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Effects of Remote *N*-(*tert*-Butoxycarbonyl) Groups on Heteroatom Directed Lithiation at Benzylic Positions[1]

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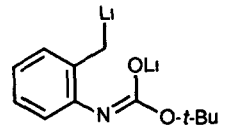
Abstract Lithiation of *N*-BOC-2-methylphenethylamine (**6**) occurs exclusively at the methyl group whereas lithiation of the phenylpropyl congener (**11**) is less regioselective *N*-BOC-phenylpropylamine (**17**) is efficiently lithiated at the benzylic position while *N*-BOC-2-methylphenylbutylamine (**23**) undergoes lithiation of the methyl group but with low conversion The results are discussed from the general perspective of heteroatom-directed metalation Several of the lithio derivatives can be converted to heterocycles, e g , tetrahydro-3-benzazepin-2-one (**10**), hexahydro-3-benzazocin-2-one (**16**) and 3-phenylpyrrolidines (**19-22**)

Benzylic anions derived from heteroatom directed lithiations of tolyl derivatives have proven to be of exceptional utility for the preparation of a number of fused heterocycles [2] For example, we have reported that lithiation of *N*-(*tert*-butoxycarbonyl)-o-toluidine and *N*-(*tert*-butoxycarbonyl)-2-methylbenzylamine affords lithio species **1**[3] and **2**,[4] respectively, and we subsequently utilized these lithiated intermediates in the synthesis of indoles,[3] oxindoles,[3] tetrahydroisoquinolines,[4] and dihydroisoquinolones.[4] It was of further interest to study the lithiation of derivatives in which the BOC group was separated by additional methylene groups from the tolyl unit to determine both the efficiency of lithiation of the methyl group and the potential for competing side chain lithiation Reported herein are the results of a study of the lithiation of such homologs which defines some of the scope and limitations of these processes and affords synthetic routes to additional nitrogen containing heterocycles



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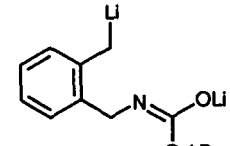
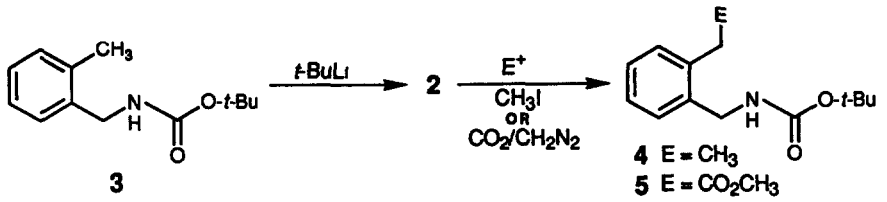


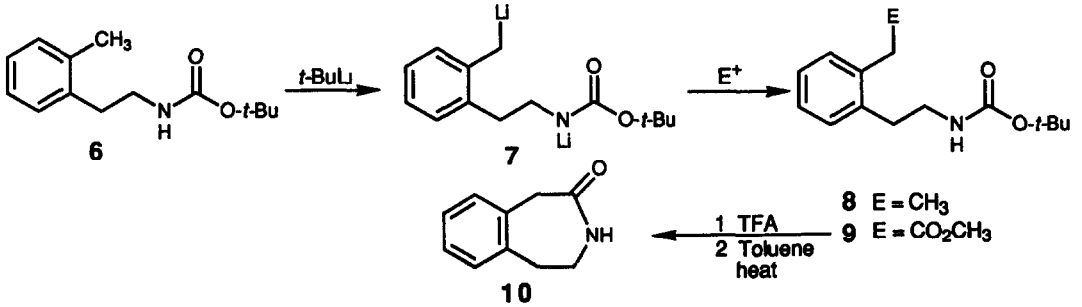
2

As previously reported,[4] treatment of BOC-2-methylbenzylamine (**3**) with strong base[5] affords dilithio species **2** For purposes of comparison with homologs of **3** (vide infra), we quenched **2** with iodomethane, which gave **4** in 80% yield, and carbon dioxide, which afforded ester **5** after esterification with diazomethane (67%) In general, quenching with iodomethane was higher yielding and furnished a more direct method for product analysis by ^{1}H NMR while carbon dioxide trapping (followed by diazomethane treatment) afforded more facile product separation and intermediates for cyclization to lactams No products derived from lithiation at alternative sites (e g., on the ring or at the benzylic methylene) were observed



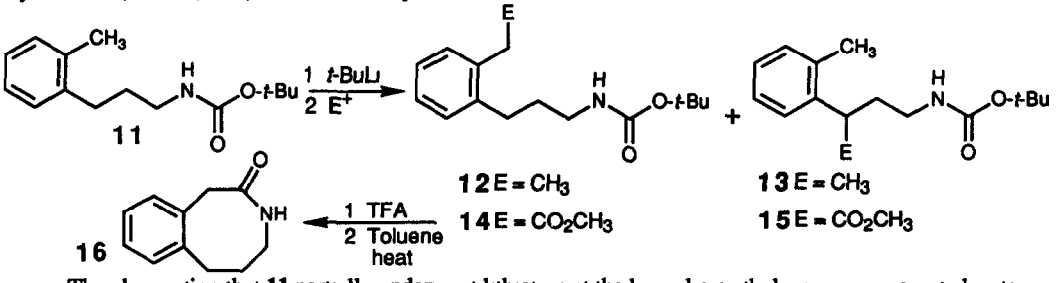
3

Under similar conditions, the BOC-phenethylamine homolog **6** underwent conversion to **7** as evidenced by the formation of **8** (80%) and **9** (67%) from iodomethane and carbon dioxide (CH_2N_2) quenches, respectively. Again there was no evidence for formation of products derived from lithiation at the benzylic methylene group. In this regard, it is of interest to note that Simig and Schlosser observed efficient benzylic lithiation of *N*-pivaloylphenethylamine with *tert*-butyllithium at -50°C[6]. The formation of derivative **9** provides a route to tetrahydro-3-benzazepin-2-ones as treatment with trifluoroacetic acid followed by heating in toluene afforded the lactam **10**.



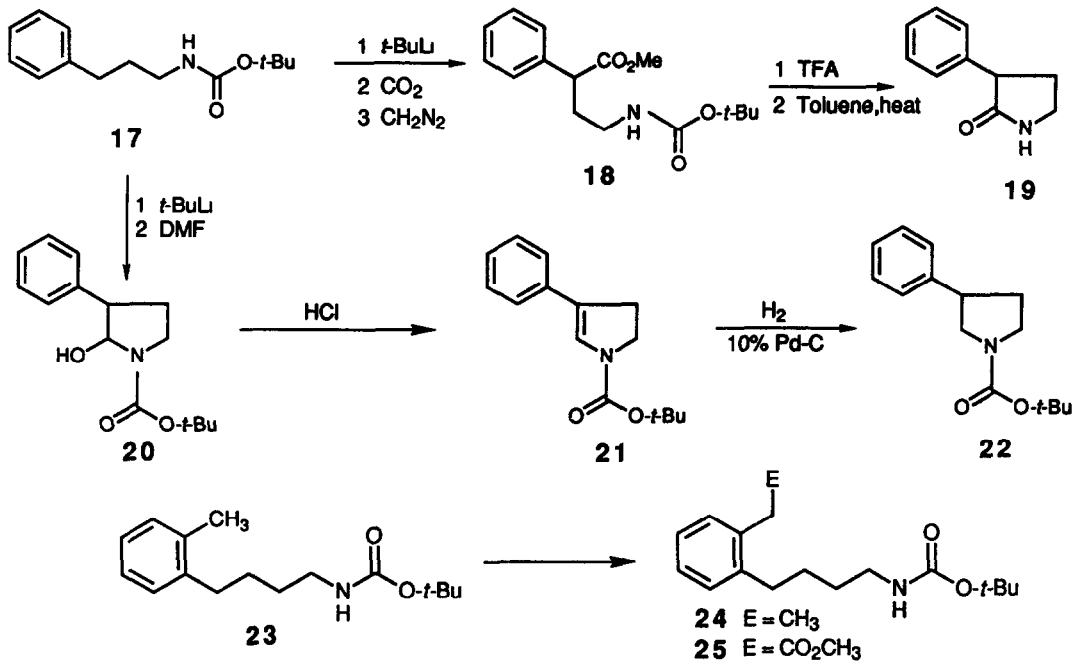
6 7 10

Extension of the *N*-BOC group to three methylenes from the tolyl moiety induced competing, albeit minor, side chain lithiation. Thus, treatment of **11** with *tert*-butyllithium at ca. -30°C. followed by iodomethane quench afforded an inseparable 4:1 mixture of products **12** and **13** (82% yield). Quench with carbon dioxide followed by esterification afforded a mixture of **14** and **15** in a similar ratio from which **14** was isolated in 45% yield by silica gel chromatography. Treatment of **14** with trifluoroacetic acid followed by cyclization (toluene, heat) afforded hexahydro-3-benzazocin-2-one **16**.



11 16

The observation that **11** partially underwent lithiation at the benzylic methylene group prompted us to investigate lithiation of *N*-BOC-3-phenylpropylamine **17**. Although the rate of dilithiation of **17** was significantly slower than the previous examples, requiring ca. 6 hours at -30°C, complete conversion to a dilithio species was achieved. Trapping with carbon dioxide, followed by esterification of the crude acid so obtained, furnished **18** in 65% yield. Removal of the BOC group from **18** (trifluoroacetic acid) followed by heating in toluene afforded 3-phenyl-2-pyrrolidinone (**19**)(90%). Condensation of the dianion from **17** with *N,N*-dimethylformamide furnished amidal **20** as a mixture of diastereomers in 73% yield. Dehydration of **20** with HCl in tetrahydrofuran gave **21** (>90%) which was hydrogenated to *N*-BOC-3-phenylpyrrolidine (**22**).



Dilithiation of **23**, in which the *N*-BOC group is extended to four methylenes from the tolyl moiety, proved to be very difficult. Treatment with *tert*-butyllithium (2.5 equivalents) for 6-8 hours at -25°C followed by trapping gave **24** and **25** in low conversion (35-40%) with the remainder being recovered starting material. Consistent with these results, *N*-BOC-4-phenylbutylamine failed to dilithiate under similar conditions as determined by >90% recovery of starting material after carbon dioxide quench.

In terms of the general concept of heteroatom-directed metalation, our results indicate that the *N*-BOC directed metalation group (DMG) can facilitate lithiation at relatively distant benzylic positions. The overall process of directed metalation is generally described as involving complexation of the alkyllithium reagent (as an aggregate) to the DMG followed by deprotonation to give the lithiated species which is generally coordinated to the DMG.[2a] For the cases presented in this paper, these concepts can be schematically described as in Figures 1 and 2. For deprotonation of an aromatic methyl group with *tert*-butyllithium, the *N*-BOC DMG operates efficiently up to, and including, the example where n=3 (Figure 1). The deprotonation is considerably less facile when n=4, presumably reflecting the increased distance of RLi from the benzylic hydrogen. For deprotonation of a benzylic methylene group (Figure 2), the limiting case is when n=2. Within these constraints, when the possibility for competition between a methyl and a methylene group exists (e g , **6**, **11**), deprotonation of the methyl group is highly favored.[7]

FIGURE 1

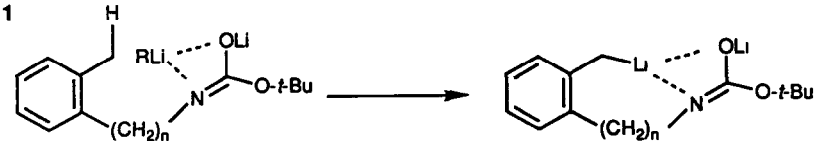
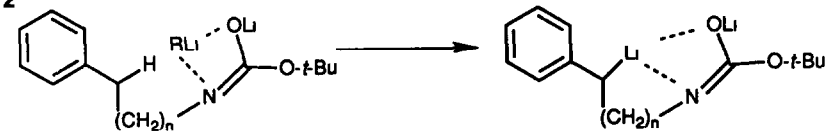


FIGURE 2



In conclusion, we have defined some of the practical limitations of benzylic lithiations directed by the *N*-BOC group From a synthetic point of view, the methodology offers potentially useful approaches to benz-fused medium ring lactams and 3-phenylpyrrolidines

Experimental

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Silica gel chromatography was performed under medium pressure with 230-400 mesh Merck Kieselgel. ^{1}H NMR spectra were measured on a Bruker WM 300 spectrometer in $CDCl_3$ solution referenced to internal tetramethylsilane. Mass spectra were recorded with an Atlaswerke CH-7 spectrometer. Infrared spectra were recorded with an IBM IR/44 Elemental analyses were performed by the Syntex Analytical Department. Tetrahydrofuran was freshly distilled from sodium-benzophenone immediately prior to use. All lithiation reactions were performed under an inert atmosphere (nitrogen or argon)

General Procedure for Lithiation-Trapping Experiments A solution of the appropriate *N*-(*tert*-butoxycarbonyl) amide (5 mmol) in tetrahydrofuran (10 mL) was cooled in an acetone-dry ice bath to ca. -60°C (internal temperature). A solution of *tert*-BuLi (8 mL of 1.5 M in pentane, 12 mmol) was added over a period of several min at such a rate as to maintain the internal temperature at ca. -40°C The resulting yellow solution was then stirred at ca. -25 to -30°C for a specified period of time: 20 min for **3**, 1.5 h for **6** and **11**; 6 h for **17**, **24**, and **27**. A CCl_4-dry ice bath was used for the longer reaction times. The solution was recooled to ca -60°C and iodomethane (0 47 ml, 7 5 mmol) or gaseous carbon dioxide (bubbled in from a lecture bottle for 30 sec) was added. The resulting reaction mixture, which often became a thick gel in the carbon dioxide reactions, was allowed to warm to ca. 0°C.

For the iodomethane trappings, workup involved addition of aqueous NH_4Cl and extraction with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4) and evaporated to afford the crude product which was purified by silica gel chromatography.

For the reactions with carbon dioxide, the reaction mixture was diluted with water, washed with EtOAc, and the aqueous layer was acidified with HCl. Extraction with CH_2Cl_2 followed by evaporation afforded the crude acid which was dissolved in ether and treated with ethereal diazomethane. Chromatography (EtOAc-hexane) of the residue obtained upon evaporation of the ether furnished the ester.

***N*-(*tert*-Butoxycarbonyl)-2-ethylbenzylamine (4).** (98%), oil, ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.51 Hz, 3H), 1 49 (s, 9H), 2.70 (q, J = 7.51 Hz, 2H),4 37 (d, J = 5.51 Hz, 2H), 4.71 (broad s, 1H, NH), 7.20 (m, 4H); IR (neat) 3348, 1701 cm^{-1}; ms (EI) m/z Anal. calcd. for $C_{14}H_{21}NO_2$. C, 71.45, H, 9.00, N, 5 95 Found. C, 71.69; H, 9.06, N, 5.98

Methyl 2-(*N*-(*tert*-butoxycarbonyl)aminomethyl)phenylacetate (5). (70%), oil, ^{1}H NMR ($CDCl_3$) δ 1 47 (s, 9H), 3 72 (s, 3H), 3.73 (s, 2H), 4 36 (d, J = 5 70 Hz, 2H), 5 0 (broad s, 1H, NH), 7 25 (m, 4H), IR (neat) 3372, 2978, 1740, 1713 cm^{-1}; ms (EI) m/z 279 (M+), 223, 222, 178, 163, 150, 146, 105, 104, 91 Anal calcd for $C_{15}H_{21}NO_4$ C, 64 49; H, 7 58; N, 5.01 Found C, 64 86, H, 7 52, N, 5.15

***N*-(*tert*-Butoxycarbonyl)-2-(2-ethylphenyl)ethylamine (8)** (80%), oil, ^{1}H NMR ($CDCl_3$) 1 24 δ (t, J = 5 74 Hz, 3H), 1 47 (s, 9H), 2 67 (q, J = 5 74 Hz, 2H), 3 80 (t, J = 5 6 Hz, 2H), 3 34 (m, 2H), 4 57 (broad s, 1H, NH), 7.15 (m, 4H), IR (film) 3400, 1700 cm^{-1}, ms (EI) m/z 249 (M+), 193, 132, 119, 105, 91 Anal. calcd. for $C_{15}H_{23}NO_2$. C, 72 25, H, 9.30, N, 5 62 Found C, 72 42, H, 9.77; N, 5 78

Methyl 2-(2-(*tert*-butoxycarbonylamino)ethyl)phenylacetate (9) (67%) m p 60-61°C (ether-hexane), ^{1}H NMR ($CDCl_3$) δ 1 43 (s, 9H), 2 84 (t, 2H, J = 7 Hz), 3 32 (m, 2H), 3 68 (s, 3H), 4 65 (broad s, 1H, NH), 7 15-7 25 (m, 4H), IR (KBr) 3380, 1737, 1688 cm^{-1} Anal calcd. for $C_{16}H_{23}NO_4$ C, 65 51, H, 7 90, N, 4.78 Found C, 65 24, H, 8.01, N, 4 40

2,3,4,5-Tetrahydro-3,1*H*-benzazepin-2-one (10) To a solution of **9** (400 mg, 1.36 mmol) in THF (10 mL) was added trifluoroacetic acid (2.5 mL) and the resulting mixture was stirred for 12 h at r.t. After concentrating the above mixture in vacuo, the residue was diluted with CH_2Cl_2 and basified with sat. Na_2CO_3 soln The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated to give a white solid This was dissolved in toluene (20 mL) and heated under reflux for 16 h. Removal of the solvent and crystallization from H_2O gave long needle-like crystals of **10** (175 mg, 57%), m.p.159-160°C); (lit.[8] m.p. 159-160°C); ^1H NMR ($CDCl_3$) δ 3.12 (dd, J = 6.32, 5.87 Hz, 2H) 3.55 (m, 2H), 3 85 (s, 2H), 6.31 (br s, 1H, NH), 7 15 (m, 4H), ms (EI) m/z 161 (M+) 132, 117, 105, 104, 91

Lithiation-iodomethane trapping of 11: 82%, oil, inseparable mixture of the regiomers **12** and **13** Integration of ^1H NMR ($CDCl_3$) signals at 1.24 (t) and 2.34 (s) for **12** and **13** respectively showed an 8 2 ratio of these isomers

Methyl 2-(3-(*N*-*tert*-butoxycarbonylamino)prop-1-yl)phenylacetate (14) and Methyl 4-(*tert*-butoxycarbonylamino)-2-(2-methylphenyl)butyrate (15) Products **14** and **15** were separated by silica gel chromatography (20% ethyl acetate-hexane). The less polar component was **15** (18%), oil; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.92 (m, 1H), 2 27 (m, 1H), 2.39 (s, 3H), 3.1 (m, 2H), 3.67 (s, 3H), 3.90 (m, 1H), 4.55 (broad s, 1H, NH), 7.15 (m, 4H), IR (neat) 3200, 1736, 1713 cm^{-1}; ms (EI) m/z 307 (M+), 251, 234, 219, 207, 175, 164, 57 Anal. calcd. for $C_{17}H_{25}NO_4$: C, 66.44; H, 8.20; N, 4.56. Found: C, 66.39, H, 8 20; N, 4.47. For **14**(45%), m.p 50-51°C; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.76(m, 2H), 2 65(m, 2H), 3.16(m, 2H), 3 65(s, 2H), 3 68(s, 3H), 4 65 (broad s, 1H, NH), 7.10-7.24 (m, 4H); IR (KBr) 3200, 1729, 1684 cm^{-1}; ms (EI) m/z 307 (M+), 251, 234, 207, 190, 175, 158, 131, 130, 117, 105, 91 Anal calcd for $C_{17}H_{25}NO_4$ C, 66 44; H, 8.20, N, 4 56; Found C, 66.39; H, 8.20, N, 4 47 For **14** (45%), m p 50-51°C; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1 76 (m, 2H), 2.65 (m, 2H), 3.16 (m, 2H), 3.65 (s, 2H), 3 68 (s, 3H), 4.65 (broad s, 1H, NH), 7.10-7.24 (m, 4H); IR (KBr) 3200, 1729, 1684 cm^{-1}, ms (EI) m/z 307 (M+), 251, 234, 207, 190, 175, 158, 131, 130, 117, 105, 91. Anal calcd. for $C_{17}H_{25}NO_4$: C, 66 44, H, 8 20, N, 4.56. Found. C, 66.30, H, 8.45; N, 4 73

1,2,3,4,5,6-Hexahydrobenzazocin-2-one (16). A solution of **14** (290 mg 0 94 mmol) and trifluoroacetic acid (2 5 mL) in THF (10 mL) was stirred for 16 h at r t. The reaction mixture was concentrated and the residue diluted with CH_2Cl_2 and made basic with sat. Na_2CO_3 soln The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 The combined CH_2Cl_2 extracts were washed with water and brine, then dried (Na_2SO_4) and solvent was removed in vacuo The residue obtained was dissolved in xylenes (20 mL) and heated under reflux for 48 h Removal of the solvent and crystallization from EtOAc gave **16** (86 mg, 52%), mp 202-206°C ^1H NMR ($CDCl_3$) δ 1 35 (m, 1H), 2 00 (m, 1H), 2 70-3 25 (m, 3H), 3 55 (m, 1H), 3 70 (s, 2H), 4 05 (m, 1H), 7 10-7 25 (m, 4H); IR (KBr) 1633 cm^{-1}, ms (EI) m/z 175 (M+), 158, 146, 132, 117, 105, 104, 91 Anal calcd. for $C_{11}H_{13}NO$ C, 75 39, H, 7 48, N, 7 99 Found· C, 75 13, H, 7 50, N, 7 95

Methyl 4-(*tert*-butoxycarbonylamino)-2-phenylbutyrate (18) (65%) oil, ^1H NMR ($CDCl_3$) δ 1 45 (s, 9H), 1 95 (m, 1H), 2 36 (m, 1H), 3.06 (m, 2H), 3 64 (t, 2H, J = 7 7 Hz), 3 68 (s, 3H), 4 56 (broad s, 1H, NH), 7 20-7 36 (m, 5H), IR (film) 3380, 1736, 1713 cm^{-1}, ms (EI) m/z 293 (M+), 237, 193, 192, 162, 161, 150 Anal calcd for $C_{16}H_{23}NO_4$ C, 65.51, H, 7.90; N, 4 78 Found C, 65.18, H, 8 05, N, 4 81

3-Phenyl-2-pyrrolidinone (19) Treatment of **18** with trifluoroacetic acid followed by cyclization in refluxing toluene as described for the preparation of **10** gave **19** (90%), m p 84-85°C (lit[9] m.p 84°C); ^1H NMR ($CDCl_3$) δ 2 20 (m, 1H), 2 58 (m, 1H), 3 42 (m, 2H), 3.65 (t, 1H, J = 9 1 Hz, H-3), 7 20-7 40 (m, 5H), 7 48 (broad s, 1H, NH)

***N*-(*tert*-Butoxycarbonyl)-2-hydroxy-3-phenylpyrrolidine (20).** Compound **17** (1.18 g, 5 mmol) was converted to the dilithio species according to the above general procedure and treated with DMF (1 mL). The reaction mixture was diluted with ether, washed with water and brine, dried (Na_2SO_4), and evaporated. Silica gel chromatography (25% ethyl acetate-hexane) afforded 0 96 g (73%) of **20** as an oil The ^1H NMR spectrum of this material displays multiple resonances due to diastereomers and *N*-BOC rotamers and therefore only selected peaks are reported: ($CDCl_3$) δ 1.52 (s, 9H), 4.16 (broad s, 1H, OH), 5.30, 5.45, 5.58 (m, 1H, sharpen to doublets with D_2O, H-2), 7.15-7.40 (m, 5H); IR (film) 3435, 1682 cm^{-1}; ms (EI), m/z 263 (M+), 207, 190, 163, 118. Anal. calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.27; H, 8.06; N, 5.24.

***N*-(*tert*-Butoxycarbonyl)-1,2-dihydro-4-phenylpyrrole (21).** A solution of **20** (350 mg, 1.33 mmol) in tetrahydrofuran (10 mL) was treated with 4 drops of conc. HCl The solution was stirred for 15 min. at room temperature. Ether was added and the mixture was washed with water and brine The ether was dried (Na_2SO_4) and evaporated to a solid residue. Silca gel chromatography (10% ethyl acetate-hexane) afforded 310 mg (95%) of **21** as a white solid; m.p. 73-74°C (hexane), ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H), 2.96 (m, 2H), 3.86 (m, 2H), 6.94 (s, 0.5 H, H-2 of one rotamer), 7.12 (s, 0.5 H, H-2 of other rotamer), 7.15-7.32 (m, 5H); IR (KBr) 1700, 1622 cm^{-1}, ms (EI) m/z 245 (M+), 190, 189, 145, 144 Anal. calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.08; H, 7.85; N, 5.57.

***N*-(*tert*-Butoxycarbonyl)-3-phenylpyrrolidine (22).** A solution of **21** (250 mg, 1 mmol) in ethanol (25 mL) was hydrogenated over 10%-Pd-C (100 mg) at 40 psi for 6 h. The catalyst was removed by filtration, and evaporation of the filtrate afforded a residue that was chromatographed on silica gel (20% ether-hexane) to give 210 mg (85%) of **22** as an oil ^1H NMR ($CDCl_3$) δ 1.49 and 1 51 (s, 9H, BOC-rotamers), 2 00 (m, 1H), 2.25 (m, 1H), 3.20-3 46 (m, 3H), 3.52-3.60 (m, 1H), 3 72-3.90 (m, 1H), 7.20-7.46 (m, 5H); IR 1697 cm^{-1}, ms (EI) m/z 247 (M+), 192, 191, 190, 174, 147, 130. Anal. calcd. for $C_{15}H_{21}NO_2$. C, 72.84; H, 8.56; N, 5.66. Found. C, 72 49; H, 8.39; N, 5.64.

Methyl 2-(4-(*tert*-butoxycarbonylamino)but-1-yl)phenylacetate (25). 38%, oil; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H), 1 56 (m, 4H), 2.63 (m, 2H), 3 15 (m, 2H), 3 68 (s, 2H), 3 71 (s, 3H), 4.55 (broad s, 1H, NH), 7.20 (m, 4H), IR (neat) 3377, 1736, 1709 cm^{-1}, ms (EI) m/z 321 (M+), 265, 248, 233, 221, 57 Anal. calcd. for $C_{18}H_{27}NO_4$: C, 67.26, H, 8 47, N, 4 26 Found C, 66 97, H, 8.27, N, 4 25.

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1 Contribution no. 859 from the Institute of Organic Chemistry.

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5. Dilithiation of **3** is efficiently obtained by treatment with either *sec-* or *tert*-butyllithium For the work reported in this paper, we utilized *tert*-butyllithium, as a number of the substrates were more difficult to lithiate.

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7 The implication is that these results (e.g , **12** **13** ratio) are determined by relative rates of deprotonation (kinetic control) and that proton transfer from initially formed anions is not involved.

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