by chloride ion addition to and elimination from the imine), it seemed plausible that, although it is operative in these cinnamylation reactions, the *cis* form of the imine (as in 1-3-cis) is simply too hindered to play a significant



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role in the reaction. We reasoned that a redesigned imine, specifically with reduced steric hindrance as in 6, might accommodate isomerization of the imine from **1-6-***trans* to the *cis*-imine form 1-6-cis, which would place the imine phenyl group in the presumably favored pseudo-equatorial position, and give rise to the anti-diastereomer. Indeed, we were delighted to discover that imine 6 performed superbly upon treatment with silane 1, giving antidiastereomer 7 in 91% yield, and with >20:1 dr and 97% ee. Thus, either diastereomer of the product may be accessed from the same cinnamylsilane 1 based solely upon the remarkably subtle difference between imines 3 and 6. Assuming our mechanistic model is correct, this constitutes the first demonstration of the ability to both induce and control imine *cis-trans* isomerization in a reaction of this type.

An examination of the scope of these cinnamylation reactions was carried out, and the results are compiled in Table 1. With only a few exceptions, both the syn- and anti-selective reactions proceed with good to excellent efficiency and diastereoselectivity, and with very high levels of enantioselectivity (products 8-19). In the syn series, we were further gratified to find that aliphatic aldehydederived imines perform well in terms of diastereo- and enantioselectivity (products 12 and 13), although the same does not hold for the anti series (typically <40% ee). This caveat notwithstanding, the results shown here represent the first general method for the highly enantioselective cinnamylation of imines, with the added and important benefit that either product diastereomer may be accessed from a single readily available chiral cinnamylsilane (1).

Our use of the *o*-hydroxybenzyl group appears to be the first such use in the context of imine addition reactions. We therefore sought to establish a simple method for the cleavage/deprotection of this group to reveal the free amine products. Hydrogenation was





<sup>a</sup> This reaction was conducted at 60 °C. <sup>b</sup> This reaction was conducted in CHCl3 at 50 °C. <sup>c</sup> This reaction was conducted in CH2Cl2 at reflux.

Scheme 3



a seemingly straightforward possibility, but initial attempts using standard protocols were unsuccessful. Eventually, it was discovered that Pd(OH)<sub>2</sub>/C-catalyzed transfer hydrogenation worked well, providing amine 20 in 73% yield from 7 (Scheme 3). A second example using o-methoxyphenyl substrate 18 proceeded smoothly as well, giving 21 in 80% yield.

We have reported the first general and highly enantioselective imine cinnamylation reaction, which provides experimentally simple and inexpensive access to high value added products containing vicinal carbinamine and benzylic stereocenters. Through the introduction of a new imine directing/activating group, a diastereochemical switch has been developed, wherein either product diastereomer may be accessed based solely upon a simple structural change to the imine. This latter discovery obviates a traditionally required-and in the present case, a problematic-synthesis of the cis reagent (2), and it may have implications for the further development of imine allylation reactions as well as other asymmetric imine addition reactions.

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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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