α-(*N*-Carbamoyl)alkylcuprate Chemistry in the Synthesis of Nitrogen Heterocycles

R. Karl Dieter* and Kai Lu

Howard L. Hunter Chemistry Laboratory, Clemson University, Clemson, South Carolina 29634-0973.

dieterr@clemson.edu

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The conjugate adducts obtained via coupling of α-(*N*-carbamoyl)alkylcuprates with α,*β*-ynoates, α-allenyl esters, or α,*β*-enoates or enimides undergo *N*-Boc deprotection and cyclization onto the ester functionality upon treatment with PhOH/TMSCl, catecholboron bromide, or trimethylsilyl triflate. This two-pot sequence provides synthetic routes to 4-alkylidinepyrrolidine-2-ones, 4-alkylidinepyrrolizidin-2-ones, and 4-alkylidineindolizidin-2-ones via allenyl esters; pyrrolin-2-ones, tetrahydropyrrolizin-2-ones, and tetrahydroindolizin-2-ones via α,*β*-ynoates; pyrrolidin-2-ones, pyrrolizidin-2-ones, and indolizidin-2-ones via α,*β*-enoates or α,*β*-enimides. The reluctance of *γ*-carbamoyl-α,*β*-enoates to undergo *E*/*Z* isomerization requires the use of (*Z*)-*β*-iodo-α,*β*-enoates readily prepared by the addition of HI to the alkynyl esters for the efficient preparation of pyrrolinones, tetrahydropyrrolizinones, and tetrahydroindolizinones. Utilization of *ω*-functionalized α,*β*-ynoates or *β*-iodo-α,*β*-enoates allows for cyclization onto the *ω*-functionality providing for a synthetic route to quinolizidines.

Introduction

Pyrrolidine and piperidine heterocycles and their fused analogues are ubiquitous in nature and display a wide range of biological activities.[1−5] Numerous synthetic routes to naturally occurring pyrrolidines,[2] piperidines,[3] pyrrolizidines,[4] indolizidines,[5] and quinolizidines[5] are detailed in several monographs and review articles. Scalemic 3-pyrrolin-2-ones are important synthetic intermediates, and the structural unit is found in natural products displaying pharmacological activity (e.g., antitumor, inhibition of platelet aggregation, and psychotropic properties).[6] Polyhydroxylated pyrrolidines and indolizidines (i.e., aza sugars) are glycosidase inhibitors, and oligosaccharide synthesis and degradation is important in a wide variety of biological phenomena involving cell−cell interactions (e.g., aggregation, differentiation, and fusion, cellular transport, tumorigenesis, metastasis, inflammation, and blood clotting).[7] Many synthetic routes to these compounds introduce the nitrogen heteroatom into a carbon framework via azide, cyanide, or ammonia substitution reactions or via reduction of imine derivatives. The development of α-aminoalkylcarbanion methodologies has begun to provide alternative strategies for the synthesis of nitrogen heterocycles offering advantages in connectivity patterns and in asymmetric synthesis. α-Lithio carbamates have been exploited in the synthesis of pyrrolidines[8a,b] and piperidines,[8b−d] while benzotriazole stabilized carbanion chemistry has been exploited in the synthesis of pyrroles,[9a−c] imidazolidin-2-ones,[9d] oxazolidinones,[9d] and pyrrolidines.[9e] The participation of N-protected α-aminoalkylcuprates (i.e., α-cuprio formamidines, carbamates, and azo compounds) in conjugate addition reactions[10] and of α-(*N*-carbamoyl)alkylcuprates in substitution reactions with vinyl triflates,[11a] vinyl

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(10) For conjugate additions to unsaturated ketones and aldehydes, see: (a) Dieter, R. K.; Alexander, C. W. *Tetrahedron Lett.* **1992**, *33*, 5693. (b) Dieter, R. K.; Alexander, C. W. *Synlett* **1993**, 407. (c) Alexander, C. W.; Lin, S.-Y.; Dieter, R. K. *J. Organomet. Chem.* **1995**, *503*, 213. (d) Dieter, R. K.; Alexander, C. W.; Nice, L. E. *Tetrahedron* **2000**, *56*, 2767. For conjugate additions to α,*β*-unsaturated carboxylic acid derivatives, see: (e) Dieter, R. K.; Velu, S. E. *J. Org. Chem.* **1997**, *62*, 3798. (f) Dieter, R. K.; Lu, K. *Tetrahedron Lett.* **1999**, *40*, 4011. (g) Dieter, R. K.; Lu, K.; Velu, S. E. *J. Org. Chem.* **2000**, *65*, 8715.

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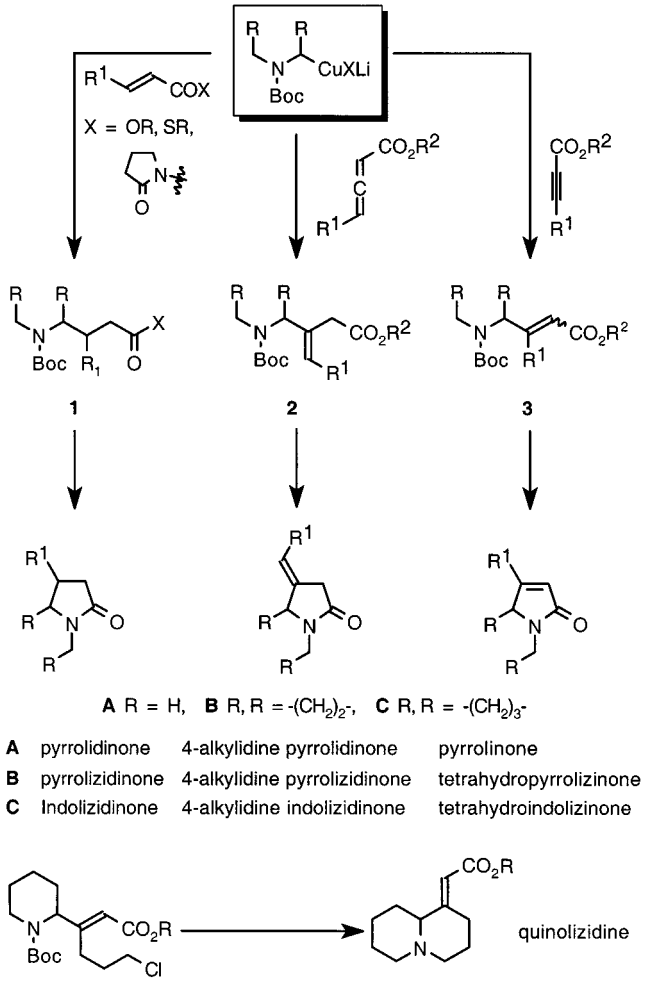
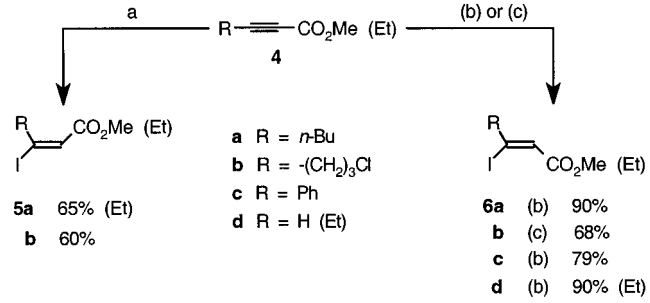
Scheme 1



iodides,[11b,c] and propargyl substrates[12] provides opportunities to exploit these reactions in the synthesis of nitrogen heterocycles. Conjugate addition reactions of α-(*N*-carbamoyl)alkylcuprates have been exploited in the synthesis of pyrroles[13] and 4-alkylidene pyrrolidinones and pyrrolizidinones.[10f] In this full account, we describe the synthesis of pyrrolidinones, pyrrolizidinones, indolizidinones, pyrrolinones, tetrahydropyrrolizinones, tetrahydroindolizinones, and quinolizidines via α-(*N*-carbamoyl)alkylcuprate chemistry.

The synthetic route to these N-heterocycles involves initial conjugate addition of α-(*N*-carbamoyl)-alkylcuprates to α,*β*-unsaturated carboxylic acid derivatives, α-allenyl esters, or α,*β*-ynoates followed by carbamate deprotection and cyclization (Scheme 1). *β*-Iodo-α,*β*-enoates can be substituted for α,*β*-ynoates and offer an alternative approach to stereocontrol in the formation of *γ*-carbamoyl-α,*β*-enoates and provide opportunities for asymmetric synthesis.[14] Cuprates derived from acyclic carbamates afford simple five-membered heterocycles while those derived from *N*-Boc-protected pyrrolidine or piperidine afford bicyclic (i.e., [3.3.0] and [4.3.0] systems

Scheme 2[a]



[a] Key: (a) (i) *n*-BuSnCu·SMe$_2$, LiBr, THF, −78 °C (from **4a**, 73%; **4b**, 69%), (ii) I_2, Et_2O, rt, overnight [**5a**, 82% (I_2), 89% (ICI); **5b**, 91% (I_2), 90% (ICI)]; (b) LiI or NaI, HOAc, 70 °C, 12 h; (c) NaI, TMSCl, H_2O (0.5 equiv), MeCN.

respectively) N-heterocycles with the N-atom at the ring fusion. Although this strategy is largely limited to formation of simple and annulated five membered N-heterocycles, *ω*-functionalized *β*-iodo-α,*β*-enoates or α,*β*-ynoates can be exploited in the synthesis of larger ring systems (e.g., quinolizidines, Scheme 1).

Results and Discussion

The requisite *γ*-carbamoyl esters (**1**), *β*-alkylidine-*γ*-carbamoyl esters (**2**), and *γ*-carbamoyl-α,*β*-enoates (**3**) were readily prepared via conjugate addition of α-(*N*-carbamoyl)alkylcuprates to α,*β*-unsaturated carboxylic acid derivatives, α-allenyl esters, and α,*β*-ynoates as previously described.[10g] (*Z*)-*β*-Iodo-α,*β*-enoates were prepared by the addition of HI to the corresponding α,*β*-ynoates. Although the use of LiI/AcOH[15] gave excellent yields of (*Z*)-isomers **6a**,**c**,**d**, the reaction gave many products with **4b** yielding only a trace of **6b** (Scheme 2). Good yields of **6b** could be obtained with in situ generated HI (i.e., Me_3SiCl, NaI, 0.5 H_2O)[16] in contrast to literature reports that treatment of α,*β*-ynones with this reagent system affords geometrical mixtures (i.e., *E*/*Z*) of *β*-iodo-α,*β*-enones,[17] the (*E*)-isomer,[18] or the deconjugated *β*-iodo-*β*,*γ*-enones[17] when excess TMSCl was employed. These results reflect, in part, the greater tendency of α,*β*-enones to undergo (*Z*)−(*E*)-isomerization[13] than the corresponding α,*β*-enoates (vide infra).[10g] (*E*)-*β*-Iodo-α,*β*-enoates were prepared via a two-step procedure involving conjugate addition of tri-*n*-butylstannylcopper to α,*β*-ynoates followed by iodination of the vinyl stannane.[19] Iodine and iodine monochloride gave comparable results in the iodination of the vinyl stannane. Although the stereochemistry was not rigorously established, the two procedures gave different geometrical isomers whose identity was confirmed in subsequent transformations (vide infra). Consequently, stereoselective routes to both the (*Z*)- and (*E*)-*β*-iodo-α,*β*-enoates are readily available for exploitation in α-(*N*-carbamoyl)alkylcuprate chemistry.

α-(*N*-Carbamoyl)alkylcuprates derived from *N*-Boc-protected dimethylamine **7a**, pyrrolidine **7b**, or piperidine **7c** underwent high-yield coupling with (*E*)- or (*Z*)-*β*-iodo-

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(17) (a) Luo, F.-T.; Kumar, K. A.; Hsieh, L.-C.; Wang, R.-T. *Tetrahedron Lett.* **1994**, *35*, 2553. (b) Luo, F.-T.; Hsieh, L.-C. *Tetrahderon Lett.* **1994**, *35*, 9585. (c) Luo, F.-T. *J. Org. Chem.* **1998**, *63*, 5656.
(18) Parsons, P. J.; Caddick, S. *Tetrahedron* **1994**, *50*, 13523.
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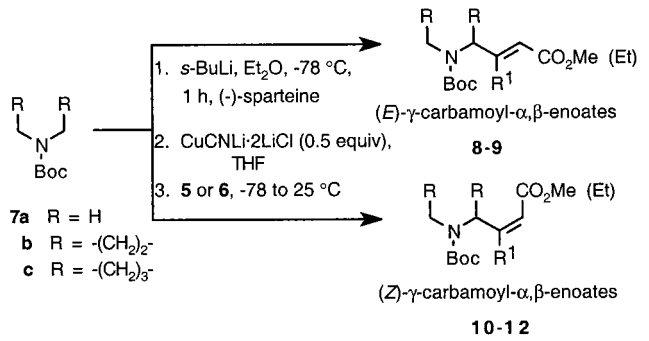
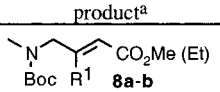
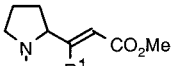
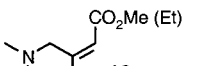
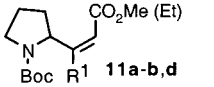
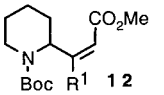
Table 1. Reaction of α-(*N*-Carbamoyl)alkylcuprates with (*E*)- or (*Z*)-β-Iodo-α,β-enoates



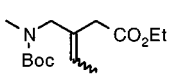
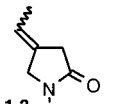
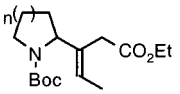
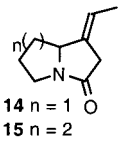
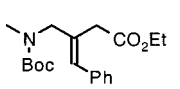
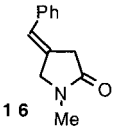
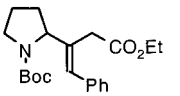
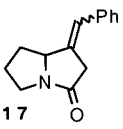
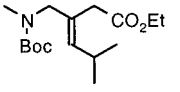
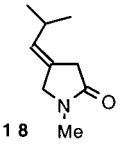
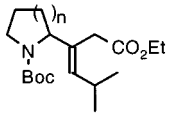
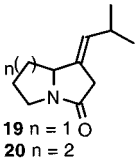
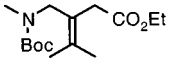
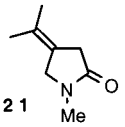
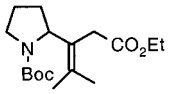
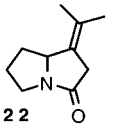
entry	*N*-Boc	vinyl iodide	R^1	product[a]	%[b] yield
1	**7a**	**5a**	*n*-Bu	 **8a-b**	56-89[c]
2	**7a**	**5b**	-$(CH_2)_3$Cl		95
3	**7b**	**5b**	-$(CH_2)_3$Cl	 **9**	71
4	**7a**	**6a**	*n*-Bu	 **10a-c**	63-82[c]
5	**7a**	**6b**	-$(CH_2)_3$Cl		81-88
6	**7a**	**6c**	Ph		59-74
7	**7b**	**6a**	*n*-Bu	 **11a-b,d**	53[d]-74[c]
8	**7b**	**6b**	-$(CH_2)_3$Cl		51
9	**7b**	**6d**	H		63-83[c]
10	**7c**	**6a**	*n*-Bu	 **12**	65

[a] The R_2CuLi reagent prepared from 2RLi + CuCN·2LiCl (0.5 equiv) was employed unless otherwise noted. Methyl ester used unless otherwise noted. [b] Yields based upon isolated products purified by flash column chromatography. [c] Ethyl ester was employed. [d] RCuCNLi was employed.

α,β-enoates (i.e., **5a**,**b** and **6a**−**d**, respectively) to afford γ-carbamoyl-α,β-enoates **8**−**12** stereospecifically in generally excellent yields (Table 1). Lower yields were generally obtained with cuprates derived from **7c** (entry 10) than from **7a**,**b**, although a low yield of vinylation product was observed with the pyrrolidinyl cuprate and **6b** (entry 8). Vinylations of α-(*N*-carbamoyl)alkylcuprates are high-yield reliable transformations[11c] that also afford high enantioselectivity[14] with scalemic *N*-Boc-pyrrolidinylcuprates.

In the initial study, the deprotection of the γ-carbamoyl-β-alkylidine esters and subsequent cyclization was achieved in a single pot using PhOH/TMSCl (Table 2).[10f] The carbamate deprotection procedure developed by Merrifield[20] called for the use of large excesses of PhOH (30 equiv) and TMSCl (10 equiv), which at times posed problems in the workup procedure. Subsequent experiments revealed that these quantities could be reduced without diminution of yields. Catecholboron bromide[21] and trimethylsilyl triflate[22] also effected the sequential carbamate deprotection and cyclization in generally somewhat higher yields (entries 2 and 3 vs 1 and 14 vs 13), although similar yields were obtained in pyrrolizidinone formation (entries 4 and 5). These protocols failed to effect cyclization to the indolizidine skeleton and required modification. Formation of indolizidinone **15** required a two-step procedure involving *N*-Boc deprotection (PhOH/TMSCl) of the γ-carbamoyl-β,γ′-enoate followed by Me_3Al-mediated cyclization[23] of the free amine onto the ester functionality to afford **15** in good yield (63%).

Table 2. Synthesis of 4-Alkylidine-2-pyrrolidinones, 2-Pyrrolizidinones, and 2-Indolizidinones from β-Alkylidine-γ-*N*-carbamoyl Esters

entry	β-alkylidine-γ-carbamoyl esters[a]	n	rxn. cond.[b]	heterocycle[c]	% yield[d]
1			A	 **13**	65[e]
2			B		83[f]
3			C		85
4		1	A	 **14** n = 1 **15** n = 2	60
5		1	D		61
6		2	E		63
7			A	 **16**	63
8			A	 **17**	92[g]
9			A	 **18**	60
10		1	A	 **19** n = 1 **20** n = 2	67
11		2	D		91
12			A	 **21**	62
13			A	 **22**	60
14			B		83

[a] Carbamate deprotonation (*s*-BuLi, sparteine or TMEDA, THF, −78 °C) followed by sequential addition of 1.0 equiv of CuCN·2LiCl (−55 °C, 45 min) and allenyl ester [TMSCl (2.5 equiv), −55 °C to rt]. [b] A = PhOH (15−30 equiv), TMSCl (5−10 equiv), CH_2Cl_2 (25 °C, 2 h). B = catecholboron bromide. C = trimethylsilyl triflate (TMSOTf, 1−2 equiv). D = TMSOTf (10 equiv). E = A and then Me_3Al (2.0 equiv), CH_2Cl_2 [0−25 °C, 3 h]. [c] Olefin diastereomeric ratio (dr) determined by ^1H NMR analysis; >95:5 unless noted. [d] Isolated yields based upon products purified by column chromatography. [e] Dr = 84:16. [f] Dr = 88:12. [g] Dr = 66:34.

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(21) Boeckman, R. K., Jr.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

(22) Hamada, Y.; Kato, S.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 3223.

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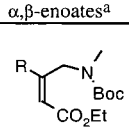
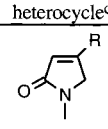
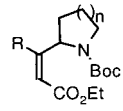
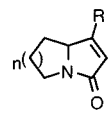
As previously reported, the conjugate addition of α-(*N*-carbamoyl)alkylcuprates to α-allenyl esters afforded the (*E*)-olefins diastereoselectively in ratios generally >95:5.[10f] This stereoselectivity is a consequence of the cuprate reagent approaching the 2,3-double bond of the allenyl ester anti to the more bulky substitutent at C-4. In two instances, where the *β*,*γ*-enoate was generated as a mixture of (*E*)- and (*Z*)-diastereomers (e.g., 86:14 and 91:9), the ratio was maintained during the deprotection and cyclization events (e.g., 84:16 and 88:12, respectively, Table 1, entries 1 and 2). Nevertheless, a phenyl-substituted (*E*)-olefin was found to undergo significant *E*/*Z* isomerization during the deprotection cyclization sequence with PhOH/TMSCl (i.e., 66:34 dr, entry 8). This isomerization occurred in the formation of pyrrolizidinone **17** (entry 8) but not during the formation of pyrrolidinone **16** (entry 7). The origin of this isomerization is curious. It seems unlikely that it occurs via protonation of the more strained and therefore more easily protonated olefin in **17** since this would reasonably be expected to afford the pyrrolin-2-one with an endocyclic double bond. The observation of *E*/*Z* isomerization in **17** but not **16** suggests that isomerization may be tied to the relative rates of cyclization. This would be consistent with the slow rate of HCl formation from PhOH/TMSCl compared to the rapid rate for carbamate deprotection.[20]

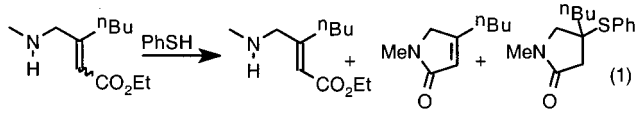
The resultant 4-alkylidinepyrrolidin-2-ones (i.e., **13**, **16**, **18, 21)**, pyrrolizidin-2-ones (**14**, **17**, **19**, **22**), and indolizidin-2-ones (i.e., **15** and **20**) contain a *β*,*γ*-unsaturated lactam functionality that can provide opportunities for enolate chemistry. Deprotonation of **13** or **14** with lithium diisopropyl amide (1.5−1.8 equiv, THF, −78 °C) followed by quenching with dimethyl sulfate (−50 to +25 °C) gave α-alkylation in good to excellent yields (90% and 70%, respectively) with no positional or stereoisomerization of the exocyclic double bond. Alkylation of **14** afforded a 1:1 mixture of diastereomers presumably arising via enolization of the methylation product by the excess base employed (1.8 equiv). Excess base was employed in these small scale reactions (<1.0 mmol) to ensure complete deprotonation.

The conjugate addition of α-(*N*-carbamoyl)alkylcuprates to α,*β*-ynoates afforded mixtures of (*E*)- and (*Z*)-α,*β*-enoates and the stereoselectivity of this reaction could not be controlled.[10g] Upon treatment of the *E*/*Z* mixture with the deprotection-cyclization protocols only the (*Z*)-diastereomer underwent cyclization and the (*E*)-isomer was recovered as unchanged amine. Reaction of the pyrrolidinyl cuprate derived from **7b** with ethyl 2-heptynoate gave **11a** and its (*E*)-isomer as a 57:43 mixture which upon treatment with PhOH/TMSCl gave **26** (53%) and the free amine of the (*E*)-diastereomer (35%) in a comparable ratio (60:40). This was in marked contrast to the *γ*-(*N*-carbamoyl)-α,*β*-enones in which both the (*E*)- and (*Z*)-diastereomers gave rise to pyrroles under the carbamate deprotection procedures,[13] illustrating the reluctance of α,*β*-enoates to undergo facile *E*/*Z* isomerization. Efforts to effect isomerization of the (*E*)-isomer to the (*Z*)-isomer with catalytic amounts of PhSSPh proved unsuccessful.[24a] Heating (*E*)-*N*-Boc-*N*-methylaminomethyl-2-heptenoate neat with 2.0 equiv of thiophenol[24c] effected (*E*)- to (*Z*)-isomerization and cyclization to afford **23** in 59% yield (eq 1). Efforts to reduce the amount of thiophenol employed gave either lower conversions of the (*E*)-isomer to **23** or increased amounts of the thiophenol conjugate adduct (eq 1). This deprotection-thiophenol protocol did not work for a *γ*-carbamoyl-α,*β*-enoate containing a pyrrolidine [i.e., ethyl (*E*)-3-(2-pyrrolidinyl)-2-heptenoate] ring system. To circumvent these difficulties, the vinylation with stereodefined *β*-iodo-α,*β*-enoates was employed for the preparation of (*Z*)-*γ*-*N*-carbamoyl-α,*β*-enoates (vide supra, Table 1).

Table 3. Synthesis of Pyrrolin-2-ones, Pyrrolizidin-2-ones, and Indolizidin-2-ones from *γ*-*N*-carbamoyl-α,*β*-enoates

entry	*γ*-*N*-Boc α,β-enoates[a]	n	R	rxn[b] cond	heterocycle[c]	cpd No.	%[d] yield
1		-	*n*-Bu	A		**23**	84
2		-	$(CH_2)_3Cl$	A		**24**	86
3		-	Ph	A		**25**	73
4		1	*n*-Bu	A		**26**	71
5		1	$(CH_2)_3Cl$	A		**27**	81
6		2	$(CH_2)_3Cl$	A		**28**	17[e]
7		2	*n*-Bu	B		**29**	<10[f]

[a] Prepared via the stereoselective vinylation of **7a**−**c** or obtained via chromatographic separation of the *E*/*Z* mixture of diastereomers resulting from reaction of **7a**−**c** with **4b**. [b] A = PhOH (15−30 equiv), TMSCl (5−10 equiv), CH_2Cl_2 (25 °C, 2 h). B = A and then Me_3Al, CH_2Cl_2. [c] **23** R = *n*-Bu; **24** R = $-(CH_2)_3Cl$; **25** R = Ph; **26** R = *n*-Bu, *n* = 1; **27** R = $-(CH_2)_3Cl$, *n* = 1; **28** R = $-(CH_2)_3Cl$, *n* = 2; **29** R = *n*-Bu, *n* = 2. [d] Yields based upon isolated products purified by column chromatography. [e] The quinolizidine **34** (Scheme 3) was formed in 56% yield. [f] Yield estimated from GC−MS ion-current trace. Uncyclized piperidine was recovered in 51% yield.



(1)

E:*Z*	PhSH (equiv), T °C, t		relative ratios (% yield)	
E	(2.0), 70, 3 h	8	81 (59)	11
E:*Z* (1:1)	(0.5), 70, 3-4 h	47	46	7
E:*Z* (1:1)	i. (0.5), 70, 3-4 h			
	ii. 100, 12 h		59	41

Treatment of the (*Z*)-*γ*-*N*-carbamoyl-α,*β*-enoates with PhOH/TMSCl effected clean carbamate cleavage and cyclization for the simple pyrrolin-2-ones (Table 3, entries 1−3) and pyrrolizidin-2-ones (entries 4−5). Indolizidin-2-ones **28** and **29** (entries 6−7) were not obtained upon treatment of the *γ*-(*N*-carbamoyl)-α,*β*-enoates with PhOH/TMSCl or TMSOTf. Although low yields of indolizidin-2-ones could be achieved by subsequent treatment with trimethylaluminum,[23] the major products were either the free amine of the (*E*)-diastereomer (entry 7) or cyclization onto an *ω*-functionality (entry 6, **34** Scheme 3).

ω-Functionalized α,*β*-ynoates provide potential opportunities for cyclization onto the *ω*-functionality as well as onto the ester moiety (Scheme 3). This synthetic strategy was probed employing α-(*N*-carbamoyl)alkylcuprates derived from *N*-Boc-protected *N*,*N*-dimethylamine (**7a**), pyrrolidine (**7b**), and piperidine (**7c**) and methyl 6-chloro-2-ynoate **4b** (prepared from 5-chloro-1-pentyne and methyl chloroformate) or (*E*)-**5b** and (*Z*)-6-chloro-3-iodo-2-enoate **6b** derived from it. The requisite

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Scheme 3

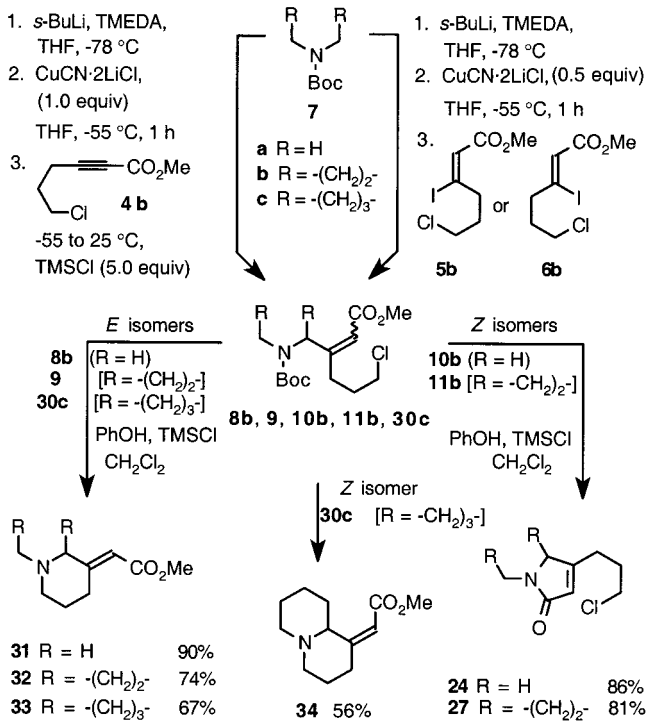
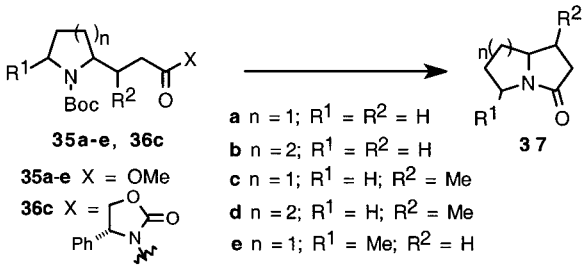


Table 4. Synthesis of Pyrrolizidin-2-ones and Indolizidinones from γ-*N*-carbamoyl Esters



entry	ester or imide	ester or imide dr[a]	rxn cond[b]	heterocycle	n	cpd No.	% yield[c] (dr)[d]
1	**35a**	-	A		1	**37a**	89
2	**35b**	-	A		2	**37b**	70
3	**35c**	60:40	A		1	**37c**	55 (65:35)
4	**35d**	69:31	B		2	**37d**	73 (86:14)
5	**36c**[e]		A		1	**37c**	63 (95:5)
6	**36c**[f]	76:24[g]	C		1	**37c**	66 (78:22)
7	**35e**	80:20	A		1	**37e**	67 (100:0)

[a] Diastereomeric ratio (dr) determined from ^{1}H NMR integrations and ^{13}C NMR peak heights. [b] A = PhOH (30), TMSCl (10), CH_2Cl_2. B = A and then ii. Me_3Al, CH_2Cl_2. C = A and then neutralize with solid K_2CO_3/CH_2Cl_2. [c] Yields determined on isolated products purified by column chromatography. [d] Dr determined from HPLC, GC−MS, ^{1}H NMR integrations, and ^{13}C NMR peak heights. [e] Conjugate addition was performed in ether. [f] Conjugate addition was performed in THF. [g] Determined by ^{1}H NMR integration on the spectrum of the HCl salt of the free amine.

γ-carbamoyl-α,β-enoates were prepared either as a separable mixture of (*E*)- and (*Z*)-diastereoisomers via conjugate addition of α-(*N*-carbamoyl)alkylcuprates to α,β-ynones or stereoselectively via vinylation of α-(*N*-carbamoyl)alkylcuprates with either (*E*)- or (*Z*)-6-chloro-3-iodo-2-hexynoate (i.e., **5b** or **6b**, respectively). Reaction of *E*/*Z* mixtures of γ-carbamoyl-α,β-enoates obtained via the conjugate addition of **7a** or **7b** with **4b** gave mixtures of products arising via the two modes of cyclization in ratios comparable to the original *E*/*Z* ratio. The reaction of **7a** with **4b** gave an *E*/*Z* mixture of diastereomers **8b**/**10b** (47:53) that upon deprotection−cyclization gave a 49:51 mixture of **31**/**24**. Similarly, reaction of the cuprate derived from **7b** with **4b** afforded a 64:36 mixture of **11b** and its (*E*)-diastereomer **9**, which upon treatment with PhOH/TMSCl gave a 74:26 ratio of **27**/**32**.

These observations were confirmed by utilization of the pure (*E*)- or (*Z*)-diastereomers obtained either by chromatographic separation or stereospecifically from the respective (*E*)- or (*Z*)-6-chloro-3-iodo-2-enoates **5b** and **6b**, respectively. Upon treatment with PhOH/TMSCl, the (*E*)-diasteromer **8b**, **9**, or **30c** underwent *N*-Boc deprotection and cyclization onto the alkyl chloride in good to excellent yields to afford the piperidine **31**, indolizidine **32**, and quinolizidine **33**, respectively. Similar treatment of the (*Z*)-diastereomers **10b** or **11b** afforded the pyrolin-2-one **24** or pyrrolizin-2-one **27**, respectively, in good yields. Reaction of the (*Z*)-diastereomer of **30c**, however, afforded quinolizidine **34** rather than the indolizin-2-one **28** (Table 3, entry 6) reflecting again the difficulty of forming indolizin-2-ones via these cyclizations. Quinolizidines **33** and **34** are diastereomeric about the carbon−carbon double bond.

Conjugate addition of pyrrolidinyl- (from **7b**) or piperidinylcuprates (from **7c**) to α,β-unsaturated esters[10g] followed by *N*-Boc deprotection and cyclization affords the fully saturated pyrrolizidin-2-ones and indolizidin-2-ones, respectively (Table 4). Conjugate addition to methyl acrylate followed by deprotection and cyclization with PhOH/TMSCl afforded both the pyrrolizidin-2-one **37a** and indolizidin-2-one **37b** in excellent to good yields (entries 1 and 2). PhOH/TMSCl effected *N*-Boc deprotection of **35d** but failed to effect cyclization to **37d**, which could be achieved in good yield by subsequent treatment with Me_3Al (entry 4). The methyl absorptions for **37d** in the ^{1}H NMR spectrum permitted assignment of the major [(1*R**,9*S**), δ 1.19 (lit.[25] δ 1.08−1.14)] and minor [(1*S**,9*S**), δ = 1.08 (lit.[25] δ 0.96−1.04)] diastereomers by comparison with previous assignments.

Utilization of methyl crotonate also afforded a mixture of diastereomeric conjugate adducts (entry 3). Deprotection and cyclization of **35c** gave a mixture of diastereomeric pyrrolizidin-2-ones **37c** in roughly the same ratio as the starting γ-carbamoyl esters (entry 3), while cyclization of **35d** gave a slightly enhanced dr of indolizidin-2-ones **37d** (entry 4) suggesting a differential cyclization efficiency for the two diastereomeric conjugate adducts. The major [(1*R**,8*S**), δ 1.12 (lit.[26a,b] δ 1.00−1.15)] and minor [(1*S**,8*S**), δ = 0.95 (lit.[26b] δ 0.98)] diastereomers of pyrrolizidin-2-one **37c** could also be assigned by comparison with a literature report. The ^{13}C absorptions for **37c** matched those reported for the (1*R**,8*S**) diastereomer.[26a] Utilization of enantiopure oxazolidinone **36c** derived from crotonic acid afforded an undetermined mixture of diastereomeric conjugate ad-

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(26) (a) Das, S.; Kumar, J. S. D.; Shivaramayya, K.; George, M. V. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1797. (b) Mori, M.; Kanda, N.; Oda, I.; Ban, Y. *Tetrahedron* **1985**, *41*, 5465.

ducts in Et_2O and a 76:24 ratio in THF (entries 5 and 6). The diastereomer ratio for the 1,4-adducts obtained in THF was determined from the ^1H NMR spectrum of the HCl salt of the free amine obtained via *N*-Boc-deprotection. The reaction of the pyrrolidinyl cuprate with enantiopure oxazolidine **36c** can afford four diastereomers which upon *N*-Boc-deprotection and cyclization with concomitant removal of the chiral auxiliary reduces to two diastereomers readily discernible in the ^1H and ^{13}NMR spectra of **37c.** The sample of pyrrolizidin-2-one **37c** obtained via deprotonation of **7b** in Et_2O, cuprate formation, conjugate addition, and cyclization was analyzed by chiral-phase HPLC, which displayed three separable components X, Y, Z (17.5:3.5:79.9 ratios, respectively). A dr of 95:5 observed in the ^1H NMR spectrum requires that the minor enantiomer of the minor diastereomer lie under either peak X or peak Z and the major enantiomer of the minor diastereomer be identified with peak Y. Even without knowing which peak conceals the minor enantiomer of the minor diastereomer, an enantiomeric excess of the major diastereomer can be placed in the range of 64−66% (i.e., 82:18−83:17 er) and approximately 40% ee for the minor diastereomer.[27a] The latter figure is extremely sensitive to errors in ^1H integration values. Chiral phase HPLC analysis thus confirms the diastereoselectivity (95:5) and establishes an upper limit for the enantioselectivity (66%, er = 83:17) of the major diastereomeric conjugate adduct. This is consistent with differential rates of reaction for a matched and mismatched pair of chiral reactants[27b] (i.e., **36c** and the chiral cuprate containing a stereogenic center bound to copper) resulting in a dynamic kinetic resolution of the racemic cuprate reagent. This interpretation is supported by the observation that reaction of the pyrrolidinylcuprate gave no enantioselectivity in conjugate addition reactions with benzyl acrylate[14] consistent with kinetic resolution of the chiral pyrrolidinylcuprate by the scalemic oxazolindinone. The excellent diastereoselectivity and good enantioselectivity under dynamic kinetic resolution suggests that the procedure may be synthetically useful. Finally, conjugate addition of the cuprate reagent derived from *N*-Boc-2-methylpyrrolidine gave an 80:20 dr of conjugate adducts from which a single diastereomeric pyrrolizidin-2-one **37e** was isolated from the deprotection cyclization sequence. The diastereomeric product obtained from **35e** could be assigned as (5*S**,8*S*) **37e** [δ = 3.43 H_5 (lit.[28] δ = 3.55), δ = 3.94 H_8 (lit.[28] δ = 3.95) rather than the (5*R**,8*S**) diastereomer [lit.[28] δ = 4.16−3.55] by comparison with literature data. These results indicate that modest to excellent diastereoselectivity can be achieved depending upon the substitution pattern of the α-(*N*-carbamoyl)-alkylcuprate and the carboxylic acid derivative employed. The use of scalemic oxazolidinones as a chiral auxiliary holds some promise for control of both relative and absolute stereochemistry in this approach to fused heterocyclic ring systems.

Summary

In summary, conjugate addition of α-(*N*-carbamoyl)-alkylcuprates to a variety of α,β-unsaturated carboxylic acid derivatives followed by *N*-Boc-deprotection and cyclization affords efficient synthetic routes to a diverse range of simple and fused nitrogen heterocycles. These include 4-alkylidine pyrrolidine-2-ones, 4-alkylidine pyrrolizidin-2-ones, and 4-alkylidine indolizidin-2-ones via allenyl esters; pyrrolin-2-ones, tetrahydropyrrolizin-2-ones, and tetrahydroindolizin-2-ones via α,β-ynoates and pyrrolidin-2-ones; and pyrrolizidin-2-ones and indolizidin-2-ones via α,β-enoates. Incorporation of an additional functional group in the α,β-unsaturated system provides opportunities for the synthesis of addition ring systems (e.g., quinolizidines) via cyclization onto this additional functionality. This strategy provides a rapid entry to the piperidinyl acetic acid **31**, which in principle, can be converted via lithium diethyl cuprate conjugate addition to 3,3-dialkylpiperidines of the type employed in a number of synthetic approaches to quebrachamine and the aspidospermidine family of alkaloids.[29] The two pot sequence of conjugate addition followed by *N*-Boc-deprotection and cyclization is efficient for the synthesis of all the ring systems examined with the exception of tetrahydroindolizin-2-ones which were formed in low yields. Utilization of chiral oxazolidinones allows for modest to excellent diastereoselectivity in both a relative and absolute sense for the synthesis of the fully saturated rings systems. Asymmetric vinylation of α-(*N*-carbamoyl)-alkylcuprates provides opportunities for the synthesis of scalemic pyrrolin-2-ones and tetrahydropyrrolizin-2-ones, which are richly functionalized for further synthetic elaboration.

Experimental Section

Materials. α,β-Alkynyl esters were commercially available (i.e., **4a**, **4d**) or readily prepared (i.e., **4a-c**) by an established procedure.[10g] γ-Carbamoyl-α,β-enoates **8a**/**10a**, **8b**/**10b**, **9**, **10c**, and **11a**,**b** were previously prepared as mixtures of (*E*)- and (*Z*)-diastereomers[10g] while **11d** was previously prepared enantioselectively.[14] The ethyl ester analogue of **12** was previously prepared.[10g] The known β-iodo enoates **5a**,[30] **6a**,[30] and **6c**[31] and the commercially available **6d**, along with **5b** and **6b**, were prepared by the stereoselective addition of HI to the corresponding α,β-alkynyl esters[15,16] or by reaction of vinylstannanes with I_2. The β-alkylidine-γ-*N*-carbamoyl esters (Table 2) were prepared as previously described.[10g] Heterocycles **22**,[33] **23**,[32] **25**,[34] **31**,[35] **37a**,[36] **37b**,[37] **37c**,[26] **37d**,[25] and **37e**[28]have been reported in the literature.

General conditions for GC−MS analysis involved utilization of an Alltech EC-1 column [100% dimethylpolysiloxane, 30 m, 0.25 i.d., 0.25 μm coating, 60/350 °C] with an initial oven temperature of 60 °C, a final temperature of 280 °C, and a heating rate of 10 °C/minute. Deuteriochloroform ($CDCl_3$) was employed as solvent for ^1H and ^{13}C NMR measurements.

(27) (a) By assuming the minor enantiomer represents a peak area *W* contributing to peak *X* or *Z*, there is a unique value of *W* that reproduces the NMR diastereomeric ratio $(X + Z - W)/(Y + W) = 95/5$. (b) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed, Engl.* **1985**, *24*, 1.

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Methyl 6-Chloro-2-hexynoate (4b). To a solution of 5-chloropentyne (2.05 g, 20 mmol) in diethyl ethyl (50 mL) at −30 °C was added a solution of *n*-BuLi in hexane (1.5 N, 13.3 mL) dropwise via syringe. The reaction mixture was stirred at −30 °C for 30 min and warmed to 0 °C for 30 min. Then the resulting white turbid mixture was cooled to −30 °C, and a solution of methyl chloroformate (1.89 g, 20 mmol) in 10 mL of ether was added dropwise via syringe. As the addition proceeded a white solid was formed. The reaction mixture was stirred at −30 °C for 20 min and warmed to room temperature during a period of 1 h. The solid LiCl was filtered, and the filtrate was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo afforded crude alkynyl ester. Kugelrohr distillation gave pure alkynyl ester **4b** as a colorless oil (3.11 g, 97%): ^{1}H NMR ($CDCl_3$) δ 2.00−2.14 (m, 2H), 2.59 (t, J = 6.9 Hz, 2H), 3.69 (t, J = 6.6 Hz, 2H), 3.73 (m, 3H); ^{13}C NMR δ 15.9, 30.1, 43.1, 52.5, 73.4, 87.3, 153.8.

(*E*)-Methyl 6-Chloro-3-iodo-2-heptenoate (5b). To a solution of diisopropylamine (0.28 mL, 2 mmol) in dry THF (2 mL) at −78 °C under nitrogen was added a solution of *n*-BuLi in hexane (1.4 mL, 1.6 N, 2.1 mmol), and the resulting solution was stirred for 20 min at −78 °C. Tri-*n*-butyltin hydride (Bu_3SnH) (0.52 mL, 2 mmol) was added to the above solution by syringe, and the mixture was stirred for 1 h. Then the complex Me_2S·CuBr (0.41 g, 2 mmol) was added quickly as a solid, and the resulant dark red solution was stirred for another 20 min at −78 °C until the cuprate was formed. A solution of α,β-ynoates (1.54 mmol) in THF (1 mL) was added to the cuprate solution, and the reaction mixture was stirred at −78 °C for 3 h before 0.5 mL of methanol was added, followed by a solution of NH_3/NH_4Cl (pH = 8). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic solution was washed with brine and dried with $MgSO_4$. Removal of solvent in vacuo gave crude stannane, which was purified by chromatography (silica gel, 100% petroleum ether followed by petroleum ether/ether (98:2). The resultant vinyl tin compound was added to a solution of iodine or monochloroiodide (1.5 equiv. in 10 mL ether) and the reaction solution was stirred overnight at room temperature. The reaction solution was then diluted with 30 mL of ether and washed with $Na_2S_2O_3$ (5%) until the color of iodine disappeared and then with brine. The organic phase was dried over $MgSO_4$. Removal of the solvent in vacuo gave crude product which was purified by chromatography (silica gel, 98:2/petroleum ether:ether, v/v) affording **5b** in 60% overall yield for the two steps as a colorless oil: ^{1}H NMR δ 1.99−2.19 (m, 2H), 3.27 (t, J = 7.2 Hz, 2H), 3.57 (t, J = 6.6 Hz, 2H), 3.70 (s, 3H), 6.69 (s, 1H); ^{13}C NMR δ 32.3, 38.9, 43.3, 51.6, 126.9, 131.9, 164.3.

(*Z*)-Methyl 6-Chloro-2-hexynoate (6b). To 10 mL of dry CH_3CN in a 50 mL round-bottomed flask at room temperature under nitrogen was added dry NaI (1.80 g, 12 mmol), and the mixture was stirred for several minutes until NaI was dissolved. TMSCl (1.54 mL, 12 mmol) was added to the solution by syringe, and the resultant solution was stirred for 15 min followed by the addition of water (95 mg). The mixture was stirred for 30 min, and a solution of methyl 6-chlorohexynoate (1.61 g, 10 mmol) was added by syringe. After being stirred for 2−3 h at room temperature, the reaction was quenched with H_2O (1−2 mL). The mixture was diluted with ether (30 mL), washed with $Na_2S_2O_3$ (5%) and brine, and dried with $MgSO_4$. Removal of solvent afforded crude product, which was almost pure vinyl iodide. Further purification by Kugelrohr distillation gave 1.95 g of **6b** as a colorless oil (68%) (0.05 mmHg, 75−80 °C oven temperature): ^{1}H NMR ($CDCl_3$) δ 1.99−2.12 (m, 2H), 2.88 (t, J = 7.2 Hz, 2H), 3.53 (t, J = 6.3 Hz, 2H), 3.75 (s, 3H), 6.43 (s, 1H); ^{13}C NMR δ 31.4, 42.8, 44.3, 51.6, 119.1, 125.9, 164.7; mass spectrum, *m*/*z* (relative intensity) EI 290 (M^+ + 2, isotope peak, 06), 288 (M^+, 19), 257 (16), 161 (M^+ − I, 48), 129 (19), 93 (25), 59 (100).

General Procedure for Reaction of α-(*N*-Carbamoyl)-alkylcuprates with β-Iodo-α,β-enoates. A solution of *N*-Boc-protected amine (i.e., **7a**−**c**, 1 mmol) and (−)-sparteine (1.3 mmol) in 3 mL of THF under an Ar or N_2 atmosphere was cooled to −78 °C. *s*-BuLi (in cyclohexane, 1.2 mmol) was added via syringe, and this mixture was allowed to stir at −78 °C for 1 h.[38] A solution of the complex CuCN·2LiCl in THF (prepared by dissolving 0.5 mmol of CuCN and 1 mmol of LiCl in 2 mL of THF) was added via syringe to the 2-lithio-*N*-Boc carbamate, and the solution was warmed from −78 to −55 °C over a period of 60 min to generate the cuprate reagent. A solution of (*E*)- or (*Z*)-β-iodo-α,β-enoate (0.5 mmol) in THF (1 mL) was added to the cuprate reagent, and the reaction mixture was stirred at −55 °C for 0.5 h followed by warming to room temperature over 3−4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL), filtered through Celite, extracted with ether (3 × 10 mL), and washed with saturated NH_4Cl (2 × 5 mL) and brine (5 mL). The extract was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the crude product, which was purified by chromatography.

(*E*)-Methyl 3-[[(1,1-Dimethylethoxycarbonyl)methylamino]methyl]-6-chloro-2-hexenoate (8b). Employing the general procedure and **7a** (1 mmol) afforded after purification by chromatography [silica gel, ether/petroleum ether, 10:90, v/v] pure **8b** as a colorless oil (145 mg, 95%): IR (neat) 2979 (m), 2944 (m), 2936 (m), 1720 (s), 1700 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (1.46) (s, 9H), 1.87−2.08 (m, 2H), 2.63 (t, J = 7.5 Hz, 2H), (2.79) 2.83 (s, 3H), 3.57 (t, J = 6.6 Hz, 2H), 3.69 (s, 3H), 3.87 (3.92) (s, 2H), 5.65 (s, 1H); ^{13}C NMR δ 27.6, 28.3, 31.4, 34.4, 44.7, 51.1, (54.1) 54.7, 80.1, 115.2, 155.4 (155.9), 157.4, 166.3 (rotamer); mass spectrum, *m*/*z* (relative intensity) EI 249 ($M^+ - C_4H_8$, 02), 232 (03), 205 ($M^+ - CO_2$, 28), 190 (11), 174 (16), 142 (27), 57 (100).

(*E*)-Methyl 3-[[(1,1-Dimethylethoxy)carbonyl]-2-pyrrolidinyl]-6-chloro-2-hexenoate (9). Employing the general procedure and **7b** (171 mg, 1 mmol) afforded after purification by chromatography [silica gel, ether/petroleum ether, 20:80, v/v] pure **9** as a colorless oil (117 mg, 71%): IR (neat) 2975 (s), 2956 (s), 2884 (m), 1725 (s), 1702 (s), 1659 (s), 1394 (s), 1169 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (1.44) (s, 9H), 1.15−1.85 (m, 3H), 1.85−2.35 (m, 4H), 2.90−3.20 (m, 1H), 3.25−3.55 (m, 2H), 3.50−3.65 (m, 2H) 3.67 (s, 3H), 4.20−4.45 (m, 1H), 5.65 (s, 1H) (rotamer); ^{13}C NMR δ 23.3, 28.0, 28.4, 31.4, 31.8, 45.0, 46.9, 51.0, 62.1, 79.9, 113.5, 154.1, 162.7, 166.7; mass spectrum, *m*/*z* (relative intensity) EI 331 (M^+, 01), 275 ($M^+ - C_4H_8$, 06), 258 (14), 231 (275 − CO_2, 24), 216 (17), 196 (48), 168 (100), 70 (48), 57 (C_4H_9, 88).

(*Z*)-Methyl 3-[[(1,1-Dimethylethoxycarbonyl)methylamino]methyl]-6-chloro-2-hexenoate (10b). Employing the general procedure and **7a** (1 mmol) afforded after purification by chromatography [silica gel, ether/petroleum ether, 10:90, v/v] pure **10b** as a colorless oil (81−88%): IR (neat) 2979 (m), 2948 (m), 2936 (m), 1720 (s), 1700 (s), 1149 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.87−2.09 (m, 2H), 2.17−2.42 (m, 2H), (2.74) 2.77 (s, 3H), 3.52 (t, J = 6.6 Hz, 2H), 3.69 (s, 3H), (4.52) 4.55 (s, 2H), (5.81) 5.83 (s, 1H) (rotamers); ^{13}C NMR δ 28.3, (29.8) 30.3, (31.7) 31.9, 35.9, 43.9 (44.1), (46.5) 48.0, 51.2, 80.0 (80.5), (119.3) 119.5, 156.0 (156.9), (158.2) 158.3, 166.7 (rotamer); mass spectrum, *m*/*z* (relative intensity) EI 249 ($M^+ - C_4H_8$, 02), 232 (06), 205 ($M^+ - CO_2$, 43), 190 (28), 172 (31), 142 (41), 110 (44), 57 (100).

(*Z*)-Methyl 3-[[(1,1-Dimethylethoxy)carbonyl]-2-pyrrolidinyl]-6-chloro-2-hexenoate (11b). Employing the general procedure and **7b** (171 mg, 1 mmol) afforded after purification by chromatography [silica gel, ether/petroleum ether, 20:80, v/v] pure **11b** as a colorless oil (84 mg, 51%): IR (neat) 2976 (s), 2880 (s), 1720 (s), 1692 (s), 1460 (s), 1169 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (1.42) (s, 9H), 1.45−1.65 (m, 1H), 1.65−2.05 (m, 4H), 2.05−2.50 (m, 3H), 3.20−3.40 (m, 1H), 3.54 (t, J = 6.3 Hz, 2H), 3.67 (3.65) (s, 3H), 3.50−3.80 (m, 1H), 5.54 (t, J = 7.5 Hz, 1H), 5.64 (s, 1H) (rotamer); ^{13}C NMR δ 24.3 (24.7), 28.2, 28.4, (30.4) 30.7, 32.4, 44.2 (44.3), 47.6 (47.8), 51.0, 58.1 (58.3), 79.6, 114.5 (117.7), 154.6, 163.9, 166.3 (rotamer); mass spectrum, *m*/*z* (relative intensity) EI 331 (M^+, 01), 274 ($M^+ - C_4H_9$, 05), 258 (14), 230 (274 − CO_2, 83), 216 (12), 198 (76), 168 (100).

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(*Z*)-Methyl 3-[[(1,1-Dimethylethoxy)carbonyl]-2-piperidinyl]-2-heptenoate (12). Employing the general procedure and **7c** (185 mg, 1 mmol) afforded after purification by chromatography [silica gel, ether/petroleum ether, 10:90, v/v] pure **12** as a colorless oil (106 mg, 65%): IR (neat) 2953 (s), 2928 (s), 2868 (m), 1720 (s), 1695 (s), 1404 (s), 1155 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, $J = 7.2$ Hz, 3H), 1.30 (s, 9H), 1.23−1.44 (m, 5H), 1.44−1.72 (m, 4H), 1.74−1.86 (m, 1H), 2.00−2.14 (m, 2H), 2.97−3.07 (m, 1H), 3.61 (s, 3H), 3.86−3.97 (m, 1H), 5.49−5.55 (m, 1H), 5.54 (s, 1H); ^{13}C NMR δ 14.0, 19.3, 22.7, 22.9, 27.8, 28.3, 29.9, 32.1, 39.9, 51.0, 54.1, 79.9, 113.3, 155.9, 166.5, 167.5; mass spectrum, *m*/*z* (relative intensity) EI 268 ($M^+ - C_4H_9$, 66), 252 (07), 224 (268 − CO_2, 93), 210 (19), 192 (49), 182 (100), 166 (33), 150 (55), 57 (C_4H_9, 70).

General Procedure A for *N*-Boc Deprotection and Lactam Formation. To a solution of PhOH (2.82 g, 30 mmol) and TMSCl (1.28 mL, 10 mmol) in 10 mL of CH_2Cl_2 at room temperature was added 1 mmol of the conjugate addition product in 2 mL of CH_2Cl_2. The mixture was stirred for 60 min and then diluted with 50 mL of ether. The solution was washed three times with 10% NaOH (20, 10, 5 mL) and one time with brine (5 mL) and then dried over $MgSO_4$. Removal of solvent gave crude product that was purified by chromatography [silica gel, ether/petroleum ether (1:1), or pure ether].

General Procedure B for *N*-Boc Deprotection and Lactam Formation. A solution of the conjugate addition product (0.5 mmol) in dry CH_2Cl_2 (2 mL) was treated dropwise with catecholboron bromide (0.2 M in CH_2Cl_2, 5 mL) at room temperature. After being stirred at room temperature for 1 h, the reaction mixture was quenched with 2 mL of H_2O, stirred for 20 min, and then diluted with an additional 30 mL of CH_2Cl_2 whereupon it was washed with 10% NaOH solution (2 × 15 mL) and brine. The organic phase was dried over $MgSO_4$. Removal of solvent gave crude product that was purified by chromatography [silica gel, ether/petroleum ether (1:1), or pure ether).

General Procedure C for *N*-Boc Deprotection and Lactam Formation. A solution of the conjugate addition product (0.5 mmol) in 5 mL of dry CH_2Cl_2 was treated with TMSOTf (1−10 equiv) at −30 °C, followed by warming the solution to room temperature over a period of 2−3 h. The reaction mixture was then diluted with 30 mL of CH_2Cl_2 and washed with $NaHCO_3$ (saturated), and the solution was dried over $MgSO_4$. Removal of solvent gave crude product that was purified by chromatography [silica gel, ether/petroleum ether (1:1), or pure ether].

General Procedure D for *N*-Boc Deprotection and Lactam Formation. Crude product (0.5 mmol) from general procedure A was dissolved in CH_2Cl_2, and the solution was cooled to 0 °C. A solution of Me_3Al in toluene (2 M, 0.5 mL, 2.0 equiv) was added dropwise to the reaction mixture via syringe. The reaction mixture was then warmed to 25 °C, stirred for 5−6 h, quenched by addition of water, and diluted with CH_2Cl_2. The organic phase was washed with aqueous HCl (5%) and dried over $MgSO_4$. Removal of the solvent in vacuo afforded crude material that was purified by column chromatography.

(*E*)-4-Ethylidene-1-methyl-2-pyrrolidinone (13). Employing general procedure A, ethyl 3-[[[(1,1-dimethylethoxy)-carbonyl]methylamino]methyl]-3-pentenoate (40 mg, 0.13 mmol) was treated with phenol (0.367 g, 3.9 mmol) and TMSCl (1.3 mmol, 0.17 mL) in 3 mL of CH_2Cl_2 to afford pure **13** (12 mg, 65%) as a colorless oil after purification by chromatography. Employing general procedure B, ethyl 3-[[[(1,1-dimethyl-ethoxy)carbonyl]methylamino]methyl]-3-pentenoate (120 mg, 0.39 mmol) was treated with catechol boron bromide (0.2 M in CH_2Cl_2, 2 mL) to afford **13** as a colorless oil (46 mg, 83%). Employing general procedure C, the 1,4-adduct (60 mg, 0.20 mmol) was treated with TMSOTf (0.05 mL) at −40 to −20 °C for 3 h in 2 mL of CH_2Cl_2 to afford **13** (24 mg, 85%): IR (neat) 2919 (s), 2868 (s), 1685 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55−1.65 (m, 3H), 2.85 (2.88) (s, 3H), 2.98 (3.04) (s, 2H), 3.94 (s, 2H), 5.36−5.52 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 29.2, 34.3, 54.7, 118.7, 127.6, 172.9; mass spectrum, *m*/*z* (relative intensity) 125 (M^+, 100), 110 ($M^+ - CH_3$, 51), 96 (13), 82 (33), 67 (88), 53 (33).

(*E*)-1-Ethylidenehexahydro-3*H*-pyrrolizin-3-one (14). Employing general procedure A, the 1,4-adduct (90 mg, 0.3 mmol) was treated with phenol (0.74 g, 7.9 mmol) and TMSCl (2.6 mmol, 0.34 mL) in 5 mL of CH_2Cl_2 to afford pure **14** (28 mg, 60%) as a colorless oil after purification by chromatography. Employing general procedure C, the 1,4-adduct (24 mg, 0.1 mmol) was treated with TMSOTf (0.15 mL) at −30 to +25 °C for 3 h, giving **14** as colorless oil (8 mg, 61%): IR (neat) 2970 (m), 2927 (m), 1702 (s), 1677 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25−1.45 (m, 1H), 1.55−1.75 (m, 3H), 1.90−2.15 (m, 3H), 3.00−3.15 (m, 1H), 3.15 (AB quartet, $\delta_A = 3.34$, $\delta_B = 2.96$, $J_{AB} = 21.0$ Hz, 2H), 3.55−3.75 (m, 1H), 4.25−4.40 (m, 1H), 5.40−5.50 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 24.2, 31.2, 37.3, 41.8, 66.2, 118.8, 134.2, 174.2; mass spectrum, *m*/*z* (relative intensity) 151 (M^+, 100), 136 ($M^+ - CH_3$, 79), 123 (77), 108 (23), 94 (58), 80 (98), 67 (33); high-resolution mass spectrum *m*/*z* 151.0993 (M^+) (calcd for $C_9H_{13}NO$ 151.0997).

(*E*)-1-Ethylidenehexahydro-2*H*-indolizin-3-one (15). Employing general procedure D, the 1,4-adduct (187 mg, 0.6 mmol) was treated with phenol (0.85 g, 9.0 mmol) and TMSCl (3.0 mmol, 0.39 mL) in 4 mL of CH_2Cl_2, followed by addition of Me_3Al solution (2 N, 0.5 mL) at 0 °C and then warming to room temperature over 5 h. Pure **15** (62 mg) was obtained as a white solid after chromatography: ^1H NMR ($CDCl_3$) δ 1.06−1.18 (m, 1H), 1.18−1.33 (m, 1H), 1.33−1.48 (m, 1H), 1.57 (d, $J = 4.5$ Hz, 3H), 1.55−1.68 (m, 1H), 1.77−1.92 (m, 2H), 2.51−2.62 (m, 1H), 2.93 (s, 2H), 3.76−3.84 (m, 1H), 4.08−4.18 (m, 1H), 5.31−5.41 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 23.6, 24.6, 32.6, 34.3, 39.7, 61.2, 117.9, 133.8, 170.9; mass spectrum, *m*/*z* (relative intensity) 165 (M^+, 49), 150 ($M^+ - CH_3$, 100), 136 (17), 122 (19), 108 (14), 94 (19), 80 (19). Anal. Calcd for $C_{10}H_{15}NO$: C, 72.70; H, 9.20; N, 8.50. Found: C, 72.48; H, 9.18; N, 8.69.

(*E*)-Hexahydro-1-(phenylmethylidene)-3*H*-pyrrolizin-3-one (17). Employing general procedure A, the 1,4-adduct (90 mg, 0.3 mmol) was treated with phenol (0.60 g, 6.4 mmol) and TMSCl (2.1 mmol, 0.27 mL) in 5 mL of CH_2Cl_2 affording pure **17** (49 mg, 92%) as a colorless oil after purification by chromatography [silica gel, ether/petroleum ether, v/v 1:1]: IR (neat) 3060 (m), 3030 (m), 2970 (s), 2894 (s), 1690 (s), 1404 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05−1.25 (m, 1H), 1.87−2.05 (m, 1H), 2.10−2.45 (m, 2H), 3.20−3.40 (m, 1H), 3.42−3.60 (m, 1H), 3.72 (s, 2H), 4.10−4.21(m, 1H), 5.75 (s, 1H), 7.15−7.55 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.8, 29.2, 36.2, 42.0, 68.6, 123.0, 126.9, 128.6, 128.8, 136.7, 164.8, 176.5; mass spectrum, *m*/*z* (relative intensity) 213 (M^+, 100), 185 (30), 170 (22), 156 (37), 122 (56), 91 ($PhCH_2^+$, 04)

(*E*)-Hexahydro-1-(2-methylpropylidene)-3*H*-pyrrolizin-3-one (19). Employing general procedure A, the 1,4-adduct (150 mg, 0.46 mmol) was treated with phenol (1.20 g, 12.8 mmol) and TMSCl (6.3 mmol, 0.80 mL) in 5 mL of CH_2Cl_2 affording pure **19** (55 mg, 67%) as a colorless oil after purification by chromatography [silica gel, ether/petroleum ether, v/v 1:1]: IR (neat) 2962 (s), 2928 (s), 2868 (m), 1711 (s), 1685 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, $J = 3.6$ Hz, 3H), 0.95(d, $J = 3.6$ Hz, 3H), 1.25−1.45 (m, 1H), 1.90−2.15 (m, 3H), 2.15−2.35 (m, 1H), 2.98−3.10 (m, 1H), 3.16 (AB quartet, $\delta_A = 3.36$, $\delta_B = 2.96$, $J_{AB} = 19.5$ Hz, 2H), 3.55−3.70 (m, 1H), 4.20−4.30 (m, 1H), 5.60−5.75 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3, 22.5, 26.1, 28.8, 31.2, 37.2, 41.7, 66.1, 131.1, 131.7, 174.1.

(*E*)-Hexahydro-1-(2-methylpropylidene)-2*H*-indolizin-3-one (20). Employing general procedure C, the 1,4-adduct (26 mg, 0.1 mmol) was treated with TMSOTf (0.15 mL) at −30 to 25 °C for 3 h in 2 mL of CH_2Cl_2 affording pure **20** (14 mg, 91%) as a colorless oil after purification by chromatography [silica gel, ether/petroleum ether, v/v 1:1]: ^1H NMR ($CDCl_3$) δ 0.96 (d, $J = 6.6$ Hz, 6H), 1.11−1.57 (m, 3H), 1.61−1.72 (m, 1H), 1.81−2.06 (m, 2H), 2.24−2.45 (m, 1H), 2.63−2.75 (m, 1H), 3.02 (d, $J = 1.2$ Hz, 2H), 3.86 (d, $J = 11.1$ Hz, 1H), 4.21 (dd, $J = 4.8$ Hz, $J = 12.6$ Hz, 1H), 5.12−5.26 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.4, 22.5, 23.6, 24.5, 28.9, 32.6, 34.1, 39.7, 61.0, 130.7, 130.9, 170.8; mass spectrum, *m*/*z* (relative intensity) 193 (M^+, 05), 192 ($M^+ - 1$, 06), 178 ($M^+ - CH_3$, 16), 150 ($M^+ -$

C_3H_7, 100), 136 (04), 122 (08); high-resolution mass spectrum *m*/*z* 193.1469 (M^+) (calcd for $C_{12}H_{19}NO$ 193.1467).

(*E*)-1-Methyl-4-(1-methylethylidene)-2-pyrrolidinone (21). Employing general procedure A, the 1,4-adduct (90 mg, 0.3 mmol) was treated with phenol (0.71 g, 7.4 mmol) and TMSCl (2.6 mmol, 0.34 mL) in 5 mL of CH_2Cl_2 affording pure **21** (27 mg, 62%) as a colorless oil after purification by chromatography [silica gel, pure ether]: IR (neat) 2928 (s), 2851 (s), 1715 (s), 1690 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (s, 3H), 1.62 (s, 3H), 2.87 (s, 3H), 2.98 (s, 2H), 3.92 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 19.5, 20.8, 29.3, 35.4, 53.6, 120.1, 125.7, 173.6; mass spectrum, *m*/*z* (relative intensity) 139 (M^+, 58), 124 ($M^+ - CH_3$, 100), 110 (10), 96 (26), 82 (30), 67 (93).

4-(3-Chloropropyl)-1,5-dihydro-1-methyl-2*H*-pyrrol-2-one (24). Employing general procedure A, the coupling product **10b** (80 mg, 0.3 mmol) was treated with phenol (0.70 g, 7.5 mmol) and TMSCl (2.3 mmol, 0.30 mL) in 3 mL of CH_2Cl_2 affording pure **24** (39 mg, 86%) as a colorless oil: IR (neat) 3087 (w), 2960 (m), 2923 (m), 1684 (s), 1445 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.94−2.13 (m, 2H), 2.52 (t, J = 7.2 Hz, 2H), 2.99 (s, 3H), 3.58 (t, J = 6.3 Hz, 2H), 3.86 (s, 2H), 5.87 (t, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.6, 28.3, 30.3, 43.9, 56.4, 122.7, 157.1, 171.7; mass spectrum, *m*/*z* (relative intensity) 175 ($M^+ + 2$, 05), 173 (M^+, 15), 110 ($M^+ - CH_2CH_2Cl$, 100), 96 (29), 82 (13); high-resolution mass spectrum *m*/*z* 173.0607 (M^+) (calcd for $C_8H_{12}ClNO$ 173.0607).

1-Butyl-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one (26). Employing general procedure A, the coupling product **6a** (156 mg, 0.5 mmol) was treated with phenol (0.71 g, 7.5 mmol) and TMSCl (2.5 mmol, 0.32 mL) in 5 mL of CH_2Cl_2 affording pure **26** (64 mg, 71%) as a colorless oil after purification by chromatography [silica gel, ether/petroleum ether, v/v 1:1]: IR (neat) 3084 (w), 2962, 2936, 2880, 1702 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3H), 1.11−1.30 (m, 1H), 1.30−1.47 (m, 2H), 1.47−1.64 (m, 2H), 2.02−2.19 (m, 2H), 2.19−2.42 (m, 3H), 3.15−3.30 (m, 1H), 3.34−3.53 (m, 1H), 4.03−4.19 (m, 1H), 5.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.4, 28.9, 29.1, 29.3, 29.4, 42.1, 69.0, 121.6, 166.5, 176.7; mass spectrum, *m*/*z* (relative intensity) 179 (M^+, 23), 136 ($M^+ - C_3H_7$, 100), 122 ($M^+ - C_4H_9$, 15), 109 (44); high-resolution mass spectrum *m*/*z* 179.1309 (M^+) (calcd for $C_{11}H_{17}NO$ 179.1310).

1-(3-Chloropropyl)-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one (27). Employing general procedure A, the coupling product **6b** (35 mg, 0.1 mmol) was treated with phenol (0.24 g, 2.5 mmol) and TMSCl (0.8 mmol, 0.10 mL) in 2 mL of CH_2Cl_2 affording pure **27** (17 mg, 81%) as a colorless oil after purification by column chromatography [silica gel, ether/petroleum ether, v/v 1:1]: IR (neat); ^1H NMR ($CDCl_3$) δ 1.06−1.20 (m, 1H), 1.94−2.15 (m, 3H), 2.15−2.35 (m, 2H), 2.38−2.62 (m, 2H), 3.15−3.32 (m, 1H), 3.36−3.50 (m, 1H), 3.57 (t, J = 6.3 Hz, 2H), 4.04−4.23 (m, 1H), 5.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.5, 28.9, 29.3, 30.0, 42.1, 43.9, 69.0, 122.2, 164.3, 176.5; mass spectrum, *m*/*z* (relative intensity) 201 ($M^+ + 2$, isotope peak, 05), 199 (M^+, 12), 164 ($M^+ - Cl$, 08), 136 ($M^+ - CH_2CH_2Cl$, 100), 122 (13), 109 (23), 80 (13).

1-(3-Chloropropyl)-5,6,7,8-tetrahydro-3*H*-indolizin-3-one (28). Employing general procedure A, the conjugate adduct (*Z*)-**30c** (150 mg) afforded pure **28** (15 mg, 17%): IR (neat) 3090 (w), 2941 (s), 2860 (m), 1758 (m), 1692 (s), 1427 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (qd, J_q = 12.3 Hz, J_t = 3.3 Hz, 1H), 1.19−1.45 (m, 1H), 1.45−1.64 (m, 1H), 1.64−1.87 (br m, 1H), 1.87−2.23 (m, 4H), 2.23−2.64 (m, 2H), 2.76 (td, J_t = 12.9 Hz, J_d = 3.0 Hz, 1H), 3.60 (td, J_t = 6.0 Hz, J_d = 1.8 Hz, 2H), 3.72 (dd, J_d = 12.0 Hz, J_d = 3.9 Hz, 1H), 4.26 (dd, J_d = 13.5 Hz, J_d = 5.1 Hz, 1H), 5.85 (s, 1H); ^{13}C 23.5, 25.0, 25.6, 30.0, 30.5, 39.0, 43.9, 62.4, 121.4, 161.3, 168.8; mass spectrum, *m*/*z* (relative intensity) 215 ($M^+ + 2$, isotope peak, 03), 213 (M^+, 09), 178 ($M^+ - Cl$, 28), 150 (100), 136 (22), 122 (14), 108 (13); mass spectrum *m*/*z* 213.0918 (M^+) (calcd for $C_{11}H_{16}ClNO$ 213.0920).

(*E*)-Hexahydro-8-(methoxycarbonyl)methylidene-7*H*-indolizidine (32). Employing general procedure A, the *E* isomer **9** (30 mg, 0.1 mmol) was treated with phenol (0.25 g, 2.7 mmol) and TMSCl (1.0 mmol, 0.12 mL) in CH_2Cl_2 at 25 °C to afford pure **32** (13 mg, 74%) after purification by column chromatography: IR (neat) 2951 (s), 2881 (s), 1715 (s); ^1H NMR δ 1.89−2.09 (m, 4H), 2.11−2.28 (m, 1H), 2.28−2.42 (m, 1H), 2.65−2.78 (m, 1H), 2.85−2.95 (m, 1H), 3.40−3.50 (m, 1H), 3.50−3.68 (m, 3H), 3.71 (s, 3H), 4.02−4.15 (m, 1H), 6.22 (s, 1H); ^{13}C NMR δ 23.0, 28.5, 30.0, 31.6, 44.7, 44.9, 51.5, 63.7, 119.4, 153.0, 165.5; mass spectrum, *m*/*z* (relative intensity) 195 (M^+, 19), 194 ($M^+ - 1$, 15), 180 ($M^+ - CH_3$, 100), 167 (16), 136 (84), 122 (21), 108 (19), 79 (11), 55 (11).

(*E*)-Octahydro-1-(methoxy)carbonylmethylidene-2*H*-quinolizine (33). Employing general procedure A, the (*E*)-isomer of methyl 3-[[(1,1-dimethylethoxy)carbonyl]-2-piperidinyl]-6-chloro-2-hexenoate (**30c**) (80 mg, 0.24 mmol) was treated with phenol (0.65 g, 6.9 mmol) and TMSCl (2.4 mmol, 0.30 mL) in 2 mL of CH_2Cl_2. The crude material was purified by column chromatography directly without washing with NaOH (10%) affording pure **33** (32 mg, 67%) as a colorless oil: IR (neat) 2945 (s), 2860 (m), 2760 (m), 1710 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19−1.42 (m, 1H), 1.47−1.68 (m, 3H), 1.68−2.04 (m, 5H), 2.11−2.36 (m, 2H), 2.36−2.50 (m, 1H), 2.92 (d, J = 11.4 Hz, 2H), 3.67 (s, 3H), 3.83 (d, J = 13.2 Hz, 1H), 5.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.2, 25.0, 25.7, 28.1, 28.4, 51.0, 56.2, 57.3, 65.6, 112.8, 160.0, 167.4; mass spectrum, *m*/*z* (relative intensity) 209 (M^+, 23), 194 ($M^+ - CH_3$, 100), 180 (16), 167 (11), 150 (45), 136 (27), 124 (15).

(*Z*)-Octahydro-1-(methoxycarbonyl)methylidene-2*H*-quinolizine (34). Employing general procedure A, the *Z* isomer of methyl 3-[[(1,1-dimethylethoxy)carbonyl]-2-piperidinyl]-6-chloro-2-hexenoate [(*Z*)-**30c**] (150 mg, 0.43 mmol) was treated with phenol (1.22 g, 13.0 mmol) and TMSCl (4.5 mmol, 0.56 mL) in 3 mL of CH_2Cl_2. The crude material was purified by column chromatography directly without washing with NaOH (10%) affording pure **34** (51 mg, 56%) as colorless oil: IR (neat) 2962 (s), 2783 (s), 2706 (s), 1725 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40−1.65 (m, 1H), 1.69−1.92 (m, 2H), 1.92−2.23 (m, 5H), 2.42−2.60 (m, 1H), 2.84−3.08 (m, 2H), 3.38−3.54 (m, 1H), 3.54−3.70 (m, 3H), 3.67 (s, 3H), 6.40 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 23.1, 28.4, 29.3, 31.5, 44.7, 45.7, 51.4, 61.8, 119.4, 155.5, 165.7; mass spectrum, *m*/*z* (relative intensity) 209 (M^+, 27), 194 ($M^+ - CH_3$, 100), 180 (17), 167 (13), 150 ($M^+ - CO_2Me$, 34), 136 (36), 124 (19).

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Supporting Information Available: Experimental procedures for the preparation of **4c**, **5a**, and **6a**. Data reduction (IR, ^1H NMR, ^{13}C NMR, mass spectrum) for compounds **4c**, **5a**, **6a**,**c**,**d**, **8a**, **10a**,**c**, **11a**,**d**, **16**, **18**, **22**, **23**, **25**, **31**, and **37b**−**e**. ^{13}C NMR spectra for **13**, **16**−**22**, **24**, **26**−**28**, and **32**−**34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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