

**A Review Of: Highly Enantioselective (-)-Sparteine-Mediated Lateral
Metalation-Functionalization of Remote Silyl Protected ortho-Ethyl
N,N-Dialkyl Aryl O-Carbamates.**



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The paper by Fassler reported the enantioselective, lateral deprotonation of ortho-protected or functionalized tertiary N,N-dialkylaryl O-carbamates and meta-protected carbamates. The influence of organolithium reagents, ratio of organolithium/(-)-sparteine pair versus N,N-dialkyl aryl O-carbamate starting materials, temperature, solvents, electrophiles, substituents located ortho or meta to the O-carbamate moiety, and O-carbamate N-substituents was investigated in this work.

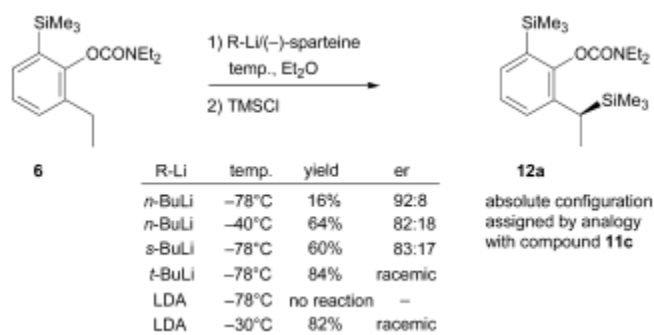


Figure 1. Sparteine-Mediated Lateral Metalation of Compound 6

The effect of base and solvent on the sparteine mediated lateral metalation of 6 will first be discussed. The yield was determined for 13 different experiments and the enantiomeric ratio was determined by CSP-HPLC. The best % yield (75%) was observed when *t*-BuOMe was used as a solvent. When toluene was used the desired enantiomeric ratio was achieved (88:12). When the *t*-BuOMe/toluene solvents were combined (1:3) the optimal yield (78%) and enantiomeric ratio (86:14) were achieved. The effect of temperature and base was also studied in tandem as seen in Figure 1. Using *t*-BuLi at -78°C displayed the highest yield (84%), but as a racemic mixture which was not the desired enantiomeric ratio. The metalation using *s*-BuLi (2.2 equiv. @ 2-3h) at -78°C displayed a lower yield (60%) but a more desirable enantiomeric ratio (83:17). The *s*-BuLi

at -78°C was chosen for all the subsequent studies in this paper. The use of less base also proved detrimental to the overall reaction. This was also observed in our laboratory experiment as we used a less concentrated sec-BuLi which could not synthesize the desired metalation reaction. Experiments were also performed to determine when the sec-BuLi should be added to optimize conditions. They concluded for this particular system, the sec-BuLi must be added at the beginning of the reaction to achieve synthetically useful yields. This was slightly different compared to the procedure followed by our lab. The general procedure for this paper began with a stirred solution of (-)-sparteine in anhydrous solvent at -78°C, then the s-BuLi was added and continued to stir for 15 minutes. A solution of the tertiary amine in anhydrous solvent was then added dropwise resulting in a yellow solution (suspension). In our procedure the tertiary amine is already present in the flask when the s-BuLi is added. It would be interesting to analyze the order of addition for the reagents in our lab.

The next topic covered involved comparing the effect of two substituents with different electronic and steric properties. The two substituents compared were MeO and TMS which were located ortho to the OCONEt₂ group of molecule **6**. The best result when MeO was the substituent was achieved with Et₂O as the solvent which produced a 46% yield and 94:6 ER. The best result obtained when TMS was the substituent was achieved under the ideal conditions (2.2 equiv s-BuLi/(-)-sparteine/Et₂O/-78 °C/2 h) produced 78% yield and 86:14 ER. These results concluded that the bulkier substituent (TMS) located ortho to the O-carbamate moiety leads to a significant loss of enantioselectivity.

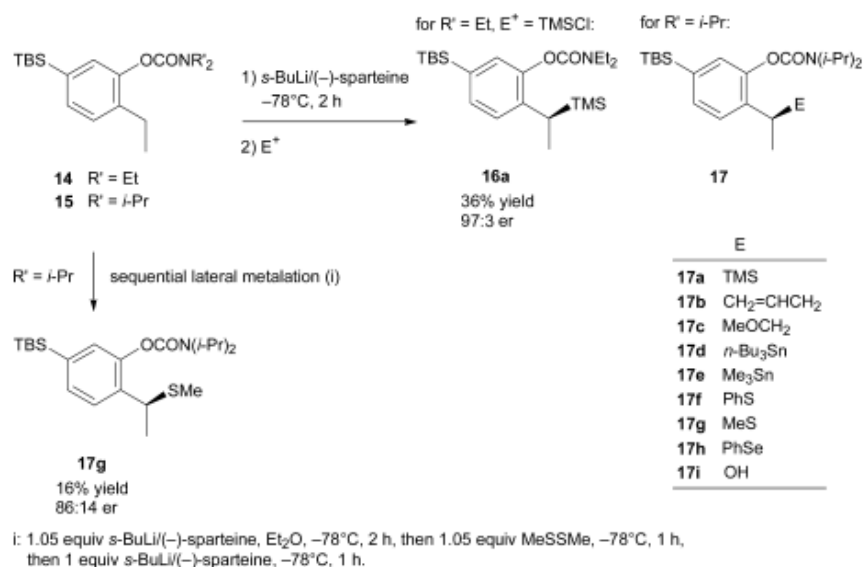


Figure 2. Lateral Metalation of 2-Ethyl Aryl O-carbamates and the effect of remote protection

The introduction of TBS was then investigated as protecting group. When compound **14** was subject to the optimized metalation conditions, followed by TMSCl quench, the product **16a** was produced with 36% yield and 97:3 ER. Although the common theme of low yield but desired ER, another route was examined to increase the yield. When compound **15** was carried out under the same conditions in hexanes (changed solvent due to solubility of **15**), the product **17a** was afforded with high yield (80%) and enantioselectivity (98:2). The absolute configuration of **17g** was further determined by x-ray crystallography studies.

Using compound **15**, a broad scope of electrophiles was introduced to identify the optimal electrophile for this reaction. The experiment produced good results with 8 of 9 of the electrophiles producing high yields (71-91%) and desired enantiomeric ratios (98:2- 94:6).

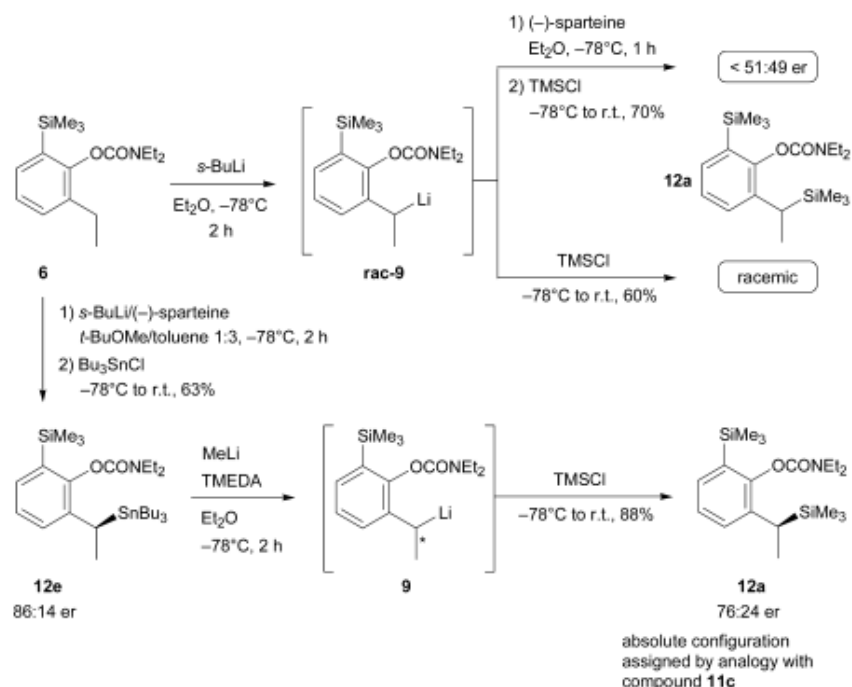


Figure 3. Lateral metalation of 6 and the origin of the observed stereochemistry

Mechanistic aspects of the reaction were studied in Figure 3 to distinguish between asymmetric deprotonation and asymmetric substitution using the protocol established by Beak². Within the lithiation-substitution pathway, asymmetry is introduced by free energy differences in either the formation or reaction of the diastereomeric lithiated species.¹ Compound **6** was metalated using *s*-BuLi in Et₂O for 2h at -78°C to synthesize lithiated product **rac-9**. The **rac-9** product was then treated with (-)-sparteine followed by TMSCl to afford **12a** (70%, 51:49). A control experiment was then performed on **rac-9** in the absence of (-)-sparteine to determine any change. In the absence of (-)-sparteine the yield was slightly less but the ER was maintained (60%, racemic). To determine the enantiodetermining step, molecule **6** was enriched using a tin-lithium exchange using the conditions in Figure 3 to obtain **12e**. The product **12e** was

synthesized with retention of (S)-configuration with good yields but decrease in the desired ER (88%, 76:24). The decrease in ER was attributed to the harsh conditions required to obtain the tin-lithium exchange. With these observations, it was determined that the racemic lithiated species **rac-9** does not lead to enantioinduction upon treatment with (-)-sparteine and the enantioenriched lithiated **9** maintains its configurational stability under these reaction conditions. Therefore, the enantiodiscriminating step in the formation of compound **12** occurs in the deprotonation and not the substitution step. These findings were in contrast to the studies of Beck², which reported leaving group-differentiated enantioselective alkylations in the (-)-sparteine mediated lateral lithiation of ortho-ethyl N,N-diisopropyl benzamides.

The authors also decided to include some aspects of computational chemistry to gain more insight into the stereochemical course of the reaction. The reactions were modeled using a series of semiempirical molecular orbital calculations (PM3) using a gas phase solvated (SMD) model. The reaction path of molecule **20** was studied which revealed three possible low-energy geometries (A, B, C).

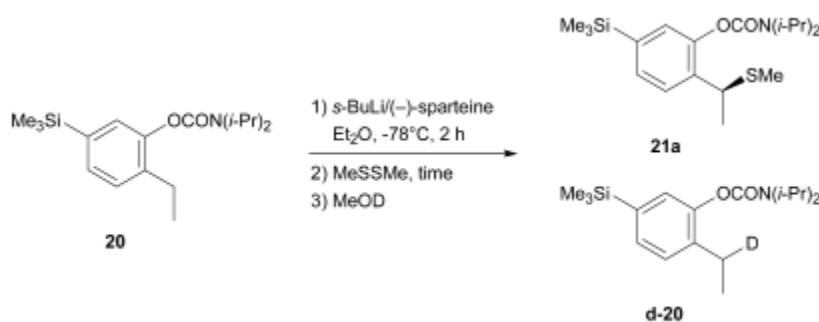
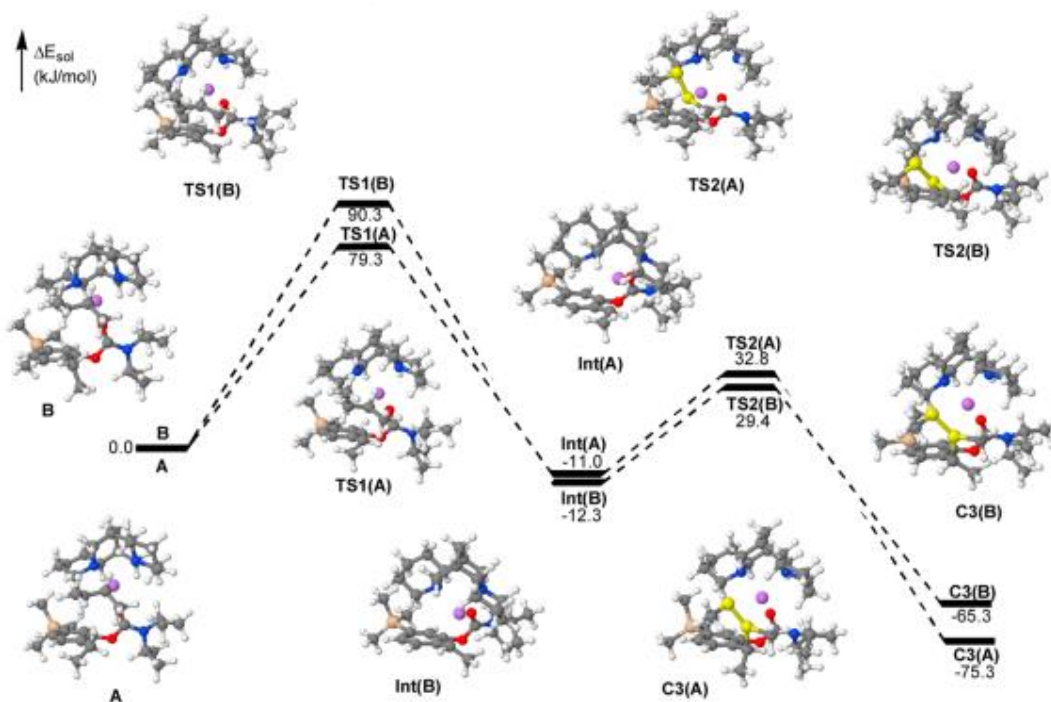


Figure 4. Molecule used in the PM3 SMD calculations



¹Atom colors: Li – purple, S – yellow, Si – pink.

Figure 5. Solvated model reaction pathway for the conversion of 20 to 21a

One of the interesting findings observed involved the TS1(A) and TS1(B). Looking at the free-energy plot the TS1(A) is more stable than TS1(B) by about 11.0 kJ. They determined that the energy difference observed in the theoretical calculations was also in qualitative agreement with the experimentally observed ER for molecule **20**.

References

¹Fassler, J.; McCubbin, A.; Roglans, A.; Kimachi, T.; Hollett, J.; Kunz, R.; Tinkl, M.; Zhang, Y.; Wang, R.; Campbell, M.; Snieckus, V. Highly Enantioselective (–)-Sparteine-Mediated Lateral Metalation-Functionalization of Remote Silyl Protected ortho-Ethyl N,N-Dialkyl Aryl O-Carbamates. *J. Org. Chem.* **2015**, *80*, 3368–3386. <https://doi.org/10.1021/jo502561m>

²Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. J. *Am. Chem. Soc.* 1994, *116*, 9755. (b) For a full account, see: Thayumanavan, S.; Basu, A.; Beak, P. J. *Am. Chem. Soc.* 1997, *119*, 8209. Review: (c) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* 1996, *29*, 552