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FULL PAPER

Arylative Allenol Cyclization via Sequential One-pot Enzyme & Palladium Catalysis

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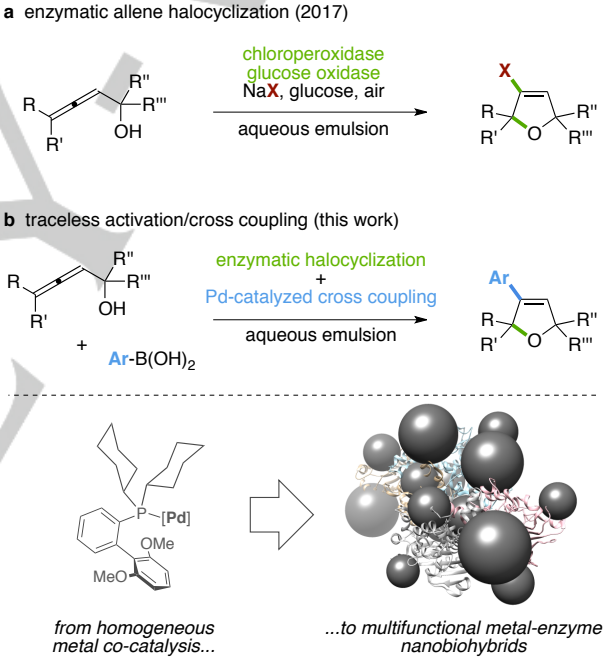
Abstract: The one-pot combination of halogenation biocatalysis and Suzuki-type cross coupling enables the direct arylative cyclization of allenic alcohols with boronic acids. This modular approach to unsaturated five-membered *O*-heterocycles proceeds in an aqueous emulsion with air as terminal oxidant. Here, the enzymatic oxidative activation of simple halide salts acts as traceless ring-closure-inducing event to trigger the subsequent C-C coupling. With the original protocol merging soluble proteins and a homogeneous SPhos-based palladium catalyst as a template, a novel heterogeneous nanobiohybrid was developed. Consisting of an oxidase matrix hosting small spherical palladium nanoparticles, this enzyme-metal hybrid exhibits catalytic competence for both the biocyclization as well as the C-C bond-forming cross coupling, underlining the potential of this new technique for streamlining chemoenzymatic approaches.

Introduction

The combination of multiple catalytic transformations in a single reaction vessel is an important objective for efficient and sustainable synthesis. These one-pot reaction designs allow for more economic process chains by eliminating waste production and time consuming work-up and purification steps.[1] In the field of biocatalysis, single vessel cascade reactions have been widely implemented due to the ease of incorporating several enzymatic transformations together.[2] Here, the biocatalysts' natural affinity towards similar process conditions, tolerance of a wide range of functional groups, and minimal disturbance towards other enzymes in the mixture are clearly rather unique properties compared to other traditional catalysts. The progress in protein engineering and directed evolution has drastically increased the desirability of biocatalysis for industrial applications in recent years.[3] Combining biocatalysis in a one-pot fashion with chemocatalysis is an attractive concept as it merges the advantages of the two fields. Even though many such applications have emerged recently, the approach suffers from daunting challenges as the process conditions for chemo- and biocatalysis are often very different.[4] The most apparent issue is the opposing requirement regarding reaction media as few enzymes stay active



Scheme 1. From biocatalytic to chemoenzymatic synthesis of substituted *O*-heterocycles.

in organic solvents, which on the other hand are most commonly the media of choice in chemocatalytic processes. Several approaches have been successfully designed to alleviate this problem, such as enzyme immobilization or the use of deep eutectic solvents, ionic liquids or colloidal media.[5]

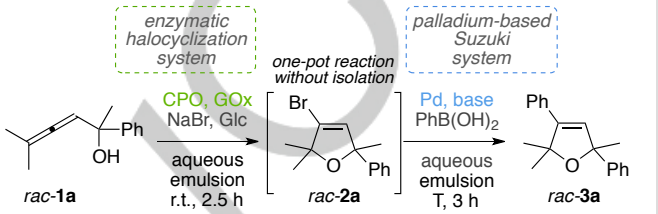
With the aim to broaden the application range of biocatalysis by enzymatic interpretations of traditional organic synthesis approaches, we recently designed a biocatalytic halocyclization of allenic alcohols and carboxylates[6] as a more sustainable alternative to the classical methods of halogenation. Taking advantage of haloperoxidases, an enzyme class, that has found wide use in both halogenation[7] and oxidation[8] reactions, the process relies on an enzymatic cascade featuring

chloroperoxidase from *C. fumago* (CPO) and glucose oxidase from *A. niger* (GOx) to catalyze the formation of halodihydrofurans while only consuming mild stoichiometric reagents sodium halide and D-glucose (Scheme 1a). A critical requirement for the reaction was the incorporation of a non-ionic surfactant, resulting in an emulsified reaction medium. As the vinyl halide handle produced in the bi-enzymatic halogenative cyclization is an obvious target for further chemical modifications through e.g. cross coupling reactions, we envisioned that this process would represent an interesting premise for generally investigating these colloidal conditions in the context of one-pot chemo/biocatalytic applications. Palladium catalyzed cross couplings and related reactions have been established as some of the most versatile and efficient tools for synthesis since being first developed in the 1970's.[9] Recently, the Pd cross coupling reactions have also found applications in one-pot chemoenzymatic approaches, including combinations with alcohol dehydrogenase[10], transaminase[11] and tryptophan halogenase[12]. These works have shown Pd-catalyzed Suzuki-Miyaura reactions to be compatible with water and biocatalytic processes, inspiring us to combine this C-C coupling with the enzymatic allenol halocyclization to produce complex arylated dihydrofurans in sequential and modular one-pot strategy (Scheme 1b). In addition to the more established homogeneous chemoenzymatic catalysis, recent developments in the field of nanotechnology have also made it possible to produce dual-active enzyme-metal nanoparticle biohybrids with great potential for heterogeneous one-pot catalysis.[13] In these nanobiohybrids, the enzyme acts as the support during the transition metal nanoparticle formation, while at the same time also retaining enzymatic activity. The enzyme-metal nanoparticle biohybrids have so far been used as dual-active heterogeneous catalysts in hydrolytic/reductive cascade reactions, as well as in a dynamic kinetic resolution of amines.[14] In this study, we explored this technique to produce oxidase/Pd nanoparticle biohybrids and evaluated them as multifunctional catalysts in the one-pot halocyclization and cross-coupling approach.

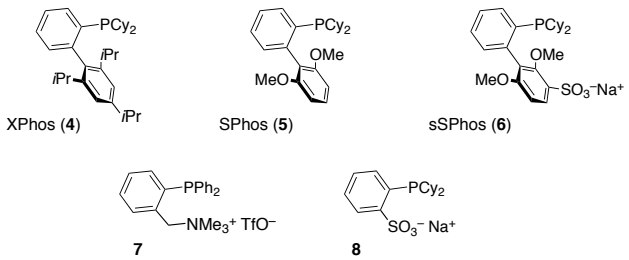
Results and Discussion

Allenic building blocks offer a unique reaction scope and have thus found broad application as versatile intermediates in organic synthesis.[15] As a starting point for our investigation on the sequential one-pot approach, the biocatalytic halocyclization of allenic alcohol **1a** was performed using the conditions found optimal in our previous studies.[6] In this first step, GOx serves as catalyst for a controlled release of hydrogen peroxide into the solution as aerial oxygen is reduced. The H_2O_2 is subsequently consumed by CPO while catalyzing the oxidation of bromide into electrophilic hypobromite species, which triggers a 5-*endo-trig* bromocyclization of the allenol. As the cyclization step was found to be fairly sensitive regarding changes in the reaction medium, the emulsion comprising of a 1:1 mixture of *n*-heptane and citrate buffer (pH 4.5) with 10 mM Brij 35 as the detergent (a non-ionic polyoxyethylene lauryl ether, also marketed as Brij L23) was also adopted for the one-pot investigation. The palladium-mediated cross coupling with phenylboronic acid was chosen as the benchmark reaction for optimizing the conditions of the enzyme-metal-catalyzed sequence. Here, after the initial biocatalytic conversion at room temperature, the reaction medium pH was increased by addition of an inorganic base prior to supplementing the mixture with Na_2PdCl_4, a monodentate phosphine ligand and phenylboronic acid as coupling partner. The first attempts using triphenylphosphine as the ligand for the Pd catalyst unfortunately resulted in a low yield of phenylated product **3a** (Table 1, entry 1). Nevertheless, the bromodihydrofuran **2a** was recovered and the combined yield of almost 90% of **2a** and **3a** indicate that no severe degradation was taking place. Unsurprisingly, the nature of the phosphine ligands had an important influence, and both XPhos

Table 1. Optimization of cross coupling parameters.



Entry[a]	Pd source (mol%)	ligand	base (eq.)	T (°C)	**2a**[b] (%)	**3a**[b] (%)
1	Na_2PdCl_4 (5)	PPh_3	K_2CO_3 (10)	80	68	19
2	Na_2PdCl_4 (5)	**4**	K_2CO_3 (10)	80	25	60
3	Na_2PdCl_4 (5)	**5**	K_2CO_3 (10)	80	4	82
4	Na_2PdCl_4 (5)	**6**	K_2CO_3 (10)	80	16	71
5	Na_2PdCl_4 (5)	**7**	K_2CO_3 (10)	80	78	11
6	Na_2PdCl_4 (5)	**8**	K_2CO_3 (10)	80	89	0
7	$Pd(OAc)_2$(5)	**5**	K_2CO_3 (10)	80	2	83
8[c]	Na_2PdCl_4 (1)	**5**	K_2CO_3 (10)	80	7	82
9	Na_2PdCl_4 (5)	**5**	K_2CO_3 (50)	80	32	47
10	Na_2PdCl_4 (5)	**5**	K_2CO_3 (2)	80	55	33
11	Na_2PdCl_4 (5)	**5**	K_3PO_4 (10)	**80**	**0**	**88**
12	Na_2PdCl_4 (5)	**5**	K_3PO_4 (10)	60	44	42
13[d]	Na_2PdCl_4 (5)	**5**	K_3PO_4 (10)	80	0	84
14[e]	Na_2PdCl_4 (5)	**5**	K_3PO_4 (10)	80	0	85

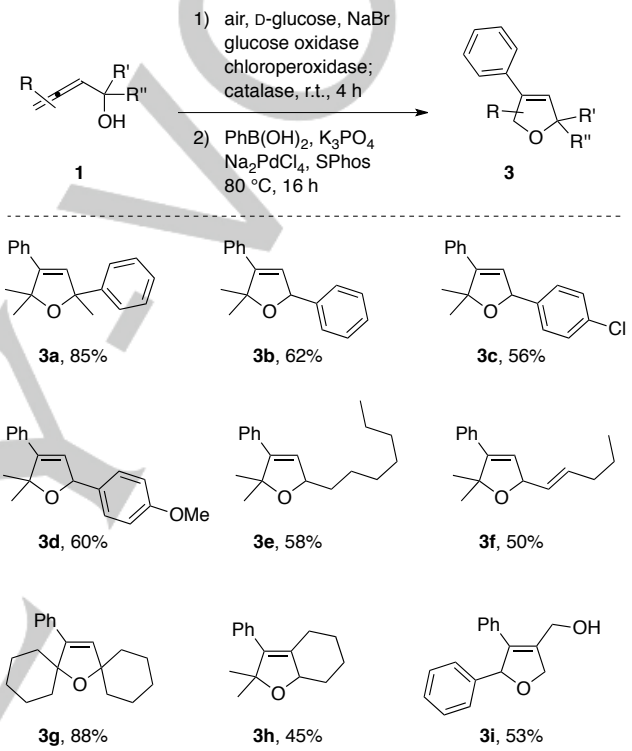


[a] Conditions: (i) 8.0 µL chloroperoxidase (*C. fumago*, 37 U/µL), 2.6 mg glucose oxidase (*A. niger*, 19 U/mg), 100 µmol allene, 300 µmol NaBr, 200 µmol D-glucose, 100 µmol Brij 35, 5 mL heptane, 5 mL citrate buffer (0.1 M, pH 4.5), room temperature, 2.5 h; (ii) 1.5 µL catalase (*M. lysodeikticus*, 131 U/µL), 15 min; (iii) Pd catalyst (5 mol%), ligand (15 mol%), 300 µmol phenylboronic acid, base, *T*, 3 h. [b] Yields determined by quantitative ^{1}H NMR against dimethyl sulfone as standard. [c] 18h reaction time. [d] No catalase addition. [e] Argon atmosphere during cross coupling.

(**4**) and SPhos (**5**) performed better (Table 1, entries 2 & 3), with SPhos giving desired arylation product **3a** with 82% yield over the two consecutive steps. In their work on successfully combining Suzuki-Miyaura cross couplings in a one-pot design with the bromination by tryptophan halogenase in aqueous medium, the group of Sewald opted to use a water-soluble ligand (sulfonated SPhos or sSPhos, **6**) as their optimal system did not involve any cosolvents.[12a] In contrast, the water-soluble phosphine ligands **6-8** (Table 1, entries 4–6) did not perform better than their non-water soluble counterparts in our colloidal biphasic medium. Across all tested reactions, approximately 10% of material is lost, possibly due to formation of more polar side products that are likely to remain in the aqueous layer in the workup of the emulsion system.

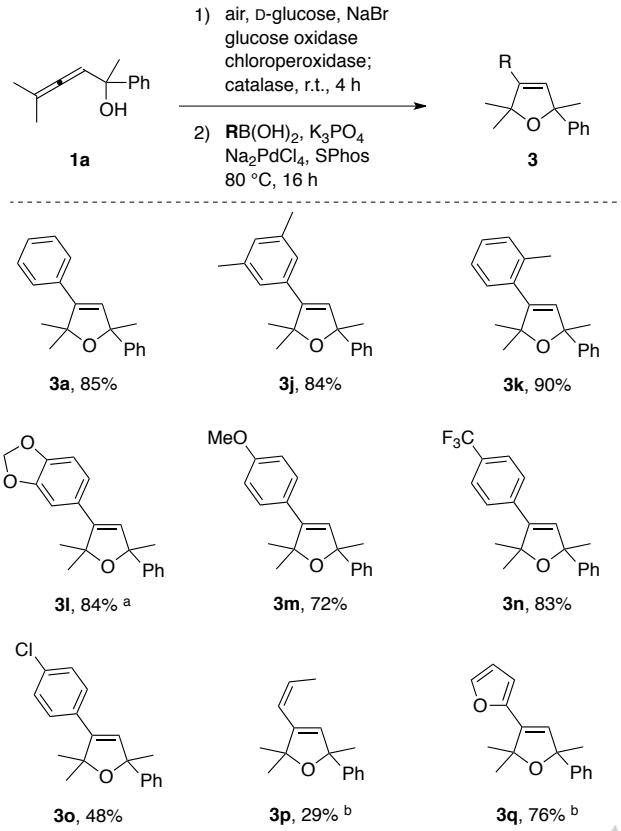
Despite involving an emulsified reaction medium stabilized by the non-ionic surfactant, the enzymatic bromocyclization of allenic alcohol **1a** could be combined in one-pot with phenylboronic acid cross coupling under fairly normal conditions for a Suzuki-Miyaura reaction. The optimal conditions resulted in a high yield of 88% over the two reaction steps, with the cross coupling reaction involving potassium phosphate as the base at a temperature of 80 °C (Table 1, entry 11). Full conversion could be reached within 3 hours of reaction time using 5 mol% palladium catalyst in the transformation. The nature of the palladium (II) source, (Na_2PdCl_4 vs $Pd(OAc)_2$) had no major effect (Table 1, entry 3 vs entry 7). Using just 1 mol% of the catalyst also results in full conversion and similar yield, yet demanded a longer reaction time of 18 h (Table 1, entry 8). Generally, a substantial amount of the inorganic base was required to overcome the citrate buffer, with a smaller amount substantially decelerating the process (Table 1, entry 10). Interestingly, when exceeding a certain level of the base concentration, destabilization of the colloidal medium and formation of larger globules was observed, also resulting in deceleration of the reaction (Table 1, entry 9). In the biocatalytic first step of the process, hydrogen peroxide is released steadily as a by-product in GOx-catalyzed glucose oxidation to avoid deactivation of the CPO caused by excess H_2O_2.[16] To eliminate the potential lingering hydrogen peroxide causing issues in the cross-coupling step, catalase from *Micrococcus lysodeikticus* was supplemented to the mixture between the steps. However, omitting this catalase addition (Table 1, entry 13) had minimal effect on the process, indicating that the H_2O_2 is not a major issue, and is likely already exhausted by the CPO. Similarly, a protective argon atmosphere to prevent potential oxidative side reactions during the cross coupling step turned out non-essential (Table 1, entry 14), underlining the robustness of the process. The change of the traceless activation agent to NaCl or NaI resulted in significantly lower overall yields (w/ NaCl: 6%; w/ NaI: 48%).

Gratifyingly, the optimized protocol translated very well to structural variations both on the allene and boronic acid part of the transformation and the one-pot process was successfully applied to generate a wide range of substituted dihydrofurans in mostly good to excellent isolated yields (Schemes 2 & 3). As stereochemistry was not the focus of this study, all chiral substrates were used as in optically inactive form, yielding racemic heterocycles. Addressing the scope of allenol substrates first, a comparative study was conducted relative to the fully α-substituted **1a** (Scheme 2). For this model substrate, the excellent of 85% of phenyldihydrofuran **3a**, compared to the yields achieved in the individual halocyclization step (85% to **2a**),[6] is synonymous with a quantitative conversion in the cross coupling step. The 85% isolated yield of **3a** also underline the good comparability with the NMR yields used in the initial screening. Although the α-monosubstituted products **3b-f** were also furnished in good yields over the two steps, these transformations fell noticeably short of the efficiency achieved previously for the isolated bromocyclization part (>80%), indicating stability issues in the elevated temperature and basic conditions of the cross coupling reaction. The very high yield of **3g**, lacking any potentially labile allylic C-H bonds, strongly supports this theory. The most palpable drop in synthetic efficiency was observed for the products **3h-i** carrying substituents in the vinylic position. Here, the added steric hinderance likely diminishes the conversion in the Pd-catalyzed reaction, resulting in mediocre overall yields.



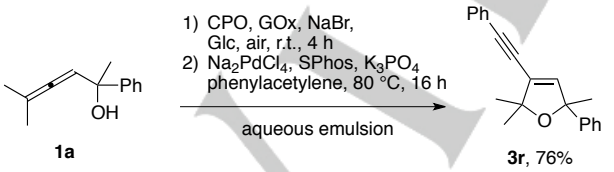
Scheme 2. Structural variation of the allenic coupling partner.

Allenol **1a** was subsequently also chosen as model substrate for the investigation on the scope of the other coupling partner, the boronic acid (Scheme 3). Eliminating the previously experienced challenges regarding steric hindrance and allylic lability, most tested boronic acids performed splendidly. A wide selection of substitution patterns on aromatic boronic acids was tolerated, giving excellent yields for simple methyl-substituted species (**3j** & **3k**) and both activating (**3l** & **3m**) and deactivating (**3n**) substituents on the arene providing the corresponding dihydrofurans with high selectivity in the one-pot process. Within this series, only *para*-chlorophenylboronic acid posed an outlier, offering a lower yield of 48% for **3o**. Although no major secondary biphenyl-type product could be detected, further activation of the chloroarene by the highly reactive SPhos-Pd system could account for slightly inferior performance. In contrast to the very effective vinyl-aryl couplings, achieving furyl or olefin substitutions was more challenging. Acceptable yields of **3p-q** using *cis*-propenyl- or 2-furylboronic acid as the cross coupling partner could only be reached after further optimization of the protocol and via continuous addition of excess boronic acid solution.



Scheme 3. Structural variation of the boronic acid coupling partner. [a] 10 eq. $RB(OH)_2$. [b] 15 eq. $RB(OH)_2$ (0.3 M in H_2O) continually added via syringe pump over 15 h.

In order to further increase the synthetic utility of the bio-metal-coupled protocol in terms of introduced functionalities, a series of alternative cross coupling approaches were tested as secondary modules to complement the halocyclization. While initial attempts to implement Stille- and Heck-type couplings have so far remained unproductive, the substitution of the boronic acids by phenylacetylene, under otherwise identical conditions, gave rise to a successful halocyclization/Sonogashira sequence. The corresponding alkynylated dihydrofuran **3r** could thus be obtained after the one-pot transformation in a high yield of 76% (Scheme 4).



Scheme 4. Chemoenzymatic alkynylation through one-pot halogenation/Sonogashira coupling.

An intrinsic challenge in chemoenzymatic strategies, where proteins and transition metal species are combined, lies in the potential mutual deactivation of the individual catalysts. As one possible solution, recently, the concept of nanobiohybrids has received significant attention. Herein, protein-based biocatalysts act as support during the formation of metal nanoparticles, rendering a hybrid material with a dual functionality as it retains the enzyme's activity while adding catalytic properties of the metal nanoparticle. Among the various applications of nanobiohybrids, a lipase-palladium hybrid has been reported as excellent mediator of Suzuki cross couplings.[14] Considering these results, we aimed to apply this concept in order to perform the previously introduced one-pot sequential process with a tailored multifunctional nanobiohybrid. From the two enzymes, chloroperoxidase and glucose oxidase, the latter was chosen as support as GOx does not depend on any metal cofactors and would therefore suffer less interference from the added metal ions. To our delight, GOx induced the formation of Pd nanoparticles smoothly and without the necessity of any external reducing agents.[13] SEM analysis of the thus obtained hybrid revealed that the formed precipitate constituted an aggregate with a mesoporous amorphous superstructure composed by palladium atoms dispersed into an organic (GOx) matrix (Fig 1a). X-ray diffraction (XRD) analysis confirmed the exclusive formation of Pd(0) species on the hybrid (Fig. 1b), and the ICP-OES analysis determined a Pd content on the hybrid of 40% (w/w). TEM analysis showed the formation of very small spherical crystalline Pd nanoparticles in the range of 2 nm (Fig. 1c-d).

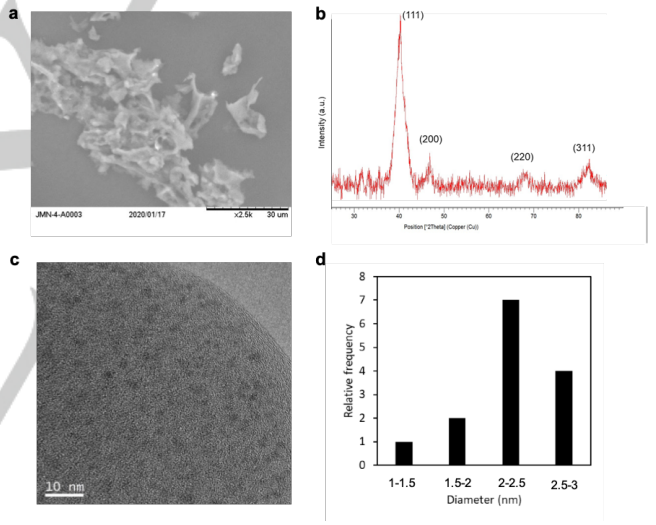
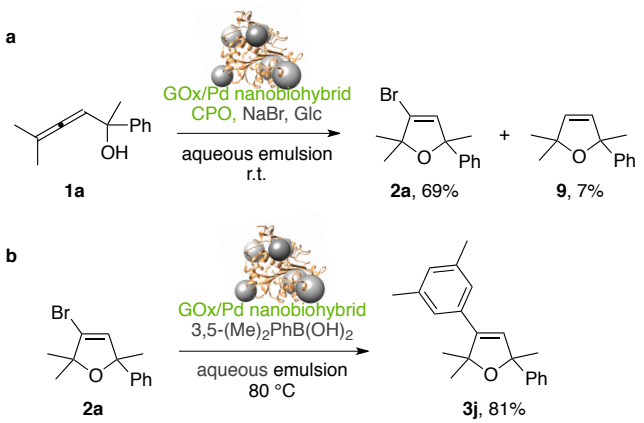


Figure 1. Characterization of the GOx/Pd nanobiohybrid: a) SEM, b) XRD pattern, c) TEM, d) Pd nanoparticles size distribution.

The specifically tailored GOx/Pd nanobiohybrid consisting of the oxidase matrix and the palladium nanoparticles was subsequently evaluated for its catalytic performance in either of the two individual reactions. Substituting the GOx from the original halocyclization protocol by the nanobiohybrid in presence of CPO, glucose and NaBr indeed led to consumption of allenol **1a** and formation of *O*-heterocyclic products in an encouraging overall yield of 76%. In addition to the expected bromodihydrofuran **2a**, however, also minor amounts of the non-halogenated 5-membered heterocycle **9** were observed (Scheme 5a). Though undesired in the context of the present study, this kind of allenol cycloisomerization, more commonly attributed to homogeneous coinage metal catalysis,[17] has been described for heterogeneous nanoparticle catalysis previously,[18] and could represent an interesting alternative application target in future investigations of palladium-based nanobiohybrids. Even more gratifyingly, also the

Suzuki coupling between the vinyl bromide intermediate **2a** and 3,5-xylyl boronic acid was catalyzed effectively by the same enzyme-metal hybrid. The arylated dihydrofuran **3j** was thus obtained in 81% yield, underlining the great potential of the nanobiohybrid concept as tool to streamline chemoenzymatic approaches. So far, early attempts to implement the GOx/Pd nanobiohydrid in a true one-pot conversion from allenols to arylated dihydrofurans have exposed certain challenges related to potential deactivation/poisoning effects, giving overall yields within a 20-30% range. A detailed follow-up study on the preparation and composition of the GOx/Pd assembly related to a more robust hybrid catalyst is currently under way.



Scheme 5. Nanobiohybrid with combined oxidase and transition metal reactivity, catalyzing both halocyclizations and Suzuki-type cross couplings.

Conclusion

Despite considerable inherent challenges to overcome, the combination of chemo- and biocatalytic techniques in streamlined one-pot processes is attracting attention following the emergence of powerful enzyme engineering techniques. The chemoenzymatic sequential halocyclization and cross coupling methods described in this work overcome the issues of incompatibility by introducing colloidal biphasic reaction media, allowing for the highly efficient conversion of allenic alcohols to densely substituted 2,5-dihydrofurans. The robustness and applicability of biocatalytic halogenations was perfectly exemplified by combinations with both Suzuki and Sonogashira couplings in homogeneous one-pot catalysis. Further, potential for performing chemoenzymatic multicatalytic reactions under heterogeneous catalysis conditions by taking advantage of the recently introduced enzyme-metal nanoparticle biohybrid concept opens interesting possibilities for advanced process development. The GOx/Pd nanobiohybrid presented here was successfully applied as catalyst for both individual reaction steps and will serve as inspiration for further optimization in the area.

Experimental Section

General remarks: All reactions carried out in dry solvents were performed under argon atmosphere using anhydrous conditions. Anhydrous solvents were acquired from an *MBraun MB*-SPS800 drying system. Commercially available reagents were used without further purification unless otherwise noted. Enzymes were obtained from: chloroperoxidase from *Caldariomyces fumago* (CPO), 37 kU/mL, Merck KGaA; glucose oxidase type II from *Aspergillus niger* (GOx), 19 kU/g, Merck KGaA; glucose oxidase from *Aspergillus niger* (GOx), Novozymes; catalase from *Micrococcus lysodeikticus*, 131 kU/mL, Merck KGaA. Synthesized products were purified by column chromatography over silica gel (Macherey-Nagel MN-Kieselgel 60, 40-60 µm, 240-400 mesh) or by distillation. Reactions were monitored by thin layer chromatography (TLC) carried out on precoated silica gel plates (Merck, TLC Silica gel 60 F_{254}) using UV light and $KMnO_4$-solution for visualization. NMR, IR and HRMS data of the synthesized compounds were recorded at the Department of Chemistry of Aalto University. ^{1}H and ^{13}C NMR spectra were recorded with a *Bruker Avance NEO 400* (^{1}H 400.13 MHz, ^{13}C 100.62 MHz). The chemical shifts are reported in parts per million (ppm) in relation to non-deuterated chloroform signal (^{1}H NMR: δ = 7.26; ^{13}C NMR: δ = 77.16). Quantitative ^{1}H NMR were recorded using delay time D = 30 s and 30 ° pulse, and are reported in relation to dimethyl sulfone internal standard signal (δ = 3.00, s, 6 H). Infrared spectra were recorded at room temperature on a *Bruker Alpha ECO-ATR* FT-IR-Spectrometer, absorption bands are reported in wave numbers [cm^{-1}]. High resolution mass spectrometry was performed on an *Agilent 6530 (Q-TOF)* mass spectrometer. Enzyme-metal hybrids were synthesized and characterized at the CSIC Institute of Catalysis and Petroleum Chemistry (ICP-CSIC). Inductively coupled plasma optical emission spectroscopy (ICP-OES) and X-ray diffraction (XRD) data was recorded by the technical staff at ICP-CSIC. Transmission electron microscopy (TEM) was done using a *JEOL JEM-2100F* field emission electron microscope. Scanning electron microscopy (SEM) was done using a *Hitachi TM-1000* tabletop microscope. *JASCO V-730* UV-visible spectrophotometer was used for enzymatic activity assays. Lyophilization of the hybrids was done using a *Telstar LyoQuest* laboratory freeze-dryer.

Representative procedure for the one-pot enzymatic halocyclization and palladium-catalyzed cross coupling: 2,2,5-trimethyl-3,5-diphenyl-2,5-dihydrofuran (3a). *n*-Heptane (5 mL) was added to a solution of Brij 35 (123 mg, 100 µmol) in an aqueous citrate buffer (5 mL, 0.1 M, pH 4.5) to form an emulsion with vigorous stirring. Sodium bromide (31 mg, 300 µmol), D-(+)-glucose monohydrate (39 mg, 200 µmol), allenic alcohol **1a** (18.5 mg, 100 µmol) and chloroperoxidase from *Caldariomyces fumago* (8.0 µL, 37 U/µL) were all added to the emulsion. Lastly, glucose oxidase from *Aspergillus niger* (2.6 mg, 19 U/mg) was added to start the reaction. The mixture was stirred vigorously under air at room temperature for 2.5 hours. Catalase from *Micrococcus lysodeikticus* (1.5 µL, 131 U/µL) was added to decompose any excess of hydrogen peroxide, and the mixture was stirred for 15 minutes. Tribasic potassium phosphate (209 mg, 1 mmol), phenylboronic acid (37 mg, 300 µmol), SPhos (6.2 mg, 15 µmol) and lastly sodium tetrachloropalladate (1.5 mg, 5 µmol) were all added to the emulsion. The mixture was heated to 80 °C and stirred vigorously for 3 hours. The reaction was allowed to cool down, and acetonitrile (6 mL) was added to enable phase separation. The mixture was extracted with *n*-pentane (4 x 20 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether 80:1) provided 2,2,5-trimethyl-3,5-diphenyl-2,5-dihydrofuran **3a** as a clear oil (22.2 mg, 84 µmol, 85% yield). $\mathbf{R_f}$ (*n*-heptane/ethyl acetate 10:1) = 0.46. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.54-7.49 (m, 2H), 7.42-7.21 (m, 8H), 6.14 (s, 1H), 1.72 (s, 3H), 1.63 (s, 3H), 1.51 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 147.5, 145.4, 134.3, 130.1, 128.5, 128.3, 127.8, 127.4, 126.7, 125.0, 88.8, 87.7, 31.0, 29.8, 28.8. **FT-IR** (neat, ATR): ν [cm^{-1}] = 3058 (w), 2973 (m), 1600 (w), 1494 (m), 1444 (m), 1363 (m), 1066 (m), 854 (m), 757 (s), 695 (s). **HRMS** (ESI): *m*/*z* $[M+H]^+$ calcd. for $C_{19}H_{21}O$: 265.1587, found: 265.1589.

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Keywords: cross coupling • chemoenzymatic • cascades • heterocycles • nanoparticles

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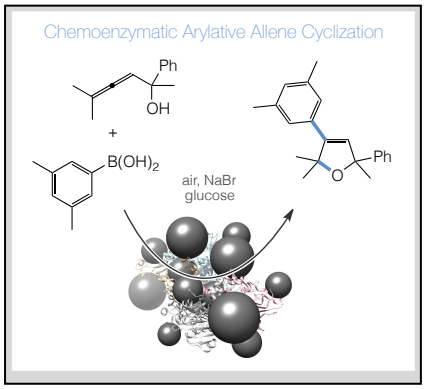

Through a chemoenzymatic one-pot approach merging halogenation biocatalysis with palladium-mediated cross coupling, allenic alcohols are converted to densely substituted O-heterocycles in an aqueous emulsified reaction medium. In addition to the modular synthetic methodology based on homogeneous catalysts, a tailor-made enzyme-metal nanobiohybrid was developed to effectively combine individual catalytic modules in a single heterogenous catalyst.