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Enantioselective Allylation of Ketone-Derived Benzoylhydrazones: Practical Synthesis of Tertiary Carbinamines

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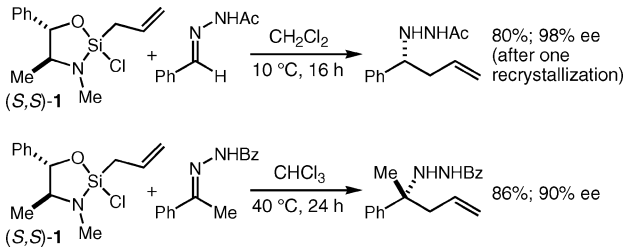
The development of practical, general, and enantioselective methods for the synthesis of tertiary carbinamines remains an important goal for organic synthesis. While many methods for the synthesis of quaternary α-amino acids have been reported,[1] far fewer reports concerning the addition of organometallics to ketimine derivatives have appeared.[2] To date, only one general method with high levels of stereoselectivity across a wide range of ketimine substrates has been described based on this approach.[3] Herein we report a practical method for the enantioselective synthesis of tertiary carbinamines based on the addition of a chiral allylsilane reagent to a structurally diverse array of ketone-derived benzoylhydrazones.

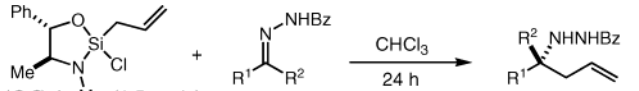
A previous report from this laboratory described the use of allylsilane **1** for the enantioselective allylation of aldehyde-derived acetylhydrazones (Scheme 1).[4] It was straightforward to interrogate allylsilane **1** for its ability to react with acetophenone-derived acylhydrazones. While all that were examined did react with allylsilane **1**, significant differences in efficiency and selectivity were noted. In contrast to the aldehyde-derived hydrazones, the benzoylhydrazone proved most effective. Under optimized conditions ($CHCl_3$, 40 °C) the product could be isolated in 86% yield and 90% ee.

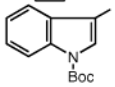
Scheme 1



Having established the viability of the reaction, we turned to a survey of the scope and generality of the method (Table 1). All hydrazones were prepared as single (*E*) isomers following recrystallization. The benzoylhydrazones derived from acetophenone, propiophenone, 2-phenylacetophenone, and methyl benzoylformate all provided good to excellent results (entries 1−4). Surprisingly, the sterically hindered isobutyrophenone-derived benzoylhydrazone was not only well-tolerated, but led to a significantly more enantioselective reaction (97% ee, entry 5). With R^2 = Me as a constant, a series of aryl and heteroaryl ketone-derived benzoylhydrazones was next examined (entries 6−12). While two of these substrates led to moderately enantioselective reactions (entries 7 and 12), the others consistently provided the hydrazides in 88−90% ee (entries 6 and 8−11). Dialiphatic ketone-derived hydrazones are effective substrates as well (entries 13 and 15). Indeed, that the benzylacetone-derived substrate provides 87% ee establishes that excellent results may be achieved even in the absence of significant steric differentiation between R^1 and R^2 (entry 13).

Table 1. Enantioselective Allylation of Ketone-Derived Hydrazones



entry	R^1	R^2	T °C	yield (%)	ee (%)[a]
1	Ph	Me	40	86	90
2	Ph	Et	40	91	89
3	Ph	CH_2Ph	40	95	84
4[b]	Ph	CO_2Me	-10	76	93
5	Ph	*i*-Pr	57	80	97
6	*p*-Br-C_6H_4	Me	23	92	89
7	*p*-MeO-C_6H_4	Me	40	70	85
8	*m*-NO_2-C_6H_4	Me	23	79	88
9	2-Naphthyl	Me	23	80	89
10		Me	40	46	88
11		Me	40	70	90
12		Me	40	64	86
13	$PhCH_2CH_2$	Me	23	86	87
14[c]	$PhCH_2CH_2$	Me	23	87	87
15	*c*-Hex	Me	23	78	94

[a] Determined by chiral HPLC. [b] Reaction time = 36 h. [c] The hydrazone starting material was a 3.8:1 *E*:*Z* mixture.

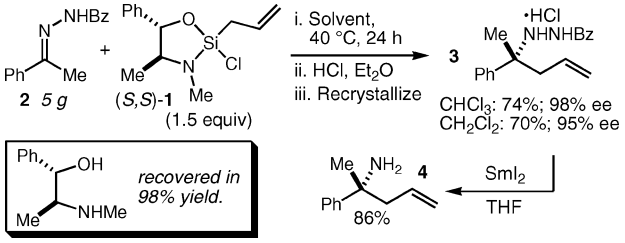
Surprisingly, when this experiment was repeated using a 3.8:1 *E*:*Z* mixture of the hydrazone, the results were identical (entry 14). Our assumption that the use of pure *E* isomers is essential for enantioselectivity was thereby disproved, and a mechanism involving *E*:*Z* isomerization was indicated (see below).

In a demonstration of the practicality of this method, the reaction of benzoylhydrazone **2** was carried out on a 5 g scale (Scheme 2). The unpurified product was acidified, and the salt was purified by a single recrystallization to give **3** in 74% yield and 98% ee. While the use of CH_2Cl_2 as solvent leads to slightly lower enantioselectivity, we nevertheless repeated this larger scale reaction in CH_2Cl_2. The recrystallization of **3** proved almost as effective (70% yield and 95% ee). Thus, for larger scale reactions, CH_2Cl_2 may be used as solvent with only minimal decrease in reaction performance. Importantly, we note as well that the pseudoephedrine controller may be recovered in 98% yield (based on amount of **1** used) by simple extraction during the workup. To establish that the free amine may easily be accessed, hydrazide salt **3** was subjected to reduction with SmI_2 to provide the free amine **4** in 86% yield.[5]

We have proposed that these reactions proceed through coordination of both the imine nitrogen and the acyl oxygen to the Lewis acidic silane reagent.[4a] However, benzoylhydrazone **2** does not react with methoxyallylsilane **5**, and *N*-methylbenzoylhydrazone **6**

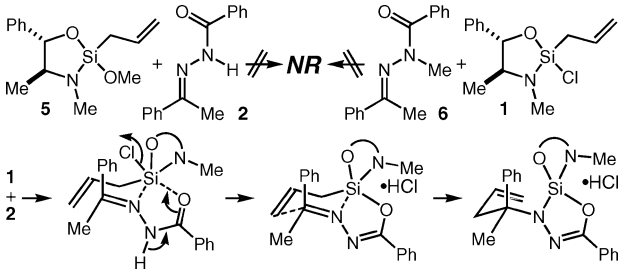
10.1021/ja0486418 CCC: $27.50

Scheme 2



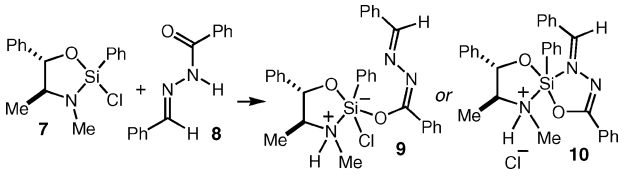
is unreactive with **1** (Scheme 3).[6] These results are consistent with a modified mechanism in which the acyl oxygen becomes covalently attached to the silane reagent by chloride displacement, and only then does allylation occur.

Scheme 3



To gain direct evidence for this hypothesis, we have prepared phenylsilane **7** (isolated as a 2:1 mixture of diastereomers). Upon reaction of **7** with hydrazone **8** in $CDCl_3$, ^1H NMR analysis shows the disappearance of **7** and **8** and the clean appearance of four new sets of signals that are consistent with structures such as **9** or **10** (Scheme 4).[7]

Scheme 4



This mixture precipitated as a white powder **11** (a single compound by ^1H NMR analysis) in 90% yield from toluene, and X-ray quality crystals were obtained by recrystallization from a CH_2Cl_2/hexanes solution (Figure 1). Not only does this structure strongly support the proposed chloride-displacement mechanism, it also represents the first X-ray structure of a silane Lewis acid−Lewis base complex directly relevant to an asymmetric reaction.[8] One particularly notable feature is the isomerization of the C=N double bond from *E* in **8** to *Z* in **11**. This provides direct evidence for the feasibility of the *E*:*Z* isomerization in these reactions that is clearly suggested by entry 14 in Table 1. In this context, it is noteworthy as well that substitution of allyl for phenyl on the silicon in structure **11** would lead to a prediction of the observed sense of induction.

This revised mechanism has profound implications for the further development of this chemistry. Certainly new substrates that carry functionality capable of adding to the silane may be imagined. In addition, while it is clear that the success of these reactions is due at least partly to the fact that the allylation is rendered intramolecular, it may also be true that the protonation of the amine of the pseudoephedrine is responsible for increased Lewis acidity of the silane as well.[9]

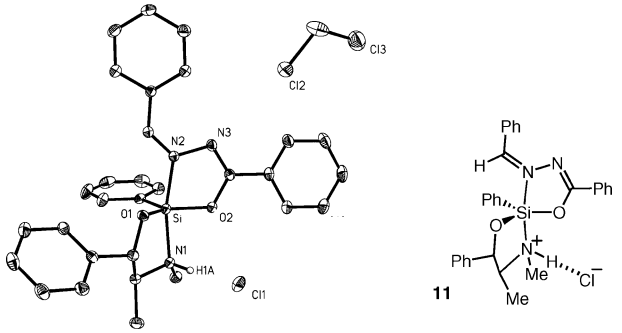


Figure 1. X-ray structure of **11**.

A highly practical method for the enantioselective synthesis of tertiary carbinamines has been reported. Reagent **1** is easily prepared in bulk, the experimental procedures are trivial, the products may be isolated (no chromatography) in high ee by crystallization, and the pseudoephedrine controller may be recovered in high yield by simple extraction.

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Supporting Information Available: Experimental procedures, characterization data, and stereochemical proofs (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Aldehydes are allylated by **5**, establishing that it is an otherwise competent allylation reagent. Leighton, J. L.; Lombardi, P. J. Unpublished results.
(7) The N−C**H**$_3$ peak is a doublet, for example. See the Supporting Information.
(8) Many X-ray structures of pentacoordinated silicon compounds have been reported. See: Holmes, R. R. *Chem. Rev.* **1996**, *96*, 927.
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