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CHIRAL INDUCTION IN ARYL RADICAL CYCLISATIONS

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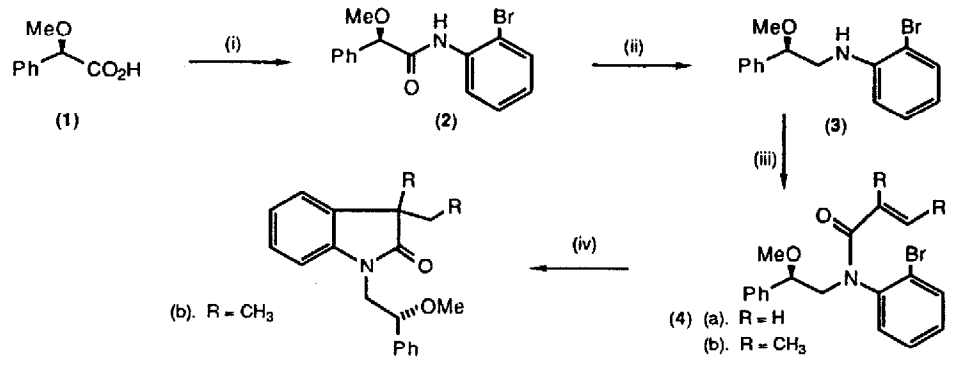
Abstract Ortho-haloacryloylanilides carrying chiral auxiliaries on the nitrogen undergo radical cyclisation to give oxindoles in optical yields up to 39%.

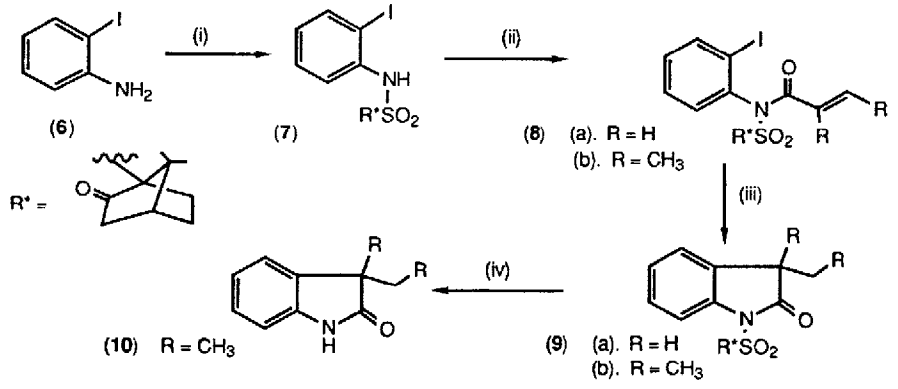
We have recently described the synthesis of 3-substituted, 3,3-disubstituted, and 3,3-spirooxindoles via cyclisation of the aryl radicals derived from o-bromoacryloylanilides[1]. The synthetic utility of this approach to oxindoles has been demonstrated by a formal total synthesis of the alkaloid geneserine[2]. In order to use this methodology in the synthesis of oxindole and indole-derived alkaloids, it is necessary to explore the possibilities for enantioselectivity. As the simple substrates contain no chiral centres, we have investigated the feasibility of chiral induction using chiral auxiliaries on the nitrogen of the starting amide. Although a considerable body of knowledge has built up recently concerning chiral induction in a variety of reactions[3], to our knowledge little work has been published concerning chiral induction in radical reactions[4].

In our earlier work on the cyclisation of these aryl radicals, we had observed that alkylation of the nitrogen of the o-bromoacryloylanilides was essential for successful cyclisation as it fixes the amide in a reactive conformation[5]. In addition, we had observed the expected broadening of signals in the ^{1}H n.m.r. caused by restricted rotation[5a]. Therefore, we believed that a chiral group on the nitrogen, even though somewhat distant from the newly-created chiral centre, would influence the relative amount of attack on the the two diastereotopic faces of the double bond. In order to investigate this hypothesis, we prepared the 6 cyclisation precursors (4a,b), (8a,b), and (14a,b) as outlined in schemes 1, 2, and 3 respectively.

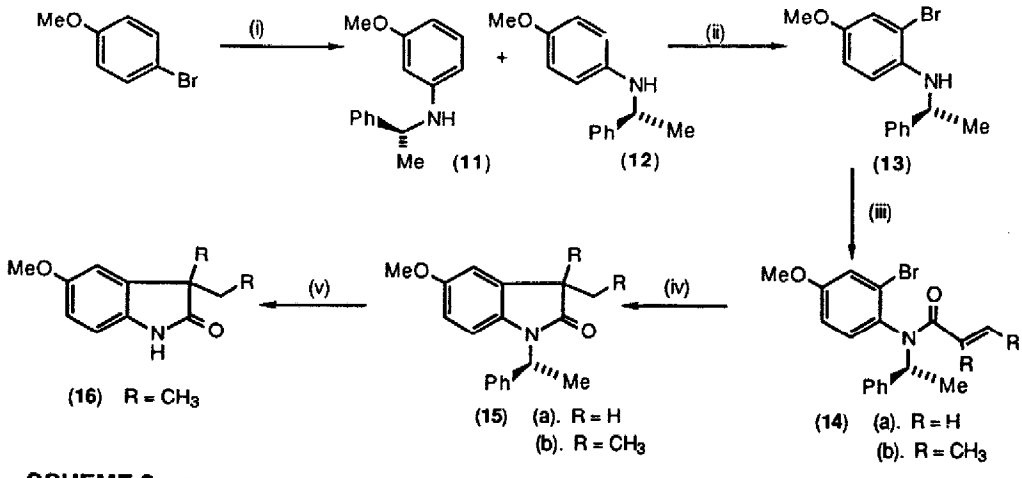
Although the mandelic acid derived chiral auxiliary in (4a,b) cannot be removed readily, it was chosen for study because of ease of synthesis. This proved to be the case and (4a) and



SCHEME 1 Reagents: (i). DCC, THF, 2-bromoaniline; (ii). BH_3.THF; (iii). RCHRCHCOCl, Et_3N, THF; (iv). Bu_3SnH, AIBN, Toluene, reflux.



SCHEME 2 Reagents: (i). 10-camphorsulphonyl chloride, Et_3N, THF; (ii). RCHRCHCOCl, KH, THF; (iii). Bu_3SnH, AIBN, Toluene, reflux; (iv). Li, NH_3



SCHEME 3 Reagents: (i). LiTMP, α-methylbenzylamine, THF; (ii). Br_2, AcOH; (iii). RCHRCHCOCl, KH, THF; (iv). Bu_3SnH, AIBN, Toluene, reflux; (v). KO^tBu, DMSO.

(4b) were prepared in overall yields of 34% and 27% respectively. The camphor sulphonyl group has been successfully used as a chiral auxiliary[6] and (8a,b) were prepared in overall yields of 48% and 45% respectively. In this case, it was found that the aryl iodide was required as the radical precursor as treatment of the corresponding aryl bromide with Bu_3SnH mainly led to cleavage of the N-acyl group. Also, acylation of the sulphonamide (7) required the use of potassium hydride rather than triethylamine. The final chiral auxiliary studied was the α-methylbenzyl group which allows the directing chiral centre to be adjacent to the nitrogen of the acryloylanilide. In this case the methoxy-substituted aromatic precursors (14a,b) were synthesised because extreme difficulty was experienced in acylating the amine corresponding to (13) and not containing the methoxy group. Also, this compound was required for a planned enantiospecific synthesis of geneserine[2]. Although the bromination of (12) proved to be critically dependant upon the reaction conditions and the initial benzyne reaction gave (11) and (12) as a ~1:1 mixture, (14a,b) were prepared in 19% and 16% overall yield.

The radical cyclisation reaction was carried out under standard conditions (1.1 equivalents of Bu_3SnH/catalytic AIBN, in refluxing toluene for 30 minutes) to give the oxindoles (5a,b), (9a), and (15a,b) in the yields shown in the Table. It is not immediately apparent why the acryloyl derivative (8a) failed to cyclise. The diastereomeric excesses also reported in the Table were measured by integration of appropriate peaks in the 360 MHz ^1H n.m.r. spectra of the oxindoles. The camphor sulphonyl auxiliary on oxindole (9b) was removed (Li/NH_3) to give N-unsubstituted oxindole (10) which proved to have an e.e. of 15% as determined using chiral shift reagent. Similarly, the α-methylbenzyl group was removed (KO^tBu, DMSO[7]) from (15b) to give (16) in a chemical yield of 75% and an e.e. of 39%.

It is apparent from the Table that substitution α-to the carbonyl group plays a crucial role in achieving a good d.e. This is not too surprising since a substituent at this position will interact strongly with the chiral group on nitrogen. As the barrier to rotation around the amide bond is of the order of 25kcals/mol[8] and the barrier to rotation around the aryl-carbon to nitrogen bond is about 20kcals/mol[9], it is reasonable to expect that the larger the α-substituent the better the chiral induction. To test this hypothesis, amine (13) was reacted with 2-ethylacryloyl chloride. Even under the most forcing conditions, no acylation could be achieved supporting the conclusion that this steric interaction is important.

In conclusion, we have defined some of the parameters for achieving chiral induction in the cyclisation of aryl radicals to give oxindoles. Clearly, there is a restriction on the size of the group at the α-position of the acryloyl moiety and carefully designed chiral auxiliaries

will be needed to maximise the optical yields of oxindoles required for the synthesis of the physostigmine alkaloids. Finally, although the optical yields in this study are relatively poor, these reactions are all carried out in refluxing toluene and it is possible that using other methods of radical initiation at lower temperatures may enhance the e.e.s of the resulting oxindoles.

TABLE

Cyclisation Substrate	Product	Yield (%)	Diastereomeric Excess (%)
4a	5a	83	7
4b	5b	79	14
8a	9a	0	-
8b	9b	65	15
14a	15a	64	2
14b	15b	59	39

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