Efficient and Highly Enantioselective Aerobic Oxidation–Michael–Carbocyclization Cascade Transformations by Integrated Pd(0)-CPG Nanoparticle/Chiral Amine Relay Catalysis

Luca Deiana,[a] Lorenza Ghisu,[a] Oscar Córdova,[a] Samson Afewerki,[b] Renyun Zhang,[b] Armando Córdova*[a,b]

[a] Department of Organic Chemistry, The Arrhenius Laboratory, Stockholm University, 106 91 Stockholm, Sweden

[b] Department of Applied Science and Design, Holmgatan 10, 851 70 Sundsvall, Sweden
Fax +46(15)4908; E-mail: armando.cordova@miun.se; E-mail: acordova@organ.su.se

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Abstract: A series of highly diastereo- and enantioselective aerobic oxidation–Michael–carbocyclization cascade transformations by integrated heterogeneous Pd(0)-CPG nanoparticle/chiral amine relay catalysis are disclosed. The heterogeneous Pd(0)-CPG nanoparticle catalysts were efficient for both the sequential aerobic oxidation and dynamic kinetic asymmetric Michael–carbocyclization transformations, resulting in 1) oxidation of a variety of allylic alcohols to enals and 2) formation of cyclopentenes containing an all-carbon quaternary stereocenter in good to high yields with up to 20:1 dr and 99.5:0.5 er.

Key words: asymmetric cocatalysis, aerobic oxidations, relay catalysis, integrated heterogeneous catalysis, integrated homogeneous catalysis, quaternary stereocenters

Typically, chemical synthesis operates through stepwise processes where each product intermediate is isolated and purified prior to the target product molecule.[1] In comparison, the biosynthesis of the cell's molecules is performed by multi-enzymatic cascade systems.[2] This has inspired researchers and led to the development of elegant tandem and cascade synthesis.[3] Recently, relay catalysis based on multi-catalyst systems have been applied for these type of transformations.[2,4] However, a challenge is the development of catalytic asymmetric relay catalysis (ARC). In this context, the combination of metal and organic catalysts has begun to receive increased attention.[5,6] Here the combined and sometimes synergistic catalysis by a metal complex and an organic molecule is a powerful approach that can improve and importantly enable transformations,[5] which are not possible by a single catalytic entity. Yet there are challenges and limitations related to compatibility problems such as different reactivity and inactivation. A way to circumvent these obstacles would be as in Nature by compartmentalization such as site-isolation via heterogeneous reaction conditions and performing catalysis in sequential steps.[7] For example, if the metal co-catalysts were supported on a solid support they could be recycled, which would prevent contamination and allow for 'green'[8] chemical synthesis. We recently demonstrated a versatile strategy for the eco-friendly synthesis of valuable molecules and expansion of chemical space in a highly selective fashion from simple alcohols using integrated heterogeneous transition metal/chiral amine multiple relay catalysis (Scheme 1).[9] Higher levels of molecular complexity were defined as how many times the heterogeneous metal catalyst was present or took part in the one-pot catalytic cascade sequences. For example, at level 1 the metal catalyst was present in one step, level 2 two steps, level 3 three steps, etc. The proof of concept was demonstrated by using heterogeneous Pd(0)-aminopropyl-mesocellular foam (AMP-MCF) nanoparticles[10] as the co-catalysts. However, the integrated heterogeneous metal/amine relay catalysis strategy is not only restricted to this type of support. Thus, it is of high interest to investigate and find other catalytic systems with good activity and selectivity that are easy to separate and recycle for this multi-catalysis concept.[11]

Porous glasses have a high mechanical, chemical, and thermal stability. They also have a variable manufacturing of pore sizes with a small pore size distribution and can be produced in different shapes. In this context, controlled pore glass (CPG) is widely used as a carrier for solid-phase synthesis of nucleotides.[12] It is also used in formulations of dental composites and as a carrier in affinity purification of antibodies. However, there are a few limited examples of the use of CPGs as supports for a noncovalently bound Pd complex[13] or Pd particles.[14] Based on the advantages of using CPG as a support in chemistry and engineering and our research interest in sequential and synergistic metal/amine catalysis,[15] we became interested in whether a CPG-supported Pd nanoparticle catalyst could act in concert with a chiral amine co-catalyst for the application in multiple ARC of complex molecules. In particular, the enantioselective construction of compounds with an all-carbon stereocenter would be challenging.[16] Herein, we disclose efficient aerobic oxidation–Michael–carbocyclization cascade reactions by integrated heterogeneous Pd(0)-CPG nanoparticle/chiral amine multiple relay catalysis for the highly enantioselective synthesis of cyclopentenes with adjacent tertiary and all-carbon quaternary stereocenters.

In initial experiments, we prepared different Pd(0)-CPG nanoparticles (see experimental for details). The amounts of immobilized Pd species were determined by elemental analysis using Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES) technique [e.g., Pd(0)-Amp-CPG, Pd = 2.18 wt%]. The sizes of the Pd-nanopar-

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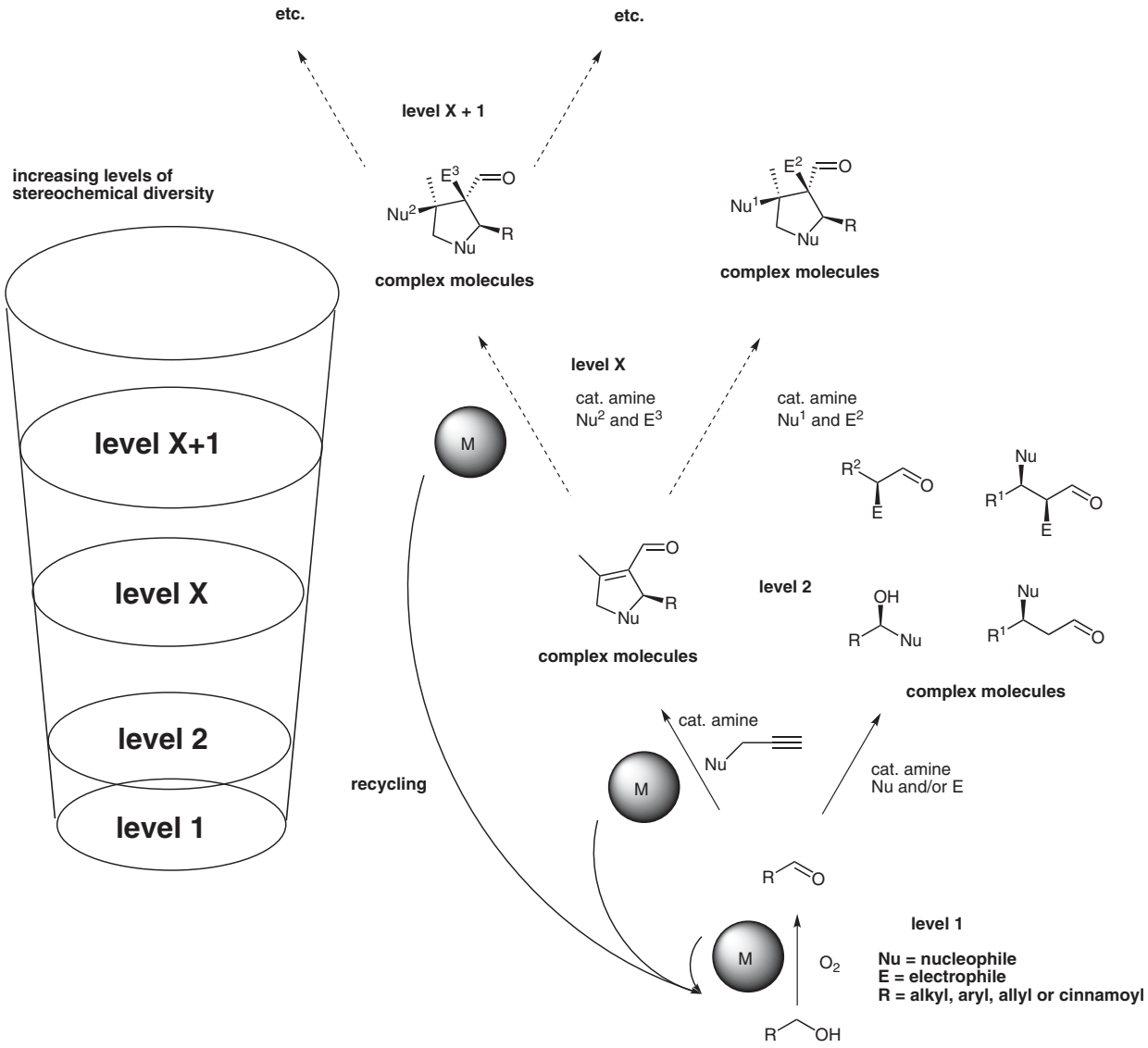
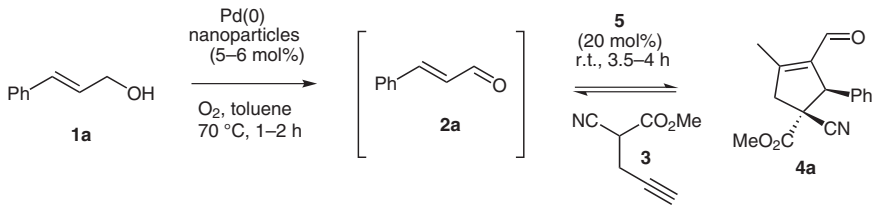


Scheme 1 Integrated heterogeneous metal/chiral amine multiple ARC

ticles were 3–5 nm as determined by transmission electron microscopy (TEM). With these Pd(0)-CPG nanoparticles in hand, their ability to catalyze the aerobic oxidation of cinnamyl alcohol **1a** in toluene at 70 °C to aldehyde **2a** followed by its co-catalytic Michael–carbocyclization[17] with propargylic ester **3** in the presence of chiral amine **5**[18] were investigated (Table 1, Scheme 2, see Supporting Information for experimental details). The later cascade step is a dynamic kinetic asymmetric transformation (DYKAT), which proceeds via a reversible amine-catalyzed Michael reaction via product intermediate **6a** followed by the irreversible synergistically metal/chiral amine co-catalyzed carbocyclization to give **4a** (Scheme 2).[17]

To our delight, all of the investigated Pd(0)-CPG nanoparticles were efficient catalysts for the conversion of **1a** to **2a** (Table 1, entries 1–7). Moreover, they were highly efficient co-catalysts for the synergistic carbocyclization of chiral enyne **Ia** to **4a** via Michael adduct **6a** and **2a** (Scheme 2). In comparison to Pd(0)-Amp-MCF (entry 8),[9] significant rate acceleration was observed for both the aerobic oxidation of **1a** to **2a** and conversion of **2a** to **4a**. Thus, the reaction time for the whole aerobic oxidation–Michael–carbocyclization cascade sequence could be reduced with up to 20 hours (from 24 to 4 h). The Pd(0)-Amp-CPG and Pd(0)-CPG-Hybrid VBC nanoparticles catalyzed the aerobic oxidation with the fastest rates (entries 3 and 5). We also found that using Pd(0)-CPG nanoparticles, which had been additionally washed with MeOH and CH_2Cl_2 after their final preparation slightly improved the stereoselectivity of the cascade sequence (entries 4 and 6). A clear cooperative affect was observed since no carbocyclization product **4a** was formed without both the presence of **5** and Pd-CPG (entries 9 and 10). The results from the screening made us investigate the scope of the integrated Pd(0)-CPG nanoparticle/chiral amine catalysis for a set of alcohols **1** using Pd(0)-Amp-CPG,

Table 1 Pd(0)-CPG-Nanoparticle Screening[a]



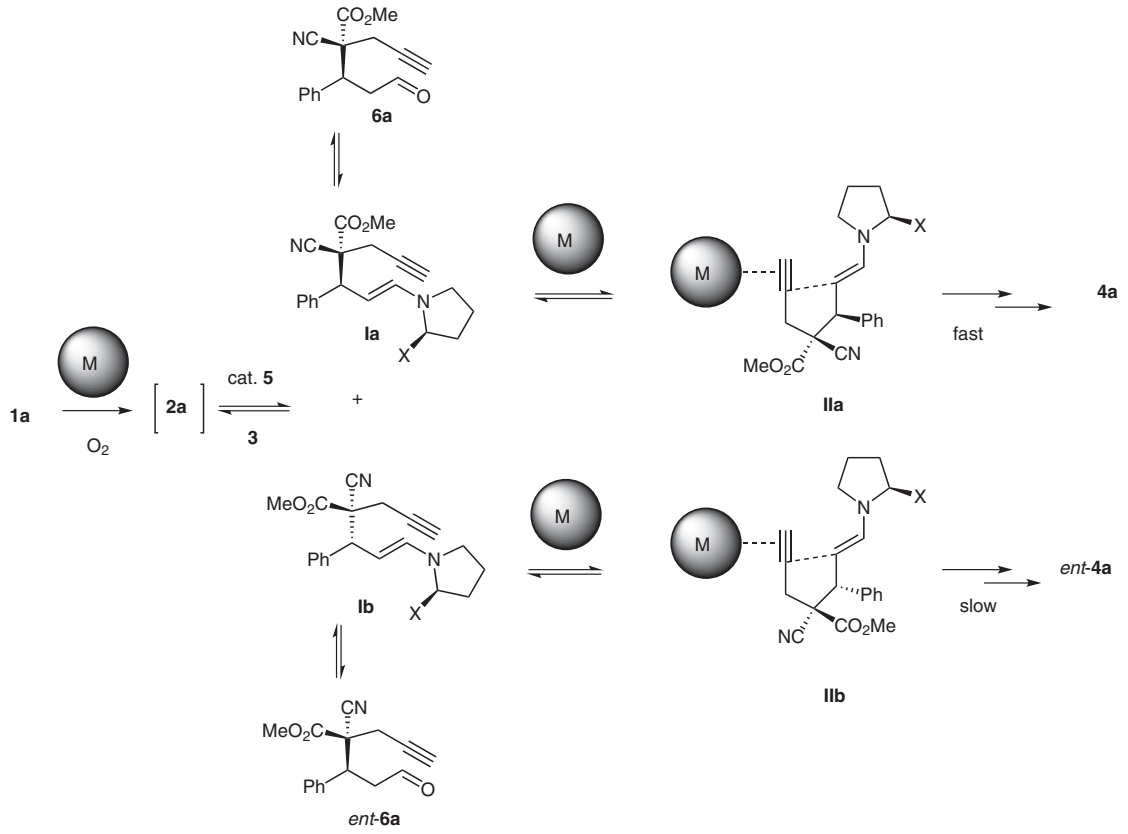
		Aerobic oxidation		Michael–carbocyclization			
Entry	Pd(0)-nanoparticle	Time (h)	Conv. (%)[b]	Time (h)	Yield (%)[c]	dr[b]	er[d]
1	Pd(0)-CPG-Hybrid	2	100	4	65	15:1	97.5:2.5
2	Pd(0)-CPG-COPO	2	100	3	60	17:1	98:2
3	Pd(0)-Amp-CPG	1	100	4	60	16:1	97:3
4	Pd(0)-Amp-CPG[e]	1	100	3.5	60	18:1	98.5:1.5
5	Pd(0)-CPG-Hybrid-VBC	1	100	3	59	15:1	97.5:2.5
6	Pd(0)-CPG-Hybrid-VBC[e]	1	100	3	69	17:1	98:2
7	Pd(0)-Amp-CPG[e,f]	1	100	3.5	62	19:1	98:2
8	Pd(0)-Amp-MCF	7	100	17	71	16:1	97:3
9	Pd(0)-Amp-CPG[e]	1	100	17[g]	–	–	–
10	Pd(0)-Amp-CPG[e]	1	100	17[h]	–	–	–
11	Pd(0)-Amp-CPG[e,i]	7	100	7	65	17:1	98.5:1.5

[a] To a suspension of Pd(0)-CPG-catalyst (5 mol% to the alcohol) in toluene (0.5 mL) placed in a vial was added **1a** (0.24 mmol, 1.2 equiv). The vial was capped, evacuated, and an O_2 balloon was connected to the reaction vessel. The reaction mixture was stirred at 70 °C for the time shown in Table 1. Next, the mixture was cooled to r.t., followed by the addition of **3** (0.2 mmol, 1 equiv) and **5** (20 mol%) and stirred for the time shown in Table 1.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Isolated yield of pure **4a**.
[d] Determined by chiral-phase HPLC analysis.
[e] Further washed (3 × MeOH, 3 × CH_2Cl_2) and dried overnight under vacuum.
[f] Toluene: 1 mL.
[g] No chiral amine **5** was added.
[h] The Pd-CPG-catalyst was removed after formation of **2a**.
[i] Pd(0)-CPG-catalyst (1 mol% to the alcohol).

which had been extra washed, and **5** as co-catalysts in toluene. The results are depicted in Table 2.

The Pd(0)/**5**-catalyzed aerobic oxidation–Michael–carbocyclization cascade transformations were highly enantioselective for all the cases investigated and the corresponding cyclopentenes **4** with an all-carbon quaternary stereocenter were isolated in good to high yields with up to 20:1 dr and 99.5:0.5 er. The catalytic aerobic oxidation of enals **1** was finished within five hours except when **1g** and **1h** were used as the starting materials (Table 2, entries 7 and 9). In particular, the oxidation of **1g** took time (entry 7). However, the aerobic oxidation of **1g** with Pd(0)-Amp-CPG as catalyst was significantly faster as compared with Pd(0)-Amp-MCF (entry 7 vs 11). The synergistic Michael–carbocyclization step of the sequence was efficient and the reaction was complete within five hours at the selected reaction conditions. The recycling of heterogeneous catalysts is an important factor for their practical applications. Thus, we investigated the possibility of recycling the Pd(0)-Amp-CPG nanoparticle catalyst after the completed multiple ARC (Table 3).

Satisfyingly, the catalytic relay sequences displayed excellent recyclability both in terms of yield and stereoselectivity. It is noteworthy that no leaching of the metal catalyst was observed. However, we noticed that the reaction rates slightly decreased for cycles 4 and 5 while the yields of **4a** somewhat increased. The latter could be due to the grinding of the Pd-CPG particles during the vigorous stirring with a magnetic stir-bar, which can result in collapse of the pore structures of the CPG particles. In fact, Prime Synthesis is not using this type of stirring in their preparation of commercially available CPGs due to this reason. The stereochemical outcome of the catalytic relay sequence is in accordance with the homogeneous Pd/chiral amine co-catalyzed dynamic Michael–carbocyclization cascade reaction.[17] Thus, the utilization of **5** as



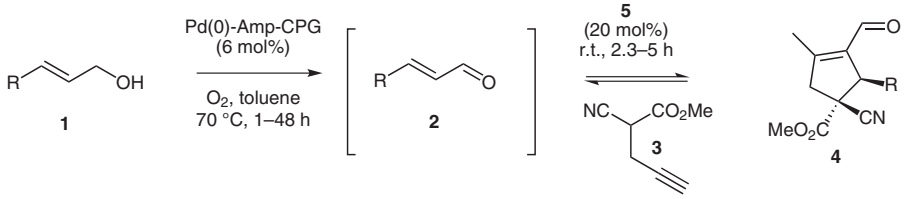
Scheme 2 The metal/chiral amine co-catalyzed aerobic oxidation–Michael–carbocyclization cascade synthesis of **4a** from **1a**

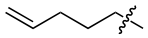
the amine catalyst in combination with the Pd(0)-Amp-CPG catalyst provides carbocycles (1*R*,2*R*)-**4** (R = aryl) with an *R*-configuration at C-1 and C-2, respectively, while the intermediate Michael adducts **6** were nearly racemic. Accordingly, we propose that the reaction proceed via synergistically Lewis acid and enamine dual-activated transition state **IIa** over **IIb** (Scheme 2) followed by hydrolysis, protonation, and isomerization to give **4a** in excellent ratios over *ent*-**4a**, respectively.

In conclusion, highly diastereo- and enantioselective aerobic oxidation–Michael–carbocyclization cascade sequences by integrated heterogeneous Pd(0)-CPG nanoparticle/chiral amine relay catalysis were developed. The heterogeneous Pd(0)-CPG nanoparticle catalysts were excellent catalysts for both steps of the catalytic relay sequence. Thus, different allylic alcohols were oxidized to enals and directly converted to cyclopentenes containing an all-carbon quaternary stereocenter in good to high yields with up to 20:1 dr and 99.5:0.5 er in one pot. Moreover, the metal catalyst can be recycled several times without any significant decrease in stereoselectivity of the reaction sequence, activity, or leaching of metal into solution, making the protocol highly stereoselective, economical, and environmentally friendly. Another important aspect of this investigation is that the Pd(0)-CPG nanoparticles that were prepared here are not only efficient catalysts for the concept of integrated heterogeneous transition metal/chiral amine multiple relay catalysis. They can also act as efficient nanoparticle catalysts for nonmulti-catalytic transformations in organic synthesis as demonstrated by the Pd(0)-CPG catalyzed aerobic oxidation of allylic alcohols. Studies towards these research lines and the development of other heterogeneous metal catalyst systems for integrated transition metal/chiral amine multiple relay catalysis are ongoing in our laboratories and will be reported in due course.

All chemicals, unless otherwise noted, were purchased from commercial sources. The control pore glass supports were obtained from Prime Synthesis Ltd. ^{1}H NMR spectra were recorded on a Bruker Avance 500 (500 MHz) spectrometer or Bruker Avance II spectrometer (400 MHz). Chemical shifts are reported in ppm from TMS with the solvent resonance resulting from incomplete deuterium incorporation as the internal standard ($CDCl_3$: δ = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (standard abbreviations), coupling constants (Hz), integration. ^{13}C NMR spectra were recorded on a Bruker Avance 500 (125.8 MHz) spectrometer or Bruker Avance II spectrometer (400 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$: δ = 77.26 ppm). High-resolution mass spectrometry was performed on a Agilent Technologies 6520-Q-TOF ESI-MS (positive mode) at the Stockholm University or Mid-Sweden University Mass Spectrometry Facility. Enantiomer ratios were determined by HPLC [Chiral Agilent Technologies Chiralpak OD, OJ-H, AS column, or Chiralcel OD-R column (4.6 mm × 250 mm)] in comparison with authentic racemic materials. Optical rotations were measured on a PerkinElmer 341 Polarimeter. Unless otherwise noted, all reactions were performed with distilled solvents under an atmosphere of N_2 in oven-dried (135 °C) or flame-dried glassware

Table 2 The Scope of the Cocatalytic Aerobic Oxidation–Michael–Carbocyclization Relay Sequence[a]



		Aerobic oxidation			Michael–Carbocyclization			
Entry	R	Time (h)	Conv. (%)[b]	Product	Time (h)	Yield (%)[c]	dr[b]	er[d]
1	Ph	1	100	**4a**	5	67	17:1	98.5:1.5
2	4-$O_2NC_6H_4$	2	100	**4b**	2.5	57	16:1	98:2
3	4-MeC_6H_4	1	100	**4c**	2.3	63	16:1	98:2
4	2-ClC_6H_4	1.5	100	**4d**	2.3	63	6:1	97.5:2.5
5	3-$O_2NC_6H_4$	5	100	**4e**	2.5	67	15:1	98:2
6[e]	*n*-Bu	4	100	**4f**	2.5	68	5:1	98:2
7[f]	4-BrC_6H_4	48	81	**4g**	2	52	12:1	99:1
8[e]	*n*-Pr	4.5	100	**4h**	3	81	4:1	98.5:1.5
9[e]		24	100	**4i**	3	63	7:1	99.5:0.5
10	4-$MeOC_6H_4$	1	100	**4j**	3	69	20:1	97.5:2.5
11[g]	4-BrC_6H_4	120	75	**4g**	16	52	12:1	99.5:0.5

[a] To a suspension of Pd(0)-Amp-CPG (6 mol% Pd to **1**, 36 mg) in toluene (0.5 mL) placed in a microwave vial was added alcohol **1** (0.12 mmol, 1.2 equiv). The vial was capped, evacuated, and an O_2 balloon was connected to the reaction vessel. The reaction mixture was stirred at 70 °C for the time shown in Table 2. Next, the mixture was cooled to r.t. Propargyl derivative **3** (0.1 mmol, 1 equiv) and the chiral amine **5** (20 mol%) were added and the reaction mixture was vigorously stirred for the time shown in Table 2.
[b] Determined by ^1H NMR analysis of the crude reaction mixture.
[c] Isolated yield of pure **4**.
[d] Determined by chiral-phase HPLC analysis.
[e] Compound **1** (0.14 mmol) and Pd(0)-Amp-CPG (5 mol%, 36 mg).
[f] Pd(0)-Amp-CPG (10 mol% to **1g**).
[g] Pd(0)-Amp-MCF (10 mol% to **1g**).

with standard vacuum line techniques. The Pd catalyst on the support was characterized for Pd loading by Inductively Coupled Plasma (ICP; Mikroanalytisches Laboratorium Kolbe, Germany). Elemental analyses on the Pd contents of the Pd-Amp-CPG were carried out by Medac LTD Analytical and chemical consultancy services (UK) by ICP-OES. The samples for TEM imaging were done by sonicating the Pd-Amp-CPG particles in EtOH, and then dropping the suspension on a standard TEM grip, and letting it dry in air. The TEM was done on a JEOL 2000FX (JEOL) microscope at an accelerate voltage of 160 KV (Figure 1S and 2S, see Supporting Information).

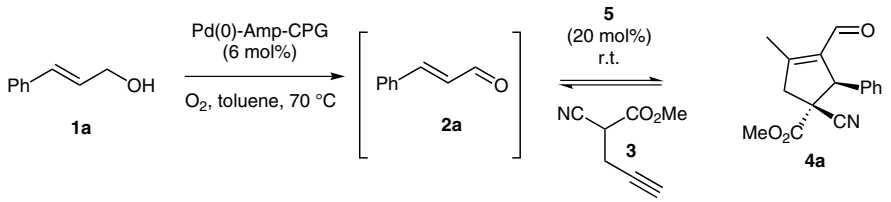
Pd(0)-CPG Nanoparticles

Amine-functionalized Amp-CPG (pore size 533 Å, amine 166 μmol/g), CPG-Hybrid VBC (pore size 526 Å, amine 398 μmol/g), CPG-Hybrid COPO (pore size 590 Å, amine 360 μmol/g), and CPG-Hybrid (pore size 1400 Å, amine 353 μmol/g) obtained from Prime Synthesis were used as supports. Thus, each amine-functionalized CPG (1 g, 1 equiv, amine content) was added to a deionized water solution (45 mL, pH 9). In parallel, Li_2PdCl_4 (2 equiv) was solubilized in a pH adjusted deionized water solution (pH 9) and next added to the suspension. After stirring for 24 h, the Pd(II)-CPG catalyst was transferred to a centrifuge vial (45 mL) and washed [3 × H_2O (40 mL), 3 × acetone (40 mL)] followed by drying overnight under vacuum. Next, the dry Pd(II)-CPG catalyst was suspended in deionized H_2O (30 mL) followed by the slow addition of $NaBH_4$ (15 equiv), which had been dissolved in deionized H_2O (15 mL) at r.t. After stirring for 30 min, the obtained Pd(0)-CPG catalyst was transferred to a 45 mL centrifuge vial, washed [3 × H_2O (40 mL), 3 × acetone (40 mL)], and dried overnight under vacuum. Some of the catalysts were also further washed [3 × MeOH (40 mL), 3 × CH_2Cl_2 (40 mL)] and dried overnight under vacuum. Elemental analyses on the Pd contents of the Pd-Amp-CPG were carried out by Medac LTD Analytical and chemical consultancy services (UK) by ICP-OES.

Pd(0)-Amp-CPG/Chiral Amine-Catalyzed Catalytic Aerobic Oxidation–Michael–Carbocyclization Relay Sequence: Typical Procedure

To a suspension of Pd(0)-Amp-CPG (6 mol% Pd to **1**, 36 mg) in toluene (0.5 mL) placed in a microwave vial was added alcohol **1** (0.12 mmol, 1.2 equiv). The vial was capped, evacuated and an O_2 balloon was connected to the reaction vessel. The reaction mixture was stirred at 70 °C for the time shown in Table 2. Next, the mixture was cooled to r.t. Propargyl derivative **3** (0.1 mmol, 1 equiv) and the chiral amine **5** (20 mol%) were added and the reaction mixture was vigorously stirred for the time shown in Table 2. After removal of the Pd catalyst, the crude mixture was directly loaded on a silica gel col-

Table 3 Recycling of the Heterogeneous Pd-CPG Nanoparticle Catalyst[a]



	Aerobic oxidation		Michael–Carbocyclization			
Cycle	Time (h)	Conv. (%)[b]	Time (h)	Yield (%)[c]	dr[b]	er[d]
1	1	100	3.5	63	19:1	98:2
2	1	100	4	60	17:1	98:2
3	1	100	5	65	18:1	98:2
4	2	100	5	67	20:1	97.5:2.5
5	4	100	6	64	18:1	98:2

[a] To a suspension of Pd(0)-Amp-CPG (6 mol% Pd to **1**, 72 mg) in toluene placed in a microwave vial (1.0 mL) was added alcohol **1** (0.24 mmol, 1.2 equiv). The vial was capped, evacuated and an O_2 balloon was connected to the reaction vessel. The reaction mixture was stirred at 70 °C for the time shown. Next, the mixture was cooled to r.t. Propargyl derivative **3** (0.1 mmol, 1 equiv) and the chiral amine **5** (20 mol%) were added and the mixture was vigorously stirred for the time shown.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Isolated yield of pure **4**.
[d] Determined by chiral-phase HPLC analysis.

umn and eluted with pentane–EtOAc to afford the corresponding products **4**.

Methyl (1*R*,2*R*)-1-Cyano-3-formyl-4-methyl-2-phenylcyclopent-3-enecarboxylate (4a)
Yield: 18 mg (67%); oil; $[\alpha]_D^{25}$ –70.9 (*c* = 1.0 $CHCl_3$).

The enantiomeric excess was determined by HPLC analysis in comparison with an authentic racemic material (ODH-column, *n*-hexane–*i*-PrOH, 85:15, λ = 210 nm, 1.0 mL/min); t_R (major enantiomer) = 19.3 min; t_R (minor enantiomer) = 29.9 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.92 (s, 1 H), 7.38–7.32 (m, 3 H), 7.17–7.15 (m, 2 H), 4.72 (br s, 1 H), 3.89 (s, 3 H), 3.41 (d, *J* = 14.8 Hz, 1 H), 3.26 (dt, *J* = 12.4 Hz, 1.2, 1 H), 2.33 (d, *J* = 0.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.2, 168.8, 157.8, 136.8, 136.6, 129.1, 128.7, 128.0, 117.4, 58.4, 54.4, 51.7, 47.9, 14.3.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{16}H_{15}NO_3$ + Na: 292.0944; found: 292.0946.

Methyl (1*R*,2*R*)-1-Cyano-3-formyl-4-methyl-2-(4-nitrophenyl)cyclopent-3-enecarboxylate (4b)
Yield: 18 mg (57%); oil; $[\alpha]_D^{25}$ –88.2 (*c* = 1, $CHCl_3$).

The enantiomeric excess was determined by HPLC analysis in comparison with an authentic racemic material (ODH-column, *n*-hexane–*i*-PrOH, 75:25, λ = 254 nm, 1.0 mL/min); t_R (major enantiomer) = 33.6 min; t_R (minor enantiomer) = 41.1 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.95 (s, 1 H), 8.22 (d, *J* = 8.8 Hz, 2 H), 7.34 (d, *J* = 8.8 Hz, 2 H), 4.82 (br s, 1 H), 3.91 (s, 3 H), 3.49 (d, *J* = 18.8 Hz, 1 H), 3.32 (d, *J* = 18.8 Hz, 1 H), 2.36 (d, *J* = 1.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.8, 168.2, 159.0, 148.1, 144.1, 136.2, 129.2, 124.2, 117.0, 57.7, 54.7, 51.3, 48.3, 14.4.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{16}H_{14}N_2O_5$ + Na: 337.0792; found: 337.0795.

Methyl (1*R*,2*R*)-1-Cyano-3-formyl-4-methyl-2-(*p*-tolyl)cyclopent-3-enecarboxylate (4c)
Yield: 18 mg (63%); oil; $[\alpha]_D^{25}$ –85.2 (*c* = 1.3 $CHCl_3$).

The enantiomeric excess was determined by HPLC analysis in comparison with an authentic racemic material (ODH-column, *n*-hexane–*i*-PrOH, 90:10, λ = 250 nm, 1.0 mL/min); t_R (major enantiomer) = 23.6 min; t_R (minor enantiomer) = 32.9 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.91 (s, 1 H), 7.16 (d, *J* = 6.4 Hz, 2 H), 7.04 (d, *J* = 6.4 Hz, 2 H), 4.68 (br s, 1 H), 3.88 (s, 3 H), 3.39 (d, *J* = 14.8 Hz, 1 H), 3.25 (d, *J* = 14.8 Hz, 1 H), 2.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.3, 168.9, 157.7, 138.4, 136.8, 133.6, 129.8, 127.9, 117.6, 58.2, 54.4, 51.8, 47.8, 21.4, 14.3.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{17}H_{17}NO_3$ + Na: 306.1101; found: 306.1104.

Methyl (1*R*,2*R*)-2-(2-Chlorophenyl)-1-cyano-3-formyl-4-methylcyclopent-3-enecarboxylate (4d)
Yield: 19 mg (63%); oil; $[\alpha]_D^{25}$ –80.3 (*c* = 1, $CHCl_3$).

The enantiomeric excess was determined by HPLC analysis in comparison with an authentic racemic material (AD-column, *i*-hexane–*i*-PrOH, 90:10, λ = 254 nm, 1.0 mL/min); t_R (major enantiomer) = 33.2 min; t_R (minor enantiomer) = 41.9 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.93 (s, 1 H), 7.47 (dd, *J* = 6.4, 1.6 Hz, 1 H), 7.29–7.20 (m, 2 H), 6.97 (dd, *J* = 6.0, 1.6 Hz, 1 H), 5.30 (br s, 1 H), 3.89 (s, 3 H), 3.41 (d, *J* = 18.8 Hz, 1 H), 3.27 (d, *J* = 18.8 Hz, 1 H), 2.34 (d, *J* = 0.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.9, 169.0, 158.4, 136.3, 134.8, 134.4, 130.3, 129.9, 128.4, 127.2, 117.3, 54.8, 54.5, 50.9, 48.9, 14.4.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{16}H_{14}ClNO_3$ + Na: 326.0554; found: 326.0562.

Methyl (1*R*,2*R*)-1-Cyano-3-formyl-4-methyl-2-(3-nitrophenyl)cyclopent-3-enecarboxylate (4e)
Yield: 18 mg (67%); oil; $[\alpha]_D^{25}$ –89.3 (*c* = 1, $CHCl_3$).

The enantiomeric excess was determined by HPLC analysis in comparison with an authentic racemic material (ODH-column, *n*-hexane–*i*-PrOH, 70:30, λ = 254 nm, 1.0 mL/min); t_R (major enantiomer) = 19.4 min; t_R (minor enantiomer) = 34.6 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.97 (s, 1 H), 8.22–8.19 (m, 1 H), 7.98 (t, *J* = 1.2 Hz, 1 H), 7.59–7.53 (m, 2 H), 4.83 (br s, 1 H), 3.92 (s, 3 H), 3.49 (d, *J* = 18.8 Hz, 1 H), 3.33 (d, *J* = 18.8 Hz, 1 H), 2.38 (d, *J* = 1.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.8, 168.2, 159.3, 148.6, 139.0, 136.1, 134.7, 130.1, 123.8, 122.8, 117.1, 57.8, 54.8, 51.3, 48.1, 14.5.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{16}H_{14}N_2O_5$ + Na: 337.0792; found: 337.0794.

Methyl (1*R*,2*R*)-2-Butyl-1-cyano-3-formyl-4-methylcyclopent-3-enecarboxylate (4f)
Yield: 17 mg (68%); oil; $[\alpha]_D^{25}$ +30.2 (*c* = 1.0 $CHCl_3$).

The enantiomeric excess was determined by HPLC analysis in comparison with an authentic racemic material (ODH-column, *n*-hexane–*i*-PrOH, 98:2, λ = 230 nm, 1.0 mL/min); t_R (major enantiomer) = 17.7 min, t_R (minor enantiomer) = 19.7 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.93 (s, 1 H), 3.83 (s, 3 H), 3.53 (br s, 1 H), 3.26 (d, *J* = 18.8 Hz, 1 H), 3.13 (d, *J* = 20.0 Hz, 1 H), 2.18 (s, 3 H), 1.99–1.90 (m, 1 H), 1.82–1.73 (m, 1 H), 1.40–1.28 (m, 4 H), 0.90 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.9, 169.5, 156.9, 137.5, 118.2, 54.2, 52.5, 49.5, 48.5, 33.4, 20.2, 14.1, 14.0.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{14}H_{19}NO_3$ + Na: 272.1257; found: 272.1270.

Methyl (1*R*,2*R*)-2-(4-Bromophenyl)-1-cyano-3-formyl-4-methylcyclopent-3-enecarboxylate (4g)
Yield:18 mg (52%); oil; $[\alpha]_D^{25}$ –55.8 (*c* = 1, $CHCl_3$).

The enantiomeric excess was determined by HPLC analysis in comparison with an authentic racemic material (AD-column, *n*-hexane–*i*-PrOH, 90:10, λ = 250 nm, 1.0 mL/min); t_R (major enantiomer) = 22.3 min; t_R (minor enantiomer) = 34.9 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.91 (s, 1 H), 7.48 (d, *J* = 6.8 Hz, 2 H), 7.09 (d, *J* = 6.8 Hz, 2H), 4.67 (br s, 1 H), 3.88 (s, 3 H), 3.42 (d, *J* = 14.8 Hz, 1 H), 3.25 (d, *J* = 12.8 Hz, 1 H), 2.32 (d, *J* = 0.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0, 168.6, 158.3, 136.5, 135.7, 132.2, 129.8, 122.8, 117.3, 57.8, 54.3, 51.3, 47.9, 14.3.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{16}H_{14}BrNO_3$ + Na: 370.0049; found: 370.0050.

Methyl (1*R*,2*R*)-1-Cyano-3-formyl-4-methyl-2-propylcyclopent-3-enecarboxylate (4h)
Yield: 19 mg (81%); oil; $[\alpha]_D^{25}$ +15.5 (*c* = 1.0 $CHCl_3$).

The enantiomeric excess was determined by HPLC analysis in comparison with an authentic racemic material (ODH-column, *n*-hexane–*i*-PrOH, 98:2, λ = 230 nm, 1.0 mL/min); t_R (major enantiomer) = 18.1 min; t_R (minor enantiomer) = 19.8 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.93 (s, 1 H), 3.83 (s, 3 H), 3.52 (m, 1 H), 3.19 (dd, *J* = 18.4, 36.3 Hz, 2 H), 2.42 (s, 3 H), 1.92 (m, 1 H), 1.75 (m, 1 H), 1.47–1.27 (m, 2 H), 0.94 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.9, 169.5, 156.9, 137.5, 118.2, 54.2, 52.5, 49.5, 48.5, 33.4, 20.2, 14.1, 14.0.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{13}H_{17}NO_3$ + Na: 258.1101; found: 258.1109.

Methyl (1*R*,2*R*)-2-(But-3-en-1-yl)-1-cyano-3-formyl-4-methylcyclopent-3-enecarboxylate (4i)
Yield: 16.5 mg (63%); oil; $[\alpha]_D^{25}$ +12.3 (*c* = 1.0 $CHCl_3$).

The enantiomeric excess was determined by HPLC analysis in comparison with an authentic racemic material (ODH-column, *n*-hexane–*i*-PrOH, 98:2, λ = 230 nm, 1.0 ml/min); t_R (minor enantiomer) = 22.5 min; t_R (majoror enantiomer) = 24.2 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.93 (s, 1 H), 5.78 (m, 1 H), 5.08–4.97 (m, 2 H), 3.83 (s, 3 H), 3.54 (m, 1 H), 3.22 (dd, *J* = 18.4, 36.3 Hz, 2 H), 2.18 (s, 3 H), 2.18–2.03 (m, 3 H), 1.88 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.9, 169.3, 157.1, 137.4, 137.3, 118.1, 115.8, 54.2, 52.0, 49.3, 48.5, 31.1, 30.5, 14.1.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{14}H_{17}NO_3$ + Na: 270.1102; found: 270.1106.

Methyl (1*R*,2*R*)-1-Cyano-3-formyl-4-methyl-2-(4-methoxyphenyl)cyclopent-3-enecarboxylate (4j)
Yield: 21 mg (69%); yellow oil; $[\alpha]_D^{25}$ –108.7 (*c* = 1.6, $CHCl_3$).

The enantiomeric excess was determined by HPLC analysis in comparison with an authentic racemic material (AS-H-column, *n*-hexane–*i*-PrOH, 85:15, λ = 210 nm, 1.0 mL/min); t_R (major enantiomer) = 43.1 min; t_R (minor enantiomer) = 73.6 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.91 (s, 1 H), 7.08 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 4.68 (br s, 1 H), 3.88 (s, 3 H), 3.79 (s, 3 H), 3.38 (d, *J* = 18.6 Hz, 1 H), 3.24 (dt, *J* = 18.6, 3.0 Hz, 1 H), 2.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.3, 168.9, 159.8, 157.6, 136.9, 129.2, 128.6, 117.6, 114.4, 57.9, 55.3, 54.4, 51.9, 47.7, 14.3.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{17}H_{17}NO_4$ + Na: 322.1050; found: 322.1051.

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