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Biocatalytic Asymmetric Cycloaddition of Benzonitrile *N*-Oxides to *N*-Vinylcarbazole†

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Baker's yeast catalyses asymmetric cycloaddition of the benzonitrile *N*-oxides **2–4** to *N*-vinylcarbazole **1** to yield optically active 4,5-dihydroisoxazoles **5–7** in good yields with an enantiomeric excess (ee) of up to 51%.

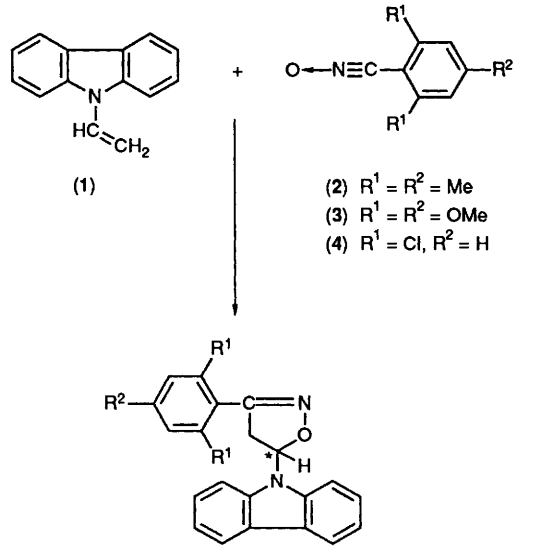
Table 1. 3-Aryl substituted 5-carbazol-9-yl-4,5-dihydroisoxazoles.

Compd. no.	Products R¹	Products R²	Yield (%)	M.p. (°C)	Molecular formula	$[\alpha]_D^{20}$ (°)[a]	Ee %[b]
5	Me	Me	78	132–133	$C_{24}H_{22}N_2O$	+127.9	50.7
6	OMe	OMe	80	236	$C_{24}H_{22}N_2O_4$	+21.3	25.4
7	Cl	H	75	229–230	$C_{21}H_{14}N_2OCl_2$	+11.4	17.6

[a] *c* 1.0 in $CHCl_3$. [b] Determined by ^1H NMR (200 MHz) spectroscopy with $Eu(hfc)_3$ as chiral shift reagent.

In continuation of our work on the utility of enzymes as catalysts in organic synthesis,[1,2] we report herein, the asymmetric 1,3-dipolar cycloaddition of the benzonitrile *N*-oxides **2–4** to *N*-vinylcarbazole **1** in the presence of Baker's yeast (*Saccharomyces cerevisiae*). This biocatalytic asymmetric cycloaddition proceeds without a chiral auxiliary in either dipole or dipolarophile and yields, for the first time, optically active dihydroisoxazoles attached to a heterocyclic nitrogen **5–7** (Scheme 1). These compounds have potential in various stereocontrolled syntheses since 4,5-dihydroisoxazoles represent the masked form of an array of different functionalities.[3,4]

This cycloaddition proceeds to yield only one regioisomer, *i.e.* 3-aryl-substituted 5-carbazol-9-yl-4,5-dihydroisoxazoles **5–7** and is a $LUMO_{(dipole)}$- $HOMO_{(dipolarophile)}$ controlled reaction.



Scheme 1.

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All the compounds were characterised on the basis of elemental analysis and ^1H NMR and mass spectral data. The structural assignments are in conformity with our earlier observations.[5]

The results for the optically active 4,5-dihydroisoxazoles **5–7** obtained are shown in Table 1. Among the compounds studied, the 4,5-dihydroisoxazole **5** formed from 2,4,6-trimethylbenzonitrile *N*-oxide **2** has shown enhanced enantioselectivity with an ee up to 51%. The higher symmetric bias observed for the cycloaddition with **2** may be due to favourable control of geometry in the approach of the dipole and dipolarophile at the 'active site'. Thus, biocatalytic cycloaddition of the *N*-oxides **2–4** to *N*-vinylcarbazole **1** proceeds with appreciable enantioselectivity and further application of this reaction is currently under study.

Experimental

Arenecarbonitrile *N*-oxides were prepared from the corresponding oximes by sodium hypobromite oxidation as described by Grundmann and Dean.[6] To Baker's yeast[7] (0.35 g) taken in pH 7.2 buffer (8.5 ml) was added *N*-vinylcarbazole **1** (1 mmol) in 30% ethanol (10 ml) followed by the benzonitrile *N*-oxide **2–4** (1 mmol) in 30% ethanol (10 ml). The mixture was incubated at 37 °C for 24 h. It was then extracted with chloroform (2 × 20 ml) and the extract dried and evaporated and the residue purified by recrystallisation from chloroform–hexane (1:1).

References

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7 Baker's yeast (*Saccharomyces cerevisiae*, Type 1) was purchased from Sigma Chemical Co., U.S.A.

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