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Amide Enolate Additions to Acylsilanes: In Situ Generation of Unusual and Stereoselective Homoenolate Equivalents

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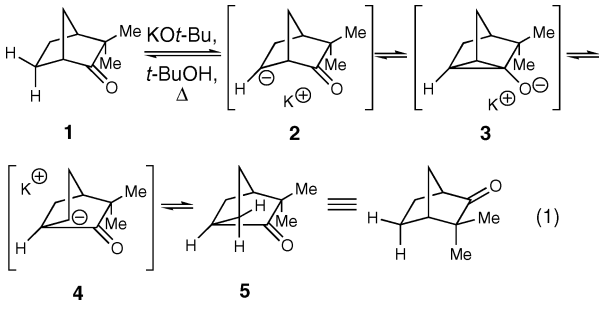
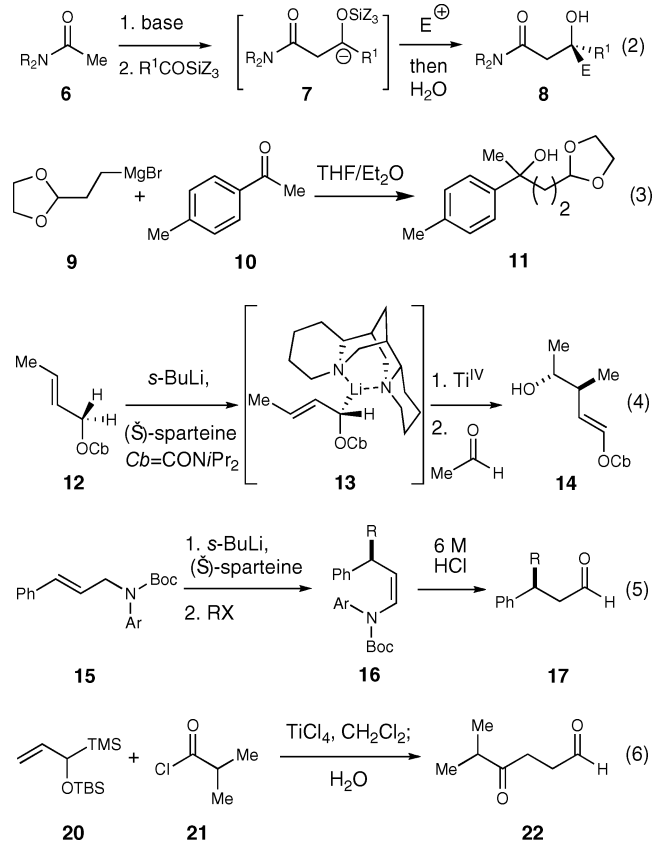
Abstract: The synthesis of β-hydroxy carbonyl compounds is an important goal due to their prevalence in bioactive molecules. A novel approach to construct these structural motifs involves the multicomponent reaction of acylsilanes, amides, and electrophiles. The addition of amide enolates to acylsilanes generates β-silyloxy homoenolate reactivity by undergoing a 1,2-Brook rearrangement. These unique nucleophiles formed in situ can then undergo addition to alkyl halides, aldehydes, ketones, and imines. The γ-amino-β-hydroxy amide products derived from the addition of these homoenolates to *N*-diphenylphosphinyl imines are generated with excellent diastereoselectivity (≥20:1) and can be efficiently converted to highly valuable γ-lactams. Finally, the use of optically active amide enolates delivers β-hydroxy amide products with high levels of diastereoselectivity (≥10:1).

Introduction

In 1962, Nickon and Lambert reported the first examples of homoenolate anion formation (eq 1).[1] Optically active camphenilone (**1**), which has no enolizable protons by classical reactivity standards, underwent racemization at elevated temperatures in the presence of potassium *tert*-butoxide. This loss of optical purity can best be attributed to the formation of an active homoenolate intermediate (**2/4**). Homoenolates are unusual nucleophiles that differ from enolates in that the negative charge is located on the β-carbon of a carbonyl system. These species are therefore less stable and more difficult to generate than the corresponding enolates due to the lack of resonance stabilization. In spite of this notable observation being almost half a century ago, researchers have been challenged in finding controllable and useful homoenolate equivalents for organic transformations.



Conceptually, the addition of a homoenolate species to an electrophile is the polarity reversal, or *Umpolung*[2] approach to a standard conjugate addition. This report describes the utilization of amide enolate additions to acylsilanes, accessing β-hydroxy-substituted homoenolate equivalents through a Brook rearrangement reaction pathway (eq 2).[3] We have found that the intermediate β-silyloxy homoenolates (**7**) undergo smooth addition to electrophiles to deliver tertiary β-hydroxy amides (**8**) in good yields and with high levels of stereoselectivity when chiral acetamides are used.



Following Nickons's seminal discovery of homoenolate formation, there have been multiple strategies to access homoenolate equivalents (eqs 3−9). The first general method for the generation and utilization of this unique reactivity pattern involved the use of acetal-masked Grignard reagents.[4] These

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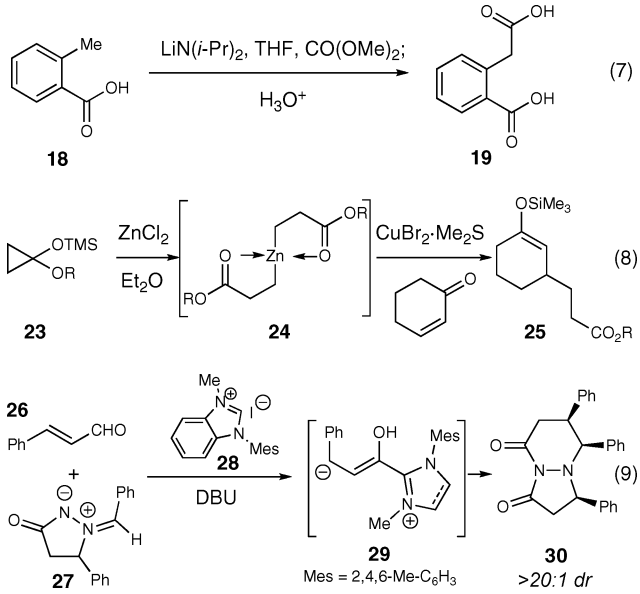
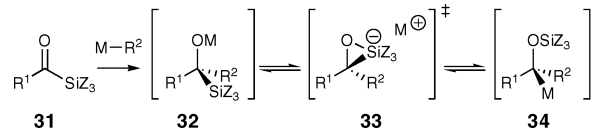


homoenolate equivalents (**9**) have been used in 1,2-addition reactions to carbonyl compounds (eq 3), acylations, and conjugate additions. The utility of these reactions has also been employed in natural product synthesis.[5−7] Approximately 20 years following Nickon's report, Hoppe employed novel sparteine-carbanion complexes of deprotonated 2-butenyl carbamates (**12**) in enantioselective homoaldol reactions (eq 4).[8−10] Beak later reported a related approach with allyl amines (**15**), which after hydrolysis, provides the corresponding β-substituted aldehydes (**17**) in good yield (eq 5).[11,12] These systems allow direct access to homoenolates and provide a manner to control the absolute stereochemistry of the products. Hauser introduced the base-induced carboxylation of aryl homoenolates,[13] which has since been successfully applied to the synthesis of several natural products (eq 6).[14] Sakurai introduced a method utilizing the Lewis acid mediated formation of homoenolates from 3-silyl-3-siloxypropenes (**20**, eq 7).[15] Nakamura and Kuwajima developed a similar approach to homoenolate anion reactivity using silyloxycyclopropanes (**23**) as a synthon (eq 8).[16] In the presence of zinc(II) chloride, the ring-opening of silyloxycyclopropane **23** occurs readily to provide a stabilized etherate intermediate (**24**). Zinc homoenolate **24** reacts with a variety of electrophiles to undergo synthetically useful carbon−carbon bond-forming reactions, while simultaneously avoiding undesired intramolecular cyclopropanation. Recently, a new approach to homoenolate generation involving nucleophilic *N*-heterocyclic carbene (NHC)-catalyzed processes has been independently investigated by several researchers, including Glorius,[17,18] Bode,[19,20] Nair,[21,22] Zeitler,[23] and our group.[24,25] For example, we recently reported the highly stereoselective formal [3 + 3] cycloaddition of enals (**26**) and azomethine imines (**27**), catalyzed by the carbene generated in situ from benzimidazolium salt **28** (eq 9).[25]

Acylsilanes and the Brook Rearrangement. From the commendable contributions from Brook, it has been known that the addition of organometallic nucleophiles to acylsilanes typically induces a reversible 1,2-silyl group migration from carbon to oxygen (eq 10).[26] In the 1,2-Brook rearrangement process, nucleophilic ($M-R^2$) addition to acylsilane **31** yields silyl alkoxide intermediate **32**, which is proposed to undergo reversible and stereospecific rearrangement via silyl epoxide transition state **33** (or intermediate, not clearly distinguished) to generate silyloxy carbanion **34**. The proposed highly ordered cyclic silyl epoxide transition state is supported by very large negative entropies of activation ($\Delta S^{\ddagger} = -35$ to -45 cal/K).[3] Overall, the unique reactivity of acylsilanes enables them to possess sequential electrophilic/nucleophilic character at the same carbon position. The additions of alkynyl lithium reagents or alkenyl Grignard reagents to acylsilanes trigger this rearrangement to access useful silyloxy carbanions.[27−30] The addition of enolates to acylsilanes has received much less attention in comparison to other organometallic nucleophiles.[31,32] If developed effectively, this method for bond construction is an alternative for the difficult analogous reaction involving the direct asymmetric addition of enolates to ketones.[33−38]



Takeda was the first to report the addition of ketone-derived enolates to acylsilanes (eq 11).[39−42] The addition of lithium enolate **36** to acylsilane **35** yields electron-delocalized allylic anion **37**, which proceeds through an intramolecular homoaldol

(1) Nickon, A.; Lambert, J. L. *J. Am. Chem. Soc.* **1962**, *84*, 4604–4605.
(2) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239–258.
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(4) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045–5050.
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(14) Shangguan, N.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9*, 1093–1096.
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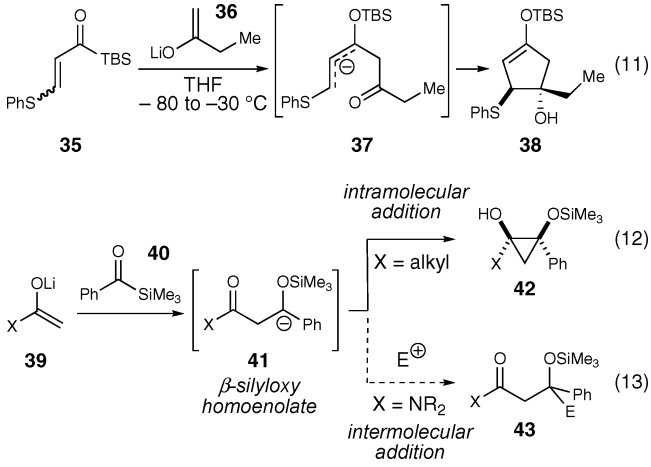
(19) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371.
(20) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873–3876.
(21) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736–8737.
(22) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507–509.
(23) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506–7510.
(24) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905–508.
(25) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334–5335.
(26) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77–84.
(27) Kuwajima, I.; Kato, M.; Mori, A. *Tetrahedron Lett.* **1980**, *21*, 2745–2748.
(28) Reich, H. J.; Olson, R. E.; Clark, M. C. *J. Am. Chem. Soc.* **1980**, *102*, 1423–1424.
(29) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065–2084.
(30) Fleming, I.; Lawrence, A. J.; Richardson, R. D.; Surry, D. S.; West, M. C. *Helv. Chim. Acta* **2002**, *85*, 3349–3365.
(31) Kuwajima, I.; Matsumoto, K. *Tetrahedron Lett.* **1979**, *20*, 4095–4098.
(32) Soderquist, J. A.; Miranda, E. I. *J. Am. Chem. Soc.* **1992**, *114*, 10078–10079.

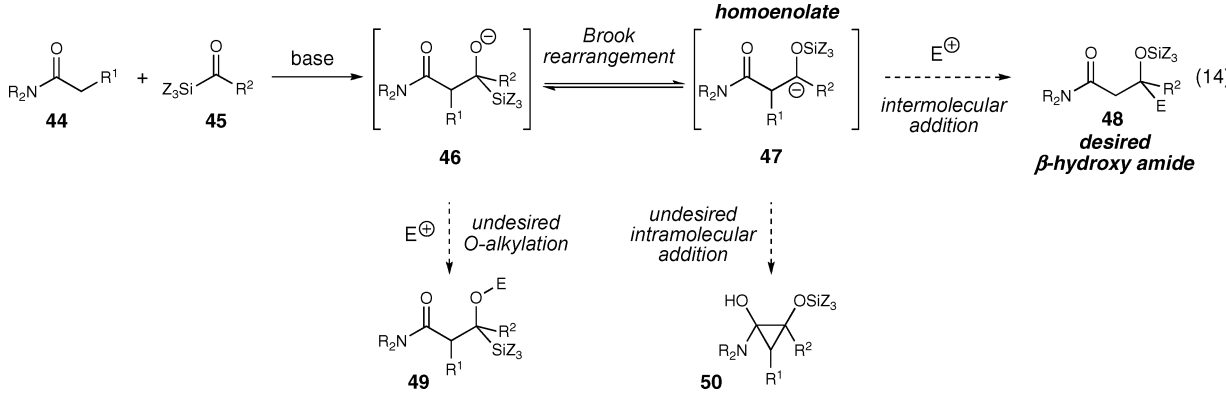
addition pathway to provide cyclized silyl enol ether **38**. However, when the acylsilane lacks α,β-unsaturation, Takeda observed the major product to be the hydroxy cyclopropane (**42**, X = alkyl, eq 12). This highly substituted carbocycle arises from the internal attack of the in situ-generated β-silyloxy homoenolate (**41**).



With our interest in developing new nucleophilic species derived from acylsilanes,[43−47] as well as homoenolate equivalents,[24,25] we chose to explore the combination of alternative enolates and acylsilanes to access stable homoenolate intermediates that could then proceed through the desired intermolecular addition pathway (eq 13). The success of this single-flask process depended on controlling the intermediates in the reaction to favor intermolecular reactivity via the β-silyloxy homoenolate (**47**, eq 14). Due to their decreased electrophilicity in comparison to ketones, we chose amide enolates (X = NR_2) to potentially disfavor the intramolecular generation of siloxy cyclopropane **50** and promote intermolecular addition and the formation of tertiary β-hydroxy amide **48**. The details of this investigation, including scope, product elaboration, and mechanism, are reported herein.[48,49]

observed (as measured by TLC), and benzyl bromide was added. This three-component reaction provided β-hydroxy amide **53** in 86% yield after desilylation.[51] Notably, the corresponding cyclopropane (**50**) or *O*-alkylation compound (**49**) was not observed. The absence of hydroxy cyclopropanes confirmed our hypothesis that the reduced electrophilicity of the amide carbonyl favors intermolecular reactivity. Methods were surveyed for product desilylation (including multiple fluoride sources and Brønsted acid), with tetrabutylammonium fluoride giving the highest yield and reaction rate. Encouraged by these results, a range of electrophiles was surveyed. Primary, allylic and benzylic halides all afford the corresponding tertiary alcohols (**53**−**57**) in good yields (entries 1−5). The β-silyloxy homoenolate intermediate also undergoes facile addition to aldehydes and ketones (entries 6 and 7). In cases where elimination (entry 5) or deprotonation (entry 7) is a possibility, the reaction proceeds surprisingly without complication. Furthermore, secondary β-hydroxy amide **60** is generated by treating the homoenolate intermediate with acidic methanol (entry 8). While the free alcohols are easily obtained by exposure of the unpurified reaction to fluoride (TBAF), it remains difficult to obtain products with the silyl-protected alcohols in tact even using mild work up conditions.

We proceeded to examine how this new process is impacted by different substituents on the acylsilane (Table 2, eq 16). The optimized reaction proceeds in good yields in the presence of both electron-deficient (entries 3, 4, and 6) and electron-rich (entry 5) aromatic systems. However, when acetyltrimethylsilane (**66**) is employed, a complex mixture primarily containing the *O*-alkylation product (no Brook rearrangement occurs) is recovered (entry 7). This observation is not surprising since aromatic substitution stabilizes the β-silyloxy homoenolate intermediate, promoting the Brook rearrangement in the previous examples (entries 1−6). Additionally, the deprotonation of an enolizable acylsilane by the parent enolate is a potentially competitive process that can interfere with the normal reaction pathway. Aliphatic dimethylphenyl acylsilanes have been previously reported to be effective Brook rearrangement precursors due to the increased stabilization of the

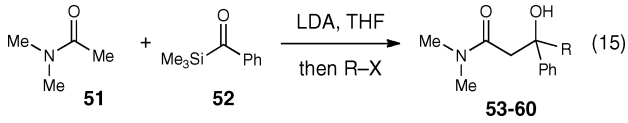


Results and Discussion

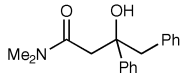
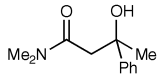
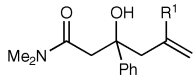
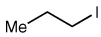
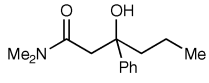
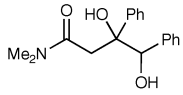
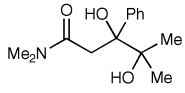
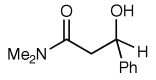
Reaction Development. Our investigation into the use of enolate additions to acylsilanes as homoenolate equivalents began by utilizing reactive and readily available starting materials. The initial reaction was conducted with dimethylacetamide (**51**) and benzoyl trimethylsilane (**52**),[50] with benzyl bromide as the electrophilic trapping reagent (entry 1, Table 1, eq 15). Amide enolate formation with lithium diisopropylamine (LDA) in THF was followed by the addition of acylsilane **52**. After 15 min at −78 °C, disappearance of acylsilane was

pentavalent silyloxy anion intermediate (**33**) from the aromatic substituent on silicon.[52−60] The β-hydroxy amide products were not observed when using dimethylphenyl acylsilanes under our developed reaction conditions (entries 8−9). As an alternative to aliphatic acylsilanes, *tert*-butyl trimethylsilylglyoxylate (**69**)[61] did prove to be effective for this transformation, providing the γ-carboxy-β-hydroxy amide (**78**) in moderate yield (entry 10). Installation of the *tert*-butyl ester provides a synthetic handle that can be potentially further functionalized to access a variety of functional groups.[62]

Table 1. Reaction with Electrophiles (R−X)[a]

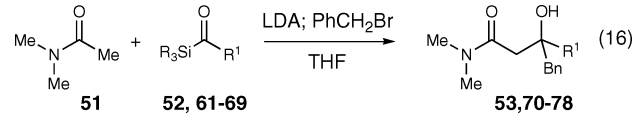


(15)

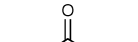
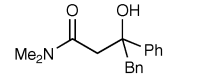
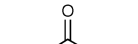
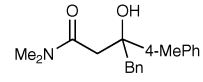
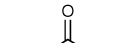
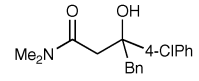
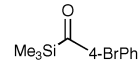
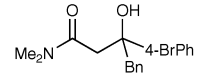
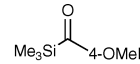
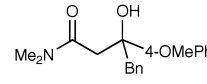
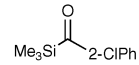
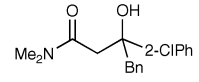
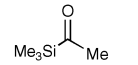
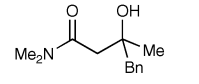
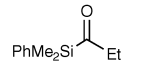
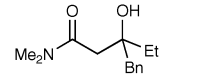
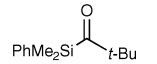
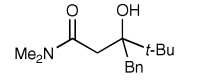
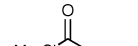
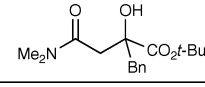
entry	R–X	product		yield (%)
1			**53**	86
2			**54**	77
3			**55** (R^1= H)	68
4			**56** (R^1= Me)	77
5			**57**	69
6			**58**	81[b]
7			**59**	78
8	AcOH/MeOH		**60**	80

[a] Acylsilane and electrophile sequentially added to a 0.2 M enolate solution in THF at −78 °C. Initial silyl ether products treated with *n*-Bu_4NF in THF prior to purification. [b] 1:1 mixture of diastereomers.

Table 2. Surveying Acylsilane Compatibility[a]



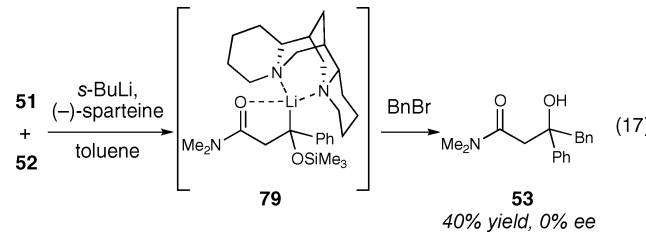
(16)

entry	acylsilane		product		yield (%)
1		**52**		**53**	86
2		**61**		**70**	73
3		**62**		**71**	73
4		**63**		**72**	69
5		**64**		**73**	75
6		**65**		**74**	67
7		**66**		**75**	0[b,c]
8		**67**		**76**	0[c]
9		**68**		**77**	0[c]
10		**69**		**78**	49

[a] See Table 1 for reaction details. [b] Minor amounts of *O*-alkylation product observed. [c] Complex mixture.

Following the development of the multicomponent homoenolate addition, investigation was directed toward the development of a stereoselective variant of this process. Drawing inspiration from the previously mentioned work of Hoppe[9,10] and Beak,[11,12] attempts were made to utilize lithium/sparteine-carbanion pairs to induce enantioselectivity (Scheme 1, eq 17). One limitation of this process was the necessity of noncoordinating solvent (e.g., toluene) to promote sparteine complexation. Under these conditions,[63] the reaction rate and yield were greatly diminished, and no enantioselectivity was observed.[64]

Scheme 1. Enantiocontrol by Sparteine Coordination

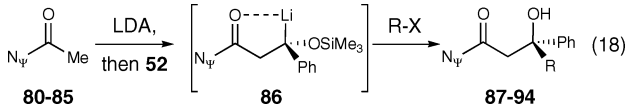


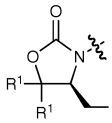
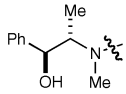
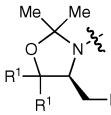
(17)

An alternative method considered for asymmetric induction involved auxiliary control by the substitution of dimethylacetamide with a chiral acetamide (Table 3, eq 18). Cyclic chiral auxiliaries were primarily considered on the basis of their rigidity and proven ability as asymmetric control elements. To this end, *N*-acyl oxazolidinones **80** and **81** were synthesized according to the procedures of Evans[65] and Davies,[66] respectively. Attempts to control the stereochemical outcome of the multicomponent reaction with these chiral oxazolidinone auxiliaries under the established reaction conditions resulted in complete decomposition of the starting materials (entries 1 and 2). This result is most likely due to inter- or intramolecular nucleophilic addition of the homoenolate intermediate (**86**) to the relatively electrophilic carbamate carbonyl of the oxazolidinone. To circumvent this problem, prolinol derived auxiliary **82**[67] and Meyers pseudoephedrine auxiliary **83**[68] were synthesized. However, these auxiliaries proved ineffective under the utilized reaction conditions (entries 3 and 4). Subsequently, *N*-acyl oxazolidines **84** and **85** were synthesized according to the procedure of Kanemasa.[69,70] Addition of the enantiopure lithium enolate of **84** or **85** to acylsilane **52**, followed by addition of benzyl bromide, afforded the desired carbinols (**91** and **92**, after desilylation) with moderate diastereoselectivity under the established kinetically controlled reaction conditions (−78 °C,

(33) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233–4235.
(34) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644–5645.
(35) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853–2873.
(36) Hatano, M.; Ishihara, K. *Synthesis* **2008**, 1647–1675.
(37) Adachi, S. H.; Harada, T. *Org. Lett.* **2008**, *10*, 4999–5001.
(38) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225–4228.

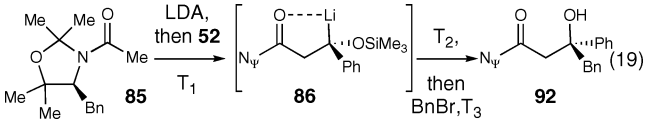
Table 3. Diastereoselective Enolate/Acylsilane Reactions[a]



entry	N_Ψ		R–X	T (°C)	yield (%)	dr[b]	product
1		**80**: R^1=H	BnBr	—78	0[c]	Š	**87**
2		**81**: R^1=Me	BnBr	—78	0[c]	Š	**88**
3		**82**	BnBr	—78 to 23	0[d]	Š	**89**
4		**83**	BnBr	—78 to 23	0[d]	Š	**90**
5		**84**: R^1=H;	BnBr	—78	77	2:1	**91**
6		**85**: R^1=Me	BnBr	—78	80	3:1	**92**
7		**85**	BnBr	—90	0[e]	10:1	**92**
8		**85**	BnBr	0	79	10:1	**92**
9		**85**	AllylBr	0	76	10:1	**93**
10		**85**	MeI	0	78	15:1	**94**

[a] Acylsilane and electrophile sequentially added to a 0.2 M enolate solution in THF. Silyl ether products treated with *n*-Bu_4NF in THF prior to purification. [b] Determined by ^1H NMR spectroscopy. [c] Decomposition. [d] 2 equiv of LDA, no addition to acylsilane. [e] No addition to benzyl bromide.

Table 4. Effect of Temperature on Diastereoselectivity[a]



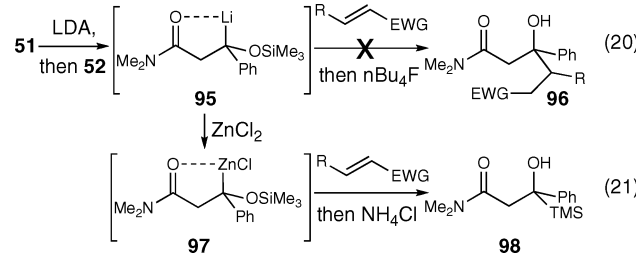
entry	T_1 (°C)	T_2 (°C)[b]	T_3 (°C)	yield (%)	dr[c]
1	−78	−78	−78	80	3:1
2	0	0	0	79	10:1
3	−78	0	−78	79	10:1

[a] Acylsilane and electrophile sequentially added to a 0.2 M enolate solution in THF. Silyl ether products treated with *n*-Bu_4NF in THF prior to purification. [b] Reaction temperature after consumption of **52** and before the addition of R−X. [c] Determined by ^1H NMR spectroscopy.

entries 5 and 6).[71] Attempts to improve the selectivity by cooling the reaction further (−90 °C) decreased the reactivity of the homoenolate, preventing alkylation (entry 7). Various bases (KHMDS and LiHMDS), additives (LiCl, HMPA, and TMEDA), and solvents (THF, Et_2O, toluene, and 1:4 THF/toluene) were investigated, with no observed improvement in yield or diastereoselectivity. However, when this sequence is carried out at elevated temperatures (0 °C), the selectivities improved to >10:1 (entries 8−10).

A further analysis of the effect of temperature on the observed diastereoselectivity was investigated (Table 4, eq 19). As noted above, when the entire reaction procedure is carried out at −78 °C, the observed diastereoselectivity for the addition process to benzyl bromide is 3:1 (entry 1). Conversely, when the entire reaction is conducted at 0 °C, an increase in diastereoselectivity

Scheme 2. Homoenolate Conjugate Addition



to 10:1 is achieved (entry 2). Importantly, high levels of stereoselectivity are also observed when only the initial homoenolate intermediate (**86**) is warmed to 0 °C for 15 min. This result suggests that a thermodynamic equilibration at this point of the reaction generates the most stable/favorable carbanion intermediate (**86**), which is the source of the observed increased stereoselectivity.[72]

On the basis of the success of our initial investigations, we decided to explore expansion of the reaction scope. Exhaustive attempts were made to effect the addition of homoenolate **95** to conjugate acceptors (Scheme 2, eq 20). Several electrophiles were surveyed for this reaction profile, but unfortunately none led to the desired 1,4-addition product. Attempted transmetalation of lithium-homoenolate **95** with $ZnCl_2$, facilitated a retro-Brook process, generating the corresponding alcohol **98** (eq 21). A small collection of epoxides and aziridines were also surveyed as potential electrophiles, although no addition to these substrates was observed.

(39) Takeda, K.; Fujisawa, M.; Makino, T.; Yoshii, E.; Yamaguchi, K. *J. Am. Chem. Soc.* **1993**, *115*, 9351–9352.
(40) Takeda, K.; Nakatani, J.; Nakamura, H.; Sako, K.; Yoshii, E.; Yamaguchi, K. *Synlett* **1993**, 841–843.
(41) Takeda, K.; Takeda, M.; Nakajima, A.; Yoshii, E. *J. Am. Chem. Soc.* **1995**, *117*, 6400–6401.
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(43) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314–2315.
(44) Mattson, A. E.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 4363–4366.
(45) Clark, C. T.; Milgram, B. C.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 3977–3980.
(46) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932–4933.
(47) Mattson, A. E.; Bharadwaj, A. R.; Zuhl, A. M.; Scheidt, K. A. *J. Org. Chem.* **2006**, *71*, 5715–5724.
(48) Lettan, R. B.; Reynolds, T. E.; Galliford, C. V.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 15566–15567.
(49) Lettan, R. B.; Woodward, C. C.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2294–2297.
(50) Yamamoto, K.; Hayashi, A.; Suzuki, S.; Tsuji, J. *Organometallics* **1987**, *6*, 974–979.
(51) Some desilylation always occurred during work-up/purification. Treatment with *n*Bu_4NF was carried out to ease characterization and yield determination efforts.
(52) Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609–5617.
(53) Lefebvre, O.; Brigaud, T.; Portella, C. *J. Org. Chem.* **2001**, *66*, 4348–4351.
(54) Buynak, J. D.; Geng, B.; Uang, S.; Strickland, J. B. *Tetrahedron Lett.* **1994**, *35*, 985–988.
(55) Takeda, K.; Ohnishi, Y.; Koizumi, T. *Org. Lett.* **1999**, *1*, 237–239.
(56) Patrocinio, A. F.; Correa, I. R.; Moran, P. J. S. *J. Chem. Soc., Perk. Trans 1* **1999**, 3133–3137.
(57) Bolm, C.; Kasyan, A.; Heider, P.; Saladin, S.; Drauz, K.; Gunther, K.; Wagner, C. *Org. Lett.* **2002**, *4*, 2265–2267.
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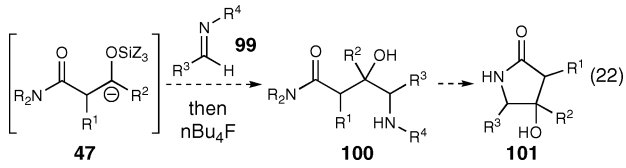
(60) Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290–11291, and references cited therein.
(61) Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 6170–6171.
(62) Claudel, S.; Olszewski, T. K.; Mutzenardt, P.; Aroulanda, C.; Coutrot, P.; Grison, C. *Tetrahedron* **2006**, *62*, 1787–1798.

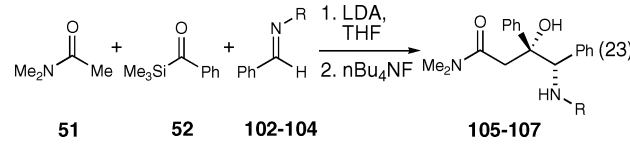
Scheme 3. Homoenolate Addition to Imines

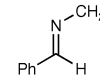
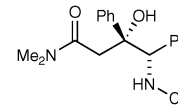
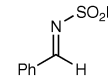
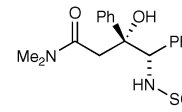
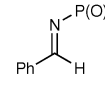
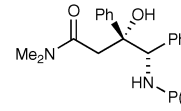
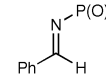
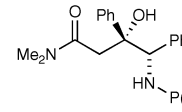


Another variant of this new strategy involved the addition of an imine as the electrophilic component (Scheme 3, eq 22). Addition of homoenolate **47** to imine **99** would permit access to highly substituted γ-amino-β-hydroxy amides (**100**). More importantly, cyclization of the amide to the corresponding γ-lactam (**101**) was envisioned to be accomplished directly upon removal of the activating group on the imine nitrogen. The synthesis of γ-lactams[73−77] is an important goal due to their application in the drug-discovery process, as key intermediates in the preparation of biologically and pharmaceutically relevant molecules.[78] Compounds containing these heterocycles have direct applications in the treatment of cancer,[78−80] fungal infections,[80] epilepsy,[81,82] HIV,[83,84] neurodegenerative diseases,[85] and depression.[86]

To evaluate the homoenolate addition to imines, we surveyed compounds with a variety of different activating groups on nitrogen (Table 5, eq 23). Following homoenolate formation,

Table 5. Synthesis of γ-Hydroxy Amides[a]



entry	imine	product	yield (%)	dr[b]
1	 **102**	 **105**	41[c]	2:1
2	 **103**	 **106**	75[c]	10:1
3	 **104**	 **107**	0[c]	—
4	 **104**	 **107**	74[d]	>20:1

[a] Acylsilane and electrophile added to a 0.1 M enolate solution in THF at −78 °C. Silyl ether products treated with *n*-Bu_4NF in THF prior to purification. [b] Determined by ^1H NMR spectroscopy. [c] Reaction warmed slowly to 23 °C following addition of the imine. [d] Reaction maintained at −78 °C following addition of the imine.

addition of *N*-benzyl imine **102**[87] gave the desired γ-amino amide (**105**) in modest yield (entry 1). The major side product of this reaction is the secondary alcohol (**60**) resulting from incomplete addition of the intermediate homoenolate to the imine after a 24 h reaction period. To increase the reactivity of the imine, *N*-sulfonylimine **103** was synthesized.[88] Exposure of imine **103** to the established reaction conditions led to the formation of desired amide (**106**) in good yield and diastereoselectivity (entry 2). In an attempt to further improve these results, while simultaneously choosing a less robust N-protecting group, we synthesized *N*-diphenylphosphinyl imine **104**.[89] Addition of the homoenolate to imine **104**, followed by warming to ambient temperature, led to an undesired rearrangement product (not shown, entry 3). Maintaining the reaction temperature at −78 °C following imine addition negated this side reaction and gave exclusively the desired γ-amino-β-hydroxy amide (**107**) in good yield and with high diastereoselectivity (>20:1) after desilylation (entry 4).

For our purposes, the *N*-diphenylphosphinyl functionality proved to be an optimal choice as an amino protecting group because of (a) its electron withdrawing properties,[90] (b) the steric magnitude associated with this functionality and its apparent stereochemical influence, and (c) the ease of removal of this group under acidic conditions,[91] increasing the potential of concomitant intramolecular cyclization to the γ-lactam. *N*-

(63) Reactions were conducted both by forming the enolate/homoenolate in the presence of (−)-sparteine and by introducing sparteine after homoenolate formation. Various reaction temperatures (−78 to 23 °C) and solvents (toluene, diisopropylether, *tert*-butylmethyl ether) were surveyed.
(64) As determined by chiral HPLC analysis.
(65) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77–82.
(66) Davies, S. G.; Sanganee, H. J.; Szolcsanyi, P. *Tetrahedron* **1999**, *55*, 3337–3354.
(67) Bishop, J. E. M., C. A.; Gerdes, J. M.; Whitney, J. M.; Eaton, A. M.; Mailman, R. B. *J. Med. Chem.* **1991**, *34*, 1612–1624.
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(70) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8645–8658.
(71) The absolute stereochemistry of β-hydroxy amide **92**, was determined by single-crystal X-ray diffraction (see Supporting Information). The absolute stereochemistry of additional β-hydroxy amides were assigned by analogy.
(72) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715–727.
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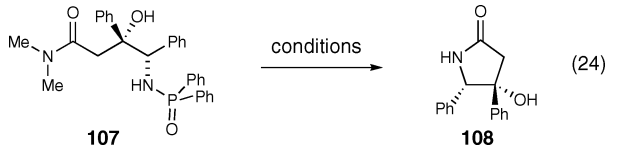
Table 6. γ-Lactam Formation[a]



entry	conditions	temp (°C)	time	yield (%)	dr[b]
1	$BF_3 \cdot OEt_2/CH_2Cl_2$	23	24 h	0[c]	–
2	$Sc(OTf)_2$/toluene[d]	115	24 h	0[c]	–
3	$Zn(OTf)_2$/toluene[d]	115	24 h	0[c]	–
4	Cu(OTf) toluene[d]	115	24 h	0[c]	–
5	concd HCl/THF	23	48 h	92	>20:1
6	concd HCl/THF	70[e]	17 h	96	>20:1
7	concd HCl/THF	150[f]	5 min	98	>20:1
8	3 M HCl/THF	150[f]	5 min	98	>20:1
9	2 M HCl/THF	150[f]	30 min	73[g]	>20:1

[a] A 0.1−0.5 M solution of the amide in solvent. [b] Determined by ^{1}H NMR spectroscopy. [c] No reaction. [d] Reaction also conducted in CH_2Cl_2; no reaction. [e] Reflux. [f] Microwave irradiation. [g] Not to complete conversion.

Diphenylphosphinyl imines have been previously used extensively as electrophiles in asymmetric reductions,[92−96] vinyl zinc additions,[97] acylanion additions,[44] and nucleophilic additions of arylboronic acids.[98]

Initial attempts to afford simultaneous deprotection and cyclization of γ-amino-β-hydroxy amide **107** to the corresponding γ-lactam (**108**) under Lewis acidic conditions were unsuccessful, even at refluxing temperatures (entries 1−4, Table 6, eq 24). Given the precedence for *N*-diphenylphosphinyl deprotection under Brønsted acid conditions,[44] the cyclization was attempted employing hydrochloric acid. There was some concern that dehydration might occur under acidic conditions to give either the α,β- or β,γ-unsaturated γ-lactams due to the potential aromatic-stabilized carbocation at the β-position prior to conducting this experiment. No elimination is observed, and desired γ-lactam **108** is recovered in excellent yield at ambient temperatures, albeit over long reaction times (2 days) and with large amounts of excess concentrated hydrochloric acid (entry 5). Conducting the reaction at reflux provides notable rate enhancement, with no product decomposition or elimination of the β-hydroxyl group (entry 6). The use of microwave irradiation promotes the concomitant deprotection and lactam formation in *only 5 min* (entry 7), and the concentration of acid could be reduced (3 M) without loss of reactivity (entry 8).

An examination of the imine scope for the formation of γ-amino-β-hydroxy amides (Table 7, eq 25) demonstrates that the reaction proceeds in good yields in the presence of both electron-deficient (entries 2 and 3) and electron-rich (entries 4 and 5) aromatic systems. A third substituent is successfully incorporated through the use of α-substituted amides (**109** and **110**), isolating the α-substituted γ-amino-β-hydroxy amides (**119**−**121**) with excellent levels of diastereoselection (entries 6−8).[99]

We next turned our attention to exploring the reaction scope as it applied to the hydrolysis of the *N*-diphenylphosphinyl amide and subsequent intramolecular cyclization to form β-hydroxy-γ-lactams, in a single efficient operation (Table 8, eq 26). Various dimethylacetamide-derived γ-amino-β-hydroxy amides (R = H) undergo cyclization in 5 min at 150 °C (condition A) to afford the corresponding γ-substituted β-hydroxy-γ-lactams in excellent yields and with retention of stereochemistry (entries 1−4). By decreasing the reaction temperature (condition B), the cyclization of 2-furyl amide **118** can be obtained without decomposition (entries 5 and 6). The α-methyl substituted γ-amino-β-hydroxy amide (**119**) provides the desired α-methyl-γ-lactam (**127**) in high yield with the higher temperature conditions (A), but with inversion of stereochemistry at the α-position (entry 7). The lower temperature conditions (B) provide the corresponding α-substituted β-hydroxy-γ-lactams in excellent yield with stereochemical retention (entries 8−10).

Our next goal was to apply the auxiliary controlled process to control the absolute stereochemistry in the synthesis of highly substituted β-hydroxy-γ-lactams (Table 9, eq 27). The use of chiral acetamide **84** in the homoenolate reaction sequence, with *N*-diphenylphosphinyl imine **112** as the electrophile, provides γ-lactam **124**, albeit with no absolute stereochemical control (entry 1). γ-Amino-β-hydroxy amide intermediate **130** was not isolated for these initial selectivity studies to ensure that enantioselectivity of γ-lactam **124** was not augmented due to inexact recovery of both diastereomers of amide **130** during the purification process. Conducting the experiment again with chiral amide **84**, this time with the optimized conditions requiring "equilibration" at 0 °C following the addition to acylsilane **52**, and prior to addition of imine **112**,[100] gives moderate enantioselectivity in the formation of **124** (entry 2). Continuing with optimization of this homoenolate process, a similar trend was observed with amide **85** (entries 3 and 4), ultimately providing **124** with high selectivity (87% ee, entry 4).[101] The γ-amino-β-hydroxy amide intermediate (**130**) was also isolated in good yield and high diastereoselectivity.[102] Hydrolysis of this sterically hindered oxazolidine auxiliary typically requires forcing conditions (refluxing 6 M H_2SO_4 in AcOH). With our products, hydrolysis of the oxazolidine under these conditions has led to elimination of the β-hydroxy functionality. The microwave irradiation protocol presented represents a more mild (3 M HCl in THF) and efficient removal of this auxiliary.

Mechanistic Details. The general mechanism for the enolate addition to acylsilanes presumably proceeds through a Brook rearrangement-mediated pathway (Scheme 4, eq 28). Enolate formation from dimethylacetamide (**51**) with LDA followed by addition to the acylsilane (**52**) provides lithium-alkoxide intermediate **131**. This intermediate then undergoes a 1,2-silyl migration (Brook rearrangement) to provide active carbanion

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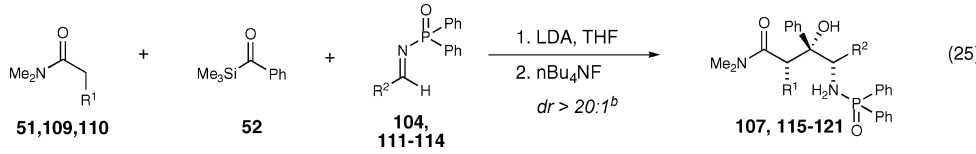
(99) Relative stereochemistry of **128** determined by ^{1}H NOE NMR spectroscopy, and further assignments were made by analogy.
(100) See experimental section and Supporting Information for details.
(101) Absolute stereochemistry of **124** determined by X-ray crystallography of the 4-bromobenzoyl imide of **124,** and further assignments were made by analogy. See Supporting Information for details.
(102) Enantiomeric excess determined by HPLC analysis (chiral stationary phase) and absolute configuration determined by X-ray crystallography. See Supporting Information for details.

Table 7. Synthesis of γ-Hydroxy Amides[a]

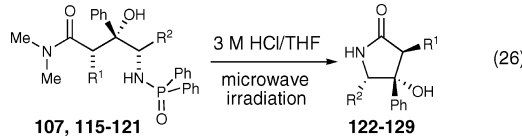


51,109,110 + 52 + 104, 111-114 → 107, 115-121

entry	amide	imine	product	yield (%)	entry	amide	imine	product	yield (%)
1	**51** R^1=H	**104**	**107**	74	5	**51**	**114**	**118**	80
2	**51**	**111**	**115**	71	6	**109** R^1=Me	**104**	**119**	84
3	**51**	**112**	**116**	70	7	**109**	**112**	**120**	78
4	**51**	**113**	**117**	71	8	**110** R^1=CH$_2$Ph	**104**	**121**	75

[a] Acylsilane and electrophile added to a 0.1 M enolate solution in THF at −78 °C. Silyl ether products treated with *n*-Bu$_4$NF in THF prior to purification. [b] Determined by ^{1}H NMR spectroscopy.

Table 8. γ-Amino-β-hydroxy Amides[a]



107, 115-121 → 122-129

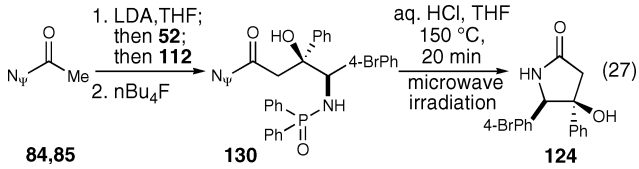
entry	amide	conditions[b]	product	yield (%)	dr[c]	entry	amide	conditions[b]	product	yield (%)	dr[c]
1	**107**	A	**122**	98	>20:1	5	**118**	A	**126**	0[d]	—
2	**115**	A	**123**	97	>20:1	6		B		97	>20:1
3	**116**	A	**124**	93	>20:1	7	**119**	A	**127**	92	1:4
4	**117**	A	**125**	94	>20:1	8		B		96	>20:1
						9	**120**	B	**128**	98	>20:1
						10	**121**	B	**129**	90	>20:1

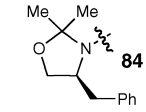
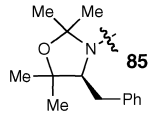
[a] A 0.1 M solution of the amide in THF/3 M aqueous HCl was heated utilizing microwave irradiation. [b] Condition *A* = 150 °C for 5 min (1:2 THF/3 M aqueous HCl); Condition *B* = 70 °C for 10 min (1:2 THF/3 M aqueous HCl). [c] Determined by ^{1}H NMR spectroscopy. [d] Decomposition.

intermediate **132**. Suitable electron stabilizing functionality (aryl, carboxylate) is needed adjacent to this carbanion to perturb the equilibrium to favor carbanion **132**. In this example, addition of carbanion **132** to benzylbromide proceeds to give β-hydroxy amide **53**, following desilylation.

The general mechanism can be applied to explain the diastereoselective homoenolate additions to imines (Scheme 5, eq 29). The proposed mechanism involves the diastereoselective addition of the *Z*-enolate of amide **133** to acylsilane **52** and subsequent stereospecific 1,2-Brook rearrangement to give

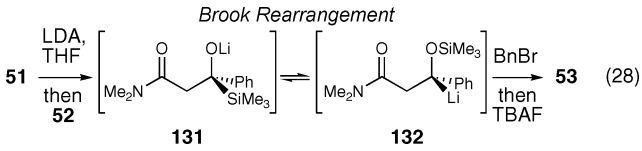
Table 9. Enantioenriched β-Hydroxy-γ-Lactams[a]



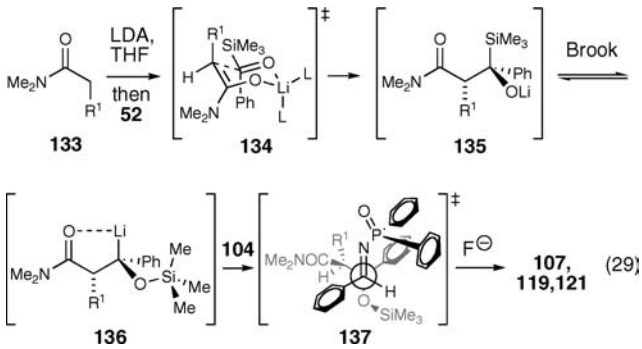
			130		124	
entry	N_Ψ	T (°C)	yield (%)	dr[b]	yield (%)	ee[c]
1	 84	−78	—	—	—	0
2		0[d]	—	—	—	34
3	 85	−78	—	—	—	23
4		0[d]	68	14:1	92(63)[e]	87

[a] See Tables 6 and 5 for reaction details. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis. [d] Brief equilibration time at 0 °C following consumption of **52**. See Supporting Information for details. [e] 92% yield from **130**, 63% from **85**.

Scheme 4. General Mechanism



Scheme 5. Diastereoselective Addition to Imines



internally coordinated carbanion intermediate **136**. Electrophilic approach of imine **104** then occurs by open transition-state **137**, at an orientation that alleviates nonbonding interactions between the *N*-diphenylphosphinyl group of the imine and the silyloxy group of the homoenolate, to yield the γ-amino-β-hydroxy amide (**107,119,121**), with higher diastereoselectivity. The overall process generates up to three contiguous stereogenic centers in a single operation with a high degree of control.

On the basis of the known relationship of temperature to diastereoselectivity and the current understanding of 1,2-silyl migrations, we have proposed a reaction pathway that accounts for the observed stereochemistry with chiral amide **85** (Scheme 6, eq 30). The current model for diastereoselection involves enolate addition to acylsilane **52** through Zimmerman−Traxler transition state **138**, minimizing nonbonding interactions between the trimethylsilyl group and the auxiliary. This initial enolate addition is the proposed source of the observed 3:1 ratio of products under kinetic control (−78 °C). For this model, it is assumed that there is no rotation about the nitrogen and carbonyl carbon bond given the high energy barrier for this process. Subsequent stereospecific Brook rearrangement (**140**)[3] rapidly occurs to give internally coordinated diastereomers **86** (major) and **141** (minor). Strongly coordinating additives (e.g., DMPU, HMPA) reduce the diastereoselectivity and yield of the reactions, supporting the proposed internal coordination of the amide carbonyl to the β-organolithium substituent. Furthermore, *O*-alkylation is not observed when the reactions are conducted at −78 or 0 °C, suggesting that the Brook rearrangement occurs rapidly to generate carbanions **86/141**. The inverse relationship of selectivity to temperature suggests that performing the reaction under thermodynamically controlled conditions (0 °C) facilitates interconversion of **86/141** prior to alkylation. Since carbanion **141** is destabilized by nonbonding interactions between the trimethylsilylether and benzyl group of the auxiliary, the reaction preferentially proceeds via thermodynamically favored intermediate **86**, to give the β-hydroxy amide (**130**), followed by desilylation.

Conclusions

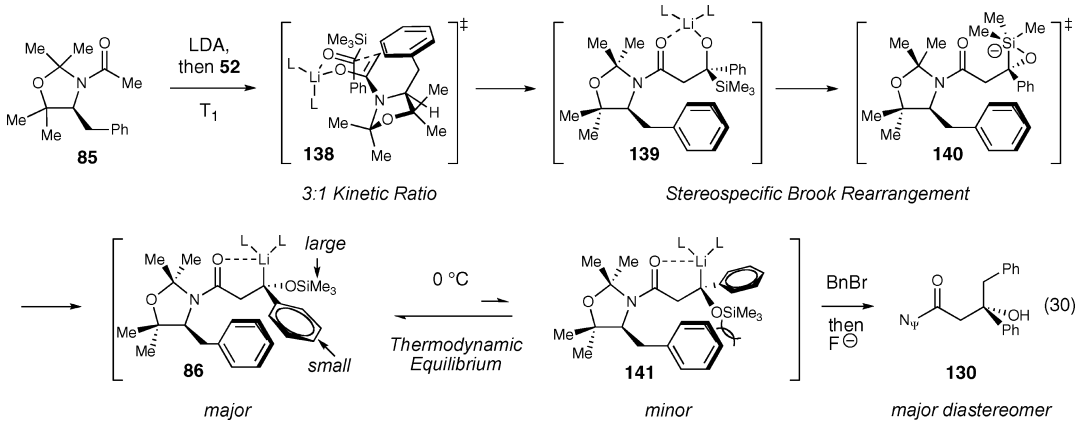
A new strategy has been developed for the synthesis of tertiary β-hydroxy amides using β-silyloxy homoenolates accessed from amide enolates and acylsilanes. These unconventional nucleophilic species undergo addition to alkyl halides, aldehydes, ketones, and imines. Amide enolates strongly favor *C*-alkylation of the homoenolate over *O*-alkylation and avoid the formation of alkoxy cyclopropane products. Homoenolate addition to imines provides the γ-amino-β-hydroxy amides in a single flask operation with good yields and excellent selectivity for each newly formed stereocenter. The use of microwave irradiation under acidic conditions promotes hydrolysis and cyclization to form the corresponding γ-lactams in excellent yields with retention of stereochemistry. The utilization of chiral acetamides allows for stereochemical control of the tertiary alcohol and subsequent γ-lactam products. This novel approach employing acylsilanes and the power of the 1,2-Brook rearrangement to access synthetically useful homoenolate reactivity is an addition to the increasing number of *Umpolung* strategies that lead to potentially useful classes of molecules.

Experimental Section

General Procedure for the Synthesis of β-Hydroxy Amides.[103] To a flame-dried flask under a positive pressure of nitrogen was added THF (2 mL) and diisopropylamine (0.79 mmol). The solution was cooled to −78 °C and *n*-butyllithium (1.5 M in hexanes, 0.73 mmol) was added by syringe. The reaction was warmed to 0 °C, stirred for 30 min, and then recooled to −78 °C. Dimethylacetamide (0.84 mmol) was added dropwise to the LDA solution, and the reaction mixture was warmed to 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was cooled to −78 °C and a −78 °C solution of the acylsilane (0.56 mmol) in THF (0.5 mL) was added via cannula. The acylsilane delivery flask was rinsed with an additional portion of THF (0.5 mL), and this rinse was transferred to the reaction flask. The resulting homogeneous solution was stirred for 30 min, after which time a solution of the electrophile (1.68 mmol) in THF (0.5 mL) was added via cannula, again rinsing the delivery flask with an additional portion of THF (0.5 mL). The reaction mixture was warmed slowly to ambient temperature over 6 h, and then stirred for an additional 6 h at the same temperature. The reaction was quenched by the addition of saturated aqueous ammonium chloride and extracted with ethyl acetate (×3). The

(103) See Supporting Information for revised experimental details as they pertain to the addition to imines.

Scheme 6. Auxiliary Controlled Diastereoselective Reactions



combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The unpurified silyl ether product was dissolved in THF (2 mL). To this solution was added tetrabutylammonium fluoride (1.0 M in THF, 1.68 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was quenched by the addition of water, extracted with diethyl ether (×3), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel.

General Procedure for the Preparation of β-Hydroxy-γ-Lactams. To a solution of the γ-amino-β-hydroxy amide (0.20 mmol) in THF (1.0 mL) was added 3 M aqueous HCl (1.0 mL). The resulting mixture was stirred for 2 min before heating at 150 °C (or 70 °C) in the microwave for 5−20 min. The resulting mixture was cooled to ambient temperature, slowly neutralized with solid sodium bicarbonate (until evolution of gas ceases), and extracted with dichloromethane. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel.

General Procedure for the Synthesis of β-Hydroxy Amides with Chiral Acetamides.[79] To a mixture of calcium sulfate (100 mg, finely ground with a mortar and pestle, and heated in a beaker at 160 °C for at least 48 h prior to use) and THF (0.5 mL) was added diisopropylamine (0.37 mmol). The resulting solution was cooled to −78 °C, and *n*-butyllithium (1.6 M in hexanes, 0.37 mmol) was added dropwise by syringe. The reaction mixture was warmed to 0 °C, stirred for 30 min, then cooled to −78 °C. To this solution of LDA was added a −78 °C solution of **85** (0.37 mmol) in THF (0.8 mL + 0.2 mL rinse) dropwise by cannulation. The resulting reaction mixture was warmed to 0 °C and stirred for 1 h. To the resulting reaction mixture was added a cooled to 0 °C solution of **52** (0.28 mmol) in THF (0.3 mL) in one portion by cannula, again rinsing the delivery flask with an additional portion of THF (0.2 mL). The resulting reaction mixture was stirred at 0 °C for 15 min, monitoring for consumption of **52** by TLC (R_f = 0.67 (10:90 ethyl acetate/hexanes)). The electrophile (0.84 mmol) was added in one portion by syringe and the reaction mixture was warmed slowly to ambient temperature over 8 h followed by stirring for an additional 4 h at ambient temperature. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (2 mL) and extracted with ethyl acetate (×3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The unpurified silyl ether product was dissolved in THF (2 mL) and treated with tetrabutylammonium fluoride (1.0 M in THF, 0.84 mmol). After 30 min, the reaction mixture was quenched by the addition of water, extracted with ethyl acetate (×3), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel.

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Supporting Information Available: Detailed experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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