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

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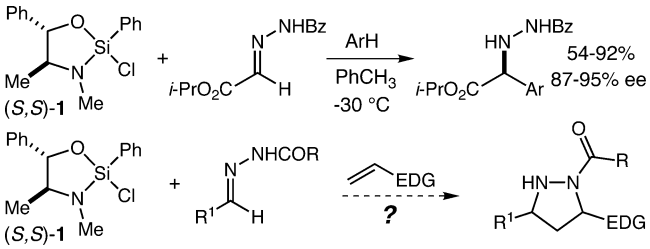
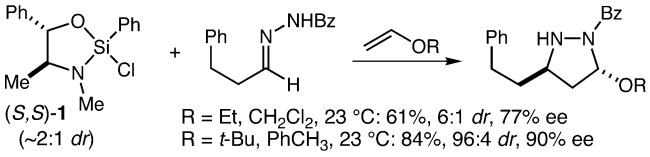
[3 + 2] Cycloaddition reactions of azomethine imines, diazoalkanes, and nitrile imines[1] provide access to medicinally important pyrazolidine and pyrazoline derivatives,[2] and both chiral auxiliary-controlled diastereoselective[3] and catalytic enantioselective[4] variants of such reactions have been 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



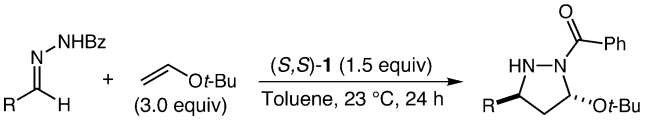
Our studies began with the benzoylhydrazone of dihydrocinnamaldehyde and ethyl vinyl ether (Scheme 2). Previously reported phenylsilanes **1** (easily prepared as a 2:1 mixture of diastereomers in a single step from pseudoephedrine and phenyltrichlorosilane) was found to mediate the cycloaddition, giving 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

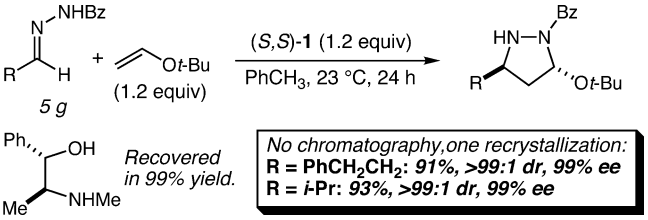


entry	R	yield (%)	dr[a]	ee (%)[b]
1	$PhCH_2CH_2$	84	96:4	90
2	$BnOCH_2$	85	>97:3	90
3	*i*-Pr	76	96:4	94
4	Cy	79	>97:3	95
5	*t*-Bu	76	>97:3	98
6[c,d]	Ph	80	>97:3	94
7[c]	*p*-F−C_6H_4	66	>97:3	93
8[c]	2-furyl	81	95:5	95

[a] Determined by ^{1}H 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

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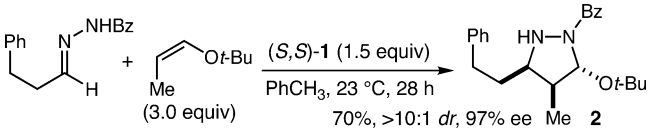
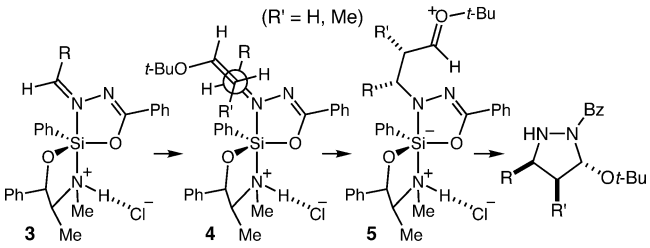
the *cis*-enol ether leads to the product with a *trans* relationship between the methyl and O*t*-Bu groups is indicative of a stepwise mechanism for these silane-promoted reactions. The possibility that the *cis*-enol ether might be isomerizing to *trans* and then engaging in a concerted reaction was 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.

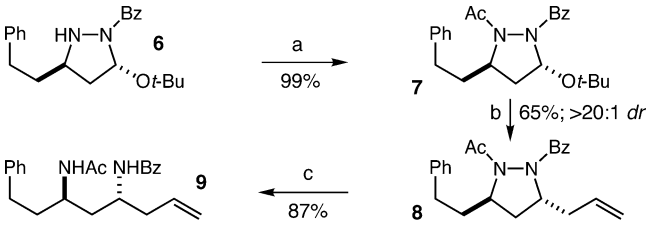
Scheme 5



That the cycloaddition products are aminals suggests an opportunity for additional C−C bond-forming reactions. This possibility has been investigated in related systems by both Carreira[9] 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 SmI_2[10] 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−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.

Scheme 6 [a]



[a] Conditions: (a) AcCl, pyridine, DMAP, CH_2Cl_2; (b) TMSOTf, $CH_2{=}CHCH_2SiMe_3$, CH_2Cl_2, −15 °C; (c) SmI_2, MeOH, THF.

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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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