Diastereoselectivity of polar and radical couplings in electrophilic substitutions of rigid 2-lithio-*N*-methylpyrrolidines†

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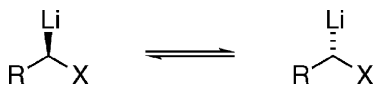
N-Methyl *trans*-fused perhydroisoindolines substituted with a tributylstannyl group in the 2-position have been prepared and used as precursors of the corresponding α-aminoorganolithiums. The steric course of the reactions of these and other conformationally rigid organolithiums with various electrophiles is summarized and compared with the steric course of the unsubstituted analogs. A mechanistic rationale for the steric course of electrophilic substitutions of these organolithiums is discussed. Pathways involving both polar electrophilic substitutions and radical couplings were observed with different electrophiles.

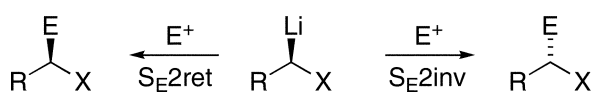
Introduction

Four recent review monographs on organolithium chemistry attest to the importance of organolithium species in organic synthesis.[1–4] Several new methods employ organolithiums in which the metal-bearing carbon atom is stereogenic and also possesses a heteroatom substituent (X in eqn (1)). Many chiral organolithium species are versatile in stereoselective synthesis due to their configurational stability and their ability to form carbon–carbon bonds, often with a high degree of stereoselectivity.[5] One of the more versatile such classes is α-aminoorganolithium compounds.[6] For example, enantiopure 'unstabilized' *N*-alkyl-2-lithiopyrrolidines and piperidines resist inversion at temperatures below −40 °C,[7] with enantiomerization barriers of 22 kcal mol^{-1} at 273 K.[8]



(1)

Stereoselectivity in electrophilic substitutions of organolithium compounds depends on the configurational stability of the carbanionic carbon as well as the mechanism of the reaction. Polar electrophilic substitutions of α-aminoorganolithiums may occur with either retention or inversion of configuration (eqn (2)).[9] The relative rates of enantiomerization and electrophilic substitution obviously affect the stereochemical outcome of the process. Other factors, such as single electron transfer (SET), may also be important in certain instances.[10] Depending on the relative redox potentials of the organolithium and the electrophile, and the rate of the competing S_E2 reaction, SET can occur to produce radicals that couple, dimerize and disproportionate. Usually, intermolecular couplings are stereorandom (eqn (3)).[10]



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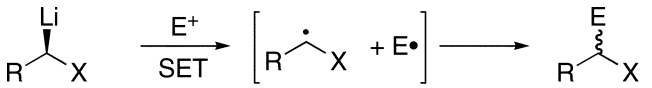
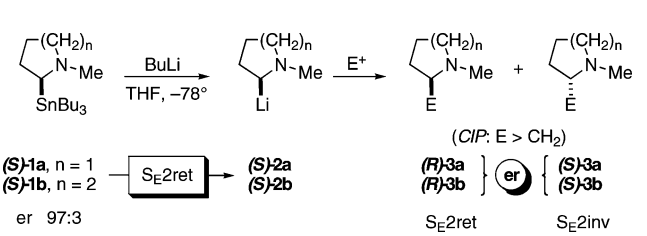


(3)

Several years ago, we studied the steric course of electrophilic substitutions of *N*-methyl-2-lithiopyrrolidines and -piperidines, which were obtained by tin–lithium exchange of the corresponding stannane (Scheme 1).[11] The scalemic stannanes **1a**,**b** were of high enantiopurity (≥97 : 3 er), and transmetallation was assumed to take place with retention of the configuration at C2, to afford organolithiums (*S*)-**2a**,**b** in enantiomeric ratio (er) similar to that of **1**. The evaluation of the configuration and er of **3a**,**b** after electrophilic quench afforded a clear picture of the steric course of the reaction. Of particular interest is the fact that both invertive ($S_E2$inv) and retentive ($S_E2$ret) substitution patterns were observed, as well as complete racemization in some cases.[11] Subsequently, we determined that the instances of complete racemization were best explained by a single electron transfer (SET) mechanism when the electrophile was easily reducible.[10] For electrophiles which underwent substitution by a polar mechanism, both invertive and retentive pathways were observed, depending on the electrophile. With carbonyl electrophiles such as carbonic acid derivatives, aldehydes and ketones, $S_E2$ret was the exclusive course; with alkyl halides, $S_E2$inv was the predominant pathway. Interestingly, with piperidines **2b**, the reaction with alkyl halides was 100% invertive, whereas with pyrrolidines **2a**, the similar reaction with the same electrophile was about 80% invertive and 20% retentive.[11] The lower stereoselectivity of the **2a** substitutions with alkyl halides was shown to *not* be the result of SET, and



Scheme 1

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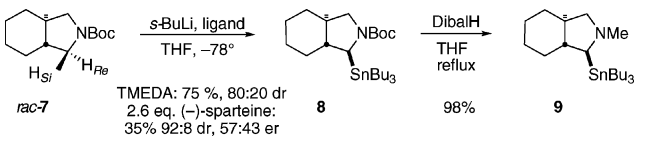
† Electronic supplementary information (ESI) available: Proton and carbon NMR spectra of **4–9** and **11a–e**, as well as GC-MS, MALDI-TOF, and HR FT-MS of **11e**. See DOI: 10.1039/b608013h

we concluded that the mechanism involved competing polar pathways.[10]

Studies such as those outlined in Scheme 1 are conceptually simple because there is only one stereocenter in stannane **1**, although the assignment of absolute configurations, and measurement of the enantiomer ratios in a large number of products **3** presented a significant challenge. Nevertheless, such studies are valuable in that they provide fundamental knowledge about the steric course of electrophilic substitutions *in the absence of any other bias*, *such as an additional stereocenter or a chiral ligand.* Such knowledge is relevant to developing methods of dynamic resolution, in which racemic organolithiums are treated first with a chiral ligand, then an electrophile, to afford enantioenriched products of electrophilic substitution.[12] Because of the variation in stereochemical outcome observed in unsubstituted heterocyclic systems, especially pyrrolidines, it is of interest to determine the stereochemical outcome in substituted lithiopyrrolidines. In this paper, we summarize our efforts in the evaluation of the steric course of electrophilic substitutions of 2-lithiopyrrolidines and 2-lithiopiperidines[13] having additional stereocenters.



Scheme 3

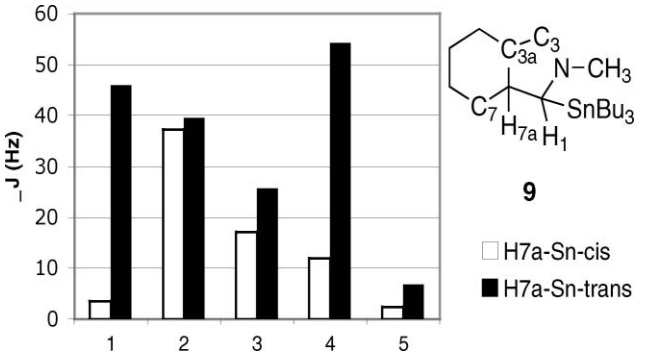


Fig. 1 Deviations between calculated and observed ^3J coupling constants in **9**: 1) Sn–C7; 2) Sn–C3a; 3) Sn–C3; 4) Sn–CH_3; 5) H1–H7a.

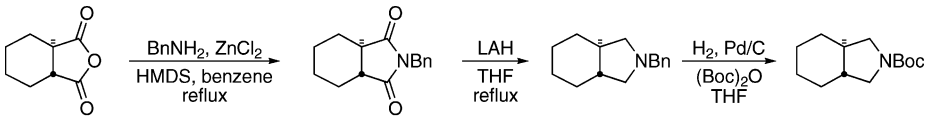
Results

Racemic, *trans*-fused perhydroisoindoline **7** was synthesized as outlined in Scheme 2. Commercially available anhydride **4** was condensed with benzyl amine, according to the procedure of Toru *et al.*,[14] to give imide **5** in 97% yield. Reduction of the imide carbonyls afforded **6** in 97% yield, and hydrogenolysis in the presence of di-*tert*-butyl dicarbonate exchanged the *N*-benzyl for an *N*-Boc in 96% yield.

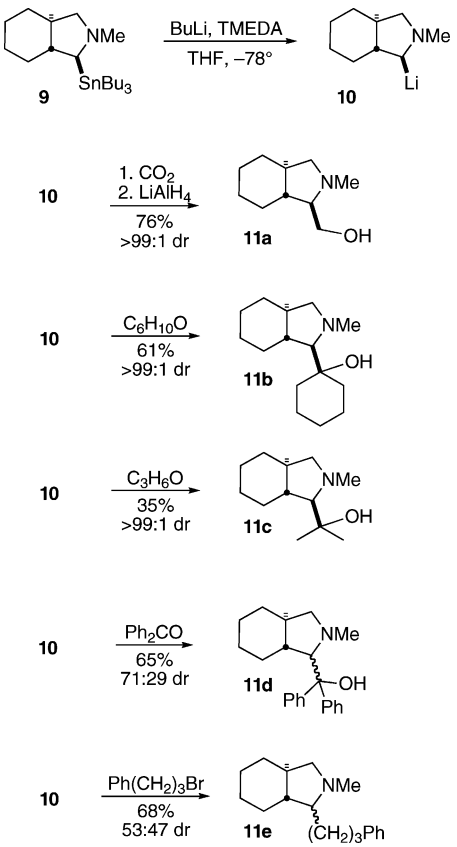
As shown in Scheme 3, *trans N*-Boc perhydroisoindoline **7** was deprotonated with *s*-butyllithium–TMEDA in ether and stannylated with tributyltin chloride to afford **8** in 75% yield and 80–90% diastereoselectivity. After chromotragraphic separation, the major diastereomer of **8** was reduced to the *N*-methyl heterocycle **9** in 98% yield. An attempt was made to achieve a kinetic resolution in the deprotonation–stannylation of racemic **7**. In the event, the yield was 35%, the diastereoselectivity was improved, but the enantioselectivity was low. Assuming that the intermediate organolithium is configurationally stable and alkylates with retention, this outcome is consistent with a higher degree of selectivity for removal of the H_{Si} proton *vs.* the H_{Re} proton in the enantiomer of **7** illustrated in Scheme 3. This proton is in a pseudoequatorial orientation in the 5-membered ring. The low enantiomer ratio indicates that excess *s*-BuLi·sparteine shows little preference for removal the pseudoequatorial H_{Si} proton of **7** *vs.* removal of the pseudoequatorial H_{Re} proton of *ent*-**7**.

The relative configuration of the major diastereomer of **9** was evaluated by measurement of the ^3J ^{1}H–^{1}H coupling (H-1/H-7a) and the ^3J ^{13}C–^{119}Sn (CH_3, C-3, C-3a, and C-6), and comparison with models (Fig. 1). Molecular mechanics calculations, in which the tributyltin was simulated by a *tert*-butyl group with the C–Sn bond fixed at 2.0 Å, provided approximate values of the relevant torsion angles in which H-7a and the Sn are either *cis* or *trans.* Coupling constants were calculated from these torsions using the Karplus relationships.[15–18] Fig. 1 shows the deviations of the calculated values from the observed NMR data. The best fit is for the diastereomer of **9** illustrated in Scheme 3, in which H-7a and the tin are *cis.* We attempted to confirm this assignment by X-ray crystallographic analysis of the methylated ammonium hexafluorophosphate salt of **9**. Due to some possible twinning and disorder in the butyl groups, the diffraction data were not adequate for a complete refinement, but the relative configuration in the partially refined structure was consistent with this assignment.

Transmetalation of stannane **9** afforded organolithium **10**, which was treated with several electrophiles as shown in Scheme 4. Addition of carbon dioxide to **10** followed by reduction gave alcohol **11a** (76%) as a single diastereomer. The relative configuration of **11a** was established by X-ray crystallography, and indicates overall retentive substitution from **9** to **11a**, consistent with the retentive reaction of **1a**,**b** with this electrophile. Addition of cyclohexanone and acetone to **10** yielded **11b** (61%) and **11c** (35%), respectively, each as a single diastereomer with retention of configuration. In all three cases (**11a–c**), the relative configuration was confirmed by evaluation of the H1–H7a ^3J coupling constant using the Karplus equation.[17] Addition of benzophenone to **10** afforded a 65% yield of **11d** as a 71 : 29 ratio of diastereomers. As a representative alkyl halide, 3-phenyl-1-bromopropane was chosen. The two step sequence of transmetalation and electrophilic quench proceeded in 68% yield to give **11e** as a 53 : 47 mixture of diastereomers, as determined by GC and ^{1}H NMR.



Scheme 2



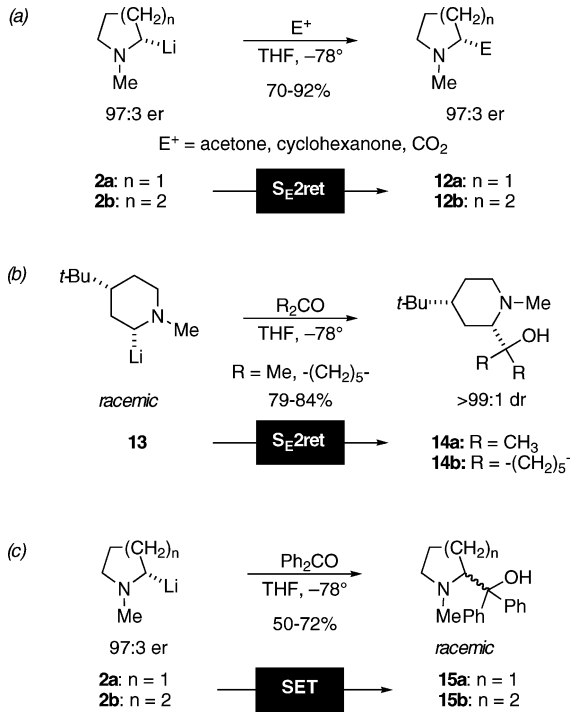
Scheme 4

Discussion

The solution structure of *N*-alkyl-2-lithiopyrrolidines can be quite complex. The solution structure of *N*-methyl-2-lithiopyrrolidine **2a** (Scheme 1) was shown to be a homochiral dimer using ^{13}C and ^{6}Li labeling.[19] However, subsequent work with other enantioenriched and racemic *N*-alkyl-2-lithiopyrrolidines shows the presence of several equilibrating species, including monomer and more than one dimer.[20] Thus lithiopyrrolidines have a number of possible solution structures. Since we do not know which of the solution species are reactive, we can only determine the stereochemical outcome of the reaction, and try to draw conclusions about mechanism as best we can. There are two electrophilic substitutions in the conversion of organostannane to product; we assume that the tin–lithium exchange reaction in these systems is stereoretentive. For simplicity, the organolithiums are drawn as monomers, and any possible bridging of lithium from carbon to nitrogen,[19] is omitted.

Carbonyl electrophiles

Substitution of carbon dioxide, cyclohexanone or acetone for lithium in **10** affords **11a–c** with >99% retention of configuration at the metal-bearing carbon (Scheme 4). The steric course of the reaction of **10** with these electrophiles is the same as that previously observed for unsubstituted pyrrolidines and piperidines **2a**,**b**, which give **12a**,**b** with retention (Scheme 5a),[11] and for substituted piperidine **13**, which gives **14a**,**b** with retention (Scheme 5b).[13] In the case of **10** and **13**, the relevant issue is diastereoselectivity, whereas with **2a**,**b**, it is enantioselectivity. All of these results are



Scheme 5

consistent with a polar process, probably occurring through a transition state in which the carbonyl oxygen coordinates to the lithium, prior to reaction with the electrophile.

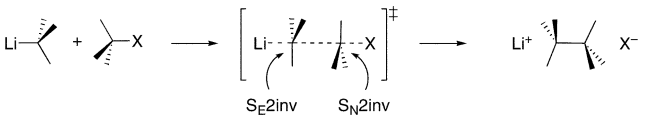
In electrophilic substitutions, benzophenone behaves differently from aliphatic ketones or benzaldehyde. Electrophilic substitution for lithium in **2a** and **2b** is stereorandom, affording racemic **15a**,**b** (Scheme 5c).[11] Electron transfer from the carbanionic carbon to the benzophenone affords a heterocyclic radical and the blue benzophenone ketyl, which can be observed visually and by EPR in the reaction mixture. Although observation of the ketyl does not place it on the reaction coordinate, by testing and eliminating other possible mechanistic pathways, we concluded that the mechanism of the coupling is *via* single electron transfer (SET).[10] Interestingly, the heterocyclic radical and the ketyl couple in remarkably high yield. When lithiopyrrolidine **10** is allowed to react with benzophenone, the reaction mixture turns blue and the substitution product **11d** is obtained in 65% yield as a 71 : 29 mixture of diastereomers. Presumably, the mechanism of this reaction is also SET, and the diastereoselectivity is due to inherent diastereofacial bias in the radical coupling.

Alkyl halide electrophiles

When **10** was allowed to react with 1-bromo-3-phenyl propane, the substitution product **11e** was a 53 : 47 mixture of diastereomers (Scheme 4). Is the low diastereoselectivity due to SET? By comparison, when unsubstituted lithiopyrrolidine **2a**, having an er of 97 : 3, was allowed to react with 1-bromo-3-phenylpropane, the substitution product **3a** had a 76 : 24 er; unsubstituted lithiopiperidine **2b** of ≥99 : 1 er afforded **3b** having 99 : 1 er. In both cases, the major enantiomer was that of inversion.[11] Radical processes due to SET were ruled out in the case of **2a** by using hexenyl bromide as the electrophile: substitution products were

obtained with similar er, but the products of radical reactions were observed in no more than trace quantities. To probe the possibility of radical processes in the reaction of **10** with alkyl halides, **10** was allowed to react with hexenyl bromide, affording a mixture of products **16–20** which were characterized by GC-MS, as shown in Scheme 6. Ten percent of the product mixture were the products of disproportionation, **16** and **17**. Two coupling products were formed, **18** and **19**, comprising 53% and 16% of the product mixture, respectively. Lastly, 21% of the product mixture consisted of four dimer diastereomers **20**. These products, and the near 50 : 50 diastereomer ratios of **18** and **19**, are clear evidence of SET, as shown by the mechanism in Scheme 6. Single electron transfer from **10** to hexenyl bromide, accompanied by loss of LiBr, affords the radicals **21** and **22**. The former partly disproportionates to give **16** and **17**; cyclization of the latter gives **23**. Coupling of **21** with **22** gives **18**, while coupling of **21** with **23** gives **19**. Dimerization of **21** gives four diastereomers of **20** of unknown relative configuration. Note that there are seven possible diastereomeric dimers of **21**: homochiral radical pairs can dimerize to produce four diastereomers of **20**, and heterochiral radical pairs can dimerize to make one racemate and two *meso* compounds, for a total of seven diastereomeric racemates. If the GC resolved all the diastereomers present, it is interesting to speculate on the presence of only four. Lithiopyrrolidine **2a** is a homochiral dimer, even when racemic.[19] One explanation could be that the homochiral dimeric aggregate of organolithium **10** is oxidized to a homochiral radical pair that dimerizes before leaving the solvent cage. Since we know[20] that 2-lithiopyrrolidines can form several aggregate types in solution, it may be that we are seeing differing reactivities for each aggregate in solution, each occurring within its own solvent cage, such as homochiral radical pairs dimerizing while heterochiral radical pairs disproportionate, *etc.* It is well established that pentamethyldiethylenetriamine (PMDTA) can act as a tridentate ligand to lithium,[21–23] so we repeated the experiment, replacing TMEDA with PMDTA. The results were similar, with a significant increase in the yield of **18**, with decreases in amount of **19** and dimer **20** (Scheme 6). This is consistent with a different reactivity profile for different organolithium aggregates.

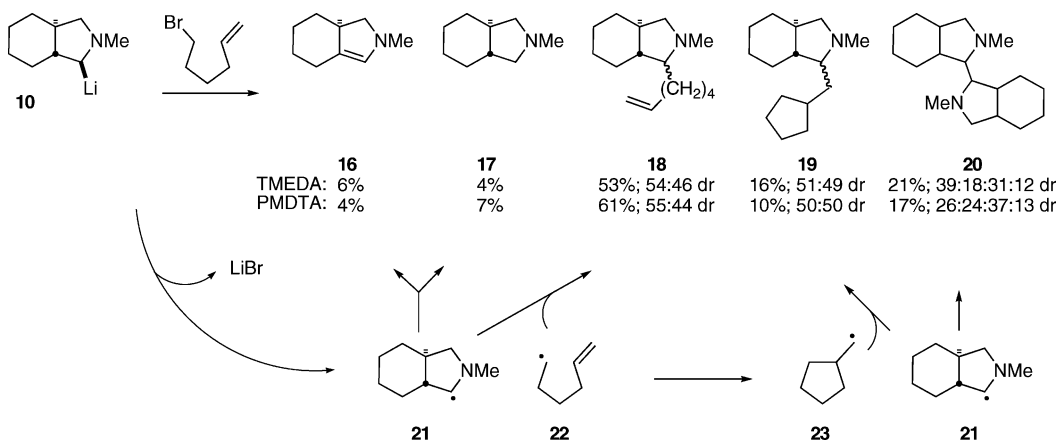
When does SET rear its ugly head? Obviously, when it is the lowest energy reaction manifold. One common circumstance is when the electrophile is easily reduced to a radical anion. With otherwise unsubstituted *N*-methyl 2-lithiopyrrolidines and 2-lithiopiperidines, this happens with electrophiles such as benzophenone (Scheme 5c), benzyl bromide, and α-bromoacetate esters.[10] Another circumstance can occur when polar processes are slowed by steric effects, such that the rate of SET becomes competitive. An invertive electrophilic substitution with an alkyl halide is a sterically demanding reaction, as it requires simultaneous inversion at two sp^3 carbons (eqn (4)). The alkyl halide electrophile must present the face opposite the leaving group to the nucleophile, while the organolithium nucleophile must present the face opposite the lithium to the electrophile. It would not take much steric interference to obstruct the two reactants from such an approach. When it is obstructed, SET can become competitive. It is useful to compare several examples to illustrate this point.



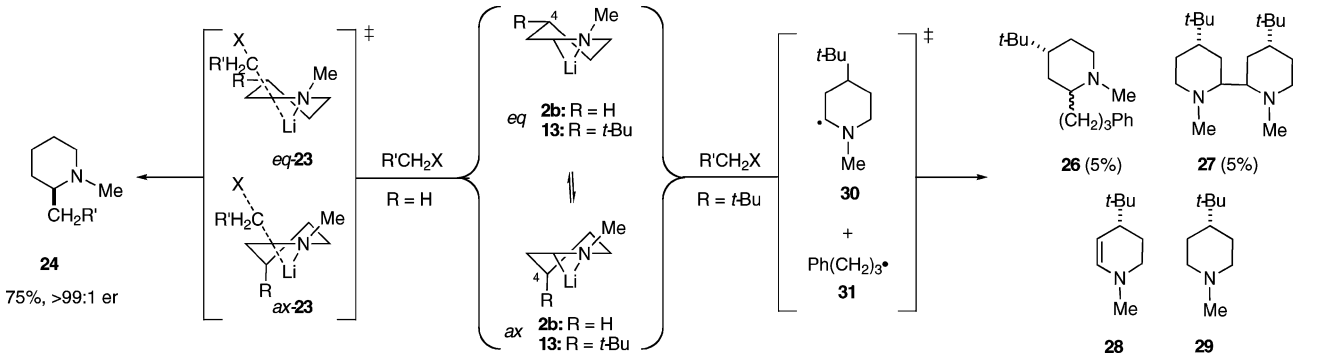
(4)

The simplest and most well defined α-aminoorganolithium solution structure is that of *N*-methyl-2-lithiopiperidine, **2b** in THF. Using ^{13}C, ^{15}N, and ^{6}Li labeling, the solution structure was determined to be monomeric, with lithium in contact with both carbon and nitrogen (R = H, Scheme 7).[19] This 3-membered ring forces the piperidine into the half-chair conformations *eq*-**2b** and *ax*-**2b**. When the piperidine ring is unsubstituted, it is likely that both are populated; when R = *tert*-butyl, as in **13**, only the *eq*-**13** conformer is energetically available. These two lithiopiperidines follow very different reaction manifolds, as shown in Scheme 7.

With **2b**, the steric course is 100% invertive, producing **24** in 75% yield.[11] It is apparent that transition structure *ax*-**23** is the less crowded of the two, since an interaction with the axial proton at C4 is avoided. With **13**, an entirely different outcome is observed.[13] Substitution product **26** was isolated in only 5% yield as a mixture of diastereomers, along with 5% yield of a dimer **27** (a single diastereomer of unknown configuration), along with **28** and **29**, the products of radical disproportionation. These four products are consistent with SET oxidation of organolithium **13**, accompanied by loss of LiBr, to radicals **30** and **31**. Examination of the transition structures **23** in Scheme 7 suggests a reasonable explanation for



Scheme 6



Scheme 7

the intervention of SET in place of invertive substitution: TS *ax*-**23** is the preferred substitution route because of less steric crowding between the electrophile and position 4 of the piperidine in TS *eq*-**23**. In **13**, the *tert*-butyl precludes population of conformer *ax*-**13** and also transition structure *ax*-**23**. Since in piperidines, the preferred steric course is invertive substitution, and since this route is precluded by the necessity of populating a boat conformation, the reaction follows the SET path.

Conclusion

Electrophilic substitutions of 2-lithio-*N*-methylpyrrolidines have been shown to proceed in good yields with carbonyl electrophiles, with retention of configuration at the metal-bearing carbon. With alkyl halides, favored invertive substitution is less facile due to steric crowding in a transition state that requires two back-to-back inversions. In these cases, single electron transfer occurs, and products of radical couplings and disproportionations are observed. With an easily reduced electrophile such as benzophenone, single electron transfer is probably the primary reaction manifold. Comparison of these trends in 2-lithio-*N*-methylpyrrolidines with previously observed trends in 2-lithio-*N*-methylpiperidines shows that the two ring systems react similarly with carbonyl electrophiles and with electrophiles that are easily reduced; with alkyl halides, some variability in reactivity patterns is apparent, most probably due to steric crowding in some cases.

Experimental

trans-2-Benzylhexahydroisoindole-1,3-dione (5)

To a suspension of *trans*-1,2-cyclohexanedicarboxylic anhydride (5.00 g, 32.4 mmol) in 100 mL benzene were added 4.90 g (36.0 mmol) $ZnCl_2$ powder at 0 °C. To this mixture were added 4.3 mL (39.2 mmol) benzylamine in 60 mL benzene followed by 10.2 mL (48.6 mmol) of 1,1,1,3,3,3-hexamethyldisilazane (HMDS). The ice bath was removed and the system was refluxed overnight. The resulting milky white reaction mixture was cooled to RT then diluted with 50 mL EtOAc followed by 60 mL 0.5 M HCl. The aqueous layer was washed with 3 × 25 mL EtOAc. The resulting organic layer was washed with 3 × 25 mL saturated $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 7.61 g (97% yield) white crystalline solid. Mp 89–91 °C; ^{1}H NMR ($CDCl_3$): δ 7.2–7.4 (m, 5H), 4.61 (Bn–CH_2, ABq, 2H, J = 14.4 Hz), 2.26–2.31 (m, 4H), 1.93 (d, 2H, J = 8.7 Hz), 1.25–1.44 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 25.18 (CH_2), 25.76 (CH_2), 41.80 (CH_2), 47.67 (CH), 127.93 (CH), 128.77 (CH), 128.85 (CH), 136.47 (C-benzyl), 176.72 (C-carbonyl). MS(EI): 243.2. Anal. calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04. Found: C, 73.91; H, 7.20%.

trans-2-Benzyloctahydroisoindole (6)

To a suspension of 3.00 g (79.1 mmol) $LiAlH_4$ in 200 mL THF at 0 °C were added 7.61 g (31.3 mmol) of **5** in 100 mL THF drop-wise *via* an addition funnel over 30 min. After a color change from grey to purple, the system was refluxed for 18 h. The mixture was cooled to −78 °C, diluted with 100 mL Et_2O, and then slowly quenched sequentially with 10 mL deionized H_2O, 15 mL 10% NaOH, and 20 mL deionized H_2O. The grey mixture was warmed to RT and stirred for 3 hours. The resulting white/grey solids were filtered and washed with Et_2O. The organic layer was dried with $MgSO_4$ and concentrated to give 6.50 g (30.2 mmol, 97% yield) of light yellow oil that was used without further purification. ^{1}H NMR ($CDCl_3$): δ 7.2–7.4 (m, 5H), 3.77 (Bn–CH_2, ABq, 2H, J = 13.2 Hz), 2.86 (ABq, 2H, J = 6.6 Hz), 2.44 (ABq, 2H, J = 9.3 Hz), 1.7–1.9 (m, 4H), 1.5 (dd, 2H, J = 6.6, 9.3 Hz), 1.2–1.3 (m, 2H), 1–1.1 (m, 2H). ^{13}C ($CDCl_3$): δ 26.3 (CH_2), 29.4 (CH_2), 45.2 (CH), 58.4 (CH_2), 62.0 (CH_2), 126.8 (CH), 128.3 (CH), 128.8 (CH), 140.3 (C). MS(EI): 215. Anal. calcd for $C_{15}H_{21}N$: C, 83.67; H, 9.83. Found: C, 83.36; H, 9.93%.

trans-Octahydroisoindole-2-carboxylic acid *tert*-butyl ester (7)

To a suspension of 10% Pd/C (1.00 g) in 500 mL THF were added 6.52 g (30.3 mmol) of **6** at −78 °C. 6.60 g (30.2 mmol) di-*tert*-butyl dicarbonate in 50 mL THF were slowly added to the reaction flask. The system was evacuated and purged with H_2 5 times. The reaction was monitored by NMR and was complete after two days. After filtration of the Pd/C, drying over $MgSO_4$, filtration and concentration, 7.53 g of a crude brown oil were obtained. Purification by column chromatography 5% EtOAc–hexanes in silica gave 6.62 g (96%) of a clear oil. ^{1}H NMR (C_6D_6): 3.65 (ABq, 1H, J = 6.6 Hz), 3.39 (ABq, 1H, J = 6.6 Hz), 2.76 (t, 1H, J = 10.2 Hz), 2.67 (t, 1H, J = 10.2 Hz), 1.54 (s, 9H), 1.46–1.53 (m, 4H), 0.85–1.1 (m, 4H), 0.60–0.80 (m, 2H). ^{13}C NMR (C_6D_6): 26.23 (3-CH_2's), 29.0 (CH_2), 29.1 (3-CH_3's), 44.26 (CH), 45.0 (CH), 51.76 (CH_2), 52.0 (CH_2), 78.6 (C-*t*-Bu), 154.7 (C-carbonyl). MS(EI): 225. Anal. calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29. Found: C, 69.54; H, 10.41%.

(1*S*,3a*R*,7a*R*)-*tert*-Butyl 1-(tributylstannyl)-hexahydro-1*H*-isoindole-2-(3*H*)-carboxylate (8)

To an Ar purged oven dry 100 mL round bottom flask, were added 3.50 mL TMEDA in 20 mL dry Et_2O and this was cooled to −78 °C. After 30 min, 16.50 mL *s*-BuLi were slowly added. After 30 min, 2.00 g **7** in 10 mL dry Et_2O were slowly added to the foggy yellow reaction mixture. After 3 h, 8.00 mL tributyltin chloride was slowly added to the dark orange suspension. The resulting yellow mixture was stirred overnight as the mixture warmed to room temperature. The reaction was quenched with 20 mL water and the aqueous layer was washed with 3 × 20 mL EtOAc. The combined organic layers were washed with 20 mL sat. NH_4Cl, dried over $MgSO_4$, filtered and concentrated to a yellow oil. Purification by column chromatography on basic alumina eluted with 0.5% EtOAc–hexanes gave 3.49 g (6.7 mmol, 75% yield) of a clear oil. ^{1}H NMR (C_6D_6): 3.56 (ABq, 1H, J = 7.2 Hz), 3.0 (d, 1H, J = 12 Hz), 2.7 (t, 1H, J = 10.2 Hz), 1.9 (dd, 1H, J = 2.1, 10.2 Hz), 1.4–1.8 (m, 26H), 1.1–1.3 (m, 2H), 0.82–1.2 (t, 9H, J = 7.5 Hz), 0.75–0.95 (m, 8H). ^{13}C NMR (C_6D_6): 11.32 (CH_2, J = 160.6 Hz, 153.8 Hz), 14.44 (CH_3), 26.52 (CH_2), 26.62 (CH_2), 28.52 (CH_2, J = 27.9), 29.09 (CH_3), 30.17 (2-CH_2's, J = 9.8), 30.18 (CH_2), 47.73 (CH, J = 20.0 Hz), 49.97 (CH, J = 4.6 Hz), 52.59 (CH_2, J = 5.2 Hz), 53.27 (CH, J = 196.0 Hz, 187.3 Hz), 78.78 (C-*t*-Bu), 154.95 (C-carbonyl). MS: (ESI/MNa) 538. Anal. calcd for $C_{25}H_{49}NO_2Sn$: C, 58.38; H, 9.60. Found: C, 58.64; H, 9.77%.

(1*S*,3a*R*,7a*R*)-1-(Tributylstannyl)-octahydro-2-methyl-1*H*-isoindole (9)

To an Ar purged, oven dried flask were added 0.200 g (0.388 mmol) of (**8**) in 5 mL dry THF. To this mixture were slowly added 0.50 mL (2.8 mmol) DIBAL-H at room temperature. After 2 days at room temperature, the mixture was cooled to 0 °C and diluted with 5 mL dry Et_2O followed by careful addition of 1 mL MeOH and 5 mL H_2O and the clear solution was stirred until a white fluffy precipitate had settled. The contents were filtered and the solids washed with 20 mL Et_2O. The resulting organic layer was dried over $MgSO_4$, filtered and concentrated to a clear oil (0.16 g, 98%) that required no further purification. ^{1}H NMR (C_6D_6): 2.81 (ABq, 1H, J = 9.9 Hz), 2.49 (ABq, 1H, J = 9.9), 2.44 (s, 3H), 2.30 (d, 1H, J = 11.4), 1.93 (m, 1H), 1.5–1.8 (m, 9H), 1.44 (m, 6H), 1.1–1.3 (m, 4H), 1.05 (m, 6H), 0.97 (t, 11H, J = 7.5 Hz). ^{13}C NMR (C_6D_6): 65.6 (t, CH, J = 230.3, 219.4 Hz), 61.8 (t, CH_2, J = 23.4 Hz), 52.3 (CH), 47.1 (t, CH, J = 22.6 Hz), 45.7 (CH_3), 30.4 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 28.4 (t, CH_2, J = 26.4), 27.11 (CH_2), 27.09 (CH_2), 14.4 (CH_3), 9.58 (t, CH_2), J = 147.8, 141.8 Hz). MS (ESI/MH+): 430.2. Anal. calcd for $C_{21}H_{43}NSn$: C, 58.89; H, 10.12. Found: C, 58.68; H, 9.91%.

General procedure for transmetalation and electrophilic substitution

To a solution of stannane (**9**) under N_2 or Ar in THF (0.1 M) at −78 °C were added TMEDA (1.3 equiv.) and *n*-BuLi (1.3 equiv. of 2.4 M in hexanes). After 20 min the electrophile was added and the reaction was stirred for 1 h. The reaction was quenched at −78 °C with 2 M HCl, and extracted with ether three times to remove neutral components. The aqueous layer was basified with powdered Na_2CO_3 and extracted with ether four times. The combined second extraction ether layers were dried with Na_2CO_3, filtered and concentrated at reduced pressure.

[(3a*R*,7a*R*)-Octahydro-2-methyl-1*H*-isoindol-1-yl]methanol (11a)

Prepared from (**9**) and CO_2 by the general procedure. Upon workup with saturated Na_2CO_3 a white solid had formed. This Na salt was then suspended in THF and cooled to 0 °C. LAH was added in one portion to the THF suspension and the reaction mixture was refluxed overnight. The solution was then cooled to 0 °C and diluted with ether. The reaction was quenched with water and stirred until solids had formed. The solids were filtered and the organic layer dried with Na_2CO_3, filtered and concentrated to a yellow oil (78% yield). After purification by radial chromatography with 10% MeOH–CH_2Cl_2 as the eluent, the product was isolated as a clear oil. ^{1}H NMR ($CDCl_3$): 0.98–1.07 (2H, m), 1.16–1.24 (2H, m), 1.37–1.54 (2H, m), 1.73–1.82 (4H, m), 2.18 (1H, ddd, J = 2.4, 3.3, 9.7), 2.39 (3H, s), 2.60 (1H, dd, J = 10.5, 8.1), 2.77 (1H, t, J = 10.5), 3.47 (1H, dd, J = 2.4, 11.1), 3.55 (1H, s, OH), 3.58 (1H, dd, J = 11.1, 3.3). ^{13}C NMR ($CDCl_3$): 25.9 (CH_2), 26.1 (CH_2), 28.8 (CH_2), 29.3 (CH_2), 42.7 (CH_3), 43.5 (CH), 46.3 (CH), 59.1 (CH_2), 60.2 (CH_2), 72.6 (CH). MS (CI, MH+): 170.

In order to establish the relative configuration, **11a** was converted to its methyliodide salt for X-ray analysis.‡ Crystals suitable for X-ray analysis were grown from the methyliodide salt through vapor diffusion with dichloromethane and hexanes. Data were collected at −100 °C for the colorless needle like crystals which ordered in the $P2_12_12_1$ (#19) space group with Z = 4. These crystals are thermally stable to air and temperature. 18 861 reflections were measured with 3087 independent reflections R_{int} = 0.037. Linear absorption μ = 2.367 mm^{-1}. Atoms were refined anisotropically in the respective space group to give a final $R1$ value of 5.46 from 2593 unique reflections $I > 2\sigma(I)$ and final w$R2$ value of 0.1033 for all data. The chemical formula is $C_{11}H_{22}NOI$. Formula weight is M_r = 311.21. Crystal system is orthorhombic with unit cell dimensions: a = 7.1485(11), b = 13.160(2), c = 14.239(2) Å. Unit cell volume is 1339.5(4) Å^3. As shown in Fig. 2, the reaction to **11a** gives retention of configuration at the lithium bearing carbon.

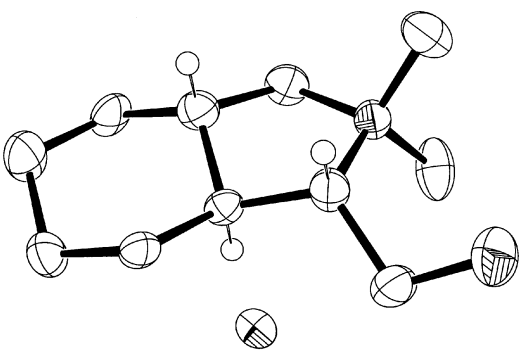


Fig. 2 ORTEP of methyliodide salt of **11a**. Ellipsoids shown at the 50% level.

‡ CCDC reference number 610644. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b608013h

[(3a*R*,7a*R*)-Octahydro-2-methyl-1*H*-isoindol-1-yl]cyclohexanol (11b)

Prepared from (**9**) and cyclohexanone by the general procedure. A colorless oil was obtained (61%) without need for further purification. ^{1}H NMR ($CDCl_3$): 1.0–1.8 (19H, m), 2.0 (1H, m), 2.1 (1H, d, $J = 8.7$ Hz), 2.5 (3H, s), 2.6 (2H, m), 3.3 (1H, s). ^{13}C NMR ($CDCl_3$): 22.4 (CH_2), 22.4 (CH_2), 25.9 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 28.8 (CH_2), 32.8 (CH_2), 33.7 (CH_2), 38.4 (CH_2), 43.8 (CH), 47.3 (CH), 48.6 (CH_3), 61.8 (CH_2), 72.6 (C), 78.6 (CH). MS (CI/MH+): 238. Anal. calcd for $C_{15}H_{27}NO$: C, 75.9; H, 11.46. Found: C, 75.89; H, 11.57%.

[(1s*,3a*I,7a*R**)-2-methyloctahydroisoindol-1-yl]propan-2-ol (11c)**

Prepared from (**9**) and acetone by the general procedure. A colorless oil was obtained (35%) without need for further purification. ^{1}H NMR ($CDCl_3$): 0.5–1.2 (4H, m), 1.1 (3H, s), 1.2 (3H, s), 1.3–1.4 (1H, m), 1.4–1.6 (1H, m), 1.7–1.8 (3H, m), 1.9–2.0 (1H, m), 2.03 (1H, d, $J = 9$ Hz), 2.48 (3H, s), 2.55 (2H, d, $J = 9$), 3.4 (1H, s). ^{13}C NMR ($CDCl_3$): 25.4 (CH_3), 25.8 (CH_2), 26.5 (CH_2), 28.7 (CH_2), 30.1 (CH_3), 32.5 (CH_2), 43.8 (CH), 48.2 (CH), 48.4 (CH_3), 61.7 (CH_2), 71.7 (C), 79.9 (CH). MS (CI/MH+): 198. Anal. calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75. Found: C, 72.91; H, 11.85%.

[(3a*R*,7a*R*)-octahydro-2-methyl-1*H*-isoindol-1-yl]diphenylmethanol (11d)

Prepared from (**9**) and benzophenone by the general procedure to give a yellow oil (65%). After purification by radial chromatography on silica gel with CH_2Cl_2 as eluent, the major diastereomer was isolated as a white crystalline solid. MP ≈ 110–113 °C. ^{1}H NMR ($CDCl_3$): 0.1–1.8 (10H, m), 2.1 (3H, s), 2.6 (1H, dd, $J =$ 10.8, 6.6), 2.8 (1H, t, $J = 10.8$), 3.3 (1H, d, $J = 9$), 5.5 (1H, s), 7.1 (1H, m), 7.2 (3H, m), 7.3 (2H, m), 7.5 (2H, m), 7.7 (2H, m). ^{13}C NMR ($CDCl_3$): 25.7 (CH_2), 26.3 (CH_2), 29.0 (CH_2), 30.9 (CH_2), 43.9 (CH), 45.7 (CH_3), 48.3 (CH), 61.9 (CH_2), 76.5 (C), 78.1 (CH), 126.4 (CH), 126.6 (CH), 126.6 (CH), 127.0 (CH), 127.9 (CH), 128.0 (CH), 144.3 (C), 148.2 (C). MS (CI/MH+): 322. Anal. calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 81.89; H, 8.55%.

(3a*R*,7a*R*)-Octahydro-2-methyl-1-(3-phenylpropyl)-1*H*-isoindole (11e)

Prepared from **9** and 3-bromo-1-phenylpropane by the general procedure to give a yellow oil (58%). After purification by radial chromatography with MeOH–CH_2Cl_2–NH_4OH 4 : 95 : 1, the major isomer was isolated as a clear oil. ^{1}H NMR ($CDCl_3$): 0.9–1.9 (14H, m), 2.0 (1H, dd, $J = 8.4$, 10.8), 2.5 (3H, s), 2.5–2.8 (3H, m), 3.2 (1H, dd, $J = 5.1$, 8.4), 7.1–7.3 (5H, m). ^{13}C NMR ($CDCl_3$): 25.8 (CH_2), 26.6 (CH_2), 27.0 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 33.5 (CH_2), 36.7 (CH_2), 43.1 (CH), 44.4 (CH_3), 48.1 (CH), 62.8 (CH_2), 67.9 (CH), 125.8 (CH), 128.4 (2-CH), 128.7 (2-CH), 143.0 (C). MS (CI/MH+): 258. HRMS: calcd: 257.2144. Found (MH+): 258.2200. Anal. calcd for $C_{18}H_{27}N{\cdot}0.25H_2O$: C, 82.54; H, 10.58. Found: C, 82.58; H, 10.63%. The trace of water could not be removed by repeated attempts at drying the sample. Multiple attempts at combustion analysis were made. All data was consistent between the analyses. Capillary GC of the samples shows only one sharp peak, indicating that the compound is pure. See supporting information for HRMS and GCMS data.†

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