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Regioselective and Stereoselective Copper(I)-Promoted Allylation and Conjugate Addition of *N*-Boc-2-lithiopyrrolidine and *N*-Boc-2-lithiopiperidine

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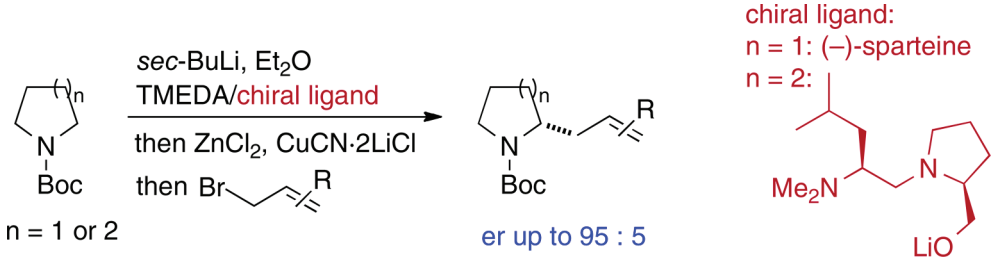
Received March 5, 2010



Copper salts have been screened for transmetalation and electrophilic quench of *N*-*tert*-butoxycarbonyl-2-lithiopyrrolidine (*N*-Boc-2-lithiopyrrolidine) and *N*-Boc-2-lithiopiperidine, formed by deprotonation of *N*-Boc-pyrrolidine and *N*-Boc-piperidine, respectively. Transmetalation with zinc chloride then (lithium chloride solubilized) copper cyanide followed by allylation typically gives mixtures of regioisomers (S_N2 and S_N2' products), whereas transmetalation with copper iodide·TMEDA then allylation occurs regioselectively (S_N2 mechanism). Addition to an enone or α,β-unsaturated ester occurs by 1,4-addition. Asymmetric deprotonation of *N*-Boc-pyrrolidine or dynamic resolution in the presence of a chiral ligand of *N*-Boc-2-lithiopiperidine followed by the zinc/copper chemistry was successful and gave the allylated pyrrolidine and piperidine products with good enantioselectivity, although use of the copper iodide chemistry resulted in some loss of enantiopurity. The chemistry provides formal syntheses of (+)-allosedridine, (+)-lasubine II, and (+)-pseudohygroline and has been used for the synthesis of (+)-coniine, (−)-pelletierine, (+)-coniceine, (−)-norhygrine, and the ant extract alkaloids *cis*- and *trans*-2-butyl-5-propylpyrrolidine.

Introduction

The formation of carbon−carbon bonds is a fundamental process in synthetic chemistry and often involves the direct interaction of nucleophilic intermediates with electrophilic partners. Organolithium compounds have emerged as very attractive nucleophilic intermediates, and their reactions have been studied extensively.[1,2] In many cases, these organolithiums give poor results with electrophiles such as Michael acceptors, allylic and aryl halides. However, the transmetalation of these species to, for example, organozinc[3−6] or organocopper[7−14] species can provide organometallic compounds with different nucleophilicities that open up wider synthetic transformations.

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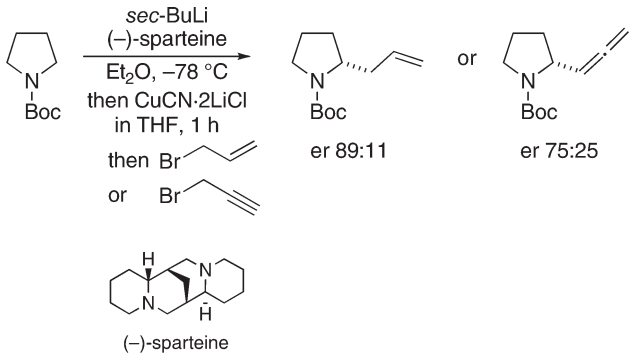
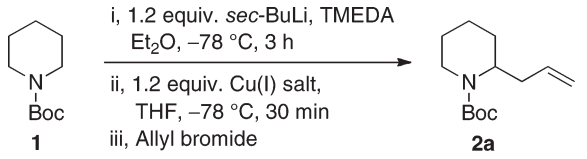
DOI: 10.1021/jo100415x Published on Web 05/14/2010

SCHEME 1. Related Results by Dieter and Co-workers (Boc = $CO_2{}^tBu$)



SCHEME 2. Formation of *N*-Boc-2-allylpiperidine 2a



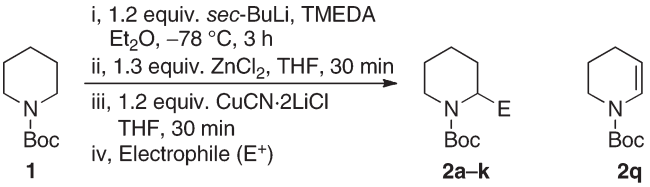
The organolithiums formed by deprotonation in the 2-position of *N*-*tert*-butoxycarbonyl-2-lithiopyrrolidine (*N*-Boc-pyrrolidine) and *N*-Boc-piperidine with *sec*-BuLi/TMEDA, developed by Beak and co-workers,[15] are important reagents due to the presence of pyrrolidines and piperidines in many natural products and pharmaceutical compounds.[16−18] Addition of these organolithiums to allyl halides results in low yields (if any) of the 2-allylated cyclic amine products. However, Dieter and co-workers have reported the transmetalation of *N*-Boc-2-lithiopyrrolidine and *N*-Boc-2-lithiopiperidine with CuCN·2LiCl and have studied the reactivity of these cuprate reagents with a range of different electrophiles.[19−24] Addition of allyl bromide or propargyl bromide to the dialkylcopper lithium species generated from enantiomerically enriched *N*-Boc-2-lithiopyrrolidine [enantiomer ratio (er) ~97:3 (*S*/*R*), formed by asymmetric deprotonation with *sec*-BuLi/(−)-sparteine][25] and CuCN·2LiCl (0.5 equiv) gave, respectively, *N*-Boc-2-allylpyrrolidine with some loss of enantiopurity (er 89:11) or *N*-Boc-2-allenylpyrrolidine with more significant loss of enantiopurity (er 75:25) (Scheme 1).[26] No substituted allyl halides were reported, so the regioselectivity issue was not addressed. In addition, no allylation reactions (racemic or asymmetric) have been reported with *N*-Boc-2-lithiopiperidine.

TABLE 1. Screen of Copper(I) Salts for Allylation

entry	Cu(I) salt	yield (%)
1	CuCN·2LiCl	52
2	CuCl	35
3	$CuBr \cdot SMe_2$	41
4	CuI	39
5	$ZnCl_2$ then CuCN·2LiCl	67[a]

[a]38% yield using diethyl allyl phosphate.

SCHEME 3. Zinc−copper-Based Reactions of *N*-Boc-2-lithiopiperidine



Recently, we showed that *N*-Boc-2-lithiopiperidine reacts with electrophiles either directly or via transmetalation to the corresponding organozinc reagent.[27−30] In order to expand the range of electrophiles amenable to this versatile reagent, we decided to study various copper(I) salts and electrophiles. We hoped to find a system that would allow regioselective allylation and reaction, using an enantioenriched organolithium, without loss of enantioselectivity. The results of these efforts are described in this paper, together with the application of this chemistry to the synthesis of a selection of simple 2-substituted pyrrolidine- and piperidine-containing natural products.

Results and Discussion

Initially, we chose *N*-Boc-2-lithiopiperidine as the nucleophile and studied a selection of conditions for allylation.[26,31−33] The results of addition of various Cu(I) salts to this organolithium followed by allyl bromide are shown in Scheme 2 and Table 1. The use of CuCN·2LiCl (1.1 equiv in comparison with the organolithium) gave the desired compound **2a** in 52% yield (yield based on the piperidine **1**). With copper halides, inferior results were obtained. Organozinc cuprates have been shown to be good nucleophiles,[34−37] and we were pleased to find an increase in the yield of **2a** when $ZnCl_2$ was added prior to CuCN·2LiCl (Table 1, entry 5). Lower yields of the product **2a** were obtained using substoichiometric amounts of CuCN·2LiCl or using diethyl allyl phosphate instead of allyl bromide as the electrophile.

Based on these preliminary results, we developed the strategy illustrated in Scheme 3. Deprotonation of *N*-Boc-piperidine

(15) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.
(16) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine: Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and Its Derivatives*; Elsevier: Amsterdam, 1991.
(17) O'Hagan, D. *Nat. Prod. Rep.* **2000**, 435.
(18) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693.
(19) Dieter, R. K.; Lu, K. *J. Org. Chem.* **2002**, *67*, 847.
(20) Li, S. J.; Dieter, R. K. *J. Org. Chem.* **2003**, *68*, 969.
(21) Dieter, R. K.; Chen, N.; Yu, H.; Nice, L. E.; Gore, V. K. *J. Org. Chem.* **2005**, *70*, 2109.
(22) Dieter, R. K.; Sharma, R. R. *Tetrahedron Lett.* **1997**, *38*, 5937.
(23) Dieter, R. K.; Topping, C. M.; Nice, L. E. *J. Org. Chem.* **2001**, *66*, 2302.
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(25) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.
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(28) Coldham, I.; O'Brien, P.; Patel, J. J.; Raimbault, S.; Sanderson, A. J.; Stead, D.; Whittaker, D. T. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2113.
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(30) Coldham, I.; Leonori, D. *Org. Lett.* **2008**, *10*, 3923.
(31) Dieter, R. K.; Velu, S. E.; Nice, L. E. *Synlett* **1997**, 1114.
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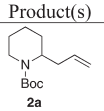
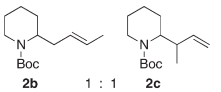
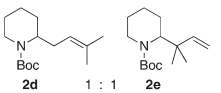
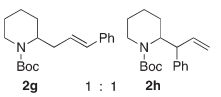
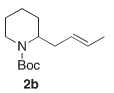
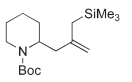
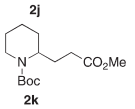
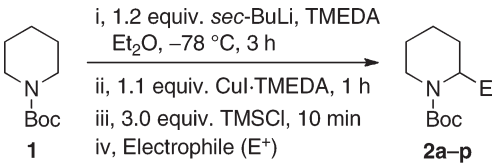
TABLE 2. Racemic Reactions of *N*-Boc-2-lithiopiperidine[a]

Entry	Electrophile	Product(s)	Yield (%)
1		 **2a**	67
2		 **2b** 1 : 1 **2c**	68[b]
3	 X = Cl or Br	 **2d** 1 : 1 **2e**	X = Cl 69 X = Br 71
4		 **2f**	58[c]
5		 **2g** 1 : 1 **2h**	54[d]
6		 **2b**	65
7		 **2i**	67
8		 **2j**	61
9		 **2k**	37[e]

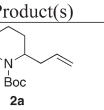
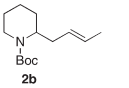
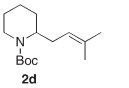
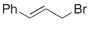
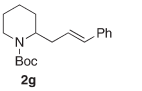
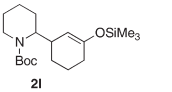
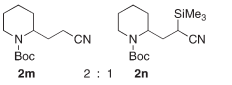
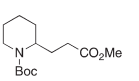
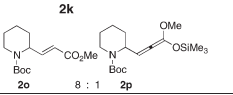
[a]Conditions as shown in Scheme 3. [b]**2c** dr 1:1. [c]**2f** dr 4:1. [d]**2h** dr 1:1. [e]For an alternative method, see Table 3.

SCHEME 4. Copper Iodide Promoted Reactions of *N*-Boc-2-lithiopiperidine



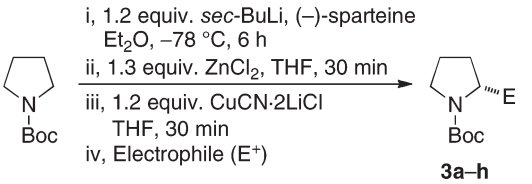
in Et_2O at −78 °C for 3 h using 1.2 equiv of TMEDA and 1.2 equiv of *sec*-BuLi was followed by addition of $ZnCl_2$ (1.3 equiv) in THF then CuCN·2LiCl (1.2 equiv) in THF. After 30 min at −78 °C, the electrophile was added and the results are summarized in Table 2. The reactions of this new mixed zinc cuprate reagent with allyl bromides and chlorides proceeded in good yields. Unfortunately, for unsymmetrical allylic halides mixtures of S_N2 and S_N2' products were usually obtained.[38−41] The regioisomers from the reaction with prenyl bromide (Table 2, entry 3) could be separated by column chromatography. Interestingly, the use of 3-chlorobut-1-ene and 1-bromobut-2-yne (Table 2, entries 6 and 7) gave only the S_N2' product (**2b** and **2i**, respectively).

TABLE 3. Racemic Reactions of *N*-Boc-2-lithiopiperidine[a]

Entry	Electrophile	Product(s)	Yield (%)
1		 **2a**	57
2		 **2b**	49
3		 **2d**	53
4		 **2g**	47
5		 **2l**	64[b]
6		 **2m** 2 : 1 **2n**	69
7		 **2k**	74
8		 **2o** 8 : 1 **2p**	73

[a]Conditions as shown in Scheme 4. [b]dr 1:1.

SCHEME 5. Zinc−Copper-Promoted Reactions of *N*-Boc-2-lithiopyrrolidine



This methodology was unsuccessful for reaction with alkyl halides or with the classical Michael acceptors such as acrylonitrile, cyclohexenone, or methyl propiolate. However, methyl acrylate gave the desired compound **2k** in modest yield. The addition of I_2 to the organozinc reagent (no copper salt) gave *N*-Boc-tetrahydropyridine **2q** (Scheme 3) in 84% yield.

To study the problem of S_N2/S_N2' attack, we tested different Cu(I) salts with prenyl bromide as the electrophile. This was aided by the ease of purification of the regioisomeric products (**2d** and **2e**). The use of CuCN·2LiCl or CuCl with or without $ZnCl_2$, or CuTC,[42] gave 1:1 mixtures of regioisomers. The presence of additives $BF_3·OEt_2$ or TMSCl also resulted in a mixture of isomers.[43−46] We were pleased to find, however, that the use of Cu(I) iodide·TMEDA complex[47] (prepared from 1.1 equiv of CuI and 1.15 equiv

(38) Goering, H. L.; Seitz, E. P.; Tseng, C. C. *J. Org. Chem.* **1981**, *46*, 5304.
(39) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063.
(40) Yoshikai, N.; Zhang, S.-L.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 12862.
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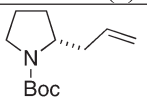
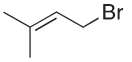
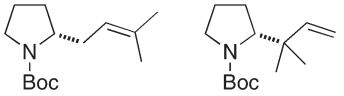
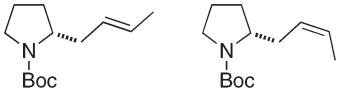
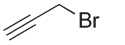
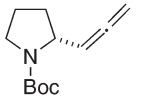
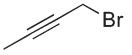
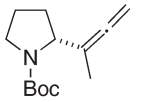
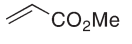
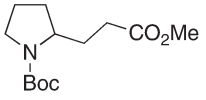
TABLE 4. Asymmetric Reactions of *N*-Boc-2-lithiopyrrolidine[a]

Entry	Electrophile	Product(s)	Yield (%)	er
1		 **3a**	81	95:5
2		 **3b** 38 : 62 **3c**	77	94:6[b]
3		 **3d** 85 : 15 **3e**	78	95:5[c]
4		 **3f**	65	95:5
5		 **3g**	76	95:5
6		 **3h**	63	50:50

[a]Conditions as shown in Scheme 5. [b]er of each regioisomer 94:6. [c]er for **3d** 95:5, for **3e** 94:6.

of TMEDA in THF) with or without TMSCl as additive gave only the S_N2 product (**2d**) in reasonable yield (51−53%).

The additive TMSCl is often used to enhance reactions of organocopper reagents, and although it may not be necessary, we opted to include TMSCl in further allylations under these conditions.[48] It is not clear why the use of the organocopper reagent derived from using CuI·TMEDA should be more regioselective, although a π-allyl Cu^{III} intermediate, which has been shown to favor S_N2 reaction, may be involved.[49] Using these reaction conditions, the same types of electrophiles were tested (Scheme 4, Table 3). The use of crotyl bromide or cinnamyl bromide gave only the S_N2 products (entries 2 and 4), in accordance with the result using prenyl bromide. In general, the yields of the allylated products (**2a**, **2b**, **2d**, **2g**) were slightly lower than those using the zinc−copper method given in Scheme 3; however, only a single regioisomer was observed in each case using the copper iodide TMEDA complex. The generation of *N*-Boc-2-lithiopiperidine by tin−lithium exchange[27] gave an improvement in terms of the yield of the allylated product (e.g., **2g**, 68%) without altering the regioselectivity. In addition to regioselective reaction with allyl bromides, we were pleased to find that this new organocuprate reagent reacted with various Michael acceptors. With cyclohexenone, the trimethylsilyl enol ether **2l** was formed in good yield as a mixture of diastereomers (Table 3, entry 5, dr 1:1). Using acrylonitrile, a mixture (ratio 2:1) of the protonated **2m** and silylated **2n** conjugate addition products was isolated. Methyl acrylate was a suitable electrophile, and the reaction provided the desired addition product **2k** in good yield (74%). This yield was a significant improvement over that obtained using the zinc cuprate reagent (Table 2, entry 8) or using the dialkylcopper lithium species (which requires 2 equiv of the organolithium).[24] The reaction with methyl propiolate gave the *trans* isomer **2o** in good yield, together with a small amount of the ketene **2p** (single diastereomer by NMR spectroscopy).

A significant aspect of this chemistry that needs addressing is the extent of asymmetric induction using the enantiomerically enriched organometallic species. This was probed for both *N*-Boc-2-lithiopyrrolidine and *N*-Boc-2-lithiopiperidine. Enantiomerically enriched *N*-Boc-2-lithiopyrrolidine (er ~97:3) can be prepared by asymmetric deprotonation using the methodology of Beak and co-workers using *sec*-butyllithium and (−)-sparteine.[25] This procedure is not amenable to the corresponding six-membered ring.[28,50,51] However, we have previously found that dynamic resolution of the organolithium under thermodynamic control in the presence of a diaminoalkoxide ligand can provide good levels of asymmetric induction after electrophilic quench (er ~85:15 using ligand **4**).[29,52] We therefore used these

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(49) Bartholmew, E. R.; Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A. *J. Am. Chem. Soc.* **2008**, *130*, 11244.
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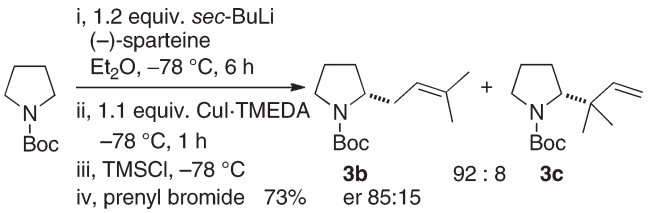
SCHEME 6. Copper Iodide Promoted Prenylation of *N*-Boc-2-lithiopyrrolidine



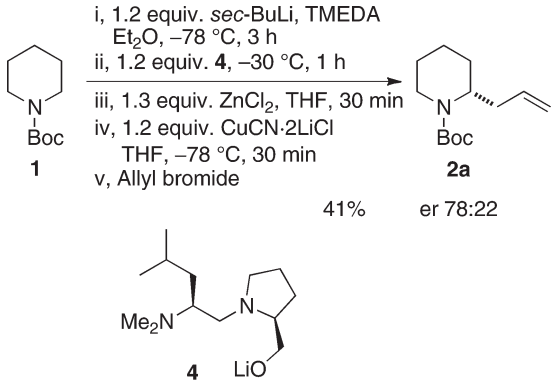
processes to test the ability to form the enantiomerically enriched 2-allylpyrrolidines and 2-allylpiperidines.

We were pleased to find that addition of zinc chloride then CuCN·2LiCl to enantiomerically enriched *N*-Boc-2-lithiopyrrolidine (prepared using *sec*-butyllithium and (−)-sparteine) followed by allyl bromide gave *N*-Boc-2-allylpyrrolidine with good yield and enantioselectivity (Scheme 5 and Table 4). This represents an improvement to the direct addition of CuCN·2LiCl to the organolithium (which results in some loss of enantiopurity, Scheme 1). The chemistry was suitable for a selection of allyl halide electrophiles to give products **3a**−**g** (Table 4). Using the unsymmetrical electrophile prenyl bromide, a mixture of regioisomeric products (**3b** and **3c**) was formed, each with high enantioselectivity. Using 3-chlorobut-1-ene and propargyl halides resulted in only the S_N2' products (entries 3−5), also with high enantioselectivity. In each case, the enantiomer ratio was determined by chiral GC analysis. The major enantiomer for the product **3a** (and by analogy for the products **3b**−**g**) is that shown ((*R*)-*N*-Boc-2-allylpyrrolidine) (vide infra) and is derived from the known *S*-*N*-Boc-2-lithiopyrrolidine by reaction with retention of configuration. Unfortunately, the electrophile methyl acrylate gave the product **3h** as a racemic mixture (entry 6). This is, however, in line with that found by Dieter and coworkers without the $ZnCl_2$.[26]

Addition of copper iodide TMEDA complex to (*S*)-*N*-Boc-2-lithiopyrrolidine gave good selectivity for the S_N2 products, but with some reduction in the enantiomer ratio. Hence, addition of prenyl bromide to this enantioenriched organocopper species gave predominantly the product **3b** with er 85:15 (Scheme 6). Use of allyl bromide gave **3a** with er 82:18, suggesting that the zinc−copper method (Scheme 5, Table 4), was preferable to avoid loss of enantiopurity. With the electrophile 3-chlorobut-1-ene only the S_N2' products (**3d** and **3e**, ratio 62:38) were formed, each with low enantioselectivity (er ∼57:43).

In a similar way to the reactions of enantiomerically enriched *N*-Boc-2-lithiopyrrolidine, we screened the extent of asymmetric induction with *N*-Boc-2-lithiopiperidine. Using ligand **4**, enantiomerically enriched *S*-*N*-Boc-2-lithiopiperidine was formed by dynamic resolution under thermodynamic control (er 85:15).[29,52] This was achieved by deprotonation of *N*-Boc-piperidine (**1**), addition of ligand **4** (which was prepared from the alcohol by deprotonation with *sec*-butyllithium), and equilibration at −30 °C for 1 h (Scheme 7). The mixture was cooled to −78 °C, and then zinc chloride and copper cyanide−lithium chloride complex in THF were added. Addition of allyl bromide gave the

SCHEME 7. Asymmetric Allylation of *N*-Boc-2-lithiopiperidine



desired *N*-Boc-2-allylpiperidine **2a** in moderate yield and with er 78:22. When CuCN·2LiCl alone (no zinc chloride) was used, the product **2a** was formed with er 71:29, and using CuI·TMEDA gave **2a** with er 62:38. Hence, some loss of enantiopurity occurs during this process, but proceeding through the zinc−copper complex can minimize the loss.

In the same way, dynamic resolution of *N*-Boc-2-lithiopiperidine with ligand **4**, followed by formation of the zinc−copper complex and addition of prenyl bromide, gave the products **2d** and **2e** (39% yield) in a ratio of 1.5:1. The enantiomer ratio of the S_N2 product **2d** was determined by chiral GC analysis (er 74:26). Using 3-chlorobut-1-ene, only the S_N2' product **2b** was formed (31% yield), but as a mixture of *E* and *Z* isomers (*E*:*Z* 63:37), with enantiomer ratios *E*-**2b** er 79:21 and *Z*-**2b** er 73:27. With the electrophile 1-bromo-2-butyne, the product **2i** was formed (29% yield) with an enantiomer ratio 79:21.

Dynamic resolution of *N*-Boc-2-lithiopiperidine with ligand **4** followed by formation of the zinc−copper species and electrophilic quench with 2-(chloromethyl)allyltrimethylsilane gave the product **2j** (34% yield, er 77:23); however, methyl acrylate gave none of the product **2k**. Using methyl propiolate as the electrophile gave the desired product **2o** (31% yield) but with zero optical rotation [lit.[53] for *S*-enantiomer: $[\alpha]_D$ −90.1 (1.0, $CHCl_3$)], suggesting that the racemic product had been formed.

With the results described above in hand, we were keen to demonstrate their use in total synthesis. Several simple substituted cyclic amine alkaloids were targeted. Wacker oxidation of the 2-allylpyrrolidine **3a** (er 95:5) gave the ketone **5** (Scheme 8). Synthesis of the ketone **5** represents a formal synthesis of (+)-pseudohygroline.[54] The specific rotation of **5**, $[\alpha]^{21}_D$ +29.5 (0.44, $CHCl_3$), matched that in the literature,[54] $[\alpha]^{23}_D$ +31.6 (2.5, $CHCl_3$), thereby demonstrating that the allylation of *S*-*N*-Boc-2-lithiopyrrolidine occurs with retention of configuration. Acid-promoted removal of the *N*-Boc group gave (remarkably) the first total synthesis of the natural product (−)-norhygrine (as its trifluoracetate salt) using only three steps from commercial *N*-Boc-pyrrolidine.[55,56] In addition to the synthesis of (−)-norhygrine,

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(53) Sánchez-Sancho, F.; Herradón, B. *Tetrahedron: Asymmetry* **1998**, *9*, 1951.

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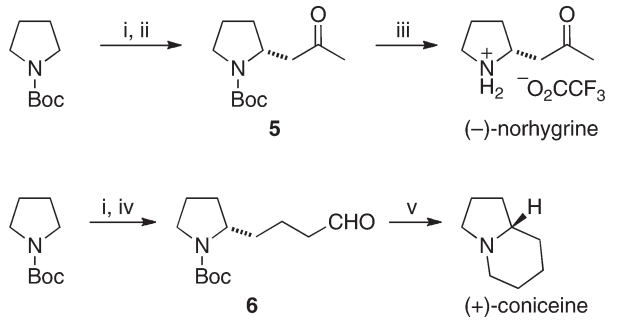
(56) Baxter, G.; Melville, J. C.; Robins, D. J. *Synlett* **1991**, 359.

SCHEME 8. Synthesis of Norhygrine and Coniceine[a]

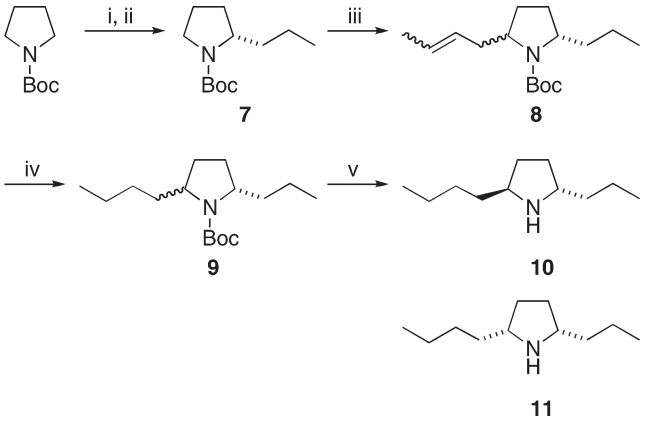


[a]Key: (i) *s*-BuLi, Et_2O, (−)-sparteine, −78 °C, 6 h, then $ZnCl_2$, THF, then CuCN·2LiCl, THF, then allyl bromide, **3a** 81%, er 95:5; (ii) $PdCl_2$, $CuCl_2$, DMF, H_2O, heat, 2 h, 56%; (iii) TFA, CH_2Cl_2, rt, 100%; (iv) H_2 (35 bar), CO (35 bar), ByPhePhos, dicarbonylacetylacetonato rhodium(I), THF, 60 °C, 24 h, 89%; (v) TFA, CH_2Cl_2 rt, then H_2 (10 bar), $Pd(OH)_2$, MeOH, rt, 24 h, 67%.

we carried out hydroformylation of the 2-allylpyrrolidine **3a** (er 95:5) to give the aldehyde **6** (Scheme 8).[57] Removal of the *N*-Boc group with trifluoroacetic acid followed directly by hydrogenation over palladium hydroxide gave (+)-coniceine.[53,58−60] The spectroscopic data matched those in the literature, including the specific rotation $[\alpha]^{21}_D$ +9.1 (1.15, EtOH), which compared well with the value reported in the literature,[61] $[\alpha]^{23}_D$ +9.3 (1.77, EtOH).

Recently, several new alkaloids including both *trans*- and *cis*-2-butyl-5-propylpyrrolidine (**10** and **11**, respectively) were isolated from extracts of the ant *Myrmicaria melanogaster*.[62] The authors state that one enantiomer was presumed to be naturally occurring (although no specific rotation data was recorded) and these compounds have been prepared only as their racemates.[62] An asymmetric synthesis of one enantiomer of each diastereomer was devised, as shown in Scheme 9. Zinc−copper-promoted allylation of (*S*)-*N*-Boc-2-lithiopyrrolidine gave the 2-allylpyrrolidine **3a** (er 95:5) (see Scheme 5). Reduction of the alkene gave *N*-Boc-2-propylpyrrolidine (**7**). A second metalation (with *sec*-butyllithium and TMEDA) followed by zinc−copper-promoted allylation with 3-chlorobut-1-ene gave the pyrrolidines **8** as a mixture of stereoisomers. Only the S_N2' allylation product was formed. Recovered starting material **7** was obtained on attempted use of *sec*-butyllithium and (−)-sparteine (in place of TMEDA) for this second metalation. Hydrogenation of the alkene gave the pyrrolidines **9**. No loss of enantioselectivity should occur during the metalation−quench process, and the stereoisomers of the products should have high er. Chiral GC analysis of the mixture of stereoisomers of the 2,5-disubstituted pyrrolidines **9** showed that the major (*trans*) diastereomer had er 97:3 (the minor diastereomer did not resolve on a β-cyclodextrin GC column). Removal of the

SCHEME 9. Synthesis of 2-Butyl-5-propylpyrrolidines[a]



[a]Key: (i) *s*-BuLi, Et_2O, (−)-sparteine, −78 °C, 6 h, then $ZnCl_2$, THF, then CuCN·2LiCl, THF, then allyl bromide, **3a** 81%, er 95:5; (ii) PtO_2, H_2 (10 bar), MeOH, rt, 24 h, 87%; (iii) *s*-BuLi, TMEDA, Et_2O, −78 °C, 3 h, then $ZnCl_2$, THF, then CuCN·2LiCl, THF, then 3-chlorobut-1-ene, 32%, dr 1.8:1 (*trans*/*cis*); (iv) PtO_2, H_2 (10 bar), MeOH, rt, 24 h, 96%; (v) TFA, CH_2Cl_2, rt, 100%.

N-Boc group gave the desired *trans*- and *cis*-2-butyl-5-propylpyrrolidines (**10** and **11**) as their trifluoroacetate salts, which were washed with NaOH to give the free bases. The *trans* and *cis* isomers **10** and **11** were separated by column chromatography. This approach represents the first asymmetric synthesis of these alkaloids. The major isomer (*trans*) (**10**) was assigned by analogy of the NMR spectra to related *trans*- and *cis*-disubstituted pyrrolidines.[63] The absolute configurations are expected to be those shown in Scheme 9, although the absolute configurations of the natural products are unknown.

The syntheses of (−)-norhygrine, (+)-coniceine, and *trans*- and *cis*-2-butyl-5-propylpyrrolidine illustrate the versatility of enantioenriched *N*-Boc-2-allylpyrrolidine. In a similar way, *N*-Boc-2-allylpiperidine was converted to two natural products (Scheme 10). Dynamic resolution under thermodynamic control of *N*-Boc-2-lithiopiperidine followed by zinc−copper-promoted allylation with allyl bromide gave enantioenriched *N*-Boc-2-allylpiperidine (**2a**), er 78:22 (Scheme 7). Hydrogenation of the alkene gave the piperidine **12**, and removal of the *N*-Boc group gave the alkaloid (+)-coniine.[60,64−69] This was formed in high yield without loss of enantiopurity, as judged by its specific rotation $[\alpha]^{23}_D$ +4.2 (1.2, EtOH) which compared well with the literature,[68] $[\alpha]^{25}_D$ +7.4 (1.0, EtOH). Although the enantiomer ratio (er 78:22) is not very high, this represents an extremely short (three-step) asymmetric synthesis of this alkaloid. Alternatively, Wacker oxidation of the allylpiperidine **2a** gave the ketone **13** (which

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(58) Hjelmgaard, T.; Gardette, D.; Tanner, D.; Aitken, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 671.
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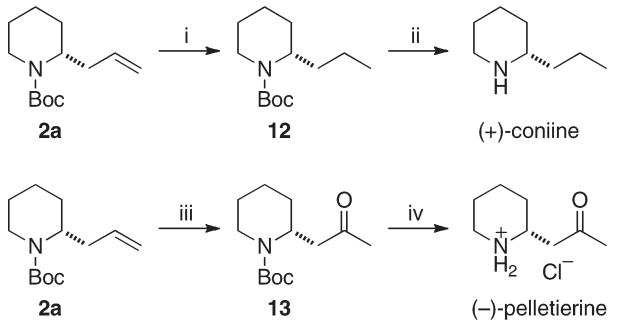
SCHEME 10. Synthesis of Coniine and Pelletierine[a]



[a]Key: (i) $Pd(OH)_2$, H_2 (1 atm), MeOH, rt, 24 h, 84%; (ii) TFA, CH_2Cl_2, rt, then NaOH, 100%; (iii) $PdCl_2$, $CuCl_2$, DMF, H_2O, heat, 2 h, 53%; (iv) HCl, dioxane, rt, 100%.

represents a formal synthesis of (+)-allosedridine and (+)-lasubine II).[54,70] Acid-promoted removal of the *N*-Boc group gave (−)-pelletierine as its HCl salt. The specific rotation of (−)-pelletierine, $[\alpha]^{23}_D$ −9.2 (1.2, EtOH), matched that for the HCl salt in the literature,[71] $[\alpha]^{21}_D$ −18.0 (0.5, EtOH).

Conclusions

We have extended the reactivity of *N*-Boc-2-lithiopyrrolidine and *N*-Boc-2-lithiopiperidine to, in particular, allylic halides. Transmetalation with $ZnCl_2$/CuCN·2LiCl allows subsequent reaction with allyl halides with good yields and enantioselectivities, but mixtures of regiosiomers using unsymmetrical allyl halides. Transmetalation with CuI·TMEDA provides high regioselectivity for the S_N2 product for unsymmetrical halides but with some loss of enantiopurity. The chemistry has been applied to short total syntheses of the natural products (−)-norhygrine, (+)-coniceine, *trans*- and *cis*-2-butyl-5-propylpyrrolidine, (+)-coniine, and (−)-pelletierine.

Experimental Section

General Experimental Methods. All reagents were obtained from commercial suppliers and were used without further purification unless otherwise specified. TMEDA and (−)-sparteine were freshly distilled from CaH_2. The ligand **4** was prepared according to a known procedure and was distilled prior to use.[29] $ZnCl_2$, CuCN, LiCl, and CuI were flame-dried under vacuum before use. *s*-BuLi was titrated before use. All of the electrophiles were distilled prior to use. Thin-layer chromatography was performed on silica plates and visualized by UV irradiation at 254 nm or by staining with an alkaline $KMnO_4$ dip. Column chromatography was performed using silica gel (40−63 μm mesh). Infrared spectra were recorded on a Fourier transform IR system. Only selected peaks are reported, and absorption maxima are given in cm^{-1}. ^1H NMR spectra were recorded at 400 MHz. Chemical shifts are reported in ppm with respect to the residual solvent peaks, with multiplicities given as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants, *J*, are quoted to the nearest 0.5 Hz. ^{13}C NMR were recorded at 100 MHz; $^1H-^1H$ and $^1H-^{13}C$ correlation spectra were run to confirm the assignment of peaks. Low and high resolution (accurate mass) mass spectra were recorded using electrospray (ES).

General Procedure with Racemic $ZnCl_2$/CuCN·2LiCl (Scheme 3, Table 2). *s*-BuLi (1.0 mL, 1.3 mmol, 1.3 M in cyclohexane) was added to the carbamate **1** (200 mg, 1.08 mmol) and TMEDA (0.19 mL, 1.3 mmol) in dry Et_2O (4.2 mL) at −78 °C. After 3 h, $ZnCl_2$ (190 mg, 1.4 mmol) in dry THF (1.7 mL) was added over 10 min. After 30 min, a solution of CuCN (115 mg, 1.3 mmol) and LiCl (109 mg, 2.6 mmol, dried at 130 °C for 48 h) in dry THF (4.3 mL) was added rapidly. The mixture was stirred at −78 °C for 30 min, and the electrophile (3.24 mmol) was added dropwise (if liquid) or as a 1.0 M solution in dry THF (if solid). The mixture was allowed to warm to room temperature slowly, and NH_4OH (10 mL, 10% aqueous) was added. Et_2O (10 mL) was added, and the mixture was stirred for 20 min. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography.

General Procedure with Racemic CuI·TMEDA (Scheme 4, Table 3). *s*-BuLi (1.0 mL, 1.3 mmol, 1.3 M in cyclohexane) was added to the carbamate **1** (200 mg, 1.08 mmol) and TMEDA (0.19 mL, 1.3 mmol) in dry Et_2O (4.2 mL) at −78 °C. After 3 h, CuI (230 mg, 1.19 mmol) and TMEDA (0.19 mL, 1.24 mmol) in dry THF (4.2 mL) were added over 10 min. The mixture was stirred at −78 °C for 1 h, and then TMSCl (0.41 mL, 3.24 mmol) was added rapidly. After 10 min, the electrophile (3.24 mmol) was added dropwise (if liquid) or as a 1.0 M solution in dry THF (if solid). The mixture was allowed to warm to room temperature slowly, and NH_4OH (10 mL, 10% aqueous) was added. Et_2O (10 mL) was added, and the mixture was stirred for 20 min. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography.

General Procedure with $ZnCl_2$/CuCN·2LiCl Asymmetric *N*-Boc-pyrrolidine (Scheme 5, Table 4). *s*-BuLi (1.2 equiv) was added dropwise to a 0.25 M solution of (−)-sparteine (1.2 equiv) in dry Et_2O at −78 °C. After 30 min, *N*-Boc-pyrrolidine (1.0 equiv) was added. After 6 h, a 0.8 M solution of $ZnCl_2$ (1.3 equiv) in dry THF was added over 10 min. After 30 min, a 0.3 M solution of CuCN (1.2 equiv) and LiCl (2.4 equiv, dried at 130 °C for 48 h) in dry THF was added rapidly. The mixture was stirred at −78 °C for 30 min, and the electrophile (3.0 equiv) was added dropwise (if liquid) or as a 1.0 M solution in dry THF (if solid). The mixture was allowed to warm slowly to room temperature, and NH_4OH (10 mL, 10% aqueous) was added. Et_2O (10 mL) was added, and the mixture was stirred for 20 min. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography.

General Procedure with CuI·TMEDA Asymmetric *N*-Boc-pyrrolidine (Scheme 6). *s*-BuLi (1.2 equiv) was added dropwise to a 0.25 M solution of (−)-sparteine (1.2 equiv) in dry Et_2O at −78 °C. After 30 min, *N*-Boc-pyrrolidine (1.0 equiv) was added. After 6 h, a 0.3 M solution of CuI (1.1 equiv) and TMEDA (1.15 equiv) in dry THF was added over 10 min. The mixture was stirred at −78 °C for 1 h, and then TMSCl (3.0 equiv) was added rapidly. After 10 min, the electrophile (3.0 equiv) was added dropwise (if liquid) or as a 1.0 M solution in dry THF (if solid). The mixture was allowed to warm slowly to room temperature, and NH_4OH (10 mL, 10% aqueous) was added. Et_2O (10 mL) was added, and the mixture was stirred for 20 min. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography.

General Procedure with $ZnCl_2$/CuCN·2LiCl Asymmetric *N*-Boc-piperidine (Scheme 7). *N*-Boc-piperidine (1.0 equiv) and TMEDA (1.2 equiv) in dry Et_2O (6 mL) were treated with *s*-BuLi (1.2 equiv) at −78 °C. After 3 h, the deprotonated ligand **4** [prepared by adding *s*-BuLi (1.25 equiv) to a 0.25 M solution of

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(71) Carlson, E. C.; Rathbone, L. K.; Yang, H.; Collett, N. D.; Carter, R. G. *J. Org. Chem.* **2008**, *73*, 5155.

the prolinol[29] (1.2 equiv) in Et_2O at 0 °C for 30 min] was added. The mixture was warmed to −30 °C. After 1 h, the mixture was cooled to −78 °C, and a 0.8 M solution of $ZnCl_2$ (1.3 equiv) in dry THF was added over 10 min. After 30 min, a 0.3 M solution of CuCN (1.2 equiv) and LiCl (2.4 equiv, dried at 130 °C for 48 h) in dry THF was added rapidly. After 30 min, the electrophile (3.0 equiv) was added dropwise (if liquid) or as a 1.0 M solution in dry THF (if solid). The mixture was allowed to warm slowly to room temperature, and NH_4OH (10 mL, 10% aqueous) was added. Et_2O (10 mL) was added, and the mixture was stirred for 20 min. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography.

***tert*-Butyl 2-(2-Oxopropyl)pyrrolidine-1-carboxylate 5.** To a stirred solution of carbamate (*R*)-**3a** (er 95:5) (250 mg, 1.2 mmol) in DMF (17 mL) and H_2O (8 mL) were added $PdCl_2$ (21 mg. 0.1 mmol) and $CuCl_2$ (350 mg, 2.6 mmol). The dark green solution was heated under reflux for 2 h and then cooled to room temperature. H_2O (100 mL) was added, the mixture was extracted with Et_2O (5 × 100 mL), and the organic layers were washed with H_2O (3 × 100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and evaporated to give carbamate **5** (150 mg, 56%) as an oil: $[\alpha]^{21}_D$ +29.5 (0.44, $CHCl_3$) [lit.[54] $[\alpha]^{21}_D$ +31.6 (2.5, $CHCl_3$)]; R_f 0.43 [petroleum ether−EtOAc (95:5)]; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 4.13−3.90 (1H, m, CH), 3.33−3.10 (2H, m, 2 × CH), 3.08−2.91 (0.6H, m, CH), 2.87−2.70 (0.4H, m, CH), 2.39−2.19 (1H, m, CH), 2.01 (3H, s, CH_3), 1.93 (1H, dd, *J* 12, 8 Hz, CH), 1.68 (2H, t, *J* 7 Hz, CH_2), 1.57−1.42 (1H, m, CH), 1.32 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 207.2 and 207.0, 154.2, 79.0, 53.3, 48.5 and 47.7, 46.4 and 45.9, 31.4 and 30.7, 30.4 and 30.2, 28.4, 23.4 and 22.7; HRMS (ES) found MH^+ 228.1605, $C_{12}H_{22}NO_3$ requires MH^+ 228.1600; LRMS *m*/*z* (ES) 228 (100). Data as reported.[54]

(−)-Norhygrine Trifluoroacetate Salt. CF_3CO_2H (0.25 mL, 3.3 mmol) was added to carbamate **5** (75 mg, 0.3 mmol) in CH_2Cl_2 (3.0 mL) at room temperature. After 2 h, the solvent was removed under pressure to give norhygrine trifluoroacetate salt (73 mg, 100%) as an oil: $[\alpha]^{21}_D$ −14.7 (0.54, $CHCl_3$); R_f 0.43 [petroleum ether−EtOAc (95:5)]; IR ν_{max} (film)/cm^{-1} 3470, 2955, 2865, 1670, 1420, 1380, 1310, 1270, 1135; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.37 (1H, br s, NH), 8.10 (1H, br s, NH), 4.02−3.74 (1H, m, CH), 3.51−3.23 (2H, m, 2 × CH), 3.09−2.93 (2H, m, CH_2), 2.32−2.18 (1H, m, CH), 2.15 (3H, s, CH_3), 2.09−1.87 (2H, m, 2 × CH), 1.83−1.55 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 208.0, 56.2, 45.9, 44.2, 29.6, 29.3, 23.1; HRMS (ES) found MH^+ 128.1073, $C_7H_{14}NO$ requires MH^+ 128.1070; LRMS *m*/*z* (ES) 128 (100). The only literature data available is the mass spectrum.[55]

***tert*-Butyl 2-(4-Oxobutyl)pyrrolidine-1-carboxylate 6.** Following a literature procedure,[57] a pressure reaction vessel with a pressure coupling closure complete with gas inlet, pressure gauge, and pressure release valve was charged with a solution of dicarbonylacetylacetonatorhodium(I) (8.0 mg, 0.54 mol %), biphephos (28 mg, 0.56 mol %), and carbamate *R*-**3a** (er 95:5) (1.2 g, 5.5 mmol) in THF (10 mL). The reaction vessel was degassed three times, filled with CO/H_2 (1:1 mixture, 70 bar), and then heated to 60 °C. After 24 h, the vessel was cooled to room temperature, the pressure was released, and the solution was concentrated. Purification by column chromatography on silica gel, eluting with petroleum ether−EtOAc (87:13) gave carbamate **6** (1.2 g, 89%) as an oil: $[\alpha]^{21}_D$ +40.0 (0.45, $CHCl_3$); R_f 0.27 [petroleum ether−EtOAc (95:5)]; IR ν_{max}/cm^{-1} 2970, 1725, 1675; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 9.73 (1H, br s, CHO), 4.07−3.87 (0.4H, m, NCH), 3.72−3.49 (0.6H, m, NCH), 3.38−3.06 (2H, m, 2 × NCH), 2.43−2.27 (2H, m, CH_2), 1.96−1.64 (6H, m, 3 × CH_2), 1.62−1.41 (2H, m, CH_2), 1.39 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 203.4 and 202.9, 155.8, 80.8 and 79.6, 57.1, 46.7 and 46.3, 44.0, 35.5 and 34.8, 32.1 and 29.2, 28.8, 24.0 and 23.3, 19.1; HRMS (ES) found MH^+, 242.1766, $C_{13}H_{24}NO_3$ requires MH^+ 242.1756; LRMS *m*/*z* (ES) 186 (100), 242 (MH^+, 10), 264 (MNa^+, 10).

(+)-Coniceine. Trifluoroacetic acid (0.9 mL, 12.0 mmol) was added to the carbamate **6** (300 mg, 1.2 mmol) in CH_2Cl_2 (12 mL) at room temperature. After 3 h, the solvent was evaporated, dry MeOH (5 mL) and $Pd(OH)_2$ (30 mg) were added, and the mixture was stirred under an atmosphere of H_2 (10 bar) at room temperature. After 24 h, the suspension was filtered on Celite, and the solvent was evaporated to give (+)-*δ*-coniceine (102 mg, 67%) as an oil: $[\alpha]^{21}_D$ +9.1 (1.15, EtOH) [lit.[61] $[\alpha]^{23}_D$ +9.3 (1.77, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.16−2.87 (2H, m, 2 × CH), 2.08−1.90 (2H, m, 2 × CH), 1.87−1.59 (8H, m, 8 × CH), 1.54−1.29 (3H, m, 3 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 63.5, 61.1, 53.3, 27.1, 23.9, 21.0, 19.4, 18.5. Data as reported.[53,58]

***tert*-Butyl 2-Propylpyrrolidine-1-carboxylate 7.** PtO_2 (50 mg) was added to the carbamate (*R*)-**3a** (1.0 g, 4.8 mmol) in dry MeOH (150 mL), and the mixture was stirred under an atmosphere of H_2 (10 bar) at room temperature. After 24 h, the suspension was filtered on Celite, and the solvent was evaporated to give the carbamate **7** (880 mg, 87%) as an oil: $[\alpha]^{21}_D$ +45.6 (0.46, $CHCl_3$) [lit.[72] $[\alpha]^{20}_D$ −34.1 (1.1, $CHCl_3$)]; R_f 0.43 [petroleum ether−EtOAc (95:5)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.88−3.60 (1H, m, CH), 3.55−3.06 (2H, m, 2 × CH), 1.99−1.71 (4H, m, 2 × CH_2), 1.70−1.56 (1H, m, CH), 1.46 (9H, s, *t*-Bu), 1.39−1.18 (3H, m, CH and CH_2), 0.92 (3H, t, *J* 7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.6, 78.8, 56.9, 46.4 and 45.0, 36.9 and 36.3, 30.6 and 29.8, 28.5, 23.0, 19.5, 14.1; HRMS (ES) found MH^+ 214.1806, $C_{12}H_{24}NO_2$ requires MH^+ 214.1807; LRMS *m*/*z* (ES) 214 (100). ^{1}H NMR data as reported.[72]

***tert*-Butyl 2-[(*E*)-But-2-enyl]-5-propylpyrrolidine-1-carboxylate and *tert*-Butyl 2-[(*Z*)-But-2-enyl]-5-propylpyrrolidine-1-carboxylate 8.** Using the general procedure for Scheme 3, carbamate **7** (880 mg, 4.1 mmol), TMEDA (0.75 mL, 4.9 mmol), *s*-BuLi (3.8 mL, 4.9 mmol), $ZnCl_2$ (730 mg, 5.4 mmol), CuCN (440 mg, 4.9 mmol), LiCl (420 mg, 9.9 mmol), and 3-chloro-1-butene (1.2 mL, 12.4 mmol) gave, after purification by chromatography on silica gel, eluting with petroleum ether−EtOAc (97:3), the carbamates **8** (360 mg, 32%), *E*:*Z* 85:15, dr of each geometrical isomer 1.8:1; data for this mixture: $[\alpha]^{21}_D$ +35.2 (0.54, $CHCl_3$); R_f 0.52 [petrol−EtOAc (95:5)]; IR ν_{max} (film)/cm^{-1} 2960, 1700, 1390, 1365, 1170, 1110; ^{1}H NMR (400 MHz, $CDCl_3$, diastereomers and rotamers) δ = 5.52−5.54 (0.15 H, m, =CH), 5.39 (0.85H, dq, *J* 14.5, 6 Hz, =CH), 5.33−5.19 (1H, m, CH=), 3.86−3.49 (2H, m, 2 × CH), 2.59−2.23 (1H, m, CH), 2.04−1.70 (4H, m, 2 × CH_2), 1.69−1.47 (5H, m, CH and 2 × CH_2), 1.40 (9H, s, *t*-Bu), 1.32−1.03 (3H, m, CH_3), 0.85 (3H, br t, *J* 7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, diastereomers and rotamers) δ = 154.7 and 153.7, 127.9 and 127.7, 127.3, and 127.2 and 127.0, 126.6, 125.8 and 125.6, 78.6, 58.2 and 57.3, 57.5, and 57.4 and 57.2, 37.9 and 37.1, 36.2, and 35.7 and 34.9, 28.5, 27.4 and 27.0, 26.4 and 26.1, 19.9, and 19.8 and 19.5, 17.9, 14.1 and 13.9; HRMS (ES) found MH^+, 268.2278, $C_{16}H_{30}NO_2$ requires MH^+ 268.2277; LRMS *m*/*z* (ES) 268 (100%).

***trans*- and *cis*-*tert*-Butyl 2-Butyl-5-propylpyrrolidine-1-carboxylate 9.** PtO_2 (18 mg) was added to the carbamates **8** (180 mg, 0.7 mmol) in dry MeOH (22 mL), and the mixture was stirred under an atmosphere of H_2 (10 bar) at room temperature. After 24 h, the suspension was filtered on Celite, and the solvent was evaporated to give the carbamates **9** (174 mg, 96%) as an oil; dr 1.8:1. Data for the mixture of diastereomers: $[\alpha]^{21}_D$ +41.2 (0.53, $CHCl_3$); R_f 0.52 [petroleum ether−EtOAc (95:5)]; IR ν_{max} (film)/cm^{-1} 2940, 1690, 1410, 1275, 1155, 1035; ^{1}H NMR (400 MHz,

(72) Blarer, D. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250.

$CDCl_3$) δ = 3.80−3.63 (1.4H, m, 2 × CH), 3.63−3.52 (0.6H, m, CH), 1.96−1.70 (3H, m, CH and CH_2), 1.67−1.49 (3H, m, CH and CH_2), 1.41 (9H, s, *t*-Bu), 1.35−1.02 (6H, m, 3 × CH_2), 0.93−0.77 (6H, m, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, diastereomers and rotamers) δ = 154.9 and 153.8, 78.5, 58.3 and 58.1, 57.5, and 57.4 and 57.2, 38.2 and 36.1, 35.6 and 34.9, 33.6 and 32.4, 29.4 and 28.9, 28.5, 27.5 and 26.6, 22.7, 19.9 and 19.5, 14.1; HRMS (ES) found MH^+ 270.2432, $C_{16}H_{31}NO_2$ requires MH^+ 270.2433; LRMS *m*/*z* (ES) 270 (100).

***trans*-2-Butyl-5-propylpyrrolidine 10 and *cis*-2-Butyl-5-propylpyrrolidine 11.** CF_3CO_2H (0.4 mL, 5.6 mmol) was added to the carbamates **9** (150 mg, 0.6 mmol) in CH_2Cl_2 (6.0 mL) at room temperature. After 2 h, the solvent was evaporated to give the mixture of pyrrolidines **10** and **11** (93 mg, 100%) as an oil. Data for the mixture of natural product as their TFA salts: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.31−8.70 (2H, m, 2 × NH), 3.78−3.28 (2H, m, 2 × CH), 2.26−2.04 (2H, m, CH_2), 1.87−1.68 (3H, m, CH and CH_2), 1.67−1.48 (3H, m, CH and CH_2), 1.42−1.18 (6H, m, 3 × CH_2), 0.95−0.76 (6H, m, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, diastereomers) δ = 60.3, 60.1, 59.8, 59.6, 34.5, 34.2, 32.1, 31.8, 30.7, 28.7, 28.5, 28.4, 22.1, 19.8, 19.7, 13.5, 13.4. This mixture was dissolved in CH_2Cl_2 (10 mL) and washed with NaOH (5 mL, 2.0 M). Evaporation of the solvent gave the free amines that were separated by column chromatography on silica gel, eluting with petroleum ether−EtOAc−Et_3N (95:5:0.5), to give the following:

(2*S*,5*S*)-2-Butyl-5-propylpyrrolidine **10** (56 mg) as an oil: $[\alpha]^{21}_D$ +2.0 (0.5, $CHCl_3$); R_f 0.52 [petroleum ether−EtOAc−Et_3N (95:5:0.5)]; IR ν_{max} (film)/cm^{-1} 3420, 2930, 2875, 1455, 1340, 1360, 1160, 1115; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.65−3.47 (2H, m, 2 × CH), 2.27−2.11 (2H, m, 2 × CH), 1.92−1.75 (2H, m, CH_2), 1.73−1.55 (4H, m, 2 × CH_2), 1.48−1.20 (6H, m, 3 × CH_2), 0.94 (3H, t, *J* 7.5 Hz, CH_3), 0.90 (3H, t, *J* 7.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 59.4, 59.2, 38.7, 36.2, 31.2, 29.7, 22.9, 20.6, 14.2, 14.0; HRMS (ES) found MH^+ 170.1904, $C_{11}H_{24}N$ requires MH^+ 170.1909; LRMS *m*/*z* (ES) 170 (100).

(2*R*,5*S*)-2-Butyl-5-propylpyrrolidine **11** (31 mg) as an oil: $[\alpha]^{21}_D$ 0.0 (0.6, $CHCl_3$); R_f 0.50 [petroleum ether−EtOAc−Et_3N (95:5:0.5)]; IR ν_{max} (film)/cm^{-1} 3415, 2930, 2870, 1455, 1340, 1365, 1165, 1115; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.07−2.89 (2H, m, 2 × CH), 2.3 (1H, br s, NH), 1.94−1.76 (2H, m, CH_2), 1.62−1.47 (2H, m, CH_2), 1.46−1.18 (10H, m, 5 × CH_2), 1.01−0.80 (6H, m, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 59.6, 59.3, 34.6, 32.2, 30.8, 28.5, 22.3, 19.8, 13.7, 13.6; HRMS (ES) found MH^+ 170.1903, $C_{11}H_{24}N$ requires MH^+ 170.1909; LRMS *m*/*z* (ES) 170 (100).

***tert*-Butyl 2-*n*-Propylpiperidine-1-carboxylate 12.** $Pd(OH)_2$ (45 mg) was added to the carbamate **2a** (200 mg, 0.9 mmol) in dry MeOH (7 mL) under an atmosphere of H_2 at room temperature. After 36 h, the suspension was filtered on Celite, and the solvent was evaporated to give the carbamate **12** (165 mg, 84%). Data as reported.[73]

(+)-Coniine. CF_3CO_2H (0.5 mL, 7.5 mmol) was added to the carbamate **12** (165 mg, 0.7 mmol) in CH_2Cl_2 (4 mL) at room temperature. After 2 h, NaOH (10 mL, 10% aqueous solution) was added, and the mixture was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give coniine hydrochloride salt (94 mg, 100%) as an oil: $[\alpha]^{23}_D$ +4.2 (1.2, EtOH) [lit.[68] $[\alpha]^{25}_D$ +7.4 (1.0, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.15 (1H, br d, *J* 12.5 Hz, CH), 2.68 (1H, br d, *J* 12.5 Hz, CH), 2.58 (1H, m, CH), 2.52−2.36 (1H, m, NH), 1.75−1.56 (4H, m, 4 × CH), 1.52−1.00 (6H, m, 6 × CH), 0.83 (3H, t, *J* 7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 55.7, 46.8, 39.4, 31.9, 26.2, 24.3, 18.9, 14.0. Data as reported.[73]

***tert*-Butyl 2-(2-Oxopropyl)piperidine-1-carboxylate 13.** To a stirred solution of the carbamate **2a** (200 mg, 0.9 mmol) in DMF (13 mL) and H_2O (6 mL) were added $PdCl_2$ (16 mg. 0.09 mmol) and $CuCl_2$ (245 mg, 1.8 mmol). The dark green solution was heated under reflux for 2 h and then was cooled to room temperature. H_2O (50 mL) was added, the mixture was extracted with Et_2O (5 × 50 mL), and the organics were washed with H_2O (3 × 50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and evaporated to give the carbamate **13** (113 mg, 53%) as an oil: $[\alpha]^{22}_D$ +5.4 (1.2, $CHCl_3$) [lit.[54] $[\alpha]^{23}_D$ +8.2 (2.0, $CHCl_3$)]; R_f 0.1 [petroleum ether−EtOAc (8:2)]; IR ν_{max}/cm^{-1} 1705, 1680, 1625, 1585, 1525, 1475, 1410, 1365, 1265, 1160, 1050; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.95−4.54 (1H, m, CH), 4.10−3.81 (1H, m, CH), 2.79 (1H, br t, *J* 13 Hz, CH), 2.67 (2H, dd, *J* 7, 2.5 Hz, CH_2CO), 2.20 (3H, s, CH_3), 1.75−1.50 (6H, m, 3 × CH_2), 1.46 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 207.6, 156.2, 80.1, 47.7, 44.8, 30.5, 30.1, 28.8, 25.7 (two CH_2), 19.3; HRMS (ES) found MH^+ 242.1759, $C_{13}H_{24}NO_3$ requires MH^+ 242.1759; LRMS *m*/*z* (ES) 186 (40), 242 (100). Data as reported.[54]

(−)-Pelletierine. HCl (0.25 mL, 1.0 mmol, 4.0 M in dioxane) was added to the carbamate **13** (113 mg, 0.4 mmol) in CH_2Cl_2 (4.0 mL) at room temperature. After 16 h, the solvent was evaporated to give (−)-pelletierine hydrochloride salt (80 mg, 97%) as an amorphous solid: mp 216−221 °C (lit.[71] mp 218−219 °C); $[\alpha]^{23}_D$ = −9.2 (1.2, EtOH) [lit.[71] for (−)-pelletierine hydrochloride, er 100:0, $[\alpha]_D$ −18.0 (0.5, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (1H, br s, NH), 9.24 (1H, br s, NH), 3.48 (2H, d, *J* 12 Hz, CH_2), 3.32−3.28 (1H, m, CH), 3.03−2.96 (1H, m, CH), 2.88 (1H, t, *J* 12 Hz, CH), 2.17 (3H, s, CH_3), 1.97−1.83 (4H, m, 2 × CH_2), 1.76−1.64 (1H, m, CH), 1.58−1.49 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 53.0, 46.0, 45.2, 30.7, 28.7, 22.2, 23.3; HRMS (ES) found MH^+ 142.1231, $C_8H_{16}NO$ requires MH^+ 142.1232; LRMS *m*/*z* (ES) 142 (100). Data as reported.[71]

Acknowledgment. We thank the EPSRC (Grant No. EP/E012272/1) and the University of Sheffield for support of this work. Mr R. J. Hanson (University of Sheffield) is thanked for help with some of the hydrogenations.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2a**−**q** and **3a**−**g**, NMR spectra for all new compounds, and GC spectra for compounds **2a**,**i**,**j** and **3a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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