−7.7. Anal. Calcd for $C_{17}H_{38}O_2Sn_2$: C, 40.0; H, 7.06. Found: C, 40.57; H, 6.77.

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**Supplementary Material Available:** Experimental procedures for compounds including **4b**, **8b**, **9b**, **10**, **14**, **16**, and **17** (3 pages). Ordering information is given on any current masthead page.

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# Complex Induced Proximity Effects: β-Lithiations of Carboxamides

Gary P. Lutz, Anne P. Wallin, Shawn T. Kerrick, and Peter Beak*

*Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801*

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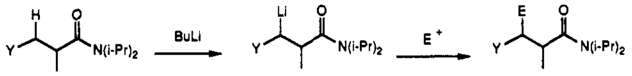
The $R^*,S^*$ and the $R^*,R^*$ diastereomers of *N,N*-diisopropyl-2,3-dideuterio-2-methyl-3-phenylpropanamide (**5**, **6**) have been used to investigate the diastereoselectivity of the β-lithiation of *N,N*-diisopropyl-2-methyl-3-phenylpropanamide (**4**). The β-lithiation of **4** is highly diastereoselective with the β-proton that is in the same relative position as the β-proton of diastereomer **6** being preferentially removed. The β-lithio species derived from **4** is shown to be a pyramidal, organolithium reagent based on $^{13}C$ NMR. Lithiation of the $R^*,S^*$ and the $R^*,R^*$ diastereomers of *N,N*-diisopropyl-2-methyl-3-(phenylthio)butanamide (**7**, **8**) and *N,N*-diisopropyl-2,3-dimethyl-4-pentenamide (**9**, **10**) occur at the β-position. Lithiation of the $R^*,S^*$ and $R^*,R^*$ diastereomers of *N,N*-diisopropyl-2-methyl-3-phenylbutanamide (**11**, **12**) occurs at the β-position for **11** and at the α-position for **12**. A conformational model is shown to correlate with these observations. The β-lithio species formed do not react diastereospecifically.

Reactions that involve specific removal of a proton from a carbon followed by reaction of the resulting carbanion with an electrophile are the basis for a wide range of synthetic strategies. Resonance and inductive effects typically dominate the deprotonation reaction, and thermodynamically favored carbanions are well-established synthetic intermediates. A growing number of kinetic deprotonations have been discovered, particularly for lithiations, and the carbanions that result from such reactions are useful as intermediates in innovative synthetic sequences.[1-13]

We have reported reactions in which tertiary amides that are activated by a phenyl, phenylthio, or vinyl group in the β-position undergo β-deprotonations in preference to the expected and well-precedented α-deprotonations to give an enolate. The observation is that **1**, when treated with an organolithium base, affords a lithiated intermediate, formally **2**, which on subsequent reaction with an electrophile provides the β-substituted product **3** diastereoselectively. In the present paper we address the issues of the actual structure of **2** and the regioselectivity and stereoselectivity of the lithiation. We provide direct evidence that **2** is correctly represented as a β-lithio amide, that the β-deprotonations are highly diastereoselective, and that the stereochemistry of the substituted products is dependent on the electrophile.



**1** **2** **3**

Y = Ph, $CH_2$=CH, PhS

The overall conversion of **1** to **3** involves formation and substitution of a homoenolate carbanion, a species that has been most usually available in masked form or from a β-halo carbonyl precursor.[3-9] Approaches similar to the direct removal of a proton in the conversion of **1** to **2** have been reported by McDougal for β-lithio acetals,[10] by Tanaka for dilithiated amides,[11] and by Watt[12] and Funk[13] for β-lithio enals.

## Results and Discussion

We have investigated the structure of the product of lithiation of *N,N*-diisopropyl-2-methyl-3-phenylpropanamide (**4**) and the stereochemistry of the deprotonations

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[1] Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356 and references cited therein.

[2] (a) Beck, P.; Hunter, J. E.; Jun, Y. M.; Wallin, A. P. *J. Am. Chem. Soc.* **1987**, *109*, 5403. The synthesis of compounds **4**, **7–8**, and **11–12** is also described here. (b) For another use of the amide as a directing group, see: Eaton, P. E.; Cunkle, G. T.; Marchioro, G.; Martin, R. M. *J. Am. Chem. Soc.* **1987**, *109*, 948. (c) The β-metalation and substitution of **4** has been performed in the presence and absence of TMEDA; the relative stereochemistry and yield of the β-substituted products were unaffected by the absence of the TMEDA.

[3] These β-lithio amides provide the synthetic equivalent of a β-lithio α-alkyl carboxylic acid. Several reviews of the β-homoenolate synthon are available.[4] Transition metal promoted cyclopropane ring openings,[5] metal insertion into a carbon–halogen bond[6] or a carbon–carbon bond,[7] destannylation,[8] and halogen metal exchange[9] are examples of different routes.

[4] For reviews on homoenolates: Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *155*, 1. Ryu, I.; Sonoda, N.; Ryu, I. *J. Synth. Org. Chem., Jpn.* **1985**, *43*, 112. Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. Stowell, J. C. *Chem. Rev.* **1984**, *84*, 409. Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205.

[5] Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, *110*, 3296 and references cited therein.

[6] Fukuzawa, S.; Sumimoto, N.; Fujinami, T.; Sakai, S. *J. Org. Chem.* **1990**, *55*, 1628.

[7] DeShong, P.; Sidler, D. R.; Rybczynski, P. J.; Slough, G. A.; Rheingold, A. L. *J. Am. Chem. Soc.* **1988**, *110*, 2575 and references cited therein.

[8] Tanaka, K.; Yoda, H.; Isobe, Y.; Kaji, A. *J. Org. Chem.* **1986**, *51*, 1856 and references cited therein.

[9] Barluenga, J.; Rubiera, C.; Fernandez, J. R.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1987**, 425. Neukom, C.; Richardson, D. P.; Myerson, J. H.; Bartlett, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 5559.

[10] McDougal, P. G.; Condon, B. D.; Laffosse, M. D., Jr.; Lauro, A. M.; VanDerveer, D. *Tetrahedron Lett.* **1988**, *29*, 2547.

[11] Tanaka, K.; Minami, K.; Kaji, A. *Chem. Lett.* **1987**, 809.

[12] Richardson, S. K.; Jeganathan, A.; Watt, D. S. *Tetrahedron Lett.* **1987**, *28*, 2335.

[13] Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1988**, *110*, 1290.

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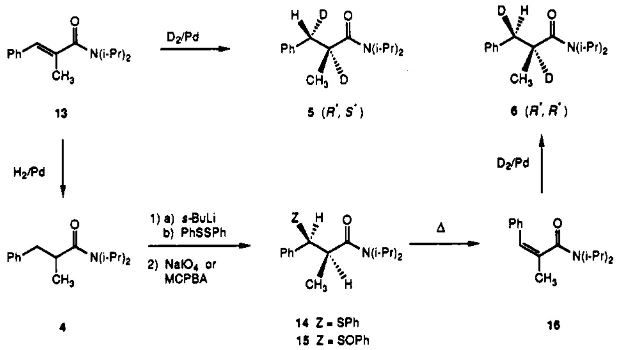
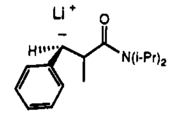
of the $R^*,S^*$ and the $R^*,R^*$ diastereomers of *N,N*-diisopropyl-2,3-dideuterio-2-methyl-3-phenylpropanamide (**5**, **6**). Also, the regiochemistry of the deprotonations of *N,N*-diisopropyl-2-methyl-3-(phenylthio)butanamide (**7**, **8**), *N,N*-diisopropyl-2,3-dimethyl-4-pentenamide (**9**, **10**), and *N,N*-diisopropyl-2-methyl-3-phenylbutanamide (**11**, **12**) have been investigated.[2a] The lithiating reagents were *sec*-butyllithium (*s*-BuLi) or *s*-BuLi/*N,N,N′,N′*-tetramethylethylenediamine (TMEDA), and methanol-$d_1$ ($CH_3OD$) was used as the electrophile to give $\beta$-deuterated products **3** (E = D) in most cases.[2c] The $CH_3OD$ reacts with consistently high efficiency, and the position of deuteration is determined by $^1H$ NMR spectrometry of the deuterium-substituted products while the extent of reaction is evaluated by the deuterium incorporation as determined by mass spectrometry.

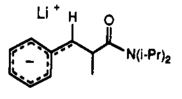
**Syntheses of 5 and 6.** The diastereomers **5** and **6** were prepared as shown. The amide **13** was synthesized from commercially available $\alpha$-methylcinnamic acid, which has the *E* configuration about the double bond, via the acid chloride. Hydrogenation of **13** with deuterium gas directly afforded the $R^*,S^*$ diastereomer **5** assuming a syn addition of deuterium to the double bond.[14,15] The deuterium content of **5** was 94% $d_2$, 5.4% $d_1$, and 0.6% $d_0$.[16] Reduction of **13** with hydrogen provided amide **4**, which upon deprotonation with *sec*-BuLi followed by reaction with diphenyl disulfide (PhSSPh) gave **14** as a single diastereomer. Oxidation of **14** gave a 1.5:1 mixture of diastereomeric sulfoxides **15**, which were separated and independently converted to the unsaturated amide **16** by a thermal syn elimination.[17] The amide **16** was obtained as a single isomer and was shown to be isomeric with **13** based on $^1H$ NMR, $^{13}C$ NMR, and GC analysis and was assigned the *Z* configuration. The stereochemistry of **14** is inferred from its conversion to the unsaturated amide **16**. Hydrogenation of **16** with deuterium gas produced the $R^*,R^*$ diastereomer **6** with a deuterium content of 90.0% $d_2$, 7.9% $d_1$, and 2.1% $d_0$.[16]



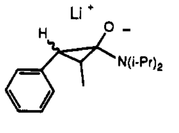
**Structure of the $\beta$-Lithiated Amide.** Although the lithiation–substitution of **4** to give the $\beta$-substituted products **3** (Y = Ph) can be represented as proceeding through the anion **2** (Y = Ph), there are at least three structures for the intermediate that would be consistent with the formation of **3**.[2a] These possibilities are the pyramidal benzylic carbanion **17**, the planar delocalized carbanion **18**, and the cyclopropyl species **19**.[18] Distinction between these structures may be made by comparison of the $^{13}C$ NMR spectrum of the intermediate organolithium species to systems of established structure.[19]



**17**

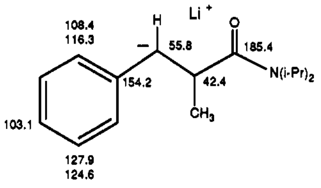


**18**



**19**

The $^{13}C$ NMR spectrum of the lithiated intermediate obtained from the reaction of **4** with *s*-BuLi at −70 °C in THF-$d_8$ has clearly identifiable signals in the region from 40 to 200 ppm, but the region between 10 and 40 ppm is obscured by excess *s*-BuLi, dissolved butane, THF-$d_8$, cyclohexane, and trace impurities. The chemical shift assignments are shown on structure **20** along with a $\Delta\delta$ that shows the changes in chemical shift of **20** relative to **4**. As can be seen, the carbonyl carbon, the ipso carbon, and the benzylic carbon resonances undergo downfield shifts. The ortho and the para carbon resonances show substantial upfield shifts and the meta carbon signals are only slightly changed in **20** relative to **4**. The chemical shift of the benzylic carbon at 55.8 ppm in the lithiated intermediate was unambiguously assigned by labeling the benzylic carbon of **4** with $^{13}C$.[20]



**20**

| | $\Delta(\delta_{20} - \delta_4)$ ppm |
|---|---|
| CON | 11.2 |
| CHLi | 16.3 |
| ipso | 12.4 |
| o | -12.6, -20.5 |
| m | -0.6, -2.3 |
| p | -23.7 |
| α | 0.8 |

Observation of the resonance assigned to the carbonyl carbon at 185.4 ppm and the pattern of chemical shift changes observed for the aromatic carbon resonances rule out **19** as a possible structure. The downfield shift of the ipso carbon signal and the relatively small downfield shift of the benzylic carbon resonance suggest the pyramidal structure **17**. The (7-phenylnorbornyl)lithium analyzed by Gruntzer, which is assigned as a pyramidal carbanion and is a model for **17**, has a chemical shift of 64.3 ppm for the benzyl carbon while the corresponding signal in the (7-phenylnorbornyl)potassium, which is a model for **18**, has a shift of 88.1 ppm.[19] In the norbornyllithium the ipso, ortho, and para carbons have chemical shifts of 157.2, 117.7, and 107.0 ppm, respectively, while in the planar norbornylpotassium the ipso, ortho, and para carbons have chemical shifts of 137.4, 107.6, and 90.6 ppm, respectively. The chemical shift evidence favors the pyramidal structure

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[14] *Chemical Abstracts, 9th Collective Index, Index Guide*; Chemical Abstracts Service: Columbus, OH, 1977; pp 1851–1881. For an early use see: McCasland, G. E. *A General System for the Naming of Stereoisomers*; Chemical Abstracts Service: Columbus, OH, 1953; p 8 ff.

[15] Jackman, L. M.; Lawn, J. W. *J. Chem. Soc.* **1962**, 3776. These authors have shown that the isomers of dimethyl cinnamatic acid undergo syn addition of hydrogen with palladium black.

[16] The initial reduction of **13** or **16** with Pd/C and deuterium gas in ethyl acetate gave low deuterium incorporations ($d_2$ < 70%). We believe that $d_0$ and $d_1$ material results from exchange of the deuterium gas with hydrogens of the solvent on the catalyst surface. This problem could be partially avoided by the addition of $D_2O$ to the reaction mixture. We believe that this exchange process accounts for the 5.4% $d_1$ and 7.9% $d_1$ material found in **5** and **6**, respectively. We have assumed that the hydrogen atoms that were incorporated into **5** and **6** are equally distributed over the $\alpha$- and $\beta$-positions.

[17] Kingsbury, C. A.; Cram, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 1810.

[18] Goswami, R.; Corcoran, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 7182.

[19] Peoples, P. R.; Grutzner, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 4709. Hoell, D.; Lex, J.; Mullen, K. *J. Am. Chem. Soc.* **1986**, *108*, 5983.

[20] The benzylic carbon signal of **20** appeared as a small broad singlet, but in the $\beta$-$^{13}C$ labeled carbanion the benzylic carbon's signal appeared as two broad overlapping singlets separated by 6.6 Hz at −70 °C. Lowering the temperature to −90 °C increased the separation of the two broad singlets to 8.5 Hz while one broad singlet was observed at −50 °C. The signals observed for the benzyl carbon are described as broad singlets because no fine splitting was observed, but we can not rule out the possibility of lithium–carbon coupling. Carbon–carbon coupling was observed for the ipso carbon (56.4 Hz), the $\alpha$-carbon (46.9 Hz), and the ortho carbons (4.8, 1.7 Hz) in the spectrum of the $^{13}C$-labeled carbanion.

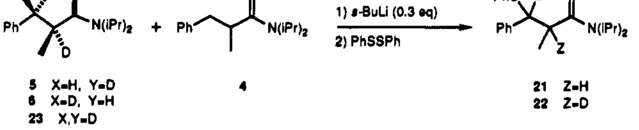
**Table I. Competition Experiments**

| mixture | reagents | initial[a] starting material | recovered[a] starting material | products[a] (21 and 22) | conversion[b] |
|---|---|---|---|---|---|
|  |  | % $d_2$, 44.2 | % $d_2$, 47.0 | % $d_2$, 39.3 |  |
| 1 | 6:4 | % $d_1$, 4.1 | % $d_1$, 3.5 | % $d_1$, 5.6 | 0.20 |
|  |  | % $d_0$, 51.7 | % $d_0$, 49.5 | % $d_0$, 55.1 |  |
|  |  | % $d_2$, 45.0 | % $d_2$, 62.3 | % $d_2$, 1.7 |  |
| 2 | 5:4 | % $d_1$, 2.8 | % $d_1$, 2.3 | % $d_1$, 6.1 | 0.33 |
|  |  | % $d_0$, 52.2 | % $d_0$, 35.4 | % $d_0$, 92.2 |  |
|  |  | % $d_3$, 45.2 | % $d_3$, 66.4 | % $d_2$, 1.8 |  |
| 3 | 23:4 | % $d_2$, 1.3 | % $d_2$, 1.7 | % $d_1$, 1.5 | 0.30 |
|  |  | % $d_1$, 0.1 | % $d_1$, 0.2 | % $d_0$, 96.7 |  |
|  |  | % $d_0$, 53.4 | % $d_0$, 31.7 |  |  |

[a] Isotopic distribution determined by FI mass spectrometry (FIMS). [b] Conversion represents the ratio of substituted products to starting material.

17 for the β-lithio intermediate. The observance of resonances for two ortho and meta carbons can be rationalized in terms of restricted rotation, but differences due to diastereomers of 17 cannot be completely ruled out.

**Diastereoselectivity of the β-Lithiation.** The β-substitution reaction of 1 via 2 to give 3 occurs with moderate to high diastereoselectivity.[2a] Either or both of the steps in the conversion of 1 to 3 could be stereoselective. In order to evaluate the diastereoselectivity of the β-lithiation we have investigated the lithiations of 5 and 6 in which deuterium provides diastereodiscrimination at the β-position. If there was no diastereoselectivity in the lithiations, 5 and 6 would be expected to proceed with a selective but equal rate of loss of the β-proton due to a deuterium isotope effect.[21] Independent lithiations of 5 and 6 indicated that the β-proton of 6 is removed more readily than the β-proton of 5. The experiments outlined below were carried out to determine the relative rates of the deprotonation of 6 compared to 5. In a typical experiment the deuterium-labeled isomer 6 and the unlabeled compound 4, in approximately a 1:1 ratio, were treated with a deficient amount of s-BuLi, and the resulting anion was allowed to react with PhSSPh to give a mixture of recovered starting materials and the substituted products 21 and 22. The ratio of 6 to 4 after reaction and the ratio of the substituted products 21 and 22 were determined by FI mass spectrometry (FIMS) isotope ratios and compared to the initial ratio of 6 to 4. A mixture of 5 and 4 and a mixture of the trideuterated isomer 23 and 4 were also independently investigated. The results of these experiments are summarized in Table I. Qualitative examination of the data in Table I shows that the dideuterated diastereomer 6 has approximately the same reactivity as the unlabeled isomer 4 while the diastereomer 5 has approximately the same reactivity as the trideuterated isomer 23. The data in Table I establish that the diastereoselective β-lithiation of 6 and 5 is at least 10:1 when the extent of reaction and the relative error in the determination of the isotopic ratios is taken into account.[22]



5 X=H, Y=D
6 X=D, Y=H
23 X,Y=D

4

21 Z=H
22 Z=D

In order to assess the stereocontrol of the sequence of lithiation and electrophilic substitution at a tertiary β-position we have investigated reactions of the diastereomeric isomer pairs 7–8, 9–10, and 11–12.

Separate treatment of either amide 7 or 8 with s-BuLi/TMEDA in THF at −78 °C for 1 h followed by addition of $CH_3OD$ gives products 24 and 25 in a 84:16 ratio in 80% yield with a deuterium incorporation of 98% from 7 and in a 87:13 ratio in 72% yield with a deuterium incorporation of 89% from 8. The position of deuteration was assigned by $^1H$ NMR, and the extent of deuterium incorporation was determined from FIMS isotope ratios. The ratios of diastereomers were determined by comparison to the retention times of authentic materials using capillary GC analysis. The relative configurations were assigned based on X-ray crystallographic analysis of 7.[23]

Amides 9 and 10 were separately treated with s-BuLi/TMEDA and subsequently allowed to react with $CH_3OD$ to give amides 26 and 27 as a mixture of isomers. The synthesis and relative configurations of 9 and 10 were based on the synthesis and assignments of Welch and Eswarakrishnan.[24a] The yield of 26 and 27 from 9 was 19% with 74% deuterium incorporation, and the yield of 26 and 27 from 10 was 47% with 76% deuterium incorporation.[24b] The ratios of 26 to 27, determined by capillary GC, were 17:83 regardless of the reactant amide. The β-deuterated amide 26 was found to have the $R^*,S^*$ configuration by comparison of the GC retention times with the retention times of the starting amides 9 and 10.

The lithiation of the β-phenyl diastereomers 11 and 12 proceeds differently than for the diastereomeric pairs 7–8 and 9–10. The $R^*,R^*$ diastereomer 11 undergoes β-lithiation to give, after reaction with $CH_3OD$, a ratio of diastereomers 29 and 30 that varies from 94:6 to 86:14 depending on the reaction conditions. The highest deuterium incorporation was found using 6 equiv of s-BuLi/TMEDA

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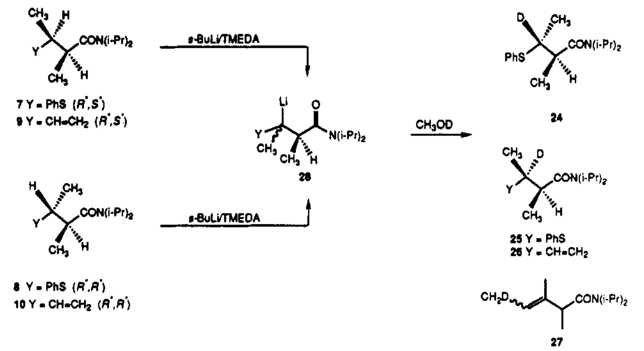
(21) (a) The theoretical primary deuterium isotope effect at −78 °C for this reaction can be estimated using the Arrhenius equation [$k_H/k_D = Ae^{(-\Delta E_a/RT)}$]. Values of $\Delta E_a$ = −1200 and −950 cal/mol were used to obtain the range of 12–22 at −78 °C.[21b,c] (b) Wiberg, K. B. *Physical Organic Chemistry*; John Wiley and Sons: New York, 1964; pp 351–364. (c) Wiberg, K. B. *Chem. Rev.* 1955, *55*, 713.

(22) The relative rates of lithiation of 4 to 5, 6, and 23 are determined using the following equation based on the substituted products obtained: $(k_H/k_D) = \{\ln [1 - (P_H/H_0)]\}/\{\ln [1 - (P_D/D_0)]\}$ where $P_H$ represents the amount of substituted product resulting from the reaction of protio material; $P_D$ represents the amount of substituted product resulting from the reaction of deuterium-labeled material; $H_0$ represents the amount of protio material initially available; and $D_0$ represents the amount of deuterium-labeled material initially available. Since the substituted products obtained when mixtures 2 and 3 were used contained very small amounts of deuterium (% $d_2$ material) and the error in determining the amount of deuterium is about 5%, values of 5% $d_2$ and 95% $d_0$ were used to give a relative rate of 20:1 for the reaction of 4 and 5 in mixture 2 and for the reaction of 4 and 23 in mixture 3.

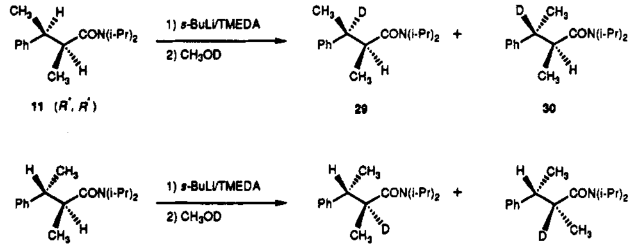
(23) Crystallographic data for 7 is contained in the supplementary material.

(24) (a) Welch, J. T.; Eswarakrishnan, S. *J. Org. Chem.* 1985, *50*, 5909. (b) Hunter, J. E. Ph.D. Thesis, University of Illinois at Urbana-Champaign, 1986. Hunter observed a similar regioselectivity when trapping allylic anions with $CH_3OD$.

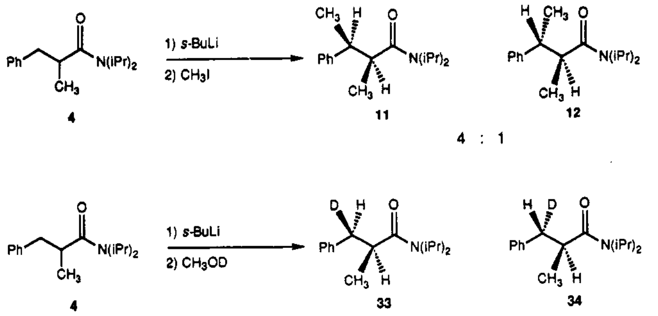


for 4–5 h at −78 °C, and these conditions give an 86:14 ratio of **29** to **30** with 88% deuterium incorporation in 97% yield. We observe only products resulting from β-deprotonation of **11** as indicated by a decrease in the intensity of the β-proton signal in the $^1$H NMR spectrum and the appearance of a quartet at the position of the α-proton signal. In contrast, metalation of the $R^*,S^*$ diastereomer **12** provides α-deprotonation. Treatment of **12** with 6 equiv of *s*-BuLi/TMEDA followed by reaction with $CH_3OD$ provides a 94:6 ratio of α-deuterated isomers **31** and **32** in 98% yield with a 94% deuterium incorporation.

These results show that β-metalation is dependent on relative stereochemistry for the β-phenyl diastereomers **11–12** but not for the β-phenylthio or β-vinyl diastereomers **7–8** and **9–10**, respectively. The $R^*,R^*$ diastereomer **11**, which undergoes β-metalation, has a β-proton with the same relative stereochemistry as the β-proton of the $R^*,R^*$ dideuterated diastereomer **6**, which also undergoes β-metalation. The $R^*,S^*$ diastereomer **12**, which undergoes α-metalation, has a β-proton with the same relative stereochemistry as the β-proton of the $R^*,S^*$-dideuterated diastereomer **5**, which does not undergo appreciable β-metalation under conditions that afford complete β-metalation of **6**.



The deprotonation reactions of **5**, **6**, **11**, and **12** are dependent on stereochemistry, while the reactions of **7–10** are less dependent on the stereochemistry of the reactants. The common products found from the lithiations of **7–8** and **9–10** show that the β-lithiated intermediates **28** lose their stereochemical identity before or upon deuteration.[25] When the anion derived from deprotonation of **4** is allowed to react with $CH_3I$, a 4:1 ratio of **11** to **12** is obtained, but when the same anion is allowed to react with $CH_3OD$, a 4:1 ratio of **34** to **33** is obtained.[2a,26] The present information suggests that the β-lithiation can be stereoselective but the stereochemical identity of the product is dependent on the electrophile used to trap the anion.



**Rationalization of Amide-Directed β-Lithiations.** It is reasonable conjecture that these directed lithiations proceed through organolithium–substrate complexes in which the primary interaction is presumably between the lithium and the carbonyl oxygen.[1,24b] In order to properly understand the present lithiation selectivities within that model, energies for the competitive transition structures for the lithiations via these complexes would be needed. Since there are considerable uncertainties about the structures of these complexes, energies for the competitive transition structures are not readily obtainable. However, analysis of conformations considered to be representative of the possible conformations of the starting amides in the transition state may be a useful approach for gaining understanding about the observed diastereoselective deprotonation. Our approach was to first do a comprehensive conformational energy minimization of structures **7–12** and **4** using MM2 approximations following earlier work by Meyers and Still.[27] The resulting low-energy conformations were then examined to determine the position of the carbonyl relative to the β-proton. Each low energy conformation was then determined to be either productive or nonproductive. A productive conformation was defined as one in which an organolithium base, while complexed to the oxygen atom of the carbonyl, could readily approach the β-proton of interest.[28] In an attempt to further mimic the transition state, the β-proton–carbon bonds of **4**, **11**, and **12** were constrained to be perpendicular to the plane of the phenyl ring.[29a] The low-energy conformations obtained from these minimizations were also analyzed as described above.

The results of the minimizations and the subsequent analysis of the low-energy conformations correlate with the

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(25) The differences in the rates of lithiation of the diastereomeric isomer pairs **7–8** and **9–10** that probably exist are not detected by these experiments.

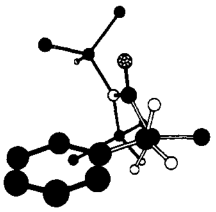
(26) Comparison of the $^1$H NMR spectra of the mixture of **33** and **34** with the $^1$H NMR spectra of **5** and **6** allowed us to assign the stereochemistry of **33** and **34**. A similar dependence of stereochemistry has been observed for the reaction of carbanions, generated at the α-position of sulfoxides, with electrophiles. Tanikaga, R.; Murashima, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2142. Biellmann, J. F.; Vicens, J. J. *Tetrahedron Lett.* **1978**, 467.

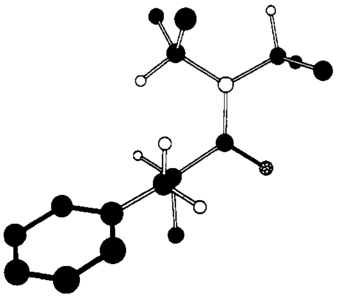
(27) Meyers, A. I.; Kunnen, K. B.; Still, W. C. *J. Am. Chem. Soc.* **1987**, *109*, 4405. MACROMODEL was used for structure input: Still, W. C.; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; DeGunst, F.; Hasel, W. MACROMODEL V3.0, Department of Chemistry, Columbia University, New York, NY 10027. The minimizations were performed using batch mode on a VMS/VAX system. The input file was generated by using the multiconformation submode with a default resolution of six for each torsional angle. All of the important torsional angles for each structure were varied. MM2(87) was the force field used and the block diagonal Newton Raphson (BDNR) minimization algorithm was used.

(28) This approach assumes that the complexation of the organolithium base would affect each conformation similarly, and therefore, the relative energies of the individual conformations would not be significantly affected with respect to one other.

(29) (a) This perpendicular orientation will presumably provide the greatest overlap of the p orbitals of the phenyl ring with the β-proton–carbon bond being broken in the transition state. The constraint was implemented in the MM2 calculations by adding the fix torsional angle (FXTA) command to the .COM file. The default V1 force constant of 1000 kJ/mol and a flat bottomed constraint well with a range of 90 ± 0° were used. (b) The phenyl ring in **35** and **36** is constrained to be perpendicular to the *pro-R* proton–carbon bond. Figure **35** represents a productive conformation while figure **36** represents a nonproductive conformation. Representations of two nonproductive conformations resulting from constraining the *pro-S* proton–carbon bond to be perpendicular to the phenyl ring are included in the supplementary material.

experimental findings. For example, we find several productive conformations for the β-proton, which is readily removed from **4** (i.e., the β-proton in diastereomer **6**) in both the constrained and unconstrained minimizations. However, there are no productive low-energy conformations for the β-proton, which is not readily removed (i.e., the β-proton in diastereomer **5**) in either the constrained or unconstrained minimizations. A representation of a constrained, productive conformation that correlates with the observed diastereoselectivity is illustrated by **35**, which is 0.3 kcal/mol above the lowest energy conformation **36**.[29b] In the lowest energy conformation the carbonyl oxygen is remote from both β-hydrogens. The β-phenyl diastereomers **11** and **12** gave similar results. Diastereomer **11**, which does undergo β-metalation, showed productive conformations in both the constrained and unconstrained minimizations. Diastereomer **12**, which does not undergo β-metalation, showed only nonproductive conformations in both minimizations. The β-phenylthio diastereomers **7** and **8** and the β-vinyl diastereomers **9** and **10**, all of which undergo β-deprotonations, exhibited at least one productive conformation. It is interesting that this model correlates the difference between the β-phenyl diastereomer **12** and the β-vinyl diastereomer **9**. In the latter a constrained, productive conformation becomes available that has no counterpart in the former. These theoretical models show good correlation between the observed selectivities for β-deprotonation and the proximity of the β-proton to the carbonyl oxygen in the low-energy conformations obtained from MM2 minimizations. While we have reservations about the many assumptions inherent in this kind of analysis, it could serve as a useful guide for selecting systems for further study.


35


36

In summary, the present work shows that the lithiation step in the amide-directed β-lithiation can be diastereoselective, that the organolithium reagent formed is correctly formulated as a β-lithio species, and that the lithiated intermediate does not necessarily retain its stereochemical identity in its reaction with electrophiles.

## Experimental Section

All reactions involving organometallic reagents were executed under a nitrogen or argon atmosphere in glassware that was either flame dried or dried in an oven and was cooled under a nitrogen atmosphere. Unless otherwise stated, the $^{1}H$ NMR chemical shifts are reported in ppm downfield from an internal tetramethylsilane standard with $CDCl_3$ as the solvent and the $^{13}C$ NMR spectra are referenced to the center resonance of $CDCl_3$ (77.0 ppm). Infrared spectra are reported in units of $cm^{-1}$. Isotopic ratio mass spectral data were obtained by computer integration of oscillographic traces of the molecular ion regions. Gas chromatography was performed using a capillary column, and chromatographic separations were performed using silica gel high-pressure (HPLC) or medium-pressure (MPLC) columns. The elemental analyses were performed by the University of Illinois Microanalytical Service. X-ray crystallographic analysis was performed by Dr. Scott R. Wilson and associates at the University of Illinois. Melting points were determined using capillary melting point apparatus and are uncorrected. All solvents and reagents were obtained from commercial sources and were used without further purification except where noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone under a nitrogen atmosphere before use. TMEDA was distilled from $CaH_2$ and stored under a nitrogen atmosphere. The *s*-BuLi was titrated using the method of Tischler and Tischler or of Suffert.[30]

**Preparation of (*R**,*S**)-2,3-Dideuterio-*N*,*N*-diisopropyl-2-methyl-3-phenylpropanamide (5).** To a solution of 0.5 g (2.0 mmol) of **13** in 50 mL of EtOAc and 3.0 mL of $D_2O$ was added 0.1 g (0.3 mmol) of 30% Pd/C. The solution was agitated under 50 psi of $D_2$ for 22 h. The mixture was filtered through Celite and concentrated in vacuo to afford a crude solid. The crude solid was purified by MPLC separation using 5% EtOAc/hexane as the solvent to afford 0.45 g (90% yield) of **5** as a white solid that was found to contain 94.0% $d_2$, 5.4% $d_1$, and 0.6% $d_0$ material: mp 33.5–35.0 °C; $^{13}C$ NMR δ 18.19, 20.49, 20.72, 20.78, 20.82, 21.34, 40.30 (t), 45.55, 46–47 (br), 125.95, 128.10, 129.05, 140.38, 175.20; $^{1}H$ NMR δ 0.86 (br d, $J = 6.4$ Hz, 3 H), 1.09 (d, $J = 6.8$ Hz, 3 H), 1.13 (s, 3 H), 1.26 (d, $J = 6.7$ Hz, 3 H), 1.33 (d, $J = 6.7$ Hz, 3 H), 2.59 (s, 1 H), 3.3–3.6 (br, 1 H), 3.84 (br m, $J = 6.6$ Hz, 1 H), 7.15–7.35 (m, 5 H).[31]

**Preparation of (*R**,*R**)-2,3-Dideuterio-*N*,*N*-diisopropyl-2-methyl-3-phenylpropanamide (6).** To a solution of 0.50 g (2.0 mmol) of **16** in 30 mL of EtOAc and 2.5 mL of $D_2O$ was added 0.1 g (0.3 mmol) of 30% Pd/C. The solution was agitated under 50 psi of $D_2$ for 48 h. The procedure used to isolate amide **5** was used to afford 0.46 g (93% yield) of **6** as a white solid that was found to contain 90.0% $d_2$, 7.9% $d_1$, and 2.1% $d_0$ material: mp 33.5–35.0 °C; $^{13}C$ NMR δ 18.10, 20.44, 20.66, 20.78, 21.26, 39.8 (br), 40.05 (t), 45.50, 46–47 (br), 125.93, 128.07, 129.09, 140.30, 175.20; $^{1}H$ NMR δ 0.85 (br d, $J = 6.4$ Hz, 3 H), 1.08 (d, $J = 6.6$ Hz, 3 H), 1.12 (s, 3 H), 1.26 (d, $J = 6.7$ Hz, 3 H), 1.32 (d, $J = 6.7$ Hz, 3 H), 2.99 (s, 1 H), 3.3–3.6 (br, 1 H), 3.84 (br m, $J = 6.6$ Hz, 1 H), 7.10–7.30 (m, 5 H).[31]

**Metalation of *N*,*N*-Diisopropyl-2-methyl-3-(phenylthio)butanamide (7).**[32] To a stirring solution of 74.5 mg (0.25 mmol) of **7** and 0.05 mL (0.30 mmol) of TMEDA in 3.0 mL of THF at −78 °C was added 0.23 mL (0.30 mmol) of *s*-BuLi. After 1 h, 2.0 mL (49 mmol) of $CH_3OD$ was added. The cooling bath was removed, and the solution was allowed to warm to room temperature before 10 mL of 2% HCl in saturated $NH_4Cl$ was added. The mixture was extracted with 20 mL of ether and washed with 10 mL of 2% HCl in saturated $NH_4Cl$ and 10 mL of brine before being dried over $MgSO_4$. Removal of the solvent in vacuo followed by HPLC separation using 5% EtOAc/hexane gave 59.8 mg, 80% yield, of **24** and **25** as a light yellow oil with a boiling point of 140 °C (0.40 mmHg). The ratio of **24** (retention time 5.17 min) to **25** (retention time 4.07 min) was found to be 84:16 as determined by capillary GC at 180 °C. The mixture was found to contain 98% $d_1$ and 2.0% $d_0$ material: $^{1}H$ NMR (for the major diastereomer **24**) δ 1.17 (d, 3 H), 1.19 (d, 3 H), 1.25 (s, 3 H), 1.30–1.40 (overlapping doublets, 9 H), 2.65 (q, 1 H), 3.35–3.65 (br, 1 H), 3.95–4.10 (br m, 1 H), 7.15–7.30 (m, 3 H), 7.40–7.45 (m, 2 H). Anal. Calcd for $C_{17}H_{26}DONS$: C, 69.32; H, 9.25; N, 4.76; S, 10.97. Found: C, 69.24; H, 9.20; N, 4.74; S, 11.02.

**Metalation of Mixture 1.**[33] To a stirring solution of 0.075 g (0.30 mmol) of a mixture of **6** and **4** (44.2% $d_2$, 4.1% $d_1$, 51.7% $d_0$ material) in 6.0 mL of THF at −78 °C under an argon atmosphere was added 0.065 mL (0.090 mmol) of *s*-BuLi. After the solution was allowed to stir for 45 min 0.33 mL (0.15 mmol) of a 0.1 g/mL solution of PhSSPh in THF was added. The resulting

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(30) Tischler, A. N.; Tischler, M. H. *Aldrichemica Acta* **1978**, *11*, 20. Suffert, J. *J. Org. Chem.* **1989**, *54*, 509.

(31) The nondeuterated isomer **4** was identified by $^{1}H$ and $^{13}C$ NMR, mass spectrum, IR, and elemental analysis. These spectra were previously reported[2a] and the spectra of the deuterated isomers **5**, **6**, and **23** are consistent with the spectra of **4**.

(32) The metalation procedure given for **7** represents the general procedure used for **8–12**. The experimental results from the metalation of **8–12** are presented in the supplementary material.

(33) The metalation procedure given for mixture 1 represents the general procedure used for mixture 2 and mixture 3. The experimental results from the metalation of mixtures 2 and 3 are presented in the supplementary material.

solution was allowed to gradually warm to room temperature overnight before 5 mL of 2% HCl in saturated $NH_4Cl$ and 5 mL of ether were added. The layers were separated, and the aqueous layer was washed twice with 5-mL portions of ether. The combined ether layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a crude oil. The extent of reaction was determined to be 0.20 by analytical HPLC techniques. The excess PhSSPh was removed by MPLC separation using 5% EtOAc/hexane as the solvent to afford 0.073 g (90% recovery) of a mixture of **6**, **4**, **21** and **22**. The recovered starting materials **6** and **4** were found to contain 47.0% $d_2$, 3.5% $d_1$, and 49.5% $d_0$ material, and the substituted products **21** and **22** were found to contain 39.3% $d_2$, 5.6% $d_1$, and 55.1% $d_0$ material.

**$^{13}$C NMR Spectrum of 20.** To a solution of 0.147 g (0.595 mmol) of **4** in 2 mL of THF-$d_8$ in a 10-mm NMR tube at −78 °C under a nitrogen atmosphere was added 0.51 mL (0.71 mmol) of *s*-BuLi. The solution was vigorously shaken by hand to insure complete mixing. The yellow anion solution was placed into the spectrometer, which had been previously cooled to −70 °C and locked on the resonance at 3.6 ppm of THF-$d_8$. The sample was allowed to equilibrate to the temperature of the probe over 15 min before the $^1$H decoupled, $^{13}$C NMR spectrum was obtained. The center peak of the downfield quintet of the THF-$d_8$ was used as the reference peak and was set to be 67.5 ppm: $^{13}$C NMR of **20** in the region from 40 to 200 ppm (75 MHz) $\delta$ 42.5, 46.7, 49.2, 55.9 (br), 103.1, 108.4, 116.3, 127.9, 129.6, 154.2, 185.4. The anion solution was quenched with excess $CH_3OD$ to give the $\beta$-deuterated product, which was found to contain 95% $d_1$ material at the $\beta$-position as determined by $^1$H NMR integration. The $^{13}$C NMR spectrum of **4** at −70 °C in THF-$d_8$ was obtained in a similar manner: $^{13}$C NMR of **4** (75 MHz) $\delta$ 19.0, 20.6, 20.9, 21.1, 21.2, 39.6, 41.6, 46.2, 49.2, 126.8, 128.9, 130.2, 141.8, 174.3.

**Acknowledgment.** We are grateful to the National Institutes of Health, the National Science Foundation, and G. D. Searle for support of this work and to Dr. Scott Wilson for the X-ray structure determination. We also thank Lithium Corporation of America for a generous gift of *sec*-BuLi and Professor W. C. Still for providing us with the updated version of MACROMODEL.

**Supplementary Material Available:** For **7**, crystal and experimental details, solution and refinement summary, ORTEP figures of the two independent molecules, atomic coordinates, thermal parameters, and bond lengths and angles; experimental procedures for the synthesis of **7**, **8**, **13–16**, and **23**; and the metalation of amides **8–12** and mixtures **2** and **3** (35 pages). Ordering information is given on any current masthead page.

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# Amine–Flavin Electron Transfer Photochemistry. Potential Models for Monoamine Oxidase Catalysis and Inhibition

Jong-Man Kim, In-Seop Cho, and Patrick S. Mariano*

*Department of Chemistry and Biochemistry, University of Maryland at College Park,*
*College Park, Maryland 20742*

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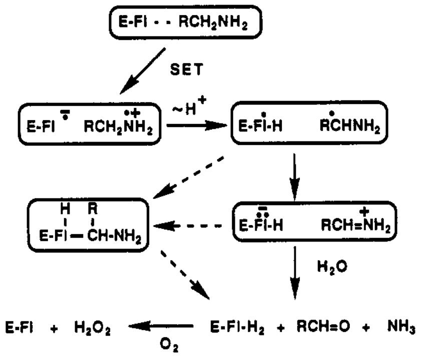
The photoreactions of 3-methyllumiflavin (3MLF) and a variety of amines have been explored. These studies have demonstrated that 3MLF undergoes efficient photoreactions with $\alpha$-silyl tertiary benzylamines to generate 4a-adducts by pathways involving sequential SET and desilylation followed by radical coupling. These adducts are unstable substances that react rapidly with nucleophiles (e.g., MeOH, $H_2O$, and $NaBH_4$) and oxygen. They are also photolabile, providing the corresponding 4a-benzyldihydroflavin upon irradiation. Non-silicon-containing primary and secondary amines also participate in SET-promoted photoreactions with 3MLF. The amine cation radicals formed in these processes undergo further transformations to produce radical intermediates by either $\alpha$-CH or NH deprotonation pathways. The potential relevance of these findings to the area of monoamine oxidase chemistry is considered.

## Introduction

**Monoamine Oxidase Biochemistry.** Monoamine oxidases (MAO) are a class of flavin-containing, membrane enzymes whose members function to control the levels of a number of biogenic amines.[1] These enzymes catalyze the oxidative deamination of their primary amine substrates (e.g. norepinephrine and serotonine) to produce aldehydes and ammonia. In recent years much attention has been given to studies of the mechanism for both catalysis by and inhibition of these enzymes. This intense interest has been stimulated by observations which show that inhibitors of these enzymes display important pharmacological properties related to their use as medicinal agents in the treatment of depression[1a,2] and Parkinson's disease.[3]

### Scheme I



Recently, reasonable radical mechanisms have been proposed for both the catalytic and inhibition reactions of the monoamine oxidases. Krantz and Lewis, for example, have formulated a single electron transfer (SET) mechanism for the pharmacologically relevant inhibition reactions of propargylic (e.g. pargyline) and related alle-

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(2) (a) Palfreyman, M. G.; McDonald, I. A.; Bey, P.; Schechter, P. J.; Sjoerdsma, A. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **1988**. (b) Squires, R. F. *Adv. Biochem. Psychopharmacol.* **1972**, *5*, 355. Neft, N. H.; Goridis, C. *Ibid.* **1972**, *5*, 307. Selikoff, I. J.; Robitzek, E. H.; Ornstein, G. G. *Q. Bull. Sea View Hosp.* **1972**, *13*, 17. Ho, B. T. *J. Pharm. Sci.* **1972**, *61*, 821. Sadler, M. *Proc. R. Soc. Med.* **1973**, *66*, 947.

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