ORGANIC LETTERS

2011
Vol. 13, No. 4
816–818

Highly Enantioselective Mannich Reactions with α-Aryl Silyl Ketene Acetals and Imines

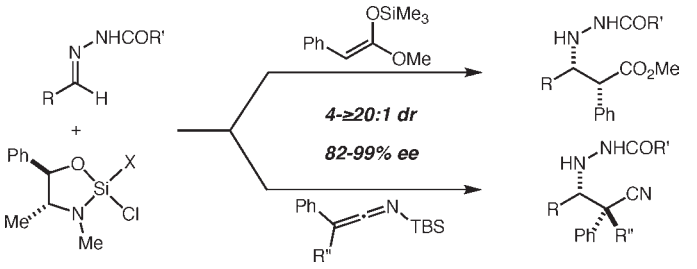
Gregory T. Notte, Jenny M. Baxter Vu, and James L. Leighton*

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

leighton@chem.columbia.edu

Received December 21, 2010

ABSTRACT



Mannich reactions with chiral silicon Lewis acid activated acylhydrazones and α-aryl silyl ketene acetals and α-aryl,α-alkyl silyl ketene imines proceed efficiently and with good to excellent levels of both diastereoselectivity and enantioselectivity. The reactions provide access to α-aryl, *β*-hydrazido esters and α-aryl,α-alkyl,*β*-hydrazido nitriles, which are valuable analogs of *β*-amino acids.

The Mannich reaction—broadly defined as the addition of an enol, enolate, or enolate equivalent to an imine—provides access to *β*-amino acids and related structures and, in recent years, has been the subject of an extraordinary amount of effort directed toward the development of efficient and highly enantioselective variants.[1] While impressive successes have been recorded using several different approaches, the substrate scope remains limited in notable ways. For example, there are relatively few reports that describe highly diastereoselective and/or enantioselective Mannich reactions of α-aryl substituted enolates (or enolate equivalents).[2] This relative paucity of general methods is particularly noteworthy as an examination of the literature reveals many examples of bioactive compounds and natural products with an α-aryl,*β*-aminocarboxyl substructure (Figure 1). This subset of Mannich reactions is thus one of fundamental synthetic importance for which there are few practical, general, and highly enantioselective solutions. Herein we report highly enantioselective Mannich reactions with α-aryl silyl ketene acetals and with α-aryl,α-alkyl silyl ketene imines that allow direct access to structures such as those depicted in Figure 1 using convenient, inexpensive, and scalable procedures.

We recently reported *neo*-pentoxychlorosilane **1** and its use in highly enantioselective Mannich reactions of aliphatic ketone-derived acylhydrazones with silyl ketene acetal (SKA) **2** (Scheme 1),[3,4] and this seemed a reasonable

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10.1021/ol103096u
Published on Web 01/14/2011

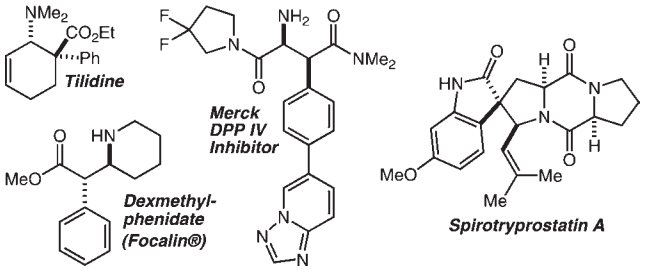
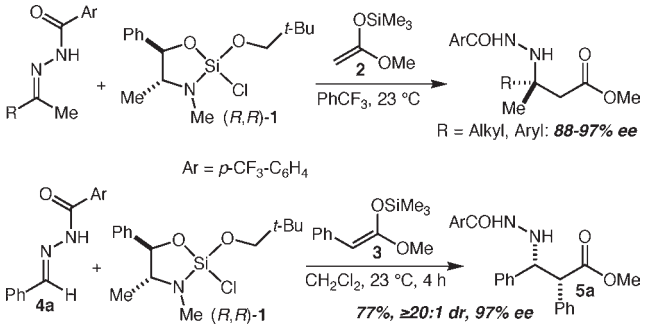


Figure 1. Examples of bioactive compounds possessing an α-aryl, β-aminocarbonyl substructure.

starting point for the present investigation. Indeed, it was quickly found that SKA **3** (prepared and employed as a 13:1 *Z*/*E* mixture) reacts smoothly with the silane **1**/hydrazone **4a** complex to give *syn*-Mannich product **5a**. Optimization was straightforward, and by performing the reaction in CH_2Cl_2 at ambient temperature for 4 h, **5a** could be isolated in 77% yield as a single diastereomer in 97% ee.

Scheme 1

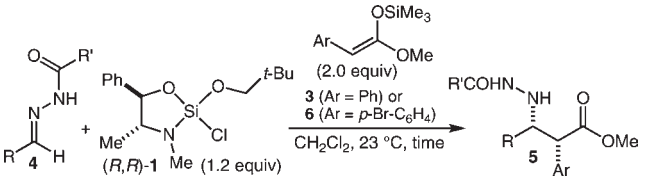


Summarized in Table 1 is a brief survey of the scope of the reaction with respect to the hydrazone substrate. Optimization focused on the nature of the group (R′) on the hydrazone, as we have found that this can have a significant effect on reaction performance. The use of both aromatic and aliphatic aldehyde-derived hydrazones resulted in excellent levels of enantioselectivity (entries 1−4), albeit with only moderate diastereoselectivity for unhindered aliphatic substrates (entries 2 and 3). As shown in entry 5, however, this moderate diastereoselectivity may be significantly improved simply by performing the reaction in $PhCF_3$. Although the reaction is slower and required a higher silane loading, the product **5b** was isolated with 13:1 dr and 94% ee. Glyoxylate-derived hydrazone **4e** (R = CO_2i-Pr, R′ = *p*-$MeOC_6H_4$) was employed as well (entry 6),

(3) Notte, G. T.; Leighton, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 6676.

(4) Silane **1** is isolated and employed as a 2.2:1 mixture of diastereomers. We have previously provided evidence that, upon reaction with a hydrazone, the diastereomers converge upon a single complex prior to the C−C bond-forming event. See ref 3.

Table 1. Highly Enantioselective Mannich Reactions with α-Aryl SKAs **3** and **6**



entry	R	R′	SKA	time (h)	product	yield (%)	dr	ee (%)
1	Ph	*p*-$CF_3C_6H_4$	**3**	4	**5a**	77	>20:1	97
2	$PhCH_2CH_2$	Ph	**3**	1	**5b**	89	5:1	95
3	*i*-$PrCH_2$	Ph	**3**	2	**5c**	86	4:1	95
4[a]	*i*-Pr	*p*-$CF_3C_6H_4$	**3**	48	**5d**	70	9:1	99
5[b]	$PhCH_2CH_2$	Ph	**3**	20	**5b**	74	13:1	94
6[c]	CO_2i-Pr	*p*-$MeOC_6H_4$	**3**	2.5	**5e**	91	5:1	82
7	$PhCH_2CH_2$	Ph	**6**	1	**5f**	79	4:1	95

[a] This reaction was run at 0 °C. [b] This reaction was run with 1.5 equiv of (*R*,*R*)-**1** and 3 equiv of SKA **3** in $PhCF_3$ at 0 °C. [c] This reaction was run with 2.4 equiv of SKA **3** in $PhCF_3$.

and although the enantiopurity of the product (**5e**) was somewhat lower with this substrate, this reaction nevertheless provides a useful and direct entry into systems such as the Merck DPP IV inhibitor[5,6] (see Figure 1). Finally, the use of a substituted aryl group (*p*-bromophenyl) on the SKA (**6**, prepared and employed as a 6:1 *Z*/*E* mixture) was demonstrated with hydrazone **4b**, which led to the isolation of **5f** (R = $PhCH_2CH_2$, R′ = Ph, Ar = *p*-Br-C_6H_4) in 79% yield (4:1 dr) and 95% ee (entry 7).

As an additional demonstration of the power of this method to allow direct and efficient access to medicinally relevant structures, hydrazone **7** was prepared and subjected to the reaction conditions described in Table 1 (Scheme 2). Prior to isolation, the unpurified Mannich product was treated with basic alumina resulting in smooth cyclization to give **8** in 78% overall yield (5:1 dr) and 95% ee. Reductive cleavage of the N−N bond was accomplished with SmI_2[7] and led to the isolation of erythro-(2*R*,2′*S*)-methylphenidate **9** as the major product of a 5:1 mixture of diastereomers in 76% yield.

Structures such as tilidine[8] and spirotryprostatin A[9] (Figure 1), and more generally the challenge of establishing quaternary carbon stereocenters in the context of complex β-amino acid derivatives, led us to examine α-aryl-α-alkyl

(5) Edmondson, S. D.; Mastracchio, A.; Mathvink, R. J.; He, J.; Harper, B.; Park, Y.-J.; Beconi, M.; Di Salvo, J.; Eiermann, G. J.; He, H.; Leiting, B.; Leone, J. F.; Levorse, D. A.; Lyons, K.; Patel, R. A.; Patel, S. B.; Petrov, A.; Scapin, G.; Shang, J.; Sinha Roy, R.; Smith, A.; Wu, J. K.; Xu, S.; Zhu, B.; Thornberry, N. A.; Weber, A. E. *J. Med. Chem.* **2006**, *49*, 3614.

(6) The Merck Research Laboratories Department of Process Research has also reported a Mannich reaction based approach to the synthesis of these bioactive compounds. See: Janey, J. M.; Hsiao, Y.; Armstrong, J. D., III. *J. Org. Chem.* **2006**, *71*, 390.

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(8) (a) Satzinger, G. *Liebigs Ann. Chem.* **1969**, *728*, 64. (b) Satzinger, G. *Liebigs Ann. Chem.* **1972**, *758*, 43.

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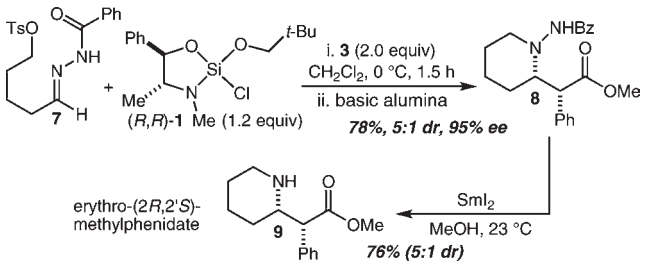
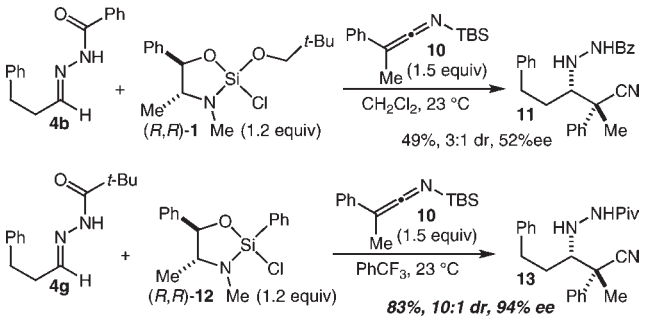
Scheme 2



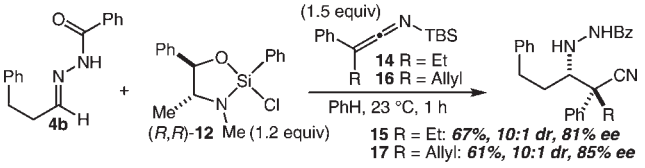
enolate equivalents.[2i] While a variety of α,α-disubstituted SKAs were found to be unreactive toward silane−hydrazone complexes, we were delighted to find that silyl ketene imine (SKI) **10**[10,11] smoothly added to the complex formed from hydrazone **4b** and silane **1** to give **11** (R = Ph) in 49% yield (3:1 dr, 52% ee) (Scheme 3). Previously described (and commercially available) phenylsilane **12**[12] was found to give improved stereoselectivity and, when paired with the bulkier pivaloylhydrazone **4g** in $PhCF_3$ as the solvent, gave **13** (R = *t*-Bu) in 83% yield (10:1 dr) and 94% ee.

Scheme 3



Attempts to expand the scope of this reaction with respect to the SKI structure revealed that this result was not general, as reactions with bulkier SKIs and pivaloylhydrazone **4g** led to poorly efficient reactions. Good results

Scheme 4



nevertheless proved attainable by employing the less hindered benzoyl hydrazone **4b**. As shown in Scheme 4, when the complex formed from **4b** and **12** was treated with ethyl-substituted SKI **14** in benzene, **15** was obtained in 67% yield (10:1 dr) and 81% ee, while under the same conditions SKI **16** led to **17** in 84% yield (10:1 dr) and 85% ee. While more work will be necessary to develop this reaction into a method that more reliably provides higher levels of enantioselectivity with a broader substrate scope, the reactions described in Schemes 3 and 4 establish that α,α-disubstituted *β*-amino acid analogs can be effectively accessed using this approach.

We have developed a series of Mannich reactions involving the addition of α-aryl silyl ketene acetals and α-aryl,α-alkyl silyl ketene imines to chiral silicon Lewis acid activated acylhydrazones. The reactions proceed efficiently and with good to excellent levels of both diastereoselectivity and enantioselectivity. We believe these reactions may find utility as a convenient entry into some relatively structurally and stereochemically complex α-aryl,*β*-amino acid analogs.

Acknowledgment. This work was supported by a grant (CHE-08-09659) from the National Science Foundation. G.T.N. is the recipient of a postdoctoral fellowship (F32-GM080859) from the National Institute of General Medical Sciences. We thank Novartis for a graduate fellowship to J.M.B. We thank Prof. Ged Parkin and Mr. Wesley Sattler (Columbia University, Department of Chemistry) for an X-ray structure analysis (see Supporting Information), and the National Science Foundation (CHE-0619638) is thanked for acquisition of an X-ray diffractometer.

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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(11) For two recent examples of the use of silyl ketene imines in asymmetric catalytic reactions, see: (a) Mermerian, A. H.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 949. (b) Denmark, S. E.; Wilson, T. W.; Burk, M. T.; Heemstra, J. R., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 14864.

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