Enantioselective 1,3-Dipolar Cycloadditions of Unsaturated Aldehydes Promoted by A Poly(ethylene glycol)-Supported Organic Catalyst

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Keywords: Catalyst immobilization / Chiral organic catalysts / Cycloadditions / Polymers

We have developed a polymer-supported version of MacMillan's catalyst by anchoring a tyrosine-derived imidazolidin-4-one by means of a spacer to the monomethyl ether of poly(ethylene glycol) (M_W = 5000 Da). The supported organic catalyst was employed in some 1,3-dipolar cycloadditions involving α,β-unsaturated aldehydes and nitrones. The products were obtained in enantiomeric excesses very similar to those observed with the non-supported catalyst, but the chemical yields were somewhat lower. Exploiting the solubility profile of the polymeric support, the catalyst was readily separated from the reaction products, recovered, and recycled. Catalyst recycling was accompanied by a very marginal erosion (if any) of the enantioselectivity and a more-substantial decrease in chemical efficiency. We ascribe the latter phenomenon mainly to the intrinsic instability of the catalyst under the reaction conditions, which is, however, a common feature of both the non-supported and supported catalysts.

Introduction

The expression "organic catalyst" has been introduced recently to define an organic compound (of relatively low molecular weight and simple structure) capable of promoting a given transformation in a substoichiometric quantity. In this context, "organic" hints to the metal-free nature of the catalyst, and emphasizes the advantages of performing a reaction under metal-free conditions. These advantages might include, inter alia, the possibility of: i) working in wet solvents and under an aerobic atmosphere; ii) dealing with a stable and robust catalyst; and iii) avoiding the problem of a (possibly) expensive and toxic metal leaching into the organic product.

Organic catalysts, and especially chiral organic catalysts,[1] can be regarded as minimalist versions of enzymes, from which they are derived conceptually and to which they are often compared.[2] Even though they rarely display the remarkable selectivity that is characteristic of enzymes, organic catalysts generally are more stable than bio-catalysts and enjoy a wider application under a variety of conditions that are unsustainable for enzymes.

In principle, organic catalysts are more readily amenable than metal-based catalysts to anchoring on a support with the aim of facilitating the separation of the product from the catalyst and the recovery and recycling of the latter.[3,4] Indeed, it has been shown repeatedly that the use of a metal-based catalyst immobilized on a support is often affected by extensive metal leaching and requires catalyst re-generation by metal replenishment before recycling.[3a][3b]

Over the last few years, we have been interested in the development of poly(ethylene glycol)-supported versions of both organic and metal-based catalysts.[5] The choice of poly(ethylene glycol) (PEG) as the support is suggested by a number of considerations, including the polymer's low cost, commercial availability, easy functionalization, and, most importantly, its very favorable solubility profile. Indeed, PEGs of $M_w \geq 2000$ Da are soluble in many organic solvents and in water, and insoluble in a few other solvents,[6] which, thus, allows catalyzed reactions to be run under homogeneous (and, likely, best-performing) conditions and the isolation and recovery of the catalyst as if it were bound to an insoluble polymer.[7]

Very recently, MacMillan and co-workers reported the use of imidazolidin-4-ones, such as **1a,b** (Scheme 1), as efficient organic catalysts for a variety of highly enantioselective reactions involving α,β-unstaurated aldehydes.[8] In a preliminary communication,[9] we have reported the immobilization of an enantiopure imidazolidin-4-one on a derivative of PEG monomethyl ether of average M_W = 5000 Da (MeOPEG) to afford an efficient supported catalyst for the enantioselective Diels–Alder reaction of α,β-unstaurated

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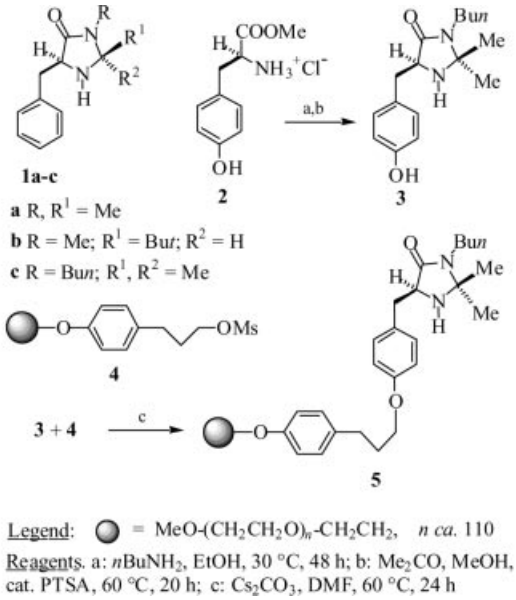


Scheme 1. Synthesis of PEG-supported imidazolidinone **5**

aldehydes with dienes.[10] Here we describe the extension of the use of the PEG-supported catalyst to the 1,3-dipolar cycloaddition of α,β-unstaurated aldehydes with nitrones.

Results and Discussion

Synthesis of the Supported Imidazolidinone

In principle, the synthesis of imidazolidin-4-ones such as **1** (Scheme 1) offers three different sites for polymer attachment: the amide nitrogen atom at position 3, the carbon atom at position 2, and the aryl residue. It was easy to recognize, however, that the introduction of a PEG/spacer fragment at position 2 would generate an additional stereocenter close to the reactive site that possibly would interfere with the stereochemical course of the reaction.[8e] On the other hand, exploitation of the amide nitrogen atom would require the ad hoc synthesis of a spacer containing a terminal amino group and its subsequent anchoring to PEG.[11]

Therefore, these options were discarded in favor of the much simpler use of (*S*)-tyrosine instead of (*S*)-phenylalanine to generate an imidazolidinone already equipped with a properly located and chemically suitable handle for PEG supporting.[12] Thus, starting from (*S*)-tyrosine methyl ester hydrochloride **2**, the imidazolidinone **3** was easily obtained in 69% yield by *N*-butyl amide formation and treatment with acetone (Scheme 1). Reaction of the Cs salt of (*S*)-**3** with the readily available mesylate **4**[13] in DMF afforded the MeOPEG-supported imidazolidinone **5** in 87% yield. Conversion of this compound to the catalytically active species involved the addition of an equimolar amount of a protic acid. While in the case of the Diels−Alder cycloadditions the supported catalyst could be prepared in situ,[9] the 1,3-dipolar cycloaddition reactions required only preformed catalyst samples.

1,3-Dipolar Cycloadditions

The synthesis of the isoxazolidine **6** by reaction of *N*-benzyl-*C*-phenyl nitrone (1 mol equiv.) with acrolein (4 mol equiv.), carried out in the presence of 0.20 mol equiv. of different **5**/HX combinations in wet nitromethane, was used as a model reaction (Scheme 2 and Table 1). The product was obtained as mixtures of *trans* (generally dominant) and *cis* isomers, the ratio of which was determined readily by ^{1}H NMR spectroscopy on the crude product and confirmed on the isolated adducts; enantiomeric excesses (*ee*) were determined by HPLC on a chiral stationary phase after quantitative reduction of aldehyde **6** to the corresponding alcohol with $NaBH_4$.[14]

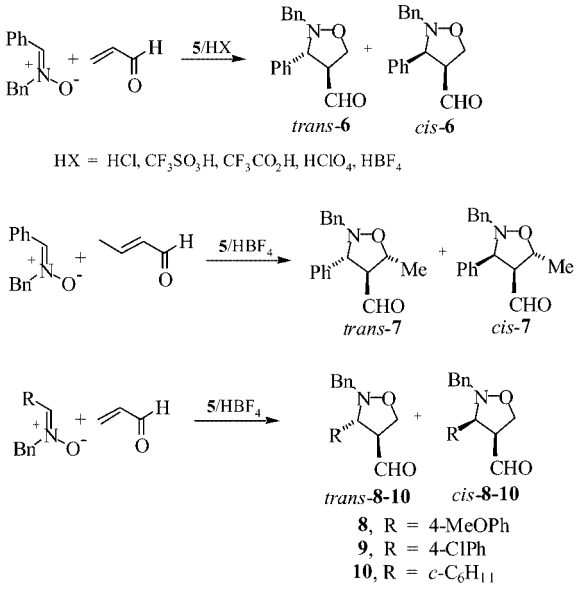
The data reported in Table 1 show a strong dependence of the efficiency of the reaction on the nature of the acid employed to generate the catalyst. We observed that catalyst samples that afford reproducible results were obtained by using HBF_4, and in particular by adding a 54% w/w solution of HBF_4 in diethyl ether to a dichloromethane solution of **5** and then isolating the catalyst by precipitation with diethyl ether. With **5**/HBF_4 as the catalyst (Entries 6−8), we obtained reasonable yields of adduct **6** with good values of *ee* for its *trans* isomer. In general, we observed that the use of lower reaction temperatures led to higher values of *ee* (Entries 5 vs. 4, and 8 vs. 7 vs. 6).

Extending the use of the supported catalyst **5**/HBF_4 to other reagents was studied by performing the reactions described in Scheme 2. The data collected in Table 2 show that

Table 1. Catalytic stereoselective synthesis of isoxazolidine **6**

Entry	Catalyst	*T* (°C)	Time (h)	Yield (%)[a]	*trans*/*cis*[b]	*trans ee* (%)[c][d]
1	**5**/CF_3CO_2H	−10	68	18	75:25	68
2	**5**/CF_3SO_3H	−10	68	22	50:50	36
3	**5**/HCl	−10	68	34	40:60	71
4	**5**/$HClO_4$	−10	68	46	86:14	85
5	**5**/$HClO_4$	−20	96	30	86:14	90
6	**5**/HBF_4	0 to 24	24	73	86:14	72
7	**5**/HBF_4	−10	68	67	81:19	78
8	**5**/HBF_4	−20	120	71	85:15	87

[a] Yields of isolated products. [b] As determined by ^{1}H NMR spectroscopy (300 MHz) on the crude products and confirmed on the isolated products. [c] As determined by HPLC on a chiral stationary phase using the corresponding alcohol; yields and values of *ee* are averages of duplicate experiments. [d] The values of *ee* of the *cis* isomers ranged from 10 to 40% (by HPLC).



Scheme 2. Synthesis of adducts **6**−**10** by 1,3-dipolar cycloaddition reactions

Table 2. Catalytic stereoselective synthesis of isoxazolidines **7**−**10** in the presence of **5**/HBF_4

T (°C)	Time(h)	Product	Yield (%)[a]	*trans*/*cis*[b]	*trans ee* (%)[c]
0 to 24	24	**7**	59	93:7	87
−20	96	**8**	64	90:10	84
−20	96	**9**	60	85:15	60
0 to 24[d]	72	**10**	41	90:10	80

[a] Yields of isolated products. [b] As determined by ^{1}H NMR spectroscopy (300 MHz) on the crude products and confirmed on the isolated products. [c] As determined by HPLC on a chiral stationary phase using the corresponding alcohol; yields and values of *ee* are averages of duplicate experiments. [d] Carried out in wet CH_3CN.

N-benzyl-*C*-phenyl nitrone reacted with crotonaldehyde to afford a 93:7 mixture of 3,4-*trans*/3,4-*cis* isomers of compound **7** in 59% yield; the major product had 87% *ee*. The cycloaddition between acrolein and the *N*-benzyl nitrones derived from 4-methoxy- and 4-chlorobenzaldehyde, and cyclohexanecarboxyaldehyde, in the presence of the same catalyst were also successful and led predominantly to *trans* adducts **8**−**10** in fair-to-good yields (41−64%) and *ee* (60−84%).[14]

A comparison of the results obtained with the PEG-supported catalyst in the 1,3-dipolar cycloaddition reactions with those obtained by MacMillan using catalysts derived from imidazolidinone **1a**,[8c] (Table 3) indicates that the major difference between the PEG-supported and the non-supported catalyst resides in the chemical, rather than the stereochemical, efficiency. Indeed, while the supported catalyst gave *trans*/*cis* ratios almost identical to, and values of *ee* only 3−6% lower than, those obtained using the non-supported catalyst (compound **9** being an exception), the difference in chemical yields was larger, ranging from 9 to 27%.[15]

Table 3. Comparison of catalysts derived from **1a** and **5** in the synthesis of adducts **6**−**9**

Catalyst (20% mol)	*T* (°C)	Product	Yield (%)	*trans*/*cis*	*trans ee* (%)
1a/CF_3SO_3H	−20	**6**	80	86:14	90
5/HBF_4	−20	**6**	71	86:14	87
1a/$HClO_4$	−10	**7**	86	94:6	90
5/HBF_4	0 to 24	**7**	59	93:7	87
1a/CF_3SO_3H	−20	**8**	83	91:9	90
5/HBF_4	−20	**8**	64	90:10	84
1a/CF_3SO_3H	−20	**9**	80	80:20	91
5/HBF_4	−20	**9**	70	85:15	60

As mentioned before, two other imidazolidinone-based catalysts precursors, namely **11**, supported on JandaJel, and **12**, supported on silica (Figure 1),[10] have recently been reported. A comparison between the catalytic efficiency of their salts with that of **5**/HX[9] was possible only in the case of the Diels−Alder cycloadditions, since **11** and **12** have not been tested in any 1,3-dipolar cycloadditions (Table 4). Considering the catalytic enantioselective syntheses of adducts **13** and **14** (Figure 1), one can see that the use of the insoluble catalyst **11**/HCl anchored on JandaJel (Entries 3/7) performed better, not only with respect to the PEG- and silica-supported catalysts, but also relative to the non-supported catalyst,[8a] in both reactions (Entries 2/6, 4/8 and 1/5, respectively). On the other hand, the catalysts immobilized on PEG and silica behaved almost identically, but slightly less efficiently, than the non-supported catalyst (Entries 2 vs. 4 vs. 1, and 6 vs. 8 vs. 5).

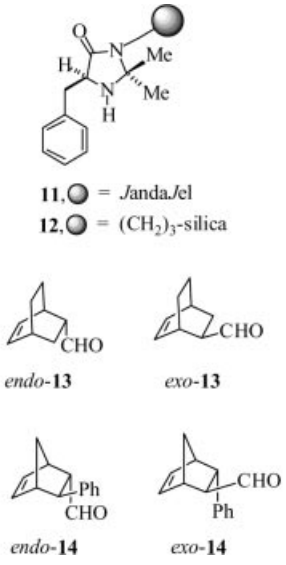


Figure 1. Structures of insoluble polymer-supported imidazolidinones **11** and **12** and of Diels−Alder adducts **13** and **14**

Catalyst Recovery and Recycling Experiments

In addition to facilitating the separation of the catalyst from the reaction products, catalyst immobilization on a polymer should allow simple recovery and recycling. In this

Table 4. Comparison of non-supported and supported catalysts in the synthesis of adducts **13** and **14**

Entry	Catalyst; mol equiv.	Support	Product	Yield (%)	*endo*/*exo*	Major isomer *ee* (%)
1	**1a**/HCl; 0.05	none	**13**	82	93:7	94
2	**5**/CF_3CO_2H; 0.10	MeOPEG	**13**	67	94:6	92
3	**11**/HCl; 0.20	JandaJel	**13**	30	93:7	98
4	**12**/HCl; 0.20	silica	**13**	83	93:7	90
5	**1a**/HCl; 0.05	none	**14**	99	43:57	93
6	**5**/HBF_4; 0.10	MeOPEG	**14**	68	44:56	88
7	**11**/HCl; 0.20	JandaJel	**14**	70	45:55	99
8	**12**/HCl; 0.033	silica	**14**	33	52:48	90

study, the separation of the catalyst was easily achieved by concentrating the reaction mixture under vacuum, dissolving the residue in a small amount of dichloromethane (2 mL/g of catalyst), and adding diethyl ether to the mixture (40 mL of diethyl ether/mL of dichloromethane). The precipitated PEG-supported catalyst was then isolated by filtration in 80−95% yield and the diethyl ether phase was worked-up to obtain the products. The recovered catalyst was then dried for a short time under vacuum to remove traces of solvent and then recycled. In contrast to the Diels−Alder cycloadditions, in which recycling was more efficient if the recycled catalyst was treated in situ with a fresh equimolecular amount of acid before adding the reagents,[9] acid addition resulted in extensive decomposition of the nitrone when the polymer was applied to the 1,3-dipolar cycloadditions. Catalyst recycling was studied by performing the synthesis of cycloadducts **6** and **7**.

The data collected in Table 5 indicate that the enantioselectivity of the recovered catalyst was maintained almost intact for at least three reaction cycles, while the chemical efficiency of the recovered catalyst slowly eroded upon its iterative re-use.

Table 5. Catalyst recycling experiments in the synthesis of adducts **6** and **7**.

Catalyst	Cycle	Product	Yield (%)	*trans*/*cis*	*trans ee* (%)
5/HBF_4 [a]	1	**6**	73	86:14	72
5/HBF_4 [a]	2	**6**	56	73:27	71
5/HBF_4 [a]	3	**6**	38	74:26	72
5/HBF_4 [b]	1	**7**	59	93:7	87
5/HBF_4 [b]	2	**7**	34	94:6	86
5/HBF_4 [b]	3	**7**	26	90:10	88

[a] Reaction conditions the same as Entry 6, Table 1. [b] Reaction conditions the same as Entry 1, Table 2.

To explain the latter phenomenon, we carried out several experiments. First, the supported catalysts were examined by ^{1}H NMR spectroscopy after each recovery, which showed that the degree of degradation increased after each cycle. The NMR spectroscopic analysis showed the appearance of broad signals close to those of the imidazolidinone moiety and the decrease of the intensity of the peaks of the imidazolidinone with respect to those of the aromatic protons of the linker, which remained unchanged; particularly evident was the partial disappearance of the imidazolidinone *gem*-dimethyl signals.

To check whether the instability of the PEG-supported catalyst was induced by the presence of the polymer, the triflate salt of imidazolidinone **1c** (Scheme 1) was kept at 24 °C for 120 h in a CD_3CN/D_2O (95:5) mixture both in the presence and in the absence of the dimethyl ether of PEG_{2000}. We did not observe degradation in either case by NMR spectroscopy, which, thus, suggests that the polymer is not playing a leading role in provoking the instability of the supported catalysts. These findings seem to point to catalyst degradation induced by the presence of the reagents. To assess this hypothesis, we prepared nitromethane solutions containing commercial **1a**/HCl (1 mol equiv.), an unsaturated aldehyde (20 mol equiv.), and water (15 mol equiv.) and kept them at 24 °C for 20 h to mimic the conditions of the 1,3-dipolar cycloaddition. After evaporation of the solvent, NMR spectroscopic analysis showed that extensive catalyst degradation occurred with acrolein, less degradation with crotonaldehyde, and essentially no degradation with cinnamaldehyde as the aldehyde.[16]

In agreement with the results of these experiments, we also observed that the non-supported catalyst **1a**/HCl showed a decrease in chemical efficiency when recycled.[17] For instance, the yield of compound **7** (obtained by a reaction involving crotonaldehyde) dropped from 64 to 49% upon one recycling, while the value of *ee* of *trans*-**7** changed from 89 to 87%. It is also interesting to note that the degradation byproducts do not interfere with the enantioselectivity of the surviving catalyst.

Conclusion

We have shown that catalysts derived from the PEG-supported imidazolidinone **5** and different acids can be employed conveniently to promote some 1,3-dipolar cycloadditions of α,β-unsaturated aldehydes with nitrones. The supported catalysts behave very similarly to their non-supported counterparts in terms of enantioselectivity, but are somewhat less efficient in terms of chemical yield. The immobilization on the polymer greatly simplifies the process of catalyst recovery. Recycling experiments showed that the supported catalyst maintains its stereochemical efficiency

for up to three reaction cycles. In contrast, the chemical efficiency slowly eroded upon recycling. In this respect, the supported and non-supported catalysts display analogous behavior. We ascribe the decrease in chemical efficiency to an intrinsic instability of the imidazolidinone catalyst that is induced by some unsaturated aldehydes.

Experimental Section

General: ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ solutions and are referenced to tetramethylsilane (TMS) at δ = 0.00 ppm. ^{13}C NMR spectra were recorded at 75 MHz and are referenced to 77.0 ppm in $CDCl_3$. IR spectra were recorded as thin films or as solutions in CH_2Cl_2.

All the PEG samples employed in the synthesis of **5** were melted at 80 °C under vacuum for 30 min before use to remove traces of moisture. Purification of the PEG-supported products involved evaporation of the reaction solvent in vacuo, dissolving the residue in CH_2Cl_2 (a few mL), and adding it to Et_2O stirred and cooled to 0 °C. After stirring at 0 °C for 20−30 min, the obtained suspension was filtered through a sintered glass filter, and the solid repeatedly washed on the filter with Et_2O.

Determining Yield and Purity of PEG-Supported Compounds: The yields of the PEG-supported compounds were determined by weight with the assumption that M_w for the PEG fragment was 5000 Da. The M_w actually ranged from 4500 to 5500. The indicated yields were for pure compounds. The purity of these compounds was determined by ^{1}H NMR spectroscopic analysis in $CDCl_3$ at 300 MHz with pre-saturation of the methylene signals of the polymer centered at δ = 3.63 ppm. In recording the NMR spectra, a relaxation time of 6 s and an acquisition time of 4 s were used to ensure complete relaxation and accuracy of the integration. The relaxation delay was selected after T_1 measurements. The signals of the PEG CH_2OCH_3 fragment at δ = 3.30 and 3.36 ppm were used as internal standards. The estimated integration error was ± 5%.

Synthesis of the Imidazolidinone 5

Synthesis of Compound (*S*)-3: (*S*)-Tyrosine methyl ester hydrochloride (1.81 g, 7.4 mmol) was added in one portion to a stirred solution of butylamine (2.5 mL, 25.3 mmol) in dry CH_3CH_2OH (3.0 mL) kept under nitrogen. The mixture was stirred at 30 °C for 48 h. The solvent was then evaporated under vacuum and the residue was treated with Et_2O (20 mL). The resulting pale-yellow solid was washed with another portion of Et_2O (20 mL), filtered, and dried under vacuum. The crude product thus obtained was suspended in saturated aqueous $NaHCO_3$ (10 mL) and stirred for 20 min. The resulting mixture was extracted with a 2% v/v solution of CH_3OH in CH_3Cl (3 × 33 mL) and the organic solution was dried and concentrated under vacuum. The residue was dissolved in a mixture of CH_3OH (15 mL) and acetone (25 mL) and PTSA (0.015 g) was added. The mixture was heated under reflux for 20 h and concentrated under vacuum to afford a crude product that was purified by flash chromatography (CH_2Cl_2/CH_3OH, 9:1). The pure product (1.411 g) was isolated in 69% overall yield. M.p. 99−101 °C. $[\alpha]_D^{23}$ = −78.2 (*c* = 0.72 in CH_2Cl_2). ^{1}H NMR ($CDCl_3$/D_2O): δ = 7.04 (B part of AB system, $^3J_{H,H}$ = 8.5 Hz, 2 H, aromatic protons), 6.74 (A part of AB system, $^3J_{H,H}$ = 8.5 Hz, 2 H, aromatic protons), 3.73 (t, $^3J_{H,H}$ = 5.8 Hz, 1 H, CHN), 3.29 (ddd, $^2J_{H,H}$ = 12.0, $^3J_{H,H}$ = 6.7, 3.2 Hz, 1 H, one H of NCH_2), 3.04 (ddd, $^2J_{H,H}$ = 12.0, $^3J_{H,H}$ = 5.8, 5.4 Hz, 2 H, Ar*CH*$_2$), 2.89 (ddd, $^2J_{H,H}$ = 12.0, $^3J_{H,H}$ = 6.2, 3.1 Hz, 1 H, one H of NCH_2), 1.43−1.49 (m, 2 H, NCH_2CH_2), 1.21−1.31 (m, 2 H, CH_3CH_2), 1.27 (s, 3 H, CMe), 1.17 (s, 3 H, CMe), 0.90 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR: δ = 174.2, 155.8, 130.7, 127.2, 115.7, 76.4, 58.9, 40.4, 35.5, 31.3, 27.8, 26.3, 20.3, 13.7 ppm. IR: $\tilde{\nu}$ = 3270, 1675, 1620 cm^{-1}. $C_{16}H_{24}N_2O_2$ (276.4): calcd. C 69.53, H 8.75, N 10.14; found C 69.71, H 8.64, N 10.23.

Synthesis of Catalyst Precursor 5: Compound (*S*)-**3** (0.200 g, 0.72 mmol) dissolved in DMF (3 mL) and Cs_2CO_3 (0.562 g, 1.725 mmol) were added to a solution of **4**[13] (3.0 g, 0.575 mmol, loading 0.192 meq/g), previously dried under vacuum at 90 °C for 1 h, in dry DMF (7 mL). After stirring at 60 °C for 24 h, the mixture was cooled to room temp., the solvent was evaporated under vacuum, and the residue was dissolved in CH_2Cl_2 (3 mL). The resulting solution was added dropwise to Et_2O (150 mL). The precipitated white solid was filtered, washed with Et_2O (2 × 25 mL), and dried under vacuum to give **5** (2.69 g, 0.50 mmol, loading 0.186 meq/g). ^{1}H NMR: δ = 7.05−7.11 (m, 4 H, aromatic protons), 6.77−6.81 (m, 4 H, aromatic protons), 4.07 (t, $^3J_{H,H}$ = 4.7 Hz, 2 H, PEG*CH*$_2$OAr), 3.84−3.88 (m, 4 H, PEGO*CH*$_2$CH$_2$Ar and $CH_2CH_2CH_2$OAr), 3.37 (t, $^3J_{H,H}$ = 5.2 Hz, 1 H, CHN), 3.30 (s, 3 H, *Me*OPEG), 3.21−3.30 (m, 1 H, one H of NCH_2), 3.04 (ddd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 5.2, 4.7 Hz, 2 H, Ar*CH*$_2$), 2.80−2.91 (m, 1 H, one H of NCH_2), 2.70 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H, PEGOAr*CH*$_2$), 1.95−2.08 (m, 2 H, $CH_2CH_2CH_2$), 1.40−1.50 (m, 2 H, NCH_2CH_2), 1.20−1.30 (m, 2 H, CH_3CH_2), 1.23 (s, 3 H, CMe), 1.13 (s, 3 H, CMe), 0.88 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_2CH_3) ppm.

General Procedure for the 1,3-Dipolar Cycloadditions: The synthesis of **4-formyl-3-phenyl-2-(phenylmethyl)isoxazolidine (6)** under the conditions of Entry 6, Table 1, is illustrative of the procedure. A 54% w/w solution of HBF_4 in Et_2O (0.026 mL, 0.186 mmol) was added to a stirred solution of **5** (0.500 g, 0.093 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at 24 °C for 1 h, and then the catalyst was precipitated by the addition of Et_2O. The precipitate was filtered and dried under vacuum to remove traces of solvent. Water (0.024 mL, 1.32 mmol) and acrolein (0.118 mL, 1.756 mmol) were added, in that order, to a mixture of the catalyst (0.480 g, 0.0877 mmol) and *N*-benzyl-*C*-phenylnitrone (0.093 g, 0.439 mmol) in nitromethane (4.4 mL) cooled to 0 °C, and then the mixture was stirred for 24 h while the temperature was allowed to rise slowly to 24 °C. The volatile materials were then evaporated under vacuum. The residue was dissolved in the minimum amount of CH_2Cl_2 and then poured in Et_2O (20 mL). The precipitate was filtered off, and the solid was washed with Et_2O (5 mL) and with an Et_2O/EtOAc mixture (9:1, 5 mL). The average recovery of catalyst ranged from 80 to 95% (0.385 to 0.455 g) after drying under high vacuum. The filtrate was concentrated under vacuum and the residue was analyzed by ^{1}H NMR spectroscopy to establish the *trans*/*cis* ratio by integrating the CHO signals at δ = 9.80 (*trans*) and 9.29 (*cis*) ppm. The crude product was then purified by flash chromatography (hexanes/EtOAc, 85:15) to give the product (0.086 g, 73%), which had ^{1}H NMR spectroscopic data in agreement with those reported.[8c] To determine *ee*, the aldehyde was converted into the corresponding alcohol by reduction with an excess $NaBH_4$ in CH_3OH at 24 °C for 1 h. The crude product (no aldehyde signals observed by ^{1}H NMR spectroscopy) was analyzed by HPLC [Chiralcel AD, flow rate 0.8 mL/min, λ = 230; hexane/CH_3CH_2OH, 92.5:7.5; for the *trans* isomer, t_R: 11.2 min (minor) and 13.4 min (major); for the *cis* isomer, t_R: 15.8 min (minor) and 20.4 min (major)].

4-Formyl-5-methyl-3-phenyl-2-(phenylmethyl)isoxazolidine (7): The crude product was analyzed by ^{1}H NMR spectroscopy to establish the *trans*/*cis* ratio by integrating the CHO signals at δ = 9.79 (*trans*)

and 9.28 (*cis*) ppm. The crude product was then purified by flash chromatography (hexanes/EtOAc, 85:15) to give a product that had ^{1}H NMR spectroscopic data in agreement with those reported.[8c] Starting from nitrone (0.439 mmol), the product was obtained (0.076 g, 0.26 mmol, 59% yield; Entry 1, Table 2). To determine *ee*, the aldehyde was converted into the corresponding alcohol by reduction with $NaBH_4$ (see above). The crude product (no aldehyde signals by ^{1}H NMR spectroscopy) was analyzed by HPLC [Chiralcel AD, flow rate 0.8 mL/min, λ = 230; hexane/CH_3CH_2OH, 95:5; for the *trans* isomer, t_R: 12.05 min (minor) and 15.5 min (major)].

4-Formyl-3-(4-methoxyphenyl)-2-(phenylmethyl)isoxazolidine (8): The crude product was analyzed by ^{1}H NMR spectroscopy to establish the *trans*/*cis* ratio by integrating the CHO signals at δ = 9.78 (*trans*) and 9.34 (*cis*) ppm. The crude product was then purified by flash chromatography (hexanes/EtOAc, 85:15) to give a product that had ^{1}H NMR spectroscopic data in agreement with those reported.[8c] Starting from the nitrone (0.439 mmol), the product were obtained (0.083 g, 0.28 mmol, 64% yield; Entry 2, Table 2). To determine *ee*, the aldehyde was converted into the corresponding alcohol by reduction with $NaBH_4$ (see above). The crude product (no aldehyde signals by ^{1}H NMR spectropscopy) was analyzed by HPLC [Chiralcel AD, flow rate 0.8 mL/min, λ = 230; hexane/CH_3CH_2OH, 95:5; for the *trans* isomer, t_R: 23.4 min (minor) and 31.2 min (major)].

3-(4-Chlorophenyl)-4-formyl-2-(phenylmethyl)isoxazolidine (9): The crude product was analyzed by ^{1}H NMR spectroscopy to establish the *trans*/*cis* ratio by integrating the CHO signals at δ = 9.78 (*trans*) and 9.29 (*cis*) ppm. The crude product was then purified by flash chromatography (hexanes/EtOAc, 85:15) to give a product that had ^{1}H NMR spectroscopic data in agreement with those reported.[8c] Starting from nitrone (0.439 mmol), the product were obtained (0.079 g, 0.26 mmol, 60% yield; Entry 3, Table 2). To determine *ee*, the aldehyde was converted into the corresponding alcohol by reduction with $NaBH_4$ (see above). The crude product (no aldehyde signals by ^{1}H NMR spectroscopy) was analyzed by HPLC [Chiralcel AD, flow rate 0.8 mL/min, λ = 230; hexane/CH_3CH_2OH, 97:3; for the *trans* isomer t_R: 39.5 min (minor) and 41.8 min (major)].

3-Cyclohexyl-4-formyl-2-(phenylmethyl)isoxazolidine (10): The crude product was analyzed by ^{1}H NMR spectroscopy to establish the *trans*/*cis* ratio by integrating the CHO signals at δ = 9.78 (*trans*) and 9.86 (*cis*) ppm. Purification by flash chromatography (hexanes/EtOAc, 90:10) gave the product as a pale yellow oil. Starting from nitrone (0.439 mmol), the product were obtained (0.049 g, 0.18 mmol, 41% yield; Entry 4, Table 2). ^{1}H NMR (*trans* isomer): δ = 9.78 (d, $^3J_{H,H}$ = 2.6 Hz, 1 H, CHO), 7.25−7.45 (m, 5 H, aromatic protons), 4.29 (dd, $^2J_{H,H}$ = 8.5, $^3J_{H,H}$ = 6.4, 1 H, one H of H_2C-5), 4.06 (t, $^2J_{H,H}$ = $^3J_{H,H}$ = 8.5 Hz, 1 H, one H of H_2C-5), 3.97 (B part of AB system, $^2J_{H,H}$ = 13.3 Hz, 1 H, one benzylic H), 3.88 (A part of AB system, $^2J_{H,H}$ = 13.3 Hz, 1 H, one benzylic H), 3.23−3.30 (m, 1 H, HC-4), 3.03−3.08 (m, 1 H, HC-3), 1.65−1.90 (m, 4 H, cyclohexyl protons), 1.40−1.60 (m, 1 H, CH of cyclohexyl), 0.87−1.30 (m, 6 H, remaining cyclohexyl protons) ppm. ^{13}C NMR (*trans* isomer): δ = 200.0, 137.1, 129.2, 128.7, 127.4, 71.2, 65.7, 61.2, 58.9, 41.3, 30.5, 29.1, 26.4 ppm. IR: $\tilde{\nu}$ = 1725 cm^{-1}. $C_{17}H_{23}NO_2$ (273.4): calcd. C 74.69, H 8.48, N 5.12; found C 74.82, H 8.66, N 5.02. To determine *ee*, the aldehyde was converted into the corresponding alcohol by reduction with $NaBH_4$ (see above). The crude product (no aldehyde signals by ^{1}H NMR spectroscopy) was analyzed by HPLC [Chiralcel AD, flow rate 0.8 mL/min, λ = 230; hexane/CH_3CH_2OH, 95:5; for the *trans* isomer t_R: 13.1 min (major) and 13.8 min (minor)].

Acknowledgments

This work was supported by CNR and MURST (Progetto Nazionale Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni).

[1] P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840−3864; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726−3748.
[2] R. Breslow, *Science* **1982**, *218*, 532−537.
[3] [3a] *Chiral Catalyst Immobilization and Recycling* (Eds.: D. E. De Vos, I. F. J. Vankelecom, P. A. Jacobs), Wiley-VCH, Weinheim, **2000**. [3b]An issue of Chemical Reviews::, *Chem. Rev.* **2002**, *102*, 3215−3289) has recently been devoted to recoverable catalysts and reagents. [3c] For an early review on supported catalysts, see: G. Manecke, W. Storck, *Angew. Chem.* **1978**, *90*, 691−705; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 657−670.
[4] For a recent review on polymer-supported organic catalysts, see: M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401−3429.
[5] [5a] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, M. Pitillo, *J. Org. Chem.* **2001**, *66*, 3160−3166. [5b] M. Benaglia, M. Cinquini, F. Cozzi, G. Tocco, *Tetrahedron Lett.* **2002**, *43*, 3391−3393, and references cited therein. [5c] M. Benaglia, M. Cinquini, F. Cozzi, A. Puglisi, G. Celentano, *Adv. Synth. Catal.* **2002**, *344*, 533−542, and references cited therein. [5d] M. Benaglia, T. Danelli, F. Fabris, D. Sperandio, G. Pozzi, *Org. Lett.* **2002**, *4*, 4229−4232. [5e] T. Danelli, R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, G. Tocco, *Tetrahedron: Asymmetry* **2003**, *14*, 461−467. [5f] M. Benaglia, T. Danelli, G. Pozzi, *Org. Biomol. Chem.* **2003**, *1*, 454−456.
[6] D. J. Gravert, K. D. Janda, *Chem. Rev.* **1997**, *97*, 489−509.
[7] [7a] For a review on PEG-supported catalysts, see: T. J. Dickerson, N. N. Reed, K. D. Janda, *Chem. Rev.* **2002**, *102*, 3325−3344. [7b] For the use of other soluble polymer-supported catalysts, see: D. E. Bergbreiter, *Chem. Rev.* **2002**, *102*, 3345−3384.
[8] [8a] For Diels−Alder cycloadditions, see: K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243−4244. [8b] A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458−2460. [8c] For nitrone cycloadditions, see: W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874−9875. [8d] For Friedel−Crafts alkylations, see: N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894−7895, and references cited therein. [8e] J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172−1173. [8f] For Mukaiyama-Michael reactions, see: S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192−1194. See also: [8g] D. W. C. MacMillan, WO 03/002491 A2, **2003**.
[9] M. Benaglia, G. Celentano, M. Cinquini, A. Puglisi, F. Cozzi, *Adv. Synth. Catal.* **2002**, *344*, 149−152.
[10] The immobilization of MacMillan-type catalysts on other supports and their use in Diels−Alder reactions has also been reported: S. A. Selkälä, J. Tois, P. M. Pihko, A. M. P. Koskinen, *Adv. Synth. Catal.* **2002**, *344*, 941−945. See Figure 1 for the structures of these catalysts.
[11] For examples of the use of the amide nitrogen atom as the handle for polymer attachment, see ref.[10].
[12] For a previous example of this strategy for anchoring a phenylalanine- containing organic catalyst to a polymer, see: H. J. Kim, W. R. Jackson, *Tetrahedron: Asymmetry* **1992**, *3*, 1421−1430.
[13] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, *Chem. Eur. J.* **2000**, *6*, 133−138.
[14] The absolute configuration of **6** and the other 1,3-dipolar cycloaddition products **7−9** was established by comparison of the sign of optical rotation with the value reported for the same compounds of known configuration (see ref.[8c]). The absolute

configuration of the previously unreported adduct **10** was assigned on the assumption that the reaction leading to **10** followed the same stereochemical course as those leading to **6**−**9**.

[15] As previously observed in the Diels−Alder reaction (see ref.[9]), in the synthesis of compounds **6** and **7** the use of either commercial **1a**/HCl or ad hoc-prepared **1a**/CF_3SO_3H resulted, in our hands, in yields and *ee* lower than those reported by MacMillan (see ref.[8c]). For instance, when **1a**/HCl was employed as the catalyst, compound **7** was obtained in 64% yield and 89% *ee*, in contrast to the reported 70% yield and 95% *ee*.

[16] In additional control experiments, we found that *N*-benzyl-*C*-phenylnitrone did not degrade **1a**/HCl, and that the degradation of **5**/HX upon recovery was independent of the catalyst's water content (from 3 to 49 equiv. of water/equivalent of catalyst; determined by Karl−Fischer titrations).

[17] The recycling of **1a**/HCl involved evaporation of the reaction mixture and addition of diethyl ether to the residue. The solvent was decanted and the residue was washed at least five times with diethyl ether to completely remove the reaction products. The combined ethereal phases were worked-up to isolate the product, and the catalyst was dried under vacuum to afford a waxy solid that was analyzed for degradation, by NMR spectroscopy, and then recycled.

Received September 10, 2003

