3-Benzylidenecamphor derivatives and their conversion into chiral auxiliaries and organocatalysts

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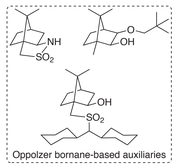
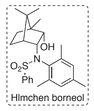
Camphor-based chiral auxiliaries

The rigid camphor system with its well defined geometry potentially possess all the key features required for a highly effective chiral auxiliary. This has been realized by Oppolzer, who developed three general *exo*-substituted bornane derivatives for use in a wide variety of reactions. Helmchen has also developed *endo*-substituted bornane-base alcohols.

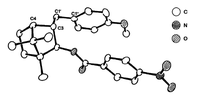


Oppolzer bornane-based auxiliaries



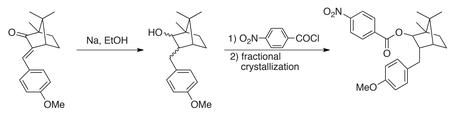
Hlmchen borneol

In earlier work, we demonstrated that the electronically complementary aromatic rings of 3-*endo*-*p*-methoxybenzylisobornyl *p*-nitrobenzoate strongly π-stack, which should make these compounds excellent chiral auxiliaries for conjugate additions and Diels-Alder cycloadditions.

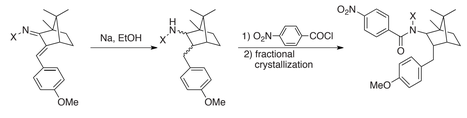


Camphor-based chiral organocatalysts: Initial approaches to targets

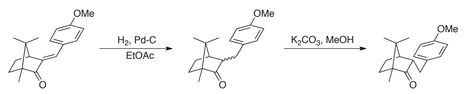
In our earlier work, we had shown that the Bouveault-Blanc reduction of *E*-3-arylmethylenecamphors gave a mixture of the corresponding saturated alcohols as a mixture of the 2-*exo*-3-*exo*, 2-*endo*-3-*endo* and 2-*endo*-3-*endo* diastereoisomers from which the 2-*exo*-3-*endo* isomer could be obtained by fractional crystallization of the mixed *p*-nitrobenzoate esters.



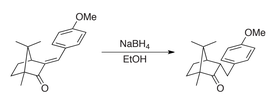
By analogy with that earlier work, we expected that the Bouveault-Blanc reduction of a similar imine derivative should premit us to obtain a *p*-nitrobenzamide derivative with similar crystallizing properties.



To obtain the required imine derivatives, it was necessary to form the 3-*endo*-benzyl ketone first. This was accomplished straightforwardly by catalytic hydrogenation over palladium, which gave a mixture containing predominantly the 3-*exo* isomer; equilibration with potassium carbonate in methanol resulted in almost complete epimerization to the 3-*endo* ketone.

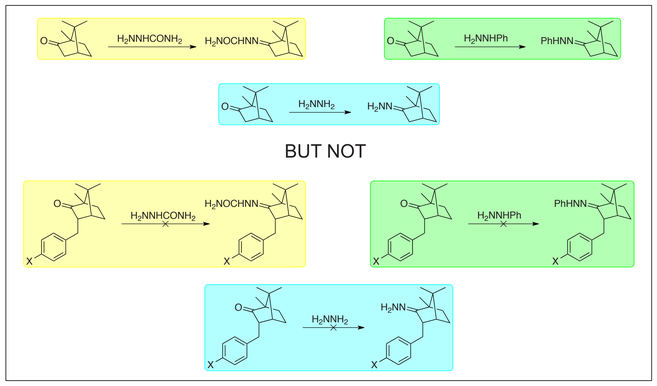


The same overall result could be obtained by direct reduction of the enone with sodium borohydride in ethanol. In this reaction, which gives the 3-*endo*-benzylisoborneol, excess reducing agent only slowly attacks the carbonyl group after the reduction of the double bond.



Reactions of benzylcamphor with nitrogen nucleophiles

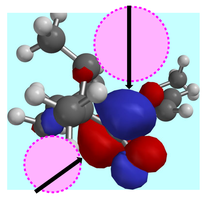
We had expected that the condensation of the benzylcamphor with nitrogen nucleophiles would proceed straightforwardly, but this has not proved to be the case. Despite the fact that camphor itself yields a semicarbazone, a phenylhydrazone and a simple hydrazone, the 3-*endo*-benzylcamphor (X = H or OMe) failed to provide any of these derivatives in isolatable yield. This may have been presaged by the fact that the sodium borohydride reduction of the benzylidenecamphor can so easily be halted at the benzylcamphor stage.

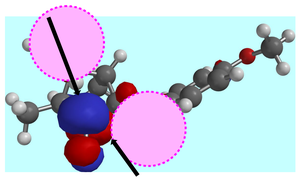


The origins of this problem may be traced to simple steric effects. With the benzyl group in the *endo* position, access to the C—O π* orbital is severely restricted:

1) access to the *endo* face of this orbital requires the nucleophile to attack from a direction where it approximately eclipses the benzyl methylene group and is also hindered by the endo hydrogen at position 6 of the norbornane ring system; and

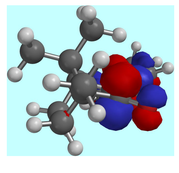
2) access to the *exo* face of this orbital is completely blocked by the 7-*syn* methyl group

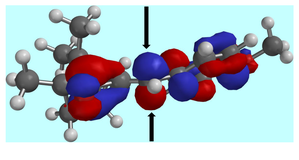




Orbitals of benzylidenecamphor

Examination of the corresponding orbitals of benzylidenecamphor suggested that the β position is sufficiently free of hindrance to allow the formation of an adduct.

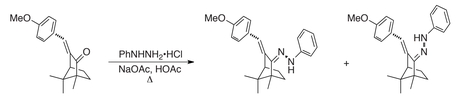




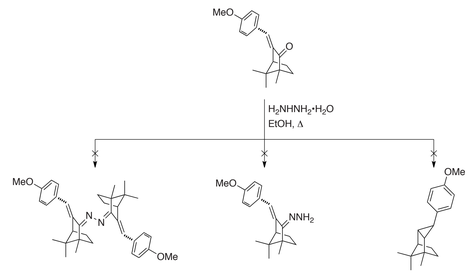
Reactions of benzylidenecamphor with nucleophiles

As an alternative to condensing the benzylcamphor itself with a nitrogen nucleophile, we tested the possibility that we could form the desired compounds from the benzylidenecamphor.

The reaction with phenylhydrazine initially gave us the expected product as a mixture of *E* and *Z* isomers, but the reaction proved to be very irreproducible. The HNMR spectrum showed that the olefinic proton was retained in the product, so the final product was not the *N*-phenylpyrazoline, as might be expected from a mechanism involving conjugate addition followed by condensation with the carbonyl group.

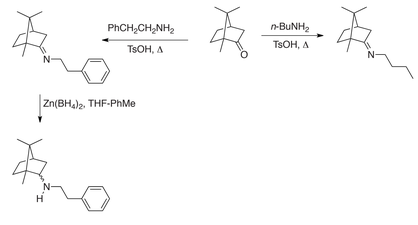


The reaction with hydrazine gave neither the hydrazone, nor the azine nor the pyrazoline. In addition, the possibility that the Kizhner cyclopropane might have been formed was investigated. None of these products was obtained, and the starting enone was the only compound recovered.



Future directions

With the almost uniform failure of our current approaches, we are now investigating the alkylation of imine anions with an appropriate benzyl halide as a means to obtain the desired imine precursor to a secondary amine. At this stage, we have completed the synthesis of both the n-butyl and 2-phenylethyl imines from camphor.



We have also demonstrated that we can reduce the imine *in situ* with zinc borohydride to give a mixture of the *N*-alkylbornylamine and the *N*-alkylisobornylamine. It is reasonable to expect that the isobornylamine will be the major diastereoisomer, but the stereochemistey has not yet been assigned.