The Steric Course of S_E2 Reactions of Unstabilized α-Aminoorganolithiums: Distinguishing between SET and Polar Mechanisms

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Abstract: The competing mechanisms that determine the steric course of electrophilic aliphatic substitution reactions (S_E2) of configurationally stable, unstabilized α-aminoorganolithiums are compared. The steric course of the reaction of lithiated pyrrolidines and piperidines with electrophiles is variable, such as when comparisons are made between two electrophiles and a single organolithium, or between two organolithiums and a single electrophile. The possible pathways considered are single electron transfer (SET) and competing polar substitutions ($S_E2$ret vs $S_E2$inv). Catalysis of organolithium racemization by the electrophile was eliminated as a possible source of racemic products. When the products are completely racemic, our evidence suggests that SET is the most likely mechanism; when polar pathways are operative, stereoselectivities vary from 75 to 100%, and may be invertive or retentive at the carbanionic carbon, depending on the electrophile.

Functionalized organolithiums such as those having an oxygen or nitrogen on the metal-bearing carbon continue to grow in importance as reactivity in electrophilic substitutions is explored (see refs 1−14 for reviews). One often puzzling aspect of such studies is the steric course of the reaction, which may proceed with retention or inversion, depending on the electrophile (the suffixes "inv" and "ret" may be used to distinguish these possibilities[15]). For example, Hoppe showed that the configurationally stable α-oxyorganolithium shown in eq 1 reacted with esters and methanol with retention, while reacting with acid chlorides and acetic acid with inversion.[16] Hammerschmidt reported that a similar α-oxyorganolithium reacts with a trialkylstannyl chloride with inversion.[17] Beak found steric dichotomy with the α-aminoorganolithium in eq 2, which reacted with acid chlorides with retention and carbon dioxide with inversion.[18] Note also the dichotomy between these two systems: acid chlorides react with inversion in eq 1 and with retention in eq 2! Both Beak and Clayden have found divergent behavior in benzylic lithiums having a chirality axis as well a chirality center on the lithium-bearing carbon, such as the example in eq 3.[14,19] All of these examples are benzylic organolithiums, and an invertive transition state will obviously be stabilized by resonance. Clearly, the steric course of an S_E2 reaction is not limited in the way an S_N2 reaction is, but the factors that determine steric course are not readily apparent.

To study the steric course of an electrophilic substitution, one must know the absolute configuration of the organolithium, and it must be configurationally stable under the conditions of the reaction. Several years ago, we reported that 2-lithiopyrrolidines and -piperidines are among the most stable of functionalized organolithiums,[20,21] which makes them ideal candidates for stereochemical studies. They also have considerable synthetic potential,[12] in that they react with a broad range of electrophiles (unlike many functionalized organolithiums) to give substitution products in good to excellent yields,[22,23] and undergo stereoselective [2,3]-sigmatropic ylide rearrangements.[24] In exploratory studies of the steric course of these reactions, we found that several trends emerged, as summarized in Scheme 1.[22] With these lithiated heterocycles, the steric course took three broadly defined paths: complete retention, varying degrees of inversion, and complete racemization, depending on the electrophile and the size of the heterocyclic ring. Note that the lithium in these compounds is not chelated by a carbonyl, as it is in the examples of eqs 1−3, although it is probably bridged to the nitrogen.[25]

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(2) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471.
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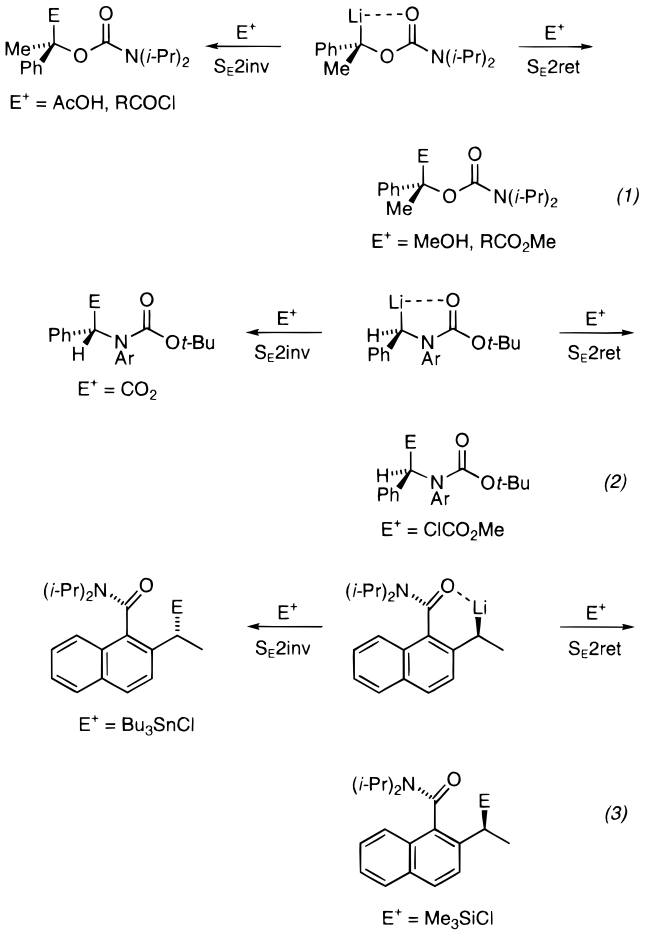


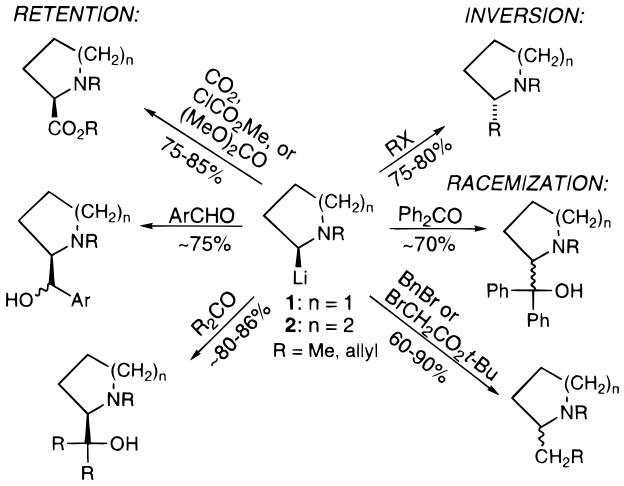
Note also that the trends we observed for these "unstabilized" α-aminoorganolithiums differ from those cited above. For example, both esters and acid chlorides proceed with retention of configuration. It is also interesting that the examples of configurational inversion that we reported in 1995[22] and 1997[23] (Scheme 1), which were proven for six examples, are distinct from those shown in eqs 1−3 in that the transition state for inversion at the carbanionic carbon is *not mesomerically stabilized.* In contrast to the examples in Scheme 1, most, if not all, nonbenzylic α-amino and α-oxy organolithiums react with retention, making these pyrrolidino and piperidino lithiums unique.

With the examples in eqs 1−3, Scheme 1, and others in the literature, the factors that determine the steric course are not clear, although hypotheses have been offered. For example, Hoppe suggests that (in his system, eq 1) a combination of anion geometry, electrophile coordinating ability, and electrophile LUMO energy come into play.[16] Beak proposes that, for the α-aminoorganolithium in eq 2, relatively unreactive electrophiles and/or electrophiles that coordinate to the lithium react with retention, while fast-reacting and/or noncoordinating electrophiles react with inversion.[18]

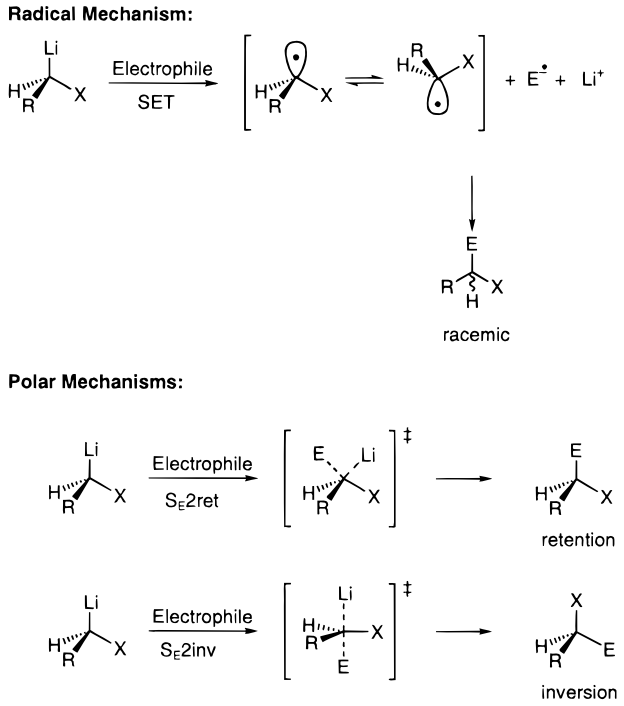
In this paper, we examine several subsets of data generalized in Scheme 1 in which the stereoselectivity is variable, or in which the steric course changes as a function of the electrophile, and examine the reasons for the differences. We interpret these results as competition between the three mechanistic pathways shown in Scheme 2: single electron transfer (SET) reactions

(25) (a) Boche, G.; Marsch, M.; Harbach, J.; Harms, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Ahlbrecht, H. *Chem. Ber.* **1993**, *126*, 1887. (b) Becke, F.; Heinemann, F. W.; Rüffer, T.; Wiegeleben, P.; Boese, R.; Bläser, D.; Steinborn, D. *J. Organomet. Chem.* **1997**, *548*, 205.

Scheme 1. Trends in the Steric Course of Electrophilic Substitutions of Lithiated *N*-Methyl and *N*-Allyl Pyrrolidines and *N*-Methyl Piperidines[22,23]



Scheme 2. Three Limiting Possibilities for Aliphatic Electrophilic Substitutions[a]

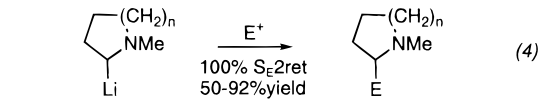


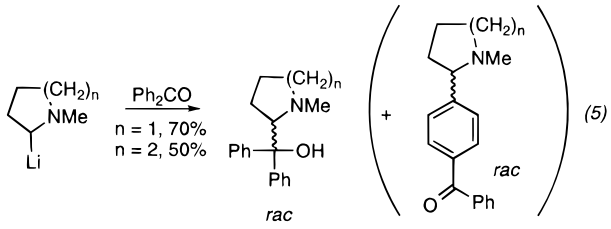
[a] X is a heteroatom substituent such as N, O, S, Se, etc.

that involve radical intermediates and form racemic products, and polar bimolecular electrophilic substitution reactions (S_E2) that may proceed with net retention (S_E2ret) or inversion (S_E2inv) of configuration at the metal-bearing carbon. A key question arises when racemic, or partly racemic products are obtained: which pathway(s) are competing, SET or nonselective polar (S_E2ret vs S_E2inv) substitutions? In this work, both the starting organolithiums and the reaction products have only one stereocenter. This is a conscious choice, whose aim is to avoid diastereomeric bias in transition states. We are currently evaluating the steric course of diastereoselective reactions, and will report these findings in due course.

Results and Discussion

Carbonyl Electrophiles. For **1** and **2**, reactions with carbon dioxide, benzaldehyde, acetone, and cyclohexanone proceed with



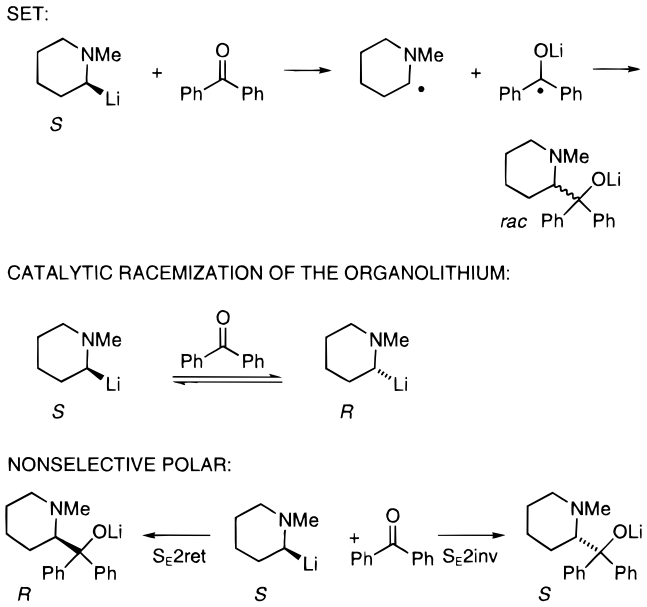


100% retention of configuration, within the limits of detection (eq 4). On the other hand, benzophenone gives addition products that are completely racemic (eq 5).[22] All of these reactions go in yields ranging from 50 to 92%. The benzophenone addition differed from the other reactions in that the reaction mixture turned blue upon addition of the benzophenone, and ESR analysis of aliquots of the reaction mixture revealed the presence of benzophenone ketyl in the reaction mixture.[22] This situation is reminiscent of earlier observations of benzophenone ketyl in organolithium additions, where presence and absence of the ketyl was correlated with the presence and absence of stereoselectivity in carbonyl addition reactions, and an SET mechanism was inferred.[26] In the addition of **1** and **2** to benzophenone, mixtures of 1,2- (**3**/**4**) and 1,6-addition products (**5**/**6**) were obtained, and both were racemic. Through an oversight, we neglected to mention this fact in our earlier paper.[22] We have since observed varying amounts of these products, the appearance of which seems to depend on the concentration of organolithium.

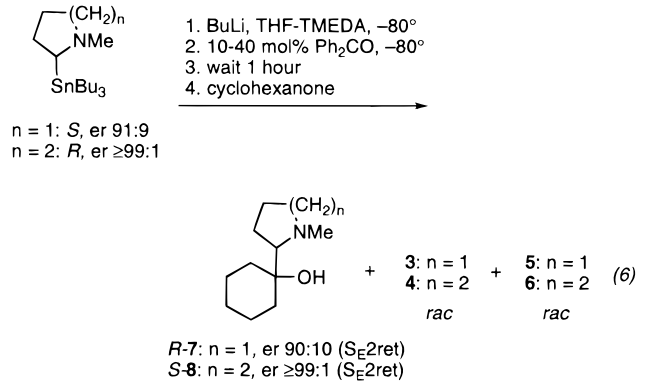
It could be argued that the presence of radicals in a reaction mixture does not necessarily place them on the reaction coordinate. To address this issue, we consider all the possible mechanisms for producing racemic products, and then seek to eliminate all but one.[27] Scheme 3 lists three possibilities: (a) single electron transfer, SET, involves oxidation of the organolithium to a radical, which couples with the benzophenone ketyl with no selectivity; (b) benzophenone catalyzes the racemization of the organolithium, and the racemic organolithium adds by a polar, $S_E2$ret mechanism; and (c) the organolithium adds by competing $S_E2$ret and $S_E2$inv pathways.

Of these possibilities, competing polar pathways seem to be the *least* likely possibility, since *all other carbonyl electrophiles* add to these organolithiums with 100% retention ($S_E2$ret). The *most* likely alternatives are SET and racemization of the organolithium, whereby racemization of the organolithium precedes a polar $S_E2$ret addition. Since organolithiums **1** and **2** are configurationally stable at −80 °C for over an hour in THF-TMEDA,[21] the benzophenone would have to catalyze its racemization for this mechanism to be operative. Racemization could occur if SET to the radical/ketyl pair were reversible, or if a lithium atom transfer reaction took place between the heterocyclic radical and the organolithium.

Scheme 3. Three Routes for Production of Racemic Benzophenone Adduct



The catalytic possibilities were tested by treating the organolithiums **1** and **2** with a substoichiometric amount of benzophenone, waiting 1 h, then quenching the reaction mixture with cyclohexanone, which adds with 100% retention. The product of the reaction contained both cyclohexanone and benzophenone adducts, and analysis of the enantiomer ratio of the cyclohexanone adduct was used to determine the degree of racemization of the organolithium (eq 6). Enantiomer ratios were



determined by NMR analysis of the crude reaction mixture in the presence of mandelic acid or Mosher acid as a chiral solvating agent.[28] This experiment has been conducted in both the pyrrolidine and the piperidine series; the results of the pyrrolidine experiment are shown in Figure 1. The enantiomer ratio of the *N*-Boc-stannylpyrrolidine precursor to **1** was determined by removal of the Boc group, acylation with benzoyl chloride, and SFC analysis on a Whelk-O Pirkle column. Comparison with authentic samples of the racemic benzophenone and cyclohexanone adducts revealed that the benzophenone adduct was racemic as expected, and that the enantiomer ratio (er) of the cyclohexanone adducts matched that of the starting stannane within the limits of experimental error. Therefore, benzophenone did *not* catalyze the racemization of the organolithium. Having reasonably eliminated two of the three possibilities, SET is left as the most likely explanation for the

(26) Rein, K. S.; Chen, Z.-H.; Perumal, P. T.; Echegoyen, L.; Gawley, R. E. *Tetrahedron Lett.* **1991**, *32*, 1941.

(27) "Eliminate all other factors, and the one which remains must be the truth." −Sherlock Holmes, in: Conan Doyle, A. In *The Sign of the Four. Edited with an Introduction by Christopher Roden*; Roden, C., Ed.; Oxford University Press: Oxford, 1993; p 8.

(28) Benson, S. C.; Cai, P.; Coilon, M.; Tokles, M. A.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 5335.

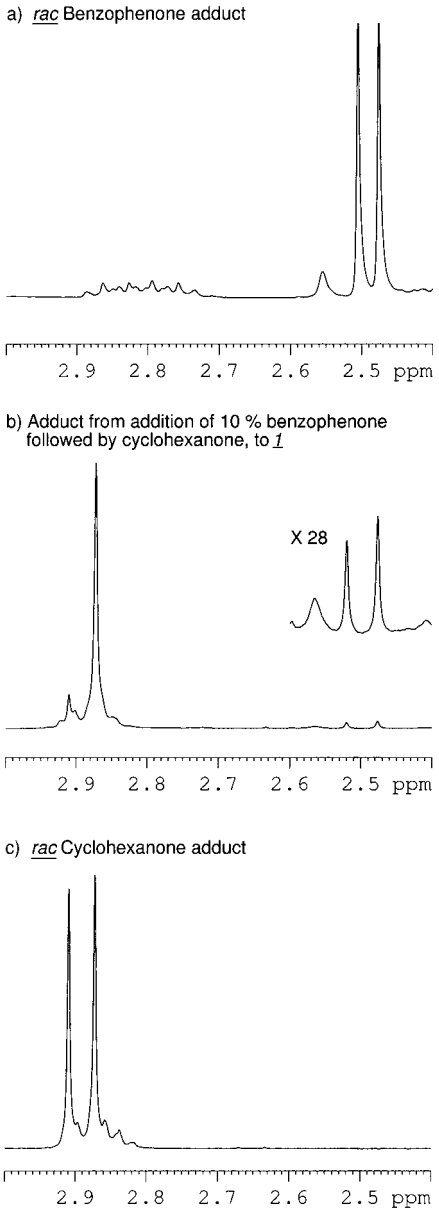
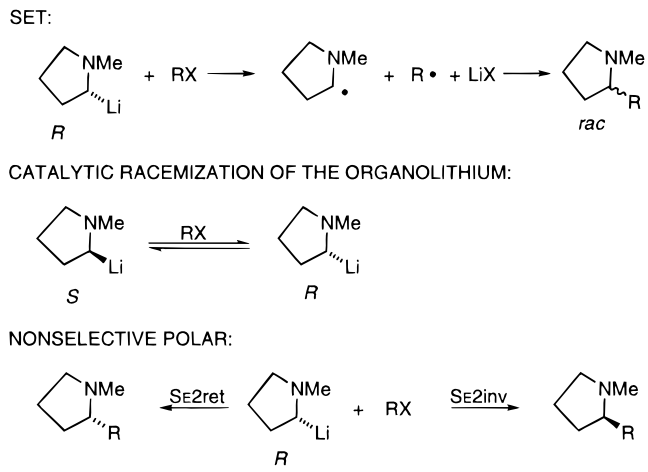


Figure 1. *N*-Methyl region of the 300 MHz ^{1}H NMR pyrrolidine addition products **3** and **5**, in the presence of Mosher acid as chiral solvating agent. (a) Paired *N*-methyl signals of diastereomeric salts of *rac*-**3**; (b) reaction mixture of eq 6; (c) paired *N*-methyls of diastereomeric salts of *rac*-**5**.

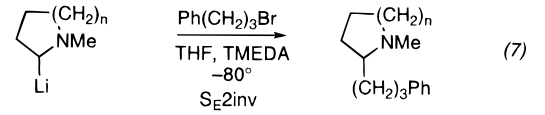
mechanistic course of these additions. This conclusion is supported by the appearance of the substitution products **5** and **6** (eqs 5 and 6) in the reaction mixture. Previous reports have shown that some organolithium[29,30] and organomagnesium[31−34] reagents add to aryl ketones by an SET radical mechanism to give mixtures of 1,2-, 1,4-, and 1,6-addition products.

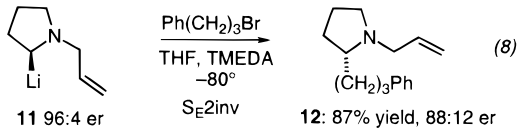
Unactivated Alkyl Halide Electrophiles. The reaction of **1** with alkyl halides is significantly less stereoselective than reactions with **2**.[22] For example, reaction of 1-bromo-3-phenylpropane with **2** (≥99:1 er) yields **10** with 100% inversion

Scheme 4. Three Possibilities for Nonselective Alkylation of **1**



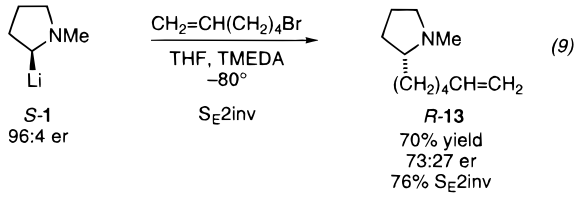
of configuration, while the same reaction with **1** (96:4 er) afforded **9** having a 75:25 er (eq 7); this corresponds to 78% inversion with **1**. Although the major trend is toward $S_E2$inv, there is considerable retention involved as well. *N*-Allylpyrrolidine **11** affords an 87% yield of alkylated product **12** in 88:12 er with the same electrophile, corresponding to 92% inversion (eq 8).[23] The steric course of the reactions shown in eqs 7 and





8 was proven for **9** and **10** by independent synthesis, and **12** by Pirkle analysis.[22,23] Again, the three most reasonable pathways leading to racemic product are SET, organolithium racemization, and competing polar pathways (Scheme 4).

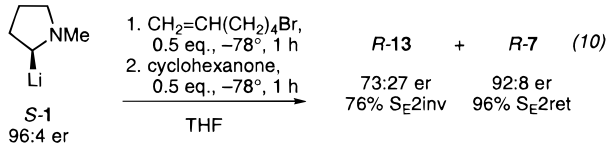
Radical probes have long been used to test SET mechanisms,[35] including alkylation of lithiated heterocycles.[36,37] We chose the most commonly used probe, hexenyl bromide, to test for SET in this system. Alkylation of **1** having an er of 96:4 to 97:3 with hexenyl bromide in THF at −78 °C afforded a 70% yield of hexenyl coupled product (**13**) with an er of 73:27 (75−76% inversion, which corresponds to 54% racemization) (eq 9). No significant amounts of cyclopentylmethyl coupled product were detected (≤10% by GC-MS). *This negative result does*



(29) Yamataka, H.; Kawafuji, Y.; Nagareda, K.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* **1989**, *54*, 4706.
(30) Olah, G. A.; Wu, A.; Farooq, O. *Synthesis* **1991**, 1179.
(31) Ashby, E. C.; Bowers, J. R., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 2242.
(32) Yamataka, H.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* **1989**, *111*, 4912.
(33) Holm, T. *Acta Chem. Scand.* **1983**, *B37*, 567.
(34) Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545.
(35) Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.
(36) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270.
(37) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.* **1989**, *54*, 175.

not prove the absence of an SET process, since the rates of the polar and radical coupling reactions have not been measured. Nevertheless, this same radical probe has been used to *demonstrate the presence of SET processes* in at least two previous studies of coupling reactions of lithiated pyrrolidines and piperidines, one of which was done in this lab.[36,37] In light of these precedents, we believe that these observations show that SET oxidation of **1** *does not occur* to an extent sufficient to account for the 54% racemization found in the production of **13**.

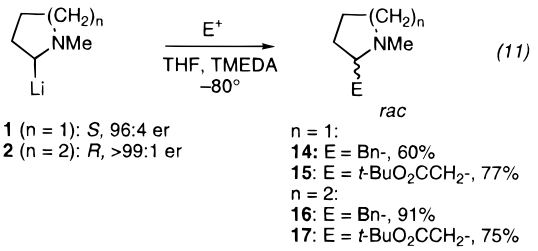
In a second experiment, half an equivalent of hexenyl bromide was added; after 1 h, the reaction was quenched with cyclohexanone (eq 10). The cyclohexanone adduct, **7**, so produced had the same er as the starting stannane (within experimental error), eliminating the possibility of racemization of the organolithium as a possible route to partial racemization. The



(10)

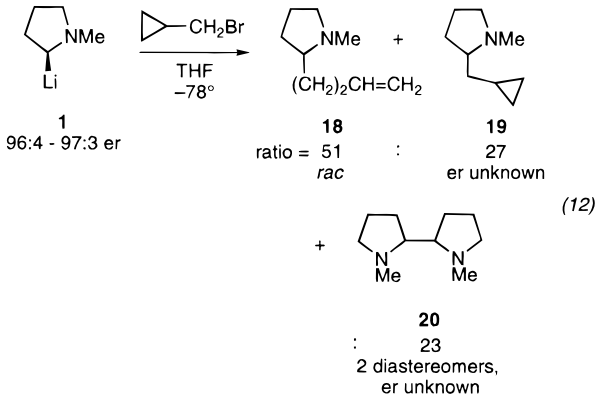
conclusion is that, for alkylation of lithiopyrrolidine **1**, SET is not involved, and the polar processes, $S_E2$ret and $S_E2$inv, compete more effectively than in the piperidine series (**2**). Most likely, this dichotomy is due to steric factors, either in the monomer or an aggregate (vide infra).

Activated Alkyl Halides. Benzyl bromide and *tert*-butyl bromoacetate, like benzophenone, afford good to excellent yields of completely racemic products **14**−**17** from **1** and **2** (eq 11).[22]



(11)

To probe the possibility of SET in this case (Scheme 4), we required a radical probe that is "activated" similar to a benzylic or allylic halide. For this we chose cyclopropylmethyl bromide. From data summarized by Ingold,[35] it can be calculated that the cyclopropylmethyl radical has a half-life of only ~1 μs at −80 °C, suffering ring-opening to butenyl radical. When **1** was allowed to react with cyclopropylmethyl bromide at −78 °C, GC-MS analysis showed a mixture containing butenyl-coupled product **18** and cyclopropylmethyl-coupled product **19** in an approximate 2:1 ratio, along with additional compounds tentatively identified as dimers **20** (eq 12). The two alkylated pyrrolidines **18** and **19** were prepared independently as proof of structure. The butenyl compound **18**, obtained as shown in eq 12, was racemic as indicated by CSP-GC; the er of **19** could not be determined. The independently synthesized racemic **19** was not resolved on CSP-GC, and NMR analysis was complicated by the presence of extra signals due to the *N*-methylpyrrolidinyl dimers, which could not be removed chromatographically. These dimers were not noticed in alkylations reported previously,[22] perhaps because they are not as prevalent when the reaction is run in the presence of TMEDA. Nevertheless, a radical process undoubtedly produces the butenylated product, and may also produce the dimers, so it appears that SET plays a major role in the stereorandom coupling of activated alkyl halides.



(12)

Competing Mechanisms. It appears that in electrophilic substitutions of **1** and **2**, the products are completely racemic when SET is operative. Why does SET intervene in some of these processes and not others? Eberson has applied Marcus theory to organic processes,[38] and notes that whether a polar mechanism or an SET mechanism is followed depends on the energy difference between the oxidation potential of a nucleophile and the reduction potential of an electrophile. This theory has been used by Arnett to support a polar process for the aldol addition of lithium pinacolonate to benzaldehyde,[39] and by Bordwell for anionic substitutions on alkyl halides.[40] The oxidation potentials of **1** and **2** are not known. The oxidation potential of benzyllithium is −1.43 V (THF/HMPA).[41] The reduction potential of benzophenone is −1.87 V ($LiClO_4$/THF),[42] and for benzaldehyde it is −1.94 V ($LiClO_4$/THF).[39] There is considerable variance in these numbers, depending on solvent and supporting electrolyte, however. If the oxidation potentials of organolithiums **1** and **2** are in the same ballpark as benzyllithium (probably more negative), the differences in redox potentials are not large enough to draw any conclusions about electron transfer rates. All we can say at this point is that SET competes with polar pathways when the electrophile is easily reduced, such as benzophenone. The addition of both **1** and **2** to benzaldehyde is retentive at the metal-bearing carbon, indicating a polar addition, while benzophenone adds by an SET mechanism. Since benzophenone is more easily reduced than benzaldehyde, relative oxidation potentials of a number of functionalized organometallics can be approximated by comparing the steric course of additions to benzophenone and benzaldehyde. Pyrrolidine **1** and piperidine **2**, which are oxidized by benzophenone but not benzaldehyde, fall between lithiated piperidinooxazolines and lithiated tetrahydroisoquinolyloxazolines, which are oxidized by both benzaldehyde and benzophenone, and lithiated BOC-pyrrolidines or magnesiated tetrahydroisoquinolyl oxazolines or pivalamides, which are not oxidized by either.[43]

Since both $S_E2$ret and $S_E2$inv processes are observed, both must be allowed by orbital symmetry.[44] Since the predominant route is $S_E2$inv, we will assume that this is the preferred mode of reaction of these α-aminoorganolithiums, and look for reasons

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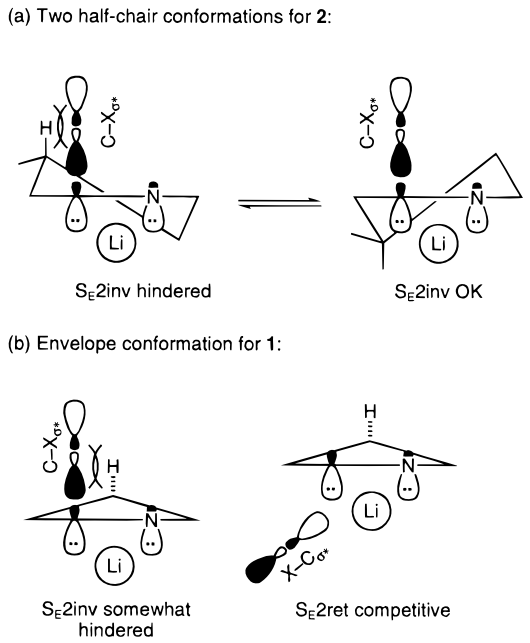

Figure 2. Competing transition structures for S_E2 reactions of **1** and **2**.

for the lower selectivity based on steric grounds. Assuming the lithium in **1** and **2** bridges the nitrogen, as was found in the solid-state structure of α-(dimethylamino)benzyllithium,[25] and as suggested by theory,[25,45] we can predict the probable conformations of **1** and **2**, and in turn offer the following explanation of the steric contribution to the stereochemical dichotomy.

Lithiopiperidine **1** can adopt two half-chair conformations, one of which is completely unhindered for an $S_E2$inv reaction, since the lithium is in the pseudoaxial conformation (Figure 2a, right). For lithiopyrrolidine **2**, envelope conformations probably predominate, with the one illustrated in Figure 2b likely being the most stable, since it places the methylene "flap" anti to the solvated cation. Here, an $S_E2$inv approach is discouraged due to the C-4$_\beta$-hydrogen shown. This steric interaction may be enough to allow the $S_E2$ret mechanism to compete. This explanation, which is illustrated for monomers of **1** and **2**, may be complicated by the aggregation states, which are currently under study.

Conclusion. Lithioheterocycles **1** and **2** appear to react with electrophiles that are not easily reduced by a polar mechanism, and with easily reduced electrophiles by an SET mechanism. Carbonyl electrophiles that are not easily reduced react exclusively by an $S_E2$ret pathway, and unactivated alkyl halides by a predominantly or exclusively $S_E2$inv pathway, depending on ring size. Lithiopyrrolidine **1** reacts with unactivated alkyl halides with about 75% $S_E2$inv and 25% $S_E2$ret, with steric factors postulated to play a role when $S_E2$inv is less favorable; lithiopiperidine **2** reacts with unactivated alkyl halides exclusively by an $S_E2$inv mechanism. With electrophiles that are easily reduced, such as benzophenone and activated halides, SET appears to be the predominant mechanism in both heterocyclic systems. In these systems, the steric course of the reaction can be used as an indicator of the mechanism: complete racemization is observed when SET is the most likely mechanism, whereas both invertive and retentive polar mechanisms may occur when SET is less likely.

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Experimental Section

Preparation of stannylpyrrolidines and piperidines and transmetalations to **1** and **2** were described previously.[21,22] Methods of er determination and products of the reactions with all electrophiles except cyclopropylmethyl bromide were reported in 1995.[22]

Procedure for Testing the Catalytic Pathways. The reaction with hexenyl bromide and cyclohexanone is typical. (*S*)-*N*-Methyl-2-(tributylstannyl)pyrrolidine (0.63 g, 1.69 mmol) was dissolved in 6 mL (0.28M) of anhydrous THF. This solution was cooled to −78 °C and BuLi (1.5 M in hexanes, 1.4 mL, 1.24 equiv) was added to the reaction by dropwise addition via syringe over 3 min. The reaction was stirred at −78 °C for 20 min. Neat 6-bromo-1-hexene (115 μL, 0.5 equiv) was added dropwise over 1 min to the reaction mixture and stirred for 1 h at −78 °C. Then neat cyclohexanone (90 μL, 0.5 equiv) was added dropwise over 1 min to the reaction mixture and again stirred for 1 h. The reaction was quenched at −78 °C with 2 mL of 2 M HCl. The reaction was warmed to room temperature and concentrated in vacuo. The biphasic mixture was extracted with ether (5 × 2 mL) to remove the stannane byproducts. The aqueous layer was then basified with 4 pellets of KOH. The basified solution was extracted with ether (5 × 2 mL). The combined organic layers were dried over anhydrous K_2CO_3, filtered, and concentrated to a light yellow oil, 0.17 g. GC-MS analysis showed 6 peaks: 2 were dimers (3 and 4%), *N*-methyl 2-(cyclopentylmethyl)pyrrolidine (3%), *N*-methyl-2-(5-hexenyl)pyrrolidine (32%), *N*-methyl-2-(1-hydroxycyclohexyl)pyrrolidine (51%), and tetrabutylstannane (7%). Retention times and MS data for the last 3 products corresponded to authentic samples.[22] NMR analysis of the reaction mixture (5.8 mg) with (*S*)-(+)-*O*-acetylmandelic acid (6.0 mg) dissolved in 0.76 mL of $CDCl_3$ indicated the enantiomers of the cyclohexanone adduct were present in a 92:8 ratio.

Reaction of 2-Lithio-*N*-methylpyrrolidine with Cyclopropylmethyl Bromide. (*S*)-*N*-Methyl-2-(tributylstannyl)pyrrolidine (0.50 g, 1.34 mmol) was dissolved in 10.5 mL (0.13 M) of anhydrous THF and cooled to −78 °C. A solution of BuLi (1.25 M in hexanes, 1.1 mL, 1 equiv) was added dropwise to the cooled solution over 1 min. The reaction was stirred for 20 min, then neat cyclopropylmethyl bromide (154 μL, 1.2 equiv) was added over 1 min. The reaction mixture was stirred for 1 h, then quenched at low temperature with 2 mL of 2 M HCl. The reaction mixture was allowed to reach room temperature and the solvent was removed in vacuo. The biphasic mixture was extracted with diethyl ether (5 × 2 mL), and the organic layers were discarded. The aqueous layer was then basified with 4 pellets of KOH and extracted with ether (5 × 2 mL). The combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated to a light yellow oil. Crude yield 0.10 g, 54%. GC-MS analysis indicated 4 products: two dimers (12% and 11%), *N*-methyl-2-(cyclopropylmethyl)pyrrolidine (27%), and *N*-methyl-2-(3-butenyl)pyrrolidine (51%). The identities of the last two products were confirmed by comparison to authentic samples.

***N*-Methyl-2-(3-butenyl)pyrrolidine.** *N*-Methyl-2-(tributylstannyl)-pyrrolidine (0.86 g, 2.30 mmol) was dissolved in 12 mL (0.2 M) of anhydrous THF. The solution was cooled to −78 °C and equilibrated for 10 min. Then BuLi (1.55 M in hexanes, 1.95 mL, 1.3 equiv) was added dropwise by syringe into the cooled solution over 3 min to give a light yellow solution that gradually deepens and lightens over a 20 min induction period. The reaction was quenched after 20 min with 4-bromobutene (316 μL, 1.3 equiv). The reaction was then stirred for 1 h at −78 °C and quenched at this temperature with 2 mL of 2 M HCl. The reaction was then allowed to reach room temperature and concentrated in vacuo. The biphasic mixture was transferred into a disposable test tube and extracted with diethyl ether (5 × 2 mL). The aqueous layer was placed in an ice bath and basified with 4 KOH pellets. This process gave a biphasic mixture and was extracted with ether (5 × 2 mL). The combined organic layers were dried over potassium carbonate, filtered, and concentrated in vacuo without heating and gave a light yellow oil (0.11 g, 33%). GCMS analysis of the crude product indicated 3 products: the *N*-methyl-2-(3-butenyl)pyrrolidine (61%) and 2 dimers (20% and 17%). The crude material was chromatographed through silica and gradient eluted with 1 to 5% methanol in dichloromethane and gave 15 mg of *N*-methyl-2-(3-

butenyl)pyrrolidine. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86−5.76 (m, 1H) (RC*H*═CH_2), 5.03−4.91 (m, 2H) (RCH═C*H*$_2$), 3.06 (dt, 1H, J = 2 Hz, 7.5 Hz) (CH_2(R)C*H*N), 2.30 (s, 3H), 2.1−1.88 (m, 5H), 1.81−1.61 (m, 3H), 1.48−1.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7 (R*C*H═CH_2), 114.4 (RCH═*C*H_2), 66.0, 57.2, 40.3 (N*C*H_3), 32.8, 30.9, 30.6, 21.8.

Independent Synthesis of *N*-Methyl-2-(cyclopropylmethyl)pyrrolidine. ***N*-Boc-2-allylpyrrolidine.** *N*-Boc-pyrrolidine (2.53 g, 14.8 mmol) and 5.8 mL (2.6 equiv) of TMEDA were dissolved into 30 mL of anhydrous ether. The solution was cooled to −78 °C and allowed to equilibrate for 30 min. Then *s*-BuLi (1.13 M in cyclohexane, 17.0 mL, 1.13 equiv) was added dropwise over a period of 7 min. The reaction was stirred for 1 h at −78 °C. The reaction mixture was then quenched with allyl bromide (1.28 mL, 1.5 equiv) by dropwise addition via syringe. The dry ice acetone bath was removed and the reaction was allowed to reach room temperature. Stirring was continued for 10 h at room temperature. The reaction mixture was quenched with 10 mL of water and extracted with 3 × 30 mL of ether. The organic layers were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated to give a light yellow liquid. The crude material was chromatographed through silica with 3% EtOAc in hexanes to give a colorless oil. Yield 1.521 g, 49%. ^{1}H NMR (400, MHz, $CDCl_3$): δ 5.71 (m, 1H), (RC*H*═CH_2), 5.00 (m, 2H), (RCH═C*H*$_2$), 3.78 (br. d, 1H), (CH_2(allyl)C*H*N), 3.26 (br. d, 2H), 2.45 (br. d, 1H), 2.09 (m, 1H), (CH_2═CHC*H*), 1.8 (m, 4H), 1.44 (s, 9H), (C*H*$_3$). ^{13}C NMR (100, MHz, $CDCl_3$): δ 154.5, (C═O),135.3, (R*C*H═CH_2), 116.9, (RCH═*C*H_2), 79.0, (O*C*(CH_3)$_3$), 56.7, 46.7−46.3, 39.0−38.2, 30.1−29.2, 23.6−22.9. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02. Found: C, 67.94; H, 10.12.

***N*-Boc-2-(cyclopropylmethyl)pyrrolidine.** Following the procedure of Suda,[46] an Aldrich diazomethane generator was charged with a solution of KOH (0.744 g, 2 equiv, in 80% EtOH). An ether solution (35 mL) of Diazald (2.84 g, 2 equiv) was added dropwise while being heated in a 65−70 °C water bath. Diazomethane was condensed with a dry ice−acetone coldfinger. The receiver flask was also cooled in a dry ice−acetone bath. After complete addition of the Diazald solution, 10 mL of ether was added dropwise to the generator. The distillate was collected until it was colorless. Neat *N*-Boc-2-allylpyrrolidine (1.33 g, 6.63 mmol) was added to the (−78 °C) diazomethane solution by syringe. The syringe was rinsed twice with 5 mL of ether. The reaction mixture was then warmed to 0 °C in an ice water bath. $Pd(OAc)_2$ (31.0 mg, 2 mol %) was added to the solution in one portion. The reaction was stirred for 30 min to give a yellow solution with a brown precipitate. The reaction mixture was filtered through a 3 cm pad of Celite, then concentrated in vacuo to give a yellow oil. The above process was repeated twice with the yellow oil. NMR spectral analysis of the crude oil indicated the absence of alkene protons. The crude oil was column chromatographed with 3% EtOAc in hexanes to give a colorless oil. Yield 1.37 g, 97%. ^{1}H NMR (400, MHz, $CDCl_3$): δ 3.81 (br q, 1H, J = 5.1 Hz) (CH_2(R)C*H*N), 3.30 (m, 2H) (CH_2C*H*$_2$N), 1.97−1.73 (m, 4H), 1.58−1.36 (m, 1H) (*C*H, cyclopropyl), 0.60−0.55 (m, 1H) (C*H*$_2$, cyclopropyl), 0.44−0.35 (m, 2H) (C*H*$_2$, cyclopropyl). ^{13}C NMR (100, MHz, $CDCl_3$): δ 154.5 (C═O), 78.8 (O*C*(CH_3)$_3$), 57.5 (*C*H_3), 46.5−46.0, 39.3−38.3, 30.5−29.8, 28.5, 23.8−23.0, 7.8 (*C*H, cyclopropyl), 4.7 (*C*H_2, cyclopropyl), 3.8 (*C*H_2, cyclopropyl). Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29. Found: C, 68.54; H, 10.21.

***N*-Methyl-2-(cyclopropylmethyl)pyrrolidine. Method A:** *N*-Boc-2-(cyclopropylmethyl)pyrrolidine (0.249 g, 1.1 mmol) was dissolved in 8 mL of anhydrous ether. The solution was cooled to −78 °C and allowed to equilibrate for 10 min. DIBAL-H (4.4 mL, 4.0 equiv, 1.0 M in cyclohexane) was added dropwise to the ether solution. The cooling bath was removed and the reaction mixture was allowed to reach room temperature. The reaction was stirred for 75 h then cooled to −78 °C and quenched with saturated sodium potassium tartrate (5 mL). The reaction mixture was stirred overnight to give two clear layers. The two layers were separated and the aqueous layer was extracted 3 times with 10 mL of ether. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo with no heating to give a light yellow oil. The oil was chromatographed through silica using a mixture of ethyl acetate, hexanes, and ethanol (1:5:0.5) to give a colorless liquid. Yield 40 mg, 26%.

Method B: *N*-Boc-2-(cyclopropylmethyl)pyrrolidine (1.03 g, 4.5 mmol) was dissolved in 5 mL of anhydrous THF. The solution was cooled to −78 °C and allowed to equilibrate for 10 min. DIBAL-H (18.3 mL, 4.0 equiv, 1.0 M in cyclohexane) was added dropwise to the THF solution. The cooling bath was removed and the reaction mixture was allowed to reach room temperature. The reaction was refluxed for 10 h then cooled to −78 °C and quenched with saturated sodium potassium tartrate (15 mL). The reaction mixture was stirred overnight to give two clear layers. The two layers were separated and the aqueous layer was extracted 3 times with 10 mL of ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo with no heating to give a light yellow oil. The oil was slowly vacuum distilled at room temperature. The distillate was collected in a tube cooled to −78 °C (dry ice, 2-propanol). The product is a clear colorless liquid. Yield 0.32 g, 50.2%. ^{1}H NMR (400, MHz, $CDCl_3$): δ 3.00 (dt, 1H, J = 2 Hz, 7 Hz), 2.24 (s, 3H), 2 (m, 3H) (RC*H*N(Me)CH_{2ax}, CH2CH_{2eq}), 1.6 (m, 2H) (CH_2C$H_2$$CH_2$N), 1.50 (m, 1H) (C$H_{2ax}$$CH_2$$CH_2$N), 1.34 (m, 1H) (cyclopropyl-CH_2), 1.20 (m, 1H) (cyclopropyl-CH_2), 0.60 (m, 1H) (C*H*, cyclopropyl), 0.38 (d, 2H, J = 8 Hz) (CH_2, cyclopropyl), 0 (m, 2H) (CH_2, cyclopropyl). ^{13}C NMR (100, MHz, $CDCl_3$): δ 66.7, 57,3, 40.5 (N*C*H_3), 39.0, 31.0, 21.8, 8.4 (*C*H, cyclopropyl), 4.8 (*C*H_2, cyclopropyl), 4.3 (*C*H_2, cyclopropyl). Anal. Calcd for $C_9H_{17}N$: C, 77.63; H, 12.31. Found: C, 75.97; H, 12.18.

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