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Vicarious Silylative Mukaiyama Aldol Reaction: A Vinylogous Extension

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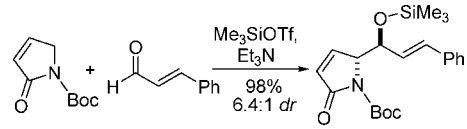
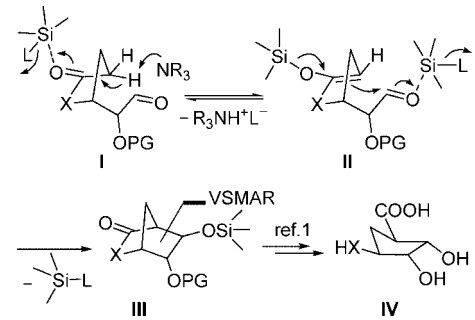


A vinylogous, silylative, and direct variant of the venerable Mukaiyama aldol reaction has been developed. Exploiting *N*-Boc-pyrrol-2(5*H*)-one as the conjugate donor, several aldehyde and ketone acceptors were scrutinized under the guidance of suitable dual Lewis acid−Lewis base activators to provide a varied repertoire of functionality-rich α,*β*-unsaturated-*γ*-amino-*δ*-silyloxy carbonyl structures, in useful yields and often with an exquisite level of diastereoselection.

Introduction

During work directed at the stereoselective synthesis of densely substituted carbacycles of type **IV**, a stage was reached where it was necessary to complete the ring construction by connecting the carbon α to the ring carbonyl to the aldehyde carbon within the precursor **I**.[1] This was achieved by an extremely productive protocol that constitutes a general method for the assembly of a variety of bicyclo[*x*.2.1]alkane structures **III**, and hence the carbacycles **IV**. Our approach, which is summarized in Scheme 1 for a generic case with five-membered rings, was based on a reaction cascade triggered by a dual silicon Lewis acid/nitrogen Lewis base system, which encompasses two main steps: (1) chemoselective deprotonation and enol-silylation to ketene acetal **II** and (2) Mukaiyama aldol-type ring closure with in situ aldolate silylation to **III**. There, the retrograde fragmentation of the formed aldolate carbon−carbon bond, a plague that often afflicts certain aldol-based maneuvers, was hampered by prompt and irreversible aldolate silyl ether formation.[2] We suggest the name "vicarious silylative Mukaiyama aldol reaction" (VSMAR) for such processes, a diction

SCHEME 1. Synthesis Itinerary to Carbacycles IV Exploiting an Intramolecular Version of the Vicarious Silylative Mukaiyama Aldol Reaction (VSMAR)[a]



[a] X = NPG, O, S; L = silicon leaving group; PG = protecting group.

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(1) (a) Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 6307–6318. (b) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2001**, *66*, 8070–8075. (c) Zanardi, F.; Battistini, L.; Marzocchi, L.; Acquotti, D.; Rassu, G.; Pinna, L.; Auzzas, L.; Zambrano, V.; Casiraghi, G. *Eur. J. Org. Chem.* **2002**, 1956–1964. (d) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2002**, *67*, 5338–5342. (e) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Gaetani, E.; Curti, C.; Casiraghi, G. *J. Org. Chem.* **2003**, *68*, 5881–5885. (f) Rassu, G.; Auzzas, L.; Zambrano, V.; Burreddu, P.; Pinna, L.; Battistini, L.; Zanardi, F.; Casiraghi, G. *J. Org. Chem.* **2004**, *69*, 1625–1628. See also: (g) Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Curti, C. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science B.V.: Amsterdam, The Netherlands, 2003; Vol. 29 (Bioactive Natural Products (Part J)), pp 449−520. (h) Rassu, G.; Auzzas, L.; Battistini, L.; Casiraghi, G. *Mini-Reviews in Organic Chemistry* **2004**, *1*, 233–247. (i) Arjona, O.; Gómez, A. M.; López, J. C.; Plumet, J. *Chem. Rev.* **2007**, *107*, 1919–2036.

(2) (a) Hatano, M.; Takagi, E.; Ishihara, K. *Org. Lett.* **2007**, *9*, 4527–4530. See also: (b) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392–393.

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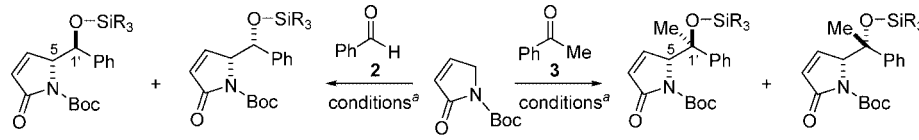
TABLE 1. Initial Screening of the Vicarious Silylative Mukaiyama Aldol Reaction (VSMAR) between Pyrrolinone 1 and Benzaldehyde (2) or Acetophenone (3)[a]



***anti*-4a**: $R_3 = Me_3$ ***syn*-4a**: $R_3 = Me_3$ ***anti*-5a**: $R_3 = Me_3$ ***syn*-5a**: $R_3 = Me_3$
***anti*-4b**: $R_3 = Et_3$ ***syn*-4b**: $R_3 = Et_3$ ***anti*-5b**: $R_3 = Et_3$ ***syn*-5b**: $R_3 = Et_3$
***anti*-4c**: $R_3 = Bu^tMe_2$ ***syn*-4c**: $R_3 = Bu^tMe_2$ ***anti*-5c**: $R_3 = Bu^tMe_2$ ***syn*-5c**: $R_3 = Bu^tMe_2$

entry	acceptor	Lewis acid (equiv)	Lewis base (equiv)	solvent (v/v)	product(s)[b]	yield (%)[c]	*anti*/*syn* ratio[d]
1[e]	**2**	TBSOTf (2.0)	DIPEA (2.0)	DCM	—[f]		
2	**2**	TBSOTf (2.0)	DIPEA (2.0)	DCM	**4c**[g]	48	5.9:1
3	**2**	TMSOTf (2.0)	DIPEA (2.0)	DCM	**4a**[g]	62	7.7:1
4	**2**	TMSOTf (2.0)	DIPEA (2.0)	Et_2O	**4a**	40	9.6:1
5	**2**	TMSOTf (2.0)	DIPEA (2.0)	Et_2O/Hex (2:1)	**4a**	67	9.5:1
6	**2**	TMSOTf (2.0)	Et_3N (2.0)	Et_2O/Hex (2:1)	**4a**	70	10.0:1
7	**2**	**TMSOTf (2.0)**	**Et_3N (1.5)**	**Et_2O/Hex (2:1)**	**4a**	**95**	**>12.0:1**
8	**2**	TMSOTf (2.0)	2,6-lutidine (1.5)	Et_2O/Hex (2:1)	**4a**	45	7.2:1
9	**2**	TMSOTf (2.0)	DBU (1.5)	Et_2O/Hex (2:1)	**4a**	<5	nd
10	**2**	TESOTf (2.0)	Et_3N (1.5)	Et_2O/Hex (2:1)	**4b**	89	4.5:1
11	**2**	TBSOTf (2.0)	Et_3N (1.5)	Et_2O/Hex (2:1)	**4c**	85	5.9:1
12	**2**	none	Et_3N (1.5)	Et_2O/Hex (2:1)	—[h]		
13	**3**	TMSOTf (2.0)	Et_3N (1.5)	Et_2O/Hex (2:1)	—[i]		
14	**3**	TMSOTf (2.0)	Et_3N (1.5)	DCM	**5a**	92	>12.1:1
15	**3**	**TMSOTf (2.0)**	**Et_3N (1.5)**	**DCM/Et_2O (9:1)**	**5a**	**95**	**27.9:1**
16	**3**	TESOTf (2.0)	Et_3N (1.5)	DCM/Et_2O (9:1)	**5b**	90	5.6:1
17	**3**	TBSOTf (2.0)	Et_3N (1.5)	DCM/Et_2O (9:1)	**5c**	95	1.1:1
18	**3**	TIPSOTf (2.0)	Et_3N (1.5)	DCM/Et_2O (9:1)	—[i]		

[a] Unless otherwise noted, the reactions were carried out in the presence of 1.3 equiv of acceptor at −78 °C for 5 h, and with a substrate concentration of 0.027 M (0.27 mmol scale). [b] Racemic substances. [c] Isolated, combined yield. [d] Determined by ^1H NMR analysis of crude reaction mixtures. [e] The reaction was carried out at 22 °C. [f] Complicated reaction mixture obtained. [g] Dehydration products also formed. [h] 90% benzaldehyde recovered. [i] Silyldienol ether from the donor solely recovered.

that evokes the cooperative role of the silicon/amine dual system in triggering formation of the silyl enol ether in situ and advancing the process by stabilizing the emerging aldolate by silylation.[3]

In this paper we disclose a vinylogous, intermolecular extension of this direct Lewis acid−base comediated aldol methodology in which nitrogen heterocycle **1** acts as the donor and aldehydes **2** and **6**−**10** or ketones **3** and **11**−**15** act as the acceptors.[4]

Results and Discussion

Synthesis. We initiated this investigation with benzaldehyde (**2**) and acetophenone (**3**) as the acceptors. For an ideal promoter system, we considered two criteria. One requirement was that the promoter should contain a basic entity that selectively deprotonates the α,β-unsaturated substrate at the γ-carbon while increasing through association the electrophilicity of the silicon reagent. The other criterion involved an electron-poor silicon component that activates the carbonyl acceptor through silicon−carbonyl association while participating in the stabilization of the aldolate by silylation.[5] We evaluated several silicon Lewis acid and amine base combinations, as well as various solvents and reaction conditions, with the results displayed in Table 1.

First of all, addition of pyrrolinone **1** to benzaldehyde (**2**) was evaluated by using a combination of TBSOTf and DIPEA (2.0 equiv each) in dichloromethane at room temperature (entry 1), one of the best conditions found during our previous investigations with aldehydo-lactams and congeners.[1a–f] Actually, the reaction proceeded rapidly, with the starting materials consumed within a few minutes; however, a complicated reaction mixture was observed, with little if any aldol products recovered. Lowering the reaction temperature to −78 °C (entry 2) or changing TBSOTf for TMSOTf at −78 °C (entry 3) was only partially productive, giving rise to the expected aldol products **4a** in moderate yields, accompanied by marginal amounts of dehydration compounds.

Reasoning that the use of ethereal, coordinative solvents in lieu of DCM would decelerate the reaction while preserving the integrity of the silylated aldol product, diethyl ether was selected and, indeed, encouraging results were obtained with neat diethyl ether (entry 4) or, better, with hexane/Et_2O mixtures (entry 5). In these instances, *anti*-configured (5*R**,1′*S**) and *syn*-configured (5*R**,1′*R**) *O*-trimethylsilyl aldols *anti*-**4a** and *syn*-**4a** formed exclusively, in moderate yield and with remarkable margin of diastereoselectivity favoring, in all instances, the anti-isomer *anti*-**4a** (∼10:1 dr).

The structural identity of compounds *anti*-**4a** and *syn*-**4a** was quickly inferred by inspection of their ^1H NMR characteristics

(3) For recent examples of direct Mukaiyama aldol-type reactions triggered by silyl triflate/tertiary amine dual systems see: (a) Downey, C. W.; Johnson, M. W. *Tetrahedron Lett.* **2007**, *48*, 3559–3562. (b) Hoye, T. R.; Dvornikovs, V.; Sizova, E. *Org. Lett.* **2006**, *8*, 5191–5194. (c) Takasu, K.; Ueno, M.; Ihara, M. *J. Org. Chem.* **2001**, *66*, 4667–4672. (d) Downey, C. W.; Johnson, M. W.; Tracy, K. J. *J. Org. Chem.* **2008**, *73*, 3299–3302. (e) Hoye, T. R.; Dvornikovs, V.; Sizova, E. *Org. Lett.* **2006**, *8*, 5191–5194.

(4) Recent reviews on vinylogous aldol and related reactions: (a) Denmark, S. E.; Heemstra, J. R., Jr *J. Org. Chem.* **2007**, *72*, 5668–5688. (b) Kalesse, M. *Top. Curr. Chem.* **2005**, *244*, 43–76. (c) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682–4698. (d) Soriente, A.; De Rosa, M.; Villano, R.; Scettri, A. *Curr. Org. Chem.* **2004**, *8*, 993–1007. (e) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929–1972.

(5) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560–1638.

where, as a general trend, a larger $^3J_{5,1'}$ coupling constant (5.2 Hz) is indicative of a 5,1′-*N*,*O*-*syn* relative stereodisposition, while a smaller $^3J_{5,1'}$ value (2.1 Hz) denotes a 5,1′-*N*,*O*-*anti* configuration.[6,7]

After further examination of several tertiary amine candidates (e.g., entries 6−9 in Table 1), the optimum condition was found, which was based on a slightly imbalanced combination of TMSOTf (2.0 equiv) and triethylamine (1.5 equiv) in a 2:1 mixture of Et_2O/hexane at −78 °C (entry 7 in Table 1), a condition that revealed aldol *anti*-**4a** predominantly (>12.0:1 dr) in a pleasing 91% isolated yield after silica gel chromatography. This reaction was clean on a 0.27 mmol scale (0.027 M), without significant side reactions, and it could be scaled up to a 2.70 mmol scale with no erosion of the overall efficiency and selectivity. Under such optimized reaction conditions, TESOTf and TBSOTf equally served as Lewis acid candidates, albeit the *anti*/*syn* diastereoisomeric ratio dropped down markedly, when passing from TMSOTf to bulkier TES- and TBS-counterparts (entry 7 vs entries 10 and 11 in Table 1). Here, *anti*- and *syn*-configured *O*-triethylsilyl and *O*-*tert*-butyldimethylsilyl carbinols **4b** and **4c** were isolated in 89% and 85% combined yields, respectively.[8] A blank experiment (entry 12 in Table 1), where the Lewis acid component was suppressed, proved unproductive, emphasizing the crucial, cooperative role of both the amine base and the silicon acid components in the dual reaction promotion.[9]

Next, the silylative, vinylogous aldol addition of **1** to acetophenone (**3**) was examined under the guidance of the TMSOTf/Et_3N system (2.0:1.5 molar ratio). Low temperature reaction in Et_2O/hexane mixture, the optimal solvent for benzaldehyde, proved extremely sluggish, and returned 1-(*tert*-butoxycarbonyl)-2-(trimethylsilyloxy)pyrrole solely, the product of enolsilylation of the donor component (entry 13 in Table 1). Actually, the intrinsic sluggish nature of the ketone acceptors, vis-à-vis the aldehyde relatives, forced us to accelerate the process, by swapping the Et_2O/hexane solvent mixture for dichloromethane. As we had hoped, the reaction proceeded smoothly (entry 14 in Table 1) giving rise to *N*,*O*-*anti*, (5*R**,1′*S**)-configured TMS-ether *anti*-**5a** in high yield and with appreciable diastereoselectivity (*N*,*O*-*syn* isomer *syn*-**5a** <8%). A further improvement was reached when 10 vol % diethyl ether was added to DCM, conditions that yielded compound *anti*-**5a** in 92% isolated yield and exquisite diastereoselectivity (entry 15 in Table 1, ∼28:1 dr).

As for the addition to benzaldehyde, screening of the Lewis acid component revealed a strict dependence of the *anti* vs *syn* diastereoselectivity upon the nature of the silicon species (entries 16−18 in Table 1), with the *anti*/*syn* ratio decreasing as the bulkiness of the silicon substituents increases. Noteworthy, when TIPSOTf was used, no reaction occurred, with complete recovery of the triisopropylsilyl dienol ether of **1** (entry 18 in Table 1).

The structural identity of the tertiary carbinol TBS-ether *anti*-**5c** (and hence of TMS- and TES-ethers *anti*-**5a** and *anti*-**5b**, by analogy) was ascertained by single crystal X-ray analysis showing a 5,1′-*N*,*O*-*anti* relative relationship, as recently reported by ourselves.[10]

Overall, these preliminary results establish a practical methodology for the direct silylative, vinylogous Mukaiyama aldol-type addition of **1** to both aromatic aldehyde **2** and ketone **3**. Interestingly, under standardized conditions, i.e., TMSOTf/Et_3N in proper solvent mixtures, the 5,1′-*anti*-configured silylated aldols or ketols mainly formed, irrespective of the nature of the acceptor component, thus suggesting a common diastereoselective mechanistic itinerary (vide infra).

With these successful results in terms of practicality and diastereoselectivity, we turned our attention to the generality of this silylative aldol technique, by scrutinizing a series of enolizable and nonenolizable aldehyde and ketone acceptors in coupling reactions to pyrrolinone **1**. Assuming that our optimal conditions might be equally operative with different carbonyl electrophiles, five aldehyde and five ketone representatives (**6**−**10** and **11**−**15**) were evaluated (Table 2).

With cinnamaldehyde **6** (entry 1 in Table 2), a totally regioselective and highly diastereoselective reaction course was observed, providing γ-substituted-5,1′-*anti*-configured silylated lactam *anti*-**16** predominantly, with no traces of any Michael-type addition product (85% yield, ∼6:1 *anti*/*syn* ratio). Reaction of (*E*)-crotonaldehyde **7**, a γ-enolizable acceptor, mimicked the cinnamaldehyde behavior, and when subjected to the same coupling procedure, afforded doubly unsaturated 1,2-adduct *anti*-**17** in moderate isolated yield (3:1 dr, entry 2 in Table 2). Addition to saturated aliphatic aldehydes **8** and **9** was next examined (entries 3 and 4 in Table 2). Thus, with isobutyraldehyde **8**, the aldol reaction again favored the formation of the *anti*-aldol compound (*anti*-**18**, 5:1 dr), while with isovaleraldehyde **9**, reversal of stereochemistry was observed, favoring *syn*-disposed adduct *syn*-**19** (0.8:1 *anti*/*syn* ratio). An attempt to rationalize this anomalous, divergent outcome on a mechanistic basis is given below.[11] As observed for benzaldehyde-derived compounds **4a**−**c**, assignment of the relative 5,1′-stereodisposition of aliphatic compounds **16**−**19** was preliminarily based on the empirical "*J*-rule" (vide supra), whereupon small values of $J_{5,1'}$ coupling constants would indicate a 5,1′-*anti* relationship (1.8−2.5 Hz), while large $J_{5,1'}$ values (5.2−5.3 Hz) would indicate 5,1′-*syn* isomers. This assumption was indisputably supported by in-depth ^{1}H NMR structural analysis of a bicyclic oxazolidinone compound, chemically derived from *anti*-**18** (Scheme S1 in the Supporting Information).

In view of our longstanding interest in Lewis acid-catalyzed crossed Mukaiyama−aldol additions involving chiral nonracemic glyceraldehyde **10** and pure, isolated dienoxypyrrole donors, addition of **1** to **10** was especially evaluated.[1d,12] Under the standard silylative conditions of the present work, a nice 85% combined yield of a nearly equimolar mixture of two diastereoisomers, (5*S*,1′*S*,4″*R*)-configured *anti,anti*-**20** and (5*R*,1′*S*,4″*R*)-

(6) Also, the H-4 proton resonance of *syn*-isomers is invariably downfield as compared to the corresponding *anti*-isomeric protons.

(7) Uno, H.; Nishihara, Y.; Mizobe, N.; Ono, N. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1533–1539.

(8) Compounds *anti*-**4c** and *syn*-**4c** are known substances (see ref 7) and provided further confirmation for the relative stereodisposition of their strictly related analogues *anti*-**4a**,**b** and *syn*-**4a**,**b**.

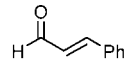
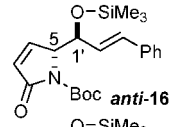
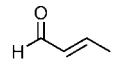
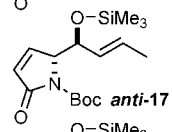
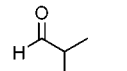
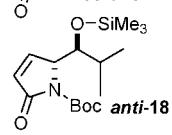
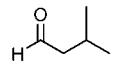
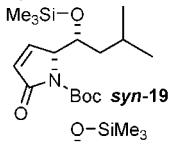
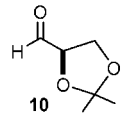
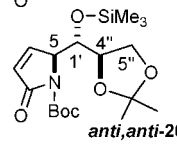
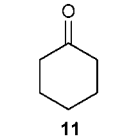
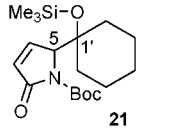
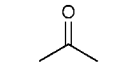
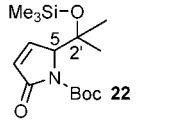
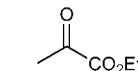
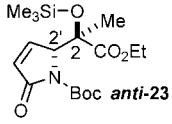
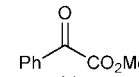
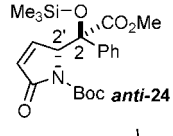
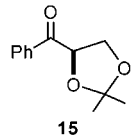
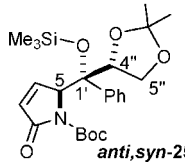
(9) Actually, one example exists dealing with free tertiary amine-promoted vinylogous aldol addition reactions involving activated furanone and pyrrolinone donors: (a) Sarma, K. D.; Zhang, J.; Curran, T. T. *J. Org. Chem.* **2007**, *72*, 3311–3318. See also: (b) Markert, M.; Mulzer, M.; Schetter, B.; Mahrwald, R. *J. Am. Chem. Soc.* **2007**, *129*, 7258–7259.

(10) Zanardi, F.; Curti, C.; Sartori, A.; Rassu, G.; Roggio, A.; Battistini, L.; Burreddu, P.; Pinna, L.; Pelosi, G.; Casiraghi, G. *Eur. J. Org. Chem.* **2008**, 2273–2287.

(11) Synthesis of *anti*-**18** and *syn*-**18** congeners has been reported (see ref 7).

(12) (a) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L. *J. Org. Chem.* **1992**, *57*, 3760–3763. (b) Rassu, G.; Casiraghi, G.; Spanu, P.; Pinna, L.; Gasparri Fava, G.; Ferrari Belicchi, M.; Pelosi, G. *Tetrahedron: Asymmetry* **1992**, *3*, 1035–1048. (c) Curti, C.; Zanardi, F.; Battistini, L.; Sartori, A.; Rassu, G.; Auzzas, L.; Roggio, A.; Pinna, L.; Casiraghi, G. *J. Org. Chem.* **2006**, *71*, 225–230.

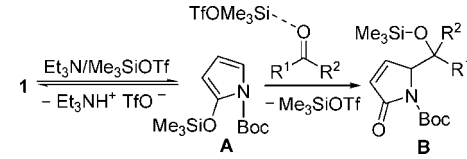
TABLE 2. TMSOTf/Et_3N Comediated VSMAR with Pyrrolinone 1 as the Donor: Variation of the Acceptor Components

entry	acceptor[a,b]	time (h)	product[c,d]	yield (%)[e]	*anti/syn* ratio[f]
1	 **6**	1	 ***anti*-16**	98	6.4:1
2	 **7**	5	 ***anti*-17**	61	3.2:1
3	 **8**	5	 ***anti*-18**	96	5.0:1
4	 **9**	5	 ***syn*-19**	90	0.8:1
5	 **10**	1.5	 ***anti,anti*-20**	85	1.2:1
6	 **11**	24	 **21**	75	
7	 **12**	24	 **22**	62	
8	 **13**	24	 ***anti*-23**	20	>12.0:1
9	 **14**	24	 ***anti*-24**	35	>15.0:1
10	 **15**	24	 ***anti,syn*-25**	70	>30.0:1

[a] All reactions were carried out in the presence of 1.3 equiv of acceptor at −78 °C, and with a substrate concentration of 0.027 M (0.27 mmol scale). [b] Entries 1−5, Et_2O/hexane (2:1); entries 6−10, DCM/Et_2O (9:1). [c] Only the major isomer is shown. [d] Except for **20** and **25**, all products are racemic substances. [e] Isolated, combined yield. [f] Determined by ^1H NMR analysis of crude reaction mixtures.

configured *syn,anti*-**20**, was obtained, from which individual isomers could be isolated and characterized. For *syn,anti*-**20**, whose optical and spectral characteristics fully matched those of a known substance,[12] the relative and absolute configuration was quickly assessed, while for its C5-epimeric counterpart

SCHEME 2. Proposed Reaction Itinerary for the Vinylogous VSMAR between 1 and Carbonyl Acceptors



anti,anti-**20**,[12a] the stereodisposition was also corroborated by clean Et_3N-induced equilibration to *syn,anti*-**20**.[13]

In spite of their alleged recalcitrant nature as acceptor substrates in aldol-type couplings, ketones proved to be pertinent acceptors in the present VSMAR methodology, with no detriment to the efficiency and diastereoselectivity of the transformation. Mirroring the optimum conditions for acetophenone (**3**) (Table 1, entry 15), reactions of symmetrical ketones **11** and **12** went cleanly and efficiently, affording the expected racemic silylated ketols **21** and **22** in 75% and 62% isolated yields, respectively (entries 6 and 7). With ketoesters **13** and **14** the reactions were less productive, affording the corresponding hindered tertiary silyl ethers in low to moderate yields. As for **13**, *N,O-anti* 2*R**,2′*R**-configured silyloxy ester *anti*-**23** was isolated in 18% yield and with good diastereoselectivity (>12:1 dr). When oxophenyl acetate **14** was employed, *N,O-anti* 2*S**,2′*R**-silylated ketol *anti*-**24** was accessed in an acceptable 33% yield and appreciable diastereoselectivity (>15:1 dr).

Noteworthy, reacting **1** with D-glyceraldehyde-derived ketone **15** returned *anti,syn*-configured (5*S*,1′*R*,4″*R*) adduct *anti,syn*-**25** as the sole stereoisomer (out of four), in an appreciable 68% isolated yield.[14]

The structural assignment of compounds **23**, **24**, and **25** was firmly ascertained by direct structural correlation to known substances,[10] as detailed in the Experimental Section.

Mechanistic Insights. As for the mechanistic itinerary of the present vicarious silylative Mukaiyama aldol reaction, we propose a tandem pathway (Scheme 2) involving first, Et_3N/Me_3SiOTf-driven generation of a dienoxy silane intermediate **A** that, in turn, couples to the appropriate carbonyl acceptor under the assistance of the silicon Lewis acid in a strict vinylogous and silylative manner. This direct approach involves simultaneous addition of all reactants (donor, acceptor, solvent, and the Lewis acid/Lewis base mixture) and markedly differs from the classical Mukaiyama aldol reaction where preformed, isolated, or in situ generated silyl enolates or dienolates react with the acceptors under the guidance of Lewis acid catalysts or promoters.[15] A decisive asset of the method is that the addition is simple to perform, direct, and reliable, and the products are recovered in a quite stable silylated form.

During the crucial carbon−carbon bond-forming stage, when prochiral carbonyl acceptors are involved ($R^1 \neq R^2$), two new stereogenic centers generate, producing *anti*- and/or *syn*-configured adducts **B**. The observed simple diastereoselection with both aldehydes and ketones can be rationalized by examining six generic transition state models: hetero-Diels−Alder-like structures **TS1** and **TS4**, open-chain antiperiplanar projections **TS2** and **TS5**, and open-chain synclinal projections **TS3**

(13) It is known that prolonged exposure of such γ-alkyl-substituted pyrrolinone species to tertiary amine bases in DCM at room temperature results in a thermodynamic equilibration between the 5,1′-*syn* and 5,1′-*anti* isomers. See, for example, ref 12b

(14) During silica gel flash chromatographic purification, partial desilylation and retrograde aldolization were observed, causing a small erosion of the isolated yield.

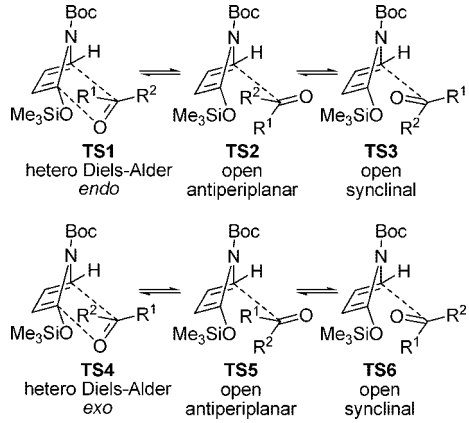


FIGURE 1. Possible transition state models for the vinylogous VSMAR of **1** to carbonyl compounds.

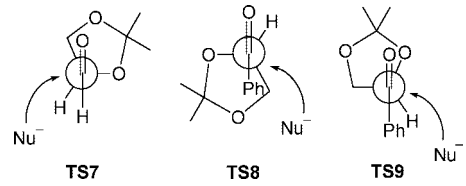


FIGURE 2. The Newman projections of staggered transition state conformers **TS7**, **TS8**, and **TS9**.

and **TS6** (Figure 1). When π-donor groups are present within the carbonyl substrates (e.g., R^1 = phenyl, styryl, propenyl, carboxyethyl), *endo* hetero-Diels−Alder-like transition states **TS1** are strongly preferred, due to the beneficial orbital overlapping of the donor and acceptor π systems, giving rise to *anti*-configured adducts.[16] When, instead, aliphatic substituents are solely involved (e.g., R^1 = isopropyl, isobutyl, dioxolanyl), concurring participation of several transition state structures can be invoked accounting for the reduced and variable *anti-*/*syn*-diastereoselectivity shown with such substrates.

As for the facial diastereoselectivity of reactions involving nonracemic prochiral acceptors **10** and **15**, a plausible rationale explaining the 1′,4″-*syn* vs *anti* preference relies on the examination of the transition states from the Newman projections **TS7**, **TS8**, and **TS9** (Figure 2). With aldehyde **10**, a classical polar Felkin-Anh model **TS7** applies, accounting for the exclusive formation of 1′,4″-*anti*-configured aldols **20** via *si*-face attack (Table 2, entry 5). However, a reverted outcome was witnessed with ketone **15**; in this case, **15** could not react via the expected **TS7**-type geometry, but would have presumably to adopt either an anti-Felkin-Anh transition state such as **TS8** or a Felkin-Anh projection **TS9**, with the CH_2O- group being considered as the large substituent.[17] In truth, the reaction yielded 1′,4″-*syn*-adduct **25** almost exclusively, via nucleophilic attack at the *re* face of the carbonyl (Table 2, entry 10).

Conclusion

In summary, we have developed a novel, direct, and vinylogous variant of the classical Lewis acid-catalyzed Mukaiyama aldol reaction applicable to both aldehyde and ketone acceptor substrates. By using pyrrolinone **1** as a prototypical "vinylogous" donor candidate, structurally and stereochemically diverse γ-substituted-α,β-unsaturated lactam silyl ethers were obtained in high yields and useful diastereoselectivities. Crucial to the success of this practical transformation was the vicarious use of a dual silicon Lewis acid/tertiary amine base promoter system triggering a reaction cascade comprising in situ formation of the actual dienoxysilane donor species, regioselective vinylogous and diastereoselective donor-to-acceptor coupling, and aldol/ketol *O*-silylation.

We are studying the applicability of the present methodology to other "vinylogous" heterocyclic and alycyclic donors to enlarge further the library of α,β-unsaturated-δ-hydroxycarbonyl structures, a relevant class of synthetically useful multifunctional compounds.[4]

Experimental Section

Representative Procedure for the Vicarious Silylative Mukaiyama Aldol Reaction (VSMAR) between Pyrrolinone 1 and Carbonyl Compounds: Preparation of (*R)-1-(*tert*-Butoxycarbonyl)-5-[(*S**)-trimethylsilanyloxy(phenyl)methyl]-1*H*-pyrrol-2(5*H*)-one (*anti*-4a) (Table 1, entry 7).** To a flame-dried, two-necked, round-bottomed flask fitted with an argon inlet adapter, magnetic stir bar, and septum was added triethylamine (Et_3N, 57 μL, 0.41 mmol) followed by anhydrous Et_2O/hexane (2:1 v/v) solvent mixture (6 mL) under argon atmosphere. The solution was cooled to −78 °C for 5 min, and trimethylsilyloxytriflate (TMSOTf, 99 μL, 0.55 mmol) was added dropwise. The resulting whitish suspension was vigorously stirred at this temperature for 5 min. To this suspension was slowly added a preformed solution of pyrrolinone **1** (50 mg, 0.27 mmol) in 4 mL of anhydrous Et_2O/hexane (2:1 v/v) solvent mixture. After the mixture was stirred at −78 °C for 5 min, benzaldehyde **2** (36 μL, 0.35 mmol) was added dropwise and the resulting whitish suspension was kept under vigorous stirring at the same temperature for 5 h. Pyridine (44 μL, 0.55 mmol) was then added at −78 °C and, after 10 min of stirring, brine (20 mL) was added. The resulting mixture was allowed to warm to room temperature (22 °C) and transferred to a separatory funnel. The aqueous layer was separated and extracted with hexane (3 × 35 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellowish oil that was directly subjected to ^{1}H NMR analysis for determination of the diastereomeric ratio (*anti:syn* ratio >12.0:1). The crude residue was purified by silica gel flash chromatography (hexane/EtOAc 85:15) to afford 92 mg (93%) of compound *anti*-**4a**. Data for *anti*-**4a**: colorless oil; R_f 0.40 (hexane/EtOAc 9:1) [silica gel, UV]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 5H, Ph), 6.79 (dd, J = 6.2, 2.0 Hz, 1H, H4), 6.08 (dd, J = 6.2, 1.3 Hz, 1H, H3), 5.52 (bd, J = 2.2 Hz, 1H, H1′), 4.70 (ddd like a q, J = 2.1 Hz, 1H, H5), 1.63 (s, 9H, *t*-Bu), 0.03 (s, 9H, TMS); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.4 (Cq, C2), 149.7 (Cq, Boc), 146.4 (CH, C4), 140.8 (Cq, Ph), 128.4 (2C, CH, Ph), 127.9 (CH, Ph), 127.6 (CH, C3), 125.6 (2C, CH, Ph), 82.9 (Cq, *t*-Bu), 71.7 (CH, C1′), 68.9 (CH, C5), 28.2 (3C, CH_3, *t*-Bu), −0.4 (3C, CH_3, TMS). Anal. Calcd for $C_{19}H_{27}NO_4Si$: C, 63.13; H, 7.53; N, 3.87. Found: C, 62.97; H, 7.71; N, 3.75.

Treatment of compound *anti*-**4a** with catalytic hydrogen (H_2, Pd/C, EtOAc) followed by citric acid (3.0 mol equiv) in MeOH quantitatively gave the corresponding known saturated and

(15) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509. (b) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011–1014. (c) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (d) Heathcock, C. H. In *Comprehensive Organic Synthesis: Additions to C-X π-Bonds, Part 2*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, UK, 1991; Chapter 1.5.

(16) With ketone acceptors, the *syn*/*anti* notation of the ketol products is sometimes ambiguous, depending on the way the formulae are written. For a uniform reading and clean rationalization of the stereochemical results, we opted to positioning the R^1 *endo*-directing group on the plane of the molecule (see compounds **5a**−**c** and **23**−**25** in Tables 1 and 2).

desilylated lactam:[7] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3−7.5 (m, 5H, Ph), 5.38 (br s, 1H, H1′), 4.35 (ddd like a dt, J = 9.4, 1.0 Hz, 1H, H5), 3.92 (br s, 1H, OH), 2.89 (ddd like a dt, J = 17.9, 10.1 Hz, 1H, H3a), 2.30 (ddd, J = 17.7, 10.1, 1.6 Hz, 1H, H3b), 2.02 (m, 1H, H4a), 1.70 (m, 1H, H4b), 1.63 (s, 9H, *t*-Bu).

The presence of minor isomer *syn*-**4a** evidenced by ^{1}H NMR analysis of the crude reaction product could no longer be detected after column chromatography purification. Data for *syn*-**4a** (taken from the reaction mixture): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 5H, Ph), 7.35 (dd, J = 6.1, 2.0 Hz, 1H, H4), 5.81 (dd, J = 6.1, 1.6 Hz, 1H, H3), 5.51 (br d, J = 5.2 Hz, 1H, H1′), 4.80 (ddd like a dt, J = 5.3, 2.0 Hz, 1H, H5), 1.54 (s, 9H, *t*-Bu), 0.10 (s, 9H, TMS).

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Supporting Information Available: Experimental procedures, compound characterization data, stereochemical assignment of *anti*-**18**, and reproductions of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800741C

(17) For a related example involving nucleophilic addition to phenyl ketone **15**, see: Roy, S.; Sharma, A.; Chattopadhyay, N.; Chattopadhyay, S. *Tetrahedron Lett.* **2006**, *47*, 7067–7069.