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Coupling Reactions of α-(*N*-Carbamoyl)alkylcuprates with Enol Triflates Derived from Cyclic *β*-Keto Esters: A Facile Approach to *γ*-Carbamoyl-α,*β*-enoates

ShengJian Li[†,‡] and R. Karl Dieter*

Howard L. Hunter Chemistry Laboratory, Clemson University, Clemson, South Carolina 29634-0973, and Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033

dieterr@clemson.edu

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α-(*N*-Carbamoylalkyl)cuprates couple with enol triflates derived from carbocyclic and heterocyclic (i.e., piperidinones) *β*-keto esters. Product yields are higher with the alkyl(cyano)cuprates [i.e., RCu(CN)Li, 56−93%] than with the dialkylcuprate reagents (i.e., $R_2CuLi{\cdot}LiCN$). An enol nonaflate works as well as the corresponding enol triflate. A facile synthetic route to *γ*-amino α,*β*-enoates not readily prepared from *γ*-keto-α,*β*-enoates is thus established. The *γ*-amino-α,*β*-enoates, available via *N*-Boc deprotection, can be cyclized to annulated pyrrolin-2-ones.

Introduction

α-(*N*-Carbamoyl)alkylcuprates[1] undergo conjugate addition[2] and substitution reactions[3−5] with a wide range of electrophiles and their reactivity profile is often complementary to the corresponding lithium reagents[6] from which they are derived. They hold considerable promise for *N*-heterocycle synthesis and are enhanced by the development of configurationally stable scalemic[5c] reagents. α-(*N*-Carbamoyl)alkylcuprates, however, either fail to undergo conjugate addition reactions with cyclic α,*β*-enoates or afford the conjugate adducts in low yields.[2b] While they do undergo substitution reactions with vinyl triflates,[5a] the reaction is very sensitive to steric factors in the electrophile. *β*-Iodo-α,*β*-enoates efficiently couple with α-(*N*-carbamoyl)alkylcuprates stereospecifically providing a solution to stereocontrol not achievable by coupling with α,*β*-alkynyl esters.[2e] This methodology was not extended to cyclic systems which potentially pose problems of steric congestion about the reactive centers of either the cuprates or the vinyl iodides.

γ-Amino carbonyl derivatives are an important class of compounds which have shown unique biological activities[7a] and they have also been used as synthons for the construction of therapeutically interesting agents.[7b−e] Numerous synthetic routes have been developed for the synthesis of this class of compounds which remain attractive intermediates in organic synthesis.[8]

Palladium chemistry effects the conversion of *β*-carboalkoxy enol triflates (e.g., **2a**) to *γ*-*N*-carbamoyl-α,*β*-enoates,[9] *β*-aminomethyl enol triflates to α,*β*-unsaturated *γ*-lactams,[10] and *β*-acyl enol triflates to *β*-acyl-α,*β*-enamides[11] which can also be converted to α,*β*-unsaturated *γ*-lactams. The tandem palladium coupling−isomerization sequence of *β*-carboalkoxy enol triflates with the *N*-methyl carbamate of 1,2-dihydropyrrole affords the *γ*-amino α,*β*-enoate with isomerization of the pyrroline double bond.[9] Utilization of a chiral binaphthyl ligand

* Address correspondence to this author at Clemson University.
† Current Address: Johnson & Johnson Pharmaceutical Research Institute, Raritan-Bridgewater, NJ.
‡ Schering-Plough Research Institute.

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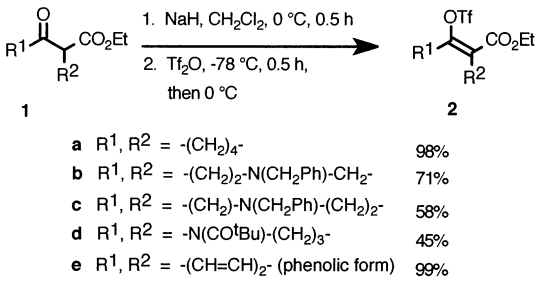
SCHEME 1



affords excellent asymmetric induction, but the reaction appears limited to pyrroline enecarbamates. In addition, the enol triflates of 4-*tert*-butyl- or 4-phenyl-2-formylcyclohexanone react with the sodium ferrate complex, $[Cp(CO)_2Fe]Na$, to form β-formyl alkenyl iron carbonyl complexes. These iron carbonyl complexes undergo a titanium-mediated carbonylative coupling with amines to afford the lactams.[12] All these procedures are significantly longer than the current method.

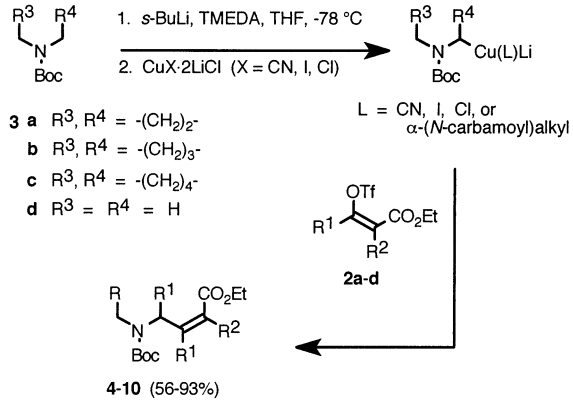
Previous efforts to couple α-(*N*-carbamoyl)alkylcuprates with the enol triflates of β-keto esters were limited to the dialkylcuprate derived from *N*-Boc-*N*,*N*-dimethylamine and the enol triflate of methyl 3-oxopentanoate (67%).[13] We now report effective procedures for the facile coupling of α-(*N*-carbamoyl)alkylcuprates with enol triflates derived from cyclic β-keto esters leading to γ-*N*-carbamoyl-α,β-enoates in good to excellent yields even when considerable steric congestion is present in the coupling components.

Results and Discussion

The enol triflates[14] or nonaflates[15] were readily prepared by modification of literature procedures in good to excellent yields (Scheme 1).

The cuprate reagents were prepared by sequential deprotonation of the carbamates according to the Beak protocol[16] followed by treatment of the in situ generated organolithium reagents with THF soluble Cu(I) salts solubilized by LiCl.[2c] Although it was not necessary to raise the temperature to guarantee complete cuprate formation, the THF solution of CuX·2LiCl was added to the α-lithiocarbamate at −78 °C, stirred at this temperature for a few minutes, and then stirred at −30 °C for 0.5 h before recooling to −78 °C. Addition to the colorless to clear yellowish cuprate THF solution of a THF solution of the enol triflate at −78 °C resulted in a yellowish-dark brown solution that was stirred at −78 °C for 1−2 h and −40 °C for 1−3 h and then briefly warmed to room temperature for 15 min (solution became dark to dark brown) before quenching the reaction with 1.0 N HCl at −78 °C. In preliminary experiments, several Cu(I) salts and cuprate reagents were examined by using pyrrolidinylcuprates derived from **3a** and vinyl triflate **2a** (Scheme 2, Table 1, entries 1−6). The lithium dialkylcuprate prepared from CuCN, CuI,[17] or CuCl uniformly gave lower yields (entries 2 vs 1, 4 vs 3, and 6 vs 5) of coupled products than the corresponding alkylcyanocuprate or alkylhalocuprate [i.e., RCu(X)Li, X = CN, I, or Cl] reagents. The alkylcyanocuprate and alkylhalocuprate reagents gave comparable yields of coupled product, but did show a small diminution of product yield across the series CuCN > CuI > CuCl (entries 1, 3, and 5) whereas the dialkylcuprate reagent gave higher yields when prepared from CuI and significantly lower yields when prepared from CuCl (entries 4 vs 6). Since the alkylcyanocuprate reagent gave the highest product yields and was also efficient in α-(*N*-carbamoyl)alkyl ligand, this reagent was employed in an examination of the scope of the reaction.

SCHEME 2



The reactions of cuprates derived from **3a** with enol triflates prepared from *N*-benzyl piperidinones were examined to probe the sensitivity of the reaction to steric factors in the substrate. These substrates would also provide a synthetic entry to substituted piperidines, a structural feature in many pharmaceuticals and biologically active nitrogen heterocycles. The effect of topological and conformational effects in the α-(*N*-carbamoyl)alkyl ligands was probed by an examination of cuprates derived from *N*-Boc-piperidine (**3b**), *N*-Boc-perhydroazapine (**3c**), and *N*-Boc-dimethylamine (**3d**).

Coupling of the alkyl(cyano)cuprate reagent derived from *N*-Boc pyrrolidine (**3a**) with the enol triflates of *N*-benzyl-3-carboethoxy-4-piperidinone (**2b**), *N*-benzyl-4-carboethoxy-3-piperidinone (**2c**), or *N*-Boc-3-carboethoxy-2-piperidinone (**2d**) proceeded uneventfully in good to excellent yield (Table 1, entries 7−9). The significant number of heteroatoms in these triflates had no negative effect upon the coupling reaction and good yields were obtained with triflate **2d** possessing significant steric congestion about the reactive site. Although deprotonation of *N*-Boc-piperidine **3b** is more difficult than the pyrrolidine analogue, good yields of cuprate formation and coupling product were achieved (entry 10) as were slightly higher yields for the *N*-Boc-perhydroazapine derived cuprate and coupling product (entry 11). The cuprate derived from *N*-Boc-*N*,*N*-dimethylamine gave

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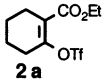
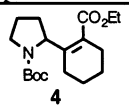
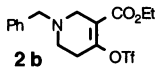
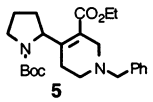
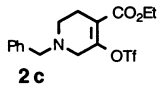
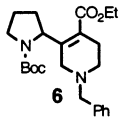
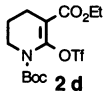
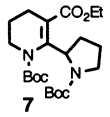
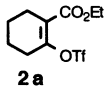
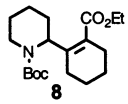
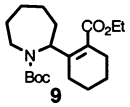
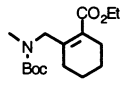
TABLE 1. Coupling Reactions of α-(*N*-Carbamoyl)alkylcuprates with Enol Triflates Derived from *β*-Keto Esters (Scheme 2)

entry[a]	RLi[b]	CuX·2LiCl[c] X	(n equiv)	cuprate reagent[d]	enol triflate[e]	product	% yield[f]
1		CN	(1.0)	RCu(CN)Li	 **2a**	 **4**	82-86[g]
2		CN	(0.5)	$R_2CuLi{\cdot}LiCN$			67
3		I	(1.0)	RCu(I)Li			82
4		I	(0.5)	$R_2CuLi{\cdot}LiI$			79
5		Cl	(1.0)	RCu(Cl)Li			73
6		Cl	(0.5)	$R_2CuLi{\cdot}LiCl$			56
7		CN	(1.0)	RCu(CN)Li	 **2b**	 **5**	93
8		CN	(1.0)	RCu(CN)Li	 **2c**	 **6**	85
9		CN	(1.0)	RCu(CN)Li	 **2d**	 **7**	82
10		CN	(1.0)	RCu(CN)Li	 **2a**	 **8**	75
11		CN	(1.0)	RCu(CN)Li		 **9**	83
12		CN	(1.0)	RCu(CN)Li		 **10**	86

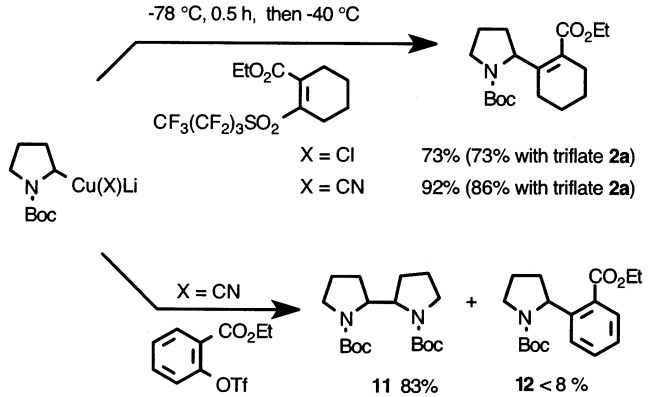
[a] The reactions were performed on a 1-mmol scale unless noted. [b] The lithium α-aminoalkyl carbanions were generated by direct deprotonation [*s*-BuLi, THF, TMEDA, −78 °C, 2 h]. [c] The RCu(X)Li (X = CN, I, Cl) or $R_2CuLi{\cdot}LiX$ cuprate reagents were generated based on the molar ratio of RLi/CuX. [d] CuCN and CuCl were obtained from a commercial source and were used as received, CuI was purified by a literature procedure (ref 17) and dried under vacuum before use. [e] The enol triflates were made by a modified literature method (refs 14 and 21). [f] The yields were based on pure products isolated after purification by column chromatography. All new compounds were characterized by their ^{1}H NMR, ^{13}C NMR, and high-resolution MS/LC-MS/MS. [g] The reaction was performed at several scales [2.0 mmol (86%), 5.0 mmol (82%), 10 mmol (83%)].

excellent yields with triflate **2a** (entry 12), which is significant since the diminished reactivity of this primary alkylcuprate reagent was observed in previous work.[2b]

Since triflic anhydride is relatively expensive, the use of cyclic vinyl nonaflates was examined. The enol nonaflate derived from **1a** gave a comparable yield of **4** upon coupling with the alkyl(chloro)cuprate derived from **3a** and a slightly higher yield with the alkyl(cyano)cuprate reagent (Scheme 3). These results coupled with the observation that the alkyl(cyano)cuprate reagents afford higher yields than the lithium dialkylcuprates suggests that moderation of cuprate and reagent reactivity is beneficial, resulting in higher yields.

The coupling reaction could not be extended to aromatic triflates. Triflate **2e** prepared from ethyl salicylate (**1e**) gave the cross-coupling product **12** in very low yield (<8%, as estimated from LC-MS analysis of the crude product mixture) affording instead the pyrrolidinyl homocoupling product **11** (the dimer of the *N*-Boc-α-pyrrolidinyl ligand) in 83% yield along with 21% of the recovered

SCHEME 3

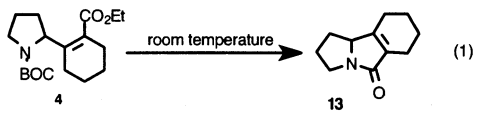


triflate **2e**. Similar homocoupling products were also observed for the other alkyl(cyano)cuprates derived from carbamates **3b**−**d**. The triflate of phenol was previously observed to be unreactive[5a] toward the lithium dialkylcuprate whereas triflate **2e** induces a coupling reaction

suggestive of SET events. Triflate **2e** contains two good electron-withdrawing groups on the aromatic ring and is apparently easily reduced by the alkyl(cyano)cuprate reagent affording an α-carbamoyl radical that combines to afford the dimer. Dimer **11**[18] has also been obtained as a mixture of diastereomers in excellent yields either by the mild oxidation of the dialkylcuprate reagent (i.e., $R_2CuLi{\cdot}2LiCl$ derived from **3a** and the homogeneous THF solution of purified CuI and LiCl) with oxidants (e.g., I_2) or by bubbling oxygen through a solution of the alkyl(cyano)cuprate.[19]

Two mechanistic pathways can be envisioned for these coupling reactions. The reaction may, in principle, proceed by either a conjugate addition−elimination pathway or a direct oxidative addition−reductive elimination pathway. Given the reluctance of α,β-enoates to participate in conjugate addition reactions and the failure of these cuprate reagents to undergo conjugate addition reactions to either α,β-enones or enoates in the absence of TMSCl,[2] we favor the latter pathway. This view is additionally supported by the observation that α-(*N*-carbamoyl)alkylcuprates give little to no enantioselectivity in conjugate addition reactions but give excellent enantioselectivity upon reaction with vinyl iodides irrespective of whether the double bond is or is not in conjugation with an ester functionality.[5c]

Finally, we note that treatment of **4** with either 50% (v/v) of trifluoroacetic acid in dichloromethane at room temperature or with 2 equiv of trimethylsilyltriflate effects *N*-Boc deprotection and cyclization to afford the tricyclic pyrroline γ-lactam **13**[20] in good to excellent yields (91% and 65%, respectively, eq 1). However, treatment of **4** with 6 equiv of PhOH and TMSCl in dichloromethane gave lactam **13** in low yield (28%) after the solution was stirred overnight.



4 13 (1)

50% CF_3COOH, CH_2Cl_2, 0.5 h 91%

TMSOTf (2 equiv), CH_2Cl_2, 1 h 65%

Conclusions

In summary, α-(*N*-carbamoyl)alkylcuprates couple with vinyl triflates derived from cyclic β-keto esters in good to excellent yields. Higher yields are achieved with the alkyl(cyano)cuprates which are efficient in α-(*N*-carbamoyl)alkyl ligand. The reaction can be achieved with the corresponding vinyl nonaflates which are less expensive to prepare. *N*-Boc deprotection and cyclization affords annulated pyrrolinones. The method thus provides for the rapid coupling of two ring systems with functionality that can react to afford a third ring system. The present work illustrates the rapid construction of highly functionalized piperidine ring systems focusing on the important role that piperidine derivatives play in pharmacology. Coupling of the scalemic pyrrolidinylcuprate[5c] provides potential opportunities for asymmetric synthetic applications.

Experimental Section

General Procedure: Enol Triflate Preparation.[21] NaH [0.240 g, 6.00 mmol, 60% (w/w) mineral oil dispersion] was washed with hexane (3 × 5.0 mL), the gray solid was flushed with a nitrogen atmosphere, whereupon CH_2Cl_2 (20 mL, dried over molecular sieves) was added and the mixture was cooled to 0 °C with an ice−water bath. The appropriate β-keto ester (5.0 mmol) was added dropwise (gray suspension became white as gas evolution proceeded) and the mixture was stirred at 0 °C for 30 min, and then cooled to −78 °C and stirred for an additional 10−15 min before triflic anhydride was added. The mixture was stirred at −78 °C for 30 min and then at 0 °C for 18 h. The reaction mixture was diluted with 50 mL of Et_2O, washed with brine (3 × 15 mL), and dried over Na_2SO_4. Concentration in vacuo afforded the enol triflates.

1,1-Dimethylethyl 2-(2-Carboethoxy-1-cyclohexen-1-yl)-1-pyrrolidinecarboxylate (4). *N*-Boc-pyrrolidine (1.7 g, 10 mmol, dried over CaH_2) was added into a flame-dried (heat gun) 100-mL round-bottom flask stoppered with a septum. TMEDA (3.0 mL, 20 mmol, commercial source, dried over CaH_2) was added via syringe, followed by 20 mL of dry THF (from a sealed bottle). The clear solution was cooled to −78 °C and stirred for ca. 5 min. *sec*-BuLi (10 mL, 13 mmol, a newly opened bottle, 1.3 M in cyclohexane/hexane 92/8, commercial source) was added via syringe dropwise. The yellowish, almost clear solution was stirred at −78 °C for an additional 2.5 h. The greenish-white powdered CuCN (0.90 g, 10 mmol, commercial source) was mixed with the colorless crystalline LiCl (0.86 g, 20 mmol, commercial source, beads <100 ppm H_2O) in another 50-mL round-bottom flask and the flask was heated with hot air and then cooled to room temperature under a N_2 atmosphere. Dry THF (20 mL) was added to the yellowish powder and the mixture was stirred at room temperature until all the solid had dissolved, whereupon the mixture became a homogeneous greenish solution that was cooled to −78 °C. At this temperature, the homogeneous Cu(I) salt dry THF solution was quickly transferred into the *N*-Boc-α-lithiopyrrolidine solution via syringe. The mixture was stirred for a few minutes, then stirred at −30 °C (yellowish clear) for 0.5 h and recooled to −78 °C (yellowish clear).

A 20-mL dry THF solution of the enol triflate of 2-carboethoxy-cyclohexanone (**2a**, 3.4 g, 2.1 mmol) was precooled to −78 °C, and was quickly taken into a syringe and added to the above *N*-Boc-α-pyrrolidinylcyanocuprate solution. The reaction mixture became deep yellow to orange in color and the solution was stirred at −78 °C for an additional 1 h (still orange), then stirred at −40 °C for 2.5 h, whereupon the color changed from orange-brown to dark brown. After being stirred at room temperature for 15 min, the dark-brown solution was recooled to −78 °C, quenched with 10 mL of 1.0 N HCl, and warmed to room temperature whereupon it was treated with $NaHCO_3$ (sat.) to afford a solution with pH 10−11. The aqueous phase was separated and extracted with Et_2O (3 × 100 mL) and CH_2Cl_2 (3 × 60 mL). The combined extracts were dried over Na_2SO_4. The crude coupling product (4.74 g, ^1H NMR showed it to be mostly the desired coupling product with minor amounts of 1-carboethoxy-2-*sec*-butylcyclohenene) was obtained as a yellowish oil. The pure coupling product **4** (colorless oil, 2.68 g, 83%) was isolated by flash column chromatography (Biotage 65 M silica gel cartridge, 10% AcOEt/Hexane, v/v, ca. 2 L): ^1H NMR ($CDCl_3$, TMS) δ 1.28 (t, J = 7.2 Hz, 3 H), 1.37 (1.46) (s, 9 H, rotamer), 1.50−2.25 (m, 9 H), 2.25−2.60 (m, 2 H), 3.18−3.40 (m, 2 H), 3.40−3.90 (m, 1 H), 4.17 (q, J = 7.2 Hz, 2 H), 4.95 (t, J = 7.8 Hz), 5.10−5.20 (br s, 1 H, rotamer); ^{13}C

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NMR ($CDCl_3$, TMS) δ 14.3, 22.0, 22.3, 24.2, 24.6 (25.0), 25.4 (25.8), 26.4, 28.4, 32.4, 45.6 (45.9), 47.5 (48.0), 59.6 (60.0), 78.9, 124.5, 150.0, 154.5, 168.6 (rotamer); HR MS (FAB, *m*/*z*) 324.2177 (MH^+) (Calcd for $M^+ + H$, $C_{18}H_{30}NO_4$, 324.2175).

1-Phenylmethyl-5-carboethoxy-4-[1-(1,1-dimethylethyloxycarbonyl)pyrrolidin-2-yl]-1,2,3,6-tetrahydropyridine (5). ^1H NMR ($CDCl_3$, TMS) δ 1.25 (t, *J* = 6.8 Hz, 3 H), 1.39 (1.48) (s, 9 H, rotamer), 1.55−2.65 (m, 8 H), 3.10−3.40 (m, 3 H), 3.40−3.75 (m, 3 H), 4.15 (q, *J* = 6.9 Hz, 2 H), 5.20 (t, *J* = 7.2 Hz), 5.25−5.55 (2 br s, 1 H, rotamer), 7.32 (s, 5 H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.8, 23.8, 24.6, 28.0, 31.7 (32.1), 46.9, 48.3, 52.8, 58.7, 59.6, 61.6, 78.7, 122.3, 126.6, 127.8, 128.3 (128.7), 137.8, 150.8, 153.9, 166.0 (rotamer); HR MS (FAB, *m*/*z*) 415.2600 (MH^+) (Calcd for $M^+ + H$, $C_{24}H_{35}N_2O_4$, 415.2595).

1-Phenylmethyl-4-carboethoxy-3-[1-(1,1-dimethylethyloxycarbonyl)pyrrolidin-2-yl]-1,2,5,6-tetrahydropyridine (6). ^1H NMR ($CDCl_3$, TMS) δ 1.26 (t, *J* = 6.9 Hz, 3 H), 1.38 (1.46) (s, 9 H, rotamer), 1.55−2.20 (m, 5 H), 2.20−3.40 (m, 6 H), 3.40−3.80 (m, 3 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 5.12 (t, *J* = 7.4 Hz), 5.20−5.60 (3 br s, 1 H, rotamer), 7.30 (s, 5 H); ^{13}C NMR ($CDCl_3$, TMS) δ 14.2, 24.2, 26.7, 28.4, 32.4 (32.6), 47.4, 49.1, 52.4 (53.0), 58.5, 60.1, (62.1) 62.3, 79.3 (81.7), 122.4, 127.1, 128.2, 129.0, 137.8, 149.8, 154.4, 167.2 (rotamer); HR MS (FAB, *m*/*z*) 415.2600 (MH^+) (Calcd for $M^+ + H$, $C_{24}H_{35}N_2O_4$, 415.2595).

1,1-Dimethylethyl 3-Carboethoxy-2-[1-(1,1-dimethylethyloxycarbonyl)pyrrolidin-2-yl]-1,4,5,6-tetrahydropyridine-1-carboxylate (7). ^1H NMR ($CDCl_3$, TMS) δ 1.25 (t, *J* = 7.1 Hz, 3 H), 1.43 (s, 9 H), 1.47 (s, 9 H), 1.60−2.05 (m, 5 H), 2.05−2.70 (m, 4 H), 2.95−3.15 (m, 1 H), 3.15−4.00 (m, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 5.22 (t, *J* = 8.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, TMS) δ 14.2, (23.8) 24.3, 24.8, 28.3, 28.5, 31.1, 32.5, 45.1, 45.8, 47.9 (48.0), 59.6 (60.1), 78.6 (78.9), 80.9 (81.2), 118.0, 153.3, 153.7, (154.4) 154.9, 167.1 (rotamer); LC-MS (EI, *m*/*z*) 6.01 min, 425.1 ($M^+ + 1$, 30%), 369.1 (20%), 325.1 (60%), 269.1 (100%), 225.1 (70%), 179.1 (90%).

1,1-Dimethylethyl 2-(2-Carboethoxy-1-cyclohexen-1-yl)-1-piperidinecarboxylate (8). ^1H NMR ($CDCl_3$, TMS) δ 1.26 (t, *J* = 6.9 Hz, 3 H), 1.38 (s, 9 H,), 1.40−1.75 (m, 9 H), 1.75−1.85 (m, 1 H), 2.00−2.30 (m, 3 H), 2.30−2.50 (m, 1 H), 3.00 (m, 1 H), 3.96 (dd, *J* = 6.3 Hz, *J* = 12.0 Hz, 1 H), 4.13 (q, *J* = 6.6 Hz, 2 H), 5.07 (t, *J* = 5.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, TMS) δ 14.2, 19.2, 22.1, 22.2, 22.8, 25.6, 26.7, 27.3, 28.3, 39.7, 55.3, 59.9, 79.2, 123.8, 151.5, 155.8, 168.5; HR MS (FAB, *m*/*z*) 338.2330 (MH^+) (Calcd for $M^+ + H$, $C_{19}H_{32}NO_4$, 338.2331).

1,1-Dimethylethyl 2-(2-Carboethoxy-1-cyclohexen-1-yl)hexahydro-azepine-1-carboxylate (9). ^1H NMR ($CDCl_3$, TMS) δ 1.27 (t, *J* = 7.2 Hz, 3 H), 1.35 (s, 9 H), 1.45 (s, 5 H), 1.46−1.62 (m, 3 H), 1.62−1.85 (m, 3 H), 1.85−2.25 (m, 4 H), 2.25−2.55 (m, 1 H), 2.75−2.95 (m, 1 H), 3.34 (dt, *J* = 18.9 Hz, *J* = 6.0 Hz, 1 H), 4.00−4.30 (m, 2 H), 5.15.(dd *J* = 4.5, *J* = 12.0 Hz), 5.36 (dd *J* = 4.5 Hz, *J* = 12.0 Hz, 1 H, rotamer); ^{13}C NMR ($CDCl_3$, TMS) δ 14.2, 22.0, 22.2, 24.4 (24.9), 26.7 (27.0), 27.4, 28.3 (28.5), 29.3 (29.4), 30.7 (30.9), 32.5 (32.7), 44.1 (44.9), 46.5 (46.9), (59.1) 59.9, 79.1, 123.4, 152.3, 156.1, 168.1 (rotamer); HR MS (FAB, *m*/*z*) 352.2491 (MH^+) (Calcd for $M^+ + H$, $C_{20}H_{34}NO_4$, 352.2488).

1,1-Dimethylethyl Ester (2-Carboethoxy-1-cyclohexen-1-ylmethyl)methylcarbamic Acid (10). ^1H NMR ($CDCl_3$, TMS) δ 1.29 (t, *J* = 7.2 Hz, 3 H), 1.45 (s, 9 H), 1.50−1.80 (m, 4 H), 2.03 (br s, 2 H), 2.29 (br s, 2 H), 2.74 (br s, 3 H), 4.18 (q, *J* = 7.2 Hz, 4 H); ^{13}C NMR δ ($CDCl_3$, TMS) 14.2, 21.8, 22.1, 26.8, (28.1) 28.4, 32.5, 49.7, 50.7, 60.3, 79.5, 127.8, 143.6, 156.0, 168.8 (rotamer); HR MS (FAB, *m*/*z*) 298.2014 (MH^+) (Calcd for $M^+ + H$, $C_{16}H_{28}NO_4$, 298.2018).

Bis(1,1-dimethylethyl) Ester [2,2′-Bipyrrolidine]-1,1′-dicarboxylic Acid (11). ^1H NMR δ ($CDCl_3$ at 7.24 ppm as internal standard) 1.44 (s, 18 H), 1.53−2.18 (br m, 8 H), 3.08−3.41 (m, 4 H), 3.41−3.61 (br s, 1 H), 3.61−3.95 (br s, 1 H); ^{13}C NMR δ ($CDCl_3$ at 77.0 ppm as internal standard) 22.7, 23.4, 28.5, 46.6 (45.9, rotamer), 59.7, 79.5 (78.5, rotamer), 155.2; HR MS (FAB, *m*/*z*) 341.2441 (MH^+) (Calcd for $M^+ + H$, $C_{18}H_{33}N_2O_4$, 341.2440).

1,2,3,6,7,8,9,9b-Octahydro-5*H*-pyrrolo[2,1-*a*]isoindole-5-one (13). ^1H NMR δ ($CDCl_3$, TMS) 1.00−1.20 (m, 1 H), 1.50−1.80 (m, 4 H), 1.95−2.10 (m, 1 H), 2.10−2.20 (m, 3 H), 2.20−2.40 (m, 3 H), 3.15−3.30 (m, 1 H), 3.30−3.50 (m, 1 H), 3.95−4.05 (m, 1H); ^{13}C NMR δ ($CDCl_3$, TMS) 20.7, 22.3, 22.5, 24.4, 28.9, 29.7, 42.4, 68.1, 132.5, 157.4, 177.3; HR MS (FAB, *m*/*z*) 178.1233 (MH^+) (Calcd for $M^+ + H$, $C_{11}H_{16}NO$, 178.1232).

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **4**−**11** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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