mmol) reacted with 7.4 mL of BuLi (1.2 M in hexane) and then with 1.92 g (10 mmol) of ethyl pentafluoropropionate. Usual workup of the reaction mixture gave 0.95 g (36%) of enol ether **9m**.

Reaction of Phosphonium Salt 1n with BuLi and Ethyl Trifluoroacetate: (*Z*)-β-(Trifluoromethyl)-β-ethoxy-2-(trifluoromethyl)styrene (8n). Similarly, phosphonium **1n** (5 g, 11 mmol) in THF (17 mL) reacted with 7.4 mL of BuLi (solution 1.47 M in hexanes) and then with 1.56 g (11.3 mmol) of ethyl trifluoroacetate. Hydrolysis and usual workup gave 1.89 g (61%) of enol ether **8n**: IR (neat) 1660 cm^{-1} (νC=C); ^{19}F NMR δ −69.7; ^1H NMR δ 1.35 (t, J = 7 Hz, 3 H), 3.9 (q, J = 7 Hz, 2 H), 6.35 (s, 1 H), 7.2–8 (m, 5 H). Anal. Calcd for $C_{12}H_{10}F_6O$: C, 50.71; H, 3.55. Found: C, 51.41; H, 3.76.

Reaction of Phosphonium Salt 1o and Ethyl Trifluoroacetate: β-(Trifluoromethyl)-β-ethoxy-4-methoxystyrene (8o). Similarly, phosphonium salt **1o** (8 g, 17.3 mmol) in THF (27 mL) reacted with 14.8 mL of BuLi (1.17 M in hexanes) and then with 2.46 g (17.3 mmol) of trifluoroacetate in THF (18 mL). After 72 h, hydrolysis and usual workup give 1.14 g (33%) of **8o**: IR (neat) 1655 cm^{-1} (νC=C); ^{19}F NMR δ −69.5; ^1H NMR δ 1.30 (t, 3 H), 3.65–4.10 (s + m, 5 H), 6.30 (s, 1 H), 6.85 (m, 2 H), 7.45 (m, 2 H). Anal. Calcd for $C_{12}H_{13}F_3O_2$: C, 58.54; H, 5.32. Found: C, 59.42; H, 5.57.

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Asymmetric Conjugate Additions to Chiral Bicyclic Lactams. Synthesis of Aracemic Trans-2,3-Disubstituted Pyrrolidines

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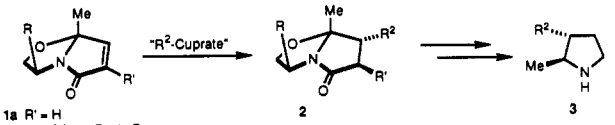
The trans-2,3-disubstituted pyrrolidine moiety, found in the pyrrolizidine alkaloids as well as other natural products, has been accessed from the α,β-unsaturated bicyclic lactams **1d** and **10**. Conjugate addition of lower order cyanocuprates to lactams **1d** and **10** resulted in endo entry of the cuprate with high diastereoselectivity. Other cuprates were investigated and resulted in diminished or opposite stereoselectivities. Further transformation of the β-substituted lactams provided the title compounds in good overall yield and high enantiomeric excess.

Conjugate additions utilizing cyanocuprates have received considerable attention in the past 20 years,[1] whereas higher order cyanocuprates have been in the spotlight for the past decade.[2] We now describe a study involving the conjugate addition of various organocuprates to the bicyclic lactams **1**[3] and the subsequent cleavage of the resultant β-substituted lactams **2** to trans-2,3-disubstituted pyrrolidines **3**.



1a R' = H
b R' = SOMe, R = i-Pr
c R' = CO_2Me, R = i-Pr
d R' = CO_2Bn, R = Ph

2 3

Initial attempts to add dialkyl organocuprates to lactam **1a** (R = i-Pr)[4] were unsuccessful due to facile 1,4-reduction to the enone furnishing the saturated lactam **4**. This reduction is not without precedent and presumably proceeds through an electron transfer from the cuprate to the π-system of the lactam (Scheme I).[5] Additional attempts to introduce alkyl groups (Gilman-type cuprates, lower order cyanocuprates, higher order cyanocuprates) with and without additives (TMSCl,[6] HMPA) to lactam **1a** (R = i-Pr, t-Bu, Ph) in a conjugate fashion also failed. However, it was observed earlier in our laboratory that addition of the lower order methyl cyanocuprate (MeCuCNLi) to lactam **1b** resulted in clean addition producing one diastereomer.[7]

Scheme I

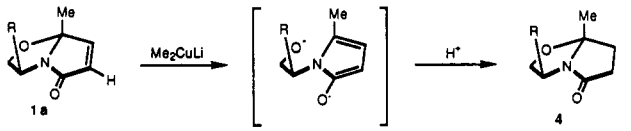


Table I. Effect of Cuprate Species on Cis/Trans Ratio of 5

lactam	cuprate	5 ratio (cis:trans)[a]
1c	Me_2CuLi	1:3
1c	$Me_2CuCNLi_2$	3:1
1c	MeCuCNLi	5:95
1d	n-PrCuCNMgBr	1:3

[a] Determined by 270- or 300-MHz NMR.

In a previous study from this laboratory the Diels–Alder cycloadditions to **1** were unsuccessful unless R′ was a

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(2) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. Lipshutz, B. H. *Synthesis* **1987**, 325. Lipshutz, B. H. *Synlett* **1990**, 119.
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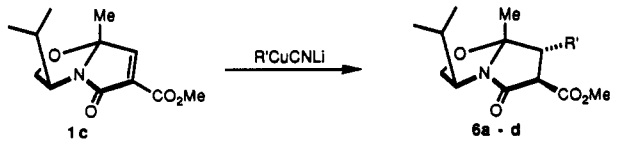
Table II. Lower Order Cyanocuprate Additions to Lactam 1c



product	R′	yield[a] (%)
6a	Me	84
6b	vinyl	84
6c	phenyl	76
6d	n-butyl	80

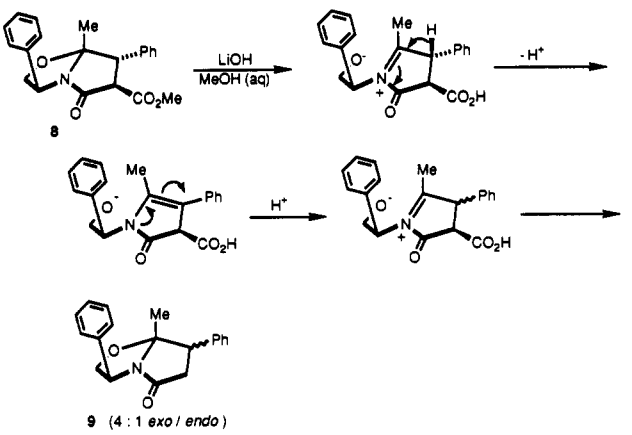
[a] The ratio of diastereomers was assessed as ~95:5 (NMR). Thus, there may be present in **6a–6d** 2–5% of the cis-diastereomer.

Table III. Attempted Decarbalkoxylations of Lactam 6a

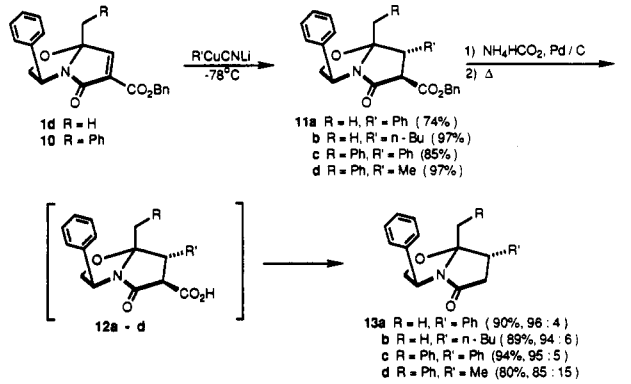
reagent	result	reagent	result
1,2-propanediol, NaOMe[14]	decomposition	TMSI[16] DMAP, Tol, pH 7, Δ[18]	51%
$Ba(OH)_2 \cdot 2H_2O/\Delta$	decomposition		
LiCl, DMSO (aq)[15]	decomposition		

carbomethoxy group.[8] When R′ was simply H no cycloadducts were formed. With this precedent in mind, α-carboalkoxy lactams **1c** and **1d** were prepared and examined as electrophilic olefins (Table I). It was found that addition of the standard "Gilman reagent"[9] to lactam **1c** resulted in a 65% yield of β-substituted lactams **5** in a 3:1 trans/cis diastereomeric ratio (based on ^1H NMR J value for the α proton) with no formal 1,4-reduction product formed.[10] In an effort to increase the selectivity of this conjugate addition, the nature of the organocuprate species was varied. Addition of the higher order methyl cyanocuprate ($Me_2CuCNLi_2$)[2,11] to lactam **1c** resulted in a reversal of the previously observed selectivity, yielding a 3:1 cis/trans ratio of **5**, whereas the lower order cyanocuprate reagent (MeCuCNLi)[12] gave a good yield of product as a 95:5 ratio of diastereomers. It should be mentioned that although the relative configurations of the cuprate addition products were assigned based on ^1H NMR analysis, the absolute stereochemical outcome of these cuprate additions was not yet known. It was also found that the addition of lower order magnesio cyanocuprates to lactam **1d** produced a 3:1 trans/cis ratio which was later shown to reflect the endo/exo selectivity at the β-position. Clearly, the best results obtained were those from the lower order lithio cyanocuprates (Table II). It is interesting to note that there have been other accounts wherein cuprate stoichiometry influenced the stereochemical outcome of conjugate additions.[13]

Scheme II



Scheme III



One of the disadvantages in using the carbomethoxy group as the "conjugate addition activator" surfaced during its attempted removal. A number of methods to effect a "one pot" decarbalkoxylation were surveyed with varying degrees of success (Table III). Many of the reaction conditions examined resulted in extensive decomposition of the lactam, presumably due to side reactions involving the acyl–iminium species.[17] The most promising reaction conditions involved reflux of lactam **6a** in a biphasic mixture of toluene/pH 7 buffer with 2.5 equiv of 4-(dimethylamino)pyridine[18] resulting in a 51% yield of lactam **7a** after 5 days. Even though this decarbalkoxylation was quite general and in all cases gave acceptable yields of product, the lengthy reaction time warranted a search for an alternative method. Treatment of the α-carbomethoxy lactam **8** with $LiOH/MeOH/H_2O$[19] followed by decarboxylation of the intermediate carboxylic acid gave rise to both epimers of **9** even though a single pure diastereomer of **8** was employed. Additionally, the β-butyl analog (Bu in place of Ph in **8**) was also observed to undergo epimerization under these conditions; thus, this property is not due solely to benzyl proton activation. This mixture was shown to arise via the basic hydrolysis conditions and may be depicted as shown in Scheme II.

As a result of the difficulty encountered to cleanly remove the α-carbomethoxy group in **8**, the benzyl esters **1d** and **10** were prepared in good yield. Cuprate additions to

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(9) House, H. O.; Chu, C.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460. Whitesides, G. M.; Fischer, W. F.; Filippo, J. S.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871.
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(16) Ho, T. *Synth. Commun.* **1979**, *9*, 233.
(17) (a) Bienz, S.; Busacca, C. A.; Meyers, A. I. *J. Am. Chem. Soc.* **1989**, *111*, 1905. (b) Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294.
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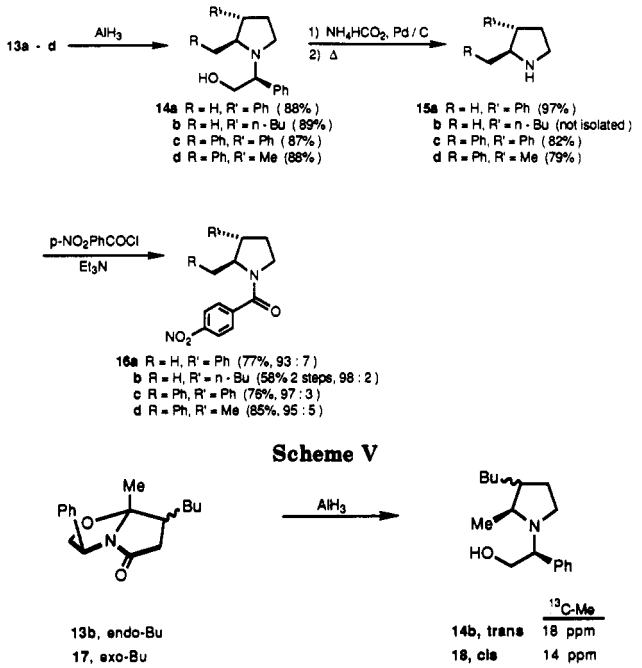
Scheme IV



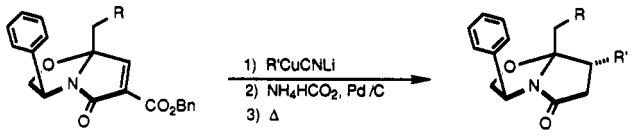
Scheme V

these lactams proceeded smoothly as in the carbomethoxy series, and as expected, the carbobenzyloxy group was easily removed via hydrogenolysis[20] followed by decarboxylation in refluxing toluene (Scheme III). The diastereomeric excess of the resultant β-substituted lactams **13a–d** was found to range between 70% and 92%. These endo/exo ratios are directly related to the facial selectivity of the initial cuprate additions since removal of the benzylic ester had no effect on the stereochemical integrity of the β-center. The absolute configuration of the newly installed stereocenter, although previously inferred via NOE, was unambiguously proven via a single-crystal X-ray structure of lactam **13a**.

The bicyclic lactams were manipulated to "reveal" the pyrrolidines **14a–d** (Scheme IV) by reductive cleavage. This was accomplished by treating stereochemically pure lactams **13a–d** (obtained by column chromatography; silica gel/ethyl acetate/hexanes) with alane ($LiAlH_4/AlCl_3$) at −78 °C in THF[17b] producing good yields of pyrrolidines in high diastereomeric purity (assessed via the benzamide derivatives, **16a–d**).

The absolute stereochemistry of the pyrrolidines **15** was initially assigned, based on a related system[17b] in which the alane reduction proceeded predominantly with retention of configuration.[17b] Furthermore, the well-documented γ-gauche effect[21] was utilized in the following manner. In separate experiments the endo and the exo diastereomers **13b** and **17**, respectively (Scheme V), were subjected to alane reduction and the resultant pyrrolidines examined by ^{13}C NMR. It was found that the resonance of the 2-methyl group for pyrrolidine **18** was shifted upfield by 4 ppm relative to pyrrolidine **14b** leading to the assignment of **18** as the *cis*-pyrrolidine and **14b** as the *trans*-pyrrolidine. Since the absolute stereochemistry of the 3-position of both pyrrolidines was known (from lactams **13b** and **17**), it followed that the absolute stereochemistry of both 2,3 disubstituted pyrrolidines must be as shown. These stereochemical assignments were later

Table IV. Effect of Temperature on the Conjugate Addition to 1d and 10



lactam	R'	addition temp (°C)	yield (%)	13 endo:exo
1d	Ph	−78	67	95:5
		0	77	96:4
1d	n-Bu	−78	87	94:6
		0	78	98:2
10	Ph	−78	80	95:5
		0	73	95:5
10	Me	−78	86	85:15
		0	84	92:8

confirmed via a single-crystal X-ray structure of *p*-nitrobenzamide **16b**.

With the N-substituted pyrrolidines **14a–d** in hand, it now remained to remove the benzyl group[20] and, due to the volatility and air sensitivity of the products, acylate the resultant pyrrolidines to their *p*-nitrobenzamides. This was readily accomplished by treatment with *p*-nitrobenzoyl chloride to provide benzamides **16a–d**. It should be noted that the diastereomeric ratios indicated for benzamides **16a–d** directly reflect the level of selectivity in the alane reduction of lactams **13a–d**.

In order to probe the relationship between the temperature at which the cuprate additions occurred and the observed diastereoselectivity, reactions were allowed to proceed at varying temperatures (Table IV). It is immediately clear there is little effect on the selectivity of the additions of cyanocuprates, and this should enhance the value of the present route to pyrrolidines.

In summary, further synthetic versatility of the bicyclic lactams **1d** and **10** is exhibited through the use of lower order cyanocuprates first utilized by Levisalles in conjugate additions over 20 years ago. Furthermore, this route should allow access to the pyrrolizidine alkaloid family, and studies are in progress with this goal in mind.

After this work was completed we became aware of the recent studies utilizing N-substituted lactams[22] and pyroglutamic acid[23] as substrates for conjugate additions leading to both racemic and enantio-enriched pyrrolidines and pyrrolidones. It is noteworthy that the products obtained from the pyroglutamic acids always contain a hydroxymethylene substituent adjacent to the lactam nitrogen whereas use of the bicyclic lactams described herein allow for a wide range of functional group variability at that position.

Experimental Section

General Procedures. Preparative flash chromatography was performed on silica gel. ^1H NMR and ^{13}C NMR were recorded at 270 or 300 MHz and 68 or 75 MHz, respectively. Infrared spectra were recorded on a Fourier transform spectrophotometer, and polarimetric measurements were taken on an automatic polarimeter. All glassware and syringe needles were oven dried, and all reaction vessels were evacuated to <1 mmHg and purged

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with argon immediately prior to use. All solvents were ACS grade and were redistilled and dried according to standard laboratory practices. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl prior to use. All alkyllithiums were titrated with 2,5-dimethoxybenzyl alcohol (except for methyllithium which was used as received) prior to use.

Unsaturated Bicyclic Lactam (+)-1d. To 511 mg (2.35 mmol) of lactam 4 (R = Ph)[3] in 25 mL of THF at −78 °C under Ar was added 4.94 mL (4.94 mmol) of 1 M LiHMDS. After 1 h, 0.34 mL (2.35 mmol) of benzyl chloroformate (passed through Na_2SO_4 prior to use) was added neat. After an additional 30 min 1.77 mmol of phenylselenyl bromide (prepared in situ from 1.77 mmol bromine/1.88 mmol diphenyl diselenide in THF) in 20 mL of THF was added and the reaction mixture stirred at −78 °C for 1 h, warmed to 0 °C for 1 h, quenched with 1 M HCl, and diluted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to a red oil which was dissolved in 25 mL of dichloromethane, cooled to 0 °C, and treated with 0.80 mL (7.06 mmol) of 30% H_2O_2. After 15 min the colorless solution was warmed to ambient temperature and stirred for 1 h at which time 1 M HCl was added and the reaction mixture was extracted into ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to 718 mg of yellow oil. Column chromatography (20–35% ethyl acetate/hexane) provided 560 mg (68%) of lactam **1d** as a clear colorless oil which solidified on standing at ambient temperature: ^1H ($CDCl_3$) δ 7.72 (s, 3 H), 7.48–7.28 (m, 10 H), 5.30 (app s, 2 H), 5.18 (app t, J = 7.2 Hz, 1 H), 4.68 (app t, J = 8.3 Hz, 1 H), 4.42 (dd, J = 6.7 Hz, 8.6 Hz, 1 H), 1.52 (s, 3 H); ^{13}C ($CDCl_3$), δ 172.1, 160.7, 156.1, 139.2, 135.2, 130.9, 128.7, 128.6, 128.4, 128.3, 127.6, 125.7, 97.9, 75.6, 67.0, 58.6, 21.7; IR (film), 3064, 2983, 1754, 1731, 1338, 738, 699 cm^{-1}; $[\alpha]_D$ = +99.7° (c 0.93, CH_2Cl_2); mp 72–74 °C.

Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48. Found: C, 72.27; H, 5.53.

α,β-Disubstituted Lactam (+)-6a. To 82 mg (0.91 mmol) of CuCN in 5 mL of THF at −78 °C under Ar was added 0.62 mL (0.87 mmol) of 1.4 M methyllithium. The tan mixture was warmed to 0 °C until a homogeneous solution resulted (5 min) and cooled to −78 °C, and 109 mg (0.46 mmol) of lactam **1c**[3] in 3 mL of THF was added dropwise. After 1 h the yellow reaction mixture was quenched with 5 mL of 10% NH_4OH/saturated NH_4Cl solution, air was blown over the reaction mixture, and the cooling bath was removed allowing the reaction mixture to warm to ambient temperature for 2 h at which time a deep blue color resulted. The aqueous layer was extracted with 2 × 15 mL of ether, and the organic layer was washed with 10 mL of brine, dried over $MgSO_4$, and concentrated in vacuo to yield 102 mg (88%) of lactam **6a**: ^1H NMR ($CDCl_3$) δ 4.09 (app t, J = 8.2 Hz, 1 H), 3.76 (dd, J = 6.4, 8.6 Hz, 1 H), 3.71 (s, 3 H), 3.60–3.51 (m, 1 H), 3.06 (d, J = 5.3 Hz, 1 H), 2.73–2.65 (m, 1 H), 1.71–1.58 (m, 1 H), 1.43 (s, 3 H), 1.06 (d, J = 7.2 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.81 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.21, 169.39, 99.48, 70.51, 62.99, 58.06, 52.61, 41.02, 33.39, 24.22, 20.42, 18.80, 13.99; IR (film), 2962, 1736, 1714, 1436, 1379, 1169, 1031 cm^{-1}; $[\alpha]_D$ = +53.0° (c 1.10, CH_2Cl_2).

Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29. Found: C, 60.98; H, 8.30.

Lactam (+)-6b. Prepared from lactam **1c** by the same procedure describing the preparation of lactam **6a** and was obtained in 84% yield: ^1H NMR ($CDCl_3$) δ 5.91–5.79 (m, 1 H), 5.27–5.21 (m, 2 H), 4.16 (dd, J = 7.8, 8.7 Hz, 1 H), 3.82–3.77 (m, 1 H), 3.80 (s, 3 H), 3.69–3.60 (m, 1 H), 3.40 (d, J = 6.6 Hz, 1 H), 3.36–3.31 (m, 1 H), 1.80–1.68 (m, 1 H), 1.53 (s, 3 H), 1.06 (d, J = 6.6 Hz, 3 H), 0.89 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$), δ 175.04, 168.96, 133.19, 118.48, 99.43, 70.22, 63.93, 55.21, 52.90, 50.06, 33.48, 23.85, 20.64, 18.91; IR (film), 2957, 2873, 1743, 1716, 1644, 1436, 1378, 1168, 1081 cm^{-1}; $[\alpha]_D$ = +87.9° (c 0.39, CH_2Cl_2).

Lactam (+)-6c. Prepared from lactam **1c** by the same procedure describing the preparation of lactam **6a** and was obtained in 76% yield after column chromatography (ethyl acetate/hexane): mp 121–123.5 °C; ^1H NMR ($CDCl_3$) δ 7.37–7.21 (m, 5 H), 4.12–4.03 (m, 1 H), 3.96 (d, J = 6.4 Hz, 1 H), 3.80–3.68 (m, 3 H), 3.78 (s, 3 H), 1.82–1.64 (m, 1 H), 1.60 (s, 3 H), 1.09 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.96, 169.03, 136.36, 128.80, 128.43, 127.80, 99.42, 70.53, 63.75, 57.20, 52.98, 51.80, 33.44, 24.56, 20.61, 18.94; IR (film), 3037, 2961, 2887, 1739, 1716, 1434, 1380, 1288, 1156, 1086, 1012, 757, 706 cm^{-1}; $[\alpha]_D$ = +185° (c 0.56, CH_2Cl_2).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30. Found: C, 67.84; H, 7.37.

Lactam (+)-6d. Prepared from lactam **1c** by the same procedure describing the preparation of lactam **6a** and was obtained in 80% yield: ^1H NMR ($CDCl_3$), δ 4.15 (dd, J = 7.8, 8.7 Hz, 1 H), 3.84–3.81 (m, 1 H), 3.79 (s, 3 H), 3.64–3.58 (m, 1 H), 3.20 (d, J = 5.2 Hz, 1 H), 2.69–2.60 (m, 1 H), 1.75–1.69 (m, 2 H), 1.52 (s, 3 H), 1.35–1.27 (m, 5 H), 1.05 (d, J = 6.6 Hz, 3 H), 0.92–0.87 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 174.41, 169.86, 99.72, 70.38, 62.75, 56.82, 52.72, 46.44, 33.57, 29.79, 28.86, 25.01, 22.57, 20.51, 18.86, 13.81; IR (film), 2959, 2874, 1747, 1715, 1469, 1434, 1378, 1166, 1019 cm^{-1}; $[\alpha]_D$ = +48.8° (c 0.67, CH_2Cl_2).

Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15. Found: C, 64.34; H, 9.08.

Unsaturated Bicyclic Lactam (+)-10. Prepared from angular benzyl analog of 4 (R = Ph)[17b] via the same procedure used to prepare lactam **1d** and was obtained in 90% yield: ^1H NMR ($CDCl_3$) δ 7.66 (s, 3 H), 7.41–7.07 (m, 15 H), 5.31–5.21 (m, 3 H), 4.73 (app t, J = 8.2 Hz, 1 H), 4.53 (dd, J = 6.3, 8.9 Hz, 1 H), 3.23 (d, J = 14.2 Hz, 1 H), 2.87 (d, J = 14.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$), δ 172.5, 160.5, 155.1, 139.0, 135.2, 134.1, 131.3, 130.0, 128.8, 128.6, 128.5, 128.3, 128.1, 127.3, 126.1, 99.9, 75.0, 66.9, 58.7, 41.3; IR (film), 3063, 2926, 1756, 1730, 1339, 737, 699 cm^{-1}; $[\alpha]_D$ = +125.7° (c 1.01, CH_2Cl_2).

Anal. Calcd for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45. Found: C, 76.04; H, 5.50.

Lactam (+)-11a. Prepared from lactam **1d** via the same procedure used to prepare lactam **6a** and was obtained in 74% yield after column chromatography (ethyl acetate/hexane): ^1H NMR ($CDCl_3$) δ 7.65–7.21 (m, 15 H), 5.36 (app t, J = 9.0 Hz, 1 H), 5.29 (d, J = 15.0 Hz, 1 H), 5.22 (d, J = 15.0 Hz, 1 H), 4.52 (app t, J = 9.7 Hz, 1 H), 4.08–3.96 (m, 3 H), 1.47 (s, 3 H); ^{13}C (benzene-d_6) δ 175.6, 168.8, 140.8, 136.7, 136.0, 129.5, 128.8, 128.7, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.5, 125.9, 100.1, 71.9, 67.5, 59.9, 57.4, 52.0, 23.5; IR (film), 3063, 2982, 1741, 1718, 1162, 738, 699 cm^{-1}; $[\alpha]_D$ = +160.0° (c 1.50, CH_2Cl_2).

Anal. Calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89. Found: C, 75.94; H, 5.94.

Lactam (+)-11b. Prepared from lactam **1d** via the same procedure used to prepare lactam **6a** and was obtained in 97% yield: ^1H NMR ($CDCl_3$) δ 7.21–7.09 (m, 10 H), 5.24–5.19 (m, 3 H), 4.58 (app t, J = 8.6 Hz, 1 H), 4.06 (dd, J = 6.9, 8.4 Hz, 1 H), 3.35 (d, J = 5.2 Hz, 1 H), 2.78–2.65 (m, 1 H), 1.83–1.71 (m, 1 H), 1.36 (s, 3 H), 1.41–1.22 (m, 5 H), 0.86 (app t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$), δ 175.0, 169.2, 140.5, 136.3, 128.4, 128.2, 128.1, 127.8, 127.1, 126.0, 100.3, 73.4, 67.9, 57.8, 56.9, 46.8, 30.0, 28.9, 24.1, 23.4, 14.2; IR (film), 3063, 3032, 2956, 1739, 1715, 1455, 1379, 1163, 734, 698 cm^{-1}; $[\alpha]_D$ = +102.9° (c 0.49, CH_2Cl_2).

Anal. Calcd for $C_{25}H_{29}NO_4$: 73.69; H, 7.17. Found: C, 73.78; H, 7.18.

Lactam (+)-11c. Prepared from lactam **10** via the same procedure used to prepare lactam **6a** and was obtained in 85% yield after column chromatography (ethyl acetate/hexane): ^1H NMR ($CDCl_3$) δ 7.47–7.12 (m, 18 H), 6.57–6.54 (m, 2 H), 5.40–5.29 (m, 3 H), 4.57 (app t, J = 8.5 Hz, 1 H), 4.27 (dd, J = 6.9, 8.8 Hz, 1 H), 4.23 (d, J = 2.2 Hz, 1 H), 3.95 (d, J = 2.2 Hz, 1 H), 3.15 (d, J = 13.9 Hz, 1 H), 3.02 (d, J = 13.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.5, 168.5, 138.9, 137.7, 135.3, 135.2, 130.8, 128.8, 128.6, 128.5, 128.3, 128.2, 128.1, 127.7, 127.2, 126.9, 125.5, 102.3, 73.5, 67.7, 59.5, 57.7, 49.0, 42.7; IR (film), 3087, 3030, 2956, 1741, 1719, 1456, 1170, 730, 698 cm^{-1}; $[\alpha]_D$ = +151.0° (c 0.41, CH_2Cl_2).

Lactam (+)-11d. Prepared from lactam **10** via the same procedure used to prepare lactam **6a** and was obtained in 97% yield: ^1H NMR ($CDCl_3$) δ 7.47–7.15 (m, 15 H), 5.37–5.31 (m, 3 H), 4.81 (app t, J = 8.6 Hz, 1 H), 4.39 (dd, J = 7.2, 8.4 Hz, 1 H), 3.32 (d, J = 3.3 Hz, 1 H), 3.09 (d, J = 14.1 Hz, 1 H), 3.05–3.01 (m, 1 H), 2.82 (d, J = 14.1 Hz, 1 H), 0.85 (d, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.0, 168.8, 139.6, 135.5, 130.3, 129.9, 128.7, 128.6, 128.4, 128.2, 128.1, 127.5, 126.7, 125.6, 102.0, 72.9, 67.4, 59.8, 58.1, 42.5, 38.7, 15.4; IR (film), 3087, 3031, 2931, 1741, 1717, 1453, 1165, 730, 699 cm^{-1}; $[\alpha]_D$ = +108.0° (c 0.30, CH_2Cl_2).

β-Substituted Lactam (+)-13a. To 141 mg (0.33 mmol) of lactam **11a** in 5 mL of methanol under Ar was added 166 mg (2.64 mmol) ammonium formate followed by 70 mg (0.066 mmol) of Pd/C. After 18 h the reaction mixture was filtered and concentrated in vacuo providing the intermediate carboxylic acid contaminated with ammonium formate which was dissolved in 25 mL of toluene and heated to reflux for 2 h. The mixture was cooled to ambient temperature and diluted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo to 87 mg (90%) of colorless oil as a 96:4 diastereomeric mixture which solidified on standing. The major diastereomer was purified by column chromatography (ethyl acetate/hexane). Spectral data for intermediate acid **12a**: ^{1}H NMR ($CDCl_3$) δ 7.24–7.04 (m, 10 H), 6.61 (br s, 1 H), 5.13 (app t, J = 8.1 Hz, 1 H), 4.29 (app t, J = 8.5 Hz, 1 H), 4.09 (d, J = 5.3 Hz, 1 H), 3.82 (app t, J = 7.0 Hz, 1 H), 3.69 (d, J = 5.2 Hz, 1 H), 1.37 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.9, 172.0, 139.8, 137.6, 128.9, 128.6, 128.2, 127.3, 127.2, 125.3, 100.2, 72.4, 59.5, 58.7, 52.3, 24.1; IR (film), 3584, 3154, 2984, 1704, 1601, 1333, 731, 699 cm^{-1}. Spectral data for lactam **13a**: ^{1}H NMR ($CDCl_3$) δ 7.37–7.21 (m, 10 H), 5.25 (app t, J = 7.2 Hz, 1 H), 4.19 (app t, J = 8.5 Hz, 1 H), 4.00 (dd, J = 5.9, 8.7 Hz, 1 H), 3.64 (dd, J = 4.2, 8.9 Hz, 1 H), 3.26 (dd, J = 8.9, 17.5 Hz, 1 H), 2.78 (dd, J = 4.3, 17.5 Hz, 1 H), 1.51 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.0, 139.8, 137.9, 128.5, 128.3, 127.3, 125.6, 101.1, 72.7, 58.1, 49.6, 39.7, 25.1; IR (film), 3063, 2926, 1715, 1376, 732, 699 cm^{-1}; $[\alpha]_D$ = +182.3° (c 0.51, CH_2Cl_2); mp 119–120 °C.

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.65; H, 6.48; N, 4.66.

Lactam (+)-13b. Prepared from lactam **11b** by the same procedure describing the preparation of lactam **13a** and was obtained in 89% yield as a 94:6 diastereomeric mixture. The major isomer was purified by column chromatography (ethyl acetate/hexane). Spectral data for intermediate acid **12b**: ^{1}H NMR ($CDCl_3$) δ 7.63 (br s, 1 H), 7.29–7.11 (m, 5 H), 5.08 (app t, J = 7.5 Hz, 1 H), 4.45 (app t, J = 8.3 Hz, 1 H), 3.95 (app t, J = 8.1 Hz, 1 H), 3.14 (d, J = 4.4 Hz, 1 H), 2.86 (d, J = 4.6 Hz, 1 H), 1.70–1.58 (m, 1 H), 1.35 (s, 3 H), 1.30–1.20 (m, 5 H), 0.87 (app t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$), δ 178.6, 172.9, 140.1, 128.7, 127.3, 125.3, 100.7, 72.3, 59.6, 58.1, 46.2, 29.9, 29.6, 24.6, 22.9, 13.9; IR (film), 3182, 2956, 1698, 1378, 730, 699 cm^{-1}. Spectral data for lactam **13b**: ^{1}H NMR ($CDCl_3$) δ 7.36–7.24 (m, 5 H), 5.18 (app t, J = 7.2 Hz, 1 H), 4.54 (app t, J = 8.3 Hz, 1 H), 4.10 (dd, J = 6.7, 8.6 Hz, 1 H), 2.94 (dd, J = 8.2, 16.8 Hz, 1 H), 2.35–2.19 (m, 2 H), 1.73–1.69 (m, 1 H), 1.39 (s, 3 H), 1.36–1.24 (m, 5 H), 0.90 (app t, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.9, 140.4, 128.6, 127.3, 125.7, 101.4, 72.6, 57.9, 43.7, 38.9, 30.1, 29.1, 24.8, 22.7, 13.8; IR (film), 3062, 3019, 2930, 2866, 1714, 1370, 700 cm^{-1}; $[\alpha]_D$ = +126.0° (c 0.96, CH_2Cl_2).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.59; H, 8.46.

Lactam (+)-13c. Prepared from lactam **11c** via the same procedure used to prepare lactam **13a** and was obtained in 94% yield as a 95:5 diastereomeric mixture. The major diastereomer was purified by column chromatography (ethyl acetate/hexane): ^{1}H NMR ($CDCl_3$), δ 7.41–7.20 (m, 13 H), 6.88–6.85 (m, 2 H), 5.29 (dd, J = 5.8, 7.3 Hz, 1 H), 4.28 (dd, J = 5.5, 8.8 Hz, 1 H), 4.13 (app t, J = 7.7 Hz, 1 H), 3.78 (d, J = 7.9 Hz, 1 H), 3.16 (d, J = 13.8 Hz, 1 H), 2.98 (d, J = 13.9 Hz, 1 H), 2.89 (dd, J = 8.7, 17.2 Hz, 1 H), 2.60 (dd, J = 1.2, 17.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 177.9, 139.1, 138.9, 135.5, 130.4, 128.8, 128.4, 127.9, 127.7, 127.1, 127.0, 126.2, 103.2, 72.7, 57.5, 47.2, 44.5, 40.5; IR (film), 3056, 3017, 2928, 1710, 1496, 1383, 783, 754, 729 cm^{-1}; mp 126–128 °C; $[\alpha]_D$ = +128.3° (c 0.35, CH_2Cl_2).

Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27. Found: C, 81.22; H, 6.26.

Lactam (+)-13d. Prepared from lactam **11d** via the same procedure used to prepare lactam **13a** and was obtained in 80% yield as an 85:15 mixture of diastereomers. The major diastereomer was purified via radial chromatography (acetone/dichloromethane): ^{1}H NMR ($CDCl_3$) δ 7.39–7.14 (m, 10 H), 5.26 (app t, J = 7.1 Hz, 1 H), 4.64 (app t, J = 8.3 Hz, 1 H), 4.43 (dd, J = 6.5, 8.8 Hz, 1 H), 3.03 (d, J = 13.9 Hz, 1 H), 2.83 (d, J = 13.9 Hz, 1 H), 2.62–2.53 (m, 2 H), 1.96 (d, J = 15.3 Hz, 1 H), 0.86 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.2, 139.5, 135.6, 130.1, 128.7, 128.2, 127.6, 126.8, 126.1, 102.9, 73.1, 57.5, 43.3, 41.9, 36.0, 15.6; IR (film), 3056, 2968, 1715, 1358, 1024, 759, 724 cm^{-1}; mp 74–76 °C; $[\alpha]_D$ = +125.3° (c 0.66, CH_2Cl_2).

Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89. Found: C, 77.92; H, 6.93.

Pyrrolidine (+)-14a. To 204 mg (1.53 mmol) of $AlCl_3$ at 0 °C under Ar was added 7 mL of THF followed by 4.60 mL (4.60 mmol) of 1 M $LiAlH_4$/THF dropwise (H_2 evolution!). The reaction mixture was warmed to ambient temperature for 20 min and cooled to −78 °C and 204 mg (0.70 mmol) of lactam **14a** was added slowly down the side of the flask. After 1.5 h, the reaction was warmed to ambient temperature for 15 min, cooled to 0 °C, and quenched slowly with 1 M HCl. The reaction mixture was diluted with H_2O and extracted with four portions of dichloromethane, and the combined organics were then washed with 10% NaOH. The aqueous layer was back-extracted with dichloromethane, and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to 173 mg (88%) of pyrrolidine **14a** as a clear colorless oil (^{1}H NMR indicates a 92:8 diastereomeric ratio at the 2-position): ^{1}H NMR ($CDCl_3$) δ 7.38–7.00 (m, 10 H), 4.14–3.99 (m, 2 H), 3.67 (dd, J = 4.0, 9.2 Hz, 1 H), 3.46 (br s, 1 H), 3.09–3.03 (m, 1 H), 2.75 (app q, J = 9.0 Hz, 1 H), 2.63–2.48 (m, 2 H), 2.26–2.13 (m, 1 H), 1.65–1.41 (m, 1 H), 1.17 (d, J = 5.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 143.7, 134.8, 129.1, 128.3, 128.2, 128.0, 127.8, 126.3, 62.9, 61.6, 60.6, 52.0, 44.2, 31.2, 17.1; IR (film) 3428, 3060, 3028, 2962, 1949, 1878, 1808, 1452, 1030, 757, 701 cm^{-1}; $[\alpha]_D$ = +108.1° (c 0.37, CH_2Cl_2).

Pyrrolidine (+)-14b. Prepared from lactam **13b** by the same procedure describing the preparation of pyrrolidine **14a** and was obtained in 89% yield as a 98:2 diastereomeric mixture: ^{1}H NMR ($CDCl_3$) δ 7.38–7.11 (m, 5 H), 4.07–3.93 (m, 2 H), 3.72–3.61 (m, 2 H), 2.94–2.87 (m, 1 H), 2.30–2.14 (m, 2 H), 1.93–1.82 (m, 1 H), 1.64–1.52 (m, 1 H), 1.22 (d, J = 6.0 Hz, 1 H), 1.18–1.05 (9m, 7 H), 0.83 (app t, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 134.6, 129.2, 128.1, 127.6, 61.9, 61.0, 60.7, 45.0, 43.7, 33.4, 30.1, 28.3, 22.8, 17.8, 14.0; IR (film), 3408, 3084, 2925, 1452, 1060, 762, 702 cm^{-1}; $[\alpha]_D$ = +46.8° (c 0.68, CH_2Cl_2).

Pyrrolidine (+)-14c. Prepared from lactam **13c** via the same procedure used to prepare pyrrolidine **14a** and was obtained in 87% yield as a 97:3 mixture of diasteromers: ^{1}H NMR ($CDCl_3$) δ 7.35–7.06 (m, 13 H), 6.78–6.75 (m, 2 H), 4.11–3.97 (m, 2 H), 3.68 (dd, J = 4.5, 9.8 Hz, 1 H), 3.21–3.15 (m, 1 H), 2.99–2.79 (m, 6 H), 2.15–2.08 (m, 1 H), 1.57–1.50 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 144.7, 139.0, 135.7, 129.7, 129.1, 128.3, 128.2, 127.9, 127.5, 126.1, 125.9, 68.2, 63.0, 61.8, 49.0, 45.0, 38.9, 32.3; IR (film), 3418, 3060, 2932, 1949, 1869, 1810, 1602, 1494, 1453, 1029, 759, 700 cm^{-1}; $[\alpha]_D$ = +43.8° (c 2.26, CH_2Cl_2).

Pyrrolidine (+)-14d. Prepared from lactam **13d** via the same procedure used to prepare pyrrolidine **14a** and was obtained in 88% yield as a 95:5 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 7.39–7.10 (m, 10 H), 4.11–3.92 (m, 2 H), 3.65 (dd, J = 8.1, 10.8 Hz, 1 H), 3.10 (app dd, J = 5.4, 13.5 Hz, 2 H), 2.89 (br s, 1 H), 2.72–2.63 (m, 1 H), 2.59–2.40 (m, 2 H), 1.95–1.81 (m, 2 H), 1.16–1.03 (m, 1 H), 1.50 (d, J = 8.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.4, 135.4, 129,4, 129.2, 128.3, 128.2, 127.9, 126.1, 68.5, 63.2, 61.4, 44.0, 40.0, 36.9, 30.9, 19.7; IR (film), 3427, 3046, 2954, 1604, 1493, 1453, 1058, 763, 739 cm^{-1}; $[\alpha]_D$ = +104.6° (c 2.40, CH_2Cl_2).

Pyrrolidine (−)-15a. To 36 mg (0.13 mmol) of pyrrolidine **14a** in 3 mL of methanol under Ar was added 65 mg (1.02 mmol) of ammonium formate followed by 27 mg (0.026 mmol) of Pd/C. After 6 h the reaction mixture was filtered through Celite and concentrated in vacuo (cool H_2O bath) to 46 mg of colorless oil. Column chromatography (60:35:5 ethyl acetate/hexane/triethylamine) provided 20 mg (97%) of pyrrolidine **15a** as a 93:7 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 7.34–7.19 (m, 5 H), 4.20 (br s, 1 H), 3.25–3.09 (m, 3 H), 2.65 (app q, J = 8.9 Hz, 1 H), 2.39–2.26 (m, 1 H), 2.08–1.93 (m, 1 H), 1.17 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.8, 128.5, 128.0, 127.5, 126.4, 62.5, 53.7, 45.5, 35.1, 18.3; IR (film), 3364, 3025, 2961, 1405, 753, 697 cm^{-1}; $[\alpha]_D$ = −4.2° (c 0.60, CH_2Cl_2).

Pyrrolidine 15c. Prepared from pyrrolidine **14c** via the same procedure used to prepare pyrrolidine **15a** and was obtained in 82% yield as a 97:3 mixture of diastereomers: ^{1}H NMR ($CDCl_3$ δ 7.34–7.12 (m, 10 H), 3.84–3.20 (m, 1 H), 3.14–3.04 (m, 2 H), 2.95–2.74 (m, 2 H), 2.62–2.51 (m, 1 H), 2.36–2.23 (m, 1 H), 1.98–1.84 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 143.3, 139.4, 129.1, 128.6, 128.4, 127.7, 126.3, 126.2, 68.1, 51.1, 45.7, 35.0; IR (film), 3337, 3060, 2931, 1947,

1870, 1758, 1494, 1453, 758, 699 cm^{-1}.

Pyrrolidine 15d. Prepared from pyrrolidine **14d** via the same procedure used to prepare pyrrolidine **15a** and was obtained in 79% yield as a 95:5 mixture of diastereomers: ^1H NMR ($CDCl_3$) δ 7.29–7.14 (m, 5 H), 2.97–2.77 (m, 3 H), 2.73–2.67 (m, 1 H), 2.60–2.53 (m, 1 H), 2.06–1.89 (m, 3 H), 1.75–1.65 (m, 1 H), 1.40–1.30 (m, 1 H), 0.97 (d, J = 6.6 Hz, 3 H); IR (film) 3342, 3060, 2953, 1402, 745, 699 cm^{-1}.

***p*-Nitrobenzamide (+)-16a.** To 76 mg (0.47 mmol) of pyrrolidine **15a** in 10 mL of dichloromethane under Ar was added 0.10 mL (0.71 mmol) of triethylamine followed by 96 mg (0.52 mmol) of *p*-nitrobenzoyl chloride. After 1 h 10% KOH was added and the mixture extracted into ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to 137 mg yellow solid. GC analysis of the crude indicated a 93:7 diastereomeric mixture of products. Column chromatography (20–50% ethyl acetate/hexane) provided 84 mg (58%) of benzamide **16a** and 29 mg (20%) of a mixture of benzamide **16a** and the minor diastereomer: ^1H NMR ($CDCl_3$) δ 8.25 (d, J = 8.4 Hz, 2 H), 7.71 (d, J = 7.6 Hz, 2 H), 7.35–7.23 (m, 5 H), 4.29–4.18 (m, 1 H), 3.74–3.45 (m, 2 H), 3.08–2.96 (m, 1 H), 2.26–2.12 (m, 1 H), 2.05–1.88 (m, 1 H), 1.41 (d, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.6, 148.7, 143.0, 140.6, 128.8, 128.5, 127.4, 127.2, 126.9, 123.7, 60.6, 52.6, 50.0, 34.0, 18.6; IR (film), 3087, 3065, 2917, 1626, 1520, 856, 760, 742, 717, 702 cm^{-1}; $[\alpha]_D$ = +119.2° (*c* 0.48, CH_2Cl_2); mp 94–96 °C.

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85. Found: C, 69.53; H, 5.82.

***p*-Nitrobenzamide (+)-16b.** Prepared from pyrrolidine **14b** by the same procedure describing the preparation of benzamide **16a** and was obtained in 60% yield from pyrrolidine **14b** as a 98:2 diastereomeric mixture. Column chromatography (20–30% ethyl acetate/hexane) provided 78 mg (58%) of benzamide **16b**: ^1H NMR ($CDCl_3$) δ 8.21 (d, J = 8.5 Hz, 2 H), 7.63 (d, J = 8.6 Hz, 2 H), 3.83–3.79 (m, 1 H), 3.43–3.32 (m, 2 H), 2.04–1.92 (m, 1 H), 1.87–1.73 (m, 1 H), 1.69–1.51 (m, 1 H), 1.35 (d, J = 6.2 Hz, 3 H), 1.30–1.21 (m, 6 H), 0.89–0.84 (m, 3 H); ^{13}C NMR ($CDCl_3$), δ 167.3, 148.4, 143.2, 128.3, 123.5, 59.2, 49.4, 46.2, 32.7, 31.3, 30.1, 22.7, 19.1, 13.9; IR (film), 3062, 2959, 2927, 1632, 1522, 1348, 867, 850, 721 cm^{-1}; mp 50–52 °C; $[\alpha]_D$ = +125.4° (*c* 0.28, CH_2Cl_2).

Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.19; H, 7.64. Found: C, 66.12; H, 7.66.

***p*-Nitrobenzamide (+)-16c.** Prepared from pyrrolidine **15b** via the same procedure used to prepare benzamide **16a** and was obtained in 75% yield as a 97:3 mixture of diastereomers. Column chromatography (20–40% ethyl acetate/hexane) provided 72% benzamide **16c**: ^1H NMR ($CDCl_3$) δ 8.29 (d, J = 8.3 Hz, 2 H), 7.96 (d, J = 8.3 Hz, 2 H), 7.71–7.07 (m, 10 H), 4.62 (m, 1 H), 3.87–3.24 (m, 3 H), 3.11–3.01 (m, 1 H), 2.92 (dd, J = 2.1, 13.6 Hz, 1 H), 2.07–2.01 (m, 1 H), 1.92–1.79 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 167.4, 148.7, 142.8, 140.9, 137.2, 130.4, 128.8, 128.4, 128.3, 127.5, 127.1, 126.7, 123.7, 64.5, 50.6, 47.1, 35.4, 34.1; IR (film) 3061, 2925, 1631, 1522, 1350, 759, 740, 701, 668 cm^{-1}; mp 159–161 °C; $[\alpha]_D$ = +59.4° (*c* 1.14, CH_2Cl_2).

Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74. Found: C, 74.34; H, 5.82.

***p*-Nitrobenzamide (+)-16d.** Prepared from pyrrolidine **15d** via the same procedure used to prepare benzamide **16a** and was obtained in 95% yield as a 98:2 mixture of diastereomers. Column chromatography (10–30% ethyl acetate/hexane) provided benzamide **16d** in 85% yield: ^1H NMR ($CDCl_3$) δ 8.24 (d, J = 8.5 Hz, 2 H), 8.15 (d, J = 8.4 Hz, 2 H), 7.63–7.15 (m, 5 H), 4.05–3.89 (m, 1 H), 3.33–3.13 (m, 2 H), 3.12–2.96 (m, 2 H), 2.24–2.09 (m, 1 H), 1.87–1.73 (m, 1 H), 1.43–1.28 (m, 1 H), 0.96 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 148.0, 143.0, 137.7, 130.1, 128.3, 128.2, 126.5, 123.6, 65.0, 49.9, 36.6, 36.4, 33.1, 18.1; IR (film), 3061, 2960, 1633, 1522, 1349, 777, 743, 722, 704 cm^{-1}; mp 72–74 °C; $[\alpha]_D$ = +127.2° (*c* 1.36, CH_2Cl_2).

Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21. Found: C, 70.27; H, 6.25.

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Asymmetric Alkylations on Chiral Formamidines. Molecular Mechanics Studies Relating to the Facial Selectivity of the Lithiated Intermediates

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Molecular mechanics studies on the lithiated chiral formamidines **1** and **3** provide an explanation for the observed degree of facial selectivity during alkylation. The energetic origin of the conformers which predominate prior to each alkylation step are found visibly to arise from angle strain and H–H repulsions.

Introduction

In a recent report from this laboratory, we presented a rationalization for the stereochemical dichotomy in first and second alkylation of chiral lithio formamidines **1** and **3**, respectively.[1] That is, alkylation of **1** occurs with very high selectivity (>99:1) on the topside (β-face) whereas the alkylation of **3** occurs with substantial facial selectivity (~9:1) predominantly from the bottomside (α-face). Our explanation of this unexpected result was based on experiments which indicated that the size of the R* group (Me, Ph, *i*-Pr, *t*-Bu) on the chiral auxiliary appeared to be playing a pivotal role in dictating the facial preference. In the first alkylation (**1** → **2**), it was found that the high level of topside selectivity was relatively insensitive to the nature of R*, whereas the bottomside selectivity observed during the second alkylation (**3** → **4**) appeared to be sensitive to the size of R*. As a result, the % de leading to **2** by varying R* could be obtained in 70–98% whereas the % de of **4** by varying R* ranged from 4 to 88%.

The reasons proposed[1] to account for the α-face alkylation of **1** and β-face alkylation of **3** (E_1 = Me) was based on there being two energetically different conformations available to the chelated lithio salts, **1** and **3**.

As semiempirical electronic structure studies[2] on complexes approaching the size of **1** through **4** have largely

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