# Palladium-Catalyzed Regioselective Allylic Oxidation of Amorphadiene, a Precursor of Artemisinin

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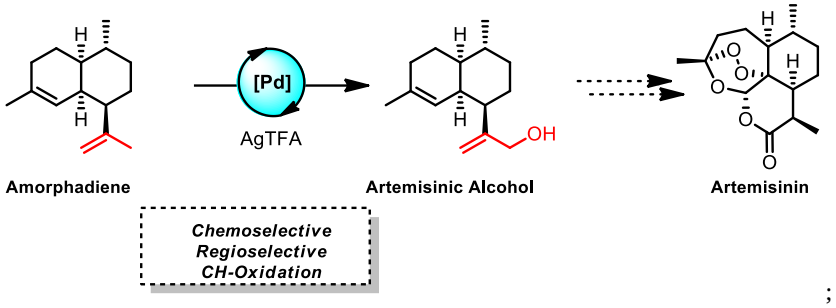


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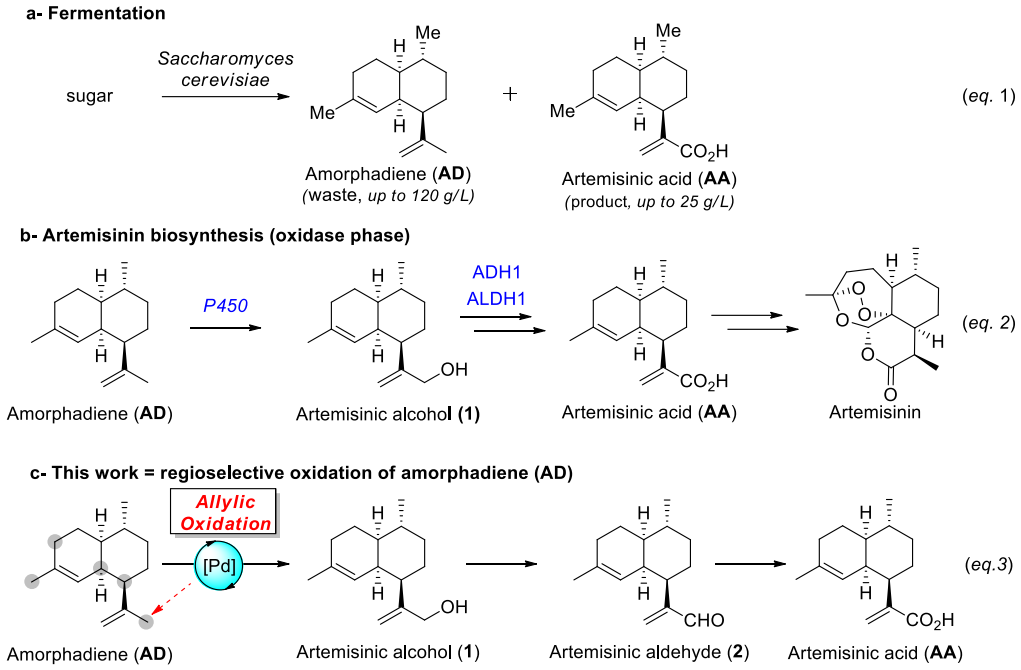
**ABSTRACT:** A regioselective Pd-catalyzed allylic oxidation of amorphadiene, a key precursor to the antimalarial drug artemisinin, is described. Amorphadiene can be obtained in high yields by fermentation, but it is currently treated as a waste in the industrial semi-synthetic artemisinin process. The catalytic step described here is a substitute to the P450 enzymes involved in the artemisinin biosynthesis and opens up new opportunities to supplement a critical step in the current semi-synthetic route and increase the potential of the fermentation process.

The remarkable efficacy of artemisinin in the treatment of malaria has driven impressive progress in synthetic biology and chemistry.[1,2] Artemisinin is a natural product isolated from *Artemisia annua L.* and its extraction from the plant is the major production pathway, producing around 100-120 tons/year. In addition, a semi-synthetic production of artemisinin has been developed on a 50-60 tons/year. Artemisinic acid (**AA**) is produced by fermentation of sugar or ethanol at titers approximating 25 g/L using *Saccharomyces cerevisiae* (Scheme 1, eq 1).[2] This **AA** intermediate is then transformed chemically to artemisinin.[3] Even if impressive breakthroughs have been made, the production cost of semi-synthetic artemisinin remains too high compared to plant extraction (around 400 $/kg).[4]

As the fermentation step produces the byproduct amorphadiene (**AD**), which is formed in high titers (up to 120 g/L),[5] its valorization could increase the market potential of the entire semi-synthetic route and has therefore been the focus of many research works either using chemical or enzymatic approaches.[5,6] To our knowledge, the non-enzymatic conversion of **AD** to artemisinic alcohol **1**, mimicking the biosynthetic pathway (Scheme 1, eq 2) and thereby complementing the final step of the fermentation route, has so far never been realized.[7]

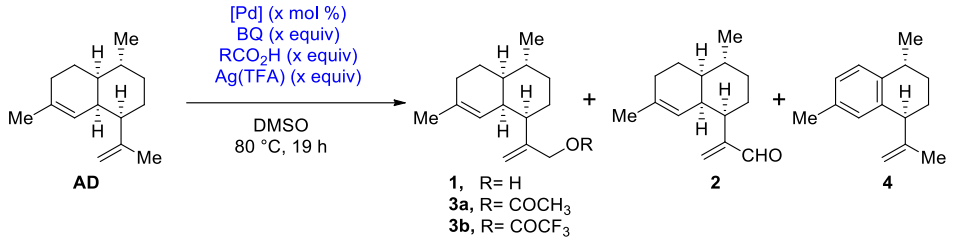
Several methods related to the allylic oxidation or "anti-Wacker" oxidation of terminal olefins have been reported. These methods require a metal catalyst, such as Cu or Pd, a ligand, a base and an oxidant.[8-19] While the process seems to be favored in the case of intracyclic double bonds, achieving high selectivity for terminal disubstitued olefins is highly challenging.[17] Beside this key endeavor, **AD** possesses five allylic positions which can potentially react, and the development of a catalytic system allowing a regioselective allylic oxidation constitutes a synthetic challenge. With this goal in mind, we report herein the development of a regioselective Pd-catalyzed oxidation of **AD** to artemisinic alcohol **1**, a key intermediate in the synthesis of **AA** and artemisinin (Scheme 1, eq 3).

**Scheme 1: a) Current fermentation process to produce AA (eq 1); b) biosynthesis of AA from AD (eq 2), and; c) This work: development of a Pd-catalyzed allylic oxidation of AD to produce AA (eq 3)**




Among the different methods reported, the regioselective oxidation of limonene published by Meier *et al.*[17] using $Pd(OAc)_2$ (15 mol %) and *p*-benzoquinone (BQ, 2 equiv), in DMSO/AcOH at 50 °C for 24 h, appeared to be the most promising method. However, our first attempts to apply the exact literature conditions to **AD** afforded poor reactivity and degradation of **AD**. Heating the reaction mixture at 80 °C for 19 h or performing the reaction under microwave irradiation did not produce **1**. Instead, the tetrahydronaphthalenic derivative **4**[18] was isolated, which corresponds to the oxidation/aromatization of the A ring of **AD.** However, the catalyst turn-over was very low as only 20% of **AD** was converted to compound **4**, and this latter was isolated in 17% yield (Table 1, entry 1). To identify suitable conditions that could produce the regioselective oxidation of the *exo*-cyclic double bond of **AD**, a screening of ligands and other parameters was performed. It is worth mentioning that for the screening of conditions, the conversion of **AD** as well as the yields of the formed products were established by GC/MS analysis of the crude reaction mixture after filtration through a small pad of silica gel, and 1,3,5-trimethoxybenzene being used as an internal standard. Several ligands were tested in an attempt to drive the selectivity towards the oxidation of the *exo*-cyclic double bond, including sulfoxides,[15] 4,5-diazafluoren-9-one (DAFO),[19] and tetrahydrothiophene (THT).[20b] However, in all cases only poor conversion of **AD** was observed. To obtain a higher conversion of **AD**, and to gain a better understanding in the chemical process, a stoichiometric quantity of Pd, *e.g.* $Pd(OAc)_2$ (1.1 equiv) was used, in the presence of BQ (2 equiv), 40 equiv of AcOH, and the reaction was performed in DMSO ($c$ = 0.2 M), at 80 °C for 19 h (Table 1, entry 2). Gratifyingly, under these conditions, even if the conversion of **AD** was moderate (40%), the major compound formed was the desired allylic acetate **3a** (32%), and only traces of the tetrahydronaphthalenic compound **4** were observed. Reducing the quantity of AcOH to 3 equivalents affected negatively the conversion of **AD** (17%), even though the regioselectivity was significantly improved as the desired allylic acetate **3a** was formed in 14% yield together with 3% of artemisinic alcohol **1.** Artemisinic alcohol **1** is presumably formed over the course of the reaction and/or by partial hydrolysis of **3a** during filtration of the crude reaction mixture on a small pad of silica gel (Table 1, entry 3). The replacement of $Pd(OAc)_2$ (1.1 equiv)/AcOH (3 equiv) by $Pd(TFA)_2$ (1.1 equiv)/TFA (3 equiv) resulted in 89% conversion of **AD** and the formation of the allylic trifluoroacetate **3b** (37%) and artemisinic alcohol **1** (28%) along with artemisinic aldehyde **2** (20%) (Table 1, entry 4).

**Table 1. Reactivity of AD in the presence of Pd catalysts and carboxylic acids.**[a]

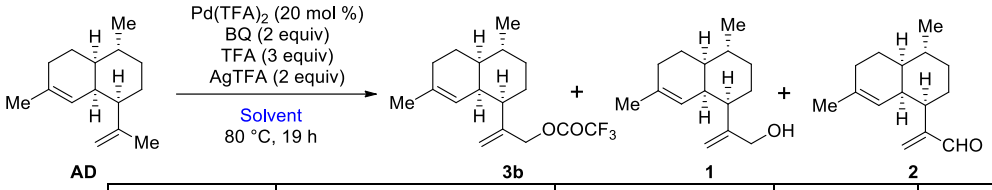



| entry | [Pd] (equiv) | oxidant (equiv) | $RCO_2H$ (equiv) | Ag(TFA) (equiv) | **AD** coversion (%)[b] | **1** or **3a**/**3b** yield (%)[b] | **2** yield (%)[b] | **4** yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (0.15) | BQ (2) | AcOH (40) | 0 | 20 | – | – | 17[c][d] |
| 2 | $Pd(OAc)_2$ (1.1) | BQ (2) | AcOH (40) | 0 | 40 | **3a**, 32 (17)[c] | – | Traces |
| 3 | $Pd(OAc)_2$ (1.1) | BQ (2) | AcOH (3) | 0 | 17 | **1**, 3 **3a**, 14 | – | – |
| 4 | $Pd(TFA)_2$ (1.1) | BQ (2) | TFA (3) | 0 | 89 | **1**, 28 **3b**, 37 | 20 | – |
| 5 | $Pd(TFA)_2$ (0.20) | BQ (2) Ag(TFA) (2) | TFA (3) | 2 | 66 | **1**, 7 **3b**, 41 | 7 | – |

[a] All the reactions were performed on a 0.2 mmol scale of **AD** in DMSO [*c* = 0.2 M]. [b] Determined by GC/MS analysis using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield. [d] Addition of molecular sieves 3 Å.

To enhance the catalytic turn-over, the introduction of a co-oxidant was then investigated. Indeed, the use of silver trifluoroacetate, Ag(TFA),[21] in conjunction with $Pd(TFA)_2$ (20 mol %), BQ (2 equiv) and TFA (3 equiv) proved to be beneficial, providing a 66% conversion of **AD**. The desired allylic trifluoroacetate **3b** was formed in 41% yield and the allylic alcohol **1** was formed in 7% yield along with artemisinic aldehyde **2** (7%) (Table 1, entry 5). With the optimized conditions in hand, [$Pd(TFA)_2$ (20 mol %), BQ (2 equiv), TFA (3 equiv) and Ag(TFA) (2 equiv), at 80 °C for 19 h in DMSO], the influence of the solvent was examined. The replacement of DMSO by $CH_3CN$ induced a better conversion of **AD** (93% *versus* 66%) but the yield in **3b** was decreased (20% *versus* 41%) (Table 2, entries 1 and 2). This result confirmed the role of DMSO in promoting the allylic oxidation toward the selective formation of **3b**/**1**. Different combinations of solvents were screened such as DMSO/$CH_3CN$ (1:1), DMSO/toluene (1:1), and DMSO/THF (1:1) to increase the conversion of **AD** to **3b** and/or **1** (Table 2, entries 3-5). When using a mixture DMSO/$CH_3CN$, the conversion of **AD** was increased from 66%, in pure DMSO, to 75% (Table 2, entry 3). Importantly, the selectivity of the allylic oxidation was improved as the combined yield of **3b** and **1** was increased from 48% to 74% [GC/MS yields: **1** (15%) + **3b** (59%)] (Table 2, entry 3). While DMSO/toluene and DMSO/THF afforded a conversion of **AD** similar to the conversion obtained in pure DMSO, the desired allylic trifluoroacetate **3b** and the allylic alcohol **1** were formed with a global yield of 53% and 58% respectively (Table 2, entries 4 and 5). Thus, the best solvent to be used is a mixture of DMSO/$CH_3CN$ in a ratio 1 to 1. The reaction was next performed on a 0.88 mmol scale in the presence of $Pd(TFA)_2$ (20 mol %), BQ (2 equiv), Ag(TFA) (2 equiv) and TFA (3 equiv) in DMSO/$CH_3CN$ (1:1) at 80 °C for 19 h (Table 3, entry 1). Under these conditions, the GC/MS analysis revealed 70% conversion of **AD** and the formation of **3b** with a yield of 70%. After an aqueous workup, the crude reaction mixture was purified by flash column chromatography on basic $Al_2O_3$, which induced the hydrolysis of **3b**, and **1** was isolated in 46% yield. In an attempt to reach full conversion of **AD**, we investigated the use of higher Ag(TFA) loadings (2, 4 and 6 equiv), in order to regenerate BQ, which is necessary to maintain the Pd(II) oxidation state (Table 3, entries 1–3). Gratifyingly, the use of 6 equivalents of Ag(TFA) led to a full conversion of **AD** and, after purification by chromatography on $Al_2O_3$, the desired allylic alcohol **1** was isolated in 70% yield (Table 3, entry 3).

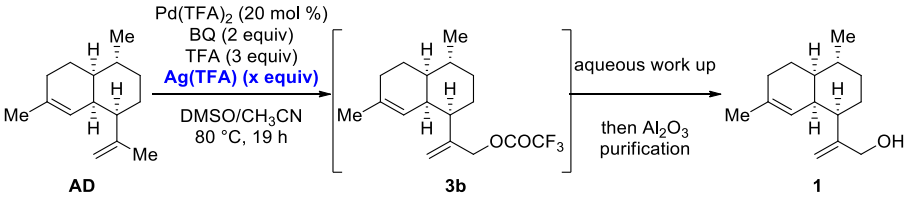
**Table 2. Solvent screening.[a]**




| Entry | Solvent | **AD** conversion (%)[b] | **1** yield (%)[b] | **2** yield **(%)**[b] | **3b** yield (%) [b] |
|---|---|---|---|---|---|
| 1 | DMSO | 66 | 7 | 7 | 41 |
| 2 | $CH_3CN$ | 93 | - | - | 20 |
| 3 | DMSO/$CH_3CN$ (1:1) | 75 | 15 | - | 59 (20)[c] |
| 4 | DMSO/Toluene (1:1) | 59 | 13 | 6 | 40 |
| 5 | DMSO/THF (1:1) | 65 | 8 | 6 | 50 |

[a] All the reactions were performed on a 0.2 mmol scale of **AD** at 0.2 M. [b] Determined by GC/MS analysis using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield.

**Table 3. Ag(TFA) equivalents screening.[a]**




| Entry | Ag(TFA) (equiv) | **AD** conversion (%)[b] | **3b** yield (%)[b] | **1** isolated yield (%)[c] |
|---|---|---|---|---|
| 1[c] | 2 | 70 | 70 | 46 |
| 2 | 4 | 82 | 78 | 56 |
| 3 | 6 | 99 | 94 | 70 [d] |

[a]Otherwise noted, all the reactions were performed on a 0.2 mmol scale of **AD** at 0.2 M. [b]Determined by GC/MS analysis using 1,3,5-trimethoxybenzene as internal standard. [c] After workup and purification on $Al_2O_3$. [d]This experiment was also performed on 0.88 mmol scale producing **1** in 68% yield.

Based on our findings and on literature precedents,[22] we hypothesized that once the Pd pre-catalyst [$Pd(TFA)_2$] is in solution, a [Pd-DMSO] complex is formed and coordinates to **AD** *via* a ligand exchange.[23d] An allylic activation is proposed to afford a $\eta^3$-allylpalladium intermediate which, in the presence of a nucleophile ($CF_3COO^-$), can lead to the desired product and to the concomitant formation of Pd(0). This latter is then oxidized to Pd(II) by BQ in the co-oxidative system, BQ/Ag(TFA). Although a complete understanding of the mechanism and the role of CH3CN have not yet been elucidated, the role of DMSO as a ligand in favor of the allylic oxidation is well accepted.[13-15, 22] In conclusion, the development of a Pd-catalyzed regioselective allylic oxidation of **AD** is described, demonstrating that a non-enzymatic route is possible to access artemisinic alcohol **1** from **AD**. This regioselective oxidation was achieved with a Pd catalytic system, enabling the formation of artemisinic alcohol **1** in 68% isolated yield on 0.88 mmol scale. Our study highlights the key role of DMSO and BQ in combination with Ag(TFA) to achieve this high level of regioselectivity, albeit with a low catalytic turn-over.

As the allylic alcohol **1** was already reported to be oxidized quantitatively into **AA**[7b] and, as this latter was transformed to artemisinin, a regioselective chemical oxidation of **AD** can now be projected as a complimentary pathway to the biosynthetic approach to produce artemisinin from **AD**. We have demonstrated the proof of concept that a palladium-catalyzed regioselective allylic oxidation of **AD** can be achieved to produce the artemisinic alcohol. As this reaction could have a great potential, the optimization of the catalyst loading, as well as the replacement of Ag(TFA) with a low-cost and earth abundant metal are currently under investigations in our laboratories.

## EXPERIMENTAL SECTION

**Materials and Methods:** Reagents were purchased from Aldrich as reagent grade and used without further purification. Reactions were performed in oven-dried glassware under an argon atmosphere. Analytical thin layer chromatography TLC were performed on silica gel plates and visualized either with a UV lamp (254 nm) or using a staining solution (*p*-anisaldehyde or $KMnO_4$). Evaporation of the solvents *in vacuo* was performed at 25-35 °C and 900-10 mbar. Flash chromatography was performed on silica gel (Merck-Kieselgel 60, 230 400 mesh) or on aluminum oxide 90

standardized Merck, Brockmann activity: II-III. Isolated yields refer to spectroscopically and chromatographically pure compounds that were dried under vacuum (0.1-0.05 mbar) before analytical characterization. $^1$H NMR spectra were recorded on a Bruker AVANCE 400 at 400 MHz and data are reported as follows: chemical shifts in ppm with the solvent peak as internal standard ($CDCl_3$, δ 7.26 ppm), multiplicity (s = singulet, d = doublet, t = triplet, q = quartet, quint = quintuplet, hex = hexuplet, hept = heptuplet, m = multiplet or overlap of non-equivalent resonances, br = broad). $^{13}$C NMR spectra were recorded on a Bruker AVANCE 400 at 100 MHz and data are reported as follows: chemical shifts in ppm with the solvent peak as internal standard ($CDCl_3$ at 77.1 ppm). Coupling constants J were measured in Hertz. Infrared (IR) spectra were recorded on a Bruker TENSORTM 27 (IRFT) and wave numbers are indicated in cm$^{-1}$. Mass spectra with electronic impact (MS-EI) were recorded with a Shimadzu GCMS-QP 2010S (70 eV). High-resolution mass spectrometry (HRMS) was obtained on a LTQ Orbitrap-XL-ETD, Thermo Scientific in the ESI mode. Amorphadiene was synthesized from dihydroartemisinic acid.[23]

**General procedure for screening experiments:** *Anhydrous solvents and oven-dried glassware were used and the reactions were performed under an argon atmosphere. Heating at 80 °C was achieved with an oil bath.*

Amorphadiene (0.2 mmol, 1 equiv), [Pd] (x equiv), *p*-benzoquinone (x equiv) and, when specified Ag(TFA) (x equiv), were sequentially charged in a reaction vessel. The solids were dissolved in the indicated solvent system [c = 0.2 M] and, AcOH or TFA (x equiv) was added to the reaction mixture. The reaction mixture was stirred at 80 °C for 19 h, allowed to cool to rt, and then diluted with EtOAc (2 mL). The organic phase was washed with brine (3 x 5 mL), dried over MgSO4, filtered and evaporated under reduced pressure. The crude was filtered through a small pad of silica gel for GC/MS analysis.

**Allylic acetate 3a** (conditions: Table 1, entry 6)

Amorphadiene (45 mg, 0.22 mmol, 1.0 equiv), $Pd(OAc)_2$ (54 mg, 0.24 mmol, 1.1 equiv), and *p*-benzoquinone (48 mg, 0.44 mmol, 2.0 equiv) were sequentially added in the reaction vessel. The solids were dissolved in a mixture of DMSO (0.5mL) and AcOH (0.5 mL, 8.7 mmol, 40 equiv) and the resulting solution was stirred at 80 °C for 19 h. The mixture was cooled to rt, and then diluted with EtOAc (2 mL). The organic phase was washed with brine (3 x 5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel (gradient of elution: hexanes to hexanes/EtOAc = 94:6) to give **3a** as a yellow oil (10 mg, 17%). $R_f$ = 0.56 ($SiO_2$; hexane/EtOAc = 4:1); $[\propto]_D^{25} - 20$ (c 0.51, $CHCl_3$); IR (ATR): $\tilde{\nu}$ = 2923, 1712, 1449, 1374, 1231, 1164, 1039 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 5.19 (br s, 1H), 5.03 (br s, 1H), 4.91 (br s, 1H), 4.59 (d, $J_{AB}$ = 13.2 Hz, 1H), 4.51 (d, $J_{AB}$ = 13.2 Hz, 1H), 2.49 (m, 1H), 2.19 (m, 1H), 2.09 (s, 3H), 1.98 – 1.66 (m, 4H), 1.59 (br s, 3H), 1.55 – 1.28 (m, 5H), 0.99 ($ddd_{app}$, J = 20.4, 12.6, 3.4 Hz, 1H), 0.89 ppm (d, J = 6.4 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 171.0, 146.1, 135.3, 120.3, 112.6, 66.7, 43.9, 41.8, 37.8, 35.4, 27.9, 26.5, 25.89, 25.79, 23.8, 21.2, 19.9 ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{26}O_2Na$ 285.1825; Found 285.1829.

**Allylic trifluoroacetate 3b** (Conditions: Table 2, entry 3)

Amorphadiene (45 mg, 0.22 mmol, 1.0 equiv), $Pd(TFA)_2$ (15 mg, 0.044 mmol, 20 mol %), *p*-benzoquinone (48 mg, 0.44 mmol, 2.0 equiv), and Ag(TFA) (93.3 mg, 0.44 mmol, 2.0 equiv) were sequentially added in a reaction vessel. The solids were dissolved in DMSO (0.5 mL) and $CH_3CN$ (0.5 mL), and anhydrous TFA (50 μL, 0.66 mmol, 3.0 equiv) was added to the mixture. The reaction mixture was stirred at 80 °C for 19 h, cooled to rt, and then diluted with EtOAc (2 mL). The organic phase was washed with brine (3 x 5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was filtered through a small pad of silica gel before GC/MS analysis (GC/MS yield = 59%). Purification by flash column chromatography on silica gel (gradient of elution: hexanes to hexanes/EtOAc = 94:6) to afford **3b** as a yellow oil (14 mg, 20%); the lowest yield of **3b** compared to the yield by GC/MS is due to the partial hydrolysis of **3b** on silica gel.

$R_f$ = 0.56 ($SiO_2$; hexane/EtOAc = 4:1); $[\propto]_D^{25} + 2.0$ (c 0.58, $CHCl_3$); IR (ATR): $\tilde{\nu}$ = 2923, 1785, 1649, 1449, 1380, 1338, 1220, 1140, 908 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 5.28 (br s, 1H), 5.03 (br s, 1H), 5.00 (br s, 1H), 4.84 (d, $J_{AB}$ = 12.8 Hz, 1H), 4.79 (d, $J_{AB}$ = 12.8 Hz, 1H), 2.48 (br s, 1H), 2.18 (m, 1H), 1.97 – 1.67 (m, 4H), 1.60 (br s, 3H), 1.58 – 1.26 (m, 5H), 1.02 (br $ddd_{app}$, J = 25.6, 12.4, 3.3, 1H), 0.90 ppm (d, J = 6.3 Hz, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 157.4 (q, $^2J_{C-F}$ = 42 Hz), 144.0, 135.8, 119.8, 114.9, 114.7 (q, $^1J_{C-F}$ = 286), 69.9, 43.7, 41.7, 37.8, 35.2, 27.8, 26.5, 25.8, 25.7, 23.8, 19.9 ppm; $^{19}$F NMR (376 MHz, $CDCl_3$) δ -74.97 ppm; GC/MS: m/z (%): 316 [9, $[M]^+$], 202 (14), 187 (6), 145 (9), 132 (22), 121 (100), 105 (15), 93 (37), 79 (25), 55 (15). HRMS (ESI) *m/z*: $[M+H]^+$ Calcd $C_{17}H_{24}F_3O_2$ 317.1723; Found 317.1723.

**Artemisinic alcohol, 1**

Amorphadiene (45 mg, 0.22 mmol, 1.0 equiv), $Pd(TFA)_2$ (15 mg, 0.044 mmol, 0.2 equiv) *p*-benzoquinone (48 mg, 0.44 mmol, 2.0 equiv) and Ag(TFA) (291 mg, 1.32 mmol, 6.0 equiv) were sequentially charged to a reaction vessel. The solids were dissolved in DMSO (0.6 mL) and $CH_3CN$ (0.6 mL), and anhydrous TFA (50 μL, 0.66 mmol, 3.0 equiv) was added to the reaction mixture. The reaction mixture was stirred at 80 °C. After 19 h, the reaction mixture was cooled to rt, and then diluted with EtOAc (2 mL). The organic phase was washed with brine (3 x 5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Aluminum oxide was added to the residue and the mixture was suspended in $CH_2Cl_2$ (10 mL). After filtration, the solvent was evaporated under reduced pressure and the resulting mixture was purified by flash column chromatography on $Al_2O_3$ using a gradient of elution from pure hexanes to hexanes/EtOAc (94:6) to give **1** as a yellow oil (34 mg, 70%). The reaction was also scaled-up to 0.88 mmol affording **1** in 68% yield**.**

$R_f$ = 0.32 ($SiO_2$; hexane/EtOAc = 4:1); $[\propto]_D^{25} - 9$ (c 1.50, $CHCl_3$); IR (ATR): $\tilde{\nu}$ = 3387, 2920, 2867, 2159, 1697, 1647, 1447, 1377, 1171, 1046, 899 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 5.19 ($t_{app}$, J= 1.2 Hz, 1 H), 5.06 (br s, 1 H), 4.84 (br s, 1 H), 4.12 (br s, 2 H), 2.49 (br s, 1 H), 2.20 (m, 1 H), 1.99 – 1.65 (m, 4 H), 1.59 (br s, 3 H), 1.55 – 1.27 (m, 5 H), 1.00 ($ddd_{app}$, J = 24.9, 12.4, 3.5, 1 H), 0.88 ppm (d, J = 6.3 Hz, 3 H), OH signal not observed; $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 151.3, 135.2, 120.6, 110.0, 65.8, 43.6, 41.8, 37.9, 35.5, 27.9, 26.6, 25.95, 25.84, 23.8, 19.9 ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{24}ONa^+$ 243.1719; Found 243.1729.

**(1R,4S)-1,6-Dimethyl-4-(prop-1-en-2-yl)-1,2,3,4-tetrahydronaphthalene, 4**[18]

Amorphadiene (45 mg, 0.22 mmol, 1.0 equiv), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol, 0.15 equiv) molecular sieves 3 Å (40 mg), *p*-benzoquinone (48 mg, 0.44 mmol, 2.0 equiv) were sequentially charged in a reaction vessel. The solids were dissolved in DMSO (0.5 mL), and AcOH (0.5 mL, 8.7 mmol, 40 equiv) and the mixture was stirred at 80 °C for 19 h. The mixture was cooled to rt, and then diluted with EtOAc (2 mL). The organic phase was washed with brine (3 x 5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting mixture was purified by flash column chromatography on silica gel (hexanes). Compound **4** was isolated as a yellow oil (7.5 mg, 17%).

$R_f$ = 0.75 ($SiO_2$; hexanes); IR (ATR): $\tilde{\nu}$ = 2955, 1427, 1376, 1248, 1112 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 7.9 Hz, 1H), 6.97 (dd, J = 7.9 Hz, 1.3 Hz, 1H), 6.91 (d, 0.7 Hz, 1H), 4.90 (m, 1H), 4.65 (m, 1H), 3.50 (dd, J = 7.6, 6.4 Hz, 1H), 2.85 (m, 1H), 2.27 (s, 3H), 2.03 – 1.90 (m, 2H), 1.80 (m, 1H), 1.74 (s, 3H), 1.45 (m, 1H), 1.28 ppm (d, J = 6.9 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz,

$CDCl_3$) δ 149.4, 139.6, 137.7, 129.4, 127.5, 127.0, 113.5, 48.1, 32.6, 30.4, 26.7, 22.7, 21.1, 20.9, 19.7 ppm.

**Artemisinic aldehyde 2**

Amorphadiene (45 mg, 0.22 mmol, 1.0 equiv), $Pd(OAc)_2$ (54 mg, 0.24 mmol, 1.1 equiv), *p*-benzoquinone (48 mg, 0.44 mmol, 2.0 equiv) were sequentially charged in a reaction vessel. The solids were dissolved in DMSO (1 mL) and then anhydrous TFA (50 µL, 0.66 mmol, 3.0 equiv) was added. The reaction was stirred at 80 °C for 19 h, allowed to cool to rt, and then diluted with EtOAc (2 mL). The organic phase was washed with brine (3 x 5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting mixture was purified by flash column chromatography on silica gel (gradient of elution from hexanes to hexanes/EtOAc = 94:6) to afford artemisinic aldehyde **2** as a yellow oil (10 mg, 21%).

$R_f$ = 0.78 ($SiO_2$; Hexanes/EtOAc = 9:1); $[\propto]_D^{25} + 9$ (c 1.1, $CHCl_3$); IR (ATR): $\tilde{\nu}$ = 2920, 2867, 1691, 1447, 1377, 1249, 1093, 940 $cm^{-1}$;

$^1H$ NMR (400 MHz, $CDCl_3$) δ 9.52 (br s, 1H), 6.18 (br s, 1H), 6.13 (br s, 1H), 4.88 (br s, 1H), 2.71 (m, 1H), 2.51 (br s, 1H), 1.97 – 1.64 (m, 4H), 1.58 (br s, 3H), 1.53 – 1.19 (m, 5H), 1.05 (m, 1H), 0.90 ppm (d, J = 6.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.6, 152.3, 135.0, 134.5, 120.0, 41.1, 39.4, 37.2, 35.0, 27.4, 26.5, 25.28, 25.22, 23.6, 19.6; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{22}ONa$ 241.1563; Found: 241.1562.

## ASSOCIATED CONTENT

The Supporting Information is available free of charge at https://pubs.acs.org/doi/ .

Detailed experimental procedures, characterization data, and spectra copies of $^1H$ and $^{13}C$ NMR (PDF).

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### Authors Contributions

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) Hale, V.; Keasling, J. D.; Renninger, N.; Diagana, T. T. Microbially derived artemisinin: a biotechnology solution to the global problem of access to affordable antimalarial drugs. *Am. J. Trop. Med. Hyg.* **2007**, *77*, 198–202.

(2) (a) Paddon, C. J.; Westfall, P. J.; Pitera, D. J.; Benjamin, K.; Fisher, K.; McPhee, D.; Leavell, M. D.; Tai, A.; Main, A.; Eng, D.; Polichuk, D. R.; Teoh, K. H.; Reed, D. W.; Treynor, T.; Lenihan, J.; Fleck, M.; Bajad, S.; Dang, G.; Dengrove, D.; Diola, D.; Dorin, G.; Ellens, K. W.; Fickes, S.; Galazzo, J.; Gaucher, S. P.; Geistlinger, T.; Henry, R.; Hepp, M. H.; Horning, T.; Iqbal, T.; Jiang, H.; Kizer, L.; Lieu, B.; Melis, D.; Moss, N.; Regentin, R.; Secrest, S.; Tsuruta, H.; Vazquez, R.; Westblade, L. F.; Xu, L.; Yu, M.; Zhang, Y.; Zhao, L.; Lievense, J.; Covello, P. S.; Keasling, J. D.; Reiling, K. K.; Renninger, N. S.; Newman, J. D. High-level semi-synthetic production of the potent antimalarial artemisinin, *Nature* **2013**, *496*, 528-533 and references therein. (b) Li, C.; Li, J.; Wang, G.; Li, X. Heterologous biosynthesis of artemisinic acid in *Saccharomyces cerevisiae*, *J. Appl. Microbiol*. **2016**, *120*, 1466-1478 and references therein; (c) Kung, S. H.; Lund, S.; Murarka, A.; McPhee, D.; Paddon, C. J. Approaches and recent developments for the commercial production of semi-synthetic artemisinin, *Front Plant Sci*. **2018**, *9*, 87-94 and references therein.

(3) Works relating to the improvement of the chemical synthesis of artemisinin: (a) Feth, M. P.; Rossen, K.; Burgard, A. Pilot plant PAT approach for the diastereoselective diimide reduction of artemisinic acid, *Org. Process Res. Dev*. **2013**, *17*, 282-293; (b) Horváth, Z.; Horosanskaia, E.; Weon Lee, J.; Lorenz, H.; Gilmore, K.; Seeberger, P. H.; Seidel-Morgenstern, A. Recovery of artemisinin from a complex reaction mixture using continuous chromatography and crystallization, *Org. Process Res. Dev*. **2015**, *19*, 624-634; (c) Fan, X.; Sans, V.; Yaseneva, P.; Plaza, D. D.; Williams, J.; Lapkin, A. Facile stoichiometric reductions in flow: an example of artemisinin, *Org. Process Res. Dev*. **2012**, *16*, 1039-1042; (d) Lee, D. S.; Amara, Z.; Clark, C.; Xu, Z.; Zeyuan, K.; Bruce, M.; Morvan, H.; Pickering, S.; Poliakoff, M.; George, M. W. Continuous photo-oxidation in a vortex reactor: Efficient operations using air drawn from the laboratory, *Org. Process Res. Dev*. **2017**, *21*, 1042-1050; (e) Amara, Z.; Bellamy, J. F. B.; Horvath, R.; Miller, S. J.; Beeby, S.; Burgard, A ; Rossen, K.; Poliakoff, M.; George, M. W. Applying green chemistry to the photochemical route to artemisinin, *Nat. Chem*. **2015**, *7*, 489-495; (f) Tambosco, B.; Segura, K.; Seyrig, C.; Cabrera, D.; Port, M.; Ferroud, C.; Amara, Z. Outer-sphere effects in visible-light photochemical oxidations with immobilized and recyclable ruthenium bipyridyl salts, *ACS Catal*. **2018**, *8*, 4383-4389. (g) Lévesque, F.; Seeberger, P. H. Continuous-flow synthesis of the anti-malaria drug artemisinin, *Angew. Chem., Int. Ed.* **2012**, *51*, 1706-1709. (h) Triemer, S.; Gilmore, K.; Vu, G. T.; Seeberger, P. H.; Seidel-Morgenstern, A. Literally green chemical synthesis of artemisinin from plant extracts, *Angew. Chem. Int. Ed*. **2018**, *57*, 5525-5528.

(4) Peplow, M. Synthetic malaria drug meets market resistance, *Nature* **2016,** *530*, 389-390.

(5) Westfall, P. J.; Pitera, D. J.; Lenihan, J. R.; Eng, D.; Woolard, F. X.; Regentin, R. Production of amorphadiene in yeast, and its conversion to dihydroartemisinic acid, precursor to the antimalarial agent artemisinin. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, E111-E118.

(6) (a) Reiling, K. K.; Renninger, N. S.; McPhee, D. J.; Fisher, K. J. .; Ockey, D. A. Conversion of amorpha-4,11-diene to artemisinin and artemisinin precursors. US2006270863 (A1), 2006. (b) Schwertz, G.; Zanetti, A.; Nascimento de Oliveira, M.; Gomez Fernandez M. A., Amara, Z.; Cossy, J. Chemo- and diastereoselectivity hydrosilylation of amorphadiene toward the synthesis of artemisinin, *J. Org. Chem.* **2020**, *85*, 9607-9613. (c) Zanetti, A.; Chaumont-Olive, P.; Schwertz, Fernandez M. A.; Amara, Z.; Cossy, J. Crystallization-Induced Diastereoisomer Transformation of Dihydroartemisinic Aldehyde with the Betti Base. *Org. Process Res. Dev.* **2020**, *24*, 850-855.

(7) Brown, G. D. The biosynthesis of artemisinin (Qinghaosu) and the photochemsitry of Artemisia annua L. (Qinghao), *Molecules* **2010**, *15*, 7603-7698.

(8) Dong, J. J.; Browne, W. R.; Feringa, B. L. Palladium-catalyzed anti-Markovnikov oxidation of terminal alkenes, *Angew. Chem., Int. Ed*. **2015**, *54*, 734-744.

(9) Ning, X.-S.; Wang, M.-M.; Yao, C.-Z.; Chen, X.-M.; Kang, Y.-B. *n*-Butyl nitrite: organic redox cocatalyst for aerobic aldehyde-selective Wacker-Tsuji oxidation, *Org. Lett.* **2016**, *18*, 2700-2703.

(10) Kim, K. E.; Li, J.; Grubbs, R. H.; Stoltz, B. M. Catalytic Anti-Markovnikov transformations of hindered terminal alkenes enabled by aldehyde-selective Wacker-type oxidation, *J. Am. Chem. Soc.* **2016**, *138*, 13179-13182.

(11) Zhang, G.; Hu, X.; Chiang, C.-W.; Yi, H.; Pei, P.; Singh, A. K.; Lei, A. Anti-Markovnikov oxidation of β-alkyl styrenes with H2O as the terminal oxidant, *J. Am. Chem. Soc.* **2016**, *138*, 12037-12040.

(12) Bäckvall, J. E.; Gogoll, A. Evidence for (π-allyl)palladium(II)(quinone) complexes in the palladium-catalyzed 1,4-diacetoxylation of conjugated dienes, *Tetrahedron Lett.* **1988**, *29*, 2243-2246.

(13) Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S. Ligand-promoted palladium-catalyzed aerobic oxidation reactions, *Chem. Rev.* **2018**, *118*, 2636-2679.

(14) Liron, F.; Oble, J.; Lorion, M. M.; Poli, G. Direct Allylic functionalization through Pd-catalyzed C-H activation. *Eur. J. Org. Chem.* **2014**, *2014*, 5863-5883.

(15) Chen, M. S.; White, M. C. A Sulfoxide-promoted, catalytic method for the regioselective synthesis of allylic acetates from monosubstituted olefins via C−H oxidation *J. Am. Chem. Soc.* **2004**, *126*, 1346-1347.

(16) Kitching, W.; Rappoport, Z.; Winstein, S.; Young, W. G. Allylic oxidation of olefins by palladium acetate, *J. Am. Chem. Soc.* **1966**, *88*, 2054-2055.

(17) von Czapiewski, M.; Meier, M. A. R. Regioselective catalytic acetoxylation of limonene, *Catal. Sci. Technol.* **2014**, *4*, 2318-2325.

(18) Ramaiah, P.; Rao, A. S. Synthesis of (+/_)-cis-Calamenene. *Synth. Commun.* **1989**, *19*, 932-942.

(19) Litman, Z. C.; Sharma, A.; Hartwig, J. F. Oxidation of hindered allylic C–H Bonds with applications to the functionalization of complex molecules, *ACS Catal.* **2017**, *7*, 1998-2001.

(20) a) Henderson, W. H.; Check, C. T.; Proust, N.; Stambuli, J. P. Allylic oxidations of terminal olefins using a palladium thioether catalyst, *Org. Lett.* **2010**, *12*, 824-827. b) Le C. Q.; Kunchithapatham, K.; Henderson, W. H.; Check, C. T.; Stambuli, J. P. A survey of sulfide ligands for allylic C-H oxidations of terminal olefins, *Chem. Eur. J.* **2013**, *19*, 11153-1157.

(21) [Cu(I)] and [Cu(II)] metal salts were tested but no improvement was observed. Several [Ag] salts were also screened and only Ag(OAc) and Ag(TFA) afforded improved conversion, with the latter being better.

(22) (a) Piera, J.; Bäckvall, J. E. Catalytic Oxidation of Organic Substrates by Molecular Oxygen and Hydrogen Peroxide by Multistep Electron Transfer—A Biomimetic Approach, *Angew. Chem. Int. Ed.* **2008**, *47*, 3506 – 3523 (b) Gigant, N.; Bäckvall, J. E. Synthesis of Conjugated Dienes via a Biomimetic Aerobic Oxidative Coupling of Two Cvinyl-H Bonds. *Chem. Eur. J.* **2013**, *19*, 10799 – 10803. (c) Gigant, N.; Bäckvall, J. E. Aerobic Double Dehydrogenative Cross Coupling between Cyclic Saturated Ketones and Simple Arenes. *Chem. Eur. J.* **2014**, *20*, 5890 – 5894. (d) Diao, T.; White, P., Guzei, ; Stahl, S. S. Characterization of DMSO coordination to palladium(II) in solution and insights into aerobic oxidation catalyst, $Pd(DMSO)_2(TFA)_2$, *Inorg. Chem.* **2012**, *51*, 11898-11909. (e) Moon, Y.; Kwon, D.; Hong, S. Palladium-Catalyzed Dehydrogenation/Oxidative Cross-Coupling Sequence of β-Heteroatom-Substituted Ketones *Angew. Chem. Int. Ed.* **2012**, *51*, 11333 –11336.

(23) Schwertz, G.; Zanetti, A.; Nascimento de Oliveira, M.; Gomez Fernandez M. A.; Dioury, F.; Cossy, J.; Amara, Z. Synthesis of amorpha-4,11-diene from dihydroartemisinic acid. *Tetrahedron* **2019**, *75*, 743-748.

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