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Asymmetric synthesis of diarylmethane derivatives by dynamic kinetic resolution

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ABSTRACT

Asymmetric allylation of *ortho*-methoxydiphenylmethane has been carried out with high yields and ee of up to 94% using the chiral ligand (−)-sparteine as an additive. Results of reactions performed under various conditions suggest that a dynamic kinetic resolution of two rapidly interconverting diastereomeric complexes is occurring.

Introduction

The substituted diarylmethane motif is found in numerous natural products and pharmacologically-relevant structures and a variety of efficient enantioselective methods have been developed for its synthesis.[1] We have previously reported an approach involving lateral lithiation of various diarylmethanes in the presence of a chiral ligand.[2] These substrates included 2-benzylanisole **1** which we were able to allylate in high yield with 60% ee (Scheme 1). Our tentative assumption of a dynamic kinetic resolution was based on the high sensitivity of the reaction to changes in electrophile and the failure of warm–cool cycles to produce high enantioselectivity.[2a]

Our original response to the moderate enantioselectivity obtained for the lateral lithiations of diarylmethane **1** was to use other stabilising groups, which gave much better results.[3] Recently, we have revisited the original substrate as part of a total synthesis and made a more thorough study of its lateral lithiation. We now report a significant improvement in the enantioselectivity of the allylation of **1** based on the use of a dynamic kinetic resolution.

Dynamic resolutions of diastereomeric complexes between an organolithium and a chiral ligand have been used by a number of groups to achieve high enantioselectivities in a variety of transformations.[4] Dynamic resolution takes place under kinetic control if the interconversion of the diastereomeric complexes (*R*)-**2** and (*S*)-**2** (Scheme 2) occurs more quickly than the reactions of the two complexes with the electrophile to give **3**. However, if the equilibration of complexes (*R*)-**2** and (*S*)-**2** is slow under the reaction conditions, a dynamic thermodynamic resolution is possible.[5]

Results

Our previous studies had shown that the organolithium/sparteine complex derived from **1** possessed a small degree of configurational instability at −78 °C.[6] This led us to assume that if higher temperatures were employed, along with slow addition of a solution of the electrophile, equilibration of the diastereomeric complexes would occur more quickly than quenching. Allyl bromide was chosen for the initial studies as the major product (*R*)-**3** had a known specific rotation for the 60% ee sample that had been confirmed by work with NMR chiral shift reagents and conversion to compounds of known absolute configuration.[7] The results of experiments at different temperatures are shown in Table 1.

Increasing the temperature up to −20 °C we observed a steady increase in the enantioselectivity with a maximum 92% ee being obtained using allyl bromide with an addition time of 150 min (achieved by the slow addition of allyl bromide (0.8 mmol) dissolved in ether (50 mL)). This result was confirmed by conversion of the product to carboxylic acid **4** and methyl ester **5** which were both known from a previous work (Scheme 3). A ytterbium shift reagent was also used with the ester, and gave results in agreement with the specific rotation measurements.[8]

At higher temperatures much lower conversion to the product was observed leading us to assume that the organolithium can be slowly quenched by solvent under these conditions since the

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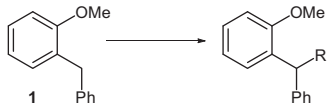
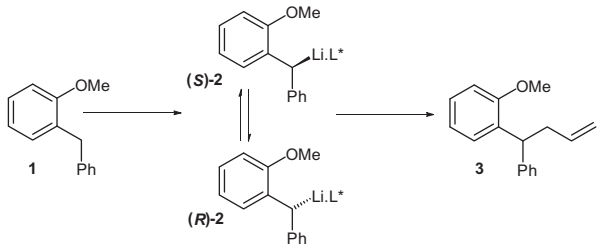
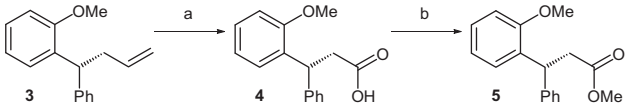


Scheme 1. Reactions of 2-benzylanisole.

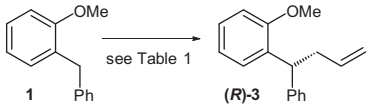


Scheme 2. Dynamic resolutions of complexes derived from **1**.



Scheme 3. Conversion of **3** to carboxylate **4** and ester **5**. Conditions: (a) $RuCl_3$, $NaIO_4$, EtOAc/H_2O/MeCN, rt, 18 h, 86%; (b) TMS–diazomethane, MeOH/toluene, rt, 1 h, 98%.

Table 1
Results of lithiation/allylation reactions



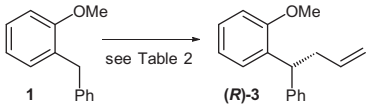
Temperature (°C)	Addition time of electrophile (min)	Yield of **3** (%)	ee of (*R*)-**3** (%)
−78	45[a]	88	60
−60	45[a]	90	58
−40	45[a]	81	66
−20	45[a]	75	84
−20	45[b]	81	93
−20	150[a]	88	92
−20	150[b]	84	94
0	45[a]	Starting material	—

Conditions: *sec*-BuLi (1.2 equiv), (−)-sparteine (1.2 equiv), Et_2O, 2 h; electrophile (1.2 equiv) then added dropwise.
[a] Allyl bromide.
[b] Allyl tosylate.

method used to generate the organolithium was the same in each case. The enantioselectivity dropped off when THF was used as solvent or TMEDA was added to the mixture (46% ee using 1.2 equiv TMEDA). Use of allyl tosylate in place of allyl bromide resulted in significant improvement in enantioselectivity, giving a 93% ee when using a 45 min addition. Our postulate is that the reaction of the organolithium with allyl tosylate is slower than that with allyl bromide allowing the equilibration of diastereomeric complexes to compete more effectively. Using allyl tosylate with the 150 min addition method resulted in a 94% ee, which was only slightly better than allyl bromide under the same conditions. The same major enantiomer (*R*)-**3** was obtained in each case.

The next study involved reactions at −20 °C using less than one equivalent of allyl bromide (Table 2). If the interconversion of

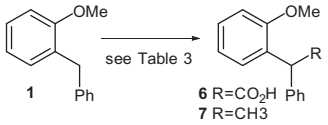
Table 2
Lithiation/allylation with sub-stoichiometric quantities of electrophile



Temperature (°C)	Equivalents of allyl bromide	Yield of **3** (%)	ee of (*R*)-**3** (%)
−20	0.1	7	71
−20	0.2	17	72
−20	0.5	40	70
−20	0.75	68	80

Conditions: *sec*-BuLi (1.2 equiv), (−)-sparteine (1.2 equiv), −20 °C, Et_2O, 2 h; electrophile then added dropwise over 45 min.

Table 3
Substitution using other electrophiles



Electrophile	R	Yield (%)	ee (%)
CO_2	CO_2H	90	80
CH_3I	CH_3	87	46
CH_3OTs	CH_3	90	61

Conditions: *sec*-BuLi (1.2 equiv), (−)-sparteine (1.2 equiv), −20 °C, Et_2O, 2 h; electrophile then added dropwise over 150 min.

diastereomeric complexes is faster than quenching we would observe similar enantioselectivities in each reaction. Conversely, if the complexes were still configurationally stable at −20 °C, there would be considerable variation between the degree and possibly the sense of enantioselection as we increased the equivalence of allyl bromide.

Although the enantioselectivities fell below our best results the ee of product **3** remained approximately constant, regardless of the amount of allyl bromide used to quench the reaction. This suggests that we are observing a dynamic kinetic resolution at this temperature.

Further experiments established that good enantioselectivity was also possible using other electrophiles (Table 3). Using the optimised conditions, carboxylation gave an 80% ee while methylation gave up to 61% ee, a major improvement on our previous results.[9] As with allylation, use of the tosylate gave the more enantioselective outcome.

In conclusion, we have improved on our earlier results for enantioselective allylation of 2-benzylanisole and provided evidence for the presence of a dynamic kinetic resolution.

Acknowledgement

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6. The organolithium/sparteine complexes derived from **1** were regenerated from a trimethyltin compound with 34% ee and quenched with allyl bromide at −78 °C. The product was obtained with the opposite configuration to the simple allylation protocol with 15% ee (see Ref. 2b).
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8. Ytterbium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] gave a significant split in the methoxy peak of **4** in $CDCl_3$. Meyers' group used a europium shift reagent in carbon tetrachloride on compound **5** but this gave no split in $CDCl_3$.
9. The enantioselectivity of the reaction leading to carboxylic acid **6** was analysed using the same method as **5**. The methyl compound **7** is a natural product with known specific rotation but not absolute stereochemistry, see Hesse, G.; Hagel, R. *Liebigs Ann.* **1976**, 996–1008. Major enantiomers are assumed to be (*R*) by analogy with allylations.