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CHIRAL α,β-UNSATURATED OXAZOLINES IN THE ASYMMETRIC DIELS-ALDER REACTION§

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Summary : α,β-Unsaturated oxazolines derived from (+)-camphor become powerful dienophiles in asymmetric Diels-Alder reaction after activation with trifluoroacetic anhydride.

In the past few years the asymmetric Diels-Alder reaction has become one of the most important tools in asymmetric synthesis. High stereochemical control has been secured by the use of chiral dienophiles, chiral dienes[1] or chiral Lewis acids as catalysts.[2] This selectivity is generally[3] due to the use of Lewis acids which increase both dienophilic reactivity and chelation control stereoselectivity. We anticipated that α,β-unsaturated oxazolines[4] could be activated with acyl halides or anhydrides to give rise to very reactive α,β-unsaturated acyl immonium intermediates. This concept has been illustrated with achiral α,β-unsaturated oxazolines[5] and we describe in the present paper the preparation of new chiral oxazolines, readily available from camphor, as well as our preliminary results in the asymmetric Diels-Alder reaction.

Camphor,[6] which is available in both enantiomeric forms, was selected as starting material. Thus, the usual SeO_2 oxidation[7] of optically pure 1R,4R-(+)-camphor gave camphoquinone (90%) whose reduction with L-Selectride[8] afforded regio- and stereoselectively the exo ketol 1 (79%). Condensation of 1 with benzylamine in the presence of 4Å molecular sieves gave the imine 2 (70%). The imino group was in turn reduced with sodium borohydride, thus affording the amino-alcohol 3 in quantitative yield. Hydrogenolysis of the N-benzyl group led to the expected amino-alcohol 4[9] (100%) (Scheme I) (overall yield from camphor 50%).

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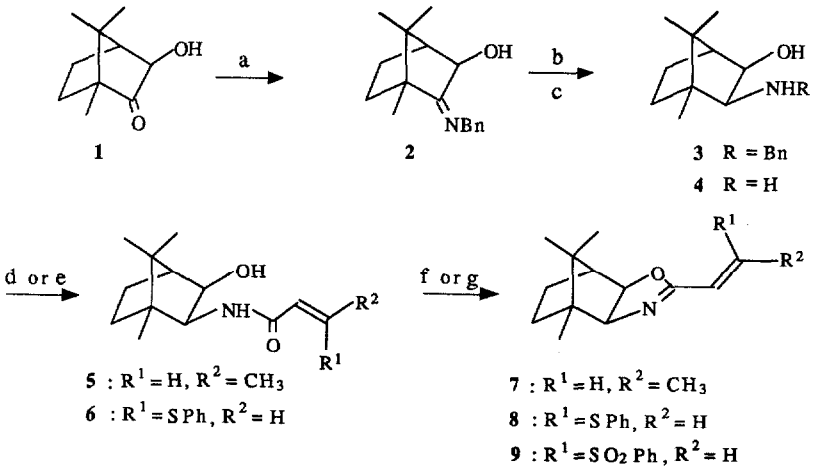
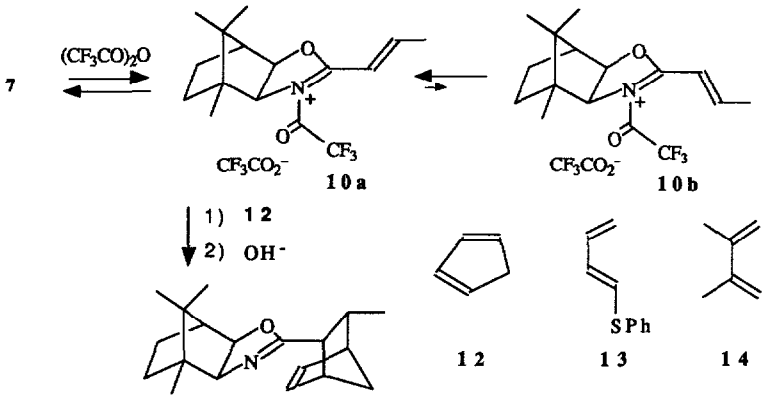
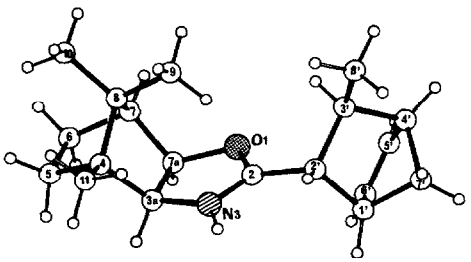
§ Dedicated to Professor D.H.R. Barton on the occasion of his 70th birthday.



Scheme I. a : $BnNH_2$, (2 eq.), THF, 4Å molecular sieves, 20°C, 48 h. b : $NaBH_4$, CH_3OH, 20°C. c : Pd-C, H_2, CH_3OH, 48 h. d : $CH_3CH{=}CHCOCl$ (1.1 eq.), CO_3Na_2 (5 eq.), CH_2Cl_2, H_2O, 20°C, 1 h. e : $PhSCH{=}CHCOCl$ (1.1 eq.), CO_3Na_2 (2 eq.), CH_2Cl_2, H_2O, 20°C, 2 h. f : 5, $POCl_3$ (4 eq.), $PhCH_3$, 100°C, 10 min. g : 6, $POCl_3$ (8 eq.), $PhCH_3$, 100°C, 1 h. h : MCPBA (2 eq.), CH_2Cl_2, 20°C, 5 h.



Scheme II.



X Ray of adduct 11

Reaction of 4 with (E)-2-butenoyl chloride under Schotten-Baumann condition afforded quantitatively the α,β-unsaturated amide 5 which was subsequently cyclized in the presence of phosphorus oxychloride to oxazoline 7 (76%). The same two-step treatment of amino-alcohol 4 with (Z)-3-(phenylthio)-2-propenoyl chloride followed by cyclization furnished oxazoline 8. Oxidation of 8 with MCPBA (2.1 eq.) generated the corresponding sulfonyl-oxazoline 9 (30%) (Scheme I).

The choice of oxazolines 7 and 9 as our synthetic goal was deduced from an examination of molecular models. It was anticipated that the treatment of oxazoline 7 with trifluoroacetic anhydride should give rise to an acyl oxazolinium intermediate, which could exist under two conformations 10a and 10b in equilibrium. The presence of a methyl group on carbon 1 and of the trifluoracetyl group on nitrogen clearly favoured the s-trans conformation 10a. An approach of the dienic compound in the endo mode from the less hindered face of the molecule should then allow a suitable control of the diastereoselectivity of the reaction, affording a single adduct 11 (Scheme II).

Thus oxazolines 7 or 9 in solution in anhydrous methylene chloride in the presence of anhydrous calcium carbonate[10] (3 eq.) and of a diene (3 eq.) were activated with *trifluoroacetic anhydride (1.1 eq.). The reaction was monitored by TLC.* The results are summarized in the Table. With a reactive diene such as cyclopentadiene 12, cycloaddition occurred at low temperature with high diastereoselectivity. It is worthy of note that trifluoroacetic anhydride appeared as the reagent of choice for such cycloadditions; acetic anhydride and methyl chloroformate are less potent, and, surprisingly, with trifluorosulfonyl anhydride we did not observe any cyclisation at low temperature and, at room temperature, cyclopentadiene was readily polymerized. With less reactive dienes like 1-phenylthiobutadiene 13 and 2,3-dimethylbutadiene 14, cycloaddition was observed at a higher temperature with trifluoroacetic anhydride.

Table

Oxazoline	Diene	Reagent (1.1 equiv.)	Adduct	Reaction Temp.[°C] (time, h)	Endo % (yield %)	d.e.
7	12	$(CF_3CO)_2O$	11	-78 (4)	100 (73)	94
7	12	$(CH_3CO)_2O$	11	-78 (1) then 20 (24)	100 (20)	>90
7	12	$ClCO_2Me$	11	-78 (2) then 20 (24)	100 (45)	>90
9	12	$(CF_3CO)_2O$	15a + 15b	*-100 (4)*	*50 (76)*	*>90*
7	13	$(CF_3CO)_2O$ (3 equiv.)	16	0 (6)	100 (47)	>90
7	14 (10 equiv.)	$(CF_3CO)_2O$ (3 equiv.)	17	18 (36)	(50)	>90

The absolute configuration of the adduct 11 was deduced from the X-ray analysis of a single crystal of the corresponding hydrobromide.[11]

It appears from the present results that chiral α,β-unsaturated oxazolines activated with trifluoroacetic anhydride are potent dienophiles in the Diels-Alder reaction. Further results obtained with more reactive acrylic oxazolines and various functionnalized dienes will be published in due course.

References and Notes

For recent reviews on the asymmetric Diels-Alder reaction, see :

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For uncatalyzed asymmetric Diels-Alder reactions, see :

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10. The use of propylene oxide in place of calcium carbonate did not improve the yield of cycloaddition.
11. Crystal data : $C_{19}H_{28}ON^{+}Br^{-}$, M = 366.34, Tetragonal, space group $P4_12_12$, Z = 8. Cell parameters : a=b=10.006(4), c=37.867(6)Å; V = 3791.25Å^3, dc = 1.28 gcm^{-3}, λ(CuKα) = 1.5418Å, F(000) = 1536, μP = 27.6 cm^{-1}. 3267 intensity data were collected on a Philips PW 110 diffractometer using graphite-monochromated CuKα radiation and the θ-2θ scan technique up to θ = 68°. Corrections were applied for Lorentz-polarization effects, a weak intensity decrease, not for absorption.

The structure was solved by the Patterson-Fourier method and refined with anisotopic thermal factors for non-hydrogen atoms by full-matrix least-squares minimizing the function $\Sigma w (Fo-/Fc/)^2$. The hydrogen atoms were located on successive Fourier-difference maps but included in refinement at idealized positions (d c-H=1.0Å) except that one linked to the nitrogen atom N-3, refined with an isotopic thermal factor equivalent to that the bonded atom. Convergence was reached at R=0.065 and wR=0.099 for the 2843 observed reflections having $I>3\sigma(I)$,$\sigma(I)$ derived from counting statistics (weighting scheme at the final stage : $\omega = 1/\sigma^2(Fo) + 0.0088\ Fo^2$, $\omega R = [\Sigma w(Fo-/Fc/)^2 \Sigma Fo^2]^{1/2}$). Calculations were performed with program SHELX76 which also provided the atomic scattering factors. Lists of fractional atomic coordinates, bond lengths and angles are available as Supplementary Material and have been deposited at the Cambridge Crystallographic Data Centre.

The molecule is shown in Fig. 1. The absolute configuration is assigned by the camphor moiety. The structure establishes clearly the stereochemistry of the Diels-Alder cycloaddition.

The bromine ion is linked to the nitrogen atom by an expected hydrogen bond N_3^{+}-Br^{-} of 3.15Å (N_3-H = 0.92Å, angle N_3-H-Br = 169.7°). There are no unusual contacts in the crystal.

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