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Asymmetric alkylation of *N*-pivaloyl-*o*-benzylaniline

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Abstract—Alkylation of 2-methoxyethoxyphenyl phenylmethane using *sec*-BuLi and (−)-sparteine has been carried out in excellent yields and up to 76% ee. The use of O'Brien's (+)-sparteine surrogate gave the opposite sense of asymmetric induction at 80% ee while the use of chiral lithium amide bases gave modest yields and ees.

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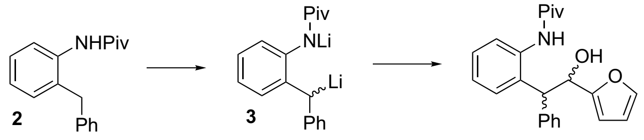
1. Introduction

In two previous papers we have reported a method for the asymmetric alkylation of prochiral alkoxy-diphenylmethane derivatives **1** using *sec*-BuLi and (−)-sparteine (Scheme 1).[1] The best stabilising group was the methoxyethoxy while an unprotected hydroxy group led to a reversal of stereoselectivity and an ee in favour of the (*S*)-product.

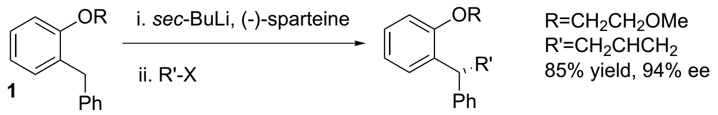
Herein we report the extension of our synthesis to a diarylmethane bearing an amino stabilising group, *N*-pivaloyl-*o*-benzylaniline **2** (Scheme 2).[2] Unlike substrates **1**, this compound has previously been subjected to lateral lithiation, with the dilithio species **3** having been generated with 2 equiv of *n*-BuLi in the presence of TMEDA and reacted with 2-furaldehyde. A 1:1 ratio of diastereomers was obtained.



Scheme 2.

2. Results and discussion

Our first experiments involved allylation reactions using *sec*-BuLi/(−)-sparteine as the chiral base system since these have been used successfully in earlier work. The results of these and other alkylations are shown in Table 1. The formation of the dilithio species required 2.4 equiv of base to be stirred with the substrate at 0 °C for 3 h after which the mixture was cooled to −78 °C before the addition of sparteine. The best results



Scheme 1.

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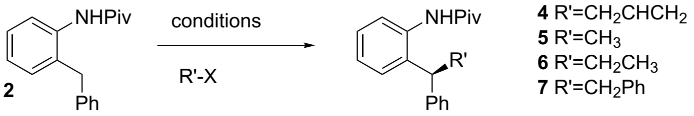
Table 1. Asymmetric alkylations of **2**



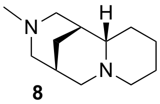
Entry	Product	R–X	Cond.	Yield (%)	Config.	Ee
1	**4**	Allyl-Br	A	90	*S*[*]	76
2	**4**	Allyl-Br	B	93	*S*[*]	71
3	**4**	Allyl-Br	C	95	*S*[*]	70
4	**5**	Me-OTs	A	41	*S*	56
5	**6**	Et-I	A	60	*S*[*]	56
6	**7**	Benzyl-Br	A	80	*S*[*]	46
7	**4**	Allyl-Br	D	89	*R*[*]	80

Conditions: (a) a mixture of **2** and *sec*-BuLi (2.4equiv) in ether is stirred at 0 °C for 3h to form anion. The mixture is then cooled to −78 °C and (−)-sparteine (2.6equiv) added dropwise. After which it is stirred at −78 °C for 2h followed by the addition of the alkylating agent (1.2equiv) and then warmed to rt. (b) (−)-Sparteine (2.6equiv) is added to preformed dilithio in ether at −78 °C, the mixture warmed to −20 °C for 1h and then recooled to −78 °C before the addition of the electrophile (1.2equiv) and warmed to rt. (c) (−)-Sparteine (2.6equiv) is added to preformed dilithio in ether at −78 °C, warmed to −20 °C for 1h and then recooled to −78 °C before the addition of the electrophile (0.5equiv). Next the mixture is warmed to −20 °C for a further 1h before recooling to −78 °C and the addition of the electrophile (0.5equiv) and warming to rt. (d) A mixture of **2** and *sec*-BuLi (2.4equiv) in ether is stirred at 0 °C for 3h to form the anion. The mixture is then cooled to −78 °C and (+)-sparteine surrogate **8** (2.6equiv) added dropwise. Next the mixture is stirred at −78 °C for 2h followed by the addition of an alkylating agent (1.2equiv) and warming to rt. Ee values were calculated using TFAE in the ^{1}H NMR.

[*] Denotes that the configuration of the major enantiomer was assigned by analogy with product **5**.

were obtained using conditions A [entry 1, dianion and (−)-sparteine stirred together at −78 °C for 2h before introduction of electrophile], which gave **4** in 90% yield and 76% ee.[3] The use of either a warm-cool cycle (entry 2) or a warm-cool cycle with batch addition of electrophile (entry 3) did not improve the ee.[4] Allyl tosylate and iodide were also used but gave poor results in terms of ee (20–30%). The use of methyl tosylate (entry 4) formed **5** in a modest yield but gave a respectable ee for the methylation of 56%. Ethyl iodide (entry 5) gave a similar ee of **6**, while benzyl bromide was disappointing in terms of enantioselectivity (entry 6).

Attempts were also made to effect the asymmetric allylation using other chiral base systems. The (+)-sparteine surrogate **8** introduced by O'Brien was utilised (entry 7) and gave the *R*-product in excellent yield and an ee slightly higher than that obtained with (−)-sparteine.[5] A selection of lithium amide bases **9**, **10** and **11** was also investigated giving modest yields and poor ees (best ee 40% with **11**).[6] These results will be discussed fully in a future paper.



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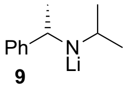

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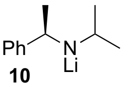

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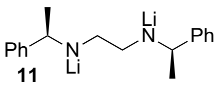

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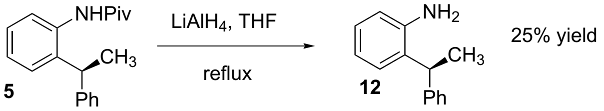


Scheme 3.

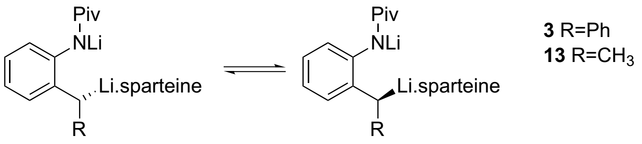
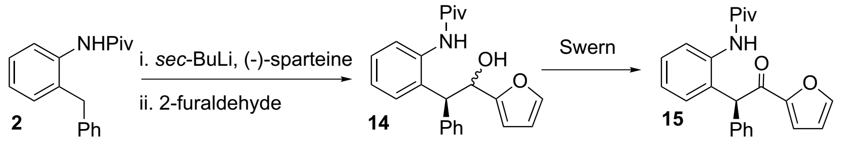


Figure 1.

The ee values for all of the reactions were obtained by the use of (−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) as a chiral shift reagent for proton NMR.[7] The sense of asymmetric induction was obtained by deprotection of the methyl derivative **5** using $LiAlH_4$ to give **12** (Scheme 3), a compound of known specific rotation.[8] The major enantiomers for **4** and **6**–**7** were assumed to be the same as for **5**.

These results suggest that the pair of diastereomeric complexes of **3** and sparteine can interconvert rapidly at −78 °C, since a warm-cool cycle had no beneficial effect on ee. Beak's work on **13** (Fig. 1) showed that this species is configurationally stable at −78 °C in the presence of (−)-sparteine. Presumably the doubly benzylic organolithium **3** has a lower barrier to inversion.

The sense of asymmetric induction in favour of the *S*-product is opposite to that found for the 2-methoxy and 2-methoxyethoxy substituted compounds studied in earlier work. It is the same as that found by Beak in reactions of **13** and as that obtained in our work on allylation of the dilithio species derived from 2-benzyl phenol.



Scheme 4.

We also repeated the reaction with 2-furaldehyde carried out by Schwartz and Yates using *sec*-BuLi/(−)-sparteine instead of *n*-BuLi/TMEDA (Scheme 4). We obtained adduct **14** in a 90% overall yield as an approximately 1:1 mixture of diastereomers. A Swern oxidation provided ketone **15** in 83% yield, which was subjected to TFAE analysis and found to have been formed in 64% ee. The sense of selectivity is assumed to be the same as for the alkylation reactions.

Future work will include screening further coordinating groups and the application of the methodology in synthesis.

Acknowledgements

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References

1. Wilkinson, J. A.; Rossington, S. B.; Leonard, J.; Hussain, N. *Tetrahedron Lett.* **2004**, *45*, 1191–1193; Wilkinson, J. A.; Rossington, S. B.; Leonard, J.; Hussain, N. *Tetrahedron Lett.* **2004**, *45*, 5481–5483.
2. Schwartz, D. A.; Yates, P. *Can. J. Chem.* **1983**, *61*, 1126–1131.
3. All new compounds gave satisfactory spectral data including HRMS. Formation of the product in all reactions of **2** was accompanied by 5–15% of 2-*tert*-butyl-3-phenyl indole. This was easily removed by flash chromatography.
4. Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575–1576; Basu, A.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 5718–5719; See also: Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 717–738, and references cited therein.
5. Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871; Hermet, J.-P. R.; Porter, D. W.; Dearden, M. J.; Harrison, J. R.; Koplin, T.; O'Brien, P.; Parmene, J.; Tyurin, V.; Whitwood, A. C.; Gilday, S.; Smith, N. M. *Org. Biomol. Chem.* **2003**, *1*, 3977–3988.
6. Amine precursors for the bases were prepared according to literature procedures: **9** and **10**: Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1989**, *46*, 523–544, **11**; Mimoun, H.; de Saint Laumer, J. Y.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158–6166.
7. Between 1 and 2 equiv of shift reagent were needed to effect full resolution. For compound **4**, the major *tert*-butyl peak was at 1.123 ppm while the minor peak was at 1.120 ppm.
8. $[\alpha]_D$ of enantiomerically pure (*S*)-isomer is +4.4 (*c* 0.32, benzene) Kinoshita, T.; Ueno, T.; Ikai, K.; Fujiwara, M.; Okamoto, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3273–3282.