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Catalytic Enantioselective Synthesis of Optically Active Phthalides

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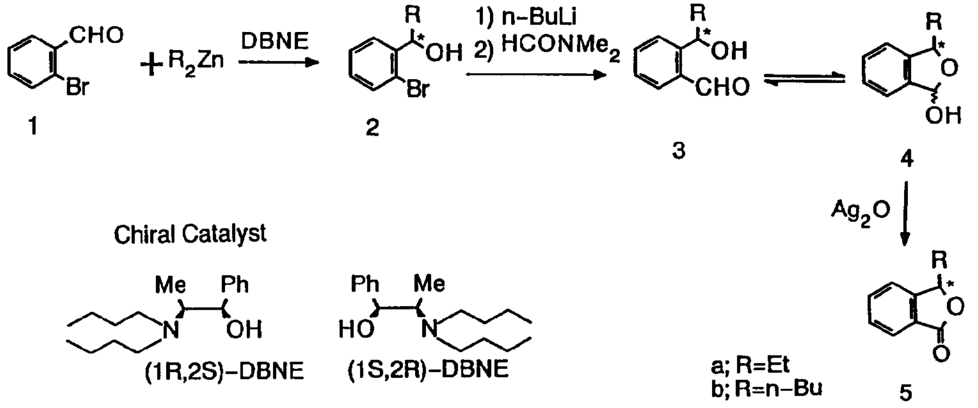
Abstract: Optically active phthalides of high enantiomeric excesses (86-90% e.e.) were synthesized from the addition of dialkylzincs to 2-bromobenzaldehyde using N,N-dibutylnorephedrine as a chiral catalyst.

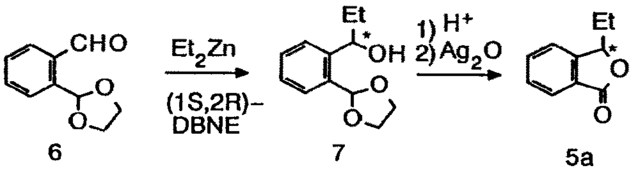
Optically active 3-alkylphthalides(5) are substances present in naturally occurring compounds such as celery oil[1] and alkaloids.[2] Although their asymmetric syntheses employing diamines,[3a,b] diols,[3c,d] and oxazolines,[3e] as chiral auxiliaries have been reported, all of the methods require stoichiometric amounts of chiral auxiliaries. Moreover, most of the conventional methods require the tedious steps for the introduction of chiral auxiliaries into the substrates via σ-bonds and the removal of the chiral auxiliaries from the substrates after the reaction.

We wish to report a catalytic enantioselective synthesis of 5 using N,N-dibutylnorephedrine(DBNE)[4] as a chiral catalyst. When 2-bromobenzaldehyde(1) was reacted with Et_2Zn (2 mol equiv.) in hexane at room temperature for 17 h in the presence of (1R,2S)-DBNE (0.2 mol



equiv.), optically active 1-(2-bromophenyl)propanol(2a) of 90% e.e. (2a) was obtained in 94% yield. Then, the alcohol(2a) was treated with *n*-BuLi, and the subsequent reaction with *N*,*N*-dimethylformamide(DMF) afforded 2-(1-hydroxypropyl)benzaldehyde(3a) and the corresponding lactol(4a)(3 and 4 were in equilibrium) in 82% yield. Oxidation of 3a and 4a with silver oxide[3a] afforded optically active 5a. In a similar manner, using $(n\text{-Bu})_2\text{Zn}$ instead of Et_2Zn, (*R*)-(+)-3-*n*-butylphthalide(5b) $[[\alpha]_D^{24}$ +29.0 (c 4.3, CHCl_3)] with 86% e.e. was obtained.[5] When (1*S*,2*R*)-DBNE was used as a chiral catalyst, (S)-(-)-5b was obtained (e.e. was determined by HPLC analysis using a chiral column. No racemization occurred during the conversion of 2 into 5).

In another experiment, the enantioselective addition of Et_2Zn to phthalaldehyde monoethyleneacetal(6) using (1*S*,2*R*)-DBNE afforded 7. The following hydrolysis of the acetal of 7 and the oxidation(Ag_2O) gave 5a of 76% e.e.



As described, the present catalytic enantioselective method provides optically active 5 of high e.e.'s.[6]

References and Notes

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5. Satisfactory results were obtained for 5a,b from ^{1}H-NMR, IR, and High Resolution MS spectra.
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