The Aza-[2,3]-Wittig Sigmatropic Rearrangement of Acyclic Amines: Scope and Limitations of Silicon Assistance

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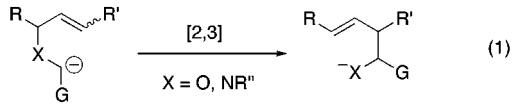
The inclusion of a C-2 trialkylsilyl substituent into allylic amine precursors allows the base-induced aza-[2,3]-Wittig sigmatropic rearrangement to proceed in excellent yield and diastereoselectivity. The rearrangement precursors require a carbonyl-based nitrogen protecting group that must be stable to the excess of strong base required for the reaction. The *N*-Boc and *N*-benzoyl group are very good at stabilizing the product anion and initiating deprotonation. The migrating groups (G) need to stabilize the intial anion by resonance and require G-CH_3 pK_a > 22 in order for the initial anion to be reactive enough for rearrangement. Products **7**, **20b**−**d**,**f**,**g**, and **23** are formed with high (10−20:1) anti diastereoselectivity. Product **23** containing the morpholine amide group is useful for preparing other carbonyl derivatives.

Introduction

Since the first observation of the [2,3]-Wittig sigmatropic rearrangement (eq 1, X = O) in only 1960,[1] this rearrangement has developed into a synthetically powerful and highly stereoselective carbanion rearrangement.[2] Despite the seemingly trivial replacement of oxygen for nitrogen, the aza analogue (eq 1, X = N) remained under developed until the beginning of the 1990s.



(1)

When trying to prepare the 3-lithio derivative of 1-benzyl-4-vinyl-2-azetidinone, Durst et al. characterized the first example of an aza-[2,3]-Wittig rearrangement and verified that the driving force for the rearrangement was the relief of ring strain in going from a four- to a seven-membered ring.[3] Over 20 years later, this seminal observation was capitalized upon first by Somfai[4] and then Coldham[5] by the use of N-substituted vinylaziridines as rearrangement precursors. These facile rearrangements were again driven by the relief of ring strain, this time in going from an aziridine to a tetrahydropyridine. The anionic aza-[2,3]-Wittig rearrangement of acyclic precursors, which do not have a latent thermodynamic driving force, have proven to be considerably more difficult. Initial attempts were thwarted by the competing [1,2] rearrangement pathway,[6] although the most successful attempt verified that the aza-[2,3]-Wittig rearrangement proceeds with inversion of configuration at the lithium-bearing carbon,[7] in accord with precedent in the oxygen series.[8] We characterized the first acyclic example of the aza-[2,3]-Wittig sigmatropic rearrangement, and from the outset argued that the resulting aza anion from the rearrangement needed to be stabilized in some way to provide some thermodynamic driving force for the reaction (eq 2, X = H).[9] The Boc protecting group seemed to achieve the best results, although Manabe also showed the efficacy of the tetramethylphosphordiamide group, with similar substrates, in terms of yield.[10] Our first example proved to be very limited, and it was only after incorporating an anion stabilizing group at the C-2 position of our substrate, to try and stabilize the transition state and dictate diastereoselection, did the reaction become more versatile, high yielding and diastereoselective (eq 2, X = $SiMe_3$).[11] Among the anion stabilizing groups surveyed,[11b] the silyl group provided the best rate acceleration and diastereocontrol in this rearrangement.

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(7) Gawley, R. E.; Zhang, Q.; Campagna, S. *J. Am. Chem. Soc.* **1995**, *117*, 11817.
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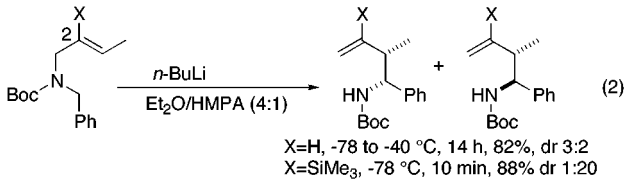
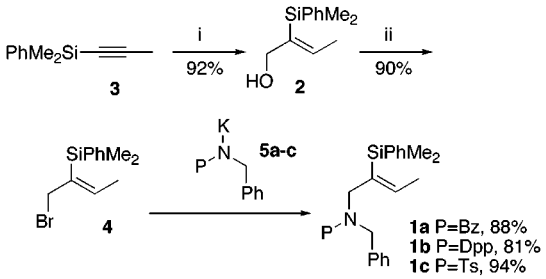


We believe the silyl substituent stabilizes α-negative charge, which develops at the central, C-2 vinyl carbon atom, during the rearrangement. Theoretical calculations of the oxy-[2,3]-Wittig process support this,[12] although other stereoelectronic arguments could apply.[13] We have also found that the phenyldimethylsilyl substituent allows facile removal of the silicon from the product terminal alkene with a combination of *t*-BuOK−18-crown-6−TBAF.[14] In this paper, we wish to report the scope and limitations of the silicon-assisted aza-[2,3]-Wittig sigmatropic rearrangement of acyclic allylic amines.

Results and Discussion

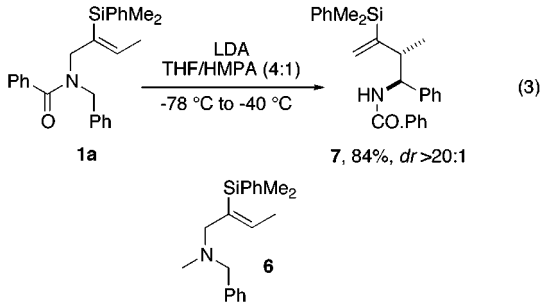
The Nature of the Nitrogen Protecting Group. A series of aza-[2,3]-Wittig precursors **1a**−**c**, based upon our initial precursor,[9] but differing only by the choice of nitrogen protecting group, were prepared according to Scheme 1. We now use a convergent synthesis for our precursors instead of the linear route reported earlier.[11a,b] Diastereomerically pure allylic alcohol **2** was prepared by hydroalumination[15] of phenyldimethylsilylpropyne (**3**),[16] formation of the *ate* complex with MeLi, and addition of paraformaldehyde. Treatment of **2** with a preformed suspension of triphenylphosphine dibromide and triethylamine in CH_2Cl_2 gave the corresponding allylic bromide **4**, which upon addition of the potassium anion of the migrating group **5a**−**c**[17] furnished the rearrangement precursors with protecting groups *N*-benzoyl **1a**,[18] *N*-diphenylphosphinyl **1b**,[19] and *N*-tosyl **1c**.

Scheme 1[a]



[a] Reagents: (i) DIBAL, MeLi, (HCHO)*n*; (ii) Br_2, Ph_3P, Et_3N.

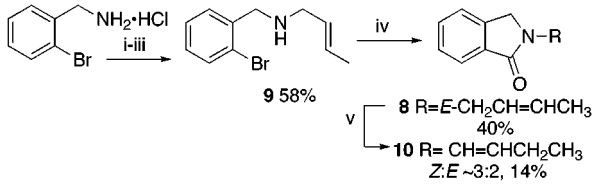
The aza-[2,3]-Wittig rearrangement precursors **1a**−**c** were subjected to our standard conditions for rearrangement. Bases *n*-BuLi and LDA were both explored with addition at −78 °C in the solvent mixture THF/HMPA (4:1) and then stirring at −40 °C overnight. Only the *N*-benzoyl analogue **1a** reacted cleanly with LDA (eq 3) to give rearranged material in 84% yield with a >20:1 diastereomeric ratio as judged by ^1H NMR. This result is very similar to the rearrangement of the corresponding *N*-Boc material. The *N*-diphenylphosphinyl **1b** and *N*-tosyl **1c** analogues both decomposed under either of the basic reaction conditions. Attempted rearrangement of a precursor possessing a methyl group instead of a protecting group led to complete recovery of starting material.[20]



From our work it would appear that a carbonyl-based protecting group on nitrogen, inert to the basic reaction conditions and which can provide some degree of stabilization of the product anion, is essential for a successful rearrangement.

As an extension to this methodology we speculated whether we could rearrange cyclic substrates where the protecting group and migrating group were tethered, as in compounds such as **8** (Scheme 2). This could lead to the functionalization of certain nitrogen heterocycles. The synthesis of *N*-benzylisoindolinone (**8**, R = Bn) is known and proceeds via the carbonylative cyclization of *N*-benzyl-2-bromobenzylamine using palladium(II) acetate catalysis.[21] Cyclization of the corresponding primary amine is low yielding, so we hoped that the but-2(*E*)-enyl group could be introduced in place of the benzyl group in the documented synthesis of *N*-benzyl-2-bromobenzylamine. It was necessary to prepare the required secondary amine using a protection-alkylation-deprotection route. Protection of 2-bromobenzylamine as its trifluoroacetyl derivative, alkylation with crotyl bromide, and deprotection[22] gave *N*-but-2(*E*)-enyl-2-bromobenzylamine (**9**) in 58% overall yield (Scheme 2). An unoptimized carbonylative cyclization furnished **8**, which when treated with *t*-BuLi, in an attempt to initiate an aza-[2,3]-Wittig rearrangement, gave only the enamine **10** as a mixture of isomers and recovered starting material (55%). This suggests that although the benzylic position is more acidic, a complex-induced proximity effect[23] involving the carbonyl group has overidden the natural thermodynamic bias of the precursor to give kinetic deprotonation. This nonproductive deprotonation upon quenching leads to double bond

Scheme 2[a]



[a] Reagents: (i) aq NaOH; $(CF_3CO)_2O$, Py; (ii) KH, (*E*)-$CH_3CH{=}CHCH_2Br$; (iii) $LiOH{\cdot}H_2O$; (iv) CO, $Pd(OAc)_2$, *n*-Bu_3N; (v) *t*-BuLi.

(15) Metz, P.; Linz, C. *Tetrahedron Lett.* **1994**, *50*, 3951.
(16) Mao, S. S. H.; Liu, F.-Q.; Tilley, T. D. *J. Am. Chem. Soc.* **1998**, *120*, 1193.
(17) For preparation of **5a**, see: Yokomatsu, T.; Arakawa, A.; Shibuya, S. *J. Org. Chem.* **1994**, *59*, 3506. For preparation of **5b**, see: Coulton, S.; Moore, G. A.; Ramage, R. *Tetrahedron Lett.* **1976**, 4005. For preparation of **5c**, see: Lerch, U.; Moffatt, J. G. *J. Org. Chem.* **1971**, *36*, 3686.
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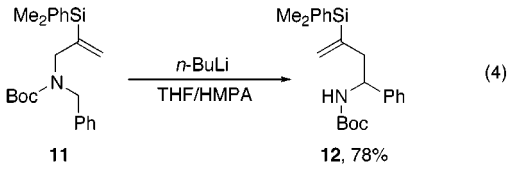
(19) Osborn, H. M. I.; Sweeney, J. B. *Synlett* **1994**, 145.

migration and starting material. This result suggests that a *N*-carbonyl protecting group, in addition to providing stabilization of the product aza anion, also plays an important part in the deprotonation step in aza-[2,3]-Wittig sigmatropic rearrangements.

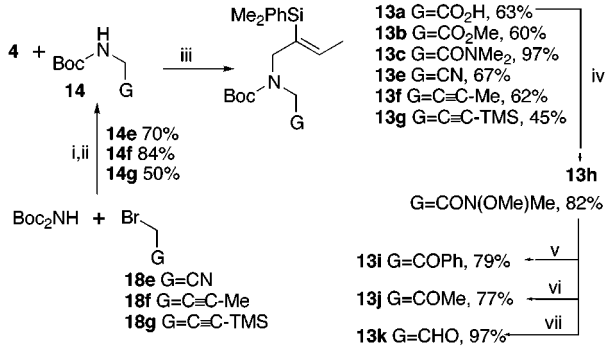
The Configuration and Substitution of the Alkene. Our standard substrate during the development of this methodology was normally an *E*(C)-alkene, and we have shown that primary or secondary alkyl substituents give good rearrangements in terms of yield and diastereoselection.[11a] The *Z*(C)-alkenes are much more difficult to synthesize, but we have shown that rearrangement of *N*-Boc-*N*-(2-trimethylsilylpent-2(*E*)-enyl)-benzylamine gave rearranged product in 62% yield with a diminished diastereoselection of 3:1 in favor of the syn diastereoisomer.[11d] According to our transition-state model, efficient access to the alternate syn diastereoisomer, from the *Z*(C)-alkene, is complicated by conflicting steric effects.[11d] However, similar types of compounds possessing the relative stereochemistry this methodology finds difficult to deliver can be prepared using Kazmaier's [3,3]-sigmatropic rearrangement of glycine ester enolates.[24] To complete this study, we have investigated the [2,3]-Wittig rearrangement of terminal alkene (**11**) rearrangement precursor. The synthesis of **11** followed a route analogous to that described for **1**, but started from phenyldimethylsilylethyne, in 52% overall yield. Rearrangement of the terminal alkene precursor **11** proceeded smoothly in 78% yield (eq 4). These results show that the rearrangement works well for terminal alkenes and *E*(C)-alkenes to give anti diastereomers such as **7**.



(4)

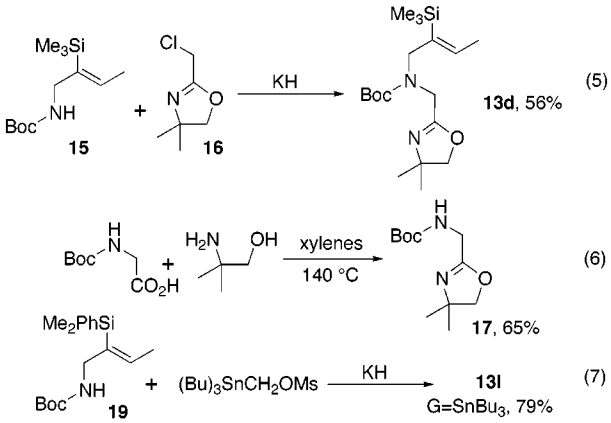
The Migrating Group. In our preliminary studies,[9] a phenyl substituent on the migrating group was optimal. Additional substituents on the phenyl group led to decreased yields with no improvement in diastereoselectivity.[25] Other more common activating substituents, upon deprotonation, were dormant toward rearrangement, which verified that the anion at the migrating carbon had to be as reactive as possible in these simple systems.[6c,9] Our main goal in this project was to be able to synthesize unnatural amino acids, which meant that the migrating groups' substituent had to be convertible to a carboxyl group, which we have demonstrated for the phenyl substituent.[9] The inclusion of a silyl group at C-2 greatly accelerated the rate of the reaction,[11] and we have subsequently explored the range of activating substituents on the migrating group which allow the aza-[2,3]-Wittig rearrangement to proceed.

Scheme 3[a]



[a] Reagents: (i) G = CN, KH; G = C≡C-CH_3 or C≡C-TMS, from corresponding OH compounds with Br_2, PPh_3, DMF then K_2CO_3 and Boc_2NH; (ii) TFA; (iii) KH; (iv) Me(MeO)NH·HCl, DIEA, DMAP, DCC; (v) PhMgCl; (vi) MeMgBr; (vii) $LiAlH_4$.

In the first cases we looked at simple carboxyl derivatives **13a**−**d**. Precursors **13a**−**c** were all derived from the alkylation of a glycine derivative **14** with **4** (Scheme 3). The oxazoline derivative **13d** was synthesized from the alkylation of *N*-Boc-2-(trimethylsilyl)but-2(*Z*)-enylamine (**15**)[11a] with 2-chloromethyl-4,4-dimethyl-1,3-oxazoline (**16**, eq 5),[26] although we have prepared similar compounds from the alkylation of **17**, itself derived from the condensation of *N*-Boc-glycine and 2-amino-2-methylpropan-1-ol (eq 6). Alternative anion stabilizing groups **13e**−**g** were synthesized in a manner similar to that for **13a**−**c**. The amido nucleophiles were derived from monodeprotection of the product from alkylation of di-*tert*-butylimidodicarbonate[27] with suitably activated methylene derivatives **18e**−**g** (Scheme 3).[28] It was not possible to prepare the corresponding ketone/aldehyde derivatives in an analogous fashion, so **13i**−**k** were prepared from the Weinreb amide **13h**, itself derived from **13a**. To generate a totally resonance unstabilized anion we required the tri-*n*-butyltin derivative **13l**, which was prepared via the alkylation of **19**[11b] with tributylstannylmethyl methanesulfonate (eq 7).[29]



Rearrangement of precursors **13a**−**l** was investigated by treatment with strong bases *n*-BuLi or LDA in THF with HMPA cosolvent at −78 °C and warming to −40 °C or room temperature for 14 h (eq 8). The amide base was

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(28) Walters, M. A.; Hoem, A. B. *J. Org. Chem.* **1994**, *59*, 2645.
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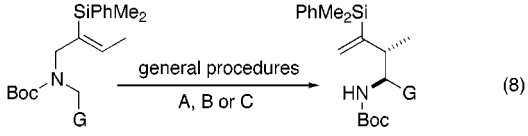
Table 1. Scope of Substituents G on Aza-[2,3]-Wittig Rearrangement



(8)

13a-l **20a-l**

precursor	equiv of base[a]	G	conditions[b]	% yield[c] (dr)[d]
13a	3.5	CO_2H	B	15 (>20:1)
13b	1.9	CO_2Me	B	70 (>20:1)
13c	1.9	$CONMe_2$	C	71 (>20:1)
13d	1.2	oxazoline	A	70[e] (>20:1)
13e	1.5	CN	B[f]	67 (3:1)
13f	1.6	C≡C-Me	A[f,g]	43 (10:1)
13g	1.5	C≡C-TMS	B[f]	77 (10:1)
13h	1.3	CON(OMe)Me	B/C	20;[h] 22[i]
13i	2.0	COPh	B/C	100[i]
13j	1.3	COMe	B/C	70[i]
13k	1.2	CHO	B/C	0
13l	1.5	$SnBu_3$	A[j]	92[k]

[a] Optimal equivalents. [b] General procedures: (A) *n*-BuLi, THF/HMPA (4:1), −78 to −40 °C, 14 h; (B) as A, but with LDA; (C) as B, but warming to room temperature, 3 h. [c] Isolated yield. [d] Ratios of unpurified products determined by ^{1}H NMR. [e] In addition recovered **13d**, 18%. [f] Reaction quenched with pH 7 buffer instead of standard MeOH. [g] ^{t}BuLi. [h] De-*N*-methoxylated precursor **13h**. [i] Starting material. [j] No HMPA, 2 h. [k] Protodestannylated **13l**.

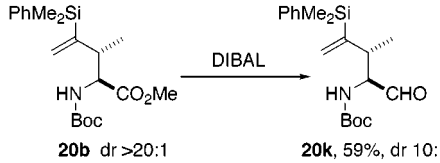
necessary for activating groups G, which were inherently reactive toward *n*-BuLi. Table 1 summarizes the results and gives the optimum reaction conditions for the most successful rearrangements.

Rearrangement of the dianion of **13a** was not particularly successful under any of the reaction conditions, although the small amount of product formed under general procedure A was essentially one diastereoisomer. The simple ester and amide function (**13b** and **13c**, respectively) rearranged in high yield and excellent diastereoselectivity. The major diastereoisomer was assigned the structure **20** based upon our transition-state model and by analogy to our previous rearrangements.[11] Additional proof was provided by a single-crystal X-ray structure determination of the major diastereoisomer of **20c**.[30] Rearrangement of the oxazoline substituent **13d** proceeded in good yield and excellent diastereoselectivity, but this product is extremely sensitive to epimerization by acid or base and could not be purified by silica gel chromatography. Cyano and acetylene functions all rearranged in moderate to good yields, but with varying levels of diastereoselection. The small linear cyano group of **13e** gave a diastereomeric ratio of 3:1, compared to ∼10:1 for the alkynyl substrates **13f** and **13g**, which are of comparable size. It has been documented in related oxy-[2,3]-Wittig rearrangement chemistry that the cyano group can interact with the developing negative charge at C-2 in the pericyclic transition state.[12] This type of interaction would electronically favor the alternate diastereomer to that drawn for **20**. The moderate yield for **13f** can be attributed to the basic reaction conditions not being wholly compatible with propargylic protons. Surprisingly, the Weinreb amide analogue **13h** would not rearrange under either set of reaction conditions. Aside from recovered starting material, only de-*N*-methoxylated precursor was isolated in 20% yield. Recovered starting material for attempted rearrangements of **13i** and **13j** suggested that the anions generated in these particular substrates were too stable for rearrangement. Aldehyde **13k** was too sensitive and was destroyed under the basic rearrangement conditions. Transmetalation of **13l** with *n*-BuLi gave protodestannylated material at −78 °C. Upon warming to −40 °C for 3 h only [1,2] migration of the *tert*-butoxycarbonyl group could be detected (15%) along with a trace of protodestannylated material (<5%) and degradation.

In this survey, HMPA was essential for the highest yield of rearrangement. We also found that the optimal amount of base varied with substrate, but in general excess base did not appear to be detrimental to the reaction yield or diastereoselection. Presumably the aza anion in the product protects the α-center from deprotonation/epimerisation.[31]

The results from the rearrangements with different activating groups G define a level of stabilization for the carbanion above which there is no rearrangement. From comparing the pK_a data of G-CH_3 compounds and assuming that the effect of the NBoc(R) substituent for all of the precursors **13** is identical, anion stabilizing groups G that exert a pK_a of less than about 22 on an adjacent methyl group do not facilitate the rearrangement.[32] This can be explained by the carbanion being too stable in these cases. However there remains an anomally that the unstabilized anion (**13l**, G = $SnBu_3$) did not rearrange.

The failure of the carbonyl precursors **13i**−**k** to rearrange was felt to be a limitation to the potential synthetic usefulness of these products. If the Weinreb amide derivative **13h** had rearranged then standard addition of an alkyl group or hydride would have furnished the required carbonyl derivative of the product. However, methyl ester **20b** can be reduced with DIBAL to give the corresponding aldehyde **20k** (eq 9) in 59% yield with a small erosion in diastereomeric ratio (>20:1 to 10:1)



(9)

20b dr >20:1 **20k**, 59%, dr 10:1

To access the corresponding keto products, we sought a more robust, but similar, activating substituent to the Weinreb amide. Morpholine amides have been introduced as a cheaper alternative to Weinreb amides for large-scale preparations of ketones from acyl derivatives.[33] The morpholine amide rearrangement precursor **21** was prepared by the standard method from the ester **14b**. Heating **14b** in anhydrous morpholine for 3 days at 80 °C gave **22**, which could be alkylated with **4** in 59% overall yield (Scheme 4). Treatment of this substrate under our normal rearrangement conditions using *n*-BuLi or LDA resulted in low yields of product. We found that moderately yielding reactions could sometimes give

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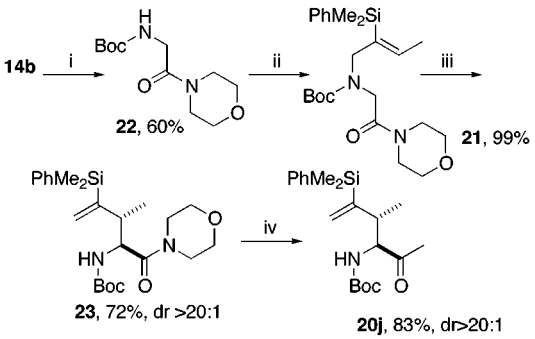
(31) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624, (see especially pp 1640−6).

(32) We know G = ester rearranges and that simple esters have pK_a(H_2O) ∼24. G = carbonyl does not rearrange, and simple ketones/aldehydes have pK_a(H_2O) ∼20 (for pK_a values, see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456 and references therein). So we make the assumption that the line of reactivity vs stability is somewhere between these two values.

(33) Martin, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett* **1997**, 1414.

Scheme 4[a]



[a] Reagents: (i) morpholine 80 °C, 3 d; (ii) KH, **4**; (iii) KH, 18-C-6; (iv) MeLi.

higher yields if a KH/18-crown-6 combination in THF was used. For example, treatment of **13c** with KH (2.4 equiv), 18-C-6 (0.5 equiv) in THF at 0 °C, with warming to room temperature for 2 h, gave a 94% (dr >20:1) of rearranged product **20c** (cf. **13c** plus LDA, 71% (dr > 20:1), Table 1). Rearrangement of **21** using KH/18-C-6 furnished the rearranged product **23** in 72% yield with essentially complete diastereoselection (>20:1 by ^{1}H NMR). Treatment with a representative alkyllithium, methyllithium, gave the methyl ketone **20j** in 83% yield with no erosion in diastereoselection.

Summary. Building upon our findings that a C-2 trialkylsilyl substituent assists the aza-[2,3]-Wittig sigmatropic rearrangement of certain acyclic allylic amines,[11] we have now determined that the nitrogen protecting group in these systems should be carbonyl based and resistant to the basic conditions employed for this rearrangement. The protecting group is implicated in the initial deprotonation of the rearrangement precursor and stabilization of the product aza anion. The rearrangement works well for terminal alkenes and primary and secondary alkyl substituted *E*(C) alkenes. The nature of the migrating group (G) is also important. A migrating group (G) which stabilizes the initial carbanion by resonance is favorable, as G = carboxylate anion (**13a**) and unstabilized carbanions derived from transmetalation of tri-*n*-butylstannane **13l** were ineffective in the rearrangement. We also propose that the initial carbanion should not be too stabilized. Migrating groups with G-CH_3 pK_a < 22 do not rearrange. Excess base (1.2−2.0 equiv) is optimal for high yields and a selection from *n*-BuLi, *t*-BuLi, LDA, or KH should be made according to the substrate and optimization. The lithium bases require HMPA as a cosolvent (20%) for good yields, but use of KH requires only 18-crown-6 as an additive. We believe these additives make the initial anions more reactive by sequestering the metal counterions. In the case of *E*(C) alkenes, anti diastereoisomers (**7**, **20**, and **23**) are formed with good stereocontrol (10−20:1), except G = CN (**13e**), which gives a diastereomeric ratio of 3:1, probably due to deleterious stereoelectronic interactions.[12] The products should be useful as building blocks in the synthesis of non proteinogenic amico acids and other nitrogen containg target molecules. Products containing the morpholine amide group (**23**) could be useful for synthesising other carbonyl derivatives not accessible from the rearrangement of their respective precursors. Enantioselective studies and applications to target synthesis are in progress and will be reported in due course.

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Supporting Information Available: Syntheses and spectroscopic data of compounds **1**, **2**−**4**, **7**−**13**, **14e**−**g**, **17**, **18**, **20a**−**g**,**j**,**k**, **23**, including ^{1}H NMR spectra of compounds **1a**−**c**, **4**, **7**, **8**, **10**−**12**, **13f**,**g**,**i**−**l**, **20a**,**b**,**e**−**g**,**j**,**k**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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