

A Simple and General Chiral Silicon Lewis Acid for Asymmetric Synthesis: Highly Enantioselective [3 + 2] Acylhydrazone–Enol Ether Cycloadditions

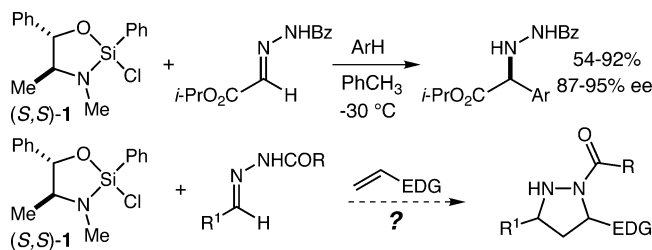
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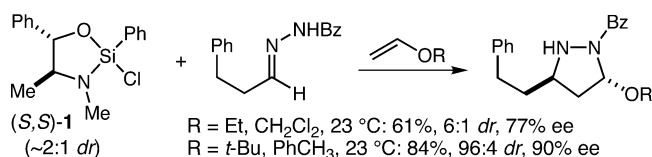
[3 + 2] Cycloaddition reactions of azomethine imines, diazoalkanes, and nitrile imines¹ provide access to medicinally important pyrazolidine and pyrazoline derivatives,² and both chiral auxiliary-controlled diastereoselective³ and catalytic enantioselective⁴ variants of such reactions have been reported. More recently, Kobayashi has established that related acylhydrazone–olefin cycloadditions may be catalyzed by (chiral) Lewis acids.⁵ We have established a program to develop chiral silicon-based Lewis acids for asymmetric synthesis, motivated by the significant practical advantages that could accrue to the use of silicon. Our strategy for inducing Lewis acidity in silanes is ring-strain, and we have documented that simply constraining allyl- and crotylsilanes in a five-membered ring leads to type I allyl-/crotylation reagents for both aldehydes and acylhydrazones.⁶ In an effort to generalize this strategy beyond allylation chemistry, we recently developed an enantioselective Friedel–Crafts reaction promoted by silanes **1** (Scheme 1).⁷ That the same simple silane Lewis acid might promote other acylhydrazone–nucleophile combinations is an attractive possibility, and we, therefore, set out to investigate acylhydrazone–olefin cycloadditions in this context.

Scheme 1



Our studies began with the benzoylhydrazone of dihydrocinnamaldehyde and ethyl vinyl ether (Scheme 2). Previously reported phenylsilanes **1** (easily prepared as a 2:1 mixture of diastereomers in a single step from pseudoephedrine and phenyltrichlorosilane) was found to mediate the cycloaddition, giving the pyrazolidine product in 61% yield with 6:1 diastereoselectivity and 77% ee. The use of *tert*-butyl vinyl ether led to an improvement in both diastereo- and enantioselectivity, and the reaction was found to perform best in toluene at room temperature. Under these conditions, the product was obtained in 84% yield with excellent (96:4) diastereoselectivity and 90% ee.

Scheme 2



Having established the feasibility of and optimal conditions for the reaction, a survey of the scope with respect to the hydrazones

was carried out (Table 1). A variety of aliphatic and aromatic and heteroaromatic aldehyde-derived benzoylhydrazones performed consistently well in the reaction, giving good yields and excellent diastereo- and enantioselectivities in every case.

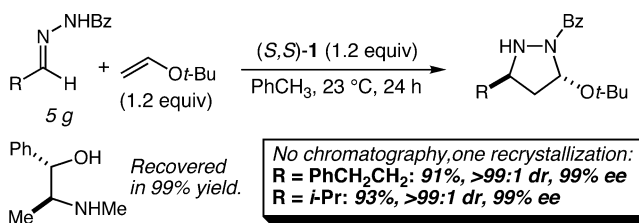
Table 1. Enantioselective [3 + 2] Cycloaddition Reactions

entry	R	yield (%)	dr ^a	ee (%) ^b
1	PhCH ₂ CH ₂	84	96:4	90
2	BnOCH ₂	85	>97:3	90
3	<i>i</i> -Pr	76	96:4	94
4	Cy	79	>97:3	95
5	<i>t</i> -Bu	76	>97:3	98
6 ^{c,d}	Ph	80	>97:3	94
7 ^c	<i>p</i> -F–C ₆ H ₄	66	>97:3	93
8 ^c	2-furyl	81	95:5	95

^a Determined by ¹H NMR spectroscopy. ^b Determined by chiral HPLC. ^c Reaction temp. = 40 °C. ^d Reaction time = 50 h.

To establish that the reaction performs well on a larger scale, entries 1 and 3 were repeated using 5 g of the hydrazone (Scheme 3). Employing only 1.2 equiv of both the vinyl ether and silanes **1**, we obtained the products after a single recrystallization in 91 and 93% yields, respectively, each as a single diastereomer in 99% ee. In addition, it proved trivial to recover the pseudoephedrine in 99% yield by simple extraction during the workup. Given this performance under near-ideal reaction conditions, it may justifiably be claimed that this is a highly practical process.

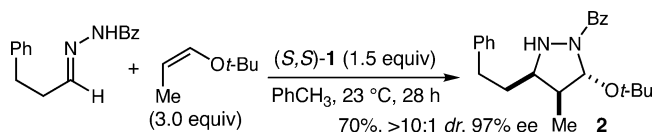
Scheme 3



It was also of interest to investigate β -substituted enol ethers as this would lead to the synthesis of pyrazolidines bearing three stereocenters. (*Z*)-*tert*-Butyl propen-1-yl ether was indeed found to be a viable dipolarophile for the reaction, leading to **2** with good diastereoselectivity and excellent enantioselectivity (Scheme 4). While Kobayashi has advanced a concerted mechanism for the Zr-catalyzed acylhydrazone–olefin cycloadditions,^{5b} this reaction represents the first example of a β -substituted dipolarophile being used in a Lewis acid-promoted version of this reaction. Such substrates can provide a direct probe of this issue, and the fact that

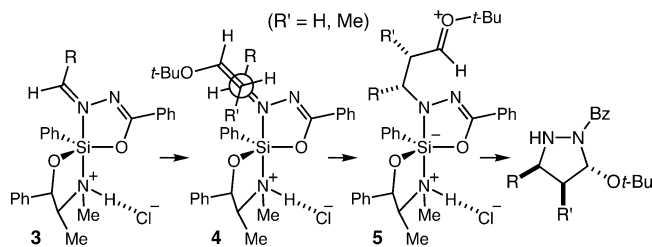
the *cis*-enol ether leads to the product with a *trans* relationship between the methyl and *OT*-Bu groups is indicative of a stepwise mechanism for these silane-promoted reactions. The possibility that the *cis*-enol ether might be isomerizing to *trans* and then engaging in a concerted reaction was excluded by the poor results (28% yield of a mixture of four products) observed when the cycloaddition was performed with the *trans*-enol ether. An additional control experiment (a sample of a cycloaddition product (Table 1, entry 1) enriched in the minor *cis* diastereomer was resubjected to the reaction conditions and was recovered unchanged) excluded the possibility that the aminal center might be equilibrating following a concerted reaction.

Scheme 4



In a previous study, it was demonstrated by X-ray crystallography that the reaction of silanes **1** with the benzaldehyde-derived benzoylhydrazone leads to structure **3** (R = Ph, Scheme 5).^{6e} Notable features of this structure include (1) the coalescence of both diastereomers of **1** into a single structure, (2) the protonation of the pseudoephedrine amino group, presumably leading to a significant increase in silane Lewis acidity,⁸ and (3) the isomerization of the C=N bond from *trans* (in the hydrazone) to *cis* (in the complex). On the basis of this structure, a plausible model may be advanced in which the enol ether approaches from the exposed *si* face of the hydrazone and is oriented so as to minimize steric interactions between the bulky *t*-BuO group and the complexed hydrazone (**4**, Scheme 5). Importantly, this model also correctly rationalizes the observed *cis* relationship between the phenethyl and methyl groups in **2** (see **4** and **5**, R' = Me). For the reactions in Table 1 (R' = H), the origin of the high levels of diastereoselectivity for the *trans* relationship between the *t*-BuO and R groups is not immediately obvious, but is presumably due to steric/conformational factors as **5** undergoes ring closure.

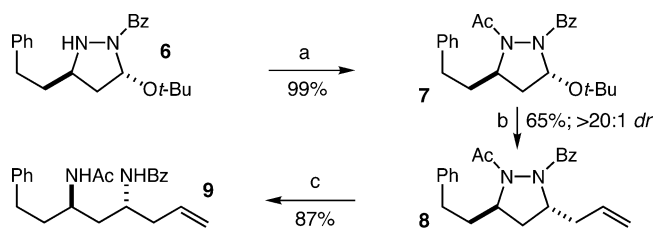
Scheme 5



That the cycloaddition products are amins suggests an opportunity for additional C–C bond-forming reactions. This possibility has been investigated in related systems by both Carreira⁹ and Kobayashi,^{5b} and it was found that in the absence of substitution at the 4 position, the diastereoselectivity was moderate at best. We were, therefore, pleased to discover that upon acetylation of **6** to **7**, a highly diastereoselective addition of allyltrimethylsilane promoted by TMSOTf could be carried out to give **8** in 65% yield (Scheme 6). Hydrazide reduction with SmI₂¹⁰ then delivered differentially protected diamine **9** in 87% yield, demonstrating that in addition to substituted pyrazolidines, this method can provide efficient access to 1,3-diamines, as well.

We have described a simple chiral silane Lewis acid for the highly diastereo- and enantioselective [3 + 2] benzoylhydrazone–

Scheme 6^a



^a Conditions: (a) AcCl, pyridine, DMAP, CH₂Cl₂; (b) TMSOTf, CH₂=CHCH₂SiMe₃, CH₂Cl₂, –15 °C; (c) SmI₂, MeOH, THF.

enol ether cycloaddition. The reactions proceed smoothly in toluene at ambient temperature. In addition, silanes **1** may be readily prepared in bulk in a single step from (*S,S* or *R,R*) pseudoephedrine and phenyltrichlorosilane. The former is inexpensive and easily recoverable, and the latter is available at a nominal cost. The process may thus lay a formidable claim to a high degree of practicality despite the requirement for a full equivalent of silanes **1**. Finally, and importantly, silanes **1** have now been shown to be highly effective chiral Lewis acids for two different reactions of acylhydrazones. The ability of silanes **1** to promote other useful transformations is under active investigation.

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Note Added after ASAP Publication. After this article was published ASAP on June 23, 2005, a processing error that caused some structures in Scheme 1 to be incorrect was discovered. The corrected version was published ASAP on June 24, 2005.

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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