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Diastereoselective Cyclobutenol Synthesis: A Heterogeneous Palladium-Catalyzed Oxidative Carbocyclization-Borylation of Enallenols

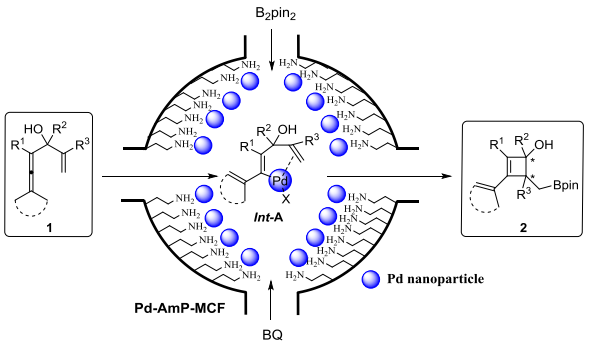
Man-Bo Li, Daniels Posevins, Karl P. J. Gustafson, Cheuk-Wai Tai, Andrey Shchukarev, Youai Qiu,* and Jan-E. Bäckvall*

Abstract: A highly selective and efficient oxidative carbocyclization-borylation of enallenols catalyzed by palladium immobilized on amino-functionalized siliceous mesocellular foam (Pd-AmP-MCF) was developed for diastereoselective cyclobutenol synthesis. The heterogeneous palladium catalyst can be recovered and recycled without any observed loss of activity or selectivity. The high diastereoselectivity of the reaction is proposed to originate from a directing effect of the enallenol hydroxyl group. Optically pure cyclobutenol synthesis was achieved by the heterogeneous strategy using chiral enallenol obtained from kinetic resolution.

After the discovery of the Wacker process in the late 1950's,[1] homogeneous palladium-catalyzed oxidations have developed rapidly and play an important role in both academia and industry.[2] Our group has had a long-standing interest in homogeneous palladium-catalyzed oxidation reactions,[2a,3a,3b] which in recent work has involved the oxidative carbocyclization of allenes.[3] In these reactions a Pd(II) salt, in most cases $Pd(OAc)_2$, is used as a homogeneous catalyst together with an oxidant (typically benzoquinone (BQ)). A drawback with $Pd(OAc)_2$ as the catalyst is that recycling is difficult, which limits its use on larger scale. Another drawback of the homogeneous Pd-catalyzed oxidations is the deactivation of active Pd catalysts because of the generation of Pd black during the catalytic cycle.[2e] Because of these limitations there is a need to develop heterogeneous catalysts that are able to mimic $Pd(OAc)_2$ in oxidation reactions. A problem and a challenge when transforming a Pd-catalyzed oxidation into a heterogeneous version[4] is to maintain high selectivity and efficiency.

Cyclobutenols are highly versatile building blocks in organic synthesis that can be readily transformed into a range of useful compounds.[5] Furthermore, they are important structural elements in a large number of biologically active compounds and natural products.[6] However, synthetic methods for their preparation are still limited.[7] For example, the most straightforward route to cyclobutene derivatives, *via* a [2+2]-cycloaddition[8] of an alkyne to an olefin, cannot be used for the direct preparation of cyclobutenols. Most of the reported methods for accessing cyclobutenols proceed *via* lengthy syntheses involving subsequent functionalization of cyclobutenones.[7a] In addition, control of diastereoselectivity during functionalization of cyclobutenones is challenging,[9] and to date only few methods are known for the distereoselective synthesis of cyclobutenols.[7b,7d] Therefore, the development of efficient methods for the stereoselective synthesis of cyclobutenols is an important and significant research task.

We have recently been involved in the use of palladium nanoparticles (NPs) immobilized on amino-functionalized siliceous mesocellular foam (Pd^0-AmP-MCF) as a heterogeneous nanopalladium catalyst in various organic transformations such as dynamic kinetic resolution,[10c] selective hydrogenation,[10d] and water-splitting.[10e] Not only has this catalyst been shown to display excellent activity, it has also proven to be associated with high recyclability.[10] Our recent extensive involvement in Pd-catalyzed oxidative carbocyclization of allenes for the construction of synthetically important carbocyclic skeletons[3] made us interested in exploring the Pd-AmP-MCF catalyst for oxidative carbocyclizations. We envisioned that enallenol **1** could be transformed into cyclobutenol **2** *via* ***Int*-A** by a Pd-catalyzed oxidative carbocyclization-borylation using Pd-AmP-MCF (Scheme 1). The hydroxyl group of enallenol **1** could potentially direct the reaction to proceed with control of diastereoselectivity. A major challenge with this approach is to activate the nanoparticle to provide access to the Pd(II) atoms required for the oxidative C–C bond formation (*via* ***Int*-A**).



Scheme 1. The strategy of heterogeneous Pd-catalyzed oxidative carbocyclization for cyclobutenol synthesis. [11]

Herein, we report on the Pd-AmP-MCF-catalyzed oxidative carbocyclization-borylation of enallenols for diastereoselective synthesis of cyclobutenols. This recyclable catalyst shows high activity and selectivity and to the best of our knowledge, it is an

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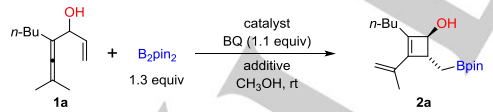
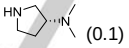
unprecedented report on a heterogeneous Pd-catalyzed oxidative carbocyclization of allenes.

Nanopalladium immobilized on amino-functionalized siliceous mesocellular foam (Pd^0-AmP-MCF) was synthesized using our previously reported procedure[10] (Supporting Information, p. S2). We initiated the investigation by using enallenol **1a** as substrate, bis(pinacolato)diboron (B_2pin_2) as trapping agent, Pd^0-AmP-MCF as the catalyst, *p*-benzoquinone (BQ) as the oxidant, and MeOH as solvent. To our delight, cyclobutenol **2a** was obtained in 8% yield with excellent regio- and diastereoselectivity (Table 1, entry 1). With these inspiring results in hand, we set out to optimize the reaction conditions for the selective formation of **2a**. After screening other solvents, such as CH_2Cl_2, $CHCl_3$, THF, EtOH, *n*-PrOH, or *t*-BuOH, which did not increase the yield, we tried to improve the outcome of the reaction by adding different additives. Interestingly, the yield of cyclobutenol **2a** increased to 45% by the use of 1.0 equiv of triethylamine (Et_3N) as an additive (Table 1, entry 2). Running the reaction more diluted (from 0.1 M to 0.05 M) improved the yield to 50%, probably due to the decrease of side-reactions (Table 1, entry 3). By lowering the amount of catalyst from 5 mol% to 1 mol%, using less Et_3N (0.1 equiv), and shortening the reaction time to 2 h, the yield of **2a** was further improved to 59% (Table 1, entry 4). To our delight, the yield of **2a** was improved to 82% (Table 1, entry 5) with replacement of Pd^0-AmP-MCF by its precursor Pd^{II}-AmP-MCF (Supporting Information, p. S2). To understand the role of Et_3N in this reaction, we studied the effect of amines on the formation of cyclobutenol **2a** (Table 1, entries 6-16). We found that trialkylamines improved the yield of cyclobutenol **2a** to a great extent (Table 1, entries 10, 14, 15). *N,N,N',N'*-tetramethyl ethylenediamine (TMEDA) as an additive completely shut down the reaction and enallenol **1a** was recovered in 92% yield (Table 1, entry 11). Interestingly, Chiral trialkylamine as an additive gave the cyclobutenol **2a** in 62% yield and 16% ee (Table 1, entry 16). These results suggest that there is an interaction between triethylamine and the Pd catalyst (e.g. coordination).[12] To be noted, 1 mol% of $Pd(OAc)_2$ as a catalyst with or without Et_3N only gave cyclobutenol **2a** in 58% or 32% yields, respectively (Table 1, entry 17 and 18), which demonstrate the high efficiency of the heterogeneous catalyst.[13]

Table 1. Selected optimization of the reaction conditions.[a]

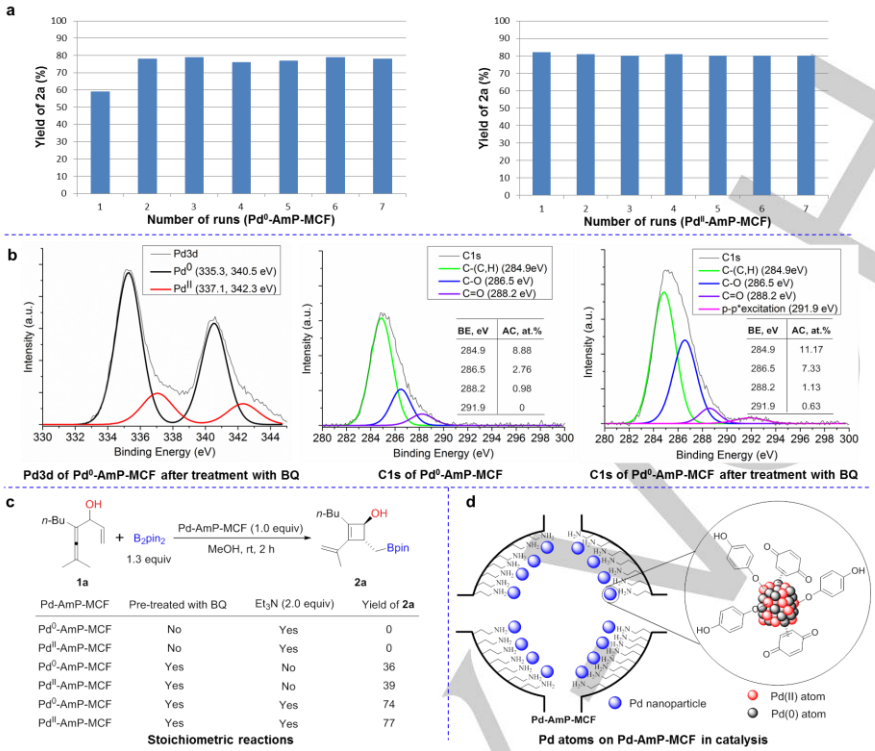


Entry	Catalyst (mol%)	Additive (equiv)	Yield (%)[b]
1	Pd^0-AmP-MCF (5)	none	8
2	Pd^0-AmP-MCF (5)	Et_3N (1.0)	45
3[c]	Pd^0-AmP-MCF (5)	Et_3N (1.0)	50
4[c,d]	Pd^0-AmP-MCF (1)	Et_3N (0.1)	59
5[c,d]	**Pd^{II}-AmP-MCF (1)**	**Et_3N (0.1)**	**82**
6[c,d]	Pd^{II}-AmP-MCF (1)	none	42
7[c,d]	Pd^{II}-AmP-MCF (1)	*n*-$BuNH_2$ (0.1)	46
8[c,d]	Pd^{II}-AmP-MCF (1)	*i*-Pr_2NH (0.1)	50
9[c,d]	Pd^{II}-AmP-MCF (1)	pyridine (0.1)	44
10[c,d]	Pd^{II}-AmP-MCF (1)	$MeN(CH_2)_4$ (0.1)	76
11[c,d,e]	Pd^{II}-AmP-MCF (1)	TMEDA (0.1)	0
12[c,d]	Pd^{II}-AmP-MCF (1)	$PhNMe_2$ (0.1)	55
13[c,d]	Pd^{II}-AmP-MCF (1)	Ph_3N (0.1)	51
14[c,d]	Pd^{II}-AmP-MCF (1)	*n*-Bu_3N (0.1)	77
15[c,d]	Pd^{II}-AmP-MCF (1)	*n*-Pr_3N (0.1)	75
16[c,d]	Pd^{II}-AmP-MCF (1)	 (0.1)	62 (16% ee)
17[c,d]	$Pd(OAc)_2$ (1)	Et_3N (0.1)	58
18[c,d]	$Pd(OAc)_2$ (1)	none	32

[a] The reaction was conducted using 0.2 mmol of **1a**, B_2pin_2 (1.3 equiv), BQ (1.1 equiv), and catalyst (1 or 5 mol%) in 1.0 mL of MeOH. [b] Determined by NMR using anisole as the internal standard. [c] 2.0 mL of MeOH was used. [d] reaction time was shorten to 2 h. [e] **1a** was recovered in 92% yield.

Furthermore, recycling and stoichiometric experiments of Pd-AmP-MCF gave us insight into the activation mode of the catalytic system. Interestingly, with Pd^0-AmP-MCF the yield of **2a** increased from 59% in the first run to 78% in the second run and was maintained around 80% from the second run to seventh run, while Pd^{II}-AmP-MCF gave more constant yield from the first to seventh run in ~80% yield (Scheme 2a). These results indicate that an activation step is required for the Pd^0-AmP-MCF catalyst. Transmission electron microscopy (TEM) images of Pd^0-AmP-MCF and Pd^{II}-AmP-MCF before the reaction are quite different, but after several recyclings they became very similar to one another (Supporting Information, p. S27). Furthermore, the deconvoluted Pd3d X-ray photoelectrons pectroscopy (XPS) spectrum of Pd^0-AmP-MCF pretreated with BQ showed that the surface of the palladium nanoparticles had a high proportion of Pd(II) (Scheme 2b). These results suggest that oxidation of the nanopalladium surface by BQ may be the activation step of Pd^0-AmP-MCF catalyst. Furthermore, the deconvoluted C1s XPS spectrum of Pd^0-AmP-MCF showed that after treatment with BQ, the atomic concentrations (AC) of C–(C,H), C–O, C=O and π-π* excitation increased from 8.88%, 2.76%, 0.98% and 0% to 11.17%, 7.33%, 1.13% and 0.63%, respectively (Scheme 2b). This result demonstrates that BQ and the reduced hydroquinone (HQ) are adsorbed on Pd-AmP-MCF after treatment with BQ. Control experiments with **1a** showed that neither Pd^0-AmP-MCF nor Pd^{II}-AmP-MCF in stoichiometric amounts did lead to any detectable formation of **2a** (Scheme 2c). However, after treatment of these two materials with 2.0 equiv of BQ for 2 h in MeOH followed by centrifugation and washing several times with MeOH, they promoted the formation of **2a** in 74% and 77% yield, respectively (Scheme 2c). These results indicate that the adsorption (or coordination) of BQ to Pd-AmP-MCF is essential for the initiation of the reaction. Based on these observations, we conclude that the active Pd(II) atoms required for the oxidative carbocylization are generated through adsorption of BQ to the palladium nanoparticles in Pd-AmP-MCF (Scheme 2d).

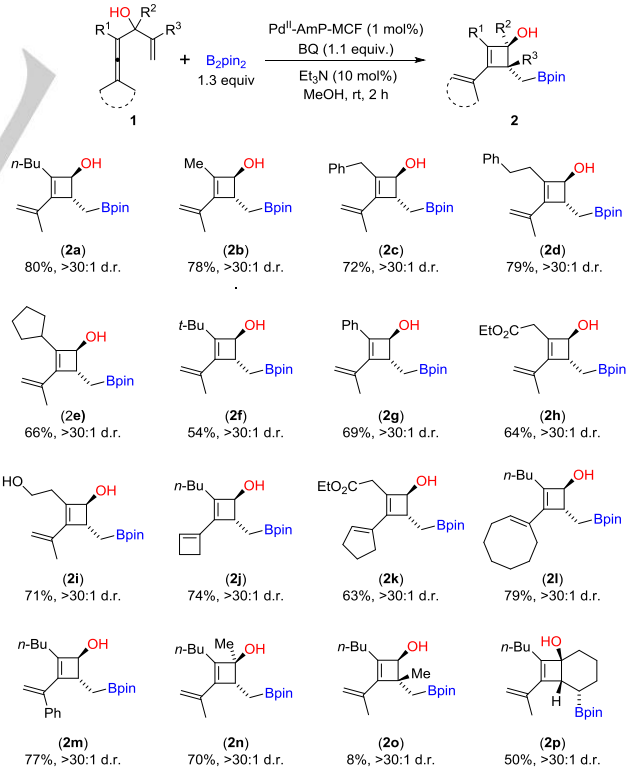
Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) analysis of a liquid aliquot taken from the Pd-AmP-MCF-catalyzed oxidative carbocyclization-borylation of enallenol **1a** showed that there were no detectable amounts of Pd in the reaction solution (< 0.1 ppm). In addition, leaching and hot filtration test (Supporting Information, p. S25) also showed that there was no detectable leaching of Pd species during the reaction, which rules out that the active catalyst for the oxidative carbocyclization-borylation of enallenols had arised from leached



Scheme 2. Recycling and stoichiometric experiments. **a**, Recycling of Pd-AmP-MCF. **b**, XPS spectra of Pd3d of Pd^0-AmP-MCF after treatment with BQ, and C1s of Pd^0-AmP-MCF before and after treatment with BQ. **c**, Stoichiometric reactions. **d**, Schematic illustration of Pd atoms on Pd-AmP-MCF in catalysis. [11]

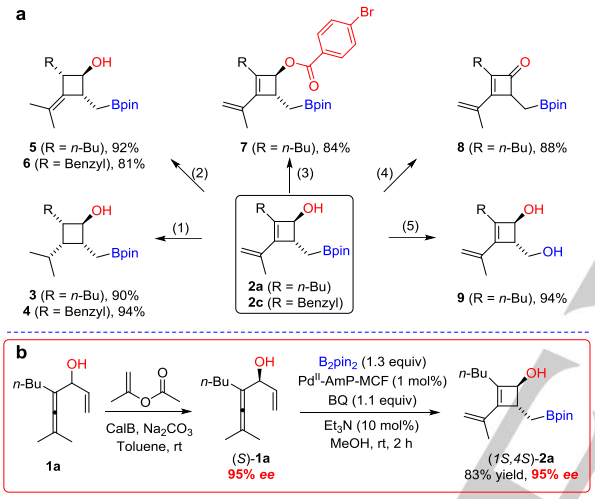
species.[14] Although we favor a heterogeneous mechanism we cannot exclude the possibility of a (temporary) dissolution of Pd(II) catalyzing a (pseudo-)homogeneous reaction inside the pores.[15]

We next studied the substrate scope of the carbocyclization-borylation of enallenols **1** to cyclobutenols **2** (Scheme 3). In addition to butyl-substituted enallenol **1a**, other alkyl groups in the R^1 position like methyl, benzyl, and phenethyl worked well to give **2b**, **2c** and **2d** in good yields. Even sterically demanding alkyl groups, such as cyclopentyl and *t*-butyl afforded the corresponding cyclobutenols **2e** and **2f** in 66% and 54% yields, respectively. Aromatic substituted substrate **1g** furnished cyclobutenol **2g** in 69% yield. The reaction tolerated functional groups like ester groups or an additional hydroxyl group to furnish the corresponding cyclobutenols, **2h**, **2i** and **2k**. Cyclobutylidene, cyclopentylidene and cyclooctylidene substituents on the allene moiety of the enallenols in place of two methyl groups also afforded the corresponding products **2j**, **2k** and **2l** in good yields. In addition, the reaction of an unsymmetrical enallenol **1m** bearing methyl and phenyl groups afforded **2m** in 77% yield. To our delight, enallenol **1n** with a tertiary alcohol afforded tertiary cyclobutenol **2n** in 70% yield. Cyclobutenol **2o** bearing an all carbon-substituted quaternary carbon was obtained from **1o** in only 8% yield under the standard conditions, probably due to the steric effects disfavoring olefin insertion to give a four-membered ring. Interestingly, bicyclic compound **2p** bearing three chiral centers was obtained in 50% yield from **1p** as a single diastereomer. It is noteworthy that all of the cyclobutenol derivatives **2** were obtained as single diastereomers in high selectivity.



Scheme 3. Substrate scope for the diastereoselective synthesis of cyclobutenols **2**.

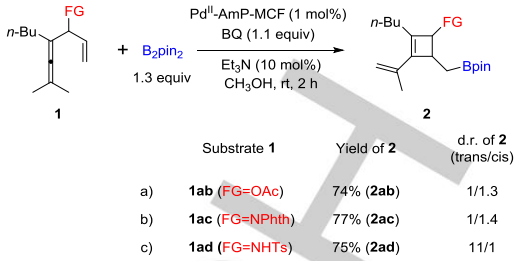
Cyclobutenols constitute a versatile platform for further chemical transformations (Scheme 4a). Hydrogenation of **2a** or **2c** using Pd/C as the catalyst afforded the corresponding tetra-substituted cyclobutane **3** or **4** bearing four chiral centers as a single diastereomer in 90% and 94% yields, respectively. A selective hydrogenation of **2a** or **2c** catalyzed by $[Ir(cod)Cl]_2$ gave C=C bond isomerized products **5** or **6** as a single diastereomer with three chiral centers. Esterification or Dess-Martin oxidation of the hydroxyl group of cyclobutenols **2a** afforded the corresponding cyclobutene ester **7** or cyclobutenone **8**, respectively. Oxidation of the boronic ester functionality in **2a** afforded diol **9** with a cyclobutene framework. Enallenol (*S*)-**1a** (95% *ee*) obtained by kinetic resolution of **1a** with *Candida antarctica* lipase B (CalB) was transformed to optically pure cyclobutenol (*1S, 4S*)-**2a** in 83% yield without any loss of optical purity (Scheme 4b). This transformation provides a simple and efficient approach to optically pure cyclobutenol derivatives.



Scheme 4. Synthetic applications of cyclobutenols **2** and synthesis of optically pure cyclobutenol **2a.** **a**, (1) Pd/C (1 mol%), H_2 (5 bar), MeOH, rt, 12 h; (2) $[Ir(cod)Cl]_2$ (1 mol%), H_2 (5 bar), DCM, rt, 12 h. (3) 4-Br-C_6H_4COCl (1.2 equiv), Et_3N (1.2 equiv), DMAP (5 mol%), DCM, rt, 12 h. (4) Dess-Martin periodinane (DMP) (1.1 equiv), DCM, rt, 2 h. (5) $NaBO_3$•$4H_2O$ (4.0 equiv), THF/H_2O, rt, 8 h. **b**, Synthesis of optically pure cyclobutenol **2**.

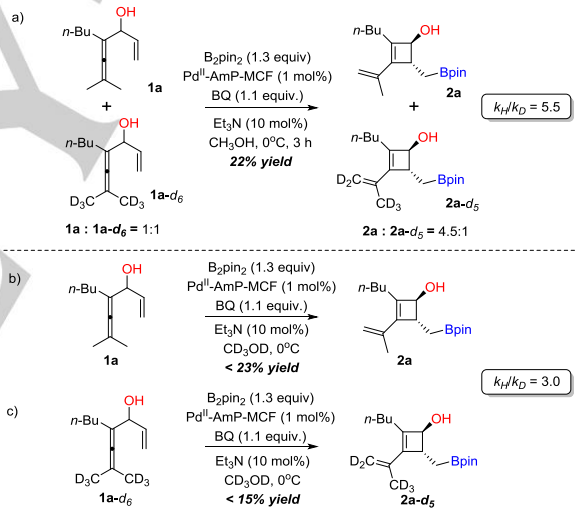
To obtain more information on the origin of the high diastereoselectivity in the formation of cyclobutenols **2**, we examined the reactivity and selectivity of substrate **1ab** in which the hydroxyl group of **1a** had been replaced by an acetoxy group. Although the reactivity of **1ab** was similar to that of enallenol **1a**, there was no diastereoselectivity in the formation of four-membered ring product **2ab** (Scheme 5a), indicating that the hydroxyl group is crucial for the diastereoselective formation of cyclobutenols **2**. We then studied the reactivity and selectivity of imide **1ac** and sulfonamide **1ad** (Scheme 5b and 5c). As with **1ab**, substrate **1ac** showed no diastereoselectivity, but interestingly, the reaction of **1ad** was diastereoselective and afforded **2ad** in a d.r. of 11:1. These results suggest that an active hydrogen (OH or NH) is required in the functional group for the control the diastereoselectivity.[16]

As the allenic C–H bond is cleaved during the reaction, we performed deuterium kinetic isotope effect (KIE) studies[17] to gain



Scheme 5. Functional groups on the diastereoselective formation of **2**.

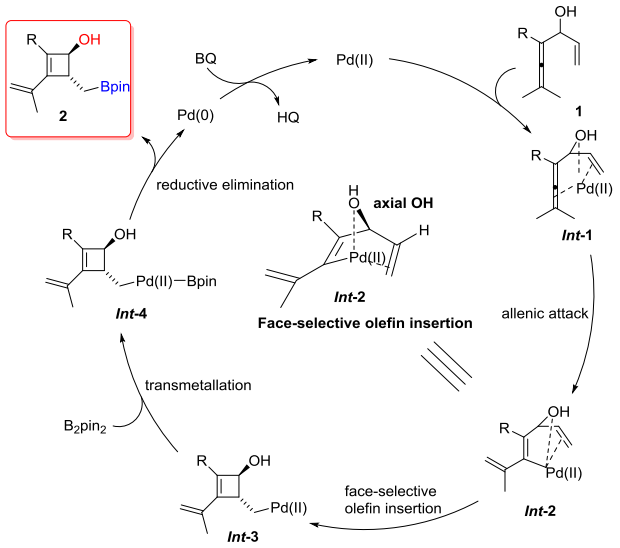
further insight into the reaction mechanism (Scheme 6). An intermolecular competition experiment was conducted using a 1:1 mixture of **1a** and **1a**-d_6 at 0 °C for 3 h (Scheme 6a). The product ratio **2a**/**2a**-d_5 measured at 23% conversion was 4.5:1, with a total 22% yield of **2a** and **2a**-d_5. From this ratio, the competitive KIE value was determined to be k_H/k_D = 5.5. Furthermore, parallel KIE experiments (from initial rate) at 0 °C afforded k_H/k_D = 3.0 (Scheme 6b and 6c). These results indicate that the initial allenic C–H bond cleavage is partially rate-limiting, and the large competitive isotope effect in the C–H bond cleavage (k_H/k_D = 5.5) requires that this step is the first irreversible step of the reaction.



Scheme 6. Kinetic isotope effect studies.

Based on the experimental results and our previous work on Pd-catalyzed oxidative carbocyclization of allene derivatives, we propose a plausible mechanism for the formation of cyclobutenols **2** (Scheme 7). Simultaneous coordination of allene, olefin, and hydroxyl group to Pd(II) center would form ***Int*-1**. The additional coordination of the olefin unit to Pd(II) is essential for the allene attack involving allenic C–H bond cleavage.[18] ***Int*-2** generated from allene attack on Pd(II), bearing an axial hydroxyl group, would promote the formation of ***Int*-3** by face-selective olefin insertion. Subsequent transmetallation of ***Int*-3** with B_2pin_2 would produce intermediate ***Int*-4**, which on reductive elimination gives the target cyclobutenol **2**. The Pd(0) is subsequently re-oxidized by BQ to active Pd(II) to close the catalytic cycle.

In conclusion, an efficient heterogeneous version of a Pd-catalyzed oxidative carbocyclization of enallenols has been



Scheme 7. Proposed reaction mechanism.

realized for the diastereoselective synthesis of cyclobutenols. The heterogeneous Pd catalyst was used at least seven times upon recycling without any loss of activity and selectivity. The coordination of the hydroxyl group of the enallenols to a Pd(II) atom on the nanoparticle is proposed to control the diastereo-selectivity of the transformation. An optically pure cyclobutenol was obtained from a chiral enallenol. This cyclobutenol preparation will be useful in synthetic chemistry, and the heterogeneous catalyst applied here may open up novel opportunities in oxidative C-C bond formation. Further studies on the use of this heterogeneous nanopalladium catalyst as a mimic for $Pd(OAc)_2$ in other oxidative cabocyclizations are currently under way in our laboratory.

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Keywords: cyclobutenols • heterogeneous palladium catalysis • diastereoselectivity • enallenols • oxidative carbocyclization

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[11] In the Scheme it looks like each nanoparticle (NP) bind to only one or two NH_2's. This is only a cartoon and in reality several NH_2's bind to each NP.

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[13] We observed Pd black on the wall of reaction tubes by using $Pd(OAc)_2$ as the catalyst. However, There are no observed generation of Pd black by using Pd-Amp-MCF as the catalyst.

[14] When studying the catalyst using synchrotron based XAS, the XANES-spectra of the catalysts before and after treatment with BQ appeared virtually the same, confirming that no significant single-site atomic palladium catalyst is formed (see Supporting Information, p. S28).

[15] If precipitation of Pd(II) on the nanoparticles is faster than diffusion in a (pseudo)homogeneous reaction the reaction may occur inside the pores. However, because of he large window size of Pd-Amp-MCF (13-14 nm) we consider such a scenario less likely.

[16] Pd^{II}-AmP-MCF catalyze the same reaction of a substrate bearing no hydroxyl group as described in ref. 3e only in 28% yield, which indicates that the hydroxyl group plays an important role not only on selectivity, but also on reactivity.

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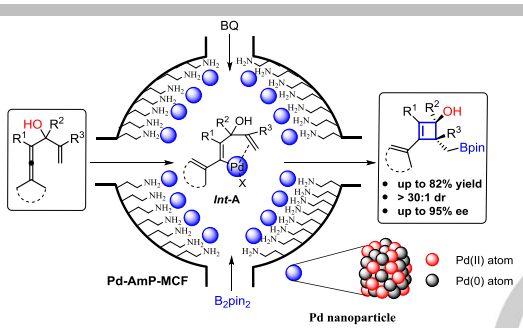
An oxidative carbocyclization-borylation of enallenols catalyzed by recoverable and recyclable heterogeneous Pd-AmP-MCF catalyst was developed for the synthesis of cyclobutenols with high diastereoselectivity.



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Diastereoselective Cyclobutenol Synthesis: A Heterogeneous Palladium-Catalyzed Oxidative Carbocyclization-Borylation of Enallenols