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Asymmetric Allylation, Crotylation, and Cinnamylation of *N*-Heteroaryl Hydrazones

Miriam Inbar Feske, Alexander Buitrago Santanilla, and James L. Leighton*

Department of Chemistry, Columbia University, New York, New York 10027

leighton@chem.columbia.edu

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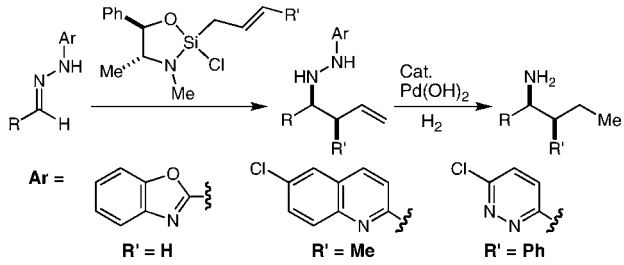
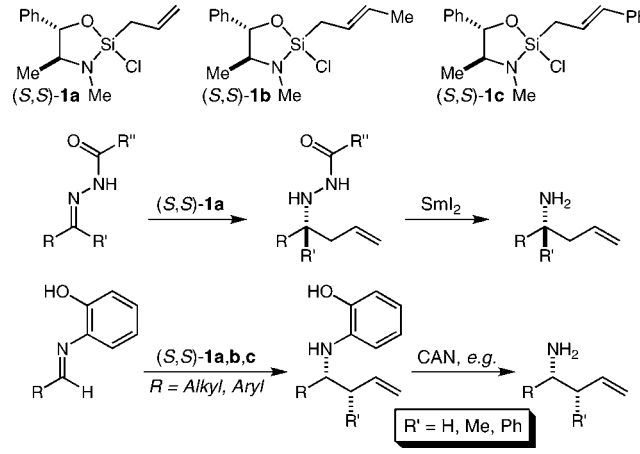
ABSTRACT



A new class of *N*-heteroaryl hydrazones has been developed as an alternative to *N*-acylhydrazones and 2-aminophenol-derived imines in asymmetric allylation, crotylation, and cinnamylation reactions with chiral allylchlorosilanes. The hydrazones are readily and inexpensively prepared, perform well in the allylation chemistry, and more importantly, the product hydrazides may be smoothly reduced by $Pd(OH)_2$-catalyzed hydrogenation to reveal the corresponding amine products.

The asymmetric allylation of imines is one of the more versatile and general methods for the synthesis of nonracemic chiral carbinamines,[1] as this approach can produce both secondary and tertiary carbinamines, as well as a second stereocenter in the allylic position of the product through the use of substituted allyl fragments. Although we have documented the utility of allylsilane **1a** in reactions with aldehyde- and ketone-derived acylhydrazones to provide chiral carbinamine products with good to excellent levels of enantioselectivity (Scheme 1),[2] two important limitations in scope were uncovered during the course of those studies: (1) most aliphatic aldehyde-derived hydrazones reacted with poor enantioselectivity and (2) acylhydrazones—with only a few exceptions—did not perform well with substituted allylsilanes **1b** and **1c**. While both limitations were successfully addressed by the use of 2-aminophenol-derived imines (Scheme 1),[3] this directing/activating group was not without its own limitation: the oxidative cleavage of the 2-hydroxyphenyl group (typically with ceric ammonium nitrate (CAN) or $PhI(OAc)_2$) from the homoallylamine products can be an

Scheme 1



(1) For two recent reviews, see: (a) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815. (b) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541.

(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.

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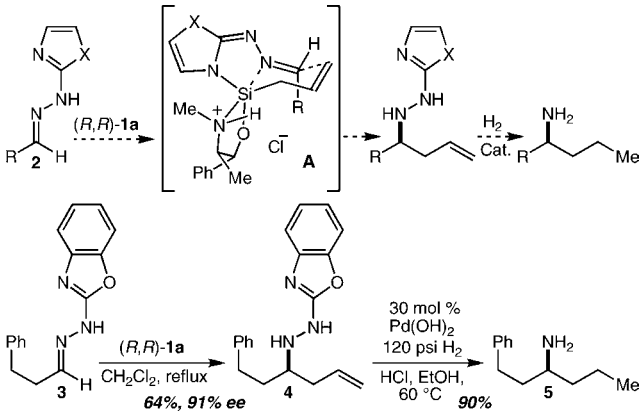
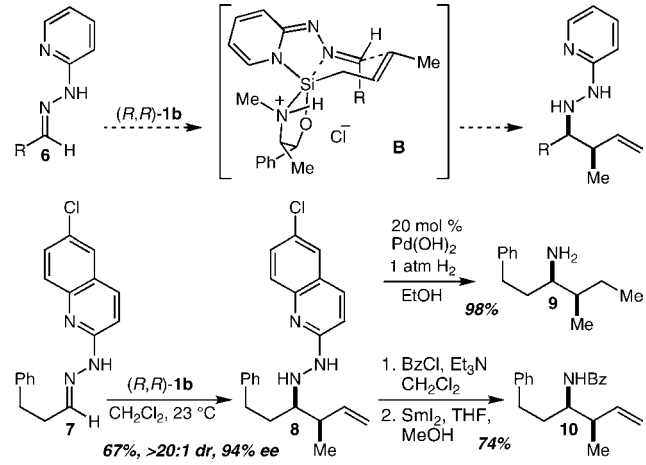
inefficient transformation. Indeed, it is often necessary to methylate the phenol and reduce the alkene first, in order to obtain acceptable yields of the free amine.[4] Our ongoing search for an effective and general directing/activating group that may be more simply, reliably, and efficiently removed has uncovered a new class of *N*-heteroarylhydrazones, and we report the details herein.

Scheme 2



N-Heteroarylhydrazones[5] such as **2** (X = O, S, N−R′) were considered because it was envisioned that they would react with our allylchlorosilanes (in analogy to the acylhydrazones and *N*-(2-hydroxyphenyl)imines) to produce a complex such as **A** (Scheme 2). Interestingly, this would require a loss of aromaticity, but as these are heteroarenes, this was predicted to be not necessarily prohibitive. Further, there was reason to be optimistic that the N−N bond in the product *N-aryl*hydrazides would be susceptible to metal-catalyzed hydrogenation.[6] Benzoxazole-derived hydrazone **3** was prepared[7] and upon treatment with (*R*,*R*)-**1a** in refluxing CH_2Cl_2 gave hydrazide **4** in 64% yield and 91% ee. Hydrogenation of the N−N bond in **4** did indeed prove feasible with $Pd(OH)_2$ as the catalyst, and this procedure produced amine **5** in 90% yield. While these two reactions represented a potential solution to the allylation of aliphatic aldehyde-derived imines, **3** did not perform well with either **1b** or **1c**. The corresponding benzothiazole and benzimidazole hydrazones were examined as well, but these proved less effective than the benzoxazole hydrazone.

Scheme 3



Our investigations focused next on heteroarylhydrazones typified by *N*-(2-pyridyl)hydrazone **6** (Scheme 3). In direct analogy to complex **A**, we envisioned that treatment of **6** with **1b** would lead to the formation of complex **B**, and we hoped that a system could be identified that would perform well in this crotylation process. While **6a** (R = CH_2CH_2Ph) did react smoothly with (*R*,*R*)-**1b**, the product was produced with poor enantioselectivity (<40% ee). Substituted pyridines and quinolines were examined, and it was eventually found that 6-chloro-2-quinoline derived hydrazone **7** provided good results. Indeed, **7** proved more reactive than **3**, reacting smoothly with (*R*,*R*)-**1b** at room temperature to give hydrazide **8** as a single diastereomer in 67% yield and 94% ee. As expected, hydrogenation under the conditions described for the reduction of **4** was effective for **8** as well giving **9** in 98% yield. Alternatively, reduction with SmI_2 (the method typically employed with the acylhydrazide products[8]) could be carried out following benzoylation of the hydrazide to give **10** in 74% overall yield.

A brief survey of substrate scope was conducted and the results are summarized in Table 1. In every case the products (**8**, **11**−**14**) were produced as a single diastereomer, and with good to excellent enantioselectivity (81−94% ee). The relatively large range in ee values observed is perhaps surprising in light of the similarity of the substrates, and is suggestive of one or more isomeric complexes (and ultimately transition states) related to **B** being relatively close in energy. Nevertheless the method does provide a useful alternative to the 2-aminophenol-derived imine crotylation reactions discussed above for aliphatic aldehyde-derived imines.

It was of interest as well to pursue an alternative for our recently reported cinnamylation protocol for 2-aminophenol-

(3) (a) Rabbat, P. M. A.; Valdez, S. C.; Leighton, J. L. *Org. Lett.* **2006**, *8*, 6119. (b) Huber, J. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2007**, *129*, 14552. (c) Huber, J. D.; Perl, N. R.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 3037.

(4) (a) Porter, J. R.; Travers, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409. (b) Sugiura, M.; Bobvieux, F.; Kobayashi, S. *Synlett* **2003**, 1749.

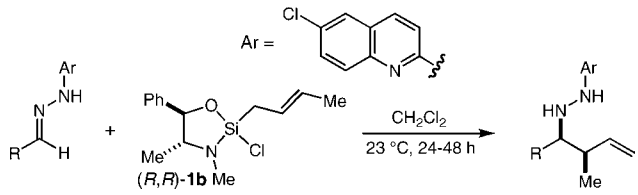
(5) We could find no examples of the use of such hydrazones in nucleophilic addition reactions. There are reports on the use of such hydrazones as ligands in coordination complexes. See, for example: (a) Tupolova, Y. P.; Lukov, V. V.; Kogan, V. A.; Popov, L. D. *Russ. J. Coord. Chem.* **2007**, *33*, 301. (b) Tang, J.; Costa, J. S.; Pevec, A.; Kozlevcar, B.; Massera, C.; Roubeau, O.; Mutikainen, I.; Turpeinen, U.; Gamez, P.; Reedijk, J. *Cryst. Growth Des.* **2008**, *8*, 1005.

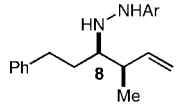
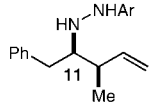
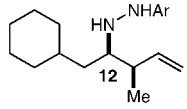
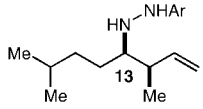
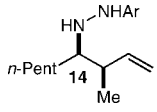
(6) (a) Hearn, M. J.; Chung, E. S. *Synth. Commun.* **1980**, *10*, 253. (b) Toti, A.; Frediani, P.; Salvini, A.; Rosi, L.; Giolli, C. *J. Organomet. Chem.* **2005**, *690*, 3641.

(7) Preparation of hydrazone **3** and all other hydrazones described herein was straightforward: the commercially available 2-chloroheteroarene is treated with hydrazine, and the resulting *N*-heteroarylhydraine is condensed with the aldehyde. See the Supporting Information for details.

(8) (a) Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* **1994**, *50*, 4399. (b) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637.

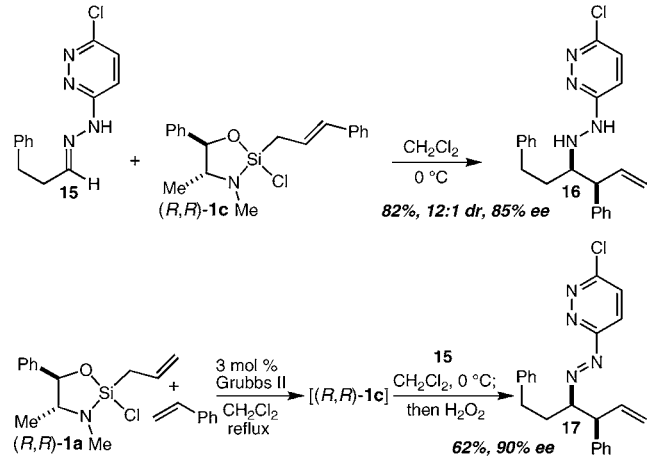
Table 1. Enantioselective Crotylation of Heteroarylhydrazones



entry	R	product	yield (%)	ee (%)
1	$PhCH_2CH_2$		67	94
2	$PhCH_2$		70	90
3	*c*-$HexCH_2$		74	81
4	*i*-$PrCH_2CH_2$		87	88
5	*n*-Pentyl		63	85

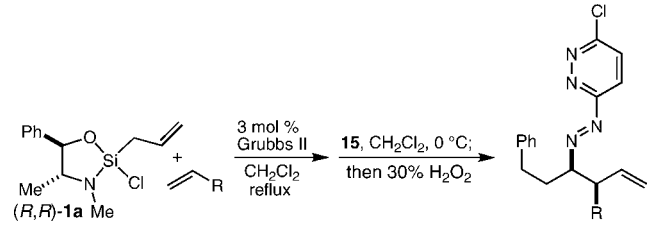
derived imines.[3b] Unfortunately, none of the substituted pyridine- and quinoline-derived hydrazones examined in the development of the crotylation reaction provided acceptable levels of enantioslectivity in reactions with (*R*,*R*)-**1c**. Our survey of heterocyclic motifs thus expanded to include pyrazines, pyrimidines, and pyridazines. While several such heteroaryl hydrazones provided promising leads, it was difficult to identify a system that provided both smooth conversion/good yields and high levels of enantioselectivity. After extensive experimentation, the 6-chloro-3-pyridazine-derived hydrazone **15** was found to provide good results upon treatment with cinnamylsilane (*R*,*R*)-**1c**, giving **16** in 82% yield (12:1 dr) and 85% ee (Scheme 4). With this promising result in hand, we next investigated the performance of the pyridazine activator in the one-pot cross-metathesis/cinnamylation procedure.[3c] While this did work, what was isolated was a ~2:1 mixture of **16** and the oxidized product **17**. This oxidation was also observed to a lesser extent in the reaction of **15** with **1c**, but it proved possible to suppress by rigorous exclusion of oxygen. Similar attempts to suppress the oxidation in the cross-metathesis/cinnamylation procedure were unsuccessful, and we therefore decided to develop a procedure in which the crude reaction product was oxidized with H_2O_2, allowing the more convenient isolation of one product instead of two. Upon optimization, this procedure allowed the one-pot synthesis of **17** (from **1a**, styrene, and **15**) in 62% yield (>20:1 dr) and 90% ee.

Scheme 4



Several examples of this one-pot cross-metathesis/cinnamylation reaction were demonstrated and the results are compiled in Table 2. The reaction is tolerant of a range of vinylarenes (entries 1−5) as well as vinylcyclohexane (entry 6). The reasons for the drop in ee observed in entry 5 and the drop in dr observed in entry 6 are not readily apparent, but may again be suggestive of one or more isomeric transition states that are relatively close in energy. As with the crotylation reactions described above, this methodology provides a viable alternative to the 2-aminophenol-derived imine cinnamylation reactions.

Table 2. Tandem Cross-Metathesis/Cinnamylation Reactions



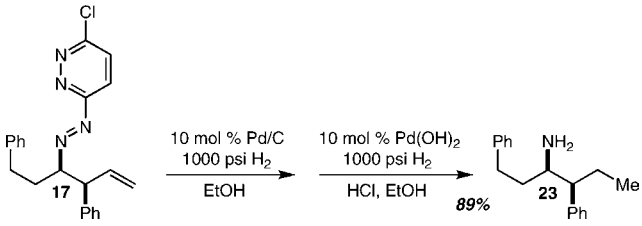
entry	R	product	yield (%)	dr	ee (%)
1	Ph	**17**	62	>20:1	90
2[a]	*o*-CH_1-C_6H_4	**18**	71	>20:1	90
3[b]	*p*-CH_3-C_6H_4	**19**	68	>20:1	86
4[a]	*m*-CF_3-C_6H_4	**20**	62	>20:1	86
5	*p*-F-C_6H_4	**21**	66	>20:1	82
6[b]	*c*-Hex	**22**	72	5:1	91

[a] This reaction was run in $CHCl_3$. [b] Part two of this reaction (the cinnamylation reaction) was conducted at 23 °C.

The N=N bond in the oxidized cinnamylation products may be hydrogenated as above (with $Pd(OH)_2$ as the catalyst), but, perhaps surprisingly, the chloride on the pyridazine ring is reduced only very slowly. Because of this the desired amine product is produced in the presence of 6-chloropyridazin-3-amine, and these two compounds react

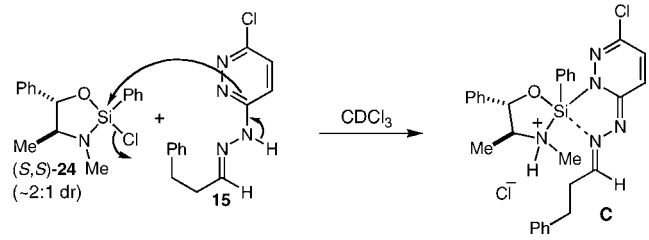
to give the substitution product. This problem is avoided by a two-stage process wherein **17** is first subjected to hydrogenation with Pd/C as the catalyst (this results in reduction of the chloride, the alkene, and reduction of R—N═N—R′ to R—NH—NH—R′), and then to hydrogenation with $Pd(OH)_2$ as the catalyst (Scheme 5). This procedure allows the reduction of **17** to give amine **23** in 89% yield.

Scheme 5



Finally, we have proposed that these hydrazones react with the chlorosilanes in direct analogy to the reactions of acylhydrazones with the chlorosilanes,[2b] and we have secured spectroscopic evidence for this notion (Scheme 6). Specifically, when hydrazone **15** is mixed with phenylsilane **24**, a single new species (assigned as **C**) is observed by ^{1}H and ^{28}Si NMR spectroscopy that grows in over the course of several hours (consistent with the idea we have previously advanced that the fact that the silanes are ∼2:1 mixtures of diastereomers is inconsequential—they react by way of a common intermediate/complex). The chemical shift of the peak in the ^{28}Si spectrum (−92 ppm) is consistent with the formation of a five-coordinate complex, and importantly, the N−C**H**$_3$ peak is a doublet in the proton spectrum, consistent with the loss of a proton from the hydrazone,

Scheme 6



displacement of chloride from silicon, and protonation of the pseudoephedrine amino group with the liberated HCl. The stereochemical details are more difficult to discuss with any authority and we note that the models for asymmetric induction implied by structures **A** and **B** are speculative.

A new class of *N*-heteroarylhydrazones has been developed for enantioselective allylation, crotylation, and cinnamylation reactions. The hydrazones are trivial to prepare, and the N−N bonds in the product hydrazides are easily cleaved by $Pd(OH)_2$-catalyzed hydrogenation. This discovery enhances the practicality and applicability of these synthetically powerful reactions, and these new hydrazones may find utility in other nucleophilic addition reactions.

Acknowledgment. This work was supported by a grant (CHE-08-09659) from the National Science Foundation. MIF is a National Science Foundation Graduate Research Fellow.

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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