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Recoverable polystyrene-supported palladium catalyst for construction of all-carbon quaternary stereocenters via asymmetric 1,4-addition of arylboronic acids to cyclic enones

Jan Bartáček, Jiří Váňa*, Pavel Drabina, Jan Svoboda, Martin Kocúrik, Miloš Sedlák

Institute of Organic Chemistry and Technology, Faculty of Chemical Technology, University of Pardubice, Studentská 573, 532 10 Pardubice, Czech Republic

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ABSTRACT

The development of recoverable catalysts based on the combination of synthetically demanding ligands with transition metals attracts a lot of attention, especially from the environmental point of view. In this paper, we describe the preparation of a recoverable polystyrene supported chiral palladium catalyst based on PyOx ligand suitable for asymmetric 1,4-addition of arylboronic acids to cyclic 3-substituted five- and six-membered enones. In the reaction, all-carbon quaternary stereocenters are formed with a high level of enantioselectivity (up to 91% ee) and conversion (up to 99%). The catalyst was used in 6 cycles with no loss of enantioselectivity and only a small decrease in conversion. A solution of the problems associated with the transition from homogeneous to heterogeneous catalytic systems is discussed.

1. Introduction

The enantioselective synthesis of compounds containing all-carbon quaternary stereocenters has been an attractive research topic in recent years [1–12]. This is mainly due to the rigid three-dimensional structure of such molecules, prepared in this manner, which may be responsible for their interesting biological activities [7,13]. One of the best understood and investigated methods for synthesis of all-carbon quaternary stereocenters is the Michael addition of carbon nucleophiles to α,β-unsaturated carbonyls catalyzed predominantly by chiral rhodium catalysts introduced by Hayashi [14–16] or by chiral palladium complexes introduced by Miyaura [17–19]. The selected products of the reaction can be utilized as important building blocks in organic synthesis [20–22]. More recently, Stoltz's group described conjugated addition of boronic acids to 3-substituted cyclic enones catalyzed by palladium complexes of (*S*)-4-(*tert*-butyl)-2-[4-(pyridin-2-yl)-4,5-dihydrooxazole (PyOx) [1] (Scheme 1). This reaction is advantageous mainly due to the formation of well-defined all-carbon quaternary stereocenters under moisture-tolerant conditions [1,23–27]. Experimental as well as computational studies showed that the enantioselectivity of the catalyst is controlled predominantly by repulsion between *t*-butyl group of the PyOx ligand and enone methylene hydrogen atoms in cationic arylpalladium(II) species (Scheme 1) [23].

In addition to the PyOx, the chiral pyridine-hydrazone [7] and *bis*-oxazoline [2,5] ligands were successfully used for palladium-catalyzed asymmetric conjugated addition of boronic acids to 3-substituted cyclohex-1-en-3-ones giving all-carbon quaternary stereocenters.

Nevertheless, all these reactions are burdened with the problems associated with the homogeneous catalysis. The fundamental problem of all catalyzed reactions consists in the necessity of separating the product from the catalyst. The regeneration of the homogeneous catalyst used can be impossible or very demanding from economic as well as technological point of view. Hence, both the chiral ligand and expensive palladium turn into dangerous waste requiring further processing or disposing [28–31]. This problem can be overcome by the application of a sustainable technology, i.e. the immobilization of the homogeneous catalysts containing such expensive ligands and toxic metals on solid carriers. The immobilization enables simple separation of the catalysts and offers the possibility for their regeneration [30,31].

Suitable carriers for immobilization of homogeneous catalysts are, among others, the spherical copolymers of styrene [32–35]. Immobilization of chiral rhodium complexes has already been performed [36,37] and a recent contribution to this topic had been made by Shen et al. They prepared recyclable catalysts based on a rhodium complex immobilized on a spherical polystyrene-poly(ethylene glycol) carrier via the post-modification strategy, starting from the commercially available copolymer TentaGel S NH_2, cross-linked by 1% DVB [38]. This catalyst was used for conjugated addition of arylboronic acid to 3-unsubstituted cyclohex-2-ene-1-ones in a batch and continuous-flow arrangement [38]. However, this type of substrates led to products with

* Corresponding author.
E-mail address: jiri.vana@upce.cz (J. Váňa).

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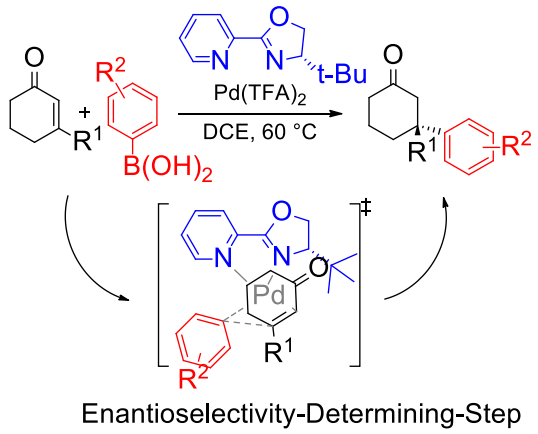
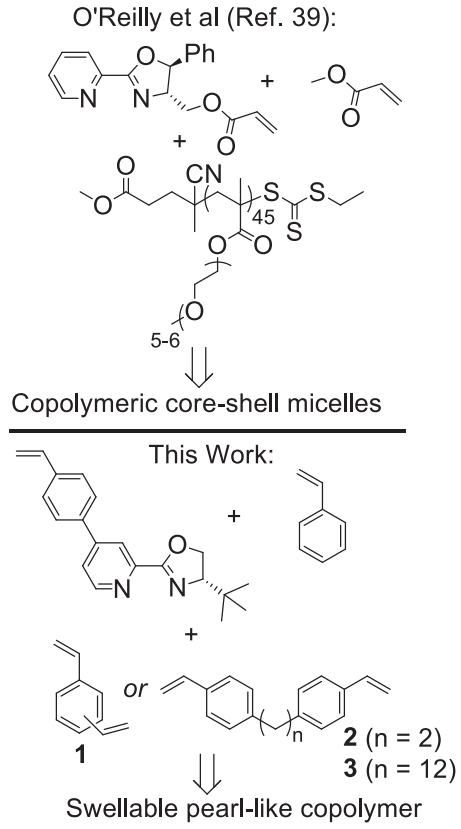


Scheme 1. Palladium-catalyzed conjugated addition of arylboronic acids to 3-substituted cyclic enones [1].



Scheme 2. Copolymerization strategy used for preparation of different copolymeric catalysts designed for asymmetric 1,4-addition of arylboronic acids to cyclic enones.

a tertiary chiral center. Further, O'Reilly et al. prepared a copolymer by RAFT copolymerization of modified PyOx-ligand. Together with palladium(II) trifluoroacetate ($Pd(TFA)_2$), this copolymer forms the so called micellar nanoreactors (Scheme 2) that were used in the synthesis of substituted chromones [39]. However, this catalyst was not recycled and only chromones were used as the substrates.

Herein, we report a development of a heterogeneous recoverable catalyst based on styrene copolymer bearing a chiral palladium complex with PyOx for asymmetric conjugated addition of aryl boronic acids to 3-substituted cyclic five and six membered enones yielding products with all-carbon quaternary stereocenters.

2. Experimental section

2.1. General

The FT-IR spectra were recorded on FT-IR Nicolet iS50 using the ATR technique. The region of diamond crystal absorption (1900–2400 cm^{-1}) was removed from the spectra. NMR spectra were measured at room temperature on Bruker AVANCE III 400 or Bruker Ascend™ 500. ^{1}H NMR spectra were calibrated to tetramethylsilane. ^{13}C NMR spectra were calibrated to the middle signal of the multiplet of used solvent. ^{13}C NMR spectra were measured with APT technique or with proton decoupling. ^{13}C NMR spectra of solid phase were measured by CP/MAS without a standard. High resolution mass spectra were measured by the „dried droplet "method using the MALDI mass spectrometer LTQ Orbitrap XL (Thermo Fisher Scientific, Bremen, Germany) equipped with nitrogen UV laser (337 nm, 60 Hz). The spectra were taken in the positive ion mode with the resolution 100,000 at $m/z = 400$. The resulting spectrum represents an average of all measurements. The used matrix was 2,5-dihydroxybenzoic acid (DHB). HPLC analysis were performed on HPLC instrument with UV–Vis diode array (200–800 nm) SYKAM 3240 and with chiral columns Daicel Chiralcel OJ-H, OD-H or Chiralpak AD-H. Optical rotation was measured on Perkin Elmer Polarimeter Model 341 with sodium-vapour lamp at the wavelength $\lambda = 589$ nm and the temperature 20 °C. The samples were analysed using scanning electron microscope JEOL JSM-5500LV. The swelling capacity of the prepared resin was measured using the method described in literature [40]. The starting chemicals were purchased from commercial resources and used without further purification. Thin layer chromatography was performed on aluminium plates coated with silica gel SiO_2 with visualization by UV light (254 or 366 nm). Flash chromatography was performed on Reveleris® X2 on silica gel packed columns. Melting points were determined in open capillaries on Buchi B-540 and were not corrected.

2.2. Preparation of monomers

2.2.1. 1,12-Bis(4-vinylphenyl)dodecane (BVPC12)

To the suspension of magnesium (0.82 g; 33.7 mmol) in dry diethyl ether (30 ml; dried over 4 Å MS) containing 3 drops of CH_3I, the 4-vinylbenzyl chloride (1.9 ml; 13.5 mmol) was added portion-wise under ultrasonication (400 W) during 1 h. The mixture was stirred for an additional one hour at room temperature. The prepared solution of 4-vinylbenzylmagnesium chloride was cannulated within 15 min to the ice-cold solution of 1,10-diiododecane (2 g; 5.1 mmol) and Li_2CuCl_4 (5.1 ml of 0.1 M solution) in dry THF (30 ml). After 16 h the reaction was quenched by a saturated NH_4Cl solution and extracted by DCM (3 × 25 ml). Combined organics layers were washed with brine, dried over $MgSO_4$ and subjected to flash chromatography (petroleum-ether). The product was obtained as a white solid (1.14 g; 3 mmol; 60%).

m.p. 51–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38–7.25$ (m, 4H), 7.21–7.02 (m, 4H), 6.69 (dd, $J = 17.5$, 10.9 Hz, 2H), 5.70 (d, $J = 17.6$ Hz, 2H), 5.18 (d, $J = 10.8$ Hz, 2H), 2.58 (t, $J = 7.5$ Hz, 4H), 1.65–1.53 (m, 4H), 1.28 ppm (d, $J = 17.1$ Hz, 16H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 142.9, 136.9, 135.2, 128.7, 126.2, 112.9, 35.8, 31.6, 29.8, 29.7, 29.7, 29.5$ ppm; FT-IR (ATR) cm^{-1}: 3124; 3087; 3003; 2978; 2916; 2846; 1911; 1820; 1705; 1630; 1510; 1462; 1406; 1122; 1014; 993; 906; 845; 814; 723; 640; 471; 455; HRMS (MALDI): m/z calcd for $C_{28}H_{38} + H^+$: 375.30518 $[M + H]^+$; found: 375.30582.

2.2.2. (S)-2-(4-bromopyridin-2-yl)-4-(tert-butyl)-4,5-dihydrooxazole

$ZnCl_2$ (5.11 g; 38.5 mmol) was melted under high vacuum and cooled down under argon atmosphere. Degassed solution of 4-bromopyridine-2-carbonitrile (2.05 g; 11.2 mmol) and L-*tert*-leucinol (1.98 g; 16.9 mmol) in chlorobenzene (50 ml; dried over 4 Å MS) was added. Resulting mixture was refluxed overnight under inert atmosphere. After cooling, the reaction mixture was decanted and solid residue was

extracted with hot DCM (20 ml). The combined organic portions were extracted with 20% NaOH (50 ml). The water layer was washed with DCM (3× 15 ml) and combined organics layer were washed with brine, dried over $MgSO_4$ and subjected to flash chromatography (hexane→AcOEt +5% TEA). The product was obtained as yellow solid (3.17 g; 10.6 mmol; 95%).

$[\alpha]_D^{20}$ –56.6 ($CHCl_3$, *c* 1 g/100 ml); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 5.2 Hz, 1H), 8.27 (d, *J* = 0.9 Hz, 1H), 7.56 (dd, *J* = 5.1, 1.3 Hz, 1H), 4.46 (t, *J* = 9.5 Hz, 1H), 4.32 (t, *J* = 8.6 Hz, 1H), 4.20–4.07 (m, 1H), 0.98 ppm (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.4, 150.4, 148.1, 133.3, 128.7, 127.3, 76.6, 69.5, 34.0, 26.0 ppm; FT-IR (ATR) cm^{-1}: 3053; 2957; 2904; 2868; 1643; 1568; 1550; 1477; 1464; 1410; 1363; 1331; 1306; 1255; 1115; 1084; 964; 914; 833; 744; 677; HRMS (MALDI): *m/z* calcd for $C_{12}H_{15}BrN_2O + H^+$: 283.04405 $[M + H]^+$; found: 283.04417.

2.2.3. (S)-4-(tert-butyl)-2-(4-(4-vinylphenyl)pyridin-2-yl)-4,5-dihydrooxazole

In 250 ml flask (*S*)-2-(4-bromopyridin-2-yl)-4-(*tert*-butyl)-4,5-dihydrooxazole (3.4 g; 12 mmol), 4-vinylphenylboronic acid (2.5 g; 16.9 mmol) and Na_2CO_3 (2.6 g; 24.5 mmol) were mixed in a THF/water mixture (4:1; 70 ml) and degassed with argon. $Pd(PPh_3)_2Cl_2$ (420 mg; 0.6 mmol) was added and the mixture was heated up to 65 °C and stirred at this temperature. After 2 days no more starting material was detectable via TLC. The reaction mixture was filtered through silica pad with AcOEt +5% TEA and evaporated. The residue was subjected to flash chromatography (hexane→AcOEt +5% TEA). The product was obtained as a yellow oil (3.8 g; 11.7 mmol; 98%).

$[\alpha]_D^{20}$ –19.8 ($CHCl_3$, *c* 1 g/100 ml); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, *J* = 5.1 Hz, 1H), 8.32 (d, *J* = 1.0 Hz, 1H), 7.73–7.62 (m, 2H), 7.59 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.55–7.47 (m, 2H), 6.76 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.84 (d, *J* = 17.6 Hz, 1H), 5.34 (d, *J* = 10.9 Hz, 1H), 4.47 (dd, *J* = 10.1, 8.9 Hz, 1H), 4.34 (t, *J* = 8.5 Hz, 1H), 4.15 (dd, *J* = 10.1, 8.4 Hz, 1H), 1.00 ppm (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.6, 150.2, 148.6, 147.6, 138.7, 136.7, 136.1, 127.3, 127.0, 123.0, 121.6, 115.3, 76.7, 69.4, 34.1, 26.0 ppm; FT-IR (ATR) cm^{-1}: 3305; 3059; 3037; 2985; 2951; 2904; 2868; 1658; 1587; 1475; 1358; 1240; 1119; 1084; 993; 955; 922; 914; 829; 746; 690; HRMS (MALDI): *m/z* calcd for $C_{20}H_{22}N_2O + H^+$: 307.18049 $[M + H]^+$; found: 307.17899.

2.3. Preparation of polymeric materials

2.3.1. Copolymers 1–3

To the Ar degassed solution of PVA (1.36 g) and NaCl (15 g) in water (400 ml) in a conical-shaped flask (500 ml) with oval magnetic stirrer (2 × 6.5 cm) was, under the inflow of N_2, suspended a solution of styrene (**1**: 2.63 g; **2**: 6.03 g; **3**: 4.03 g), (*S*)-4-(*tert*-butyl)-2-(4-(4-vinylphenyl)pyridin-2-yl)-4,5-dihydrooxazole (**1**: 0.6 g; **2**: 1.7 g; **3**: 0.82 g), crosslinker (0.9 mol% - **1**: 65.7 mg of DVB; **2**: 135 mg of BVPE; **3**: 142 mg of BVPC12), dibenzoylperoxide (**1**: 0,16 g; **2**: 0.29 g; **3**: 0.16 g) and bromobenzene (0.6 mL·g^{-1} monomers). Stirring was adjusted to 250 min^{-1} and the mixture was heated to 95 °C within 30 min and stirred for 4 days. After cooling the suspension was poured into water (0.5 l) and the sedimented copolymer was decanted repeatedly from water (3 × 500 ml). The crude pearl-like copolymer was gradually washed with water (3 × 200 ml), methanol (100 ml), THF (50 ml) and DCM (50 mL) and extracted with THF-water mixture (2:1) in Soxhlet extractor for 24 h. The final pearl-like copolymer was obtained after drying in vacuo (**1**: 2.35 g – 81% yield; **2**: 4.5 g – 70% yield; **3**: 3.3 g – 68% yield). Ligand content was calculated from microanalysis (**1**:0.571; **2**:0.732; **3**:0.464 mmol·g^{-1}).

1: FT-IR (ATR) cm^{-1}: 3373; 3103; 3082; 3059; 3026; 2991; 2924; 2850; 1720; 1670; 1601; 1514; 1493; 1452; 1265; 1066; 1028; 906; 829; 758; 737; 696; 540; elemental analysis (%) found C 85.98, H 7.68, N 1.60; swellability (ml·g^{-1}) 1,2-DCE: 3.8, AcOEt: 2.3.

2: ^{13}C CP/MAS NMR (20 kHz rotation, 126 MHz): δ = 164, 147, 128, 76, 68, 41, 34, 27, 26 ppm; FT-IR (ATR) cm^{-1}: 3379; 3107; 3082; 3059; 3026; 3003; 2922; 2852; 1720; 1672; 1601; 1514; 1493; 1452; 1365; 1066; 1028; 906; 829; 756; 696; 540; elemental analysis (%) found C 86.36, H 7.70, N 2.05; swellability (ml·g^{-1}) 1,2-DCE: 5.3, AcOEt: 2.

3: FT-IR (ATR) cm^{-1}: 3379; 3103; 3082; 3059; 3026; 3001; 2922; 2850; 1720; 1676; 1601; 1514; 1493; 1452; 1365; 1068; 1028; 906; 829; 756; 696; 538; elemental analysis (%) found C 88.51, H 7.77, N 1.30; swellability (ml·g^{-1}) 1,2-DCE: 8.8, AcOEt: 2.7.

2.3.2. Copolymeric complexes 1–3*Pd

Copolymers **1–3** and $Pd(TFA)_2$ were placed into flask. Next, a solvent (1,2-DCE or AcOEt; 20 ml *per* 1 g of polymer) was added and after ultrasound homogenization (400 W; 1 min) the mixture was heated up to 60 °C and stirred at this temperature. After 3 days, the copolymer was filtered, washed with DCM, dried and precisely weighted. The weight difference of the copolymer before and after complexation, was identified with amount of complexed Pd and its content was estimated (mmol·g^{-1}). 13 mol% of this complex was used in catalytic experiments.

1*Pd: FT-IR (ATR) cm^{-1}: 3352; 3103; 3082; 3059; 3026; 3001; 2920; 2848; 1714; 1676; 1601; 1493; 1452; 1265; 1194; 1138; 1066; 1028; 906; 829; 756; 735; 696; 536; **2*Pd(a-c)** (same bands of different intensity): FT-IR (ATR) cm^{-1}: 3103; 3082; 3060; 3026; 3003; 2922; 2850; 1716; 1684; 1601; 1514; 1493; 1452; 1369; 1192; 1142; 1028; 906; 827; 756; 696; 534; **3*Pd**: FT-IR (ATR) cm^{-1}: 3103; 3082; 3059; 3026; 3003; 2922; 2850; 1714; 1693; 1601; 1493; 1452; 1369; 1192; 1142; 1028; 906; 829; 756; 696; 538.

2.4. Catalytic experiments

2.4.1. General procedure for catalytic experiments

Arylboronic acid (0.91 mmol), enone substrate (0.45 mmol), catalyst (0.06 mmol of Pd) and HFIP (2.27 mmol) were mixed in 1,2-DCE (6 ml) and heated to 60 °C in a flask. The catalyst turned from a yellowish color to dark black immediately after the heating was initiated. After 24 h, catalyst was filtered off, washed with DCM and EtOH, conversion was determined by ^{1}H NMR and the product was directly isolated by flash chromatography (hexane→THF). Enantiomeric excess was determined by chiral-phase HPLC.

2.4.2. Catalyst reactivation

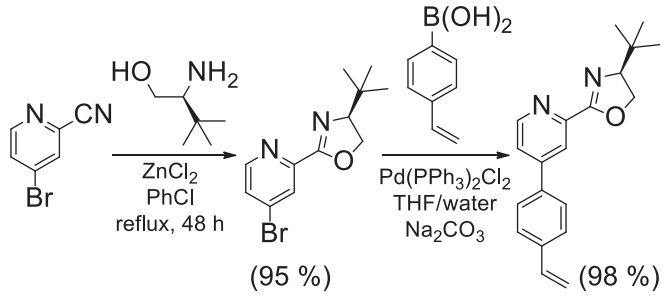
Previously used catalyst (0.06 mmol Pd) was mixed with *p*-chloranil (37 mg; 0.15 mmol) and 10 drops of TFA in 1,2-DCE and stirred for 4 days at 60 °C. Next, the catalyst was filtered, washed with DCM and after drying used in the next cycle.

3. Results and discussion

3.1. Synthesis and characterizations of copolymers 1–3

The PyOx monomer (*S*)-4-(*tert*-butyl)-2-[4-(4-vinylphenyl)pyridin-2-yl]-4,5-dihydrooxazole was synthetized from the commercially available 4-bromopyridine-2-carbonitrile in two steps with the overall yield of 93%. The used methodology consists in the formation of a chiral oxazoline ring from cyano-group and L-*tert*-leucinol catalyzed by $ZnCl_2$ [41], followed by the introduction of a 4-vinylphenyl group via Suzuki-Miyaura cross-coupling reaction (Scheme 3) [42–45].

We gradually prepared copolymers **1–3** by suspension copolymerization of a PyOx monomer, i.e. (*S*)-4-(*tert*-butyl)-2-[4-(4-vinylphenyl) pyridin-2-yl]-4,5-dihydrooxazole, with styrene and one of the three different cross-linkers (1%) (Scheme 4). The type and amount of cross-linker used for production of polymers **1–3** were selected in order to achieve samples with various swellability. It represents an important parameter for easy diffusion of reactants to the catalytic centers



Scheme 3. Synthesis of PyOx monomer (*S*)-4-(*tert*-butyl)-2-[4-(4-vinylphenyl) pyridin-2-yl]-4,5-dihydrooxazole.

[40,46]. Thus, we used three structurally similar cross-linkers differing in molecular length: divinylbenzene (DVB) **1**, 1,2-bis(4-vinylphenyl) ethane (BVPE) **2** and 1,12-bis(4-vinylphenyl)dodecane (BVPC12) **3**. Expectably, the elongation of the side chain of cross-linkers causes a distinct increase in the swellability of the prepared pearl-like copolymers **1–3** in the following order: **1**: 3.8; **2**: 5.3; **3**: 8.8 ($ml \cdot g^{-1}$ in 1,2-dichloroethane (1,2-DCE)). The subsequent complexation reaction of the copolymers **1–3** with various amounts of $Pd(TFA)_2$ gave final catalysts **1–3*Pd**.

The prepared copolymers **1–3** and their complexes **1–3*Pd** were characterized by FT-IR (Fig. 1). In spectra of **1–3** the only significant bands of PyOx fragments are 1671 cm^{-1} (ν C=N) and 829 cm^{-1} (δ_{oop} 1,4-disubstituted phenyl). The most intensive band 696 cm^{-1} belongs to phenyl groups (δ_{oop}). In spectra of Pd complexes **1–3*Pd**, valence vibrations of C–F bonds at 1193 and 1141 cm^{-1} from a trifluoroacetate ligand are propagated (Fig. 1).

Copolymer **2** was also characterized using ^{13}C CP/MAS NMR at rotation frequency of 20 kHz without a standard. In the spectra (Fig. 2) current signals can be assigned: 164 ppm (quaternary oxazoline O–C=N carbon), 147 ppm (quaternary aromatic carbons), 128 ppm (aromatic CH carbons), 76 ppm (oxazoline CH_2), 68 ppm (oxazoline CH), 41 ppm (polymeric backbone CH), 36 ppm (polymeric backbone CH_2), 27 and 26 ppm (CH_3 from *t*Bu group). Broad signal at 61 ppm is probably a spinning sideband.

The SEM images confirm the spherical character of the prepared resins, whose size below ca. 300 μm in a dry state allows for easy manipulation (Fig. 3).

3.2. Optimization of reaction conditions

We performed the addition of phenylboronic acid to 3-methylcyclohex-2-en-1-one under selected reaction conditions (24 h; 60 °C) for mutual comparison of the activity of the catalysts and the effect of

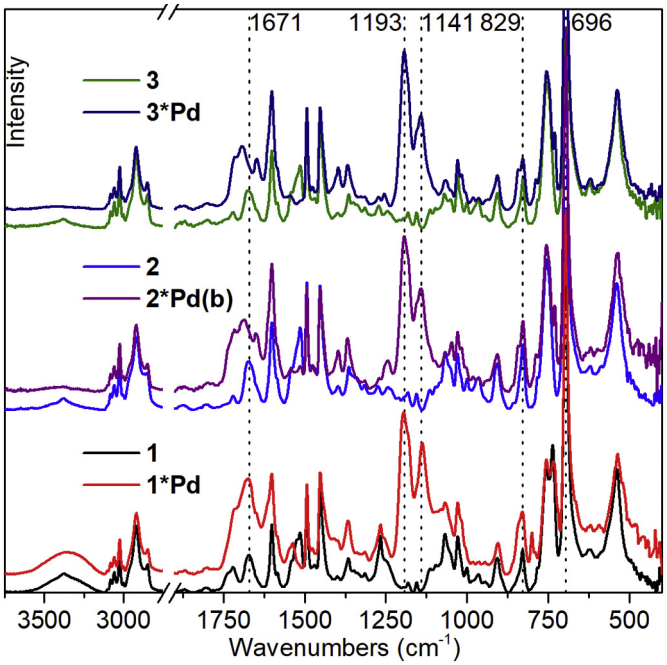
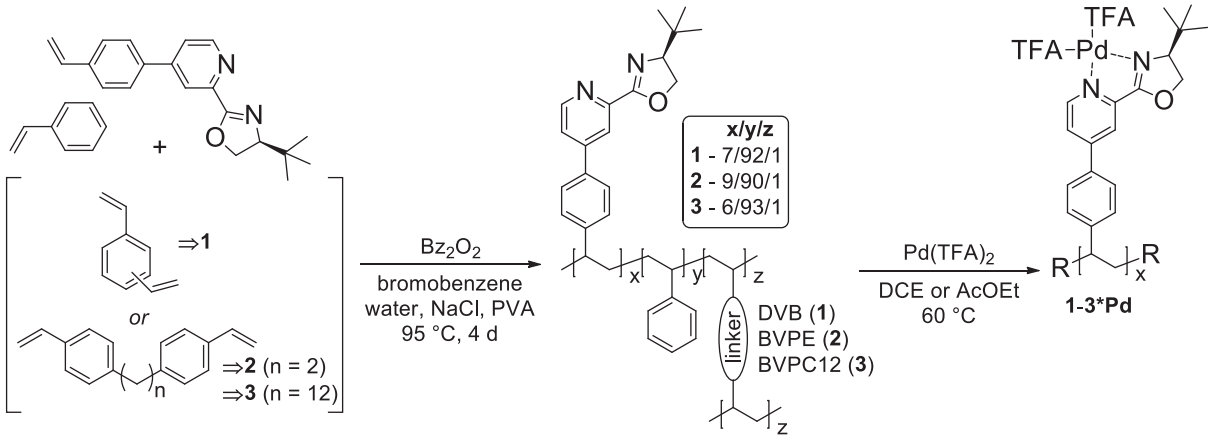


Fig. 1. FT-IR spectra of PyOx polymers **1–3** and their complexes **1–3*Pd**.

additives. It follows from literature, that 1,2-DCE is the most convenient solvent for this reaction [26]. Furthermore, the presence of an acid is necessary for successful product formation. The protonation at the position 2- of formed 3,3-disubstituted cyclohexanone occurs during the reaction, which was confirmed by deuteration experiment [23]. However, the application of water as a source of the proton in our initial experiments led to unreproducible results. This finding can be explained by the hydrophobic character of heterogeneous catalysts **1–3*Pd**. Therefore, we also tested less polar additives, i.e. 2,2,2-trifluoroethanol (TFE, pK_a = 12.5 [47]) and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP, pK_a = 9.3 [48]) respectively. The presence of HFIP led to approximately 20% higher conversions, compared to TFE (99% vs 82%) (Table S1). The performed deuteration experiment confirmed, that HFIP acts as the source of the proton (S4–6). Thus, we have used HFIP in further experiments.

Table 1 summarizes the results of initial experiments using catalysts **1*Pd** complexed with 1.4 equivalents (calculated to the amount of PyOx in copolymer) of $Pd(TFA)_2$. The first experiment (entry 1) gave almost quantitative 96% conversion and enantioselectivity 73%. For comparative purposes, a similar experiment running under homogeneous conditions (PyOx/$Pd(TFA)_2$, 1,2-DCE, 10 equiv. H_2O, 12 h,



Scheme 4. Synthesis of PyOx polymers **1–3** and their complexes **1–3*Pd**.

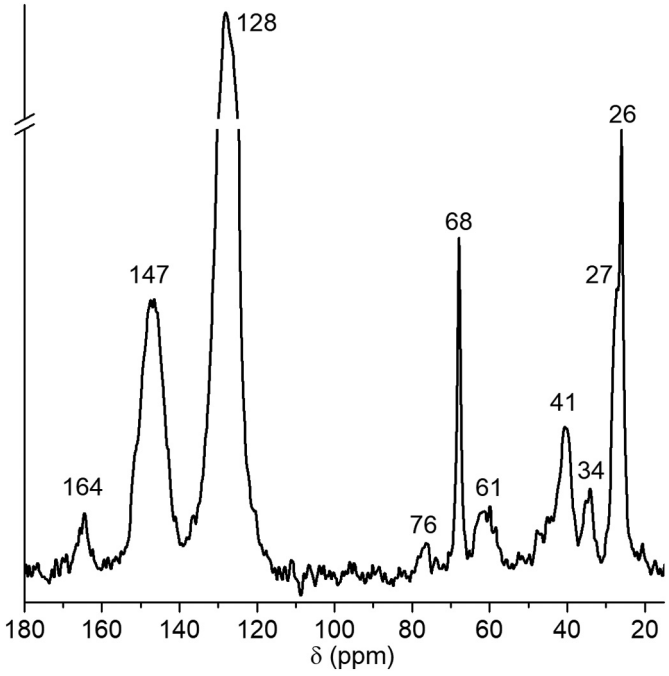


Fig. 2. ^{13}C CP/MAS NMR of copolymer **2**.

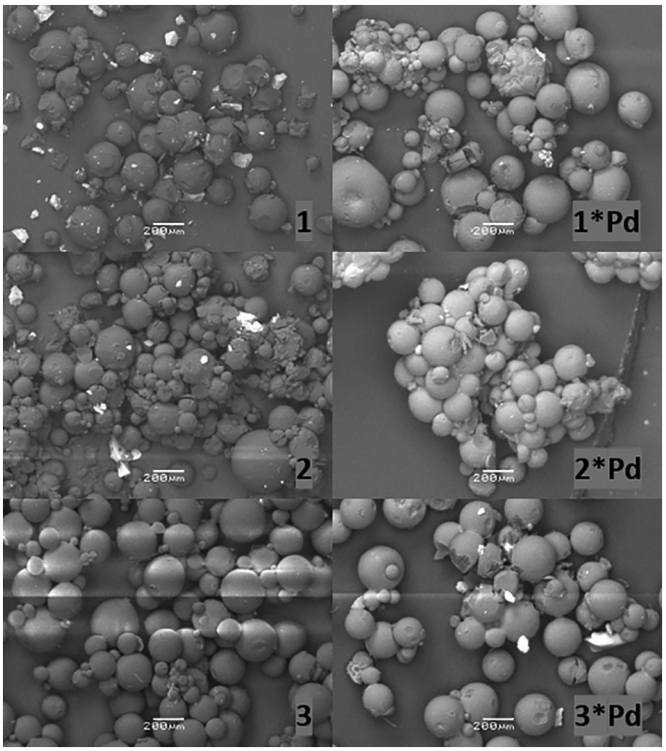
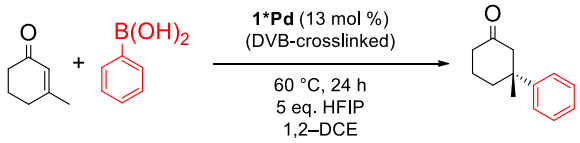


Fig. 3. SEM images of PyOx polymers **1–3** and their complexes **1–3*Pd**.

60 °C) gave conversion 93% and 92% ee [26]. In the second cycle (entry 2), the enantioselectivity increased to 81% ee, however the conversion slightly decreased to 88%. The observed catalyst deactivation via possible leaching of catalytic complex from the polymer carrier [49,50] was excluded by Sheldon's test (S3) [50]. Leaching of Pd was observed only after 1st cycle (presumably washing out of the adsorbed Pd $(TFA)_2$). In next cycles, amount of Pd on beads was stable (Table S2). We also evaluated the possibility of loss of the catalyst's activity due to the reduction of active Pd(II) to Pd(0) [12,51]. Thus, before the third

Table 1
An overview of recycling experiments with 1*Pd on model addition of phenylboronic acid to 3-methylcyclohex-2-ene-1-one.



Run	NMR Yield (%)[a]	ee (%)[b]
Homogeneous[c]	93	92
1st	96	73
2nd	88	81
3rd*	77	81

[a] The conversion was determined after 24 h by ^{1}H NMR spectroscopy.
[b] The enantiomeric excess was determined by HPLC.
[c] PyOx/Pd$(TFA)_2$, 1,2-DCE, 10 equiv. H_2O, 12 h, 60 °C, isolated yield, Ref. [26].
* Reoxidation by *p*-chloranil was performed before this cycle.

catalytic cycle, the catalyst **1*Pd** was reoxidized by treatment with *p*-chloranil. However, the usage of a reoxidized catalyst (entry 3) did not improve the yield (77%, 81% ee). The most probable explanation for the catalyst's deactivation may be the accumulation of all reaction species in the polymer matrix, which inhibits the diffusion of the reactants to the catalytic centers.

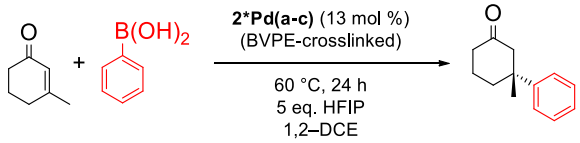
Taking these findings into account, we prepared catalyst **2*Pd(a)** containing longer cross-linker by a complexation reaction of copolymer **2** (1 eq.) with Pd$(TFA)_2$ (2 eq.). As mentioned above, the longer cross-linker causes a better swellability of the polymeric matrix, which could facilitate diffusion of reactants to the catalytic center as well as removing of products form the polymer matrix. Based on the obtained results (Table 2, A), a slight decrease in conversion within four consecutive cycles (95 to 89%) followed by a dramatic drop of conversion in the fifth cycle (66%) is observed (Table 2, A, entry 1–5). However, the subsequent reoxidation of catalysts **2*Pd(a)** by treatment with *p*-chloranil caused an increase in conversion to 96% without any change in enantioselectivity (83% ee) (Table 2, A, run 6). The usage of catalyst **3*Pd** based on the longest cross-linker did not improve the conversions. Thus, we used catalyst based on 1,2-bis(4-vinylphenyl)ethane cross-linker in further experiments.

Notably, both the catalyst **1*Pd** and catalyst **2*Pd(a)** gave slightly lower enantioselectivity than the homogeneous version of the catalyst (91% ee vs. 83% ee). Stoltz et al. found out that an important factor affecting the enantioselectivity is the ratio of PyOx/Pd$(TFA)_2$ [23]. Therefore, we prepared another catalyst **2*Pd(b)** derived from copolymer **2**, where the complexation reaction was performed in 1,2-DCE with the ratio of reactants 2:1 (PyOx/Pd$(TFA)_2$). We found out, that this modification of the catalyst caused an increase in enantioselectivity up to 89% ee (Table 2, B), while the conversion remained unchanged (93%). In the second cycle, comparable enantioselectivity (90% ee) was observed. Unfortunately, the conversion dropped to 54%.

Obtained results showed that an excess of ligand related to palladium content facilitates achieving better enantioselectivity. However, reoxidation of palladium after each cycle is necessary.

Due to economic demands regarding the relatively difficult ligand synthesis, we have prepared the catalyst **2*Pd(c)** by complexation of 1.3 equivalents of copolymer **2** with 1 equivalent of Pd$(TFA)_2$. The result obtained with catalyst **2*Pd(c)** in the first catalytic cycle (Table 2, C) indicates its high catalytic activity (conversion 99%), but only moderate enantioselectivity (73% ee). Interestingly, the enantioselectivity was increased to 87% ee upon the second catalytic cycle and then, it was oscillating around this value in the next cycles. This finding can be explained by a possible rearrangement of the catalytic centers, which has been previously observed in literature [52]. In this

Table 2
An overview of recycling experiments with **2*Pd(a-c)** on model addition of phenylboronic acid to 3-methylcyclohex-2-ene-1-one.



	Catalyst Ligand/Pd ratio in 2Pd					
	(A) 2*Pd(a) 1: 2		(B) 2*Pd(b) 2: 1		(C) 2*Pd(c) 1.3: 1	
Run	NMR Yield (%)[a]	ee (%)[b]	NMR Yield (%)[a]	ee (%)[b]	NMR Yield (%)[a]	ee (%)[b]
1st	95	70	93 (79)[c]	89	99	73
2nd	95	80	54	90	90*	87
3rd	84	82	–	–	99*	88
4th	89	82	–	–	89*	89
5th	66	83	–	–	54*	89
6th	96*	83	–	–	69*	87

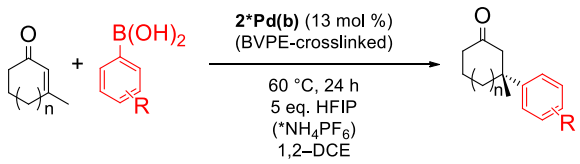
[a] Determined after 24 h by ^{1}H NMR spectroscopy.
[b] The enantiomeric excess was determined by HPLC.
[c] Isolated yield from independent experiment.
* Reoxidation by *p*-chloranil was performed before this cycle.

case, the catalyst was reoxidized by treatment with *p*-chloranil after each cycle to give high conversions.

3.3. Reaction scope

With the optimized reaction conditions at hand, we examined the reaction with various arylboronic acids (Table 3). With regards to the achieved higher enantioselectivity in the 1st runs (Table 2, the 1st runs), we applied the catalyst **2*Pd(b)**. In the case of less reactive boronic acids, we added 30 mol% of NH_4PF_6 due to its known positive effect on the reaction rate caused by stabilization of cationic palladium [26].

Table 3
An overview of catalytic experiments on model additions of various arylboronic acids to different enone substrates under optimized conditions.



Product		Catalyst			
		Homogeneous		2*Pd(b)[e]	
n	R	Yield (%)	ee (%)	NMR Yield (%)[a]	ee (%)[b]
1	4-CH_3	99 (12*h*)[c]	87	94	75
1	4-CF_3	99 (12 h)[c]	96	85*	91
1	4-Cl	94 (18 h)[c]	95	78*	91
1	4-Ac	99 (18 h)[c]	96	52*	90
1	4-OBn	96 (18 h)[c]	74	59*	58
1	3-COOMe	91 (24 h)[c]	95	38*	nd
0	H	84 (12 h)[c]	91	99	79
0	4-CH_3	99 (24 h)[d]	77	92* (96 h)	67
0	3-COOMe	99 (24 h)[d]	89	99* (96 h)	90
0	4-COOMe	99 (24 h)[d]	96	91* (72 h)	91

[a] Determined after 24 h by ^{1}H NMR spectroscopy.
[b] The enantiomeric excess was determined by HPLC.
[c] Results from Ref. [26].
[d] Our result; 5 mol% $Pd(TFA)_2$, 6 mol% (*S*)-*t*Bu-PyOx, 5 eq. water, 60 °C, 24 h, 1,2–DCE.
[e] Ligand / Pd ratio 2:1.
* With addition of 30 mol% of NH_4PF_6.

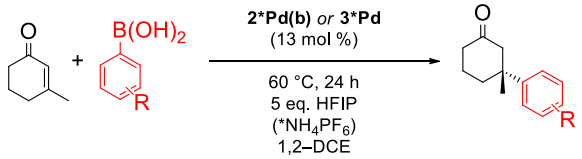
The comparison of our results with the previously obtained values with homogeneous systems [26] shows lower catalytic activity of the catalysts **2*Pd(b)**. Nevertheless, it exhibited only a slightly lower degree of enantioselectivity. The effect of substituents on achieved enantioselectivity reproduces the trends found for the homogeneous systems. Thus, the presence of electron-donating substituents reduces the enantioselectivity [1]. Lower conversions could be caused by still not enough efficient diffusion of reactants to the catalytic centers, especially in the case of bulky substrates. Satisfied with enantioselectivities achieved by **2*Pd(b),** we prepared catalyst **3*Pd** based on a copolymer **3**, cross-linked by an even longer cross-linker in order to increase conversions. Unfortunately, the results obtained with the catalyst **3*Pd** were comparable to or even worse than the results obtained with catalyst **2*Pd(b)** (Table 4). Thus, the lower conversions are not only affected by insufficient diffusion, but other unfavorable effects take place.

We have extended the study by the substrates differing in enone ring size. The catalysts **2*Pd(b)** gave high conversions and enantioselectivities with five-membered substrates, however prolongation of reaction time was necessary.

4. Conclusion

In summary, we have prepared polystyrene based pearl-like copolymers **1–3** containing the PyOx type chiral ligand. The polymers differ in the used cross-linkers, therefore they possess diverse swellability. Upon the complexation reaction of polymers **1–3** with $Pd(TFA)_2$, the obtained heterogeneous catalysts were used for asymmetric 1,4-addition of arylboronic acids to cyclic 3-substituted five- and six-membered enones and successfully recycled. To the best of our knowledge, this is the first recoverable palladium catalyst used for this type of reaction. The optimization experiments showed that the addition of HFIP (proton source), an excess of ligand to Pd and reoxidation of the catalysts **2*Pd (a-c)** after each cycle with *p*-chloranil yield conversions and enantioselectivities comparable to the homogeneous catalyst. The obtained results are promising not only for experiments performed in a batch arrangement, but they also open the way for using the prepared catalysts in flow reactors.

Table 4
Comparison of catalysts **2*Pd(c)** and **3*Pd**.



Product	Catalyst	
	2*Pd(b)[b]	3*Pd[b]
R	NMR Yield (%)[a]	NMR Yield (%)[a]
H	99	89
4-Ac	52*	50*
4-COOMe	57*	51*
4-OBn	59*	41*

[a] Determined after 24 h by ^{1}H NMR spectroscopy.
[b] Ligand / Pd ratio 2:1.
* With addition of 30 mol% of NH_4PF_6.

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Data availability

The raw data required to reproduce these findings are included in the article and in the Supplementary data file.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reactfunctpolym.2020.104615.

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