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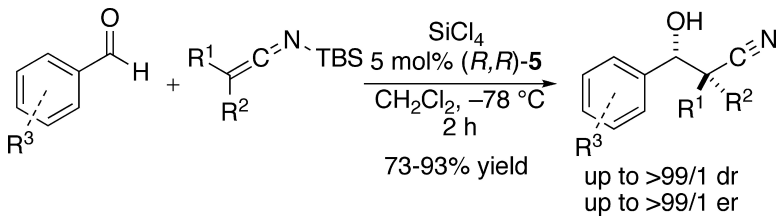

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Enantioselective Construction of Quaternary Stereogenic Carbons by the Lewis Base Catalyzed Additions of Silyl Ketene Imines to Aldehydes

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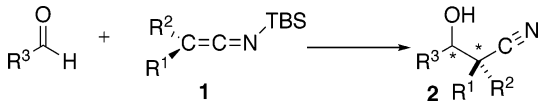
The development of catalytic, enantioselective methods for the construction of quaternary stereogenic centers represents a continuing challenge in organic chemistry.[1] Creating these centers rapidly and selectively is difficult because of the steric repulsion that is encountered in the C−C bond-forming event. Moreover, achieving high levels of enantiotopic face selectivity is difficult because of the relatively similar steric environments presented by the non-hydrogen substituents. The need for more general methods is underscored by a growing number of biologically active natural products and pharmaceutical agents that possess quaternary stereogenic carbon atoms.

Quaternary stereogenic centers can be generated through the aldol addition of α,α-disubstituted enolates to aldehydes, and given the edifice of work on catalytic, enantioselective aldol-type reactions, this strategy seems logical.[2] However, this approach is limited by the need for and inability to obtain geometrically defined α,α-disubstituted enolate or enolate equivalents.[3] To solve this problem and empower the aldol addition for the selective synthesis of quaternary centers would require either (1) controlling the geometry of disubstituted enolates, (2) developing other nucleophile classes, or (3) identifying catalysts that dominate the facial selectivity. Herein we describe an aldol addition process that combines the latter two strategies.

A class of nucleophiles that avoids the issues associated with enolate geometry is the silyl ketene imine (**1**). The key structural feature of these species is the pair of orthogonal substituent planes which imparts an axis of chirality when R^1 and R^2 are dissimilar.[4] Aldol-type reactions of these nucleophiles would generate *β*-hydroxy nitriles (**2**) containing an α-quaternary stereogenic center (Scheme 1).[5] These compounds are versatile synthetic intermediates due to the wide range of functionalities that are accessible through manipulation of the cyano group.[6]

Scheme 1

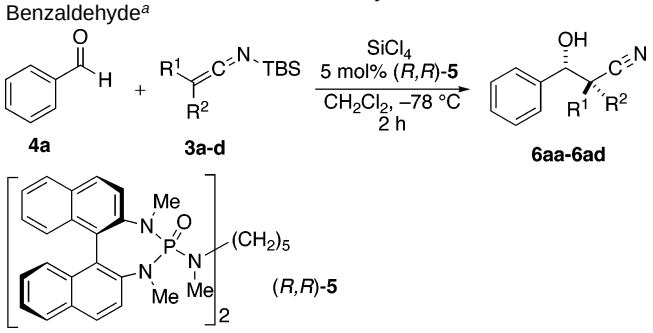


Although silyl ketene imines (SKIs) are well-known, only a few reports have described their use as nucleophiles.[7] Frannett et al. established that SKIs undergo exothermic additions to both aldehydes and acid chlorides.[8] More recently, Fu et al. have described the enantioselective acylation of SKIs, catalyzed by a chiral 4-(pyrrolidino)pyridine derivative.[9]

Recent studies from these laboratories have described the $SiCl_4$-promoted, Lewis base catalyzed, enantioselective aldol-type addition reactions of enoxysilane derivatives with aldehydes.[10] Generally, the products are isolated in good yield and with high diastereo- and enantioselectivities; however, the formation of only secondary and tertiary stereocenters has been achieved. Quaternary centers have proven more difficult to create because of the reduced reactivity of the α,α-disubstituted enolate equivalents with this catalyst.[10c] We hypothesized that a silyl ketene imine might be suitable to participate in this reaction because a significant portion of their steric bulk resides in a plane perpendicular to and distal from the nucleophilic carbon.

To test this hypothesis, SKI **3a** was prepared (by lithiation of α-phenylpropionitrile followed by trapping with TBSCl) and its reactivity was assayed in the addition to benzaldehyde (**4a**) using the $SiCl_4$/bisphosphoramide catalyst system (Table 1, entry 1). Gratifyingly, nitrile product **6aa** was isolated in good yield and with high levels of both diastereo- and enantioselectivity. Furthermore, in situ IR studies with 1-naphthaldehyde revealed that complete conversion was achieved in less than 50 s at −68 °C with catalyst loadings as low as 1 mol %! In contrast, the analogous silyl ketene acetal derived from ethyl 2-phenylpropanoate proved unreactive under identical reaction conditions. In light of this promising result, a wide range of disubstituted silyl ketene imine structures was next surveyed.

Table 1. Aldol Addition Reaction of Aryl-Substituted SKIs with Benzaldehyde[a]



entry	SKI	R^1	R^2	product	yield %[b]	dr[c]	er[c]
1	**3a**	Ph	Me	**6aa**	87	95:5[d]	98.5:1.5
2	**3b**	4-$CF_3C_6H_4$	Et	**6ab**	73	97:3	99.5:0.5
3	**3c**	4-$MeOC_6H_4$	Me	**6ac**	90	99:1	99.1:0.9
4	**3d**	2-MeC_6H_4	Me	**6ad**	74	87:13[d]	94.2:5.8[e]

[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of silyl ketene imine, 0.05 equiv of (*R*,*R*)-**5** at 0.25 M in CH_2Cl_2 at −78 °C for 2 h. [b] Yield of analytically pure material. [c] Determined by CSP-SFC. [d] Determined by ^1H NMR analysis. [e] Determined by CSP-HPLC after derivatization with 3,5-dinitrobenzoyl chloride.

The first series of nucleophiles investigated the scope of the aldol addition with respect to the aryl substituent of the silyl ketene imine (Table 1). Electron-rich, electron-poor, and hindered aryl-substituted ketene imines were prepared and then tested in the addition to **4a**. Each nucleophile reacted at a comparable rate, and the aldol products were isolated in high yields and with excellent selectivities. The nitrile products derived from the additions of electron-rich and electron-poor aryl-substituted ketene imines exhibited higher diastereo- and enantioselectivities than those observed with hindered aryl substituents, most likely because of an achiral background reaction for slower reacting substrate **3d**.

The next survey of nucleophile structure examined the scope of this process with respect to the alkyl substituent of the SKI (Table 2). First a series of α-alkylbenzylnitrile-derived ketene imines **3e**−**g**

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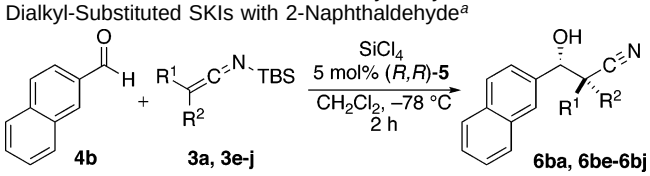
was prepared and tested in the addition to 2-naphthaldehyde (**4b**). The results show that, although steric bulk can be well tolerated at this position, the presence of an α-branched substituent leads to a drop in both the diastereomeric and enantiomeric purity of the product (compare entries 1−3 to entry 4). More importantly, a synthetically useful allyl-substituted silyl ketene imine **3h** was well tolerated in the reaction providing a nitrile product in good yield and high selectivity (entry 5). To further expand on the nucleophile scope, two dialkyl-substituted SKIs that do not contain an aryl ring were prepared and tested in the addition to **4b**. The cyclohexane-derived ketene imine **3i** provided an aldol product with a nonstereogenic quaternary carbon in good yield and enantioselectivity (entry 6). Silyl ketene imine **3j**, containing disparate alkyl groups, reacted to give a 60:40 mixture of enantiomerically enriched diastereomers in good yield (entry 7). The high enantiomeric ratio observed within each diastereomer suggests that the source of the low dr was the insufficient steric differentiation in the alkyl substituents of the silyl ketene imine.

Table 2. Aldol Addition Reaction of Aryl, Alkyl-Substituted, and Dialkyl-Substituted SKIs with 2-Naphthaldehyde[a]

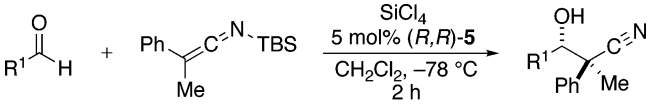


entry	SKI	R^1	R^2	product	yield %[b]	dr[c]	er[c]
1	**3a**	Ph	Me	**6ba**	90	98:2	98.7:1.3
2	**3e**	Ph	Et	**6be**	78	97:3	92.7:7.3
3	**3f**	Ph	*i*-Bu	**6bf**	90	99:1	99.6:0.4
4	**3g**	Ph	*i*-Pr	**6bg**	73	61:39	78.9:21.1[d]
5	**3h**	Ph	allyl	**6bh**	79	94:6	97.5:2.5
6	**3i**	$-(CH_2)_5-$		**6bi**	85	N/A	91.2:8.8
7	**3j**	*i*-Pr	Me	**6bj**	92	60:40	92.1:7.9[e]

[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of silyl ketene imine, 0.05 equiv of (*R*,*R*)-**5** at 0.25 M in CH_2Cl_2 at −78 °C for 2 h. [b] Yield of analytically pure material. [c] Determined by CSP-SFC. [d] Enantiomeric ratio of the minor diastereomer was 71.4:28.6. [e] Enantiomeric ratio of the minor diastereomer was 96.6:3.4.

To further elaborate the scope of this reaction, a survey of the aldehyde structure was undertaken (Table 3). The addition of SKI **3a** to a wide range of aromatic aldehydes **4c**−**i** was examined, and in general, the aldol products were isolated in high yields and with excellent selectivities. Electron-poor and electron-rich aromatic aldehydes reacted with similar rates and selectivities to benzaldehyde (entries 1−3). Hindered aromatic aldehydes, such as 2-tolualdehyde and 1-naphthaldehyde, also yielded products in good yields

Table 3. Aldol Reaction of α-Phenylpropionitrile-Derived SKI **3a** with Aromatic Aldehydes[a]



entry	R^1	product	yield %[b]	dr[c]	er[c]
1	4-$CF_3C_6H_4$ (**4c**)	**6ca**	88	>99:1[d]	99.3:0.7
2	4-BrC_6H_4 (**4d**)	**6da**	93	99:1	98.9:1.1
3	4-$CH_3O_2CC_6H_4$ (**4e**)	**6ea**	93	>99:1	98.6:1.4
4	4-$CH_3OC_6H_4$ (**4f**)	**6fa**	78	96:4	96.6:3.4
5	2-$CH_3C_6H_4$ (**4g**)	**6ga**	84	>99:1	99.2:0.8
6	1-naphthyl (**4h**)	**6ha**	76	>99:1	98.4:1.6
7	2-furyl (**4i**)	**6ia**	92	99:1	94.9:5.1

[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of **3a**, 0.05 equiv of (*R*,*R*)-**5** at 0.25 M in CH_2Cl_2 at −78 °C for 2 h. [b] Yield of analytically pure material. [c] Determined by CSP-SFC. [d] Determined by ^1H NMR analysis.

and high selectivities (entries 5 and 6). Additionally, only a slight diminution in the enantioselectivity was observed for the electron-rich heteroaromatic aldehyde, 2-furaldehyde (entry 7). Despite the high rate of reaction observed for the addition of SKIs to aromatic aldehydes, aliphatic aldehydes remain unreactive.[11]

The absolute and relative configurations of the products were established by single-crystal X-ray crystallography for the nitrile product **6da**, obtained from the addition of SKI **3a** to 4-bromobenzaldehyde.[12] The *S*-configuration at the alcohol center confirms that the nucleophile adds to the *Re* face of the aldehyde, in agreement with the sense of asymmetric induction observed in other reaction manifolds reported for this catalyst.[10c]

In conclusion, a novel Lewis base catalyzed aldol reaction for the construction of quaternary stereogenic centers via the addition of SKIs to aromatic aldehydes has been described. The products are isolated in good yields and with excellent diastereo- and enantioselectivities. Furthermore, the reaction exhibits broad substrate scope in both the SKI and the aromatic aldehyde. Future work will focus on new classes of ketene imine nucleophiles and other electrophiles.[13]

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Supporting Information Available: Full characterization of all aldol products along with representative procedures for the addition reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews, see: (a) Trost, B. M.; Chunhui, J. *Synthesis* **2006**, 369−396. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363−5367. (c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146. (d) For a recent monograph, see: *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Germany, 2005.

(2) For reviews on catalytic asymmetric aldol reactions, see: (a) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 29.1. (b) Carreira, E. M.; Fettes, A.; Marti, C. *Org. React.* **2006**, *67*, 1−216. (c) For a recent monograph, see: *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004.

(3) For a discussion on quaternary carbon synthesis via aldol reaction, see: ref 1d, Chapter 3.

(4) However, studies on both *N*-alkyl and *N*-aryl ketene imines reveal a low barrier to racemization; see: (a) Jochims, J. C.; Lambrecht, J.; Burkert, U.; Zsolnai, L.; Huttner, G. *Tetrahedron* **1984**, *40*, 893−903. (b) Lambrecht, J.; Gambke, B.; Seyerl, J.; Huttner, G.; Nell, G.; Herzberger, S.; Jochims, J. C. *Chem. Ber.* **1981**, *114*, 3751−3771.

(5) For an example of this catalytic, enantioselective process, see: Kuwano, R.; Miyazaki, H.; Ito, Y. *J. Organomet. Chem.* **2000**, *603*, 18−29.

(6) Tennant, G. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Sutherland, I. O., Eds.; Pergamon: New York, 1979; Vol. 2, pp 539−550.

(7) (a) West, R.; Gornowicz, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 1714−1720. (b) Watt, D. S. *Synth. Commun.* **1974**, *4*, 127−131.

(8) (a) For additions to aldehydes, see: Cazeau, P.; Llonch, J.-P.; Simonin-Dabescat, F.; Frainnet, E. *J. Organomet. Chem.* **1976**, *105*, 145−156. (b) For additions to acid chlorides, see: Cazeau, P.; Llonch, J.-P.; Simonin-Dabescat, F.; Frainnet, E. *J. Organomet. Chem.* **1976**, *105*, 157−160.

(9) Mermerian, A. H.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 949−952.

(10) (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2007**, in press. (b) Denmark, S. E.; Fujimori, S. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; Vol. I, Chapter 7. (c) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774−3789.

(11) The reduced reactivity of aliphatic aldehydes can be attributed to an unfavorable equilibrium that exists between the activated aldehyde complex and an inactive α-chlorotrichlorosilyl ether; see ref 10c.

(12) The crystallographic coordinates of **6da** have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 659734. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; www.ccdc.cam.ac.uk/conts/retrieving.html or deposit@ccdc.cam.ac.uk.

(13) Preliminary results from reactions of SKIs with α,β-unsaturated aldehydes show exclusive 1,4-addition with moderate diastereoselectivity.

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