Functionalization of *N*-[(Silyl)methyl]-β-lactam Carbanions with Carbon Electrophiles

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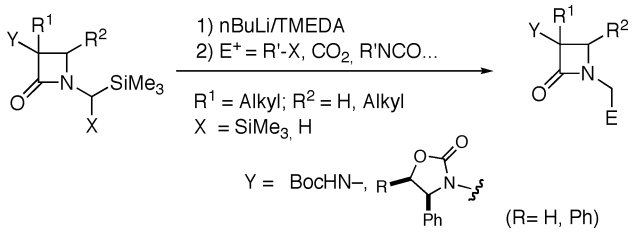

Latent acidity of α-alkyl-α-amino-*N*-[(silyl)methyl]-β-lactams enabled a concise entry to lithium nonenolate *N*-methyl-azetidinone carbanions lithiated α′ to the β-lactam nitrogen, owing to the stabilizing "α-effect" of one or two trimethylsilyl groups. ^{n}BuLi/TMEDA and ^{t}BuLi/TMEDA were the bases of choice for complete deprotonation of di- and monosilylated β-lactams, respectively. Trapping of the resulting carbanions with alkyl halides provided the corresponding *N*-[(α′-silyl)-alkyl]-β-lactams, while carbon dioxide and related electrophiles such as benzyl chloroformates or isocyanates, afforded the corresponding silicon-free *N*-carboxymethyl-, *N*-benzyloxycarbonylmethyl-, and *N*-amidomethyl-β-lactams in a single synthetic step. Likely structures of these unprecedented lithiated *N*-[(silyl)methyl]-β-lactams were studied by MO calculations (B3LYP/6-31G*), and the origin of their relative stability was briefly discussed.

Introduction

Since the advent of semisynthetic antibiotics in the early 1970s α′-metalated β-lactams *N*-carboxymethyl enolates **1** and their sulfonyl and phosphoryl analogues have been used extensively as intermediates to prepare bicyclic cephem-, clavam-, or carbapenems and tricyclic trinem nuclei via α′−β cyclization reactions.[1] In addition, their stereoselective alkylation has been employed to prepare synthons en route to nonproteinogenic amino acids.[2] Surprisingly, the chemistry of simple β-lactam carbanions metalated α′- to the azetidin-2-one nitrogen atom, has been virtually ignored[3] and, to the best of our knowledge, only α′-lithiated *N*-benzyl β-lactams **2** (Figure 1) fall into this category. In a seminal work, Durst[4] reported more than 30 years ago the LDA-promoted formation of α′-lithiated β-lactams **2** as well as their transformation into cycloexpanded γ-lactams **3**, and several [2,3]-shift rearranged ϵ-lactams **4** (from **2**, R^4 = vinyl). The well-acknowledged β-lactam ring strain was believed to be at the origin of this reactivity, and, accordingly, different cleavage-recombination processes for cycloexpansions (**2** → **3**) have been proposed thereafter to explain it, either involving the intermediacy of radical−radical

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(1) General review on β-lactam synthesis can be found in the following: (a) Backes, J. In *Houben-Weyl, Methoden der Organischen Chemie, Band E16 B*; Muller, E., Bayer, O. Eds., Thieme: Stuttgart, 1991; p 31. Cyclization methodologies to bicyclic β-lactams can be found in the following: (b) Kant, J.; Walker, D. G. in *The Organic Chemistry of β-Lactams*, Georg, G. I., Ed.; VCH Publishers: New York, 1993; pp 121−196. Additional representative examples on the use of *N*-carboxymethyl-β-lactam enolates to prepare polycyclic β-lactams can be found in the following: (c) Jacobsen, M. F.; Turks, M.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2002**, *67*, 2441−2417. (d) Alcaide, B.; Polanco, C.; Saez, E.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 7125−7132. (f) Chmielewski, M.; Kaluza, Z.; Furman, B. *Chem. Commun.* **1996**, 2689−2696. (g) Roland, S.; Durand, J. O.; Savignac, M.; Genet, J. P. *Tetrahedron Lett.* **1995**, *36*, 3007−3010. (h) Crocker, P. J.; Karison-Andreasson, U.; Lotz, T.; Miller, M. J. *Heterocycles* **1995**, *40*, 691−716.

(2) (a) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377−386. (b) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383−389. (c) Ojima, I. in *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1992; p. 197−255.

(3) α′-Deprotonation in β-lactams stabilized by a remote conjugate ester group has been described: Ruano, G.; Anaya, J.; Grande, M. *Synlett* **1999**, 1441−1443.

(4) Durst, T.; Van der Elzen, R.; LeBelle, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 9261−9263.

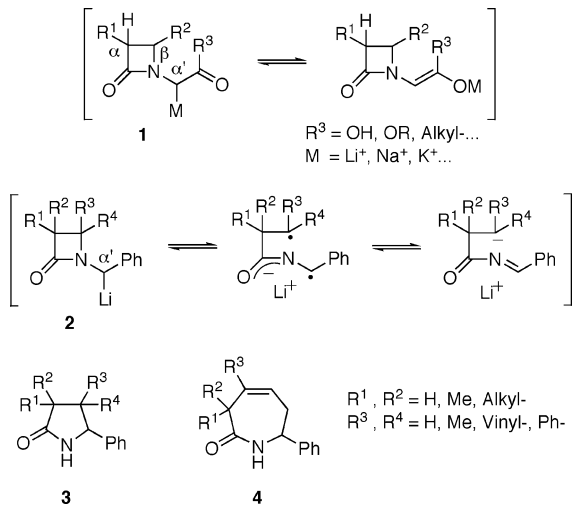


FIGURE 1. α′-Metalated *β*-lactams stabilized by enolate formation and benzylic effect.

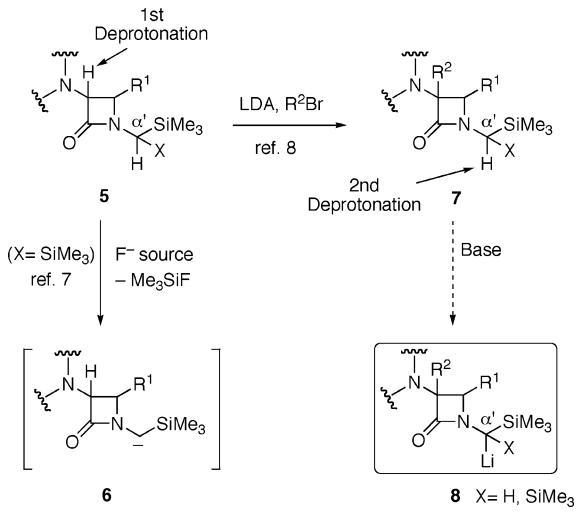


FIGURE 2. Desilylation and sequential deprotonation of α-amino-α,*β*-disubstituted-*N*-[(trimethylsilyl)methyl]-*β*-lactams.

anions, or the participation of *N*-acyl imine *β*-carbanions.[5] As a result of their instability, examples of the intramolecular reaction of benzyl anions **2** with electrophiles are very rare: only single examples of α′-deuteration[4] and α′-acylation[5(b)] have been described.

As part of our ongoing interest for 3-amino-*N*-[(trimethylsilyl)methyl]-2-azetidinones **5**,[6] we have established previously their usefulness as a source of naked *N*-[(trimethylsilyl)methyl]-*β*-lactam carbanions **6** (Figure 2). These species are generated under formally neutral conditions, through fluoride ion-promoted desilylation, and can be trapped "in situ" with carbonyl compounds to afford Peterson-like olefination products.[7] Recently, we also have described the completely stereocontrolled α-alkylation of *β*-lactams **5** to α-alkyl-α-amino-*N*-[(trimethylsilyl)methyl-*β*-lactams **7**,[8] demonstrating their utility as precursors of *β*-turned peptidomimetic *β*-lactam surrogates.[9]

On the basis of the existing methods to metalate amides or carbamates adjacent to the nitrogen atom,[10] and considering the well-known ability of silyl groups to facilitate weak α-carbanion stabilization in *N*-[(trimethylsilyl)methyl]-α-amino derivatives,[11] we envisaged to study the base-promoted α′-metalation of *β*-lactams **7**. Herein we report the first access to enantiopure *β*-lactams **8** lithiated α′ to the *β*-lactam nitrogen and their reaction with carbon electrophiles to afford a variety of α′-functionalized *N*-methyl azetidin-2-ones.

Results and Discussion

To establish the conditions and scope of metalation (**7** → **8**), a set of structurally different *N*-silylmethyl-*β*-lactams **10**−**17** was prepared according to procedures previously described in our laboratory (Scheme 1). Suitable *β*-lactams with the α-amino function protected as cyclic carbamate (Xc) or alkyl carbamate (BocHN-) were selected, bearing either α-alkyl- or α,*β*-dialkyl substitution patterns at the azetidin-2-one ring and having one or two trimethylsilyl groups at the *N*-methyl position.

Some of the *N*-[(silyl)methyl]-*β*-lactams prepared were first submitted to a test α′-deprotonation reaction with alkyllithium bases, followed by in situ trapping of the intermediate carbanions using deuteriomethanol or highly reactive carbon electrophiles (e.g., MeI, BnBr) (Table 1).

It was found that α-monoalkyl-bis-silyl-*β*-lactam **10** was cleanly deprotonated with ^{s}BuLi at −78 °C in THF (entry 1). Attempted deprotonation with ^{n}BuLi under similar conditions caused product decomposition, whereas ^{t}BuLi resulted in residual deuteration (<5% by NMR) and recovery of the starting material. Deprotonation of *β*-lactam **10** could also be driven with LDA or LHMDS bases, but they only led to partial

(5) (a) Ahn, C.; Shin, D.-S.; Park, J.-H. *J. Korean Chem. Soc.* **1999**, *43*, 489−490. (b) Escalante, J.; Gonzalez-Tototzin, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 981−985. (c) Park, J.-H.; Ha, J.-R.; Oh, S.-J.; Kim, J.-A.; Shim, D.-S.; Won, T.-J.; Lan, Y.-F.; Ahn, C. *Tetrahedron Lett.* **2005**, *46*, 1755−1757.

(6) In contrast to other *N*-aryl- or *N*-alkyl-substituted conventional azetidinones, *β*-aryl-, *β*-alkyl-, *β*-unsubstituted *β*-lactams **5** are accessible in a fully stereocontrolled manner from *N*-[bis(trimethylsilyl)methyl]imines. See the following for example: (a) Palomo, C.; Aizpurua, J. M.; Legido, M.; Mielgo, A.; Galarza, R. *Chem. Eur. J.* **1997**, *3*, 1432−1441. (b) Palomo, C.; Aizpurua, J. M.; Legido, M.; Galarza, R.; Deya, P. M.; Dunogues, J.; Picard, J. P.; Ricci, A.; Seconi, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1239−1241.

(7) Palomo, C.; Aizpurua, J. M.; García, *Tetrahedron Lett.* **1990**, *31*, 1239−1241.

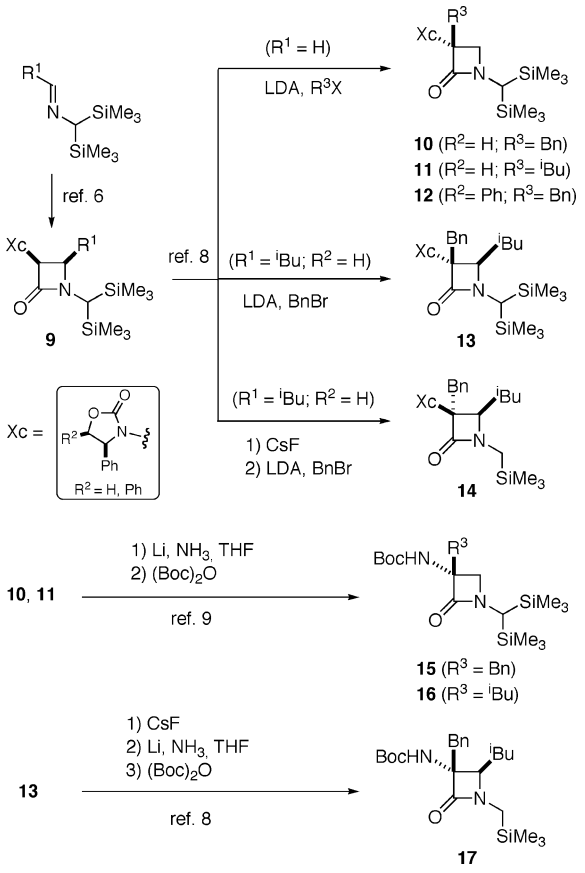
(8) (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Benito, A.; Cuerdo, L.; Fratila, R. M.; Jimenez, A.; Loinaz, I.; Miranda, J. I.; Pytlewska, K. R.; Micle, A.; Linden, A. *Org. Lett.*, **2004**, *6*, 4443−4446. (b) Palomo, C.; Aizpurua, J. M.; Galarza, R.; Benito, A.; Khamrai, U. K.; Eikeseth, U.; Linden, A. *Tetrahedron*, **2000**, *56*, 5563−5570. For the preparation of related racemic α-alkyl-α-amino-*β*-lactams, see: (c) Wu, Z.; Georg, G. I.; Cathers, B. E.; Schloss, J. V. *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 983−986. (d) Broadrup, R. L.; Wang, B.; Malachowski, W. P. *Tetrahedron*, **2005**, *61*, 10277−10284.

(9) (a) Palomo, C.; Aizpurua, J. M.; Benito, A.; Miranda, J. I.; Fratila, R. M.; Matute, C.; Domercq, M.; Gago, F.; Martin-Santamaria, S.; Linden, A. *J. Am. Chem. Soc.* **2003**, *125*, 16243−16260. (b) Palomo, C.; Aizpurua, J. M.; Benito, A.; Galarza, R.; Khamrai, U. K.; Vazquez, J.; de Pascual-Teresa, B.; Nieto, P. M.; Linden, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3056−3058.

(10) (a) Whisler, M. C.; Macneil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206−2225. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanyan, S. *Acc. Chem. Res.* **1996**, *24*, 552−560.

(11) For reviews on silyl carbanions, see (a) Wang, D.; Chan, T. H. Silylmethyl Anions. In *Science of Synthesis: Houben-Weyl, Methods of Molecular Transformations*, Fleming, I., Ed.; Thieme: Stuttgart-New York, 2002; Vol. 4, p 481−498. (b) J. S. Panek, Silicon Stabilization. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 1, p. 579. (c) Itami, K.; Kamei, T.; Mitsudo, K.; Nokami, T.; Yoshida J. *J. Org. Chem.* **2001**, *66*, 3970−3976 and references therein. For metalation of *N*-(silylmethyl)amides and carbamates, see (d) Sieburth, S. M. N.; Somers, J. J.; O'Hare, H. K., *Tetrahedron* **1996**, *52*, 5669−5682.

SCHEME 1. Preparation of *N*-[(silyl)Methyl]-*β*-lactams 10−17



deuteration (typically 60−80%), even when 2−3 equiv of base were used. To our satisfaction, when *β*-lactam **10** was deprotonated with ^{s}BuLi/TMEDA at −78 °C or with ^{n}BuLi/TMEDA at −100 °C, the resulting carbanion was trapped with MeI and BnBr to give α′-alkylated *N*-[bis(silyl)methyl]-*β*-lactams **19**−**21** in fair to good isolated yields (entries 2−5). Nonactivated primary alkyl iodides (e.g., ^{n}BuI, entry 6) also gave successful trapping, whereas secondary ones (e.g., ^{i}PrI) failed to react with the carbanion. As ^{n}BuLi/TMEDA proved to be slightly more efficient than ^{s}BuLi/TMEDA, it was adopted as the standard base for successive deprotonations. Lithiation of α,*β*-dialkyl-substituted bis-silyl *β*−lactam **13** failed[12] (entry 8), and its monosilyl analogue **14** provided the unexpected *N*-benzyl-*β*-lactam **23** (entry 9), likely through the desilylmethylation of intermediate α′-lithio carbanion to the corresponding *β*-lactam *N*-lithio amide. Metalation was compatible with the presence of an additional acidic proton from the BocHN group, provided 2.5 equiv of base were used. Under none of the conditions tested did α′-lithiated *β*-lactams **10**−**16** produce any detectable pyrrolidones arising from eventual cycloexpansion reactions, neither any byproducts from the competitive deprotonation of $SiMe_3$ methyl groups nor *β*-lactam ring-opening side products from butyllithium nucleophilic attack to the azetidin-2-one carbonyl.[13]

It was worth mentioning that, irrespective of the base used, a very characteristic deep color (purple, red, or green) developed from carbanions bearing an α-benzyl group at the *β*-lactam ring (compounds **10**, **14**, and **15**, respectively), whereas α-isobutyl *β*-lactams **11** and **16** showed the typical pale-yellow or pale-brown colors of ordinary α-carbanions of *N*-[(silyl)methyl]-amides or carbamates.[11(c)] These observations suggested that, at least in the former instances, α′-lithiated *β*-lactam species might have a complex structure involving some radical delocalization within the α-benzyl moiety. Conversely, participation of the phenyl group of the oxazolidinyl cyclic carbamate (Xc) in such delocalization seemed to be not essential to carbanion formation (compare entries 7 and 10).

Next, we extended the scope of the reaction to other carbon electrophiles such as carbon dioxide, benzyl chloroformate, and isocyanates[14] (Table 2). They were reacted with *N*-[(silyl)-methyl]-*β*-lactam carbanions, generated under optimized conditions, to furnish moderate to good yields of the corresponding desilylated[15] and α′-functionalized *N*-methyl-*β*-lactams **26**−**36**. Interestingly, the method was applicable to all the α,*β*-substitution and *N*-protection patterns studied, including monosilyl-*β*-lactams **14** and **17**, and some of the α-*N*-Boc-α′-carboxy-*β*-lactams prepared (e.g., **34**−**36**) could be considered as internally constrained peptidomimetics, ready for incorporation into peptide chains by standard peptide synthesis techniques.[16]

Depending on the bases selected to deprotonate the *β*-lactams or the reaction conditions used to trap the carbanions, unexpected products were obtained in some instances. For example, attempted acylation of the carbanion derived from **10** with benzyl chloroformate (entry 2) afforded exclusively the α′-methylated product **19** instead of the expected benzyl ester **27**. The transformation was rationalized by means of a reaction pathway involving the participation of a TMEDA/$ClCO_2Bn$ complex (Scheme 2) as the methylating agent.[17] Indeed, carrying out the same reaction using TMEDA-free ^{s}BuLi to deprotonate the *β*-lactam **10** gave the expected product **27** (entry 3). For the reaction of the carbanion derived from **11** with trimethylsilyl isocyanate, different products (nitrile **30** or amide **31**) were obtained, depending on the trapping reaction temperature (entries 6 and 7). The expected amide **31** was obtained in good yield only when the trapping reaction was conducted entirely at −78 °C and was quenched at the same temperature, whereas performing the trapping step at room-temperature resulted in the exclusive formation of nitrile **30**.

A key question arising from the successful α′-deprotonation of *N*-[(silyl)methyl]-*β*-lactams disclosed above was the likely

(12) Additional deprotonation trials conducted with several butyllithium/TMEDA combinations at temperatures up to −30 °C provided no evidence of carbanion formation. Above this temperature, only decomposition of compound **12** was observed.

(13) Nucleophilic addition of alkyllithiums to amide carbonyls can be blocked by increasing the steric hindrance at the Cα position: (a) Schlecker, R.; Seebach, D.; Lubosch, W.; *Helv. Chim. Acta*, **1978**, *61*, 512−516. (b) Schlecker, R.; Seebach, D.; *Helv. Chim. Acta*, **1977**, *60*, 1459−1471. For azetidin-2-one ring opening with alkyllithium reagents, see (c) Pearsons, P. J.; Camp, N. P.; Underwood, J. M.; Harvey, D. M. *Tetrahedron*, **1996**, *52*, 11637−11368.

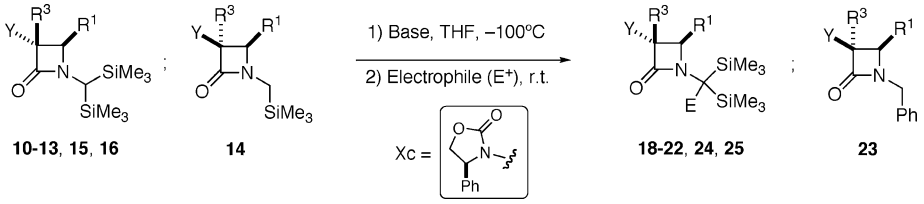
(14) We previously described the α′-carbamoilation of **11** with trimethylsilyl isocyanate, see ref 9a.

(15) Spontaneous desilylation of α-trimethylsilyl-carbonyl compounds under acidic aqueous workup conditions is a well-established process. See, for example, the following: Landais, Y. α-Silyl Carbonyl Compounds. In *Science of Synthesis: Houben-Weyl, Methods of Molecular Transformations;* Fleming, I., Ed.; Thieme: Stuttgart-New York, 2002; Vol. 4, p 757−772.

(16) An alternative four-step transformation of *N*-[bis(trimethylsilyl)-methyl]-*β*-lactams into *N*-(carboxymethyl)-*β*-lactams was developed previously in our laboratory, involving Ce(IV)-promoted degradation of bis-(trimethylsilyl)methyl group and *N*-alkylation of intermediate NH-*β*-lactams with benzyl iodoacetate (see ref 9). For a related approach to α-alkyl-N-carboxymethyl-*γ*-lactams, see the following: Raghavan, B.; Johnson, R. L. *J. Org. Chem.* **2006**, *71*, 2151−2154.

(17) A similar reaction using ^{s}BuLi/TMEDA base and $(Boc)_2O$ electrophile also gave α′-methylated *β*-lactam **19** as the only reaction product, instead of the expected *N*-[(*tert*-butoxycarbonyl)methyl]-*β*-lactam.

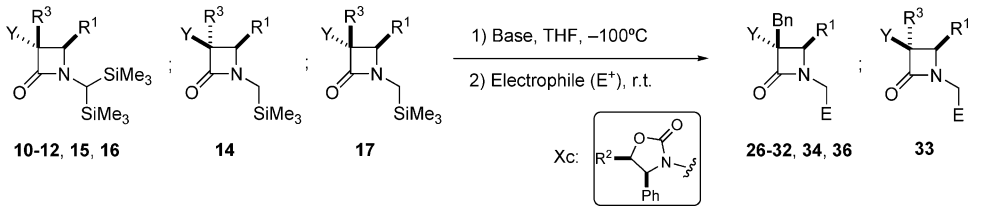
TABLE 1. Deprotonation of *N*-[(silyl)Methyl]-Substituted *β*-Lactams with Alkyllithium Bases[a]



entry	*β*-lactam	Y	R^1	R^3	base	anion color[b]	electrophile	product	E	yield (%)[c]
1	**10**	Xc	H	Bn	^{s}BuLi	A	MeOD[d]	**18**	D	82
2	**10**	Xc	H	Bn	^{s}BuLi	A	MeI	**19**	Me	40
3	**10**	Xc	H	Bn	^{s}BuLi/TMEDA	A	MeI	**19**	Me	51
4	**10**	Xc	H	Bn	^{s}BuLi/TMEDA	A	BnBr	**20**	Bn	61
5	**10**	Xc	H	Bn	^{n}BuLi/TMEDA	A	BnBr	**20**	Bn	70
6	**10**	Xc	H	Bn	^{n}BuLi/TMEDA	A	^{n}BuI	**21**	^{n}Bu	40
7	**11**	Xc	H	^{i}Bu	^{n}BuLi/TMEDA	B	BnBr	**22**	Bn	77
8	**13**	Xc	^{i}Bu	Bn	^{n}BuLi/TMEDA	B	MeOD[d]			(<5)[e]
9	**14**	Xc	^{i}Bu	Bn	^{n}BuLi/TMEDA	C	BnBr	**23**		50[f]
10	**15**	BocHN	H	Bn	^{n}BuLi/TMEDA[g]	D	MeOD[d]	**24**	D	75
11	**16**	BocHN	H	^{i}Bu	^{t}BuLi/TMEDA[g]	B	MeOD[d]	**25**	D	67

[a] Deprotonation step was run with 1.3 equiv of base during 30 min at −100 °C for ^{n}BuLi/TMEDA and at −78 °C for other bases. After addition of the electrophiles (2 equiv), trapping was conducted at room temperature for 5 h. [b] A: deep purple; B: slight yellow−orange; C: deep red; D: deep green. [c] Yields of isolated pure products. [d] 20 equiv of MeOD used. [e] Conversion determined by ^{1}H NMR (500 MHz) analysis of the reaction crude. [f] Unchanged starting material partially recovered (40%). [g] 2.5 equiv of base used.

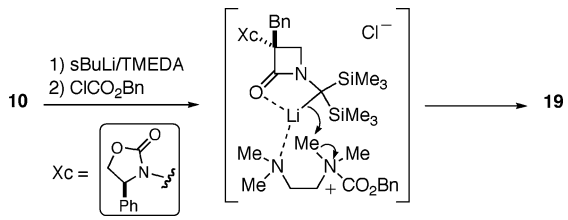
TABLE 2. Functionalization of *N*-[(silyl)Methyl]-*β*-lactams with Carbon Dioxide and Related Electrophiles



entry	*β*-lactam	Y	R^1	R^2	R^3	base	electrophile[a]	product	E	yield (%)[b]
1	**10**	Xc	H	H	Bn	^{s}BuLi (−78)	CO_2	**26**	CO_2H	58
2	**10**	Xc	H	H	Bn	^{s}BuLi/TMEDA (−78)	$ClCO_2Bn$	**19**		77
3	**10**	Xc	H	H	Bn	^{s}BuLi (−78)	$ClCO_2Bn$	**27**	CO_2Bn	45
4	**10**	Xc	H	H	Bn	^{n}BuLi/TMEDA (−100)	PhNCO	**28**	CONHPh	63
5	**11**	Xc	H	H	^{i}Bn	^{n}BuLi/TMEDA (−100)	CO_2	**29**	CO_2H	90
6	**11**	Xc	H	H	^{i}Bn	^{n}BuLi/TMEDA (−100)	Me_3SiNCO	**30**	CN	60
7	**11**	Xc	H	H	^{i}Bn	^{n}BuLi/TMEDA (−100)	Me_3SiNCO[c]	**31**	$CONH_2$	80
8	**12**	Xc	H	Ph	Bn	^{n}BuLi/TMEDA (−100)	PhNCO	**32**	CONHPh	74
9	**14**	Xc	^{i}Bn	H	Bu	^{t}BuLi/TMEDA (−78)	CO_2	**33**	CO_2H	81
10	**15**	BocHN	H	H	Bn	^{n}BuLi/TMEDA[d] (−100)	CO_2	**34**	CO_2H	64
11	**16**	BocHN	H	H	^{i}Bu	^{n}BuLi/TMEDA[d] (−100)	CO_2	**35**	CO_2H	68
12	**17**	BocHN	^{i}Bu	H	Bn	^{t}BuLi/TMEDA[d] (−78)	CO_2	**36**	CO_2H	45[e]

[a] Trapping with electrophiles (2 equiv; excess for CO_2 gas) was conducted warming the mixture to room temperature for 5 h. [b] Yields of isolated pure products. [c] Trapping reaction conducted at −78 °C. [d] A total of 2.5 equiv of base used. [e] Unchanged starting material partially recovered (38%).

SCHEME 2. Reaction Pathway to α′-Methylated *β*-Lactam 19



role played by the carbonyl groups of the *β*-lactam and oxazolidinone moieties on the stabilization of α′-lithiated *β*-lactams. To shed light on this problem, some ab initio B3LYP/6-31G* calculations[18] were conducted on structures **37**−**39** (Figure 3), featuring two simplified SiH_3 groups and a α-methyl substitution to discard additional conformational complexity around the *β*-lactam ring. Geometry of the lithium cation was assumed to be tetrahedral, monocoordinated to the *β*-lactam or

(18) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

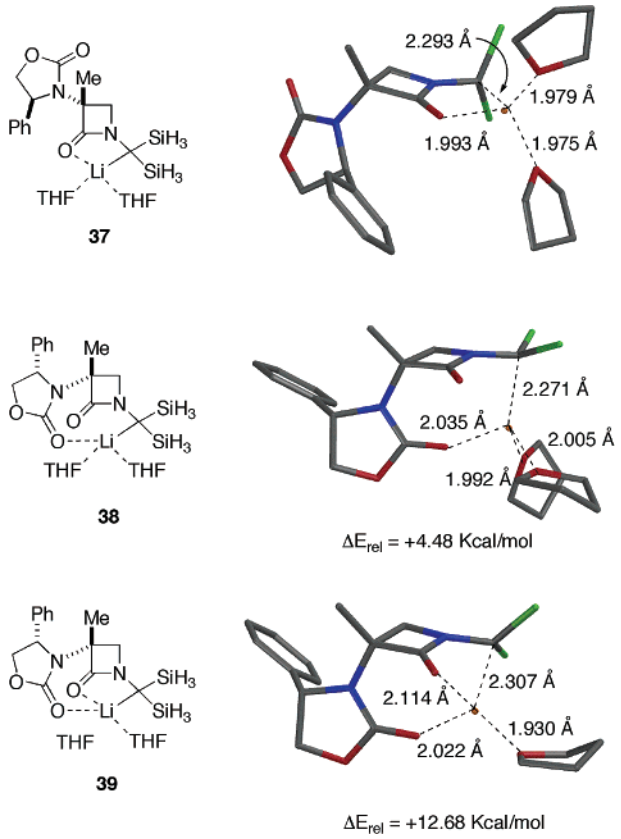


FIGURE 3. Relative B3LYP/6-31G* energies of α′-lithio-*N*-[bis(silyl)-methyl]-*β*-lactams **37**−**39** solvated with two molecules of THF. Hydrogen atoms omitted for clarity.

the oxazolidinone carbonyl groups in **37** and **38**, respectively, or chelated to both carbonyl oxygen atoms in **39**. Two additional THF molecules were incorporated as lithium cation solvates, one of them external to the complex in the case of **39**. Computation was conducted following standard geometry-optimization and energy-minimization protocols and yielded relative destabilization of 4.48 and 12.68 kcal/mol for **38** and **39** with respect to the more stable structure **37**. This energy difference might arise from the considerable pyramidalization strain imposed to the *β*-lactam planar nitrogen atom to reach the structures **38** and **39** and also from the increased electronic repulsion between the oxazolidinone and *β*-lactam carbonyl oxygen electron lone pairs in the latter complex. While the present results strongly suggested that coordination imparted by the oxazolidinone (or Boc-) carbonyls is not strictly necessary for α′-carbanion formation in α-alkyl-α-amino-*N*-[(silyl)-methyl]-*β*-lactams, extension of the lithium carbanion model **37** to α-benzyl substituted *β*-lactams of the type **10**, **12**, or **14** could not be necessarily straightforward. Indeed, some additional interaromatic *π*-stacking or even charge-transfer complex formation between the benzylic and oxazolidinone phenyl groups could come into play in these cases.

Finally, X-ray analysis of compounds **10** and **13**,[19] α-alkylated and α,*β*-dialkylated, respectively (Figure 4), provided an additional indication of the relevant stabilizing effect of the

(19) The crystallographic data for structures **10** and **13** have previously been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-113859 and 132758, respectively, in connection with refs 9b and 9a.

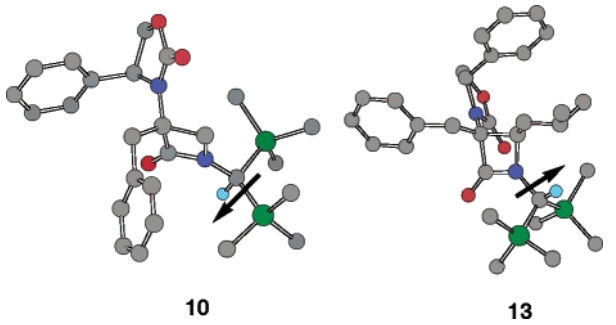


FIGURE 4. X-ray crystal structures for the *N*-[bis(silyl)methyl]-*β*-lactams **10** (*β*-unsubstituted) and **13** (*β*-substituted), showing the opposite spatial disposition of the C<u>H</u>(SiMe$_3$)$_2$ methine protons.

β-lactam carbonyl on α′-lithiated carbanions. A detailed inspection of the crystal structures of **10** and **13** revealed that in the former case the C<u>H</u>(SiMe$_3$)$_2$ proton was pointing toward the *β*-lactam carbonyl group, whereas in **13** the steric hindrance between the *β*-isobutyl and trimethylsilyl groups blocked the methine C−H bond into the opposite spatial orientation. It was logical to assume that a similar conformational trend could be kept up in the corresponding α′-lithiated carbanion from **13**, preventing any coordination between the lithium cation and *β*-lactam carbonyl. As commented above (see Table 1, entry 8) this agreed fully with the experimental observation that compound **13** was the only *N*-[(silyl)methy]-*β*-lactam studied unable to undergo α′-deprotonation. Indeed, cancellation of such *β*-isobutyl/trimethylsilyl steric hindrance by elimination of one trimethylsilyl group, restored the reactivity of the monosilylated analogue **14** (see Table 1, entry 9 and Table 2, entry 9).

Conclusion

We have demonstrated that α-alkyl-α-amino-*N*-[(silyl)-methyl]-*β*-lactams can be regarded as new *N*-methyl-*β*-lactam cryptocarbanion sources. Compared to previously reported nonenolate *N*-benzyl-*β*-lactams, the α-lithiated derivatives of *N*-[(silyl)methyl]-*β*-lactams are remarkably stable, with no apparent tendency to nucleophilic ring opening or ring-cyclo-expansion side reactions. According to MO calculations and experimental observations, the origin of such stability seems to lie primarily on the coordination of the lithium cation by the *β*-lactam carbonyl, and in a less extent, on the "α-effect" of the trimethylsilyl groups. Alkylation at the α′-position preserving the silyl moiety represents a new entry to elaborated *N*-substituted *β*-lactams, potentially reactive under fluoride ion-triggered conditions, while the spontaneous loss of the silyl groups after trapping with carbon dioxide-derived electrophiles, renders the *N*-[(trimethylsilyl)methyl]- groups directly amenable to a variety of carboxylic acid derived functional groups. The synthetic utility of the method has been illustrated with the direct preparation of some dipeptide *β*-lactam surrogates, ready for incorporation into inverse turn peptidomimetics under standard peptide synthesis conditions.

Experimental Section

General Procedure for the α′-Functionalization of *N*-[(trimethylsilyl)methyl]-azetidin-2-ones. A 0.60 M solution of ^{n}BuLi/TMEDA in THF was prepared under nitrogen by adding dried TMEDA (1.2 mmol, 0.18 mL) and 2.5 M ^{n}BuLi (1.2 mmol, 0.48 mL) to anhydrous THF (1.30 mL) cooled to −100 °C (MeOH/liquid nitrogen bath). This solution was immediately used after

preparation. In a separate flask, the corresponding 1-[(trimethylsilyl)methyl]-azetidin-2-one (1 mmol) was dissolved in anhydrous THF (3 mL), cooled to −100 °C (methanol/liquid nitrogen bath) under nitrogen, and 0.60 M ^{n}BuLi/TMEDA solution (1.2 mmol, 2.0 mL) was added dropwise. The mixture was stirred at −100 °C for 30 min and a 1 M solution of the corresponding electrophile (2−10 mmol) in THF was added. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature for 5 h. For carboxylation reactions CO_2 gas was collected in a balloon, dried through a molecular sieves tube, and bubbled into the carbanion solution until color disappearance (1−2 min). The reaction mixture was quenched with saturated aqueous NH_4Cl (4 mL) and extracted with CH_2Cl_2 (5 mL x 3), and the resulting organic phase was dried ($MgSO_4$) and evaporated. For the carboxylation reaction, the crude was redissolved in CH_2Cl_2 (5 mL) and extracted again with NaOH (0.2 M, 10 mL). The aqueous phase was separated, acidified with 6 M HCl, and extracted with CH_2Cl_2 (5 mL x 3) to yield the pure carboxylic acid. Analytically pure samples were obtained after purification by column chromatography (silica gel, eluent: EtOAc/hexanes).

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Supporting Information Available: Physical and spectroscopic data for compounds **10**−**36**. This material is available free of charge via the Internet at http://pubs.acs.org.