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Conversion of Five-, Six-, and Seven-Membered Lactams to Racemic or Scalemic 2-Substituted Heterocycles by Amidoalkylation

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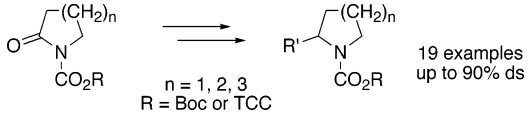

An efficient method for the synthesis of 2-alkyl- and 2-aryl pyrrolidines, piperidines, and azepanes from lactams, in either racemic or enantiopure form, is presented. The lactam nitrogens are acylated with either Boc anhydride or *trans*-cumylcyclohexyl (TCC) chloroformate. Selective reduction of the lactam carbonyl to the carbinolamide is followed by treatment with benzotriazole. Substitution of the benzotriazole is accomplished by treatment with organometallics, yielding the 2-substituted heterocycles. With TCC, up to 90% diastereoselectivity is achieved. After diastereomer purification, reductive removal of the auxiliary affords enantiopure 2-substituted heterocycles. A mechanistic hypothesis is presented that details the conformational equilibria of the key step.

Introduction

N-Acyliminium ions[1] and iminium ions[2] are extremely versatile synthetic intermediates. In the context of intermolecular addition of nucleophiles to iminiums having a chiral auxiliary on nitrogen, considerable work has been done in the area of dearomatizing additions to pyridinium and isoquinolinium ions, for example, by the groups of Polniaszek,[3] Comins,[4] Streith,[5] and Wanner[6] (Figure 1). Achieving diastereoselectivity in additions to pyridiniums presents a particularly difficult challenge because of the symmetry of the ring. Comins' approach is to block approach of a nucleophile at the 2-position with a triisopropylsilyl group at the 3-position, but Streith and Wanner have addressed the problem through the design of an auxiliary that is meant to simultaneously block one face of the ring and deliver the nucleophile regioselectively to the other via coordination to a proximal carbonyl oxygen.

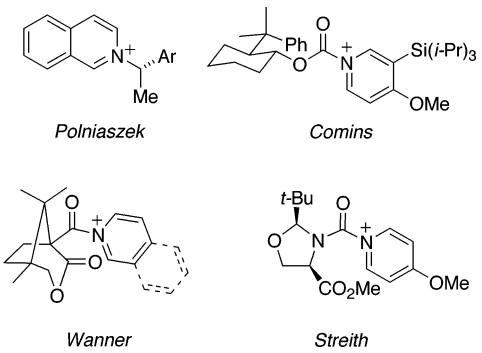

FIGURE 1.

N-Acyliminium ions of nonaromatic heterocycles have been generated in a number of ways (Scheme 1). For example, Wanner has converted enamides to α-chloroheterocycles which form iminium ions when treated with a Lewis acid.[7] Suga and Yoshida used electrochemical oxidation of 2-(trimethylsily)heterocyclic carbamates to generate *N*-acyliminium ions for subsequent reaction with nucleophiles such as allyl silanes and Grignard reagents.[8] Meyers[9] used 2-methoxy heterocycles as pre-

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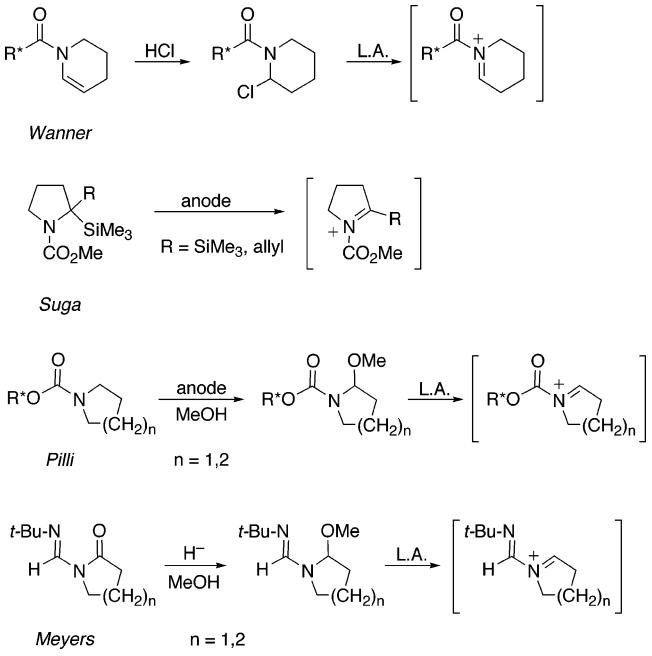
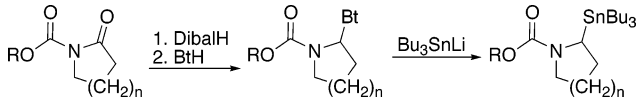
SCHEME 1



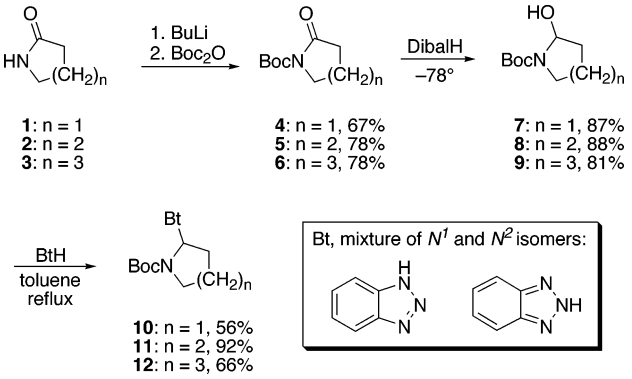
SCHEME 2



cursors to *N*-formamidinyl iminium ions and Pilli[10] has used them as precursors to *N*-carbamoyl iminium ions. Pilli generated the methoxy compounds by anodic oxidation of the saturated heterocycle, whereas Meyers accessed the methoxy compounds by Red-Al reduction of the *N*-formamidinyl lactam. Of these methods, only the Wanner and Pilli methods have been tested for diastereoselectivity in organometallic additions using a chiral auxiliary. The Wanner method affords >90% diastereoselectivity in additions of organoaluminum and organozinc compounds.[7]

Recently, we demonstrated that five- and six-membered *N*-carbamoyl lactams could be converted to *N*-carbamoyl-2-(tributylstannyl) heterocycles,[11] which are useful precursors to α-aminoorganolithium compounds (Scheme 2).[12] This method begins with reduction of *N*-carbamoyl lactams to the carbinolamide according to the method of Dieter,[13] but in contrast to the work of Pilli and Meyers noted above, optimal yields were obtained using a benzotriazole leaving group, as reported by Katritzky and Pearson.[14] With a Boc group on the nitrogen the products are racemic. With use of *trans*-cumylcyclohexanol (TCC) as a chiral auxiliary, the method afforded moderate diastereoselectivity, but the diastereomers were separable, providing either enantiomer of enantiopure 2-(tributylstannyl)pyrrolidines and -piperidines. In this paper, we extend this method to the synthesis of 2-alkyl- and 2-arylpyrrolidines, piperidines, and azepanes in either racemic or enantiopure form. Unrelated methods for the preparation of enantioenriched 2-substituted heterocycles include electrophilic substitutions of scalemic heterocycles metalated at position 2,[15,16] sparteine-mediated anionic cyclizations,[17] and enantioselective additions of lithiated allyl sulfonates to sulfinylamines followed by a ring-closing metathesis.[18]

SCHEME 3



Results

In the racemic series, we acylated the nitrogen with a Boc group because of its easy removal. Thus (Scheme 3), acylation of the lithium salts of lactams **1**−**3** afforded the Boc lactams **4**−**6**. Low-temperature reduction of the lactam carbonyl of imides **4**−**6**[13] was achieved selectively over the urethane carbonyl to give **7**−**9**, and replacement of the hydroxyls with benzotriazole[14] gave **10**−**12**, the precursors to the presumed *N*-acyliminium ion intermediates in the addition of organometallic nucleophiles.

The results of several Grignard additions to the five-, six-, and seven-membered ring heterocycles **10**−**12** are listed in Table 1. An excess of the organometallic was required to achieve the yields shown. Optimization experiments revealed that the reaction does not proceed at lower temperatures, and the external Lewis acids $AlCl_3$, $EtAlCl_2$, and Et_2AlCl failed to facilitate the addition, either by enhancing the yields or by permitting a

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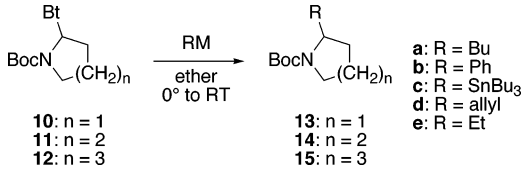
TABLE 1. Preparation of Racemic 2-Substituted Heterocycles



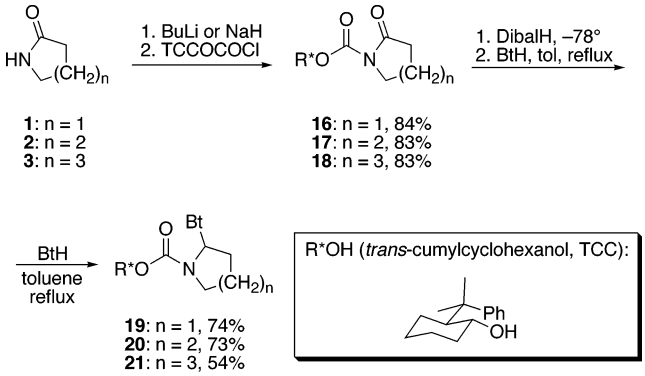
10: n = 1
11: n = 2
12: n = 3

13: n = 1
14: n = 2
15: n = 3

substrate	RM	yield (%)
10	BuMgBr	**13a**, 61
10	PhMgBr	**13b**, 59
10	Bu_3SnLi[a]	**13c**, 78
11	BuMgBr	**14a**, 62
11	PhMgBr	**14b**, 62
11	Bu_3SnLi[a]	**14c**, 44
11	AllylMgBr	**14d**, 48
11	EtMgBr	**14e**, 52
12	BuMgBr	**15a**, 65
12	PhMgBr	**15b**, 58

[a] THF solvent (ref 11).

SCHEME 4



smaller excess of organometallic. The yields are moderate to good, and are of isolated and purified product.

Preliminary experiments with a menthol-derived carbamate chiral auxiliary, with tributyltin lithium as the nucleophile, revealed a total lack of diastereoselectivity,[11] so we turned to commercially available *trans*-cumylcyclohexanol (TCC) as auxiliary. Scheme 4 illustrates the procedure for the conversion of lactams **1**−**3** into imides **16**−**18**, and then into benzotriazoles **19**−**21**, using methodology analogous to the Boc compounds in the racemic series.

The addition of organometallics to *N*-acyliminium ions derived from **19**−**21** was successful in all cases studied, as detailed in Table 2. The yields indicated are of the diastereomer mixture. The diastereomer ratio was determined by supercritical fluid chromatography (SFC). In all cases but one, the diastereomers were separable on a preparative scale by recrystallization or chromatography, and the homogeneity of the major diastereomer was confirmed by SFC. Reductive removal of the auxiliary from the major diastereomer afforded enantiopure 2-substituted heterocycles. Of these, rotations for **25b**,**c** and **26b**,**c** have been reported, and the absolute configurations were established by comparison.[11,19−21] The rotations we found for these oily amines corresponded closely for **25c** and **26c**,[11] but not for **25b** and **26b**. The literature rotations of **25b** and **26b** were reported for neat samples obtained by resolution, but we did not make sufficient material to attempt duplication. However, we used the sign of rotation only to establish absolute configuration. Moreover, two reports of the specific rotation of neat *R*-**25b** (both obtained by resolution) differed significantly (+13.65[19] and +156.5[20]), but both were dextrorotatory. Enantiopurity of our compounds is assured, since the amines were obtained by reduction of single diastereomers. Previous work in these laboratories has shown that Dibal-H reduction of enantioenriched 2-(tributylstannyl)-pyrrolidine carbamates and 2-(tributylstannyl)piperidine ureas occurs with no racemization.[16] Moreover, we have recently confirmed the absolute configuration of *S*-2-(tributylstannyl)pyrrolidinium iodide by anomalous dispersion X-ray analysis.[22] The relative configurations of the four corresponding TCC adducts (**22b**,**c** and **23b**,**c**) are therefore established. The relative configurations of the remaining five compounds are assigned by analogy.

Discussion

For the strategy of converting a lactam to an *N*-acyliminium ion, none of the existing strategies outlined in the Introduction were suitable. The closest possibilities were the Wanner or Streith auxiliaries (Figure 1). The advantage of these auxiliaries would be the possibility of intramolecular delivery of organometallic following coordination of the metal to a carbonyl oxygen. However, both of these alternatives presented the problem of chemoselectively reducing a lactam in the presence of an ester or lactone, so we chose to investigate the methodology using a Boc carbamate first, and then extend the methodology to the TCC auxiliary.

Following Dieter's precedent,[13] the selective reduction of the lactam carbonyl over the carbamate carbonyl was routine at low temperature for both Boc (**4**−**6**) and TCC carbamates (**16**−**18**), although the yields were somewhat lower with the TCC carbamate. In both cases, conversion of the carbinols to the benzotriazoles **10**−**12** and **19**−**21** afforded products with complex NMR spectra because of the mixture of N^1 and N^2 constitutional benzotriazole isomers (see Scheme 3). With **19**−**21**, additional complexity is imparted by the possibility of diastereomers as well: each of the two constitutional isomers may exist as two diastereomers. After the addition of the organometal, the spectra of the products **13**−**15** and **22**−**24** are considerably simpler.

The proposed mechanism is shown in Scheme 5. Beginning with the benzotriazoles **10**−**12** and **19**−**21**, in addition to the two possible constitutional benzotriazole isomers, there are two possible rotamers (indicated in Scheme 5 as *cis* and *trans* **10**−**12** and **19**−**21**). In the case of **19**−**21**, there are additionally two possible diastereomers due to the TCC auxiliary. Expulsion of the benzotriazole moiety then affords the intermediate *N*-acyliminium ions **28** and **29**, which may also exist as rotamers, noted as *s-cis* and *s-trans*. Addition of the organometallic to *N*-Boc iminium ions **28a**−**c** affords compounds **13**−

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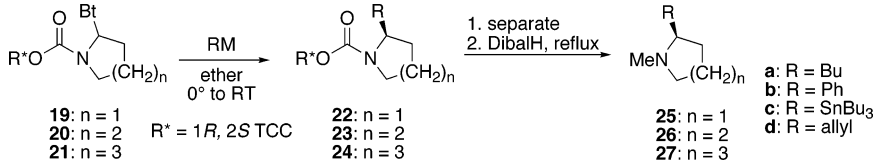
(22) Gawley, R. E.; Narayan, S.; Vicic, D. A. *J. Org. Chem.* **2005**, *70*, 328−329.

TABLE 2. Preparation of Scalemic 2-Substituted Heterocycles



19: n = 1
20: n = 2
21: n = 3

R* = 1*R*, 2*S* TCC

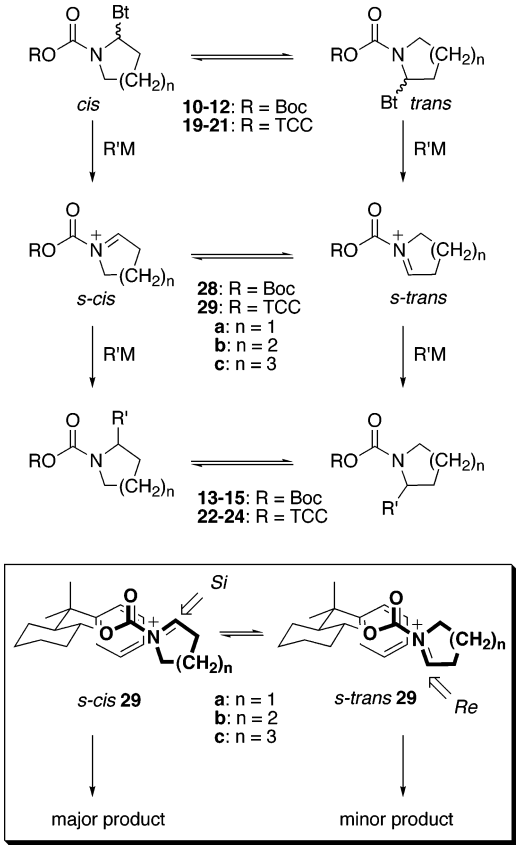
22: n = 1
23: n = 2
24: n = 3

25: n = 1
26: n = 2
27: n = 3

substrate	RM	step 1, yield (%)	dr	step 2, yield[a] (%)
19	BuMgBr	**22a**, 41	79:21	**25a**, 66
19	PhMgBr	**22b**, 54	84:16	**25b**, 65
19	Bu_3SnLi[b]	**22c**, 51	80:20	**25c**, 70
19	AllylMgBr	**22d**, 48	72:28	**25d**, 62
20	BuMgBr	**23a**, 47	88:12	**26a**, 70
20	PhMgBr	**23b**, 51	90:10	**26b**, 68
20	Bu_3SnLi[b]	**23c**, 43	70:30	**26c**, 76
21	BuMgBr	**24a**, 68[c]	54:46[c]	*d*
21	PhMgBr	**24b**, 64	74:26	*d*

[a] Yield of reduction, after removal of minor diastereomer. [b] THF solvent (ref 11). [c] Diastereomers inseparable. [d] Not done.

SCHEME 5



15 as racemates, and the equilibria between *cis*/*trans* **10**−**12**, and *s-cis*/*s-trans* **28** are irrelevant.

The absolute configuration of the major product after reductive removal of the chiral auxiliary of several of the pyrrolidines and piperidines revealed that the addition occurred to the *Si* face of the iminium ion. This is consistent with the approach as illustrated in the *s-cis* conformation of **29a**−**c** on the left of the inset of Scheme 5.

It is likely that the *cis*/*trans* equilibrium of **10**−**12** and **19**−**21**, and of the *s-cis*/*s-trans* equilibrium **28/29a**−**c**, at the temperature of the reaction, is fast in comparison to the rate of the overall conversion of benzotriazole to product. The free energy rotational barrier in pyrrolidine and 2-pyrroline carbamates similar to **10**−**12** is 15−17 kcal/mol.[23,24] We are not aware of any data on the free energy barrier to C−N bond rotation in *N*-acyliminium ions. However, it is almost certainly less than that of the carbamates, since the nitrogen lone pair is delocalized away from the carbonyl. Such effects can be seen in both amides and carbamates. For example, *N*-acetylpyrrolidines have rotational barriers in the range of 17.4−18.7 kcal/mol,[23,25] whereas *N*-acetylpyrrole has a free energy barrier of 12.1 kcal/mol,[26] or 5.3−6.6 kcal/mol less than *N*-acetylpyrrolidines. The barrier to rotation in *N*-methyl-*N*-Boc anilines is 11−13 kcal/mol,[27,28] and is lowered by electron withdrawing substituents on the phenyl ring. If the phenyl is replaced by a π-deficient heterocycle, the barrier falls even further. For example, the barrier for rotation in *N*-methyl-*N*-Boc-2-aminopyrimidine is less than 9 kcal/mol, and is still undergoing fast exchange in a 500 MHz NMR at −90 °C.[27] On the basis of these data, a conservative upper limit estimate of the free energy barrier for the *s-cis*/*s-trans* interconversion of *N*-acyl iminium ions **28** and **29** is 12 kcal/mol, which corresponds to a rate constant of 1500 s^{-1} at 0 °C. If the TCC auxiliary hinders rotation and increases the barrier by 2 kcal/mol, the rate would be 33 s^{-1} at 0 °C. The experimental conditions described in this paper call for overnight stirring from 0 °C to room temperature for complete conversion. We do not know whether the ionization of the benzotriazolyl carbamates **19**−**21** or the addition of organometallic to iminium ions **29a**−**c** is rate determining, but the *s-cis*/*s-trans* equilibrium is probably faster.

The organometallic addition to *N*-acyliminium ions **29a**−**c** is the stereochemically defining step. If the *s-cis*/*s-trans* equilibrium of **29a**−**c** is faster than the organometallic addition, Curtin−Hammett kinetics[29] apply.

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Possibly, coordination of the organometallic to the urethane carbonyl and intramolecular delivery of the carbanion nucleophile to the *Si* face of *s-cis* **29** accounts for the configuration of the major product. Interestingly, the steric course of this reaction is in contrast to that of the *N*-acylpyridiniums developed by Comins, in which addition occurs predominantly to the *Re* face of C_6 of the pyridinium (see Figure 1).[30]

In conclusion, the conversion of lactams to 2-substituted heterocycles has been achieved in both racemic and enantiopure forms. Up to 90% ds was found with use of the TCC auxiliary. The goal of achieving higher selectivity in additions by using a TCC auxiliary is likely complicated by the multiple equilibria involving the intermediates in the key step. Nevertheless, in all but one case, the diastereomers were easily separable, affording enantiopure *N*-methyl heterocycles after reductive removal of the auxiliary, which may be recovered.

Experimental Section

***tert*-Butyl 2-(Benzotriazolyl)azepane-1-carboxylate, 12.** To a well-stirred solution of *tert*-butyl 2-(hydroxy)azepane-1-carboxylate (**9**)[13,31] (2.4 g, 11 mmol) in toluene (40 mL) were added benzotriazole (2.0 g, 16.5 mmol) and molecular sieves 4 Å and the reaction mixture was refluxed for 4 h. The resulting suspension was filtered through Celite and the organic layer was washed with 15% NaOH and brine, and then dried over $MgSO_4$. Solvent removal under reduced pressure gave the crude product that was purified by flash chromatography (ethyl acetate/hexane, 1:8) to give the desired product (2.3 g, 66%). LRMS: *m/z* 339 ($M{\cdot}Na^+$). This compound was used directly without further purification or characterization.

2-(2-Phenylpropan-2-yl)cyclohexyl 2-Oxoazepane-1-carboxylate, 18. To a solution of ϵ-caprolactam (1.1 g, 9.7 mmol) in dry THF (20 mL) at −78 °C under N_2 atmosphere was added BuLi (3.9 mL, 2.5 M, 9.7 mmol) dropwise and the reaction mixture was warmed to 0 °C and stirred for 15 min. The reaction mixture was again cooled to −78 °C and to this, a solution of (1*R*,2*S*)-2-(2-phenylpropan-2-yl)cyclohexyl chloroformate[2] (3.3 g, 11.7 mmol) in dry THF (60 mL) was added. The reaction mixture was stirred overnight, gradually warming to room temperature, and diluted with 5% $NaHCO_3$ solution (50 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 × 40 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography (ethyl acetate/hexane, 1/5) to give the title compound (3.2 g, 83%) as an oil. ^{1}H NMR δ 0.86−1.08 (m, 2H), 1.14 (s, 3H), 1.25 (s, 3H), 1.41−1.62 (m, 8H), 1.84−2.06 (m, 2H), 2.43 (t, 2H), 3.18 (t, 2H), 4.79 (dt, 1H), 6.96−7.24 (m, 5H); ^{13}C NMR δ 23.4, 24.7, 25.4, 25.8, 27.1, 27.7, 28.6, 29.1, 33.3, 39.3, 39.9, 45.7, 50.9, 77.2, 125.0, 125.5, 127.9, 151.5, 152.6, 175.3. IR 1766, 1714 cm^{-1}. LRMS *m/z* 380 ($M{\cdot}Na^+$). Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74. Found: C, 73.42; H, 8.82.

2-(2-Phenylpropan-2-yl)cyclohexyl 2-(Benzotriazolyl)-azepane-1-carboxylate, 21. To a well-stirred solution of **18** (1.0 g, 2.8 mmol) in dry THF (30 mL) at −78 °C was added DIBAL-H (1.0 mL, 5.6 mmol) under a blanket of N_2 atmosphere. The reaction mixture was stirred for 1 h at this temperature and then diluted with a saturated solution of potassium acetate (2 mL) and the mixture was stirred for 10 min. Then it was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were thoroughly washed with brine and dried ($MgSO_4$). After rotary evaporation under reduced pressure, the product (800 mg, 80%) was obtained as an oil. ^{1}H NMR δ 0.74-0.91 (m, 6H), 1.01−1.66 (m, 30H), 1.71−2.11 (m, 4H), 2.74−2.98 (m, 2H), 3.32−3.51 (m, 2H), 4.49 (m, 1H), 4.71−4.86 (m, 3H), 5.41 (m, 1H), 6.05−7.24 (m, 10H) (for 2 diastereomers); ^{13}C NMR δ 22.62 and 22.67, 22.75 and 2318, 24.79 and 24.86, 25.83 and 26.07, 26.98 and 27.48, 28.17, 28.96 and 29.44, 29.58 and 29.73, 34.06 and 34.15, 34.85, 39.69 and 40.43, 40.91 and 41.18, 50.93 and 51.06, 75.90 and 76.21, 78.83 and 80.10, 124.88 and 125.03, 125.38 and 125.53, 127.86 and 127.95, 151.03 and 152.78, 154.85 and 156.59 (for 2 diastereomers). IR 3427, 1673 cm^{-1}. *m/z* 382 $(M + 23)^+$. Anal. Calcd for $C_{21}H_{33}NO_3$: C, 73.50; H, 9.25. Found: C, 73.53; H, 9.56.

To a well-stirred solution of the above lactol (700 mg, 1.95 mmol) in toluene (40 mL) were added benzotriazole (350 mg, 2.9 mmol) and molecular sieves 4 Å and the reaction mixture was refluxed for 3 h. The orange suspension was filtered through Celite and the organic layer was washed with 15% NaOH and brine, and then dried over $MgSO_4$. Solvent removal under reduced pressure gave the crude product that was purified by flash chromatography (ethyl acetate/hexane, 1/10) to give the desired product (600 mg, 67%) as an oil. This compound was used without further purification or characterization. LRMS *m/z* 483 ($M{\cdot}Na^+$).

General Procedure for the Grignard Addition. To a well-stirred solution of 2-benzotriazolyl-*N*-carbamoyl heterocycle (1 equiv) in dry Et_2O (8 mL) was added appropriate Grignard reagent (4 equiv) dropwise at 0 °C under nitrogen atmosphere. The reaction mixture was stirred overnight while allowing it to attain room temperature. It was then diluted with a saturated solution of NH_4Cl (1 mL) and extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and then dried ($MgSO_4$). After rotary evaporation, the crude product was purified by flash chromatography (ethyl acetate/hexane, 1:10). For the compounds resulting from addition to TCC iminiums (from **19**−**21**), the diastereomer ratios were determined by HPLC or SFC. The diastereomers were then separated before reduction.

***N-tert*-Butoxycarbonyl-2-(butyl)pyrrolidine**, **13a**,[32] was prepared from **10**[11] (200 mg, 0.7 mmol) and *n*-butylmagnesiumchloride (1.4 mL, 2.0 M, 2.8 mmol) in 61% yield as a colorless oil after flash chromatography. ^{1}H NMR δ 0.74 (t, 3H), 1.12 (m, 5H), 1.30 (s, 9H), 1.47 (m, 1H), 1.66 (m, 2H), 3.14 (m, 2H), 3.56 (m, 1H); ^{13}C NMR δ 14.0, 22.6 and 23.0, 28.5, 29.8 and 30.6, 33.8 and 34.2, 46.0 and 46.3, 57.2, 78.6, 154.5. LRMS *m/z* 250 ($M{\cdot}Na^+$).

***N-tert*-Butoxycarbonyl-2-(butyl)piperidine**, **14a**,[33] was prepared from **11**[11] (200 mg, 0.66 mmol) and *n*-butylmagnesium chloride (1.3 mL, 2.0 M, 2.64 mmol) in 62% yield as a colorless oil after flash chromatography. This compound is known in the patent literature (*Chem. Abstr.* 136:294967),[33] but spectral data have not been reported. ^{1}H NMR δ 0.84 (t, 3H), 1.09−1.36 (m, 3H), 1.40 (s, 9H), 1.44−1.67 (m, 5H), 2.69 (dt, 1H), 3.91 (m, 1H), 4.14 (m, 1H); ^{13}C NMR δ 14.1, 19.1, 22.7, 25.7, 28.4, 28.5, 28.6, 29.4, 38.7, 50.4, 79.1, 155.2. LRMS *m/z* 264 ($M{\cdot}Na^+$). HRMS *m/z* 264.1922 ($M{\cdot}Na^+$), calcd for $C_{14}H_{27}NO_2Na$ 264.1939; *m/z* 186.1488 ($MH^+ - C_4H_9$), calcd for $C_{10}H_{20}NO_2$ 186.1494.

***N-tert*-Butoxycarbonyl-2-(butyl)azepane**, **15a**, was obtained by the reaction of **12** (500 mg, 1.6 mmol) and butylmagnesium chloride (3.2 mL, 2.0 M, 6.4 mmol) in 65% yield as an oil after flash chromatography (ethyl acetate/hexane, 1:15). ^{1}H NMR δ 0.68 (m, 6H), 0.93−1.19 (m, 13H), 1.26 and 1.27 (s, 18H), 1.31−1.64 (m, 5H), 1.85 (m, 2H), 2.46 (dt, 2H), 3.37−3.92 (m, 4H) (for 2 rotamers); ^{13}C NMR δ 14.0, 22.6 and 22.7, 24.8 and 25.1, 28.4, 28.9, 29.9, 34.44 and 34.67, 34.70

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and 34.78, 41.08 and 41.44, 54.1, 55.0, 78.35 and 78.61, 155.59 and 155.78 (for 2 rotamers). LRMS *m/z* 278 ($M{\cdot}Na^+$); HRMS *m/z* 278.2106 ($M{\cdot}Na^+$), calcd for $C_{15}H_{29}NO_2Na$ 278.2096; *m/z* 200.1650 ($MH^+ - C_4H_9$), calcd for $C_{11}H_{22}NO_2$ 200.1651.

(1*R*,2*S*,2′*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl 2′-(phenyl)pyrrolidine-1-carboxylate, **22b**, was prepared from **19**[11] (400 mg, 0.92 mmol) and phenylmagnesium bromide (5.5 mL, 1.0 M, 5.5 mmol) in 54% yield as an oil after flash chromatography (ethyl acetate/hexane, 1:25) to remove major byproducts: SFC column, Chiracel OD-H; modifier, 10% ethanol; flow rate, 3.0 mL/min; temperature 30 °C; diastereomeric ratio (dr), 16:84; retention time, 12.08:15.99 min, respectively. Further purification by radial chromatography (ethyl acetate/hexane, 0.5:25) afforded the major diastereomer. ^{1}H NMR δ 0.38 (m, 1H), 1.02 (m, 4H), 1.15 (s, 3H), 1.36 (s, 3H), 1.71 (m, 6H), 1.98 (m, 2H), 3.11 (m, 1H), 3.49 (m, 2H), 4.62 (m, 1H), 7.18−7.32 (m, 10H); ^{13}C NMR δ 23.2, 24.2, 24.8, 26.2, 27.1, 29.0, 34.5, 34.8, 39.9, 46.1, 51.4, 61.1, 75.5, 115.6, 119.9, 126.7, 127.9, 128.4, 129.5, 152.7, 154.3, 156.6. IR 1694 cm^{-1}. LRMS *m/z* 414 ($M{\cdot}Na^+$). Anal. Calcd for $C_{26}H_{33}NO_2$: C, 79.76; H, 8.50. Found: C, 79.70; H, 8.52.

(1*R*,2*S*,2′*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl 2-(phenyl)piperidine-1-carboxylate, **23b**, was obtained from reaction of **20**[11] (400 mg, 0.9 mmol) and phenylmagnesium bromide (3.6 mL, 1.0 M, 3.6 mmol) in 51% yield as a colorless oil after flash chromatography (ethyl acetate/hexane, 1:25) to remove major impurities: SFC column, Chiracel OD-H; modifier, 10% ethanol; flow rate, 3.0 mL/min; temperature 30 °C; diastereomeric ratio, 10:90; retention time, 9.93:14.08 min, respectively. Further purification by radial chromatography (ethyl acetate/hexane, 0.5:25) afforded major diastereomer. ^{1}H NMR δ 1.02 (m, 1H), 1.31 (s, 3H), 1.35 (s, 3H), 1.48 (m, 6H), 1.86 (m, 1H), 2.09 (m, 2H), 2.35 (d, 1H), 2.71 (m, 1H), 3.66 (m, 1H), 4.87 (m, 1H), 5.49 (m, 1H), 7.01−7.37 (m, 10H); ^{13}C NMR δ 19.5, 24.9, 25.8, 26.2, 27.7, 28.4, 34.5, 40.2, 40.4, 51.3, 53.3, 76.3, 125.2, 125.6, 126.4, 126.7, 128.1, 128.6, 140.1, 151.6, 155.7. IR 1682.6 cm^{-1}. LRMS *m/z* 428 ($M{\cdot}Na^+$). Anal. Calcd for $C_{27}H_{35}NO_2$: C, 79.96; H, 8.70. Found: C, 79.09; H, 8.66.

(1*R*,2*S*,2′*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl-2-(phenyl)azepane-1-carboxylate, **24b**, was prepared from 145 mg of **21** (0.315 mmol) and phenylmagnesium chloride (1.26 mL, 1.260 mmol of a 1.0 M solution in THF) in 65% yield after flash chromatography (ethyl acetate/hexane 1:25). The oil crystallized on standing. SFC column, Chiracel OD-H; modifier, 10% ethanol; flow rate, 3.0 mL/min; temperature 30 °C; diastereomeric ratio 26:74; retention time, 11.47:16.22 min, respectively. Recrystallization from ether afforded a single diastereomer by SFC, mp 104−106 °C. ^{1}H NMR δ 0.62−2.00 (m, 25H), 2.26−2.37 (m, 2H), 2.79−2.98 (m, 2H), 3.80−4.11 (m, 1H), 4.72−4.80 (m, 1H), 5.00−5.08 (p, 1H), 6.98−7.28 (m, 10H); ^{13}C NMR δ 24.6, 24.7, 25.7, 25.8, 26.1, 27.6, 29.0, 29.5, 29.6, 29.6, 30.0, 30.7, 34.2, 34.4, 35.7, 37.0, 30.6, 40.7, 43.4, 44.0, 51.06, 51.10, 59.6, 60.0,125.09, 125.12, 125.54, 125.59, 125.74, 126.50, 126.54, 127.75, 127.96, 128.33, 128.44, 143.8, 144.3, 150.6, 151.3, 156.1, 156.4. IR 2927, 2252, 1674, 1450, 908 cm^{-1}. HRMS: *m/z* 442.2721 ($M{\cdot}Na^+$), calcd for $C_{28}H_{37}NO_2$ 442.2722. $[\alpha]_D$ + 51.3 (*c* 0.265, CH_2Cl_2). Anal. Calcd for $C_{28}H_{37}NO_2$: C, 80.15; H, 8.89; N, 3.34. Found: C, 80.14; H, 8.93; N, 3.37.

General Procedure for Reductive Removal of TCC Auxiliary. To a well-stirred solution of the 2-substituted *N*-TCC heterocycle (1 equiv, 0.7 mmol) in dry THF (15 mL) was added DibalH (6 equiv, 4.2 mmol) under nitrogen atmosphere. The reaction mixture was refluxed overnight while stirring. It was then quenched with MeOH (1 mL), 15% NaOH solution (2 mL), and water (2 mL). Removal of solvent under reduced pressure gave the crude product that was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). After rotary evaporation, the crude product was purified by flash chromatography (ethanol/ethyl acetate/hexane; 0.5:1:5).

(*R*)-1-Methyl-2-(phenyl)pyrrolidine, **25b**,[19,34,35] was prepared from **22b** (R = phenyl) in 65% yield as an oil after flash chromatography: ^{1}H NMR δ 1.25 (m, 1H), 1.63−1.98 (m, 4H), 2.15 (s, 3H), 3.01 (t, 1H), 3.32 (dt, 1H), 7.18−7.32 (m, 5H); ^{13}C NMR δ 22.5, 35.2, 40.5, 57.1, 71.7, 127.0, 127.5, 128.3, 143.3. $[\alpha]_D$ + 82.5 (*c* 2.0, $CHCl_3$) (lit. *R*-(+) $[\alpha]_D$ +156.5 (neat),[34] +13.65 (neat)[19]).

(*R*)-1-Methyl-2-(phenyl)piperidine, **26b**,[34] was prepared from **23b** (R = phenyl) in 68% yield as an oil after flash chromatography: ^{1}H NMR δ 1.36 (m, 1H), 1.51−1.85 (m, 5H), 1.98 (s, 3H), 2.08 (m, 1H), 2.72 (m, 1H), 3.01 (m, 1H), 7.17−7.30 (m, 5H); ^{13}C NMR δ 25.1, 26.3, 36.0, 44.7, 57.6, 71.2, 127.0, 127.5, 128.4, 145.0. $[\alpha]_D$ + 143.0 (*c* 2.0, $CHCl_3$) (lit. *R*-(+) $[\alpha]_D$ +82.7 (neat)[34]).

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Supporting Information Available: General experimental details, references to all previously reported compounds, details of the synthesis, and characterization of **13b**, **14b**, **14d**, **14e**, **15b**, **22a**, **22d**, **23a**, **24a**, **25a**, **25d**, and **26a**, and proton and carbon NMR spectra of **13a**, **13b**, **14a**, **14b**, **14d**, **14e**, **15a**, **15b**, **18**, **22a**, **22b**, **22d**, **23a**, **23b**, **24a**, **24b**, **25a**, **25b**, **26a**, and **26b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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