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A New Silicon Lewis Acid for Highly Enantioselective Mannich Reactions of Aliphatic Ketone-Derived Hydrazones

Gregory T. Notte and James L. Leighton*

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

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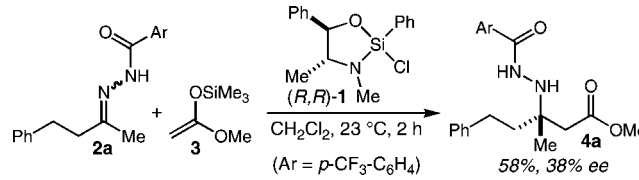
β-Amino acids have long been recognized as important building blocks in natural products synthesis and medicinal chemistry[1] and oligomers thereof as peptidomimetics.[2] As a direct result, massive effort has in recent years been devoted to the development of enantioselective Mannich reaction methodologies, and numerous impressive successes have been recorded.[3] With only very few exceptions, however, these successes have been limited to the use of aldimines as the electrophilic reaction component. Only a few examples of highly enantioselective Mannich reactions with ketimines have been reported,[4,5] and to our knowledge, there are no reported examples of highly enantioselective reactions of alipahtic ketone-derived imines. Due to the success of our strained silane Lewis acid platform with aliphatic ketone-derived hydrazones in other reactions,[6] we decided to examine whether we could address this important gap in the scope of enantioselective Mannich reactions.

Phenylsilane **1** has been shown to be effective both for acylhydrazone Friedel−Crafts reactions[7] and for acylhydrazone enol ether [3 + 2] cycloaddition reactions,[8] and it was hoped that this success would extend to the addition of silyl ketene acetals (SKA) to aliphatic ketone-derived hydrazones. Unfortunately, although **1** was found to promote the reaction between hydrazone **2a** and SKA **3**, the reaction gave **4a** with only moderate efficiency and poor enantioselectivity (Scheme 1).

Upon consideration of what changes could be readily made to the silane Lewis acid to render it more effective, replacement of the phenyl group with a more electronegative and sterically tunable group seemed an attractive option (Scheme 2). Alkoxy groups fit the bill on both counts and were also attractive in practical terms due to the ready availability of alkoxytrichlorosilanes.[9] Thus, reaction of **5** and **6** with pseudoephedrine provided alkoxysilanes **7** and **8** in 70 and 95% yields, respectively, and as 2.5:1 and 2.2:1 mixtures of (unassigned) diastereomers, respectively. With these new silanes in hand, our test reaction with hydrazone **2a** was reexamined, and gratifyingly, silanes **7** and **8** provided dramatically improved performance, giving **4a** in 81% and 74% ee, respectively. Upon optimization, it was found that the use of $PhCF_3$ as solvent provided another boost in enantioselectivity, and under these conditions (**2a** + silane in $PhCF_3$, 23 °C, 30 min; add SKA **3**, 30 min), silane **8** led to the production of **4a** in 89% yield and 90% ee. Given this performance, and its experimentally trivial, inexpensive, and high-yielding preparation, silane **8** was deemed most effective.

With optimal conditions identified, we set out to examine the scope of the reaction with respect to the hydrazone structure (Table 1). A range of aliphatic ketone-derived hydrazones **2a**−**f** participated smoothly in the reaction, giving β,β-dialkyl-β-hydrazidoesters **4a**−**f** in good yields and with high levels of enantioselection (entries 1−6). Remarkably, the hydrazone derived from 2-butanone (**2c**) is a highly effective substrate, giving **4c** in 91% ee (entry 3). To the best of our knowledge, this is the highest enantioselectivity achieved for a nucleophilic addition to a 2-butanone-derived imine.[10] More

Scheme 1



Scheme 2

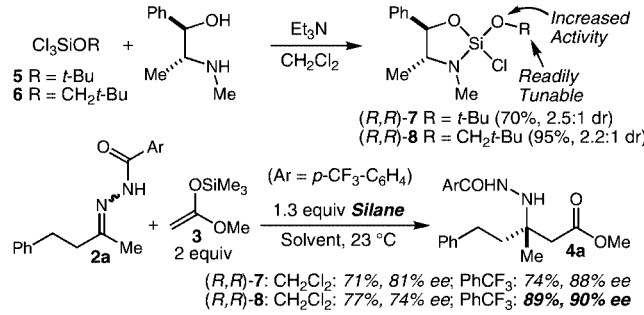
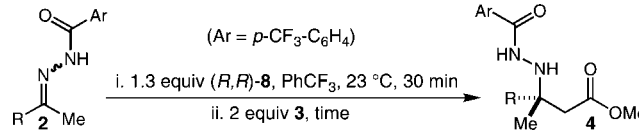


Table 1. Highly Enantioselective Mannich Reactions with Ketimines



entry	R	time[a]	yield (%)	ee (%)
1	$PhCH_2CH_2$ (**a**)	30 min	89	90
2	$PhCH_2$ (**b**)	30 min	89	96
3	Et (**c**)	30 min	84	91
4	$CH_2{=}CHCH_2CH_2$ (**d**)	30 min	74	89
5	*i*-$PrCH_2CH_2$ (**e**)	30 min	83	92
6	$TBSOCH_2CH_2$ (**f**)	30 min	66	91
7[b]	*i*-$PrCH_2$ (**g**)	22 h	74	96
8[c]	Cy (**h**)	22 h	71	97
9[d]	Ph (**i**)	22 h	60	88

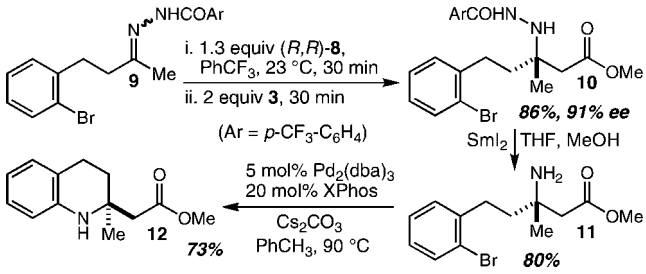
[a] Refers to reaction time after addition of **3**. [b] 3 equiv of **3**, 1.6 equiv of **8**, 0 °C. [c] 4 equiv of **3**, 2 equiv of **8**, in CH_2Cl_2. [d] Ar = *p*-NO_2−C_6H_4, 10 °C.

highly substituted aliphatic substrates (**2g**,**h**) are well tolerated and give superior enantioselectivities (entries 7 and 8), albeit in sluggish reactions that require higher loadings of **8** and the SKA. Finally, although it is not the focus of this study, we note that the acetophenone-derived hydrazone **2i** is an effective substrate, as well (entry 9).

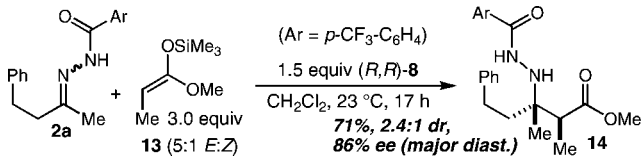
As one demonstration of the utility of this new and effective method for aliphatic ketimine substrates, we have developed an approach to an unusual 1,2,3,4-tetrahydroquinoline, a ring system of importance in organic and medicinal chemistry.[11] Thus, the

10.1021/ja800830h CCC: $40.75

Scheme 3



Scheme 4



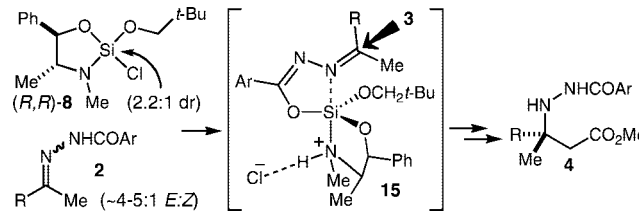
Mannich reaction of hydrazone **9** proceeded to give **10** in 86% yield and 91% ee (Scheme 3). Hydrazide reduction with SmI_2[12] gave **11** in 80% yield, and intramolecular Buchwald−Hartwig amination[13] gave 1,2,3,4-tetrahydroquinoline **12** in 73% yield.

We are aware of only a few examples of asymmetric Mannich reactions of substituted enolates with ketimines.[4a,b,d] SKA **13** (5:1 *E*:*Z*) was therefore prepared and employed in the Mannich reaction (Scheme 4). Although the diastereoselectivity of the reaction was low, we were gratified to find that the reaction proceed reasonably efficiently (71% yield) and in 86% ee.

As noted above, silane **8** is prepared and utilized as a 2.2:1 mixture of diastereomers. In addition, hydrazones **2** are synthesized and utilized as ∼4−5:1 mixtures of *E* and *Z* isomers (except **2h**, which is a ≥20:1 mixture).[14] Variation of the stoichiometry of **8** (0.5, 1.3, 2.0, and 4.0 equiv) under the otherwise standard conditions for the reaction of hydrazone **2a** led to only slight variations in the enantioselectivity of the reactions (89, 90, 92, and 92% ee, respectively). These data allow us to exclude the possibility that the silane diastereomers react through separate pathways with significantly different rates and enantioselectivities. While the yields in Table 1 do not allow us to exclude the possibility that only the major silane diastereomer is active, it will be noted that the 89% yields obtained for **4a** and **4b** are exactly the theoretical maximum for such a scenario. As for the hydrazone *E* and *Z* isomers, those same 89% yields for **4a** and **4b** establish that both isomers must be participating in the reaction. Indeed, when the reaction of **2a** was run with 2.0 equiv of **8** (and with only a 10 min complexation time), **4a** was isolated in 97% yield and 92% ee.

Taken together, these data suggest that silanes **8** and hydrazones **2** converge on a common complex, and that the reactions proceed through a single common pathway.[15] While we have thus far been unsuccessful in our attempts to characterize a relevant silane−hydrazone complex by X-ray crystallographic analysis, it will be noted that we have done so previously with the complex derived from (*S*,*S*)-**1** and the benzoyl hydrazone of benzaldehyde.[6] That structure established (1) the convergence of both silane diastereomers on a single complex upon treatment with a hydrazone, and (2) isomerization of the hydrazone *trans* isomer to *cis* in the complex. On the basis of this precedent, it is reasonable to propose the formation of a single complex **15** from silanes **8** and hydrazones **2** (Scheme 5). Attack of SKA **3** on the exposed front face of complex **15**—the back face being effectively blocked by the *neo*-pentyl group—correctly predicts the observed sense of absolute stereochemical induction.

Scheme 5



We have developed a new silane Lewis acid (**8**) that is effective for the highly enantioselective Mannich reaction of SKAs with aliphatic ketone-derived hydrazones. Silane **8** is trivial to prepare on large scale at a nominal cost, and neither its preparation nor use presents any significant environmental or toxicity issues. Ongoing efforts will address both increased scope in this Mannich reaction and a more detailed understanding of the mechanism.

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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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(15) It is consistent with this proposal that in the reaction of **2a** under the standard conditions the product ee is constant throughout the reaction. See the Supporting Information.

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