Poly(ethylene glycol)-Supported Chiral Imidazolidin-4-one: An Efficient Organic Catalyst for the Enantioselective Diels–Alder Cycloaddition

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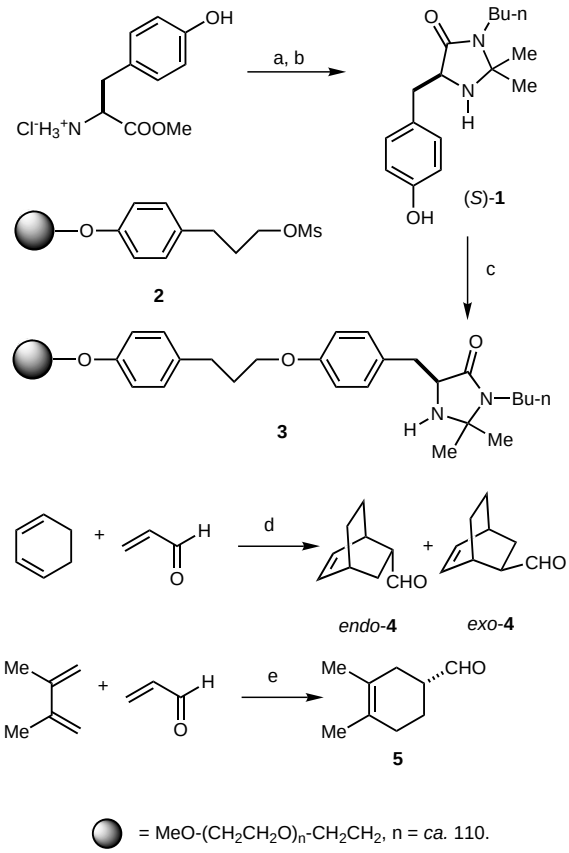
Abstract: A tyrosine-derived imidazolidin-4-one was immobilized on a modified poly(ethylene glycol) and converted *in situ* into a soluble polymer-supported catalyst for the enantioselective Diels–Alder cycloaddition of acrolein to 1,3-cyclohexadiene (up to 92% ee) and 2,3-dimethyl-1,3-butadiene (73% ee). Catalyst recycling (up to four cycles) was accompanied by some loss of the chemical efficiency and marginal erosion of the enantioselectivity.

Keywords: asymmetric catalysis; catalyst immobilization; chiral organic catalysts; Diels–Alder cycloadditions; soluble polymers.

The immobilization of chiral catalysts on polymer matrixes has recently emerged as a practical method which allows easy recovery and recycling of often expensive catalysts while facilitating product isolation and purification.[1] In this context, readily functionalized poly(ethylene glycol)s (PEGs) of $M_w > 2000$ Da offer distinctive advantages over other polymers. These supports, being soluble in many organic solvents and in water and insoluble in a few other solvents,[2] allow us to run a catalyzed reaction under homogeneous (and likely best performing) conditions and to isolate and recover the catalyst as if it were bound to an insoluble polymer.[3]

While immobilization of chiral ligands on PEGs has been reported,[1,3a,4] the synthesis of PEG-supported catalysts has been much less studied.[1,3b] Chiral organic (i.e., metal-free) catalysts[5] seem particularly attractive for supporting on polymer, since they cannot suffer from metal leaching upon recycling, a major drawback associated with the use of polymer-bound, metal-based catalysts.[6] As a part of a project devoted to the development of PEG-supported organic catalysts,[7] we now report that immobilization of an enantiopure imidazolidin-4-one on a derivative of PEG_{5000} monomethyl ether afforded an efficient and recyclable catalyst for the enantioselective Diels–Alder cycloaddition.[8]



Reagents and conditions:
a: *n*-$BuNH_2$ (4 mol equiv), EtOH, RT, 20 h
b: Me_2CO (excess), MeOH, cat. PTSA, 60 °C, 20 h;
c: **2** (0.8 mol equiv), Cs_2CO_3 (3 mol equiv), DMF, 60 °C, 24 h
d: **3**/HX (0.1 mol equiv; X = Cl, CF_3COO, CF_3SO_3), CH_3CN/H_2O, 95/5, 24 °C
e: **3**/TFA (0.1 mol equiv), CH_3CN/H_2O, 95/5, 24 °C

Scheme 1. Synthesis of PEG-supported catalyst precursor **3** and enantioselective Diels–Alder cycloadditions.

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Starting from (*S*)-tyrosine methyl ester hydrochloride, imidazolidin-4-one **1** was easily obtained[8a] in 58% yield (Scheme 1). Reaction of the Cs salt of (*S*)-**1** (1.25 mol-equiv) with the readily available mesylate **2**[9] in DMF (60 °C, 24 h) afforded the supported imidazolidin-4-one **3** in 87% yield.[10] *In situ* conversion of this compound to the catalytically active species involved the addition of an equimolar amount of different acids (see Table 1). The resulting ammonium salts (0.1 mol-equiv) were employed, under different conditions, in the Diels–Alder cycloaddition between cyclohexadiene (1 mol-equiv) and acrolein (3 mol-equiv) to afford mixtures of *endo*- (largely major) and *exo*-cycloadducts **4.** The results are reported in Table 1, together with those obtained using the non-supported catalysts derived from (*S*)-**1** and its methyl ether (**1**-OMe). Yields were determined on the isolated products; diastereoisomeric ratios were determined by 300 MHz ^{1}H NMR analysis of the crude products, exploiting the CHO signals at $\delta = 9.46$ (*endo*) and 9.75 (*exo*) ppm, and confirmed on isolated compounds; enantiomeric excesses (ee) were obtained by HPLC analysis on a chiral stationary phase carried out on the *N,N*-diphenylhydrazones derived from **4** in $>95\%$ yield; the (*R*) absolute configuration of *endo*-**4** was established by reduction to the corresponding alcohol and comparison of the sign of optical rotation with the value reported for a sample of known configuration.[11]

The efficiency of the non-supported catalyst was preliminarily established (entries 1 – 3). Best results were obtained using the trifluoroacetate salt of **1**-OMe, that, at a 10% molar loading, led to *endo*-**4** in 75% yield, 92/8 diastereoselectivity, and 84% ee. These results were inferior to those obtained by MacMillan et al. working under similar conditions with 5% molar of (*S*)-5-benzyl-2,3,3-trimethylimidazolidin-4-one hydrochloride as the catalyst (82% yield, 93/7 diastereoselectivity, 94% ee).[8a] However, by using the supported catalyst derived from **3**, and by properly selecting the reaction parameters (entry 8), results comparable to MacMillan's were obtained (67% yield, 94/6 diastereoselectivity, 92% ee).

The acid employed to generate the catalyst was important (entries 4, 6, 7), with **3**/HCl securing better yields and **3**/TFA higher stereocontrol. Independently of the catalyst counterion, a longer reaction time increased the yield (entries 4 vs. 5, 7 vs. 8). Decreasing the catalyst loading to 5% molar slowed down the reaction, but preserved the stereoselectivity (entry 8 vs. 9). The use of pre-formed catalysts (entries 11 and 12) did not improve the efficiency of the process while making it less practical.

Finally, the reaction was successfully extended to the acyclic 2,3-dimethylbutadiene which, when reacted with acrolein under the conditions of entry 8, afforded cycloadduct **5**,[11] $[\alpha]_D^{23}$: $+170.0$ (*c* 0.20, CH_2Cl_2), in 75% yield and 73% ee (by HPLC, see above).

Table 1. Catalytic enantioselective synthesis of cycloadduct **4** at 24 °C in CH_3CN/H_2O (95/5).

Entry	Catalyst	Time [h]	Yield [%][a]	*endo/exo*[b]	*endo* ee %[c]	*exo* ee %[c]
1	**1**/HCl	22	35	90/10	68	undetermined
2	**1**/TFA	22	39	91/9	82	undetermined
3	**1**-OMe/TFA	22	75	92/8	84	undetermined
4	**3**/HCl	22	63	91.5/8.5	70	60
5	**3**/HCl	40	81	91/9	73	undetermined
6	**3**/TfOH	22	27	94/6	88	84
7	**3**/TFA	22	50	94/6	92	undetermined
8	**3**/TFA	40	67	94/6	92	86
9	**3**/TFA[d]	40	45	94/6	90	undetermined
10[e]	**3**/TFA	40	10	91/9	undetermined	undetermined
11	**3**/HCl[f]	40	61	92/8	70	undetermined
12	**3**/TFA[f]	40	52	93/7	84	undetermined
13	**3**/TFA[g]	40	61	94/6	87	undetermined
14	**3**/TFA[h]	40	50	94/6	87	undetermined
15	**3**/TFA[i]	40	38	94/6	85	undetermined

[a] Yields of isolated products.
[b] As determined by 300 MHz ^{1}H NMR spectroscopy on the crude products and confirmed on the isolated products.
[c] As determined by HPLC on a chiral stationary phase on the corresponding *N,N*-diphenylhydrazones; yields and ee are average of duplicate experiments.
[d] 0.05 mol-equiv of catalyst.
[e] Carried out in $MeOH/H_2O$.
[f] Carried out with a pre-formed sample of catalyst.
[g] Carried out with a catalyst sample recycled after use in entry 8.
[h] Carried out with a catalyst sample recycled after use in entry 8 and 13.
[i] Carried out with a catalyst sample recycled after use in entry 8, 13, and 14.

The relevant issue of recovery and recycling of the catalyst was then addressed. The catalyst was recovered from the reaction mixture by evaporation of the solvent under reduced pressure, precipitation with diethyl ether, and filtration. The recovered material was then dried at 90 °C under high vacuum to eliminate traces of water that the hygroscopic PEG could have absorbed from the solvent. The recovery yields ranged between 70 and 80%. NMR analysis showed that the recovered material was a mixture of protonated and unprotonated **3**. As such, this material was found to promote a sluggish cycloaddition reaction. However, addition of TFA regenerated an active catalyst that was successfully employed in a second cycle affording the product in 61% yield, 94/6 *endo/exo* ratio, and 87% ee (Table 1, entry 13). Iteration of the recovery/recycling protocol was possible for other two cycles, both occurring in almost unchanged stereoselectivities but in decreasing yields (entries 14 and 15). When the catalyst was used in a fifth cycle, the yield was very low (10–15% after 60 h).

The decrease in chemical efficiency of the recovered catalyst was confirmed by repeating the recycling experiments and using an internal-standard calibrated GC analysis to asses the reaction yield without being hampered by the problems associated with the isolation of the relatively volatile adduct **4**.[12] ^{1}H NMR analysis of the recovered samples of **3** indicated extensive degradation after three cycles, showing broadening of the signals of the imidazolidinone moiety and a decreased intensity of its peaks with respect to those of the aromatic protons of the linker, which remained virtually unchanged.[13] Thus, it seems possible that prolonged exposure of **3** to the acidic reaction medium led to catalyst degradation resulting in the observed decreased yields upon recycling. The fact that the ee of the product did not change as dramatically as the chemical yield (1st cycle, 92% ee; 4th cycle, 85% ee) suggests that the catalyst degradation product(s) did not affect the steric course of the reaction. Catalyst stability and recycling are undergoing further studies.

In conclusion, these results showed that a modified PEG is a convenient support of an organic catalyst for the enantioselective Diels–Alder cycloaddition. The supported catalyst secured stereoselectivity very similar to that observed with a related, non-immobilized catalyst. Simple catalyst recovery and recycling was also demonstrated, although only for a limited number of cycles. These findings can be useful in designing practical enantioselective catalytic reactions with continuous catalyst recycle, and widen the scope of PEGs as convenient supports for chiral organic catalysts.

Experimental Section

Compound 2

Mp 99–101 °C; $[\alpha]_D^{23}$: −78.2 (*c* 0.72, CH_2Cl_2); IR: $\nu = 3270$, 1675, 1620 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3/D_2O$): $\delta = 7.04$ (B part of AB system, 2H, $J = 8.5$ Hz, aromatic protons), 6.74 (A part of AB system, 2H, $J = 8.5$ Hz, aromatic protons), 3.73 (t, 1H, $J = 5.8$ Hz, CHN), 3.29 (ddd, 1H, $J = 12.0$, 6.7, 3.2 Hz, one H of NCH_2), 3.04 (ddd, 2H, $J = 15.0$, 5.8, 5.4 Hz, ArCH_2), 2.89 (ddd, 1H, $J = 12.0$, 6.2, 3.1 Hz, one H of NCH_2), 1.43–1.49 (m, 2H, NCH_2CH_2), 1.21–1.31 (m, 2H, CH_3CH_2), 1.27 (s, 3H, CMe), 1.17 (s, 3H, CMe), 0.90 (t, 3H, $J = 7.3$ Hz, CH_2CH_3); Anal.: found: C 69.71, H 8.64, N 10.23; $C_{16}H_{24}N_2O_2$ (276.4) requires: C 69.53, H 8.75, N 10.14.

Synthesis of Catalyst Precursor 3

To a solution of **2** (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), compound (*S*)-**1** (0.200 g, 0.72 mmol) dissolved in DMF (3 mL) and Cs_2CO_3 (0.562 g, 1.725 mmol) were added. After 24 h stirring at 60 °C, the mixture was cooled at room temperature, the solvent was evaporated under vacuum, and the residue was dissolved in CH_2Cl_2 (3 mL). The resulting solution was poured dropwise in Et_2O (150 mL). The precipitated white solid was filtered, washed with Et_2O (2 × 25 mL), and dried under vacuum to give **3**; yield: 2.69 g (0.50 mmol, loading 0.186 meq/g). ^{1}H NMR (300 MHz, $CDCl_3$, with presaturation of the PEG methylene signals at $\delta = 3.63$; relaxation delay: 6 s; acquisition time: 4 s): $\delta = 7.05–7.11$ (m, 4H, aromatic protons), 6.77–6.81 (m, 4H, aromatic protons), 4.07 (t, 2H, $J = 4.7$ Hz, PEGCH_2OAr), 3.84–3.88 (m, 4H, PEGOCH_2CH_2Ar and $CH_2CH_2CH_2$OAr), 3.37 (t, 1H, $J = 5.2$ Hz, CHN), 3.33 (s, 3H, *Me*OPEG), 3.21–3.30 (m, 1H, one H of NCH_2), 3.04 (ddd, 2H, $J = 15.0$, 5.2, 4.7 Hz, ArCH_2), 2.80–2.91 (m, 1H, one H of NCH_2), 2.70 (t, 2H, $J = 7.8$ Hz, PEGOArCH_2), 1.95–2.08 (m, 2H, $CH_2CH_2CH_2$), 1.40–1.50 (m, 2H, NCH_2CH_2), 1.20–1.30 (m, 2H, CH_3CH_2), 1.23 (s, 3H, CMe), 1.13 (s, 3H, CMe), 0.88 (t, 3H, $J = 7.2$ Hz, CH_2CH_3).

General Procedure for the Diels–Alder Cycloaddition

To a stirred solution of compound **3** (0.500 g, 0.093 mmol) in a 95/5 CH_3CN/H_2O mixture (10 mL), trifluoroacetic acid (7.2 μL, 0.095 mmol) was added and the mixture stirred for 5 min at 24 °C. Freshly distilled acrolein (0.186 mL, 2.79 mmol) and 1,3-cyclohexadiene (0.086 mL, 0.93 mmol) were added in this order. The mixture was stirred at 24 °C for 40 h. Na_2SO_4 was then added, the mixture was filtered, and the organic solvent evaporated under vacuum. The residue was dissolved in the minimum amount of CH_2Cl_2 and then poured in Et_2O (30 mL). The precipitate was filtered off, and the solid was washed with Et_2O (5 mL). Average recovery of catalyst ranged from 70 to 80% (0.360 to 0.400 g) after drying under high vacuum. The filtrate was concentrated under vacuum and the residue was purified by flash chromatography with an 80:20 hexanes: Et_2O mixture as eluent to give the product; yield: 0.085 g (67%). The ^{1}H NMR data were in agreement with those reported.[14] Conversion of the product to the corre-

sponding *N,N*-diphenylhydrazone (*N,N*-diphenylhydrazine, EtOH, $MgSO_4$, 24 °C, 15 h, >95% yield) was necessary for ee determination by HPLC [Chiralcel OD, flow rate 0.8 mL/min, $\lambda = 230$; for the *endo* isomer: hexane/*i*-PrOH = 99:1; t_R: 5.40 min (minor) and 5.80 min (major); for the *exo* isomer: hexane/*i*-PrOH = 95:5; t_R: 12.60 min (minor) and 13.30 min (major)].

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[12] The GC yields (cycle, at 24 h, at 40 h, isolated) were the following: 1, 64%, 77.5%, 67%; 2, 60%, 73%, 60%; 3, 26%, 51%, 48%; 4, undetermined, 35%, 33%. The GC analysis did not show the presence of any degradation products. *Endo/exo* ratios were identical to those reported in entries 8, 13 – 15. In the reactions carried out with recycled catalysts the amounts of reagents and solvents for a new cycle were adjusted to the amount of recovered **3.**

[13] Interestingly, an analogue of (*S*)-**1** having a benzyl instead of the 4-hydroxybenzyl group at C-5, did not show any degradation when exposed to excess TFA in 95/5 CD_3CN/D_2O at room temperature for 120 h either in the absence or in the presence of the bismethyl ether of PEG_{2000}.

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