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Highly Enantioselective Cascade Transformations by Merging Heterogeneous Transition Metal Catalysis with Asymmetric Aminocatalysis

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The concept of combining heterogeneous transition metal and amine catalysis for enantioselective cascade reactions has not yet been realized. This is of great advantage since it would allow for the recycling of expensive and non-environmentally friendly transition metals. We disclose that the use of a heterogeneous Pd-catalyst in combination with a simple chiral amine co-catalyst allows for highly enantioselective cascade transformations. The preparative power of this process has been demonstrated in the context of asymmetric cascade Michael/carbocyclization transformations that delivers cyclopentenes bearing an all carbon quaternary stereocenters in high yields with up to 30:1 dr and 99% ee. Moreover, a variety of highly enantioselective cascade hetero-Michael/carbocyclizations were developed for the one-pot synthesis of valuable dihydrofurans and pyrrolidines (up to 98% ee) by using bench-stable heterogeneous Pd and chiral amines as co-catalysts.

Traditionally, organic syntheses are based on stepwise processes in which isolation and purification of key intermediates are needed before further transformations can be accomplished[1]. Domino and cascade reactions on the other hand can be performed in a one-pot fashion and allowing for the possible access to a myriad of complex molecules in an efficient, atom-economical and green manner[2,3]. However, the development of catalytic asymmetric domino and cascade reactions is very challenging and has previously been propelled predominantly by using transition metal catalysts[4–6]. Lately these types of transformations have begun to benefit from the rapidly growing field of organocatalysis[7–9].

In recent years, the concept of combining transition metal catalysis and organocatalysis in one process, so called "organo-metal cooperative catalysis", has attracted considerable attention and has emerged as a promising strategy for developing new and unprecedented transformations, not possible by using the transition metal or the organic catalysts alone[10]. Despite its advantages, the number of organo-metal cooperative catalyzed reactions that have been developed is by far less than those in which a single catalyst is employed. One major factor that contributes to this disparity is the incompatibility between transition metals and organocatalysts. Thus, the design and discovery of novel cooperative catalytic systems to conquer this challenge are particularly pressing. In 2006, we discovered that C-C bond formation could be achieved by combining homogeneous transition-metal catalysis with aminocatalysis, and have since then developed dual catalytic systems for reactions, such as enantioselective α-allylic alkylaion of various carbonyl compounds[11,12], enantioselective β-alkylation of α,β-unsaturated aldehydes[13], carbocyclizations of various enynes[14,15] and for the synthesis of homoallylboronates[16]. While successful, this methodology still suffers from drawbacks, the main being related to the use of homogeneous catalysts that are tedious to remove, resulting in inefficient separation, purification and recycling of the catalyst[17–21]. However, there are several examples in the literature where this problem has been circumvented *e.g.* by the use of heterogeneous catalysis[22]. Therefore, we were interested to investigate whether it was possible to implement a heterogenous

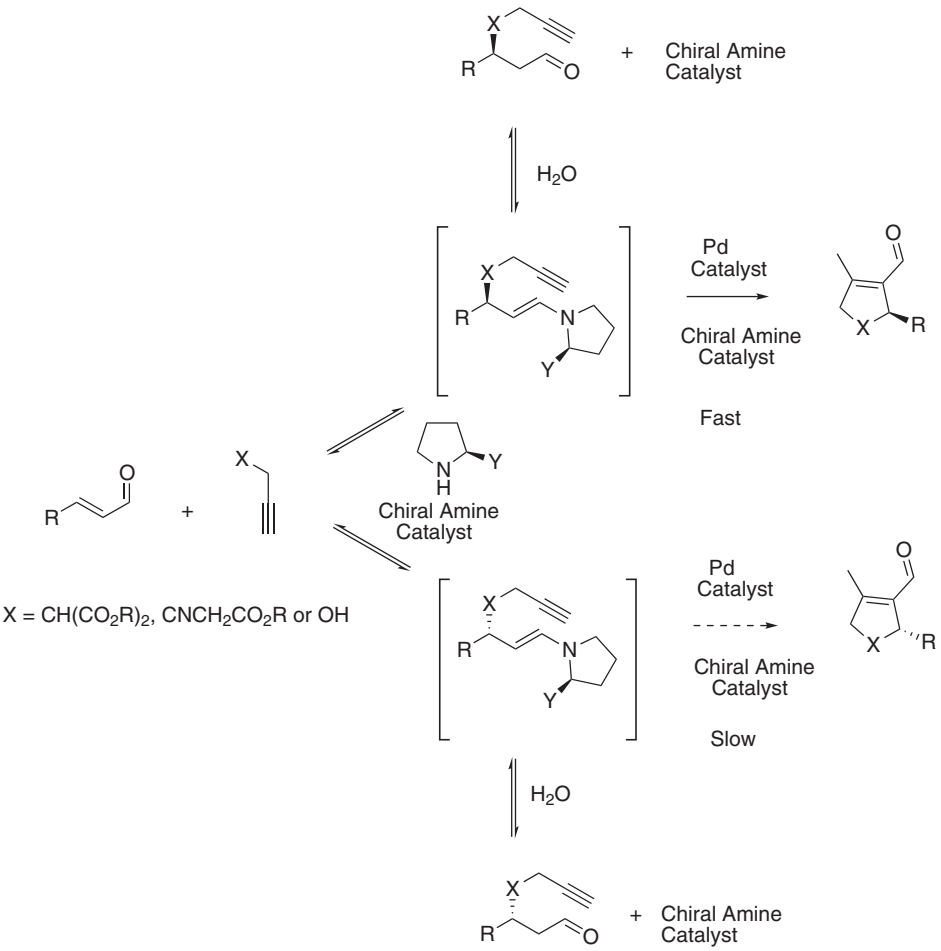


Figure 1 | **Pd-Amine co-catalyzed DYKAT.**

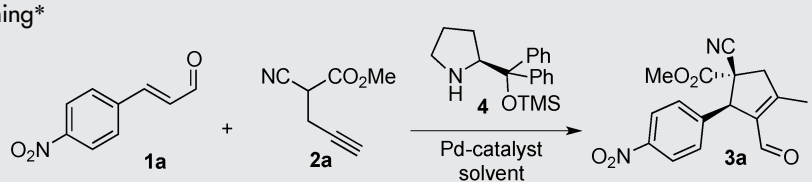
Pd-catalyst in combination with an organocatalyst in the development of novel cascade and domino reaction protocols. To the best of our knowledge, we herein report on the first example in which heterogeneous Pd catalysis has been merged with amine catalysis for highly enantioselective cascade transformations.

Results

Initial screening. We have recently reported on a one-pot homogeneous dynamic kinetic asymmetric transformation (DYKAT) employing chiral amines and $Pd(PPh_3)_4$ or $PdCl_2$ as co-catalysts for the preparation of a wide range of cyclopentenes and dihydrofurans in high yields (Figure 1)[14,15].

These dynamic cascade reactions proceed *via* an initial reversible amine-catalyzed conjugate addition followed by carbocyclization were the synergistic catalysis is essential (Figure 1)[15]. Thus, the initial reversible 1,4-addition, which proceeds through catalytic iminium activation of an enal, forms two diastereomeric catalytic enamine intermediates (X = $CH(CO_2R^1)_2$ or OH). Next, an irreversible Pd and amine co-catalyzed intramolecular enantioselective C-C bond-formation[23–26] occurs *via* activation of the alkyne moiety, and the stereochemical outcome of the reaction is determined by the different rates of cyclization for the two diastereomeric enamine intermediates. When using 2-substituted-4-pentynoate esters (*e.g.* X = $CNCHCO_2R^1$) as substrates, the transformation generates an all-carbon stereocenter, which has proved to be a challenging task in organic synthesis[27]. However, this cascade reaction is very difficult to control since the initial reversible 1,4-addition step to the enal results in the formation of two nearly racemic diastereomeric Michael intermediates. Thus, four stereoisomers are formed, Next, one of these four Michael stereoisomers has to react at a significantly higher rate as compared to the others during the metal-co-catalyzed carbozyclization step in order to make the reaction both highly diastereo- and enantioselective[14]. Based on the advantages associated with heterogeneous metal catalysis (e.g. recycling, simpler purification, and reduction of metal-contamination), we became interested in developing this type of DYKAT cascade process in a heterogeneous fashion for the synthesis of cyclopentenes containing an all-carbon quaternary stereocenter. To our delight, we found that by carrying out the reaction of enal **1a** and the cyanoacetate derivative **2** in CH_3CN, in the presence of 1.5 mol% of a heterogeneous Pd(II)-catalyst[28] and prolinol **4**[29], the desired cyclopentene **3a** could be isolated in 37% yield after 22 h (Table 1, Entry 1). Furthermore, the reaction proceeded with a high stereoselectivity, resulting in a *dr* of 16 : 1 and an *ee* of 90%, respectively. By increasing the loading of Pd to 3.0 mol% (Table 1, Entries 2–6), the yield of the reaction could be significantly increased while retaining high stereoselectivity. Performing the reaction in CH_2Cl_2 and toluene provided the highest stereoselectivity (up to 16 : 1 dr and 96% ee) for the co-catalyzed cascade reaction and delivered the corresponding product **3a** in high yield (Entries 3–6). It should be mentioned that the diastereoselectivity increased with prolonged reaction time. The reaction employing a heterogeneous Pd(0)-catalyst[29] also proved to be highly stereoselective in CH_2Cl_2, toluene and *p*-xylene (Entries 9–12). For example, the corresponding product **3a** was isolated in 75% yield with up to 15 : 1 dr and 95% *ee* (Entry 11). It is noteworthy that an increase in stereoselectivity could be observed when heterogeneous

Table 1 | Condition screening*



Entry	Time (h)	Solvent	Metal Cat.	Yield (%)§	dr¶	ee (%)†
1	22	CH_3CN	Pd(II)-AmP-MCF (1.5 mol%)	37	16 : 1	90
2	24	CH_3CN	Pd(II)-AmP-MCF (3.0 mol%)	68	21 : 1	86
3	21	CH_2Cl_2	Pd(II)-AmP-MCF (3.0 mol%)	80	16 : 1	94
4	3.5	CH_2Cl_2	Pd(II)-AmP-MCF (3.0 mol%)	73	10 : 1	96
5	23	toluene	Pd(II)-AmP-MCF (3.0 mol%)	76	9 : 1	94
6	18	toluene	Pd(II)-AmP-MCF (3.0 mol%)	67	10 : 1	94
7	4	CH_2Cl_2	$PdCl_2$ (3 mol%)	81	18 : 1	94
8	23	toluene	$PdCl_2$ (3 mol%)	76	9 : 1	94
9	42	CH_3CN	Pd(0)-AmP-MCF (3.0 mol%)	67	17 : 1	86
10	18	CH_2Cl_2	Pd(0)-AmP-MCF (3.0 mol%)	70	16 : 1	91
11	18	toluene	Pd(0)-AmP-MCF (3.0 mol%)	75	15 : 1	95
12	18	*p*-xylene	Pd(0)-AmP-MCF (3.0 mol%)	72	15 : 1	92
13	18	toluene	$Pd(PPh_3)_4$ (3 mol%)	71	10 : 1	91
14	41	CH_3CN	$Pd(PPh_3)_4$ (3 mol%)	76	12 : 1	86
15‡	23	CH_2Cl_2	Pd(II)-AmP-MCF‡ (3.0 mol%)	0	-	-
16€	23	CH_2Cl_2	-	0	-	-

*Experimental conditions unless otherwise noted: A mixture of **2** (0.24 mmol), Pd (3 mol%) in solvent (0.5 mL) was stirred for 5 min. To this, aldehydes **1** (0.2 mmol) and amine **4** (20 mol%) were added and the reaction was stirred at room temperature for the time given in the table.
§Isolated yield of **3a**.
¶Determined by ^{1}H NMR.
†Determined by chiral-phase HPLC analysis.
‡No chiral amine **4** was added.
€Only chiral amine catalyst was **4**. The conjugate addition intermediate was formed with a 2 : 1 dr.

Pd-sources were used as catalysts instead of homogeneous ones (Entries 7, 8, 13 and 14). Moreover, it was established that the chiral amine and the heterogeneous Pd catalysts have to operate in concert for product **3a** to be formed (Entries 15 and 16).

Substrate scope. The scope of the reaction was studied and a variety of substrates were tested under the optimized reaction conditions described above for the dual catalytic system (Table 2). The protocol proved to tolerate a wide range of α,β-unsaturated aldehydes **1** with both electron-withdrawing (Entries 1–6), electron-donating (Entry 9) and heteroaromtic substituents (entry 10), giving the corresponding cyclopentenes **3a–3g** in high yields with high *dr's* (up to 30 : 1) and *ee's* (91–99%). The reaction also proceeded with high stereoselectivity when the aryl substituent was replaced with an aliphatic group (Entry 11). The stereochemistry of the products **3** was established by NMR NOE experiments, chiral-phase HPLC analyses and by comparison with the literature[14].

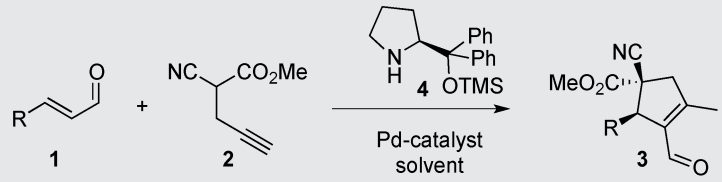
It is noteworthy that our dual catalytic system involving the heterogenous Pd-catalysts also proved to be successful for the synthesis of hetrocycles with important structural motifs. Thus, by replacing the enolate-type nucleophile **2** with either propargylic alcohol **5** or propargylic amine **6**[15,30], it was possible to obtain dihydrofurans **7** and dihydropyrroles **8** generally in good to high yields and high *ees*, respectively (Table 3).

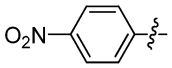
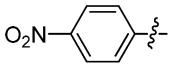
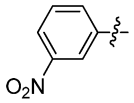
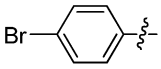
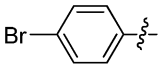
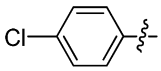
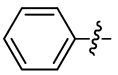
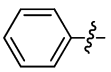
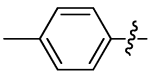
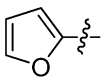
Since the recycling and life-time of heterogeneous catalysts are significant issues for practical applications, the reusability of the heterogeneous Pd(II)-catalyst was investigated in great detail for the reaction between enal **1a** and cyanoacetate **2**, in both CH_2Cl_2 (Table 4) and CH_3CN (Table 1S, supplementary information). During the recycling study, the conversion of starting material was monitored by NMR and after completion of the transformation, the reaction mixture was centrifuged at 4°C. The supernatant was isolated by syringe and analyzed by elemental analysis, confirming the absence of palladium, and demonstrating that all of the palladium is retained on the support. Furthermore, the recovered catalyst was successfully reused 8 times in CH_2Cl_2 under the same reaction conditions without any decrease in activity (Table 4).

Discussion

To determine the Pd species in our catalytic system a hot filtration tests was performed. Thus, the Pd(0)-AmP-MCF catalyst was filtered off after 20% conversion and the solid free filtrate was allowed to stir for 5 h under identical reaction conditions. Analysis of the catalyst-free reaction by NMR analysis determined that no further conversion of the substrate had occurred. Elemental analysis showed that no Pd had been leached in to the solution. The same type of experiment was made for the cascade reaction with the Pd(II)-AmP-MCF co-catalyst. Thus, the Pd-catalyst was filtered off after 5 min (20% conversion) and the solid free filtrate was allowed to stir for 5 h under equal reaction conditions. Once again analysis of the catalyst-free reaction by NMR determined that no further conversion of the substrate had occurred. However, elemental analysis of the filtrate showed a Pd content of 80 ppm, indicating leaching of Pd into solution during the reaction that was re-deposited after completion and recycling of the catalyst by centrifugation. To ensure that the catalytic reaction operates *via* a heterogeneous pathway and not *via* the participation of homogeneous Pd-species, a control experiment with corresponding amounts of homogeneous $PdCl_2$ (80 ppm) was performed. Gratifyingly, only trace amounts of product were observed within 4 h while the same reaction with the heterogeneous Pd(II)-catalyst was completed within this time (Table 1, Entry 4). This result is in correlation to that of the former analysis of the catalyst-free reaction, demonstrating that the heterogeneous pathway truly catalyzes the carbocyclization. It is also in accordance with our results from the Pd(0)-AmP-MCF[28] co-catalyzed carbocyclizations were the heterogeneous Pd-catalyst mediated the transformations. It is noteworthy that the efficiency of the cascade reactions in CH_2Cl_2 with the Pd(II)-AmP-MCF co-catalyst increased during the recycling and that the stereoselectivity also slightly improved (Table 4).

Table 2 | The scope of the co-catalytic asymmetric cascade reaction using a heterogeneous Pd and chiral amine catalyst*



Entry[a]	R (Prod.)	Time (h)	Yield (%)§	dr¶	ee(%)†
1‡	 (**3a**)	18	75	15 : 1	95
2£	 (**3a**)	20	80	16 : 1	94
3£	 (**3b**)	5	74	21 : 1	91
4£	 (**3c**)	16	83	18 : 1	96
5‡	 (**3c**)	18	78	19 : 1	99
6£	 (**3d**)	16	85	19 : 1	96
7‡	 (**3e**)	18	70	15 : 1	91
8£	 (**3e**)	16	84	12 : 1	96
9£	 (**3f**)	16	86	24 : 1	96
10£	 (**3g**)	18	81	12 : 1	91
11‡	*n*Pr (**3h**)	23	67	5 : 1	96

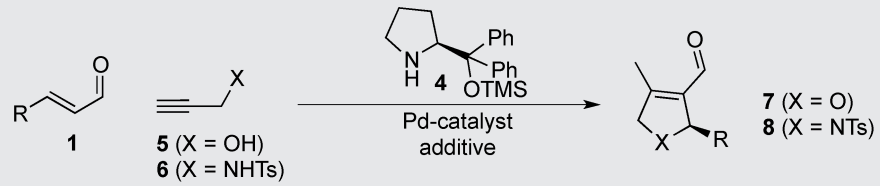
*Experimental conditions unless otherwise noted: A mixture of **2** (0.24 mmol), Pd(II)-AmP-MCF (3 mol%) in solvent (0.5 mL) was stirred for 5 min. To this, aldehydes **1** (0.2 mmol) and amine **4** (20 mol%) were added and the reaction was stirred at room temperature for the time given in the table.
§Isolated yield of **3**.
¶Determined by ^{1}H NMR.
†Determined by chiral-phase HPLC analysis.
‡Reaction performed with Pd(0)-AmP-MCF in toluene.
£Reaction performed with Pd(II)-AmP-MCF in CH_2Cl_2.

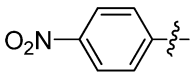
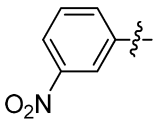
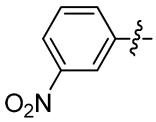
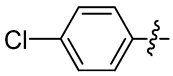
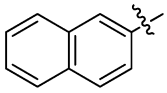
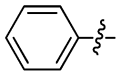
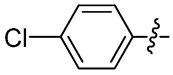
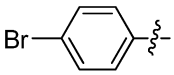
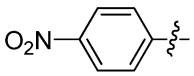
In conclusion, the concept of merging heterogeneous metal catalysis with asymmetric amino catalysis for highly enantioselective cascade transformations has been demonstrated. This type of co-catalysis enabled the diastereo- and enantioselective synthesis of highly substituted cyclopenetenes, bearing an all carbon quaternary stereocenter (up to 24 : 1 dr and 99% ee). In addition, synergistic co-catalysis allowed for the highly enantioselective synthesis of functionalized dihydrofurans and dihydropyrrolidines. The heterogeneous Pd co-catalysts were readily recycled and the efficiency and stereoselectivity slightly increased after the first two cycles in CH_2Cl_2. The ability of recycling expensive and non-environmentally friendly transition metal catalysts and their use as co-catalysts together with simple chiral metal-free catalysts for one-pot, multi-step reactions possess a great promise in the development of greener and more sustainable chemistry. Further studies towards this direction are ongoing in our laboratories.

Methods

General procedure for the cascade Michael/carbocyclization between 1 and 2. To a stirred solution of **2** (0.375 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was added

Table 3 | The scope of the co-catalytic asymmetric cascade reaction using a heterogeneous Pd and chiral amine catalyst



Entry	R	Alkyne	t [h]	Prod.	Yield [%]¶	ee [%]‡
1*		**5**	17	**7a**	82	92
2*		**5**	17	**7b**	69	89
3£		**5**	40	**7b**	85	93
4†		**5**	22	**7c**	59	94
5†		**5**	25	**7d**	59	98
6§		**6**	22	**8a**	53	92
7§		**6**	20	**8b**	59	94
8§		**6**	22	**8c**	53	96
9§		**6**	20	**8d**	67	94
10§	Me	**6**	23	**8e**	84	77

*A mixture of propargyl alcohol **5** (0.375 mmol), Pd(II)-AmP-MCF (3 mol%) in $CHCl_3$ (0.5 mL) was stirred for 5 min. Aldehydes **1** (0.25 mmol), amine **4** (20 mol%) and benzoic acid (20 mol%) were then added and the reaction was stirred at 4°C for appropriate time.
£Pd(0)-AmP-MCF (5 mol%) in toluene (0.5 mL) at room temperature. Otherwise identical to*.
†THF (0.25 mL) and 5 (0.75 mmol) otherwise identical to *.
§A mixture of propargyl amine **6** (0.30 mmol), Pd(II)-AmP-MCF (5 mol%) in toluene (1.0 mL) was stirred for 5 min. Aldehydes **1** (0.20 mmol), amine **4** (20 mol%), sodium acetate (2.5 equiv) and water (1 equiv) were added and the reaction was stirred at room temperature for the time given in the table.
¶Isolated yield.
‡Determined by chiral-phase HPLC analysis.

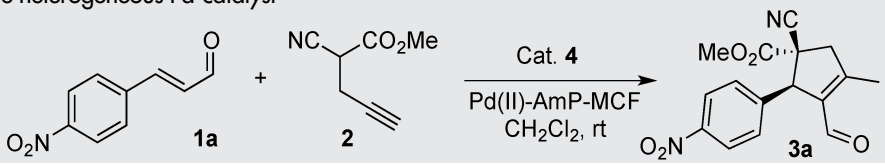
Pd-catalyst (3 mol%). After stirring for 5 minutes at room temperature, the chiral pyrrolidine catalyst **4** (20 mol%) and the enal **1**(0.25 mmol, 1 equiv) were added sequentially. The reaction was vigorously stirred for the time shown in the table. Next, after removal of the Pd-catalyst by filtration, the crude reaction mixture was directly loaded on a silica-gel column and next chromatograph (pentane/EtOAc) afforded the corresponding product **3**. All ^{1}H-NMR spectra and ^{13}C-NMR spectra of the products **3** can be found in the supplementary information. Detailed description of the conditions used (HPLC) for the ee determination of compounds **3** as well as HPLC traces are given in the Supplementary Information.

General procedure for the cascade Michael/carbocyclization between 1 and 5. To a stirred solution of propargyl alcohol **5** (0.375 mmol, 1.5 equiv)) in $CHCl_3$ (0.5 mL) was added Pd-catalyst (3 mol%). After stirring for 5 minutes, the chiral pyrrolidine catalyst **4** (20 mol%), benzoic acid (20 mol%) and the enal **1** (0,25 mmol, 1 equiv) were added sequentially. The reaction was vigorously stirred at 4°C for the time shown in the table. Next, after removal of the Pd-catalyst by filtration, the crude reaction mixture was directly loaded on a silica-gel column and next chromatography (pentane/ EtOAc) afforded the corresponding product **7**. All^{1}H-NMR spectra and ^{13}C-NMR spectra of the products **7** can be found in the supplementary information. Detailed description of the conditions used (HPLC) for the ee determination of compounds **7** as well as HPLC traces are given in the Supplementary Information.

General procedure for the cascade Michael/carbocyclization between 1 and 6. To a stirred solution of *N*-tosyl propargylamine **6** (0.3 mmol, 1.5 equiv) in toluene (1 mL) was added Pd-catalyst (5 mol%). After stirring for 5 minutes, the chiral pyrrolidine catalyst **4** (20 mo%), sodium acetate (0.5 mmol, 2.5 equiv), water (0.2 mmol, 1 equiv) and the enal **1** (0,25 mmol, 1 eq) were added sequentially. The reaction was vigorously stirred at room temperature for the time shown in the table. Next, after removal of the Pd-catalyst by filtration, the crude reaction mixture was directly loaded on a silica-gel column and next chromatography (pentane/ EtOAc) afforded the corresponding product **8**. All ^{1}H-NMR spectra and ^{13}C-NMR spectra of the products **8** can be found in the supplementary information. Detailed description of the conditions used (HPLC) for the ee determination of compounds **8** as well as HPLC traces are given in the Supplementary Information.

Procedure for recycling of the Pd nanoparticles. To a stirred solution of CH_2Cl_2 (1.5 mL) and **2** (0.72 mmol, 1.2 equiv) in a vial (5 mL), was added Pd-catalyst (3 mol%). After stirring for 5 minutes at room temperature, the chiral pyrrolidine catalyst **4** (20 mol%) and the enal **1a** (0.6 mmol, 1 equiv) were added sequentially. The reaction was vigorously stirred for the time shown in Table 4. Next, the reaction mixture was transferred to a 14 mL centrifuge vial and CH_2Cl_2 (5 mL) was added. After centrifugation for 10 minutes, a syringe removed the supernatant and the Pd-catalyst was washed with CH_2Cl_2 (2×6 mL). The supernatant and the liquid phases

Table 4 | Recycling of the heterogeneous Pd-catalyst*



Cycle	Time (h)	Yield (%)§	dr (%)¶	ee (%)†
1	20	73	13 : 1	92
2	17	73	19 : 1	93
3	17	78	23 : 1	92
4	16	82	21 : 1	93
5	19	82	23 : 1	93
6	17	78	30 : 1	94
7	16	92	18 : 1	94
8	16	81	16 : 1	94
9	16	89	17 : 1	94

*Experimental conditions unless otherwise noted: A mixture of **2** (0.72 mmol), Pd(II)-AmP-MCF (3 mol%) in CH_2Cl_2 (1.5 mL) was stirred for 5 min. To this aldehyde **1a** (0.6 mmol) and amine **3** (20 mol%) were added and the reaction was stirred at room temperature for the time given in the table. §Isolated yield.
¶Determined by ^{1}H NMR.
†Determined by chiral-phase HPLC analysis.

were combined together, the solvent removed under reduced pressure and the resulting mixture was directly loaded on a silica gel column. Chromatography (pentane/EtOAc mixtures) gave the corresponding product **3a**. The recovered catalyst was than successfully reused under the same reaction conditions following the same work-up procedure. **(1*R*,2*R*)-methyl 1-cyano-3-formyl-4-methyl-2-(4-nitrophenyl)cyclopent-3-enecarboxylate 3a:** oil. **^{1}H NMR (400MHz, $CDCl_3$):** δ 9.94 (s, 1H), 8.21 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 4.81 (bs, 1H), 3.90 (s, 3H), 3.48 (d, J = 18.8 Hz, 1H), 3.32 (d, J = 18.8 Hz, 1H), 2.36 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** 185.8, 168.1, 159.1, 144.1, 136.2, 129.2, 124.2, 117.0, 57.7, 54.7, 51.3, 48.2, 14.4; **HRMS (ESI)** : calcd for [M+Na] ($C_{16}H_{14}N_2O_5$) requires m/z 337.0792, found 337.0795; $[\alpha]_D^{25} = -86.1$ (c=1, $CHCl_3$). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH-column, *n*-hexane/*i*-PrOH = 75/25, λ = 250 nm, 1.0 ml/min) t_r (major enantiomer) = 34.0 min, t_r (minor enantiomer) =43.7 min.

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Author contribution

L.D., S.A. and C.P.-N. planned, conducted and analyzed the experiments. E.J. and O.V. prepared the Pd-AmPMCF catalysts. E.J. and A.C. designed and directed the project as well as wrote the paper.

Additional information

Supplementary information accompanies this paper at http://www.nature.com/scientificreports

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