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(4*S*)-*p*-Hydroxybenzyl-1,3-oxazolidin-2-one as a solid-supported chiral auxiliary in asymmetric 1,3-dipolar cycloadditions

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Abstract

Evans' chiral auxiliary was grafted onto both Merrifield and Wang resins and, after functionalisation, they were used as chiral dipolarophiles in a 1,3-dipolar cycloaddition involving both a nitrile oxide and a nitrone. The cycloadducts were cleaved and analysed by chiral HPLC: the recovered supported chiral oxazolidinone was functionalised and reused in further cycloadditions. The stereochemical results as well as the possibility of recycling the chiral linker supports the applicability of solid-supported chiral auxiliaries.

Keywords: asymmetric induction; cycloadditions; oxazolidinones; solid-phase synthesis.

Asymmetric synthesis by 1,3-dipolar cycloaddition (1,3-DC) has gained increasing attention in recent years and can be approached either by the use of a chiral catalyst or by running the reaction with a dipolarophile having a chiral auxiliary group.[1] The first method is the most attractive one for performing asymmetric reactions because a catalytic amount of chiral material is required, and the target product is directly obtained without any further manipulation. Nevertheless the limitations involved in asymmetric synthesis by the use of chiral auxiliaries tempted us to exploit the virtues of the solid phase organic chemistry (SPOC) approach.

The use of polymer-supported chiral auxiliaries gives some benefits: easy separation and recovery of the expensive chiral material; simple isolation of the desired chiral adduct; and possible extension to a continuous flow system.[2] Among the different chiral auxiliaries proposed in the literature, one of the most important was introduced by Evans,[3] and more recently a resin-bound version has been used in several processes such as alkylation,[4] conjugate and aldol additions,[5,6] and Diels–Alder cycloadditions.[7] Here we wish to report the use of a resin-bound Evans' auxiliary as a chiral dipolarophile in 1,3-DC involving either mesitonitrile oxide (MNO) or diphenylnitrone (DPN) as 1,3-dipoles.

The chiral linker was obtained starting from commercial L-tyrosine following a general protocol described for similar compounds (Scheme 1).[8] After esterification of **1**, the amino group was protected

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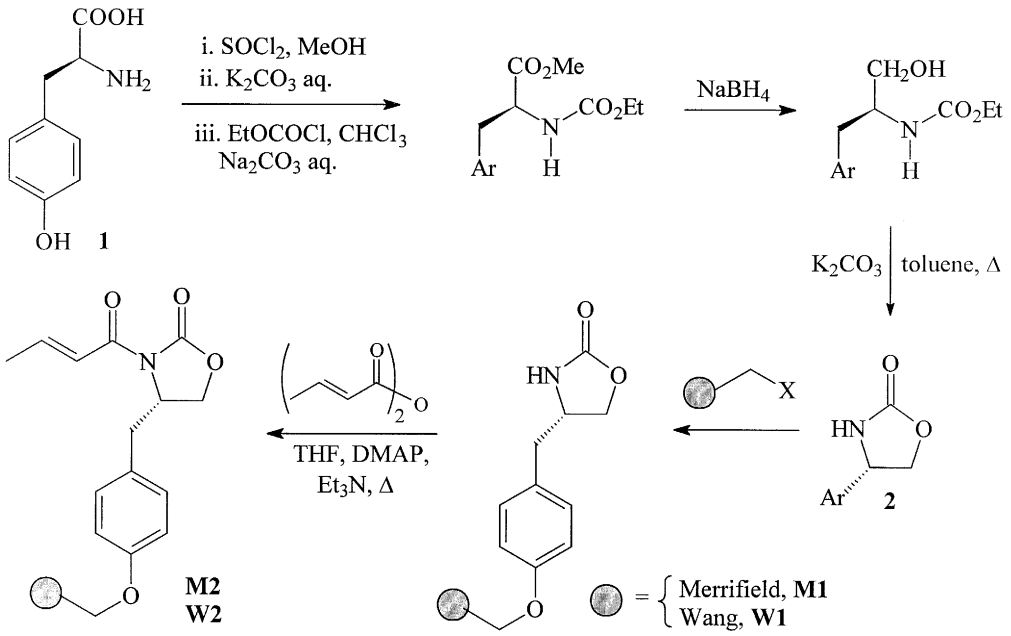
as the *N*-ethoxy carbonyl derivative and the ester group reduced with $NaBH_4$. The resulting alcohol was cyclised under thermal conditions in the presence of K_2CO_3 to give **2** in a 55% overall yield on 0.1 molar scale.[9] The chiral linker was attached directly onto both a Wang resin under Mitsunobu conditions and a chlorobenzyl Merrifield resin by nucleophilic substitution. The resin-bound oxazolidinones **W1** and **M1** were then acylated under mild conditions by reaction with *trans*-crotonic anhydride in THF in the presence of catalytic DMAP and triethylamine at reflux for 72 hours.[11] The loading of **W1** and **M1** was verified by cleavage and recovery of the chiral linker and was found to be 0.89 and 1.02 mmol/g, respectively.

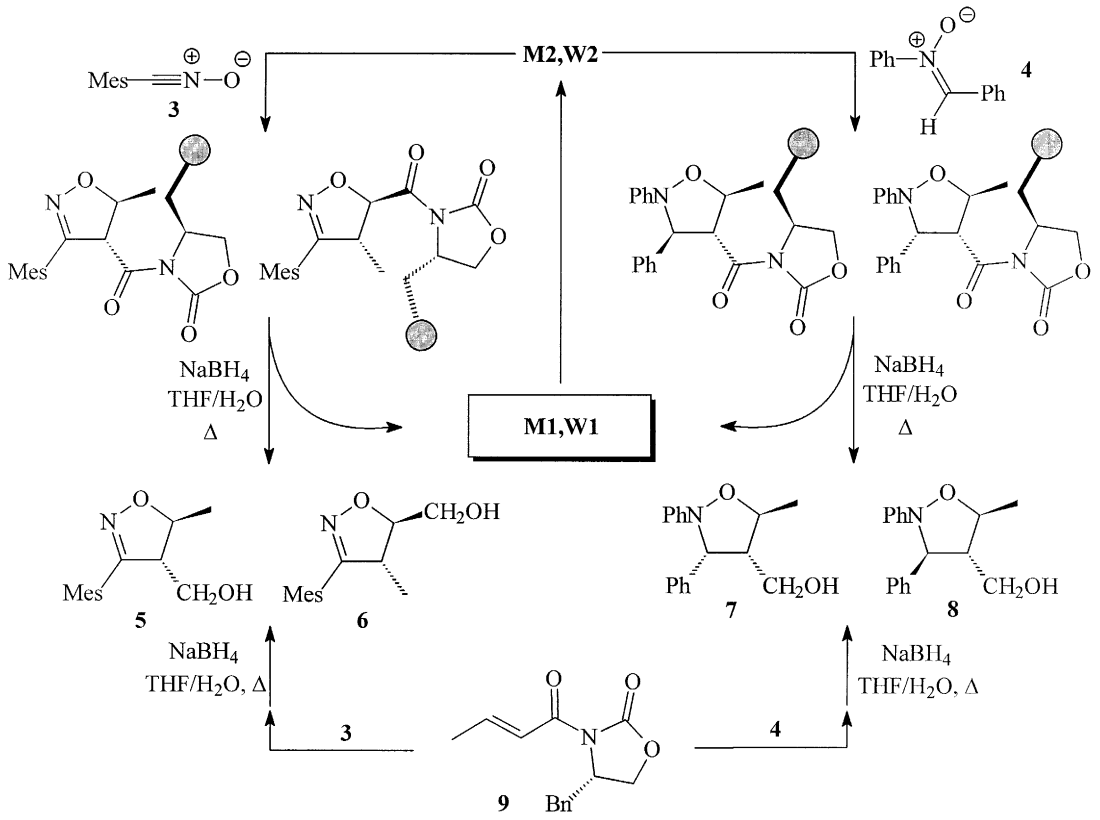


Scheme 1.

The functionalised resins **M2** and **W2** were then allowed to react for the required time at room temperature with both MNO-**3** and DPN-**4** under uncatalysed or catalysed conditions. The cycloadducts were then cleaved from the resin by following a racemisation-free method for the reductive removal of 2-oxazolidinones recently outlined in the literature (Scheme 2)[12] by reduction with $NaBH_4$ in THF/H_2O at ambient temperature. The methanol derivatives **5**–**8** obtained from SPOC and from **9** with the more classic solution chemistry, were analysed by an HPLC equipped with either a Chiralpak AD (**5**, **6**) or a Chiralcel OD (**7**, **8**) column, and the results are collected in Table 1.

Moving from solution to solid phase, the yields of the MNO cycloadducts do not change significantly (entry 1 versus 2–7) nor do the regioisomer ratios. The data in entries 2–7 clearly show the absence of any catalytic effect of Lewis acid as in that observed in solution,[14] but an interesting degree of enantioselection was observed in the formation of **5**, while product **6** was always formed as a racemic mixture. Merrifield resin was found to work better than Wang resin and in entry 4 the results obtained in the presence of $Sc(OTf)_3$ perfectly match the solution ones (entry 1). The remarkably different enantioselectivities in the formation of **5** and **6** can be rationalised in terms of steric interactions between the benzyl substituent on the auxiliary and the mesityl group; this effect arises during the formation of **5** and is absent in the MNO approach leading to **6**.

In the cycloadditions of DPN **4** some relevant differences are found. First of all, the low reactivity of **4** requires longer reaction times and, in the SP conditions, the reaction yields are less satisfactory than



Scheme 2.

those observed in the case of MNO cycloadditions, probably due to DPN decomposition. Moreover, the response of the catalyst in solution or in SP reactions displays a notable difference. In fact, in solution the presence of Mg(II) or Sc(III) deeply influences reactivity, stereo- and enantioselectivity,[13] while the presence of 10% mol of catalyst was ineffective in the reactions run under SP conditions. Presumably the nitrone **4**, which is used in excess (4 equiv.), coordinates to the metal cation and this fact leads to both a decreased Lewis acidity of Mg(II) and Sc(III) and an enhanced competitive decomposition of **4** giving low yields of adducts **7**, **8**, as clearly observed in entries 11 and 14.

As previously stated, the results in DPN reactions depend on the resin employed. The *exo* selectivity observed in solution under uncatalysed conditions (83%) decreases to about 50% in the case of **M2**, while the **W2** reactions turn into *endo* selectivity (~70%). A similar trend is also observed for the *ee* of the *endo*-adduct **8**: excellent for the solution, poor for **M2**, and negligible for **W2**. In contrast, the *exo* adduct is always obtained with the same good enantioselectivity.

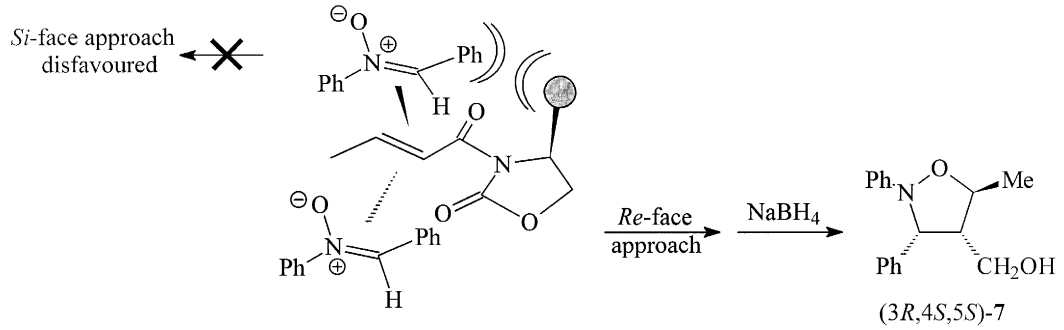
The differences in enantioselectivity as a function of the *exo* or *endo* approach may be rationalised by considering that the two DPN approaches in an *endo*-TS display weaker steric interactions than those for an *exo*-TS. This is confirmed by the absolute configuration of **7** corresponding to the nitrone joining the less hindered *Re*-face of the dipolarophile (Scheme 3).

The resins **M1** and **W1**, recovered after reductive cleavage, were checked by gel-phase ^{13}C NMR,[15] and then **M2, W2** were freshly prepared and tested in the MNO cyloadditions. Cycloadducts **5** and **6** were obtained in comparable yields and selectivities with the Merrifield resin, while the selectivities obtained with the recycled **W2** showed an increased regioisomeric **5**:**6** ratios (75:25) and a diminished

Table 1
Reaction conditions, yields, and product distribution of 1,3-DC of **9**, **W2**, **M2** with **3**, **4** at rt in CH_2Cl_2[a]

n	Dipolarophile	Dipole	Catalyst[b]	time / yield	**5** (*%ee*) : **6**	**7** (*%ee*) : **8** (*%ee*)
1	**9**	**3**	---	4 d / 85%	71 (***63***) : 29	---
2	**M2**	**3**	---	4 d / 54%	67 (***46***) : 33	---
3	**M2**	**3**	$Mg(ClO_4)_2$	4 d / 61%	68 (***55***) : 32	---
4	**M2**	**3**	$Sc(OTf)_3$	4 d / 62%	70 (***60***) : 30	---
5	**W2**	**3**	---	4 d / 55%	72 (***26***) : 28	---
6	**W2**	**3**	$Mg(ClO_4)_2$	4 d / 62%	68 (***33***) : 32	---
7	**W2**	**3**	$Sc(OTf)_3$	4 d / 51%	67 (***35***) : 33	---
8	**9**[c]	**4**	---	15 d / 95%	---	83 (***84***) : 17 (***>99***)
9	**M2**	**4**	---	40 d / 38%	---	53 (***89***) : 47 (***22***)
10	**M2**	**4**	$Mg(ClO_4)_2$	40 d / 43%	---	56 (***81***) : 44 (***24***)
11	**M2**	**4**	$Sc(OTf)_3$	40 d / 25%	---	53 (***86***) : 47 (***29***)
12	**W2**	**4**	---	40 d / 25%	---	31 (***83***) : 69 (***6***)
13	**W2**	**4**	$Mg(ClO_4)_2$	40 d / 27%	---	30 (***81***) : 70 (***6***)
14	**W2**	**4**	$Sc(OTf)_3$	40 d / 20%	---	33 (***81***) : 67 (***7***)

[a]Reactions in entries 2-7 and 9-14 were carried out on 0.5 g of resin. [b]Catalysts magnesium perchlorate and scandium triflate were used in 10% mol respect to the loading of each resin. [c]Data was taken from ref. 13.



Scheme 3.

enantioselectivity of up to 14% *ee*. Nevertheless, the good results obtained with the recovered **M2** support the applicability of solid-supported chiral auxiliaries.

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