# ASYMMETRIC DIALKYLATION OF CHIRAL 2-BENZAZEPINE FORMAMIDINES†

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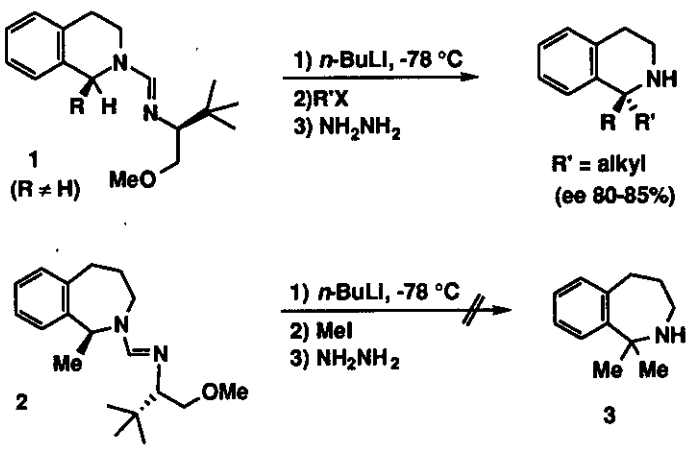
***Abstract*** *- Repeated metallation and alkylation of an (S)-(+)-tert-leucinol derived 2,3,4,5-tetrahydro-1H-2-benzazepine formamidine leads to the corresponding 1,1-dialkyl-2-benzazepines in good yields and with excellent enantioselectivities.*

Previously, we reported that metallation and alkylation of chiral 2,3,4,5-tetrahydro-2-benzazepine formamidines (**5**) provided the corresponding monoalkylated 2-benzazepines (**6**) in good yield and with high enantioselectivities (84-96% ee).[1] At that time, the absolute stereochemistry of the major isomer resulting from these alkylations was tentatively assigned the *S*-configuration.[2] This assignment has subsequently been confirmed by anomolous dispersion single crystal X-ray analysis[3] and was found to be in agreement with the predicted assignment (as shown for **6**). Our continued studies in this area have now been extended to a synthesis of the related quaternary substituted compounds (**7**).

It was earlier shown[4] that treatment of the *tert*-leucine methyl ether isoquinoline formamidine (**1**) with *n*-butyllithium in THF at -78 °C provides a 3° α-amino anion which can be alkylated with a variety of simple electrophiles. Suprisingly, an attempt to alkylate the benzazepine formamidine (**2**) under similar conditions failed to provide the corresponding 1,1-dimethylbenzazepine (**3**). This suggested that, a) either **2** was not deprotonated under these conditions; or b) that approach of the electrophile (MeI) was severely hindered in this system.

† Dedicated to the memory of Professor Yoshio Ban whose important contributions to organic chemistry will not be forgotten.




It was subsequently confirmed by a deuterium quenching study, that **2** was, indeed, not deprotonated by *n*-butyllithium at -78 °C (Table 1). Additionally, it was found that both *t*-butyllithium and *sec*-butyllithium failed to deprotonate this compound at -78 °C, although the reaction with *sec*-butyllithium provided partial deuterium incorporation after 1 h (~10% by $^1$H nmr). It was found after some experimentation, that treatment of **2** with *sec*-butyllithium (-78 °C) and then warming to -40 °C (1 h) provided **4** with > 95 % deuterium incorporation ($^1$H nmr analysis).

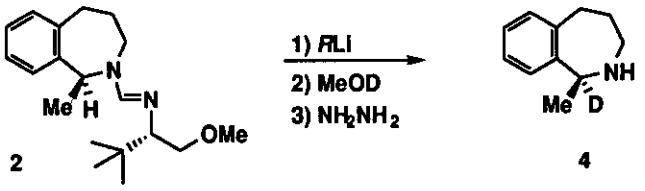



**Table 1.** Various conditions for deprotonation of **2**.

| Entry | Base (RLi) | Temp (Time) | % Deuterium |
|---|---|---|---|
| 1 | *n*-BuLi | -78 °C (1.0 h) | 0 |
| 2 | *t*-BuLi | -78 °C (1.0 h) | 0 |
| 3 | *sec*-BuLi | -78 °C (1.0 h) | ~10 |
| 4 | *sec*-BuLi | -78 °C → -40 °C (1.0 h) | >95 |

Having now developed suitable conditions to effect a second deprotonation of the monoalkylated benzazepine formamidine (**2**), a series of enantiomerically enriched 1,1-dialkyl-2,3,4,5-tetrahydro-2-benzazepines (**7**) were prepared from the chiral benzazepine formamidine (**5**) (Table 2). Thus, metallation (*n*-BuLi, THF, -78 °C) and alkylation (-90 °C, $R^1X$) of (**5**) provided the crude monoalkylated formamidines (**6**) which were filtered through a short column of silica gel (hexanes/ethyl acetate/$Et_3N$ 50:45:5) and immediately subjected to a second metalation-alkylation sequence (*sec*-BuLi, THF, -40 °C, 1h; -90 °C, $R^2X$).[5] Thereafter, methanol quench (-90 °C) and removal of the chiral auxiliary (EtOH/$NH_2NH_2 \cdot H_2O$/HOAc (17:2:1), 60 °C, 6 h) provided the dialkylated amines (**7**) in good yields and with moderate to excellent enantioselectivities.

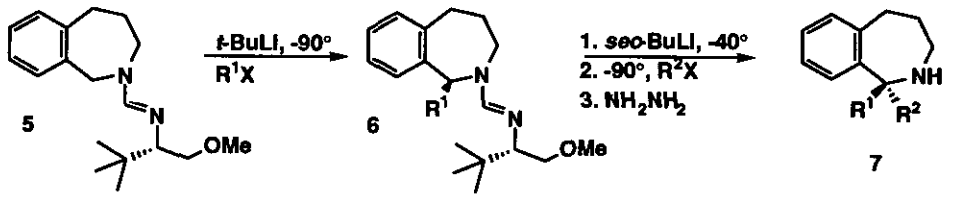



**Table 2**. Asymmetric dialkylation of *t*-leucinol benzazepine formamidine (**5**).

| Entry | $R^1X$ | $R^2X$ | Yield **7** (%) | Ratio of **7** (S:R)[a] |
|---|---|---|---|---|
| 1 | MeI | MeI | 53 | ------- |
| 2 | MeI | *n*-PrBr | 84 | 25:75[b] |
| 3 | *n*-PrBr | MeI | 80 | >99:1[b] |
| 4 | MeI | BnBr | 56 | 65:35[c] |
| 5 | BnBr | MeI | 60 | >99:1[c] |
| 6 | $I(CH_2)_3OTBS$ | MeI | 76 | >99:1[d] |
| 7 | *n*-PrBr | $MeOCH_2Cl$ | 84 | 2:98[e] |
| 8[f] | *n*-PrBr | $MeOCH_2Cl$ | 70 | 6:94[e] |

a) Unless otherwise indicated ratios were determined by Chiral hplc using a Diacel Industries Chiracel OD column. b) Analysis of *p*-methoxybenzamide (Chiracel OJ), Hexane/Isopropanol (96:4), Flow = 0.75 ml/min. c) Analysis of *p*-methoxybenzamide, Hexane/Isopropanol (95:5), Flow = 0.55 ml/min. d) Analysis of *p*-methoxybenzamide, Hexane/Isopropanol (98:2), Flow = 0.60 ml/min. e) Analysis of naphthamide, Hexane/IEthanol (98:2), Flow = 0.75 ml/min. f) alkylation of (*S*)-valine methyl ether benzazepine formamidine.

As indicated above, alkylation of the intermediate monoalkylated formamidines (**6**) occurred predominately from the α-face with net retention of configuration.[6,7] This sense of addition is consistent with earlier studies involving the isoquinoline formamidines.[2] The enantiomeric excesses for the 2-benzazepine alkylations, however, were significantly higher (10-20%) than in the corresponding isoquinoline system (Entries 3, 5-8). Moreover, it was found that the extent of asymmetric induction in the 2-benzazepines was significantly attenuated by the nature of the R-group at C-1. Thus, when $R^1X$ was iodomethane (Entries 2 and 4), the second alkylation occurred with greatly decreased levels of diastereoselection, indicating a previously unobserved steric effect. On the other hand, introduction of iodomethane in the second alkylation step gave excellent stereoselectivity (Entries 3, 5, 6). A change from the *tert*-leucinol derived formamidine to the valinol derived formamidine (Entries 7, 8) showed only a negligible effect on the overall level of diastereoselection and this represents a significant deviation from the previously studied isoquinoline system, which experienced an additional 10% drop in selectivity under these conditions.[2] Finally, these data appear to indicate that conformational "flexibility" in the 7-membered benzazepine ring plays an important role in determining the level of diastereoselection for the dialkylation process. Additional studies of this system are in progress.

## ACKNOWLEDGEMENT

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## REFERENCES

1. A. I. Meyers and R. H. Hutchings, *Tetrahedron,* 1993, **49**, 1807.
2. For a recent review of formamidine chemistry including a mechanistic rationale for asymmetric induction see: A. I. Meyers, *Tetrahedron,* 1992, **48**, 2589.
3. *Unpublished* X-Ray data.
4. A. I. Meyers, M. A. Gonzalez, V. Struzka, A. Akahane, J. G. Guiles, and J. S. Warmus, *Tetrahedron Lett.,* 1991, **32**, 5501.
5. Attempts to carry out a "one pot" dialkylation of **5** gave predominantly monoalkylated products with low yields of dialkylated material.
6. The absolute sense of addition was confirmed by anomalous dispersion single crystal X-ray analysis of **7** ($R^1$ = Bn, $R^2$ = Me) (HBr salt).
7. Note the apparent reversal in selectivity for entries 7 and 8 reflects a change in priority due to the methoxymethyl group.

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