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Lewis Base Activation of Lewis Acids. Vinylogous Aldol Addition Reactions of Conjugated *N,O*-Silyl Ketene Acetals to Aldehydes

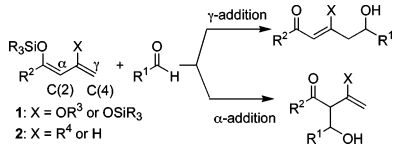
Scott E. Denmark* and John R. Heemstra, Jr.
Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801
Received October 2, 2005; E-mail: denmark@scs.uiuc.edu

The potent biological activity and structural diversity of the polyketide class of natural products has provided attractive targets for total synthesis as well as potential leads for the development of promising pharmaceutical agents.[1] The structural characteristic common to these natural products is the complex polyol subunits residing within their core, and one of the most widely applied methods for polyol synthesis is the aldol addition reaction. The selectivity, generality, and predictability obtainable with current aldol technology have elevated this reaction to strategy-level status in natural product synthesis.[2]

Whereas the normal aldol addition provides access to 1,3-difunctional relationships, the vinylogous extension[3] of this reaction allows 1,5-difunctional subunits to be constructed. This vinylogous modification of the aldol reaction is possible when γ-enolizable α,β-unsaturated carbonyl substrates are employed as "extended dienolates". This process leads to the formation of δ-hydroxy-β-keto esters or δ-hydroxy-α,β-unsaturated carbonyl compounds in which up to two stereocenters and one double bond can be created simultaneously.[4]

Although similar to simple aldol additions, the vinylogous aldol reaction overlays the challenge of site selectivity onto the already-present issues of diastereo- and enantioselectivity. Addition of a dienolate to an aldehyde has the possibility of generating a mixture of both the α- and γ-addition products (Scheme 1). A strategy that allows for γ-site selectivity is the use of silyl dienolates as nucleophiles in Lewis acid promoted vinylogous Mukaiyama aldol additions.[2] For example, silyl dienol ether **1** is a synthetic equivalent of a diketone or keto ester dianion that reacts with exclusive γ-site selectivity owing to the high nucleophilicity at C(4). However, silyl dienol ethers derived from α,β-unsaturated carbonyl compounds (**2**) are not as electronically biased, and steric effects from both the dienolate and catalyst structure are needed to achieve high site selectivity. Indeed, both α- and γ-addition products have been observed in vinylogous aldol reactions employing ester-derived dienol ethers.[4,8]

Scheme 1



Recent disclosures from these laboratories have demonstrated that the catalytic action of chiral bis-phosphoramide (*R,R*)-**3**[5] and silicon tetrachloride promotes the addition of simple α,β-unsaturated ester-[6] and ketone-derived[7] dienol ethers to aldehydes with almost exclusive γ-site selectivity for a variety of substitution patterns on the dienol ether while maintaining high enantio- and diastereoselectivity. However, two limitations persisted for the addition of ketone-derived dienolates.[7] First, the dienolates were found to be unreactive with aliphatic aldehydes under Lewis base catalysis. Furthermore, although the formation of cross-conjugated dienolates is overwhelmingly favored under conditions of kinetically controlled enolization, the extended dienolates of α,β-unsaturated ketones are difficult to obtain when α'-protons are present and mixtures of the cross and extended conjugated dienolates are typically isolated.[8] To address the issue of nucleophile reactivity, we have explored the potential of dienol ethers derived from α,β-unsaturated amides in the vinylogous aldol addition to aldehydes. Amide-derived silyl enol ethers are known to be highly reactive species.[9] Moreover, the ability to transform the amide function into either ketones or aldehydes provides indirect access to aldol products derived from these α,β-unsaturated carbonyl compounds.[10] We report herein a general, catalytic, and enantioselective vinylogous addition of silyl dienol ethers derived from α,β-unsaturated amides to aldehydes.[11]

Previous studies in these laboratories with ester-derived dienolates demonstrated that the site selectivity of the addition is largely influenced by the size of the alkoxy substituent.[6] Therefore, amides derived from various amine structures were chosen to probe their effect on site (as well as stereo-) selectivity. Surprisingly, at the outset of these studies, a general procedure for the synthesis of conjugated *N,O*-silyl ketene acetals was absent in the literature. However, these dienolates are easily accessed by deprotonation of the corresponding α,β-unsaturated amide with 1.1 equiv of potassium hexamethyldisilazide (KHMDS) at −78 °C followed by trapping of the resulting potassium dienolate with TBSCl. This protocol allowed for the synthesis of *tert*-butyldimethylsilyl dienol ethers **5**−**8** in good to high yields (Table 1). These dienolates are distillable oils with a wide range of stabilities. Whereas dienolate **6** shows significant decomposition at −15 °C within a week of synthesis, morpholine-derived dienolate **8** could be stored indefinitely at this temperature without any noticeable sign of decomposition. In all cases, the products were obtained as single geometrical isomers determined to be of the 1*Z* configuration by analysis of their ^{1}H nOe NMR spectra. The reactivity of these conjugated *N,O*-silyl ketene acetals was assayed in the addition to hydrocinnamaldehyde (**4**), an aldehyde that resisted addition by ketone-derived dienolates (Table 1).[12] Gratifyingly, the corresponding aldol products were isolated in uniformly high yield; however, the enantioselectivity of the addition was highly dependent on the structure of the nitrogen substituents. Whereas the acyclic amine-derived dienolates reacted with modest enantioselectivity (Table 1, entries 1 and 2), the cyclic amines afforded higher selectivity. Indeed, the morpholine-derived silyl dienol ether **8** reacted with exclusive γ-selectivity and excellent enantioselectivity (Table 1, entry 4). In all cases, the resulting aldol product was exclusively of the *E* configuration.

The addition of the morpholine-derived silyl dienolate **8** was next surveyed with a variety of aldehyde structural types (Table 2). Reactions with linear, α-, and β-branched aliphatic aldehydes afforded the γ-addition products exclusively in good to high yields and excellent enantioselectivities (entries 1−4). Both aromatic and heteroaromatic aldehydes reacted rapidly (entries 5−8), providing vinylogous aldol adducts in high yields and selectivities. With a

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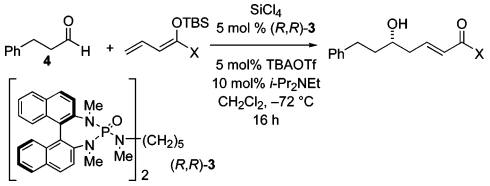
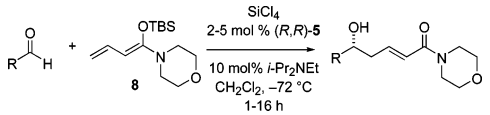
Table 1. Vinylogous Aldol Reactions of Amide-Derived Dienolates with Hydrocinnamaldehyde[a]



entry	dienolate (yield, %)[b]	X	product	yield %[c]	γ: α[d]	er[e]
1	5 (77)	NMe_2	**9**	69	92:8	91.0:9.0
2	6 (89)	NEt_2	**10**	78	95:5	84.8:15.2
3	7 (80)	$N(CH_2)_5$	**11**	70	93:7	96.0:4.0
4	8 (78)	$N(CH_2CH_2)_2O$	**12**[f]	80	>99:1	99.0:1.0

[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of dienolate, 0.05 equiv of (*R*,*R*)-**3**, 0.1 equiv of *i*-Pr_2NEt, 0.05 equiv of TBAOTf at 0.1 M in CH_2Cl_2 at −72 °C for 16 h. [b] Yields of dienolate synthesis. [c] Yields after chromatography. [d] Determined by ^1H NMR analysis. [e] Determined by CSP-SFC. [f] *S* absolute configuration.[13]

Table 2. Vinylogous Aldol Reactions of Morpholine-Derived Dienolates **8** with Aldehydes[a]



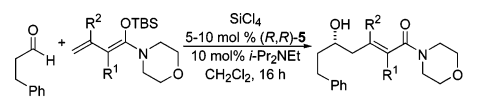
entry	R	product	yield, %[b]	γ: α[c]	er[d]
1[e]	$PhCH_2CH_2$	**12**	80[f]	>99:1	99.0:1.0
2[e]	$CH_3(CH_2)_4$	**13**	79[f]	>99:1	94.3:5.7
3[e]	$(CH_3)_2CHCH_2$	**14**	84[f]	>99:1	99.7:0.3
4[e]	cyclohexyl	**15**	63	>99:1	99.4:0.6
5	C_6H_5	**16**	95	>99:1	97.2:2.8
6	4-$CH_3OC_6H_4$	**17**	95	>99:1	99.0:1.0
7	4-$CF_3C_6H_4$	**18**	93	>99:1	95.4:4.6
8	2-furyl	**19**	94	>99:1	93.8:6.2
9[g]	(*E*)-PhCH═CH	**20**	94	>99:1	98.2:1.8
10	(*E*)-PhCH═C(CH_3)	**21**	91	>99:1	75.5:24.5

[a] All reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of **8**, 0.05 equiv of (*R*,*R*)-**3**, 0.1 equiv of *i*-Pr_2NEt at 0.1 M in CH_2Cl_2 at −72 °C. [b] Yield of analytically pure material. [c] Determined by ^1H NMR analysis. [d] Determined by CSP-SFC. [e] 0.05 equiv of TBAOTf was added. [f] Yield after chromatography. [g] Reaction employed 0.02 equiv of (*R*,*R*)-**3**.

catalyst loading of only 2 mol %, the addition of dienolate **8** to cinnamaldehyde afforded γ-addition product in excellent yield, site-, and enantioselectivity (entry 9). Unfortunately, α-methyl branched olefinic aldehydes continue to afford low enantioselectivity (entry 10). Although aliphatic aldehydes require longer reaction times compared to that of conjugated aldehydes, the fact that aliphatic aldehydes afford the highest selectivity is particularly noteworthy as these are typically the least selective substrates in this catalytic system.[6]

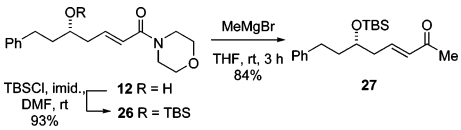
In a preliminary survey of structural generality, we have prepared ketene acetals **22** and **23** bearing methyl groups on the α and β atoms of the dienyl unit, respectively.[14a] These nucleophiles also reacted with exclusive γ-selectivity to afford the addition products in high yield and high geometrical[14b] and excellent enantioselectivity with hydrocinnamaldehyde (Scheme 2).[15]

Scheme 2



Coincidentally, of all the amides employed, the morpholine derivative is also the most effective at the acylation of organometallic nucleophiles to form ketones.[16,17] After protection of **12** as a *tert*-butyldimethylsilyl ether, MeMgBr cleanly converted the morpholine amide **26** to the methyl ketone **27** in high yield without any evidence for the formation of the tertiary alcohol arising from overaddition (Scheme 3).

Scheme 3



These findings represent the first catalytic and enantioselective vinylogous aldol reactions that employ silyl ketene acetals derived from α,β-unsaturated amides. Further studies are underway to extend this method to other morpholine-derived amides and for the synthesis of complex polyol-containing natural products.

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Supporting Information Available: Full characterization of all dienol ethers and 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.

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(12) The addition of tetrabutylammonium trifluoromethanesulfonate and diisopropylethylamine to the solution was found to increase the yield of the aldol adducts. For a discussion of the role of these additives, see ref 6a.
(13) Absolute configuration of **12** was determined by chemical correlation to (3*S*)-5-phenylpentane-1,3-diol (O_3 then $LiAlH_4$). Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928−1932.
(14) (a) *N*,*O*-Silyl ketene acetal **22** is formed as a 2.6:1, *E*/*Z* mixture, whereas **23** is a 19:1 *Z*/*E* mixture. (b) Product **24** formed as a single *E* isomer whereas **25** is formed as an 88:12, *E*/*Z* mixture.
(15) Ketene acetals **22** and **23** also reacted with excellent yield and enantioselectivity with benzaldehyde (90−97% yield, 98.4:1.6−98.6:1.4 er) and cinnamaldehyde (95−97% yield, 98.9:1.1−99.3:0.7 er).
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