Steric and Electronic Influences on the Diastereoselectivity of the $Rh_2(OAc)_4$-Catalyzed C−H Insertion in Chiral Ester Diazoanilides: Synthesis of Chiral, Nonracemic 4-Substituted 2-Pyrrolidinones

Andrew G. H. Wee,* Baosheng Liu, and Douglas D. McLeod

Department of Chemistry, University of Regina, Regina, Saskatchewan S4S 0A2, Canada

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A series of N-substituted *N*-(4-methoxyphenyl)-α-(alkoxycarbonyl)-α-diazoacetanilides, **10** and *ent*-**10**, wherein the alkoxy unit is a chiral auxiliary group [(−)-**7** or (+)-**8**)], was prepared. The $Rh_2(OAc)_4$-catalyzed intramolecular C−H insertion reaction of **10** and *ent*-**10**, under optimized reaction conditions, was investigated as a route for the preparation of chiral, nonracemic 4-substituted 2-pyrrolidinones. The cyclization reaction led only to 2-pyrrolidinone and 2-azetidinone products; the former products were obtained as major and, in a few cases, as exclusive products. The type and nature of the N-substituent in **10** or *ent*-**10** was found to govern the diastereoselectivity of the reaction. With *N*-alkyl groups, steric effects play an important role in determining the diastereoselectivity of the reaction. However, with *N*-arylethyl substituents, electronic effects transmitted by the aryl substituents influenced the diastereoselectivity of the C−H insertion reaction. Specifically, electron-donating substituents were found to markedly attenuate the diastereoselectivity of the reaction. The diastereoselectivity of the reaction ranged from moderate to high (37−98%). A transition-state model to explain the observed diastereoselectivity is provided. The synthetic utility of the method is demonstrated by the stereoselective synthesis of the medicinally important, unnatural amino acid *trans*-4-cyclohexyl-L-proline **23**.

Introduction

Rhodium(II) carbenoids, generated from the reaction of α-diazocarbonyl compounds with catalytic amounts of dirhodium(II) complexes, undergo a wide range of synthetically useful transformations.[1] In particular, the intramolecular Rh(II) carbenoid mediated C−H insertion reaction is now a well-established method for the facile construction of five-membered carbocycles and heterocycles. Recently, there has been a growing interest in the development of methods, based on asymmetric rhodium(II) carbenoid C−H insertion, for the synthesis of chiral, nonracemic cyclic molecules.[2] In general, two approaches have been investigated. The first approach entails the incorporation of a readily removable, chiral auxiliary group into the α-diazocarbonyl compound.[3] Intramolecular rhodium(II) carbenoid-mediated C−H insertion and subsequent excision of the auxiliary group from the cyclic product results in an (net) enantioselective route to cyclic molecules. The second approach uses either chiral dirhodium(II) carboxylates or carboxamides to catalyze the cyclization of achiral diazocarbonyl compounds.[2a−c,4] However, the stereoselectivities of these reactions were found to vary with both the type of chiral rhodium(II) catalyst and the structure of the diazocarbonyl compound. The most effective chiral catalysts developed to date are the rhodium(II) carboxamide-based catalysts, $Rh_2(5S/5R\text{-MEPY})_4$ and $Rh_2(4S\text{-MEOX})_4$[2a,b] which not only provide good to excellent enantio- and/or diastereocontrol but also effect excellent regiocontrol in the C−H insertion reaction. These catalysts were found to be especially useful for the cyclization of select α-diazoacetates to give γ-lactone derivatives in high enantiomeric excess (91−97%).[2b] However, in cases where lower enantio- and diastereoselectivities were obtained, the use of the newly designed catalysts, $Rh_2(MACIM)_4$ and $Rh_2(MPPIM)_4$, resulted in excellent stereocontrol.[4f] The results from these studies have been used in the synthesis of natural products.[4f,5]

On the other hand, fewer studies have reported on the intramolecular asymmetric C−H insertion in diazoamides. Doyle and co-workers described the Rh_2(5S/5R-

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(2) Reviews: (a) Doyle, M. P.; McKervey, M. A. *Chem. Commun.* **1997**, 983. (b) Doyle, M. P. *Aldrichim. Acta* **1996**, *29*, 3. (c) Hashimoto, S.-i.; Watanabe, N.; Anada, M.; Ikegami, S. *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 114. (d) Brunner, H. *Angew. Chem., Intl. Ed. Engl.* **1992**, *31*, 1183.

(3) (a) Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28 and references cited. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; Chapter 12, p 862.

(4) Selected examples of homochiral Rh(II) complexes used in intramolecular C−H insertion: **Rh(II) Carboxylates**: (a) Watanabe, N.; Ohtake, Y.; Hashimoto, S.-I.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1995**, *36*, 1491 and references therein. (b) Sawamura, M.; Sasaki, H.; Nakata, T.; Ito, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2725. (c) McKervey, M. A.; Ye, T. *Chem. Commun.* **1992**, 823 and references cited. **Rh(II) "Carboxamides"**: (d) Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosch, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968. (e) Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Daniel, K. L. *Tetrahedron Lett.* **1992**, *33*, 7819. (f) Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L.; Bode, J. W.; Simonsen, S. H.; Lynch, V. *J. Org. Chem.* **1995**, *60*, 6654 and references cited. **Rh(II) Phosphate**: (g) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992**, *33*, 5983.

(5) For example: (a) Pyrrolizidine alkaloid: Doyle, M. P.; Kalinin, A. V. *Tetrahedron Lett.* **1996**, *37*, 1371. (b) Lignan lactones: Bode, J. W.; Doyle, M. P.; Protopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, *61*, 9146.

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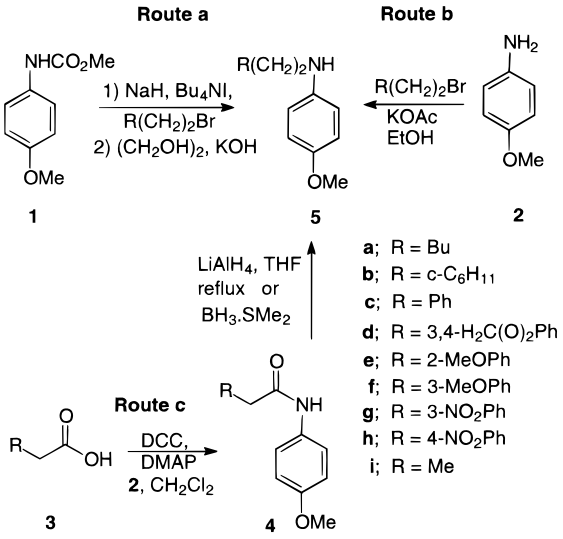
Scheme 1

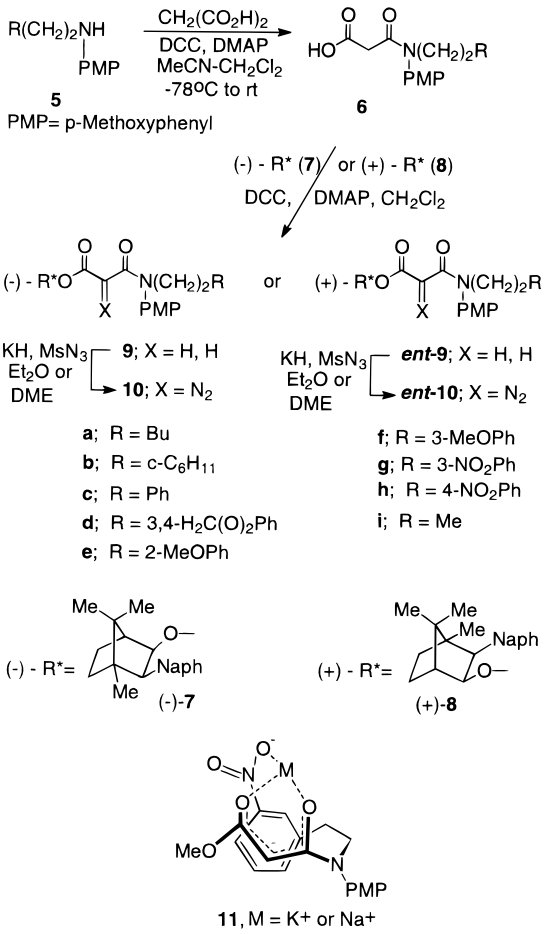


MEPY)$_4$ and Rh$_2$(4S-MEOX)$_4$-catalyzed reactions of *N*-alkyl-*N*-*tert*-butyldiazoamides[4d,e] to give 4-substituted 2-pyrrolidinones with ee's in the range 58−78%. 2-Azetidinones (ee 20−80%) were also obtained as minor products. In connection with our interest in the intramolecular C−H insertion of acyclic N-substituted *N*-PMP diazoanilides (PMP = *p*-methoxyphenyl),[6] we became interested in developing a route for the synthesis of chiral, nonracemic 4-substituted 2-pyrrolidinones.[7a] We reasoned that diastereoselective rhodium(II) carbenoid-mediated C−H insertion would be achieved if a chiral auxiliary group was incorporated into the ester moiety of our diazoanilides. Herein, we describe the details of our investigation into the Rh$_2$(OAc)$_4$-catalyzed asymmetric C−H insertion reaction of chiral ester diazoanilides of type **10** and *ent*-**10**, where R* represents the (+)-camphor- or (−)-borneol-derived auxiliary (−)-**7** or (+)-**8**. This type of approach for the preparation of optically active 4-substituted 2-pyrrolidinones has not been reported before. We found that the chiral auxiliary group was readily removed from the 2-pyrrolidinone products by decarbalkoxylation and was recovered unchanged and in good yields. Overall, the reaction proceeded with good regioselectivity and excellent chemoselectivity. The diastereoselectivity of the reaction was found to vary with the type and nature of the N-substituent in **10** and *ent*-**10**.

Results and Discussion

I. (a) Preparation of Chiral Ester Diazoanilides 10 and *ent*-10. The diazoanilides **10** and *ent*-**10** used in this study were prepared according to the routes shown in Schemes 1 and 2. The *p*-anisidine derivatives **5** were prepared, as summarized in Scheme 1, using either previously developed routes (a and b, **5a**,**c**,**i**)[6] or via the anilides **4** (route c, **5b**,**d**,**e**,**f**,**h**) using standard chemical transformations. *N*-[(3-Nitrophenyl)ethyl]-*p*-anisidine **5g** was prepared starting from *m*-nitrobenzaldehyde. Treatment of the latter with (methoxymethylene)triphenylphosphorane gave the enol−ether, which was hydrolyzed (*i*-PrOH−HCl) to generate the corresponding aldehyde. Without isolation, the aldehyde was directly reacted with *p*-anisidine in the presence of NaCNBH$_3$[8] to afford the product **5g**.

Scheme 2



The unstable anilines **5** were immediately condensed with malonic acid, under optimal reaction conditions (DCC, cat. DMAP, MeCN−CH$_2$Cl$_2$, −40 °C),[9a] to give good yields (60−70%) of the amide acids **6**[9b] (Scheme 2). Compounds **6** were then coupled (DCC, DMAP)[11a,b] to the appropriate chiral auxiliary, (−)-**7**[3a,c] or (+)-**8**,[12] to afford the ester amides **9** or *ent*-**9** in good yields (75−95%).

The conversion of the ester amides **9** to the diazo derivatives **10** was not trivial. The usual diazotization

(6) Wee, A. G. H.; Liu, B.-S.; Zhang, L. *J. Org. Chem.* **1992**, *57*, 4404.

(7) (a) Preliminary communication: Wee, A. G. H.; Liu, B.-S. *Tetrahedron Lett.* **1996**, *37*, 145. (b) For a related enantioselective synthesis of 4-substituted 2-pyrrolidinones, see: Anada, M.; Hashimoto, S.-i. *Tetrahedron Lett.* **1998**, *39*, 79.

(8) (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. (b) Danheiser, R. L.; Morin, J. M., Jr.; Salaski, E. J. *J. Am. Chem. Soc.* **1985**, *107*, 8066.

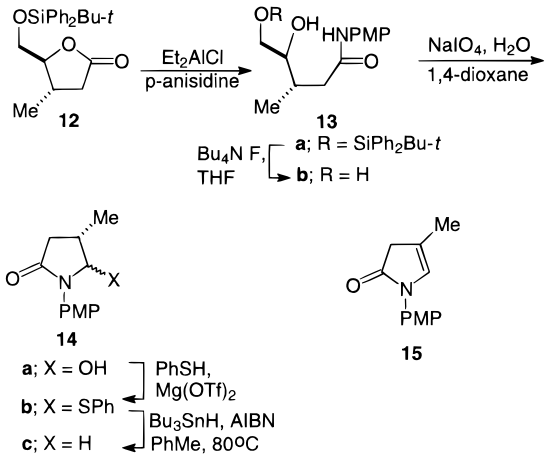
(9) (a) Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 897. (b) Other routes were also examined: Condensation of *p*-anisidine either with α-methyl(4-methoxybenzyloxycarbonyl)acetic acid or α-(*tert*-butyloxycarbonyl)acetic acid followed by deprotection of the α-methyl(4-methoxybenzyl)[10] or *tert*-butyl (TFA−CH$_2$Cl$_2$, 1:10 v/v) groups.

(10) Yoo, S.-E.; Kim, H. R.; Yi, K. Y. *Tetrahedron Lett.* **1990**, *31*, 5913.

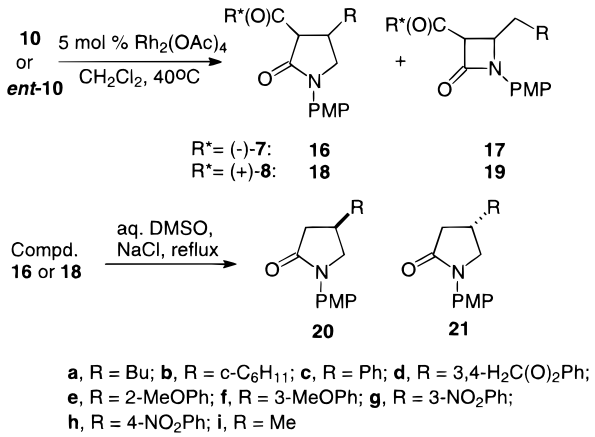
(11) (a) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. (b) Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241. (c) The carboxylic acids were either prepared using standard chemical transformations (e.g., hydrolysis of nitriles; oxidation of primary alcohols) or were commercially available.

(12) (a) Coxon, J. M.; Hartshorn, M. P.; Lewis, A. *Aust. J. Chem.* **1971**, *24*, 1017. (b) (−)-Camphor was prepared by oxidation of (−)-borneol according to Stevens' procedure (Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980**, *45*, 2030.) It was converted to (+)-**8** following the same sequence of steps[3a] used for the synthesis of (−)-**7**.

Scheme 3



Scheme 4



a, R = Bu; **b**, R = c-C_6H_{11}; **c**, R = Ph; **d**, R = 3,4-$H_2C(O)_2$Ph; **e**, R = 2-MeOPh; **f**, R = 3-MeOPh; **g**, R = 3-NO_2Ph; **h**, R = 4-NO_2Ph; **i**, R = Me

method (MsN_3[13] and DBU as the base),[6,14] which had served us well in other cases, was found to be inefficient; only low yields (25%) of diazo compounds **10** were obtained. We reasoned that the α-methylene hydrogens in the *β*-dicarbonyl unit may be sterically shielded by the auxiliary group, and consequently, approach of the bulky DBU base to the α-hydrogen may be hindered. After many experiments, we found that **9** or *ent*-**9** was efficiently diazotized by the use of KH in either dry ether or DME. Consistently good yields (75−90%) of diazo products **10** or *ent*-**10** were obtained with the exception of **10g**. In the latter case, no diazo product was obtained from **9g** under the improved conditions, and only starting material was recovered (90%). The use of catalytic amounts (10 mol %) of 18-crown-6 as a phase-transfer catalyst did not yield positive results. Eventually, we found that the use of NaH as the base-promoted diazotization and **10g** was obtained in 40% yield. No further attempts were made to optimize the yield of **10g**.

The inefficiency in the diazotization of **9g** may be attributed to the formation of an insoluble, stable potassium chelate such as **11** that does not further react with MsN_3 to give **10g**. On the other hand, the formation of the sodium chelate is less likely because of its lower stability due to the smaller size of the sodium ion. As a result, diazotization is observed.

(b) Preparation of (*S*)-(−)-*N*-(4-Methoxyphenyl)-4-methyl-2-pyrrolidinone (14c). We next diverted our attention to the preparation of the reference compound (*S*)-(−)-**14c**[15a] that was used in the HPLC analysis of **20i** and **21i** (vide infra; note that **14c** and **21i** are the same). It should be noted that (*S*)-(−)-4-methyl-2-pyrrolidinone has been reported[15b] previously but the *N*-PMP derivative is unknown.

The known[16] *γ*-lactone **12** [$[\alpha]^{23}_D$ +29.2 (*c* 3.9, $CHCl_3$) (lit.[16] $[\alpha]^{23}_D$ +30.5 (*c* 1.2, $CHCl_3$)] was subjected to ring opening[17] with Et_2AlCl−*p*-anisidine complex to give the secondary alcohol **13a** (Scheme 3). Desilylation of **13a** produced the diol **13b**, which was subjected to glycol cleavage using $NaIO_4$[18] in aqueous dioxane to give the cyclic amide alcohol **14a** as a mixture of diastereomers.

Various attempts at deoxygenating the C-5 position in **14a** were futile. For example, reduction of **14a** or its trifluoroacetate derivative with Et_3SiH mediated by $BF_3{\cdot}OEt_2$[19a] or CF_3CO_2H[19b] only gave low yields of the desired (*S*)-**14c**. The major product formed was **15**, which resulted from an E1-type elimination from the acyliminium ion intermediate.[20] It was decided that deoxygenation under neutral conditions may be more conducive for the formation of (*S*)-**14c**. Toward this end, the phenylthio derivative **14b** was prepared by treatment of **14a** with thiophenol in the presence of $Mg(OTf)_2$,[21] a mild Lewis acid. Reduction of **14b** with tributyltin hydride under free-radical reaction conditions[22] gave (*S*)-(−)-**14c** ($[\alpha]^{23}_D$ −1.66 (*c* 4.5, $CHCl_3$) in 95% yield. The ee of (*S*)-(−)-**14c** (t_R = 14.0 min) was >98% on the basis of HPLC analysis.

II. (a) Optimization Studies: $Rh_2(OAc)_4$-Catalyzed C−H Insertion Reaction of *ent*-10a and 10c. Our initial efforts (Scheme 4) were aimed at establishing optimal reaction conditions for the C−H insertion reaction. We were interested in determining the regioselectivity[23] of the reaction (2-pyrrolidinone **16c**/**18a**: 2-azetidinone **17c**/**19a**) and, in particular, the diastereoselectivity of the C−H insertion in the formation of the 2-pyrrolidinone **16c** or **18a**. Compounds *ent*-**10a** and **10c** also permitted us to assess the influence of the N-substituent on the outcome of the reaction and especially whether metallocarbenoid addition[24] to the aryl moiety would be competitive with C−H insertion in the reaction of **10c**.

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(21) Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169.
(22) Neumann, W. P. *Synthesis* **1987**, 655.
(23) Although we found[6] that 2-pyrrolidinone products are usually favored, we felt that it was necessary to reevaluate the regioselectivity in these systems because it is well-known that structural changes in the diazo substrate can have a significant influence on the regioselectivity of the reaction. For example, see Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820 and references therein.
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Table 1. $Rh_2(OAc)_4$-Catalyzed C−H Insertion in Compounds *ent*-10a and 10c

					20/21	
entry	compound	solvent, *T* (°C)	yield[a] (%)	**16**:**17** or **18**:**19**[b]	yield[c] (%)	% ee[d]
1	*ent*-**10a**	$(CH_2Cl)_2$, rt	83	7.3:1	80	40
2	*ent*-**10a**	$(CH_2Cl)_2$, 83	75	2.3:1	88	42
3	*ent*-**10a**	CH_2Cl_2, rt	70	4.3:1	92	47
4	*ent*-**10a**	CH_2Cl_2, 40	64	2.6:1	80	55
5	**10c**	$(CH_2Cl)_2$, rt	90	29:1	94	67
6	**10c**	$(CH_2Cl)_2$, 83	88	17:1	82	57
7	**10c**	CH_2Cl_2, rt	86	28:1	87	64
8	**10c**	CH_2Cl_2, 40	96	23:1	84	79

[a] Combined yield of **16**/**17** or **18**/**19**. [b] Ratio is based on the isolated yields of 2-pyrrolidinone and 2-azetidinone. [c] Isolated yields of **20** or **21**. [d] Determined by HPLC analysis of **20** or **21** on a Chiralcel OB column.

The reactions were catalyzed by 5 mol % of $Rh_2(OAc)_4$[25a] in either dry CH_2Cl_2 or $(CH_2Cl)_2$[25b] for 16−20 h. In these studies, only the 2-pyrrolidinone and 2-azetidinone derivatives were formed, and we did not detect the formation of δ-lactam and cycloaddition products in the reaction of *ent*-**10a** and **10c**, respectively. The less polar 2-azetidinone and more polar 2-pyrrolidinone products were separated using flash chromatography and were each obtained as a mixture of diastereomers. In the case of the 2-pyrrolidinone products, their formation should in principle result in four possible diastereomers; however, TLC analysis of the 2-pyrrolidinone **18a** revealed the presence of at least two very closely moving diastereomers. No further attempts were made, at this stage, to separate the two (or more) diastereomers because **18a** would be decarboxylated at a later stage. Due to the complex nature of the ^1H NMR spectra of each of the diastereomeric mixtures, it was not possible to determine the ratio of the diastereomers in the 2-azetidinone and 2-pyrrolidinone products.

The decarboxylation[27a] of **16c** and **18a** proceeded efficiently to give 2-pyrrolidinones **20c** and **21a**. As well, the chiral alcohol (−)-**7** or (+)-**8** were recovered in good yields (85−95%). Unfortunately, the decarboxylation of the 2-azetidinones under the same conditions led only to the decomposition of starting material, and consequently, we did not further pursue this area. Compounds **20c** and **21a** were subjected to HPLC analysis using a Chiralcel OB column, and the results are shown in Table 1.

It is evident that the regioselectivity in the reaction of compound *ent*-**10a** is more sensitive to the type of solvent[28] used and the reaction temperature than **10c**. At rt, the regioselectivity of the reaction in $(CH_2Cl)_2$ is much higher than in CH_2Cl_2; however, at reflux, the regioselectivity was markedly lower, and similar in both solvents (compare Table 1, entries 1, 3 and 2, 4). In **10c**, the regioselectivity of the reaction was neither affected by the type of solvent nor the reaction temperature (compare Table 1, entries 5, 7 and 6, 8). In all conditions examined, excellent regioselectivity was obtained.

The diastereoselectivity of the reaction in *ent*-**10a** and **10c** showed a dependence on the type of solvent used and the reaction temperature. In *ent*-**10a**, there was a tradeoff between regioselectivity and diastereoselectivity in the reaction. In general, a lower diastereoselectivity was realized in $(CH_2Cl)_2$ than in CH_2Cl_2 regardless of whether the reaction was conducted at room temperature or at reflux temperature (compare Table 1, entries 1, 2 and 3, 4). The best diastereoselectivity was achieved when the reaction was conducted in CH_2Cl_2 at 40 °C (Table 1, entry 4). For compound **10c**, it was found that the diastereoselectivity of the reaction at room temperature was similar in $(CH_2Cl)_2$ and CH_2Cl_2 (compare Table 1, entries 5 and 7); however, at reflux temperature, there was a significant decrease in diastereoselectivity when $(CH_2Cl)_2$ was used as the solvent. In contrast, high diastereoselectivity was obtained in refluxing CH_2Cl_2 (compare Table 1, entries 6 and 8).

From the above studies, it was concluded that the conditions that are conducive for optimal regio- and diastereoselections in the reaction of compounds of type **10** are the use of CH_2Cl_2 as solvent and a reaction temperature of 40 °C.

(b) $Rh_2(OAc)_4$-Catalyzed Cyclization of Compounds 10a,b,d−i and *ent*-10c,d,h,i. The Rh(II)-catalyzed reaction of compounds with different N-substituents (Scheme 4) was studied to determine the influence of steric and electronic effects on the diastereoselectivity of the reaction. The diazo compounds were cyclized under the optimized reaction conditions, and the results are summarized in Table 2. In general, the 2-pyrrolidinones, **16** or **18**, were produced as major and, in a few cases, as exclusive products. An exception, however, was noted in the case of **10e** (compare Table 2, entry 8 to entries 6, 7, 9, and 11). Its cyclization gave an equal amount of 2-pyrrolidinone **16e** and 2-azetidinone **17e** products. The absence of regioselection in this case is attributed to the *o*-methoxy methoxy group,[29] which sterically hinders approach of the metallocarbenoid to the benzylic C−H bond. Consequently, this makes the enthalpically less favorable 2-azetidinone pathway more competitive. As expected, we did not detect any cycloaddition products from the reaction of the *N*-arylethyl systems.

The 2-pyrrolidinones **16** and **18** were decarboxylated and then subjected to HPLC analysis as before. From the results in Table 2, it is apparent that the diazoanil-

(25) (a) Oxindole derivatives that resulted from aromatic substitution were also formed in the $Rh_2(acam)_4$-catalyzed reactions of *ent*-**10a** and **10c**. This outcome is in accord with literature results.[26a] The oxindole products were decarboxylated, and the diagnostic features in their ^1H NMR spectra are the aromatic (3H) proton signals in the region δ 6.70−6.90 and the singlet due to the C-3 methylene hydrogens at δ 3.48−3.50.[26b] (b) When dry benzene was used, TLC analysis of the reaction mixture showed that the reaction was not as "clean".

(26) (a) Brown, D. S.; Elliot, M. C.; Moody, C. J.; Mowlem, T. J.; Marino, J. P., Jr.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 2447. (b) Wee, A. G. H.; Liu, B.-S. *Tetrahedron* **1994**, *50*, 609.

(27) (a) Krapcho, A. P. *Synthesis* **1982**, 805 and 893. For other decarboxylation methods, see: Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814 and references therein.

(28) For a discussion on the dramatic influence of solvent polarity on the chemoselectivity of the Rh(II)−carbenoid mediated reaction, see: Davies, H. M. L.; Matasi, J. J.; Ahmed, G. *J. Org. Chem.* **1996**, *61*, 2305 and references therein.

(29) Charton, M. *Prog. Phys. Org. Chem.* **1971**, *8*, 235.

Table 2. $Rh_2(OAc)_4$-Catalyzed Reaction of 10 and *ent*-10: Regioselectivity and Diastereoselectivity

		2-pyrrolidinone/2-azetidinone		**20** or **21**			
entry	compound	yield[b] (%)	**16**:**17**[c] or **18**:**19**[c]	yield[d] (%)	ee[e] (%)	$[\alpha]_D$	config
1	**10a**	75	3.4:1	80	45	+1.69	(*R*)-**20**
2	*ent*-**10a**[a]	64	2.6:1	92	47	−2.10	(*S*)-**21**
3	**10b**	84	5:1	84	98	+4.45	(*S*)-**20**
4	**10c**[a]	96	23:1	98	79	−10.5	(*S*)-**20**
5	*ent*-**10c**	90	44:1	87	80	+9.98	(*R*)-**21**
6	**10d**	85	100:0	84	50	−15.2	(*S*)-**20**
7	*ent*-**10d**	78	100:0	96	52	+15.9	(*R*)-**21**
8	**10e**	74	1:1	84	37	+4.13	(*S*)-**20**
9	**10f**	90	100:0	76	67	−6.20	(*S*)-**20**
10	**10g**	82	nd[f]	70	77	−5.88	(*S*)-**20**
11	*ent*-**10h**	76	100:0	80	75	+4.83	(*R*)-**21**
12	**10i**	81	4:1	75	30	−0.51	(*S*)-**21**
13	*ent*-**10i**	75	4:1	78	32	+0.58	(*R*)-**20**

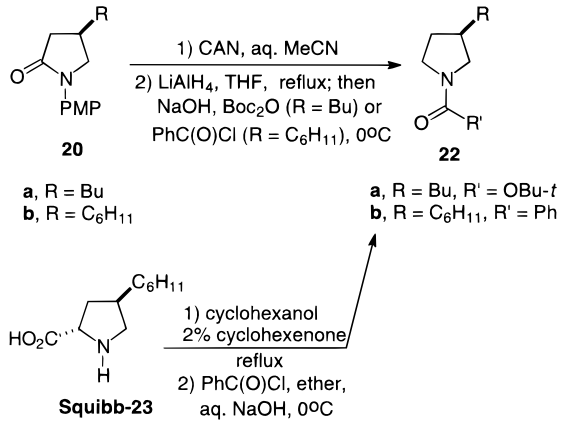
[a] Results from Table 1, entries 4 and 8, respectively, were included for comparison. [b] Isolated, combined yield of 2-pyrrolidinones and 2-azetidinones: **16**/**17** or **18**/**19**. [c] Ratio was based on the isolated yields of **16**:**17** or **18**:**19**. [d] Isolated yields of **20** or **21**. [e] Determined using a Chiralcel OB column. [f] Not determined. Obtained as an inseparable mixture of **16g** and **17g**. The presence of **17g** was evidenced by the 2-azetidinone ν_{max}(C=O) at 1761 cm^{-1}. Ratio could not be determined by ^1H NMR because of extensive signal overlap.

ides **10a** and *ent*-**10a**, with the linear *N*-hexyl group, reacted with modest diastereoselectivity (Table 2, entries 1 and 2), whereas **10b**, possessing a sterically more demanding *N*-(cyclohexyl)ethyl group, reacted with very high diastereoselectivity (Table 2, entry 3). More interestingly, the diastereoselectivity in the reaction of the *N*-(arylethyl)diazoanilides was found to be dependent on the nature of the substituent(s) in the phenyl moiety. In the unsubstituted **10c** and *ent*-**10c**, the products **20c** and **21c** were obtained in 80% ee (Table 2, entries 4 and 5). The presence of electron-donating methoxy substituents in the phenyl ring attenuated the diastereoselectivity of the reaction (Table 2, entries 6−9). Specifically, lower ee's of **20** and **21** were obtained when a methoxy group was located ortho and/or para to the benzylic position (Table 2, entries 6−8). Moving the methoxy group to the meta position resulted in a significant increase in the diastereoselectivity (Table 2, entry 9). In contrast, the presence of an electron-withdrawing NO_2 group that is located either meta or para to the benzylic position was found to have little influence on the diastereoselectivity of the reaction. Thus, **10g** and *ent*-**10h** afforded 2-pyrrolidinones **20g** and **21h**, which had ee's in the range of 75−77%. This outcome is comparable to the result obtained for **10c** and *ent*-**10c** (Table 2, entries 10, 11 vs 4, 5).

In the case of **10i** and *ent*-**10i**, the cyclization proceeded with low diastereoselectivity to afford the 2-pyrrolidinones **20i** and **21i**, respectively (Table 2, entries 12 and 13). The low diastereoselectivity may be due to the small steric size of the *N*-propyl group. Unexpectedly and unlike the results obtained from the reaction of **10a**,**c** and *ent*-**10a**, it was found that the sense of induction at the new C-4 stereocenter in **20i** and **21i** was *reversed*.

(c) Assignment of Absolute Configuration at C-4. The absolute configuration of C-4 in compounds **20a**−**c** and **21c** was assigned by comparison of the specific optical rotation of their derivatives with those reported for known compounds. Thus, **20a** was converted, as summarized in Scheme 5, to **22a** ($[\alpha]^{23}_D$ +11.1; *c* 1.6, CH_2Cl_2). Compound **22a** was dextrorotatory, whereas the known[15b] (*S*)-enantiomer ($[\alpha]^{23}_D$ −30.5) was levorotatory. Further, the specific optical rotation of compound **22b** that was prepared from **20b** (Scheme 5), and Squibb-**23**[30a,b] showed excellent agreement in both the sign and magnitude. As well, compounds **20c** and **21c** were N-deprotected to give the known (*S*)-4-phenyl-2-pyrrolidinone [$[\alpha]^{23}_D$ +27 (*c* 0.74, MeOH) (lit.[31] $[\alpha]_D$ +37.5)] and (*R*)-4-phenyl-2-pyrrolidinone [$[\alpha]^{23}_D$ −28.3 (*c* 0.5, MeOH) (lit.[31] $[\alpha]_D$ −37.8)], respectively. With the exception of **20i** and **21i**, the absolute configuration of C-4 in **21a** was inferred from that of **20a** and in **20d**−**g** and **21d**,**h** from that of **20c** and **21c**, respectively. From these results, we conclude that the chiral ester diazoanilides of type **10** undergo cyclization to give 2-pyrrolidinones of type **20**, whereas diazoanilides *ent*-**10** cyclize to give **21**.

Scheme 5



In the case of the cyclization of **10i** and *ent*-**10i**, HPLC analysis (see Experimental Section) showed that for the decarboxylated 2-pyrrolidinone product derived from **10i**, the ratio of **20i** to **21i** is 1:1.8, whereas for the decarboxylated 2-pyrrolidinone product derived from *ent*-**10i** the ratio of **20i** to **21i** is 2:1. The results indicate that the sense of induction at C-4 for the cylization of **10i** and *ent*-**10i** is *S* and *R*, respectively.

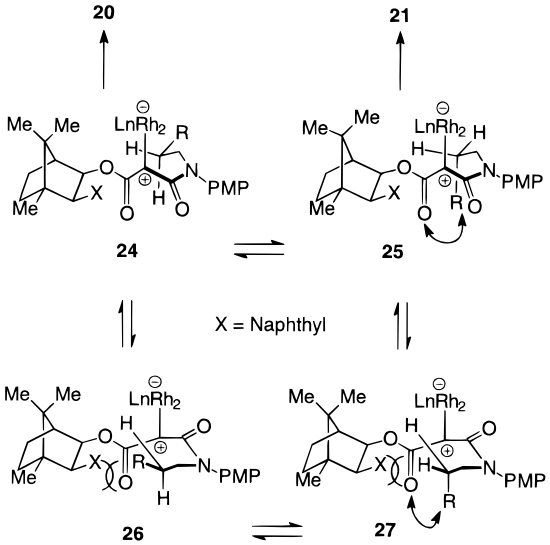
III. Reaction Pathway. The four chairlike,[1g] rapidly interconvertible[32] transition-state conformers **24**−**27** (Chart 1) can be considered to be involved in the cyclization of **10**. (For the sake of clarity, we have shown only the transition states for the reaction of the diazoanilide **10**. The enantiomeric transition states would apply for

(30) (a) Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140. (b) Squibb-**23** was decarboxylated according to the procedure described by: Hashimoto, M.; Eda, Y.; Osanai, Y.; Iwai, T.; Aoki, S. *Chem Lett.* **1986**, 893. The pyrrolidine product was then benzoylated to give **22b**.

(31) Zelle, R. E. *Synthesis* **1991**, 1023.

(32) Seeman, J. I. *Chem. Rev.* **1986**, *86*, 42.

Chart 1



ent-**10a**,**c**,**d**,**h**.) The transition states **26** and **27**, however, are destabilized by the presence of severe nonbonded interactions: in **26**, there is an R/naphthyl interaction, and in **27**, there are the syn R/CO_2R* as well as H/naphthyl interactions. Therefore, the cyclization of **10** should proceed preferentially via the lowest and second lowest energy transition states **24** and **25**. However, it should be noted that the involvement of **26** and **27** cannot be ruled out.

We envisaged the C−H insertion in **24** and **25** is initiated by the interaction of the vacant p-orbital of the rhodium(II) carbenoid carbon with the target C−H bond.[33] The degree of interaction depends on the "electron-richness" of the C−H bond. That is, for a less electron-rich C−H bond the interaction occurs farther along the reaction coordinate, which would result in a more compact transition state (TS). On the other hand, for a more electron-rich C−H bond the interaction occurs earlier along the reaction coordinate, which would result in a less compact (open) TS.

For compounds **10a**,**b**,**c**,**g**, compact transition states are involved, which means that any destabilizing steric interactions present in the transition states **24** and **25** will be fully manifested. The TS **25a**,**b**,**c**,**g** would be destabilized because of the presence of a steric interaction between the CO_2R* group and a pseudoaxial substituent R. This would lead to the preferential formation of compounds **20a**,**b**,**c**,**g** via **24**. The highest diastereoselectivity was realized for the *N*-(cyclohexyl)ethyl system **10b**, and we attribute this to a strong preference of the bulky cyclohexyl moiety for the pseudoequatorial position that is possible only in TS **24b** (R = C_6H_{11}). On the other hand, the reaction of compounds **10d**−**f** is envisaged to involve less compact transition states **24d**−**f** and **25d**−**f** due to the activating influence of the methoxy groups[33b] on the benzylic C−H bond. Consequently, any destabilizing steric interactions that are present will be small and the energy difference between **24** and **25** will decrease. Carbon−hydrogen insertion via both transition states will become competitive, resulting in an attenuation of diastereoselectivity. The poorer diastereoselectivity observed for the reaction of **10e** may further be attributed to the "ortho" effect[29] of the methoxy group.

The above model, however, cannot reconcile the results obtained for the cyclization of **10i** (and *ent*-**10i**) in which the sense of induction is reversed. We do not have an explanation for this unusual phenomenon at this time.

IV. Synthesis of (2*S*,4*S*)-4-Cyclohexyl-2-pyrrolidinecarboxylic Acid (*trans*-4-cyclohexyl-L-proline) (23). The pyrrolidine moiety is widespread in nature and is found in many alkaloids[34a−e] as well as in natural[34f] and unnatural amino acids.[34g−k] Because of the biological activity usually associated with these molecules,[35] there is strong interest in developing new methods for the synthesis of this important ring system. The above-described method permits the ready preparation of chiral, nonracemic 4-substituted 2-pyrrolidinones from simple starting materials. Since 2-pyrrolidinones are versatile intermediates for the synthesis of pyrrolidine-type compounds, we explored the possibility of using compound **20b** for the synthesis of *trans*-4-cyclohexyl-L-pyrrolidine **23**,[30a] an unnatural amino acid that is used in the synthesis of the antihypertensive agent Fosinopril Sodium.[30a,34g]

The adopted approach was to prepare the cyclic hemiaminal **29a** from compound **20b**. Cyanation at C-2 in **29a** using acyliminium chemistry[20] followed by hydrolysis of the cyano group should complete the installation of the carboxylic acid function. However, the diastereoselectivity of the cyanation reaction is also of interest to us because literature precedence[36] indicates that the diastereoselectivity of the reaction of Δ^1-pyrrolidinium ions with nucleophiles depends not only on the structure of each of the reactants but, more importantly, on the type of N-substituent. For example, with an *N*-acyl substituent, there is a preference for the incoming nucleophile to add cis to a preexisting substituent,[36a,b] whereas with a *N*-benzyl group, there is a preference for nucleophilic addition to occur trans to a preexisting substituent.[36c]

To address the synthesis of **23** (Scheme 6) and the diastereoselectivity question, compound **20b** was N-deprotected to give (*S*)-4-cyclohexyl-2-pyrrolidinone, which

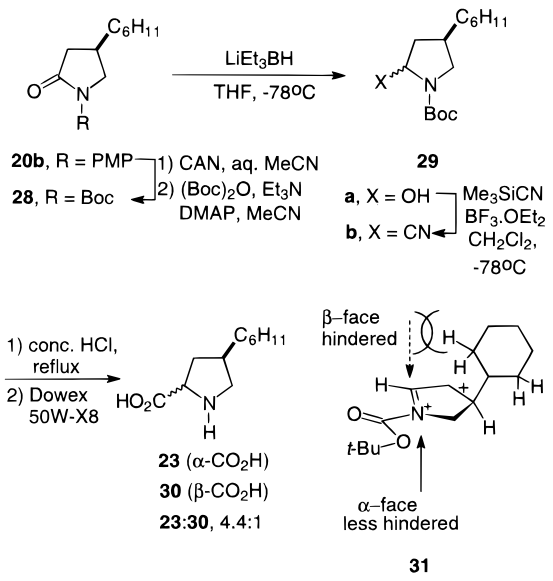
(33) (a) Doyle, M. P.; Westrum, L. J.; Wendelmoed, N. E. W.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958. (b) Taber, D. F.; Song, Y. *J. Org. Chem.* **1996**, *61*, 6706.

(34) (a) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31, p 194. (b) Massiot, G.; Delaude, C. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986, Vol. 27, p 270. (c) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, p 252. (d) Yang, M.-H.; Chen, Y.-Y.; Huang, L. *Phytochemistry* **1988**, *27*, 445. (e) Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **1991**, *32*, 2625. (f) Shinozaki, H. In *Kainic Acids As A Tool In Neurobiology*; McGeer, E. G., Olney, J. W., McGeer, P. L., Eds.; Raven Press: New York, 1978; pp 17−35. (g) Sasaki, N. A.; Dockner, M.; Chiaroni, A.; Riche, C.; Potier, P. *J. Org. Chem.* **1997**, *62*, 765 and references cited. (h) Anderson, N. G.; Lust, D. A.; Colapret, K. A.; Simpson, J. H.; Malley, M. F.; Gougoutas, J. Z. *J. Org. Chem.* **1996**, *61*, 7955. (i) Thaisrivongs, S.; Pals, D. T.; Furner, S. R.; Knoll, L. T. *J. Med. Chem.* **1988**, *31*, 1369. (j) Karanewski, D. S.; Badia, M. C.; Cushman, D. W.; Deforrest, J. M.; Dejeneka, T.; Lee, V. G.; Loots, M. J.; Petrillo, E. W. *J. Med. Chem.* **1990**, *33*, 1459. (k) Kennewell, P. D.; Mathani, S. S.; Taylor, J. B.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2542.

(35) For example: Neuroexcitatory activity: (a) Reference 34f. Glycosidase inhibitors: (b) Fleet, G. W. J.; Witty, D. R. *Tetrahedron: Asymmetry* **1990**, *1*, 119. (c) Horenstein, B. A.; Zabinski, R. F.; Schramm, V. L. *Tetrahedron Lett.* **1993**, *34*, 7213. Fungiside: (d) Eckert, J. W.; Rahm, M. L.; Koldezen, M. J. *J. Agric. Food Chem.* **1972**, *20*, 104.

(36) (a) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590. (b) Renaud, P.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1704. (c) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229.

Scheme 6



was N-acylated with Boc_2O under Grieco conditions[37] to afford **28**. Selective reduction of the lactam carbonyl with $LiEt_3BH$[38] at −78 °C gave the alcohol **29a** as an inseparable mixture of diastereomers. This alcohol was directly treated with Me_3SiCN in the presence of $BF_3{\cdot}OEt_2$ to give the cyano derivative **29b** again as an inseparable mixture of diastereomers. The use of $TiCl_4$ as the Lewis acid in this reaction only resulted in the decomposition of alcohol **29a**. Unfortunately, we were not able to ascertain the diastereoselectivity of the reduction and cyanation reactions by ^1H NMR analysis of products **29a**,**b** because of extensive signal overlap and complication from the rotational isomerism arising from restricted rotation about the *N*-Boc moiety.

Treatment of **29b** with concentrated HCl at reflux caused hydrolysis of the cyano unit and the *N*-Boc protecting group to give a mixture of the HCl salts, **23**·HCl and **30**·HCl, in quantitative yield. At this juncture, we also prepared the HCl salt of Squibb-**23** and compared its ^1H NMR spectrum in D_2O with that of **23**·HCl/**30**·HCl. This revealed that the desired *trans*-4-cyclohexyl-L-proline was formed as the *major* diastereomer. The ratio of trans/cis diastereomers was 4.4:1 on the basis of the integration of the H-2 double doublet centered at δ 4.38 (trans) and δ 4.29 (cis). The mixture **23**·HCl/**30**·HCl was desalted (Dowex 50W-X8) to afford the amino acids **23**/**30** in quantitative yield. An analytical sample of pure synthetic-**23** was obtained by recrystallization from water and it showed $[\alpha]_D$ and spectroscopic properties identical to those obtained for Squibb-**23**.

The observed diastereoselectivity for the cyanation step is interesting in light of the results that have been reported[36] for similar reactions. It has been shown[36c] that acid hydrolysis of the cyano group does not lead to epimerization of the α-carbon (C-2 in this case). On the basis of this fact, we conclude that the cyanation step (**29a** → **29b**) had also occurred with a 4.4:1 trans/cis diastereoselectivity. Geometry optimization of the pyrrolidinium ion intermediate **31**,[15a] which is involved in the conversion **29a** → **29b**, at the AM1 level[39] showed that one of the cyclohexyl α-methylene units is directed toward the center of the pyrrolidinium moiety. The *β*-face (i.e., cis to cyclohexyl group) of the iminium moiety is, therefore, more hindered because of steric shielding by the hydrogens of the α-methylene unit. Consequently, preferential attack by the cyanide anion from the less hindered α-face is observed to afford *trans*-**29b** as the major product.

Conclusions

With one exception (**10e**), the $Rh_2(OAc)_4$-catalyzed C−H insertion reaction of diazoanilides **10** and *ent*-**10** proceeds efficiently to give predominantly 4-substituted 3-(alkoxycarbonyl)-2-pyrrolidinones. The reaction was highly regioselective and showed excellent chemoselectivity. The diastereoselectivity of the reaction is dependent on the type and nature of the N-substituent. With *N*-alkyl groups, steric effects govern the diastereoselectivity of the reaction. However, with *N*-arylethyl substituents, electronic effects transmitted by the aryl substituents influenced the diastereoselectivity of the C−H insertion reaction. Specifically, electron-donating substituents were found to attenuate the diastereoselectivity of the reaction. The 4-substituted 3-(alkoxycarbonyl)-2-pyrrolidinones were readily decarboxylated to give good yields of chiral, nonracemic 4-substituted 2-pyrrolidinones, and the chiral alcohols, (−)-**7** and (+)-**8**, were recovered in high yields. Although the sense of asymmetric induction in the newly created C-4 stereocenter in compounds **20** and **21a**−**h** is predictable on the basis of the type of chiral ester auxiliary [(−)-**7** or (+)-**8**] that was used, we found that this trend was *reversed* in the case of the cyclization of compounds **10i** and *ent*-**10i**. This outcome may represent a limiting case for this method for the synthesis of chiral nonracemic 4-substituted 2-pyrrolidinones. Studies on the use of homochiral Rh(II) carboxylates for catalyzing the C−H insertion of compounds **10** is in progress, and the results will be reported at a later date. The synthetic utility of the method is demonstrated by the stereoselective synthesis of the medicinally important, unnatural amino acid (2*S*,4*S*)-4-cyclohexyl-2-pyrrolidinecarboxylic acid **23**. The readily accessible **20b** was converted in five steps (51% overall yield) to give synthetic-**23** and its (2*R*,4*S*)-epimer in a ratio of 4.4:1.

Experimental Section

General Methods. Only diagnostic absorptions in the infrared spectrum are reported. ^1H (200 MHz) and ^{13}C (50.3 MHz) NMR spectra were recorded in $CDCl_3$ unless stated otherwise. Tetramethylsilane ($\delta_H = 0.00$) and the $CDCl_3$ resonance ($\delta_C = 77.0$) were used as internal references. Where applicable, the positions of the signals of minor diastereomers are enclosed in square brackets. Elemental analyses and high-resolution electron impact (70 eV) and chemical ionization mass spectral analyses were performed at the Chemistry Department, University of Saskatchewan, Canada. Reaction progress was monitored by thin-layer chromatography on Merck silica gel 60_{F254} precoated (0.25 mm) on aluminum-backed sheets. Air- and moisture-sensitive reactions were

(37) (a) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2224. (b) Hansen, M. M.; Harkness, A. R.; Coffey, D. S.; Bordwell, F. G.; Zhao, Y. *Tetrahedron Lett.* **1995**, *36*, 8949.

(38) Pedregal, C.; Ezquera, J.; Escribano, A.; Carreno, M. C.; Ruano, J. L. C. *Tetrahedron Lett.* **1994**, *35*, 2053.

(39) Calculations performed using Hyperchem v. 4.0. $\Delta H_f = +53.8582$ kcal/mol.

conducted under a static pressure of argon. All organic extracts were dried over anhydrous Na_2SO_4. Chromatogarphic purification implies flash chromatography,[40] which was performed on Merck silica gel 60 (230−400 mesh). HPLC analysis of compounds **20** and **21** was performed using a Chiralcel OB column (1.5 mm × 250 mm) with in-line UV detection (λ = 254 nm). The eluent was hexane/2-propanol (70:30 v/v) unless otherwise stated, and a flow rate of 1.5 mL/min was used. Rhodium(II) acetate [$Rh_2(OAc)_4$] was purchased from Strem Chemicals Inc. (Newburyport, MA) and was dried under high vacuum (0.05 Torr) at 100 °C before use. Dichloromethane, 1,2-dichloroethane, chloroform, DME, and acetonitrile were dried by distillation from calcium hydride. THF and diethyl ether were dried by distillation from sodium using sodium benzophenone ketyl as indicator.

General Procedure for the Decarboxylation of 2-Pyrrolidinones 16 or 18. A diastereomeric mixture of **16** or **18** (1 mmol), NaCl (2 mmol), and aqueous DMSO (6 mL, 3:1 v/v DMSO−H_2O) was refluxed under Ar for 4−12 h. The reaction was diluted with water (6 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (3 × 5 mL), dried, filtered, and evaporated. The crude product **20** or **21** was purified by chromatography. The chiral auxiliary (−)-**7** or (+)-**8** was recovered unchanged in 85−95% yield.

(*R*)-(+)-4-Butyl-1-(4-methoxyphenyl)-2-pyrrolidinone (20a). Yield: 88%. Mp (Et_2O/petroleum ether): 69−70.5 °C. $[\alpha]^{23}_D$ +2.07 (*c* 1.2, $CHCl_3$). IR ν_{max}: 3079, 1691, 1645, 1614, 1514 cm^{-1}. ^1H NMR, δ: 0.93 (t, 3H, *J* = 7.6 Hz), 1.23−1.60 (m, 6H), 2.26 (dd, 1H, *J* = 15.7, 7.1 Hz), 2.41 (quintet, 1H, *J* = 7.1 Hz), 2.70 (dd, 1H, *J* = 15.7, 7.1 Hz), 3.45 (dd, 1H, *J* = 9.3, 6.8 Hz), 3.78 (s, 3H), 3.87 (dd, 1H, *J* = 9.3, 6.8 Hz), 6.88 (d, 2H, *J* = 8.8 Hz), 7.48 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR, δ: 14.0, 22.5, 29.5, 31.5, 34.1, 39.0, 54.8, 55.3, 114.0, 121.6, 132.6, 156.4, 173.3. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.83; H, 8.56; N, 5.67. Found: C, 72.74; H, 8.93; N, 5.48.

(*S*)-(+)-4-Cyclohexyl-1-(4-methoxyphenyl)-2-pyrrolidinone (20b). Yield: 87%. HPLC: hexane/2-propanol 90:10. $[\alpha]^{23}_D$: + 4.45 (*c* 0.85, $CHCl_3$). IR ν_{max}: 3054, 1689, 1513 cm^{-1}. ^1H NMR, δ: 0.88−1.10 (m, 2H), 1.16−1.44 (m, 5H), 1.62−1.87 (m, 4H), 2.20 (dd, 1H, *J* = 15.1, 8.0 Hz), 2.24−2.41 (m, 1H), 2.63 (dd, 1H, *J* = 15.1, 8.0 Hz), 3.54 (t, 1H, *J* = 8.3 Hz), 3.77−3.87 (m, 1H), 3.80 (s, 3H), 6.99 (d, 2H, *J* = 8.8 Hz), 7.49 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR, δ: 25.9, 26.0, 26.3, 30.6, 31.0, 37.3, 37.7, 42.2, 53.4, 55.4, 114.0, 121.7, 132.6, 156.5, 173.6. EIMS (*m*/*z*, rel intensity): 273 (M, 82), 136 (M − c-$C_6H_{11}CH{=}CH_2$ − CO, 100). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.68; H, 8.49; N, 5.13. Found: C, 74.42; H, 8.84; N, 5.04.

(*S*)-(−)-1-(4-Methoxyphenyl)-4-phenyl-2-pyrrolidinone (20c). Yield: 84%. Mp (EtOAc/petroleum ether): 92.5−95 °C. $[\alpha]^{23}_D$ −10.5 (*c* 2.2, $CHCl_3$). IR ν_{max}: 3053, 1692, 1604 cm^{-1}. ^1H NMR, δ: 2.68 (dd, 1H, *J* = 16.7, 8.7 Hz), 2.92 (dd, 1H, *J* = 16.7, 8.7 Hz), 3.50−3.79 (m, 1H), 3.70 (s, 3H), 3.77 (t, 1H, *J* = 8.2 Hz), 4.06 (t, 1H, *J* = 8.2 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 7.13−7.35 (m, 5H), 7.43 (d, 2H, *J* = 8.8 Hz). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.37; H, 6.41; N, 5.24. Found: C, 76.17; H, 6.40; N, 5.62.

(*S*)-(−)-1-(4-Methoxyphenyl)-4-[3,4-(methylenedioxy)phenyl]-2-pyrrolidinone (20d). Yield: 84%. HPLC: ethanol. Mp (EtOAc/petroleum ether): 119.5−121.5 °C. $[\alpha]^{23}_D$ −15.5 (*c* 1.0, $CHCl_3$). IR ν_{max}: 3053, 1691, 1610, 1512 cm^{-1}. ^1H NMR, δ: 2.71 (dd, 1H, *J* = 16.6, 8.8 Hz), 2.96 (dd, 1H, *J* = 16.6, 8.8 Hz), 3.63 (quintet, 1H, *J* = 8.8 Hz), 3.79 (t, 1H, *J* = 8.8 Hz), 3.80 (s, 3H), 4.10 (t, 1H, *J* = 8.8 Hz), 5.96 (s, 2H), 6.69−6.83 (m, 3H), 6.91 (d, 2H, *J* = 8.8 Hz), 7.50 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR, δ: 37.0, 40.3, 55.5, 56.2, 101.1, 107.1, 108.5, 114.1, 120.0, 121.8, 132.2, 135.0, 146.7, 148.1, 156.7, 172.5. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.43; H, 5.51; N, 4.51. Found: C, 69.59; H, 5.48; N, 4.43.

(*S*)-(+)-1-(4-Methoxyphenyl)-4-(2-methoxyphenyl)-2-pyrrolidinone (20e). Yield: 84%. HPLC: hexane/2-propanol, gradient elution, 90:10, 80:20, 60:40. $[\alpha]^{23}_D$: +4.13 (*c* 4.2, $CHCl_3$). IR ν_{max}: 3048, 1693, 1601, 1586, 1513 cm^{-1}. ^1H NMR, δ: 2.82 (dd, 1H, *J* = 17.2, 8.6 Hz), 2.92 (dd, 1H, *J* = 17.2, 8.6 Hz), 3.72−3.98 (m, 2H), 3.75 (s, 3H), 3.80 (s, 3H), 4.12 (t, 1H, *J* = 7.5 Hz), 6.89−6.99 (m, 2H), 6.90 (d, 2H, *J* = 8.8 Hz), 7.18−7.31 (m, 2H), 7.52 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR, δ: 32.0, 38.1, 54.5, 55.1, 55.2, 110.5, 113.8, 120.5, 121.6, 127.1, 128.1, 129.3, 132.4, 156.3, 157.2, 173.0. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.69; H, 6.44; N, 4.71. Found: C, 72.49; H, 6.51; N, 4.67.

(*S*)-(−)-1-(4-Methoxyphenyl)-4-(3-methoxyphenyl)-2-pyrrolidinone (20f). Yield: 76%. HPLC: ethanol. $[\alpha]^{23}_D$: −6.29 (*c* 0.8, $CHCl_3$). IR ν_{max}: 3054, 1693, 1602, 1586, 1513 cm^{-1}. ^1H NMR, δ: 2.78 (dd, 1H, *J* = 16.8, 8.1 Hz), 3.00 (dd, 1H, *J* = 16.8, 8.1 Hz), 3.67 (quintet, 1H, *J* = 8.1 Hz), 3.82 (s, 3H), 3.82 (s, 3H), 3.86 (dd, 1H, *J* = 8.1, 7.1 Hz), 4.15 (t, 1H, *J* = 8.1 Hz), 6.78−6.96 (m, 3H), 6.92 (d, 2H, *J* = 8.8 Hz), 7.24 (m, 1H), 7.51 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR, δ: 37.2, 40.0, 55.2, 55.5, 56.0, 112.2, 112.9, 114.1, 119.0, 122.0, 130.0, 132.3, 143.4, 156.7, 160.0, 172.6. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.69; H, 6.44; N, 4.71. Found: C, 72.41; H, 6.45; N, 4.62.

(*S*)-(−)-1-(4-Methoxyphenyl)-4-(3-nitrophenyl)-2-pyrrolidinone (20g). Yield: 70%. HPLC: ethanol. $[\alpha]^{23}_D$ −5.88 (*c* 0.9, $CHCl_3$). IR ν_{max}: 3058, 1693, 1612, 1583, 1530, 1513 cm^{-1}. ^1H NMR δ: 2.70 (dd, 1H, *J* = 16.2, 8.1 Hz), 3.01 (dd, 1H, *J* = 16.2, 8.1 Hz), 3.70−3.81 (m, 1H), 3.74 (s, 3H), 3.81 (t, 1H, *J* = 7.4 Hz), 4.17 (t, 1H, *J* = 7.4 Hz), 6.85 (d, 2H, *J* = 8.8 Hz), 7.43 (d, 2H, *J* = 8.8 Hz), 7.46 (d, 1H, *J* = 7.8 Hz), 7.56 (t, 1H, *J* = 7.8 Hz), 8.09 (d, 1H, *J* = 7.8 Hz), 8.11 (s, 1H). ^{13}C NMR δ: 37.0, 40.0, 55.7, 114.3, 122.1, 122.1, 122.5, 130.2, 132.0, 133.0, 144.0, 157.1, 162.8, 171.8. Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.36; H, 5.17; N, 8.97. Found: C, 65.56; H, 5.16; N, 8.66.

(*R*)-(+)-4-Methyl-1-(4-methoxyphenyl)-2-pyrrolidinone (20i). Yield: 78%. $[\alpha]^{23}_D$ +0.58 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.21; H, 7.37; N, 6.83. Found: C, 70.34; H, 7.56; N, 6.68.

(*S*)-(−)-4-Butyl-1-(4-methoxyphenyl)-2-pyrrolidinone (21a). Yield: 87%. $[\alpha]^{23}_D$: −1.79 (*c* 1.4, $CHCl_3$). EIMS (*m*/*z*, rel intensity): 247 (M, 58), 136 (M − C_6H_{12} − CO, 100).

(*R*)-(+)-1-(4-Methoxyphenyl)-4-phenyl-2-pyrrolidinone (21c). Yield: 87%. Mp (EtOAc/petroleum ether): 92−94 °C. $[\alpha]^{23}_D$: +9.98 (*c* 3.0, $CHCl_3$). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.37; H, 6.41; N, 5.24. Found: C, 76.30; H, 6.31; N, 5.38.

(*R*)-(+)-1-(4-Methoxyphenyl)-4-[3,4-(methylenedioxy)phenyl]-2-pyrrolidinone (21d). Yield: 96%. HPLC: ethanol. $[\alpha]^{23}_D$ +15.9 (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.43; H, 5.51; N, 4.51. Found: C, 69.43; H, 5.51; N, 4.51.

(*R*)-(+)-1-(4-Methoxyphenyl)-4-(4-nitrophenyl)-2-pyrrolidinone (21h). Yield: 81%. HPLC: ethanol. $[\alpha]^{23}_D$: +4.83 (*c* 1.0, $CHCl_3$). IR ν_{max}: 3054, 1694, 1606, 1514 cm^{-1}. ^1H NMR δ: 2.76 (dd, 1H, *J* = 16.0, 6.8 Hz), 3.09 (dd, 1H, *J* = 16.0, 6.8 Hz), 3.73−3.95 (m, 1H), 3.80 (s, 3H), 3.89 (t, 1H, *J* = 6.9 Hz), 4.24 (t, 1H, *J* = 6.9 Hz), 6.92 (d, 2H, *J* = 8.2 Hz), 7.48 (d, 2H, *J* = 8.2 Hz), 7.52 (d, 2H, *J* = 8.2 Hz), 8.23 (d, 2H, *J* = 8.2 Hz). ^{13}C NMR δ: 37.0, 39.7, 55.4, 114.2, 122.0, 124.3, 127.7, 131.8, 147.2, 149.4, 156.9, 171.6. Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.36; H, 5.17; N, 8.97. Found: C, 65.21; H, 5.23; N, 8.83.

(*S*)-(−)-4-Methyl-1-(4-methoxyphenyl)-2-pyrrolidinone (21i). Yield: 81%. $[\alpha]^{23}_D$: −0.51 (*c* 1.0, $CHCl_3$). IR ν_{max}: 3050, 1690, 1612, 1586, 1513 cm^{-1}. ^1H NMR, δ: 1.21 (d, 3H, *J* = 5.9 Hz), 2.23 (dd, 1H, *J* = 15.9, 7.3 Hz), 2.45−2.65 (m, 1H), 2.74 (dd, 1H, *J* = 15.9, 8.3 Hz), 3.40 (dd, 1H, *J* = 9.4, 5.8 Hz), 3.79 (s, 3H), 3.90 (dd, 1H, *J* = 9.4, 7.4 Hz), 6.90 (d, 2H, *J* = 8.3 Hz), 7.49 (d, 2H, *J* = 8.3 Hz). ^{13}C NMR, δ: 19.5, 26.3, 40.7, 55.4, 56.2, 113.9, 121.7, 132.6, 156.4, 173.4. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.21; H, 7.37; N, 6.83. Found: C, 70.35; H, 7.37; N, 6.59.

4-Butyl-1-(*tert*-butyloxycarbonyl)-2-pyrrolidine (22a). CAN (444 mg, 0.81 mmol) was dissolved in water (2.5 mL) and added to a solution of **20a** (67 mg, 0.27 mmol) in MeCN (5 mL) at 0 °C. After 30 min, excess solid Na_2SO_3 was added to destroy unreacted CAN. Then the solvent was evaporated, the

(40) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

organic residue taken into EtOAc (10 mL), and the organic layer washed with brine (10 mL), dried, filtered, and evaporated. Chromatographic purification gave 4-butyl-2-pyrrolidinone (79%). IR ν_{max}: 3244, 1696 cm^{-1}. ^{1}H NMR δ: 0.91 (t, 3H, J = 7.6 Hz), 1.18−1.54 (m, 6H), 2.00 (dd, 1H, J = 19.2, 10.3 Hz), 2.26−2.53 (m, 2H), 3.02 (dd, 1H, J = 8.8, 6.4 Hz), 3.49 (t, 1H, J = 8.8 Hz).

A solution of 4-butyl-2-pyrrolidinone (30 mg, 0.21 mmol) in dry THF (5 mL) was cooled to 0 °C, under Ar, and then treated with $LiAlH_4$ (16 mg, 0.41 mmol). After being stirred briefly at 0 °C, the cooling bath was removed and the mixture was warmed to room temperature and then refluxed for 15 h. The reaction mixture was treated with 1 M aqueous NaOH (1.5 mL) at 0 °C, and then ether (2 mL) was added followed by Boc_2O (137 mg, 0.63 mmol). The mixture was stirred for 4 h at room temperature and then filtered through a short pad of anhydrous Na_2SO_4. The filtrate was evaporated, and the residue was chromatographed to give **22a** (66%). $[\alpha]^{23}_D$: +11.1 (*c* 1.6, CH_2Cl_2) [for the (*S*)-enantiomer, lit.[15b] $[\alpha]^{23}_D$ −30.5 (*c* 0.83, CH_2Cl_2)]. IR ν_{max}: 1698, 1542 cm^{-1}. ^{1}H NMR δ: 0.91 (br t, 3H, J = 7.6 Hz), 1.21−1.45 (m, 7H), 1.50 (s, 9H) 1.89−2.20 (m, 2H), 2.85 (br q, 1H, J = 8.3 Hz), 3.12−3.65 (m, 3H).

1-Benzoyl-4-cyclohexylpyrrolidine (22b) from 2-Pyrrolidinone (20b). The *N*-PMP in **20b** (39.5 mg) was oxidatively removed (239 mg of CAN in 1 mL of water and 3 mL of MeCN] according to the procedure as described for the conversion of **20a** to **22a**. The crude 4-cyclohexyl-2-pyrrolidinone (18 mg) was dissolved in dry THF (2 mL), and $LiAlH_4$ (6.4 mg) was added. The mixture was refluxed for 10 h and then cooled to 0 °C, and aqueous 1 M NaOH (1.5 mL) was added. After being stirred briefly at 0 °C, ether (3 mL) was added followed by benzoyl chloride (0.1 mL). Workup as described previously followed by chromatographic purification gave **22b** in 18 mg (77%). HPLC: hexane/2-propanol, 90:10; t_R = 14.9 min. $[\alpha]^{23}_D$: +99.4 (*c* 0.9, CH_2Cl_2). Mp: 60.5−63 °C. IR ν_{max}: 1718, 1637, 1581 cm^{-1}. ^{1}H NMR (1:1 mixture of rotamers) δ: 0.78−1.39 (m, 6H), 1.41−2.22 (m, 8H), 3.10 and 3.25 (t, 1H, J = 10.0 Hz), 3.38−3.68 (m, 2H), 3.74−3.94 (m, 1H), 7.32 (m) and 8.10 (d, J = 6.5 Hz) (5H). ^{13}C NMR, δ: 25.96, 26.02, 26.03, 26.33, 28.73, 30.58, 31.31, 31.50, 31.90, 32.00, 41.33, 41.71, 44.04, 45.94, 46.39, 49.79, 50.50, 53.85, 127.04, 127.07, 128.19, 129.70, 129.74, 129.97, 133.01, 136.92, 137.18, 163.93, 169.56. HRMS: calcd for $C_{17}H_{23}NO$ 257.1779, found 257.1778.

1-Benzoyl-4-cyclohexylpyrrolidine (22b) from Squibb-23. Squibb-**23**[30a] (35 mg, 0.15 mmol) was suspended in cyclohexanol (0.5 mL). Then a mixture of cyclohexanol and 2-cyclohexenone (0.3 mL, 50:1 v/v)[30b] was added, and the mixture was immersed into an oil bath set at 158 °C. There was gas evolution, and the color of the mixture turned brown. After 10 h, the mixture was cooled to room temperature, ether (3 mL) was added, and the mixture was extracted with 1 M HCl (3 × 2 mL). Fresh ether (3 mL) was added to the acidic, aqueous layer followed by benzoyl chloride (0.1 mL). The mixture was cooled to 0 °C, and aqueous 10% NaOH (3 mL) was added. After 10 min, the ether layer was separated, the aqueous phase was re-extracted with ether (2 × 3 mL), and the combined organic phases were washed with brine (5 mL), dried, filtered, and evaporated. The crude product was chromatographed (initially using 20:1 petroleum ether−ether then 2:1 petroleum ether−EtOAc) to give the 13.6 mg of product (35%). Mp: 58−60 °C. $[\alpha]^{23}_D$: +102 (*c* 0.50, CH_2Cl_2). HRMS: calcd for $C_{17}H_{23}NO$ 257.1779, found 257.1778. Mixed mp: 58.5−61.5 °C. NMR data are identical to **22b** prepared from **20b**.

HPLC Analysis of Decarboxylated 2-Pyrrolidinones Derived from Cyclization of 10i and *ent*-10i. Racemic **14c**, which was prepared by the decarboxylation of the known (±)-3-(carbomethoxy)-1-(4-methoxyphenyl)-4-methyl-2-pyrrolidinone,[6] was used for determining conditions for optimal separation. A baseline separation of the two enantiomers was achieved. Each of the two decarboxylated 2-pyrrolidinones (from **10i** and *ent*-**10i**) showed two peaks, one at t_R = 10 min and the other at t_R = 14 min. A comparison of the retention times with that obtained for the reference compound (*S*)-**14c** (t_R = 14 min) identified the slower eluting component as **21i**. The faster eluting component was assigned to **20i**. The 2-pyrrolidinone derived from **10i** showed the ratio (based on relative peak areas) of **20i**:**21i** is 1:1.8, whereas the 2-pyrrolidinone formed from *ent*-**10i** indicated the ratio of **20i**:**21i** is 2:1. Addition of a small amount of (*S*)-**14c** to the 2-pyrrolidinone derived from **10i** caused an increase in the peak area of the slower moving component **21i** (t_R = 14 min).

(*S*)-1-(*tert*-Butyloxycarbonyl)-4-cyclohexyl-2-pyrrolidinone (28). Compound **16b** (565 mg, 0.976 mmol) was decarboxylated [NaCl (171 mg, 2.93 mmol); 25 mL DMSO−water (10:1 v/v)] to afford after chromatography (6:1 petroleum ether/EtOAc), 232 mg (87%) of crystalline **20b**. Compound **20b** (322.8 mg, 1.182 mmol) was oxidized using CAN (1.98 g, 3.612 mmol) as described above (**20b** → **22b**) to give 4-cyclohexyl-2-pyrrolidinone (179 mg, 91%). A small amount of sample for spectroscopic characterization was purified by chromatography (8:1 then 2:1 CH_2Cl_2/acetone). Mp: 125−125.5 °C (CH_2Cl_2/acetone). $[\alpha]^{22}_D$: −5.56 (*c* 0.9, $CHCl_3$). IR ν_{max}: 3418, 3215, 1697, 1449 cm^{-1}. ^{1}H NMR, δ: 0.72−1.38 (m, 6H), 1.52−1.88 (m, 5H), 1.90−2.44 (m, 3H), 3.07 (t, 1H, J = 8.3 Hz), 3.43 (t, 1H, J = 8.7 Hz), 6.62 (br s, 1H). ^{13}C NMR, δ: 26.0, 26.4, 30.7, 31.2, 41.3, 42.3, 46.6, 178.1.

4-Cyclohexyl-2-pyrrolidinone (224 mg, 1.33 mmol) was dissolved in dry CH_2Cl_2 (2.7 mL), and dry Et_3N (0.24 mL, 1.33 mmol), DMAP (164 mg, 1.34 mmol), and Boc_2O (600 mg, 2.75 mmol) were added sequentially at room temperature. After being stirred for 17 h, the solvent was removed and the residue was columned (20:1 petroleum ether/EtOAc) to yield 257 mg of **28** (72%). Mp: 90.5−90.8 °C (EtOAc/petroleum ether). $[\alpha]^{23}_D$: −1.68 (*c* 1.5, $CHCl_3$). IR ν_{max}: 1785, 1753, 1714, 1368, 1316 cm^{-1}. ^{1}H NMR, δ: 0.75−1.37 (m, 6H), 1.52 (s, 9H), 1.58−1.89 (m, 5H), 1.89−2.38 (m, 1H), 2.24 (dd, 1H, J = 16.7, 10.7 Hz), 2.66 (dd, 1H, J = 16.7, 8.3 Hz), 3.33 (dd, 1H, J = 10.8, 8.6 Hz), 3.86 (dd, 1H, J = 10.8, 8.0 Hz). ^{13}C NMR, δ: 26.0, 26.2, 28.0, 30.5, 31.0, 37.0, 38.0, 42.0, 50.6, 82.8, 150.2, 174.1. HRMS: calcd for $C_{15}H_{25}NO_3$ (M − 15) 252.1599, found 252.1600.

(2*S*,4*S*)- and (2*R*,4*S*)-1-(*tert*-Butyloxycarbonyl)-2-cyano-4-cyclohexylpyrrolidine (29b). Compound **28** (126 mg, 0.47 mmol) was dissolved in dry THF (12 mL) and cooled to −78 °C. A 1 M solution of $LiEt_3BH$ (0.6 mL, 0.56 mmol) was added slowly, and the reaction was stirred for 1.5 h at −78 °C. The mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL) and warmed slowly to 0 °C. H_2O_2 (30%, 5 drops) was added, and the mixture was stirred for 20 min. Then THF was evaporated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried, filtered, and evaporated. The crude alcohol **29a** was obtained in quantitative yield and was used without purification in the next step. IR ν_{max}: 3562−3175, 1681, 1393, 1366 cm^{-1}.

Alcohol **29a** (82 mg, 0.31 mmol) was dissolved in dry CH_2Cl_2 (5 mL), and Me_3SiCN (91 μL, 0.632 mmol) was added. The mixture was cooled to −78 °C, and $BF_3{\cdot}OEt_2$ (83 μL, 0.67 mmol) was added dropwise to the mixture. After 2 h, the reaction was quenched at −78 °C with saturated aqueous $NaHCO_3$ (2 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried, filtered, and evaporated, and the residue was purified by chromatography (20:1 petroleum ether/EtOAc) to give recovered alcohol **29a** (10 mg) and the oily cyano product **29b** (66 mg, 78%; 89% based on recovered starting material) as a mixture of diastereomers. Cyano product **29b**: IR ν_{max}: 2239, 1704, 1478, 1450, 1393 cm^{-1}. ^{1}H NMR, δ: 0.82−1.37 (m, 6H), 1.50 (s, 9H), 1.57−1.98 (m, 6H), 2.10−2.42 (m, 2H), 2.82−3.06 (m, 1H), 3.48−3.89 (m, 1H), 4.56 (dd, 1H, J = 19.8, 8.1 Hz). ^{13}C NMR, δ: 26.2, 27.0, 28.3, 31.4, 31.8, 34.8, 35.5, 41.2, 43.3, 44.4, 47.7, 50.0, 50.3, 81.3, 118.5, 183.1. HRMS: calcd for $C_{16}H_{26}N_2O_2$ (M^+) 278.1994, found 278.2002.

(2*S*,4*S*)- and (2*R*,4*S*)-4-Cyclohexyl-2-pyrrolidinecarboxylic acid·HCl (23·HCl/30·HCl). Compound **29b** (44 mg, 0.16 mmol) was dissolved in concentrated HCl (2 mL) and then heated to reflux. The reaction was stirred at reflux for 22 h. Then the reaction mixture was washed with Et_2O (2 × 5 mL).

The aqueous layer was evaporated to give **23**·HCl/**30**·HCl in quanititative yield (37 mg). At this stage, we also prepared the HCl salt of Squibb-**23** and compared its ^{1}H NMR spectrum with that of our synthetic material. Synthetic Sample. $[\alpha]^{22}_D$: −4.9 (*c* 1.0, MeOH). ^{1}H NMR, δ (D_2O): 0.70−1.32 (m, 6H), 1.36−1.73 (m, 5H), 1.85−2.13 (m, 2H), 2.31 (dd, J = 5.3, 3.4 Hz) and [2.41, m] (1H), 2.94 (t, 1H, J = 10.9 Hz), 3.55 (dd, J = 11.2, 6.4 Hz) and [3.45, d, J = 7.8 Hz] (1H), 4.38 (dd, J = 9.1, 3.9 Hz) and [4.29, dd, J = 10.7, 7.8 Hz](1H). ^{13}C NMR, δ (D_2O): 29.2, [29.5], 34.6, 34.9, [35.0], 36.1, [36.5], 43.8, [44.0], 46.3, [47.9], 53.2, [53.1], 63.3, 176.1. Squibb-**23**·HCl. $[\alpha]^{22}_D$: −5.6 (*c* 2.2, MeOH). ^{1}H NMR, δ (D_2O): 0.70−1.32 (m, 6H), 1.36−1.73 (m, 5H), 1.85−2.13 (m, 2H), 2.16−2.41 (m, 1H), 2.94 (t, 1H, J = 11.2 Hz), 3.55 (dd, 1H, J = 11.3, 6.4 Hz), 4.38 (dd, 1H, J = 8.9, 4.1 Hz). ^{13}C NMR, δ (D_2O): 29.2, 29.5, 34.6, 34.9, 36.0, 43.9, 46.3, 53.3, 63.2, 175.8.

The mixture of **23**·HCl/**30**·HCl was subjected to ion-exchange chromatography (Dowex 50W-8X, 200−400 mesh) using 5% aqueous NH_4OH as the eluent. The amino acid fractions were evaporated to dryness and extracted with hot MeOH. The methanol extracts were evaporated to give **23**/**30** in quantitative yield. An analytical sample of synthetic-**23** was obtained by recrystallization from H_2O. Mp (H_2O): 265.3−265.5 °C (lit.[30a] mp 265−267 °C). $[\alpha]^{22}_D$: −40.0 (*c* 0.5, MeOH) [lit. $[\alpha]^{30a}_D$ −39.5 (*c* 1.14, MeOH)]. IR ν_{max} (KBr): 3272−2801, 1618, 1385, 1349 cm^{-1}. ^{1}H NMR δ (CD_3OD): 0.83−1.42 (m, 6H), 1.51−2.08 (m, 7H), 2.22−2.46 (m, 1H), 2.88 (t, 1H, J = 10.5 Hz), 3.53 (dd, 1H, J = 11.3, 6.7 Hz), 3.92−4.10 (m, 1H). ^{13}C NMR δ (CD_3OD): 27.2, 27.4, 32.8, 33.1, 34.9, 42.3, 44.7, 50.7, 62.6. HRMS: calcd for $C_{11}H_{19}NO_2$ (M − 15) 152.1439, found 152.1435.

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Supporting Information Available: Procedure for the preparation and spectroscopic and/or analytical data for compounds **5g**, **6**, **9**, **10**, and **13**−**19** as well as a ball and stick rendering of AM1-minimized pyrrolidinium ion **31** (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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