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Carbamoyl Anion Addition to *N*-Sulfinyl Imines: Highly Diastereoselective Synthesis of α-Amino Amides

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Supporting Information

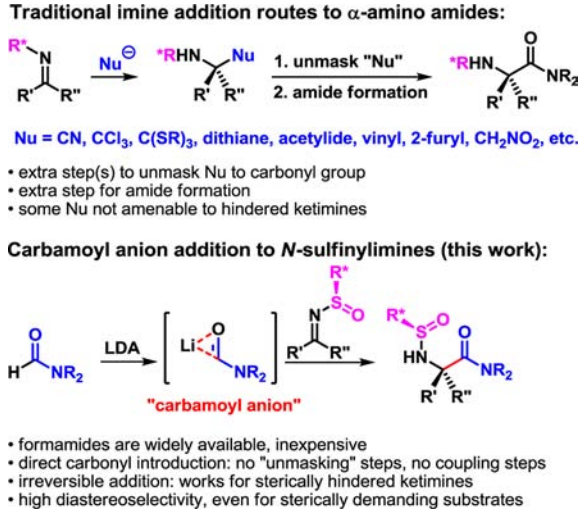
ABSTRACT: Carbamoyl anions, generated from N,N-disubstituted formamides and lithium diisopropylamide, add with high diastereoselectivity to chiral *N*-sulfinyl aldimines and ketimines to provide α-amino amides. The methodology enables the direct introduction of a carbonyl group without the requirement of unmasking steps as with other nucleophiles. The products may be converted to α-amino esters or 1,2-diamines. Iterative application of the reaction enabled the stereoselective synthesis of a dipeptide. Spectroscopic and computational studies support an anion structure with η^2 coordination of lithium by the carbonyl group.

The introduction of carbonyl functionality by umpolung reagents has been extensively explored over the past several decades.[1] The majority of reagents for this purpose require one or more steps to "unmask" the carbonyl group after an initial nucleophilic reaction. Less explored are the true carbonyl anions, in part because of challenges associated with their preparation and their low stability.[2] These species have the advantage of direct introduction of a carbonyl group without the need for subsequent unmasking steps. Carbamoyl anions are among the most stable of the carbonyl anions.[3] The first generation of a carbamoyl anion occurred in 1967 when Schöllkopf and Gerhart treated bis(diethylcarbamoyl)mercury with *n*-BuLi and trapped the purported diethylcarbamoyllithium with carbonyl electrophiles as well as MeI and Bu_3SnCl.[4] In 1973, Banhidai and Schöllkopf demonstrated that carbamoyllithiums can be generated directly from formamides by deprotonation with lithium diisopropylamide (LDA), and the resultant anions can be added to aldehydes and ketones.[5] In the same year, Enders and Seebach reported the analogous reaction of thioformamides to form thiocarbamoyllithiums.[6]

Surprisingly, there have been no reports on the use of carbamoyllithiums in asymmetric reactions, and the addition of carbamoyllithiums to imines has not been reported either.[7] Addition of carbamoyllithiums to chiral imines would provide an attractive asymmetric route to α-amino amides (Scheme 1). As the basic subunit of peptides, α-amino amides are of fundamental importance in biology and chemistry.[8] They are also a common structural feature in many pharmaceutical agents.[9] Their stereocontrolled synthesis has been researched extensively by numerous methods.[10] Protocols based on stereoselective additions to imines offer a convenient avenue for synthesizing structurally diverse chiral α-amino amides.[11] Limitations of the traditional pool of nucleophiles are the requirements for additional steps to unmask the carbonyl synthon and for subsequent amide formation by coupling. In addition, many common nucleophiles (−CN, $-CCl_3$, $-CH_2NO_2$) add reversibly and can give low conversions and/or low stereoselectivities for hindered imine substrates.[12] Ellman's *N*-*tert*-butanesulfinyl (TBS) imines have been shown to be exceptionally versatile chiral imines for the preparation of amines by addition of nucleophiles.[13] The *N*-2,4,6-triisopropylphenylsulfinyl (TIPPS) imines developed by Han and Senanayake have often demonstrated complementary utility as chiral imines.[14] These two classes of *N*-sulfinyl imines therefore seemed to be promising substrates for investigating an asymmetric carbamoyl anion addition. We report herein the highly diastereoselective addition of carbamoyl anions, derived from readily available formamides, to *N*-sulfinyl imines to provide structurally diverse α-amino amides.

Exploratory experiments utilized pivaldehyde-derived TBS imine **1a** and TIPPS imine **1b** as electrophiles and *N*,*N*-

Scheme 1. Conversion of Imines to α-Amino Amides



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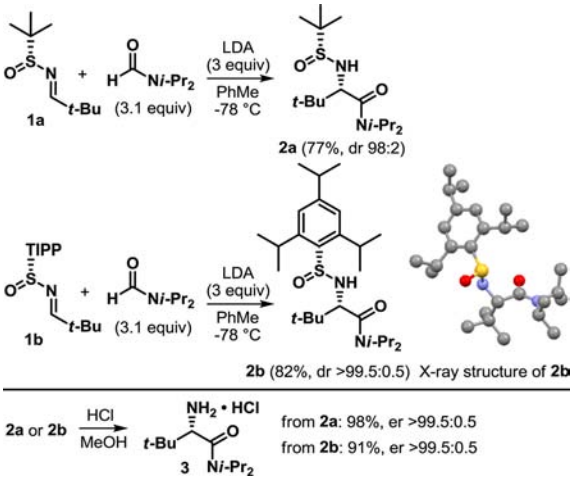
diisopropylformamide as the pronucleophile (Scheme 2). Under optimal conditions, a solution of **1a** and *N*,*N*-diisopropylforma-

Scheme 2. Synthesis of *tert*-Leucine Amides 2a and 2b



mide (3.1 equiv) in toluene cooled to −78 °C was treated with LDA (3 equiv).[15] After 10 min, HPLC analysis indicated the consumption of **1a** and the formation of the α-amino amide product **2a** as a 98:2 mixture of diastereomers. Following workup and chromatographic purification, diastereopure **2a** was isolated in 77% yield. When TIPPS imine **1b** was employed under the same reaction conditions, adduct **2b** was formed in >99.5:<0.5 diastereomeric ratio and isolated in 82% yield. Single-crystal X-ray structure analysis of **2b** confirmed the relative stereochemistry. Sulfinyl deprotection with HCl in MeOH afforded α-amino amide hydrochloride salt **3** in high yield without loss of optical purity. Both **2a** and **2b** gave the same *S* enantiomer of **3**, confirming that the (*R*)-TBS group directed the addition with the same stereochemistry as the (*R*)-TIPPS group. The stereochemistry is consistent with that observed for other organolithium additions to *N*-sulfinyl aldimines and can be explained by an open transition state model.[13,16]

The scope of the carbamoyl anion addition was first explored with sulfinyl aldimines (Table 1). The addition of *N*,*N*-dimethylformamide (DMF) anion to TBS imine **1a** gave amide **4a** with 93:7 diastereoselectivity (entry 1), while the addition to TIPPS imine **1b** proceeded with 98:2 diastereoselectivity (entry 2). The reaction proceeded equally well using dimethylthioformamide (entry 3), furnishing thioamide **5b** in 84% yield with 99:1 diastereoselectivity. Addition of *N*-formylmorpholine was effective (entries 4 and 5), which should prove useful since morpholine amides may undergo controlled organometallic additions to give ketones.[17] The use of enolizable imines with one (entry 6) or two (entry 7) α-protons was possible. In the case of sulfinimine **10**, optimal conversion was obtained when the carbamoyllithium was generated first and the solution of **10** was subsequently added. Reactions of aryl (entries 8−10) and heteroaryl sulfinimines (entries 11 and 12) gave access to aryl glycinamides. In general, the bulky TIPPS auxiliary gave slightly higher diastereoselectivities than the TBS auxiliary.

Organometallic additions to sulfinyl ketimines often proceed with lower selectivity relative to aldimines.[13] Nonetheless, the present reaction worked well for a variety of ketimine substrates (Table 2). The reaction of ketimine **20** (entry 1) with DMF gave **21** in 78% yield with 98:2 diastereoselectivity. The relative stereochemistry of **21** determined by X-ray crystal structure

Table 1. Formamide Addition to *N*-Sulfinyl Aldimines[a]

entry	sulfinimine	formamide	product (yield)[b]	dr[c]
1	**1a** (R = *t*-Bu)		**4a** (X = O, 72%)	93:7
2	**1b** (R = TIPP)		**4b** (X = O, 83%)	98:2
3	**1b** (R = TIPP)		**5b** (X = S, 84%)	99:1
4	**6a** (R = *t*-Bu)		**7a** (76%)	93:7
5	**6b** (R = TIPP)		**7b** (82%)	97:3
6	**8**		**9** (79%)	97:3
7	**10**		**11** (71%)	99:1
8	**12a** (R = *t*-Bu)		**13a** (83%)	90:10
9	**12b** (R = TIPP)		**13b** (77%)	96:4
10	**14**		**15** (78%)	98:2
11	**16**		**17** (90%)	99:1
12	**18**		**19** (81%)	96:4

[a]Typical reaction conditions: 1 equiv of sulfinimine, 3.1 equiv of formamide, 3 equiv of LDA, PhMe, −78 °C. [b]Isolated yields. [c]Determined by HPLC comparison to authentic diastereomers.

analysis is consistent with the observed stereochemistry for organolithium additions to *N*-sulfinyl ketimines.[13,18] Other sterically demanding α-quaternary ketimines reacted to give α-quaternary β-quaternary amino amides with uniformly high diastereoselectivities (entries 2−4, 7, and 8). Importantly, these highly hindered compounds are not readily accessible by other methods, particularly with high chiral purity. The reaction was amenable to cyclopropyl- (entry 4), alkenyl- (entry 6), and alkynyl-substituted (entry 7) ketimines. Enolizable ketimine **28** (entry 5) was reacted with preformed carbamoyl anion to give adduct **29** in good yield with high diastereoselectivity (97:3). The reaction of trifluoromethyl TIPPS imine **34** gave CF_3-substituted adduct **35** in 76% yield with >97:3 diastereoselectivity (entry 8).

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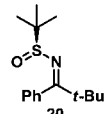
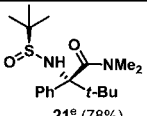
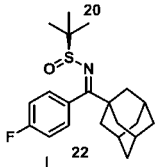
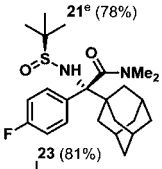
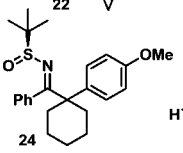
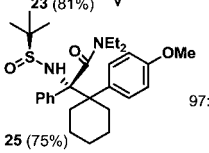
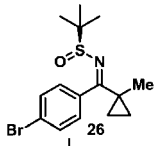
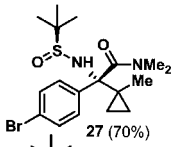
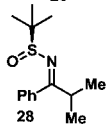
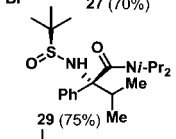
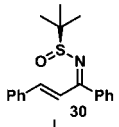
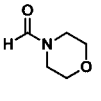
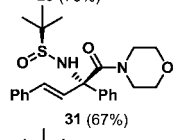
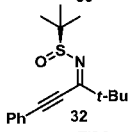
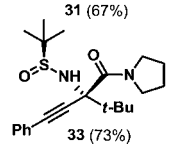
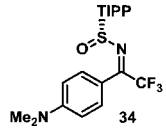
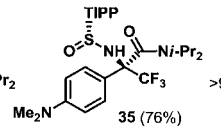
Table 2. Formamide Addition to *N*-Sulfinyl Ketimines[a]

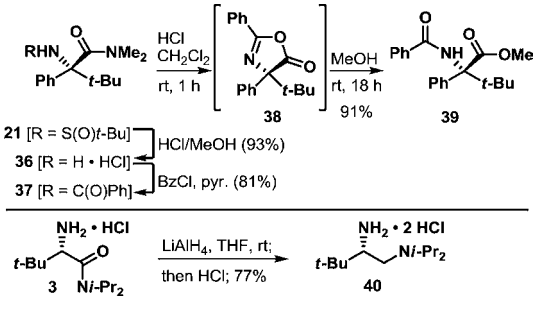
entry	sulfinimine	formamide	product (yield)[b]	dr[c]
1[d]	 **20**		 **21**[e] (78%)	98:2
2	 **22**		 **23** (81%)	97:3
3[f]	 **24**		 **25** (75%)	97:3
4	 **26**		 **27** (70%)	95:5
5	 **28**		 **29** (75%)	97:3
6	 **30**		 **31** (67%)	92:8
7[f]	 **32**		 **33** (73%)	94:6
8	 **34**		 **35** (76%)	>97:3[g]

[a]Typical reaction conditions: 1 equiv of sulfinimine, 3.1 equiv of formamide, 3 equiv of LDA, PhMe, −78 °C. [b]Isolated yields. [c]Determined by HPLC comparison to authentic diastereomers. [d]10.1 equiv of DMF, 10.0 equiv of LDA. [e]Stereochemistry was assigned from the X-ray crystal structure. [f]6.1 equiv of formamide, 6.0 equiv of LDA. [g]Determined by ^{1}H NMR analysis.

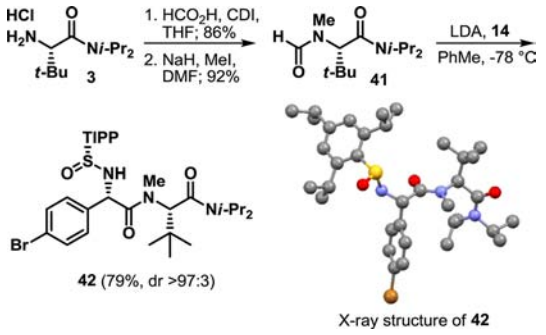
The amide moiety of the products could conveniently be converted to an ester or amine (Scheme 3). The ester conversion was accomplished by the oxazolone procedure of Heimgartner.[19] Deprotection of the sulfinyl group of **21** and subsequent N-benzoylation afforded diamide **37**. Treatment of **37** with HCl in CH_2Cl_2 at room temperature effected intramolecular cyclization to give the intermediate oxazolone **38**, which was opened with methanol to give ester **39** (91% yield). The mild conditions for this conversion for such a sterically demanding substrate are notable. Reduction of **3** with $LiAlH_4$ and subsequent treatment with HCl gave diamine **40** as its dihydrochloride salt in 77% yield. Diamine **40** and related compounds have been used as chiral ligands for asymmetric reactions.[20]

Iterative application of the addition reaction enabled the synthesis of a dipeptide (Scheme 4). Amino amide **3**, prepared as

Scheme 3. Amino Ester or Diamine Synthesis



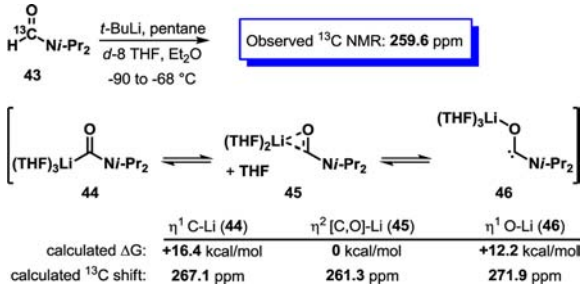
Scheme 4. Stereocontrolled Dipeptide Synthesis



shown in Scheme 2, was sequentially N-formylated and N-methylated to give **41**. Treatment of formamide **41** with LDA in the presence of TIPPS imine **14** gave dipeptide **42** in 79% yield with >97:3 dr. The relative stereochemistry of **42** determined by X-ray crystal structure analysis is consistent with control of the addition by the sulfinimine auxiliary. This synthesis demonstrates the power of the methodology as a versatile and highly stereocontrolled process for peptide construction.

The structure of the carbamoyl anion has historically been depicted as a C-lithiated anion (**44**), although an O-lithiated dialkylamino carbene resonance form (**46**) has also been postulated (Scheme 5).[4,5] Furthermore, in their ab initio studies

Scheme 5. Characterization of the Anion of 43



of formyllithium, Schleyer and Streitweiser found η^2 coordination of Li to be favored.[21] The analogous η^2 carbamoyl anion structure (**45**) is shown canonically as intermediate between **44** and **46**. Interestingly, several stable aminooxy carbenes have been prepared by Alder and co-workers.[22] These species showed characteristic low-field ^{13}C NMR shifts of 262−278 ppm for the carbenic carbons. We explored the deprotonation of *N*,*N*-diisopropylformamide by low-temperature ^{13}C NMR spectroscopy with a broad sweep width to ascertain whether any diagnostic low-field signal characteristic of a carbene such as **46** was generated. To enhance the signal of the key carbonyl carbon, >99% ^{13}C-labeled **43** was synthesized. Formamide **43** was deprotonated with *t*-BuLi at −90 °C, and the ^{13}C NMR spectrum

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was recorded starting at −68 °C.[23] A strong signal was observed at 259.6 ppm. Computational modeling of structures **44**−**46** at the B3LYP level of theory with the 6-311G+(d,2p) basis set was performed using Gaussian 09.[24] To preserve the coordinative saturation of Li, **44**, **45**, and **46** were coordinated with three, two, and three molecules of tetrahydrofuran (THF), respectively.[25] The calculations showed that among the optimized structures, η^2-coordinated **45** had the lowest free energy. The η^1-C−Li structure **44** was 16.4 kcal/mol higher in free energy, while the carbenic η^1-O−Li structure **46** was 12.2 kcal/mol higher. The ^{13}C chemical shifts of **44**−**46** were calculated using the individual gauges for atoms in molecules (IGAIM) method [B3LYP/6-311G+(d,2p)] within Gaussian 09.[24] The calculated shift for η^2-coordinated anion **45** (261.3 ppm) was closest to the observed shift of 259.6 ppm. The free energy calculations together with the observed and calculated ^{13}C NMR shifts suggest that the η^2-coordinated structure **45** is the most favored form of the anion.

In summary, we have described the highly diastereoselective addition of carbamoyl anions to *N*-sulfinyl aldimines and ketimines. The process represents the first use of carbamoyl anions in an asymmetric reaction and the first addition of carbamoyl anions to imines. The reaction provides simple, atom-economical, and direct access to diverse chiral α-amino amides from readily available formamides and either *N*-*tert*-butane- or *N*-2,4,6-triisopropylphenylsulfinyl imines. Sterically hindered α-quaternary-β-quaternary α-amino amides not readily available by other methods are accessible with high diastereoselectivity. Importantly, the products may be easily converted to α-amino esters or 1,2-diamines, which further adds to the utility of the methodology. By iterative application of the reaction, a dipeptide was prepared with high diastereoselectivity and control of the new stereocenter by the sulfinyl auxiliary. Finally, ^{13}C NMR and computational analysis suggested η^2 coordination of lithium by the carbamoyl anion. Further applications of carbamoyl anions in asymmetric reactions will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Procedures, additional data, and complete ref 24 (as SI ref 4). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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