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Solid supported chiral auxiliaries in asymmetric synthesis. Part 2: Catalysis of 1,3-dipolar cycloadditions by Mg(II) cation☆

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Abstract—1,3-Dipolar cycloadditions of supported Evans' chiral auxiliary with nitrile oxides and nitrones in the presence of Mg(II) cation as catalyst were evaluated. The presence of acetonitrile as co-solvent was found to be fundamental for the Lewis acid catalysis on solid-phase. The regio- and stereochemical outcome of nitrile oxide cycloadditions is influenced by nearly stoichiometric quantities of the cation, whilst catalytic amounts of Mg(II) influence both the reactivity and the stereoselectivity of the nitrone cycloadditions. The results obtained support a reaction mechanism involving the coordination of the Mg(II) to the dicarbonyl fragment of the chiral auxiliary.

1. Introduction

A useful approach to asymmetric synthesis is offered by the use of temporary linked chiral information. Among the examples in the literature, one of the most useful chiral auxiliaries has been developed by Evans,[2] finding wide applications in several C–C bond forming reactions[3] and, in particular, in the field of cycloadditions.[2–4]

The extensive use of chiral oxazolidinones in asymmetric synthesis is due to their fulfilment of several requirements: easy preparation, high induced selectivities, and ability to interact with several metal cations. The latter feature is particularly relevant since catalysed reactions usually yield increased reactivities and selectivities; the suitable choice of the catalytic system can lead to the selective formation of only one of the possible diastereoisomers.

Chiral oxazolidin-2-ones are easily prepared either starting from natural amino acids or by using a modified sharpless asymmetric aminohydroxylation strategy.[5] When the oxazolidin-2-one is synthesised starting from tyrosine, it can be grafted to a polymer through the phenolic group.[6] A solid-phase approach allows some practical advantages, since the chiral information could be easily recycled for further processes.[1,7]

Despite the increasing relevance of solid phase synthesis in contemporary organic chemistry, only few examples of cycloadditions involving solid supported dienophiles or dipolarophiles have been reported,[1,7d,8,9] and even fewer are the reports investigating catalysed supported cycloadditions.[7d,9a,10] To the best of our knowledge, the only paper referring to the catalysis of cycloadditions involving a supported chiral oxazolidin-2-one derivative is related to a Diels–Alder reaction of the solid supported *N*-crotonyl oxazolidone with cyclopentadiene.[7d] The cycloaddition was efficiently catalysed by Et_2AlCl (1.4–2.8 equiv.), giving results very similar to those observed under classic solution conditions (*endo*/*exo* ratio, 21:1; ee *endo*-adduct, 86%), when Merrifield resin was used. The Wang-resin supported dienophile was unstable in the presence of Al(III) and the catalysed cycloaddition did not yield any of the desired reaction products.

In a previous communication, we reported the synthesis and the reactivity of polymer grafted chiral oxazolidin-2-ones derived from tyrosine in 1,3-dipolar cycloadditions.[1] 1,3-Dipolar cycloaddition reactions of **1a**,**b** with either mesitonitrile oxide **3** (Scheme 2) or diphenyl nitrone **4** (Scheme 3) evidenced good reactivities and selectivities, but the cycloadditions were not influenced by the presence of Lewis acids such as Mg(II) or Sc(III) cations. This behaviour strongly argued with classical solution

☆ See Ref. 1.

Keywords: asymmetric induction; 1,3-dipolar cycloaddition; catalysis; solid-phase synthesis.

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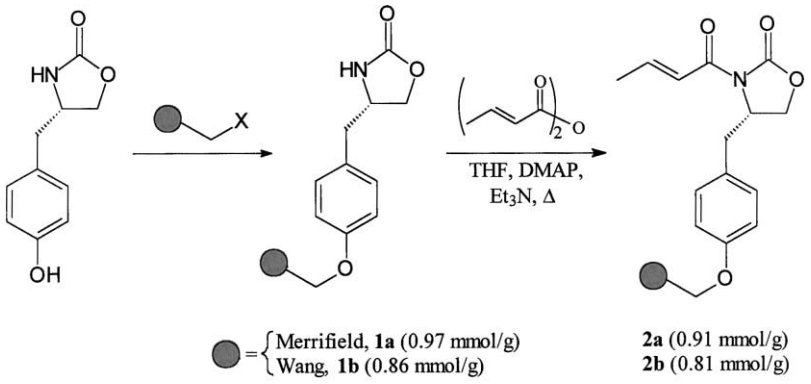


Scheme 1.

conditions, where both stereo- and enantioselectivity were deeply influenced by the presence of Lewis acids.[4c]

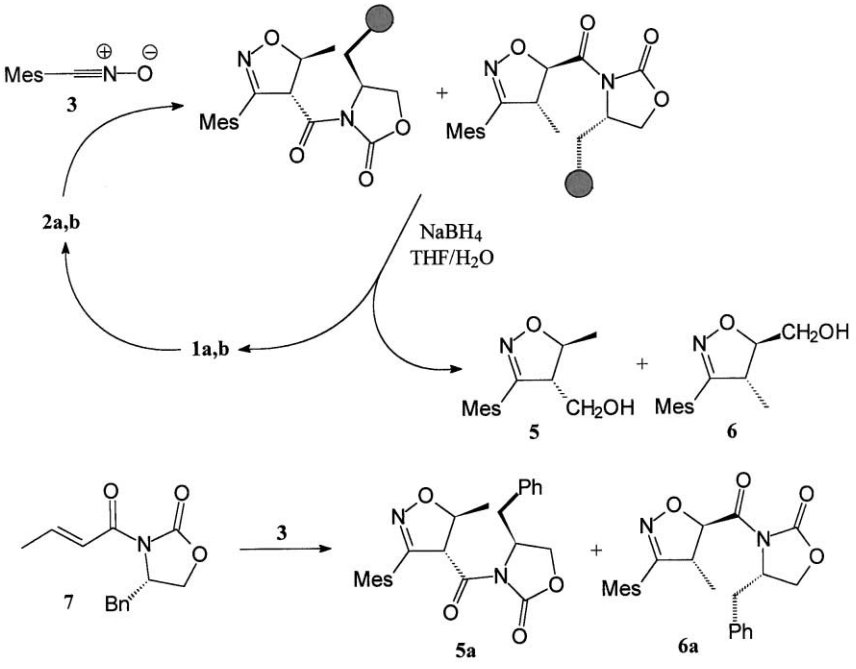
2. Results

(4*S*)-*p*-Hydroxybenzyl-1,3-oxazolidin-2-one was obtained starting from commercial L-tyrosine by optimising a general protocol described for similar compounds (40% overall yields, see Section 5 for details).[11] The chiral auxuliary was attached directly onto both Wang resin (X=OH) under Mitsunobu conditions and Merrifield resin (X=Cl) by nucleophilic substitution (NaH in DMF).[12,13] Resin-bound oxazolidinones **1a**,**b** were then mildly acylated by reaction with *trans*-crotonic anhydride in THF in the presence of catalytic DMAP and triethylamine under reflux for 72 h (Scheme 1).

2.1. Reactions of resin-bound chiral oxazolidinones 2a,b with mesitonitrile oxide

As previously reported, substrates **2a**,**b** reacted with both mesitonitrile oxide **3** to give the corresponding cycloadducts, which can be cleaved by reduction with $NaBH_4$ and analysed by chiral HPLC (Scheme 2). When the cycloadditions were run in the presence of $Mg(ClO_4)_2$ or $Sc(OTf)_3$ in dichloromethane the strong catalytic influence observed in solution was not detected.[1] The bis-coordinanting ability of the oxazolidinone moiety, usually observed in solution, was most likely prevented by its grafting on the solid support. Hence, we reasoned that more appropriate reaction conditions could help the interaction of the dicarbonyl fragment with the metal cation and the following optimisation protocol was tested.

Resins **2a**,**b** were suspended in DCM and increasing amounts of 1 M magnesium perchlorate–CH_3CN solution were added. Mesitonitrile oxide was then added portionwise and after 7 days the resins were filtered, washed with DCM, methanol, THF, and dried under vacuum. The filtered resins were suspended in THF and then a solution of $NaBH_4$ in H_2O was added. The mixtures were shaken at room temperature for 15 h, the resins were filtered and washed with THF and DCM. The filtered solvents were evaporated



Scheme 2.

Table 1. Reaction conditions, yields, and product distribution of the 1,3-DC of **2a**,**b** and **7** with **3** at rt in DCM with increasing amounts of 1 M MP–CH_3CN solution

n	Dipolarophile	Equiv. of catalyst	Time (days)/yield	**5**:**6**	%ee **5**	%ee **6**
1	**7**[a]	–	4/quant.	71:29	63	n.r.
2		0.1	4/quant.	55:45	18	5
3		0.2	4/quant.	46:54	−22	7
4		0.3	4/quant.	42:58	−30	11
5		0.5	4/quant.	45:55	−70	13
6		2.0	4/quant.	43:57	−86	25
7	**2a**	–	4/54%	67:33	60	n.r.
8		0.2	7/48%	70:30	56	n.r.
9		0.5	7/53%	59:41	38	7
10		1.0	7/49%	36:64	−41	18
11		2.0	7/47%	26:74	−55	20
12	**2b**	–	4/55%	72:28	60	n.r.
13		0.1	7/51%	60:40	48	6
14		0.2	7/49%	54:46	41	7
15		0.3	7/53%	41:59	7	7
16		0.5	7/43%	29:71	−24	8
17		1.0	7/41%	23:77	−41	17
18		2.0	7/44%	20:80	−44	16

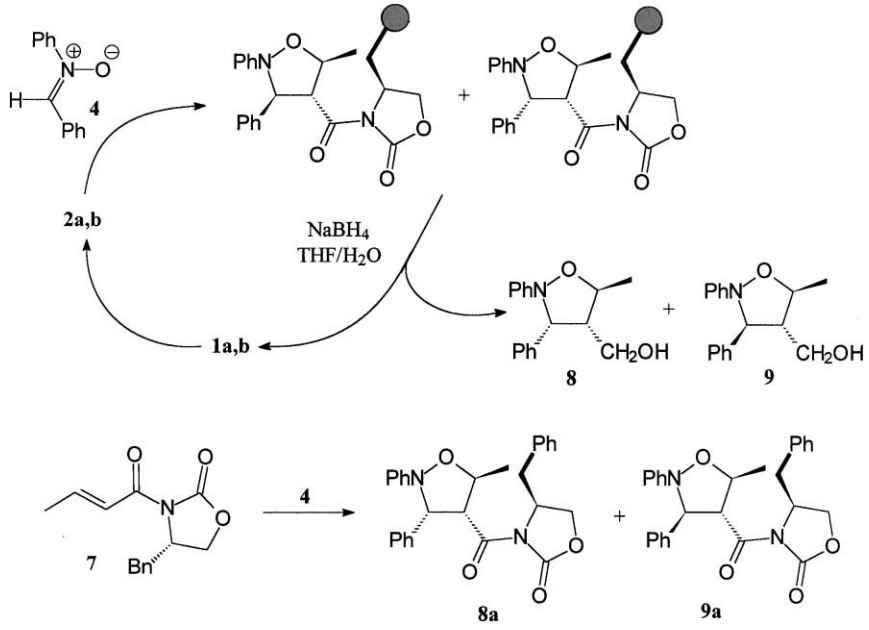
[a] The data related to the 1,3-DC involving **7** are referred to products **5a** and **6a** and the values in the last two columns are de.

to dryness, and the residue was analysed by HPLC (see Section 5 for details). The obtained results are reported in Table 1.

In order to compare these results with those obtained in solution, the cycloaddition of (4*S*)-benzyl-*N*-crotonyl-oxazolidin-2-one (**7**) with **3** was run under analougous conditions (Scheme 2). The diastereomeric cycloadducts **5**,**6a** were directly submitted to HPLC analysis without any further purification (see Table 1 for results).

The results in Table 1 indicate some interesting features. Reactivity was not affected by the presence of the Mg(II) cation, whilst cycloaddition regioselectivity changed in favour of cycloadduct **6** (Table 1, entries 10, 11, 16–18). A similar trend was also observed in the cycloaddition of **7** (solution conditions), even if the regioselectivity drift was lower (Table 1, entries 2–6). Enantioselectivity was also influenced by the presence of the cation, providing an inversion in the enantioselective formation of **5**. In the case of **6** the increase in the ee values was only moderate (Table 1, entries 3–6, 10, 11, 16–18).

Wang-supported dipolarophile **2b** seems to be more sensitive to the cation concentration. In fact, 0.3–0.5 equiv. of Mg(II) were enough to invert both regio- and enantioselectivity of the cycloaddition, whereas in the case of the Merrifield resin **2a** higher salt concentrations [1.0 equiv. of Mg(II)] were required to observe similar effects. Data in Table 1 seem to rank dipolarophiles as **7**>**2b**>**2a** in terms of their response to cation concentration.



Scheme 3.

Table 2. Reaction conditions, yields, and product distribution of the 1,3-DC of **2a,b** and **7** with **4** at rt in DCM with increasing amounts of 1M MP–CH_3CN solution

n	Dipolarophile	Equiv. of catalyst	Time (days)/yield	**8**:**9**	%ee **8**	%ee **9**
1[a]	**7**[a]	–	15/quant.	83:17	83	>99
2		0.1	2.5/quant.	85:15	−93	>99
3	**2a**	–	40/12%	53:47	88	22
4		0.1	7/20%	58:42	90	27
5		0.2	7/29%	28:72	−85	78
6		0.3	7/30%	23:77	−85	78
7		0.5	7/24%	20:80	−80	80
8		1.0	7/26%	20:80	−80	80
9		2.0	7/26%	16:84	−84	75
10	**2b**	–	40/12%	46:54	86	9
11		0.1	7/19%	29:71	−86	80
12		0.2	7/20%	23:77	−85	74
13		0.3	7/18%	18:82	−85	77
14		0.5	7/18%	10:90	−87	77
15		1.0	7/19%	13:87	−75	77
16		2.0	7/19%	15:85	−70	78

[a] The data related to the 1,3-DC involving **7** are referred to products **8a** and **9a** and the values in the last two columns are de and are taken from Ref. 4c.

2.2. Reaction of resin-bound chiral oxazolidinones 2a,b with diphenyl nitrones

The encouraging results obtained using **3** prompted us to test the same solid phase protocol in the 1,3-dipolar cycloadditions of **2a**,**b** with diphenylnitrone **4** (Scheme 3). The obtained results, together with those previously reported for the reaction of **7** with **4**,[4c] are collected in Table 2.

The reactions involving nitrone **4** exhibit more evident catalytic effects than the ones involving nitrile oxides. The presence of $\leq$0.2 equiv. of Mg(II) gave rise to an increase in reactivity (higher yields in shorter reaction times), in stereo- and in enantioselectivity. The *endo* adduct **9** became the favoured product (*endo*/*exo* ratio with up to 90:10), and was obtained with ees ranging from 75 to 80%.

By analogy with the results shown in Table 1, the Wang-supported dipolarophile **2b** was more sensitive to the salt concentration, since 0.1 equiv. of Mg(II) showed significant catalytic effects (Table 2, entry 11), whereas in the case of the Merrifield-supported derivative **2a** a higher salt concentration was required (Table 2, entry 5).

2.3. Reusability of resin-bound chiral oxazolidinones 2a,b

Next we addressed the key issue of polymer reusability. In our preliminary communication,[1] the resins **1a**,**b** recovered after a 1,3-dipolar cycloaddition reactions were characterised by gel-phase ^{13}C NMR spectroscopy,[14] transformed again into **2a**,**b**, and re-used in a further 1,3-dipolar cycloaddition reaction with **3**. The recycled Merrifield resins **2a** gave comparable reaction yields and selectivities, while the recycled Wang resin **2b** yielded an increased regioselectivity, but the enantioselectivity diminished up to 14% ee.

Recycling of the supported chiral auxiliary was checked on a semi-preparative scale under catalytic conditions. Resins **2a**,**b** (1 g) were allowed to react with both **3** and **4** under the previously described protocol [1.0 equiv. of Mg(II)]. After reductive cleavage, **1a**,**b** were again converted into **2a**,**b** and allowed to react with either **3** or **4**. This sequence was repeated and the results of the three cycloadditions are listed in Table 3.

The first run of each reaction set reproduced with acceptable

Table 3. Reaction conditions, yields, and product distribution of the 1,3-DC of recovered **2a,b** with **3** (entries 1–6) and **4** (entries 7–12) at rt in DCM with 1.0 equiv. of MP–CH_3CN solution

n	Dipolarophile	Equiv. of catalyst	Time (days)/yield	**5**:**6**	%ee **5**	%ee **6**
1	**2a**	1.0	7/42%	29:71	−68	22
2	1st recycle	1.0	7/43%	29:71	−55	20
3	2nd recycle	1.0	7/40%	34:66	−45	18
4	**2b**	1.0	7/40%	23:77	−43	12
5	1st recycle	1.0	7/41%	25:75	−40	16
6	2nd recycle	1.0	7/43%	40:60	−17	8
				8:**9**	%ee **8**	%ee **9**
7	**2a**	1.0	7/32%	14:86	−81	80
8	1st recycle	1.0	7/33%	6:94	−70	80
9	2nd recycle	1.0	7/30%	36:64	−67	73
10	**2b**	1.0	7/28%	5:95	−80	78
11	1st recycle	1.0	7/30%	5:95	−70	73
12	2nd recycle	1.0	7/25%	7:93	−55	73

accuracy the data reported in Tables 1 and 2 for smaller scale experiments. Only a few runs showed a small increase in regio-, stereo-, and enantioselectivity (Table 3, entries 1 and 10). When the recycled resins **2a**,**b** were used in a first recycling run, the observed reactivities and selectivities were substantially confirmed. However, a measurable drop in regio-, stereo-, and enantioselectivity was generally observed in the second recycling run (Table 3).

A further experiment was set up in order to verify the stability of the chiral auxiliary through all the reaction sequences. The Wang-supported dipolarophile **2b** (1 g) was reacted with **3** in the presence of 1 equiv. of magnesium perchlorate in CH_3CN. After reductive cleavage (no changes in reaction yield and selectivities were observed), the chiral oxazolidinone was recovered by treatment of **1b** with CF_3COOH/DCM, purified by column chromatography and recrystallised from methanol. The optical rotation of the recovered chiral auxiliary was in full accordance with the literature value, confirming that no racemisation of the chiral auxiliary occurred (see Section 5). The same reaction sequence was repeated after the second recycling run and the chiral auxiliary was again recovered with unaffected optical purity.

3. Discussion

3.1. Nitrile oxide cycloadditions

In order to achieve selective nitrile oxide cycloadditions to chiral β-substituted α,β-unsaturated carbonyl derivatives two distinct levels of control have to be satisfied: regio- and stereoselectivity. The first one is the more difficult to control since, in the 1,3-dipolar cycloaddition of crotonoate derivatives, mixtures of 4- and 5-acyl isoxazolines are generally obtained in ratios close to 50:50.[15] In the case of crotonamides regioselective formation of both 4- and 5-acyl isoxazolines can be observed, depending on several factors such as nitrogen substituents.[16] Data available in the literature on regio- and stereoselectivities obtained in 1,3-dipolar cycloadditions involving β-substituted chiral dipolarophiles are summarised in Chart 1. 1,3-Dipolar cycloadditions with bornyl[17] and Sultan[18] crotonoates did not allow the regioselective formation of cycloadducts, obtained with negligible to good diastereomeric excesses (de). In the case of Rebeck benzoxazole[19] the excellent diastereoselectivity was not associated with a good level of regioselectivity. The use of chiral imidazoline[20] was highly efficient both in terms of regio- and diastereoselectivity, and depended on the nitrogen atom substituent.

The only substrate able to achieve complete regio- and diastereoselectivity was a β-borane derivative of Sultan crotonoate[21] and this strategy was usefully applied in the synthesis of optically active 4-hydroxy-Δ^2-isoxazolines.

None of the previously reported 1,3-dipolar cycloaddition reactions was tested in the presence of a catalyst; a single example is found in the 1,3-dipolar cycloadditions involving chiral 1,3-dithiane-1-oxide.[22] The cycloaddition was completely regioselective and the low diastereoselectivity was depending on both the solvent and the catalyst. Use of Mg(II) and Zn(II) allowed reversal of diastereoselectivity. Other attempts to catalyse analogous 1,3-dipolar cycloaddition reactions were reported by Kanemasa,[23] but both regio- and diastereoselectivity were not improved in the presence of metal cations such as Zn(II) and Ti(IV).

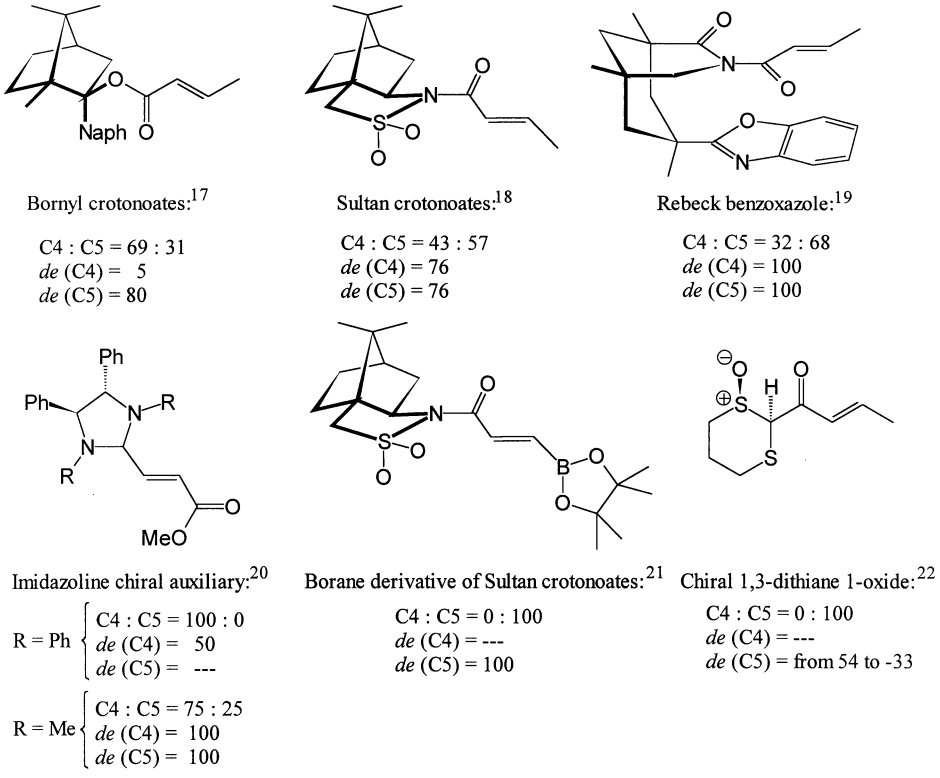


Chart 1.

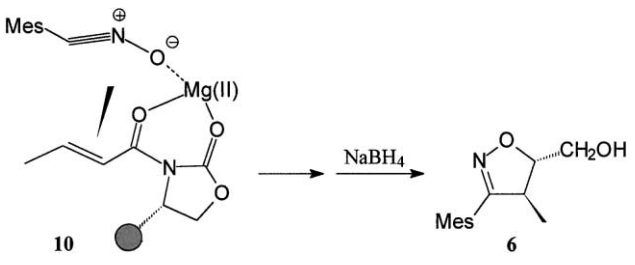
The low number of papers on metal assisted 1,3-dipolar cycloadditions of nitrile oxides is probably the consequence of the difficulty to control their stereoselectivity. This derives from two distinct problems. First, 1,3-dipoles are usually generated in situ in the presence of a base, conditions that are not compatible with a catalyst. Furthermore, nitrile oxides are low-lying FMOs species and therefore attempts to use cations to activate α,β-unsaturated carbonyl compounds are ineffective.[4a]

Data reported in Table 1 demonstrate that the catalysis of these cycloadditions (Scheme 2) can influence the observed selectivities on solid phase as well as in solution. In nitrile oxide cycloadditions, a stronger effect was observed on chemoselectivity, since an inversion of regiochemistry was clearly evidenced by the presence of the Mg(II) cation. The cycloaddition in solution involving **7** was only moderately affected by the presence of the salt, and a value of about 60% was obtained with 0.3 or more equiv. of salt. Solid phase catalysed cycloadditions involving **2a**,**b** showed a stronger regiochemistry drift, and **6** became the largely predominant product. Thus, the lower reactivity associated to solid phase synthesis with respect to classical solution chemistry allowed to emphasise the catalytic effects.

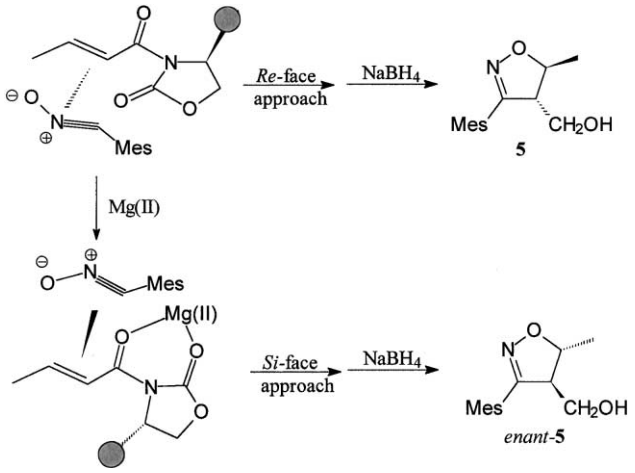
The regiochemistry shift in response to low salt concentrations observed with Wang resin **2b** was similar to that observed in solution, but the increase in the yield of **6** is observed with an amount of Mg(II) up to 1 equiv. The Merrifield resin was less sensitive to the catalyst concentration than the Wang resin since higher Mg(II) concentrations were required in the reaction of **2a** to obtain high yields of **6**.

The change in regiochemistry was consistent with a mechanism analogous to that proposed by Kanemasa[23] in the catalysed 1,3-dipolar cycloadditions between nitrile oxides and allylic alcohols. The Mg(II) cation coordinated both carbonyl oxygen atoms of the chiral oxazolidinone and the oxygen atom of the nitrile oxide to give complex **10**, which favoured the formation of the 5-acyl-substituted isoxazoline that, after the reductive cleavage, led to **6** (Scheme 4).

Complex **10** rationalises the inversion in the enantioselectivity observed in the formation of the 4-substituted oxazoline **5** (Scheme 5). In the uncatalysed cycloaddition, the preferred conformation of the reacting dipolarophile had the two carbonyls in the *s-trans* disposition. The chiral information on the C4 of the oxazolidinone ring hindered the C-α *Si*-face of the CC double bond and, therefore, the



Scheme 4.



Scheme 5.

nitrile oxide approached the dipolarophile from the opposite *Re*-face to give **5** after reductive cleavage.

When the Mg(II) cation coordinated the oxygen carbonyl atoms, the carbonyl groups in the reacting substrate assumed a *s-cis* conformation, and nitrile oxide approached the double bond from the less hindered *Si*-face to yield enant-**5**.

The same reversion in enantioselectivity was not observed in the case of regioisomer **6** that, moreover, did not show significant levels of enantioselectivity in all the tested conditions. The latter result was the consequence of the loss of the steric interaction between the mesityl group and the chiral information on the oxazolidinone ring, interaction that is discriminant in determining the stereochemical outcome.

As a matter of fact, the Mg(II) cation drove regioselectivity to the formation of the C5-acyl substituted isoxazoline, but the latter product was obtained with a low control of the enantioselectivity, being less sensitive to steric information. This intrinsic disadvantage was overcome in the cycloaddition involving a nitrone dipole.

3.2. Nitrone cycloadditions

Several examples of syntheses involving either (chiral substrate–achiral catalyst) or (achiral substrate–chiral catalyst) combinations have been proposed in the literature for nitrone cycloadditions.[4a] Cycloaddition involving dipolarophile bearing the Evans chiral auxiliary are catalysed by Mg(II) and Sc(III) cations and, with an appropriate choice of the catalytic system, *exo* and *endo* cycloadducts can be selectively obtained with good to excellent control of the diastereoselectivity.[4c,24]

Data reported in Table 2 clearly evidence that both reactivity and selectivity are influenced by the presence of the Mg(II) cation.

Reactivity. The coordination of the metal cation, acting as a Lewis acid, to the conjugated carbonyl lowered the LUMO energy of the alkene with respect to the uncoordinated

olefin. The increase in reaction yields observed within shorter reaction times is fully consistent with such a mechanism.

Stereoselectivity. The stereochemical outcome of the cycloaddition was influenced by:

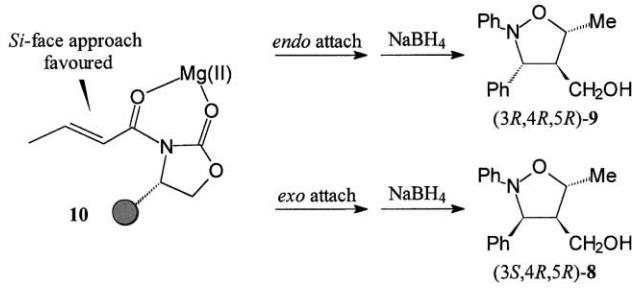
a. the polymer grafted to the reacting dipolarophile;
b. the coordination of the Mg(II) cation.

A tentative rationale of point (a) involves a change in the steric demand of the reacting olefin from solution to solid phase chemistry, since a decrease in the *exo* preference was observed going from solution (reaction of **7**) to solid phase chemistry (reactions of **2a**,**b**).

Under classical solution conditions, catalysis with magnesium perchlorate did not influence the stereoselectivity and the *exo* cycloadduct was again obtained as major product.[4c] *endo* Selectivity was observed only when the salt was used with molecular sieves. In the case of solid supported dipolarophiles **2a,b**, the addition of increasing amounts of Mg(II), without molecular sieves, drove stereoselectivity towards the formation of the *endo* cycloadduct (*endo*/*exo* with up to a ratio of 9:1). The Wang support showed an higher sensitivity to salt concentrations than the Merrifield resin, and also exhibited higher levels of selectivity.

Enantioselectivity. The uncatalysed cycloaddition of diphenylnitrone and **2a**,**b** showed good enantioselectivity only in the formation of the *exo* adduct. However, when it was performed in the presence of Mg(II) the favoured product became the *endo* adduct, which was obtained with up to 80% ee. These results strongly paralleled those observed under standard solution conditions. The inversion in the *exo* enantioselectivity, as well as the increase in the *endo* one, was observed with 0.1 (Wang support) or 0.2 equiv. of cation (Merrifield support). This result is a further evidence that **2b** has a more solution-like behaviour than **2a**, pointing out the relevance of the distance between reaction sites and resin bulk in determining the substrate ability to interact with the metal cation.

The absolute stereochemistry of the adducts **8** and **9** were determined by correlation with compounds **8a** and **9a** of known configuration, and confirmed a mechanism involving **10** as the reacting complex, since both *endo* and *exo* cycloadducts derived from the approach of nitrone to the less hindered *Si*-face of the dipolarophile (Scheme 6).



Scheme 6.

An important factor in both catalysis and solid phase synthesis is the reaction solvent. Chlorinated media such as chloroform and DCM are frequently used because of their low coordinating abilities and good swelling properties. Nevertheless, the same reactions were tested in a more coordinating solvent (THF) by adding either increasing volumes of magnesium perchlorate–acetonitrile solution or directly the solid salt. Quite surprisingly, such conditions optimised the stereochemical outcome: with 0.5–1.0 equiv. of Mg(II) cation the *endo*/*exo* ratio was 98:2, and the ee of the *endo* adduct was 90%.

3.3. Polymer reusability

Polymer reusability was tested by performing three sequential cycloadditions between **2a**,**b** and either **3** or **4**. The first recycling of the supported chiral oxazolidinone gave, in general, acceptable results in terms of regio-, stereo-, and enantioselectivities (Table 3, entries 2, 5, 8, and 11), but the second recycle gave disappointing results. Nitrile oxide cycloadditions evidenced a decrease in both regio- and enantioselectivity (Table 3, entries 3, 6), as did the nitrone cycloaddition of the Merrifield-supported dipolarophile **2a** (decrease in both stereo and enantioselectivity). Only the Wang support gave reproducible results, at least in terms of both stereoselectivity and enantioselectivity of the major *endo* adduct. Since the recovered chiral auxiliary did not show any drop in optical purity, a possible explanation may involve the presence of traces of moisture able to modify the catalyst activity. Further studies are required to better understand this phenomenon.

4. Conclusion

A carrier of the cation is needed in solid phase chemistry to allow the Lewis acid to interact with grafted bis-coordinating dipolarophile and to simulate classical catalysis conditions in solution. The transfer of Mg(II) from the swelling solution to the bead reacting sites can be achieved by using small volumes of Mg(II)-acetonitrile solution added to DCM (a solvent with good swelling properties). Under these conditions, the 1,3-dipolar cycloaddition reactions involving solid supported chiral dipolarophiles are effectively catalysed by the Mg(II) cation.

Even if nitrile oxide cycloadditions are less sensitive to cation catalysis than those involving nitrones, stoichiometric amounts of salt influence both regioselectivity (shift toward the formation of the 5-acyl-substituted isoxazoline) and stereoselectivity (reversion in the enantioselectivity of the 4-acyl-substituted isoxazoline). In the case of nitrone cycloadditions catalytic amounts of Mg(II) are sufficient to strongly influence both reactivity and selectivity, which are increased in the presence of 0.1–0.2 equiv. of Mg(II). In particular, stereoselectivity is enhanced and the *endo* adduct becomes the largely predominant one with ee higher than 90%.

All results are consistent with a reaction mechanism involving a reacting complex with the dicarbonyl fragment of the chiral oxazolidinone coordinated by the Mg(II) cation. Such a coordination deeply influences the selectivity

(regio- stereo- and enantioselectivity) of 1,3-dipolar cycloadditions and, at least in the case of nitrone cycloadditions, also the reactivity is significantly increased.

5. Experimental

All melting points are uncorrected. Elemental analyses were done on a Carlo Erba 1106 elemental analyser. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 spectrometer (solvents specified). Chemical shifts are expressed in ppm from internal tetramethylsilane (δ) and coupling constants are in Hertz (Hz): b, broad; s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; qi, quintet; m, multiplet. IR spectra (nujol mulls for standard compounds, and diffuse reflectance—DR—for resins) were recorded on an FT-IR Perkin–Elmer Paragon 1000 spectrophotometer and absorbtions (ν) are in cm^{-1}. The optical rotations were determined on a Perkin–Elmer 241 polarimeter. Column chromatography and TLC: silica gel H60 and GF_{254} (Merck), respectively. The cycloadduct ratios were determined by HPLC on either a Chiralcel OD or a Chiralpack AD.

5.1. Synthesis of the chiral auxiliary

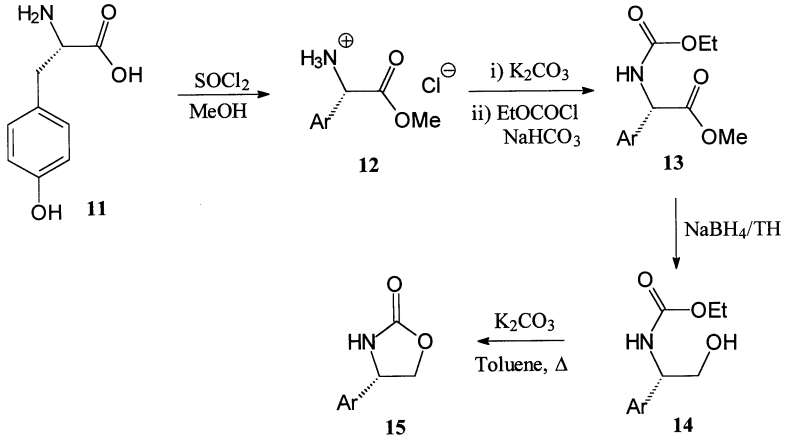
The synthesis of the chiral oxazolidinone was optimised on the basis of a protocol described for analogous derivatives[11] following the procedure depicted in Scheme 7. The synthetic method reported in literature[25] for the synthesis of **15** gave less satisfactory results.

5.1.1. (2*S*)-2-Amino-3-(4-hydroxyphenyl)-propionic acid methyl ester hydrochloride (12). Thionyl chloride (39.3 g, 0.33 mol) was added dropwise to ice cooled methanol (300 mL) over 20 min, keeping the temperature below −10°C. L-Tyrosine (50 g, 0.28 mol) was added and the solution was stirred at room temperature for 2 days. The solvent was removed by evaporation and the residue was twice triturated with methanol and concentrated, dissolved in hot methanol, diluted with ether and left to crystallise. Compound **12** was obtained in quantitative yield as white crystals: mp 190–191°C (lit.[26] 189–191°C); $[\alpha]_D^{20}=+70.9$ (*c* 1.1, pyridine) [opposite enantiomer, lit.[26] $[\alpha]_D^{20}=-68.0$ (*c* 1.0, pyridine)].

5.1.2. (*S*)-2-Amino-*N*-ethoxycarbonyl-3-(4-hydroxyphenyl)-propionic acid methyl ester (13). The ester hydrochloride **12** (23.7 g, 0.10 mol) was dissolved in water (50 mL) and K_2CO_3 (13.8 g, 0.10 mol) was added portionwise. DCM (100 mL) was added to the obtained suspension, and ethyl chloroformate (10.0 mL, 0.105 mol) was then added dropwise under vigorous stirring. After 10 min, saturated solution of $NaHCO_3$ (50 mL) was added and the mixture was stirred for 2 h. The aqueous phase was separated and extracted with DCM (150 mL), and the organic layers, dried over $MgSO_4$, were concentrated under vacuo to give **13** (26.7 g, quantitative yield) as a pale yellow oil, that was used in the next step without any further purification. ^{1}H NMR ($CDCl_3$): 6.96 (d, 2H, J=7.5 Hz, Ar), 6.72 (d, 2H, J=7.5 Hz, Ar), 5,78 (s, 1H), 5.15 (d, 1H, J=8 Hz, NH), 4.6 (m, 1H, CH–CO), 4.10 (q, 2H, J=6.5 Hz, OCO–CH_2), 3.23 (s, 3H, COO–CH_3), 3.02 (m, 2H, CH_2–Ar), 1.23 (t, 3H, J=6.5 Hz, CH_3).

5.1.3. (2*S*)-2-Amino-*N*-ethoxycarbonyl-3-(4-hydroxyphenyl)-propanol (14). Product **13** (26.7 g, 0.10 mol) was dissolved in THF (200 mL) and $NaBH_4$ (15 g, 0.40 mol) was added portionwise. The suspension was stirred for 1 h at room temperature and then refluxed overnight. The mixture was cooled at 0°C and 10% HCl (50 mL) was added with caution. The solid was filtered and treated with acetone. Aqueous and organic layers were collected and concentrated under vacuum. The residue was extracted with DCM (150 mL), the organic layers were washed with brine, dried on $MgSO_4$ and concentrated to give a pale yellow oil, which was filtered through a silica plug (25 g of silica gel, ethyl acetate as eluant). Compound **14** (19.1 g, 82% yield) was obtained as a colourless viscous oil, which was directly used in the next reaction. ^{1}H NMR ($CDCl_3$): 8.15 (s, 1H, OH), 7.06 (d, 2H, J=7.5 Hz, Ar), 6.74 (d, 2H, J=7.5 Hz, Ar), 5.90 (d, 1H, J=7 Hz, NH), 4.00 (q, 2H, J=7.5 Hz, $OCOCH_2$), 3.75 (m, 1H, CH), 3.52 (t, 2H, J=6 Hz, CH_2–O), 2.9–2.6 (m, 2H, CH_2–Ar), 1.12 (t, 3H, J=7.5 Hz, CH_3).

5.1.4. (4*S*)-(4-Hydroxybenzyl)-1,3-oxazolidin-2-one (15). The previously obtained product **14** (19.1 g, 0.082 mol) was dissolved in toluene (100 mL) and K_2CO_3 (2.0 g, 0.015 mol) was added. The mixture was refluxed in a Dean–Stark apparatus for 4 h. Toluene was removed and ethanol was added to the sticky residue. After 1 h, the insoluble material was



Scheme 7.

filtered off and the filtrate concentrated leaving a viscous oil which solidified by treatment with 5 mL of 1:1 EtOH/HCl conc. The white solid was recrystallised from methanol to give 7.7 g of **15** (50% yield, total yield of the three steps, 40%). Mp 178–179°C (lit.[25] 175–178°C). $[\alpha]_D^{20}=+11.8$ (*c* 0.5, ethanol) [lit.[25] +8.6 (*c* 0.5, ethanol)].

5.2. Preparation of the supported chiral auxiliary

5.2.1. Merrifield resin. The chiral auxiliary **15** (7.5 g, 38 mmol) was dissolved in dry DMF (10 mL) and Merrifield resin (10 g, 12 mmol) was added to the solution. The suspension was cooled at 0°C and NaH (1.9 g, 38 mmol) was added portionwise under gentle stirring. After three days of vigorous shaking at room temperature the suspension was filtered. Resin **1a** was washed with DMF, with methanol and THF, and then with DCM before drying under vacuum. FT-IR (DR), ν: 3278, 1772 cm^{-1}. Gel-phase ^{13}C NMR spectrum, δ ($CDCl_3$): 159.5, 158.2, 115.2, 69.5, and 53.9.

5.2.2. Wang resin. The chiral auxiliary **15** (5.95 g, 30.9 mmol) and triphenylphosphine (7.98 g, 30.9 mmol) were dissolved in dry THF (100 mL); 10 g of Wang resin (1.03 mmol g^{-1}, 10.3 mmol) were then added to the solution. The suspension was cooled at 0°C and DEAD (4.8 mL, 30.9 mmol) in dry THF (10 mL) was added dropwise under gentle stirring, in such a rate to maintain the solution colourless. After three days of vigorous shaking at room temperature the suspension was filtered. Resin **1b** was washed several times with methanol and THF, and then with DCM before drying under vacuum. FT-IR (DR), ν: 1754 cm^{-1}. Gel-phase ^{13}C NMR spectrum, δ ($CDCl_3$): 67.8 and 55.3.

5.2.3. Functionalisation of resins 1a,b. General procedure. Resin portions corresponding to 1.2 mmol of chiral auxiliary (1.0 g for **1a** and 1.35 g for **1b**) were swollen in dry THF (10.0 mL for **1a**, 13.5 mL for **1b**). DMAP (0.3 g, 2.4 mmol) and TEA (0.8 mL, 6 mmol) were added to the suspension that was then cooled in an ice bath. *Trans*-crotonic anhydride (0.7 mL, 4.8 mmol) was added dropwise and, after 1 h of gentle stirring, the ice bath was removed and the mixture refluxed for three days. The solvent was filtered, and the resin was washed several times with THF and methanol, until the washing phase was colourless, and then with DCM before drying under vacuum. **2a**: FT-IR (DR), ν: 1718.2 cm^{-1}. Gel-phase ^{13}C NMR spectrum, δ ($CDCl_3$): 164.8, 66.1, 55.3 and 18.6. **2b**: FT-IR (DR), ν: 1778 and 1730 cm^{-1}. Gel-phase ^{13}C NMR spectrum, δ ($CDCl_3$): 164.9, 146.9, 121.8, 66.0, 55.2, and 18.5.

5.2.4. Standard protocol for the 1,3-dipolar cycloaddition. A measured volume of 1 M solution of magnesium perchlorate in acetonitrile (from 15 to 300 μL) was added to 200 mg of **2a**,**b** swollen in 10 mL g^{-1} of dry DCM, and the suspension shaken for 15 min. Then 1.1 equiv. of the 1,3-dipole were added (for **2a**: 37 mg of **3** and 45 mg of **4**; for **2b**: 33 mg of **3**, 37 mg of **4**). The reaction was shaken at room temperature for seven days. The solvent was filtered off and the resin was washed with DCM, methanol and THF. The obtained resins were swollen in THF (2 mL) and 30 mg of $NaBH_4$, dissolved in water (0.3 mL), were added.[26] The suspension was shaken overnight at room temperature. The solvent was recovered by filtration and the resin washed with THF and DCM. The combined organic layers were washed with water (15 mL), dried over anhydrous magnesium sulphate and the residue obtained was analysed by HPLC.

5.3. Nitrile oxide cycloadducts 5,6

They were analysed on a Chiralpak AD Column; eluant: *n*-hexane/*i*-propanol=96:4; flow, 1 mL min^{-1}. Retention times: **5**, 40.0 and 49.3 min; **6**, 35.7 and 56.8 min.

5.3.1. *trans*-5-Methyl-3-mesityl-2-isoxazoline-4-methanol (5). The product was obtained as colourless oil. IR (neat) 3405 and 1612 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.50 (3H, d, *J*=6.3 Hz, –Me), 1.76 (1H, bs, –*OH*), 2.26 (6H, s, –CH_3Mes), 2.30 (3H, s, –CH_3Mes), 3.30–3.37 (1H, m, *H*-4), 3.63 (2H, AB syst., –CH_2OH), 4.72 (1H, dq, *J*=7.0, 6.3 Hz, *H*-5), 6.88 (2H, s, –Arom.); ^{13}C NMR ($CDCl_3$) δ 20.0, 20.7, 21.0, 60.6, 61.3, 80.2, 125.4, 128.7, 136.8, 138.7, 157.8. Elem. Anal.: found C, 72.0; H, 8.2; N, 6.0. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00.

5.3.2. *trans*-4-Methyl-3-mesityl-2-isoxazoline-5-methanol (6). The product was obtained as colourless oil. IR (neat) 3406 and 1612 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.13 (3H, d, *J*=7.3 Hz, –Me), 2.25 (6H, s, –CH_3Mes), 2.29 (3H, s, –CH_3Mes), 2.76 (1H, bs, –*OH*), 3.55 (1H, qi, *J*=7.3 Hz, *H*-4), 3.72 (1H, dd, *J*=12.2, 4.4 Hz, –CH_2OH), 3.89 (1H, ddd, *J*=12.2, 4.4, 1.5 Hz, –CH_2OH), 4.36 (1H, m, *H*-5), 6.88 (2H, s, Arom.); ^{13}C NMR ($CDCl_3$) δ 15.6, 20.0, 20.8, 47.3, 62.6, 87.8, 125.1, 128.5, 136.9, 138.5, 162.0. Elem. Anal.: found C, 72.1; H, 8.1; N, 5.9. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00.

5.4. Nitrone cycloadducts 8,9

They were analysed on a Chiralcel OD Column; eluant: *n*-hexane/*i*-propanol=90:10; flow, 1 mL min^{-1}. Retention times: **8**, 10.4 (3*S*,4*R*,5*R*) and 14.9 min (3*R*,4*S*,5*S*); **9**, 12.3 (3*S*,4*S*,5*S*) and 18.1 min (3*R*,4*R*,5*R*).

5.4.1. (3*R*,4*S*,5*S*) (3*S*,4*R*,5*R*)-5-Methyl-2,3-diphenyl-isoxazolidine-4-methanol (8). The product was obtained as colourless oil. IR (neat) 3420, 1596 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.44 (3H, d, *J*=6.2 Hz, –Me), 2.61–2.71 (1H, m, *H*-4), 3.38 (2H, AB syst., –CH_2OH), 4.30 (1H, qi, *J*=6.2 Hz, *H*-5), 4.76 (1H, d, *J*=8.9 Hz, *H*-3), 7.53 (2H, m, *o*-Ph–N), 6.8–7.6 (10H, m, Arom.); ^{13}C NMR ($CDCl_3$) δ 18.7, 55.6, 61.2, 71.1, 76.4, 115.3, 121.5, 127.5, 127.7, 128.4, 128.7, 138.2, 150.9. Elem. Anal.: found C, 75.7; H, 7.0; N, 5.3. $C_{17}H_{19}NO_2$ requires C, 75.81; H, 7.11; N, 5.20.

5.4.2. (3*R*,4*R*,5*R*) (3*S*,4*S*,5*S*)-5-Methyl-2,3-diphenyl-isoxazolidine-4-methanol (9). The product was obtained as colourless oil. IR (neat) 3422, 1597 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.47 (3H, d, *J*=6.2 Hz, –Me), 2.47–2.38 (1H, m, *H*-4), 3.78–3.65 (2H, AB system, –CH_2OH), 4.17 (1H, dq, *J*=8.6, 6.2 Hz, *H*-5), 4.53 (1H, d, *J*=8.6 Hz, *H*-3), 6.7–7.6 (10H, m, Arom.); ^{13}C NMR ($CDCl_3$) δ 17.6, 61.1, 63.1, 73.4, 77.2, 113.9, 121.1, 126.5, 127.4, 127.5, 128.8, 142.5,

152.2. Elem. Anal.: found C, 75.9; H, 7.0; N, 5.2. $C_{17}H_{19}NO_2$ requires C, 75.81; H, 7.11; N, 5.20.

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