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Markovnikov Wacker-Tsuji Oxidation of Allyl(hetero)arenes and Application in a One-Pot Photo-Metal-Biocatalytic Approach to Enantioenriched Amines and Alcohols

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Abstract: The Wacker-Tsuji aerobic oxidation of various allyl(hetero)arenes under photocatalytic conditions to form the corresponding methyl ketones is presented. By using a palladium complex [$PdCl_2(MeCN)_2$] and the photosensitizer [Acr-Mes]ClO_4 in aqueous medium and at room temperature, and by simple irradiation with blue led light, the desired carbonyl compounds were synthesized with high conversions (>80%) and excellent selectivities (>90%). The key process was the transient formation of Pd nanoparticles that can activate oxygen, thus recycling the Pd(II) species necessary in the Wacker oxidative reaction. While light irradiation was strictly mandatory, the addition of the photocatalyst improved the reaction selectivity, due to the formation of the starting allyl(hetero)arene from some of the obtained by-products, thus entering back in the Wacker-Tsuji catalytic cycle. Once optimized, the oxidation reaction was combined in a one-pot two-step sequential protocol with an enzymatic transformation. Depending on the biocatalyst employed, i.e. an amine transaminase or an alcohol dehydrogenase, the corresponding (*R*)- and (*S*)-1-arylpropan-2-amines or 1-arylpropan-2-ols, respectively, could be synthesized in most cases with high yields (>70%) and in enantiopure form. Finally, an application of this photo-metal-biocatalytic strategy has been demonstrated in order to get access in a straightforward manner to selegiline, an anti-Parkinson drug.

Keywords: Wacker-Tsuji oxidation; photocatalysis; palladium chemistry; biocatalysis; sequential transformations

Introduction

Wacker-Tsuji oxidation is probably one of the most studied transformations in organic chemistry due to its relevance, since it affords carbonyl compounds from readily available alkenes. This reaction, discovered by Smidt and co-workers at Wacker Chemie company at late 50s,[1] is based on the use of a palladium(II) salt as catalyst, which is reduced into Pd(0), thus requiring the presence of a copper(II) salt under aerobic and acidic conditions to provide the desired compounds to a large extent.[2] Under these conditions, the Markovnikov addition of water is usually achieved,[3] affording the corresponding methyl ketones when terminal alkenes are employed as substrates. However, soon it became clear that the utilization of Cu(II) in a catalytic or stoichiometric amount produced undesired effects such as larger quantities of waste and lower selectivities and atom efficiencies, accompanied by the use of toxic organic co-solvents under harsh reaction conditions. In this field, important efforts have been carried out in order to develop more efficient and safer strategies to replace the copper(II) salt. Hence, it has been described the use of other co-oxidants including peroxides,[4] organic molecules such as benzoquinone,[5] *tert*-butyl nitrite,[6] hypervalent iodine atoms,[5c,7] or inorganic salts,[8] among others. Never-

theless, all of them present serious drawbacks since at least stoichiometric amounts of these reagents are required.

The employment of oxygen as final electron acceptor to recycle the catalytically active Pd(II) species releasing hydrogen peroxide or water as co-product is the best choice from an environmental point of view. Unfortunately, this aerobic transformation usually requires harsh conditions (high oxygen pressures and elevated temperatures), polar solvents with high boiling points such as dimethylsulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF) or *N*,*N*-dimethylacetamide (DMA), and the addition of ligands, to avoid Pd(0) deactivation due to precipitation as palladium black.[9] In this context, it is known that soluble Pd(0) complexes are in equilibrium with (soluble) palladium nanoparticles (NPs) before aggregation, acting as reservoir of catalytically active palladium species as demonstrated in cross-coupling reactions.[10] Stabilized or immobilized Pd NPs are indeed excellent catalysts, which have been applied to different transformations including cross-coupling reactions,[11] reductions and hydrogenations[12] or alcohol oxidations.[13]

The fact that palladium NPs are the catalytically active species in the aerobic Wacker oxidation of olefins has been disclosed decades ago,[14] and finally demonstrated by applying them in this oxidative reaction.[15] The pioneering contribution of Ishida, Tokunaga and co-workers demonstrated that the Wacker oxidation of various styrene compounds into the corresponding acetophenones was catalyzed by immobilized Pd NPs on ZrO_2, and also by soluble Pd(0) complexes under both co-catalyst and acid-free conditions at 80 °C and 2 atm of oxygen, implying the formation of catalytically active NPs.[16] Doris and Namboothiri groups have also shown that supported Pd NPs can catalyze the same reaction in the presence of CuCl under very mild reaction conditions.[17]

In a continuous search for more sustainable chemical processes, photocatalysis has emerged, especially in the last two decades, as a powerful tool that can be applied to the selective synthesis of valuable organic compounds.[18] Thus, visible-light is used to initiate different organic transformations under very mild conditions through single-electron transfer (SET) or energy-transfer (EnT) mechanisms, depending on the photocatalyst and reagents employed. Obviously, redox processes can be largely influenced by light irradiation, providing a unique reaction environment, affecting to the redox state of the chemical species involved. In metal-catalyzed methodologies, the addition of a photosensitizer has allowed the design of novel transformations usually under mild conditions due to the cooperative action between the photo- and the metal catalysts, but the direct activation of soluble metal complexes under light irradiation is also possible.[19] Particularly the photoactivation of Pd complexes is a well-established method to mediate C–C bond coupling reactions generally via one electron redox chemistry.[20] Also, immobilized Pd NPs on photosensitive materials such as TiO_2 or graphitic carbon nitride (g-C_3N_4), or in combination with an external photocatalyst, have promoted different transformations including water splitting,[21] hydrogen peroxide production,[22] or radical C–C bond formation.[23]

In the last years, the synthesis of carbonyl compounds starting from alkenes has been achieved under photocatalyzed conditions. For instance, Lei and co-workers described the anti-Markovnikov addition of water to alkenes combining 9-mesityl-10-methylacridinium perchlorate ([Acr-Mes]ClO_4) as SET photosensitizer and a cobalt complex at room temperature using blue led light in a mixture of acetonitrile (MeCN):water (10:1 *v*/*v*), providing the desired carbonyl compounds through a radical mechanism.[24] Later, Fabry *et al.* developed the Wacker-Tsuji oxidation of various terminal alkenes to produce the corresponding methyl ketones, by mixing a palladium(II) salt and [Ir(ppy)$_2$(bpy)]PF_6 as SET photocatalyst under white light in a DMF:H_2O (6:1 *v*/*v*) mixture at 120 °C. In this particular case, the photosensitizer reoxidized the palladium center transferring the electrons to the oxygen and closing the oxidative cycle.[25] It must be emphasized that the addition of the photocatalyst was strictly necessary.

Due to the mildness of both synthetic strategies, the combination of photo- and biocatalytic methodologies has been successfully implemented, providing efficient and selective pathways to valuable derivatives in a one-pot sequential or cascade fashion.[26] Examples of photocatalyzed processes involving the action of alcohol dehydrogenases (ADHs)[27] or amine transaminases (ATAs)[27,28] towards the synthesis of enantioenriched alcohols and amines, respectively, can be highlighted.[29]

Enantiopure 1-(hetero)arylpropan-2-ols and 1-(hetero)arylpropan-2-amines (amphetamines) are privileged motifs with a wide spectrum of biological properties, and have also been employed as precursors of pharmaceutical compounds for the treatment of, e. g. obesity (Benzphetamine), Parkinson (Selegiline), the attention deficit hyperactive disorder (Dextroamphetamine and Lisdexamfetamine), and asthma (Formoterol). These high-added value derivatives have been obtained following different synthetic approaches including non-biocatalytic[30] and enzymatic[31] syntheses. Also, multienzymatic – deracemization,[32] amination of racemic alcohols[33] or dynamic kinetic resolution processes[34] – and chemoenzymatic – organo-bio[35] or metal-bio[36] – cascade transformations have allowed the enantioselective synthesis of these derivatives.

In this field, two remarkable contributions have been disclosed involving a Wacker-type oxidation of alkene substrates in a multi-step sequence to obtain 1-

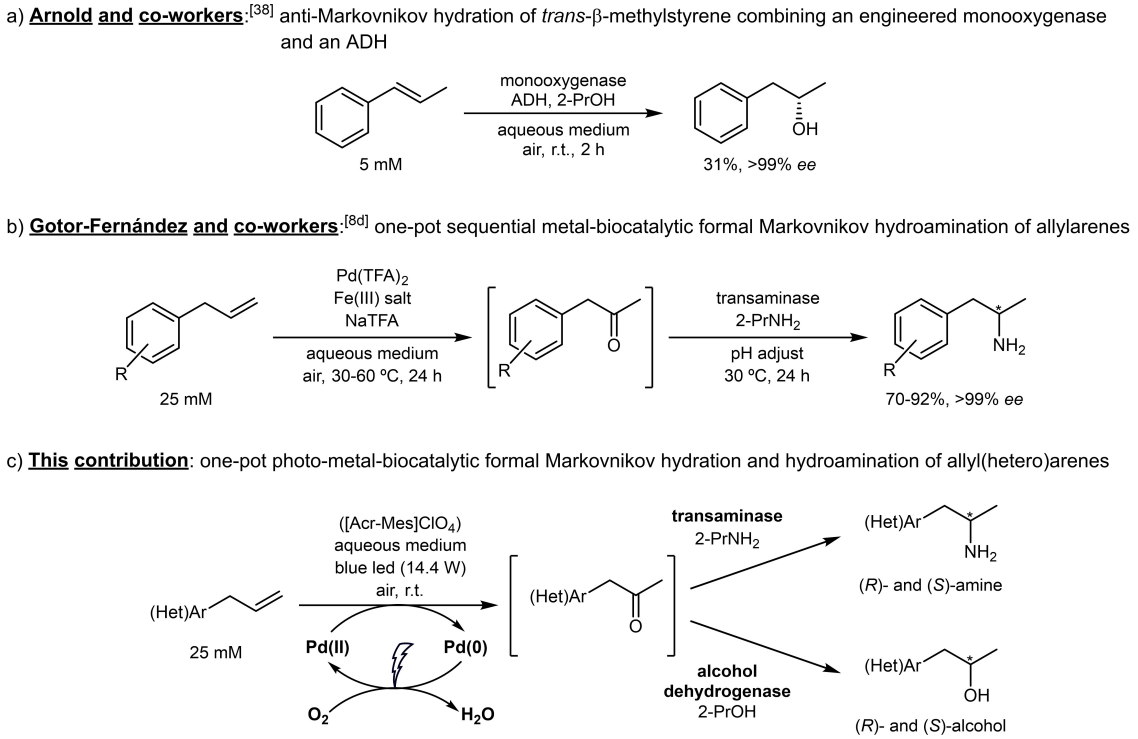
arylpropan-2-ols or 1-arylpropan-2-amines in aqueous medium under aerobic conditions.[37] Arnold and co-workers reported the anti-Markovnikov oxidation of a series of alkenes catalyzed by an engineered P450 monooxygenase enzyme followed by an ADH-catalyzed reduction to afford the enantioenriched alcohols (Scheme 1a). Among the different substrates included in this study, *trans*-β-methylstyrene provided 1-phenylpropan-2-ol although at low extent.[38] Our research group recently developed the stereoselective synthesis of a family of 1-arylpropan-2-amines in good yields starting from allylarenes following a sequential strategy which involved a Wacker-Tsuji oxidation and a biotransamination step (Scheme 1b).[8d] Interestingly, palladium(II) trifluoroacetate and an iron(III) salt, used as co-oxidant, in the presence of sodium trifluoroacetate efficiently catalyzed the formation of the ketone intermediates at 30–60 °C, which were subsequently aminated by an amine transaminase. With these precedents, here the development of the Wacker-Tsuji oxidation of various allyl(hetero)arenes is described under very simple and mild photocatalytic conditions, in addition to its integration with a stereoselective biocatalyzed process to synthesize in a straightforward manner valuable enantiopure *sec*-alcohols or primary amines (Scheme 1c).

Results and Discussion

As a first step, commercially available allylbenzene (**1a**, 25 mM) was considered as the model substrate to optimize a light-driven Wacker transformation. Hence, various Pd catalysts and photosensitizers were tested (Table 1) to obtain 1-phenylpropan-2-one (**2a**) under blue light irradiation.

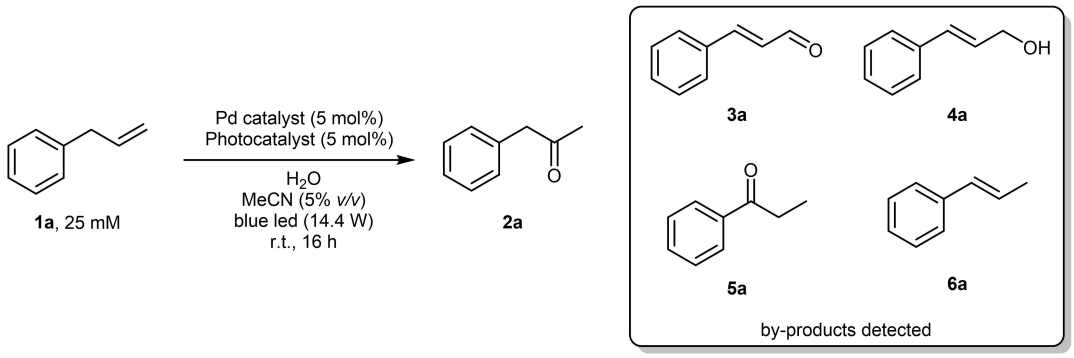
Based on our previous experience developing this reaction,[8d] we performed the photocatalyst screening under blue led activation using $Pd(TFA)_2$ as catalyst in a water:MeCN (95:5 *v/v*) mixture (entries 1–5) at r.t. These conditions were selected as they can be compatible with a second biocatalytic reaction. Among the different pairs screened, $Pd(TFA)_2$/$[Acr\text{-}Mes]ClO_4$ afforded the highest conversion into the desired product **2a** (34%) after 16 h. $[Acr\text{-}Mes]ClO_4$ is a SET sensitizer belonging to the acridinium family,[39] and it can promote or mediate Wacker-type transformations activating alkene derivatives[24,40] or oxygen to form radical anion superoxide.[39a,41]

Cinnamaldehyde (**3a**), cinnamyl alcohol (**4a**), propiophenone (**5a**), and a non-oxygenated compound such as *trans*-β-methylstyrene (**6a**) were detected as by-products of these transformations, although at very low extent. Next, different Pd(II) and Pd(0) complexes were examined under the same conditions (entries 6–11), finding the best results with $PdCl_2(MeCN)_2$, which gave **2a** in a very high conversion (75%). It was



Scheme 1. Chemo- and multienzymatic approaches to obtain enantioenriched 1-(hetero)arylpropan-2-ols or 1-(hetero)arylpropan-2-amines through multi-step reactions starting from alkene derivatives.

Table 1. Aerobic light-driven Wacker-Tsuji oxidation of allylbenzene (**1a**).[a]



Entry	Pd catalyst [5 mol%]	Photocatalyst [5 mol%]	**1a** [%][b]	**2a** [%][b]	**3a** [%][b]	**4a** [%][b]	**5a** [%][b]	**6a** [%][b]
1	$Pd(TFA)_2$	$Ru(bpy)_3Cl_2$	86	7	1	< 1	< 1	6
2	$Pd(TFA)_2$	$Ir(ppy)_3$	72	19	3	< 1	1	5
3	$Pd(TFA)_2$	Eosin Y	66	23	5	< 1	2	4
4	$Pd(TFA)_2$	Rose Bengal	86	8	4	< 1	1	1
5	$Pd(TFA)_2$	$[Acr\text{-}Mes]ClO_4$	59	34	7	< 1	< 1	< 1
6	$PdCl_2(MeCN)_2$	$[Acr\text{-}Mes]ClO_4$	21	75	2	1	< 1	1
7	$Pd(OAc)_2$	$[Acr\text{-}Mes]ClO_4$	66	27	5	1	< 1	1
8	$Pd(OAc)_2(PPh_3)_2$	$[Acr\text{-}Mes]ClO_4$	60	23	14	3	< 1	< 1
9	$Pd(dba)_2$	$[Acr\text{-}Mes]ClO_4$	67	22	7	2	1	1
10	$Pd(PPh_3)_4$	$[Acr\text{-}Mes]ClO_4$	68	15	11	2	1	3
11	Pd/C	$[Acr\text{-}Mes]ClO_4$	69	1	11	17	1	1
12[c]	**$PdCl_2(MeCN)_2$**	**$[Acr\text{-}Mes]ClO_4$**	**10**	**79**	**7**	**1**	**1**	**2**

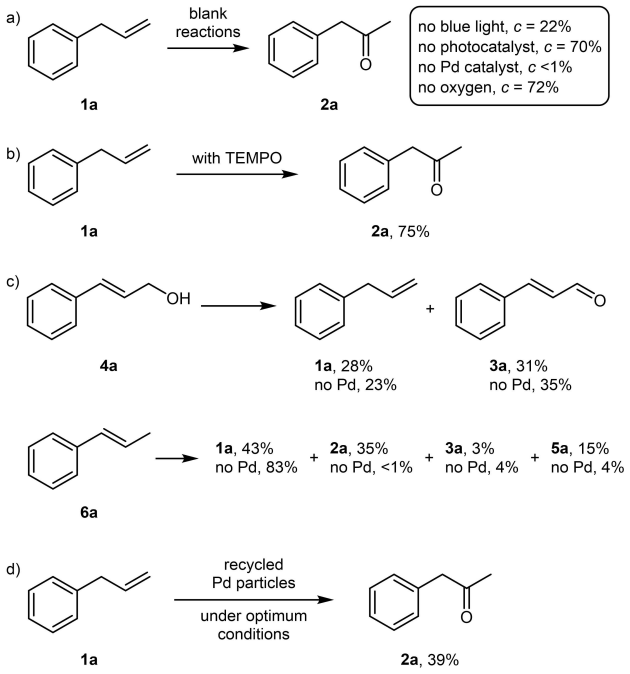
[a] Reaction conditions: Pd catalyst (5 mol%) and photocatalyst (5 mol%) were placed into a glass vial (3.5×2.4 cm) and dissolved in MeCN (5% *v/v*, 150 µL). Next, allylbenzene (**1a**, 0.075 mmol, 25 mM) and H_2O (2.85 mL) were added to the reaction mixture. The reaction was magnetically stirred under blue led light (14.4 W) for 16 h at room temperature.
[b] Percentages of compounds were measured by GC analysis (see details in the Supporting Information).
[c] 10 mol% $PdCl_2(MeCN)_2$.

remarkable that also soluble Pd(0) catalysts afforded **2a** although at lower extension (15–22%), in agreement with previous results.[16] However, Pd on charcoal did not catalyze the oxidation of **1a** into **2a**. It must be noticed that among all Pd sources tested, $PdCl_2(MeCN)_2$ is the one with the more labile ligands.

Subsequently, a reaction optimization (see Table S1 in the Supporting Information) was achieved. The amounts of photo- and metal-catalysts (5–10 mol%) and acetonitrile concentration (0–15% *v/v*) were modified, attaining a slightly better conversion into ketone **2a** (79%) when the quantity of the palladium catalyst was increased up to 10 mol% (Table 1, entry 12). Also, transformations at higher substrate concentration were performed, and while conversions close to 60% were still attained at 50 mM of **1a**, a considerable drop of activity was observed at 100–150 mM. The use of other organic co-solvents [tetrahydrofuran (THF), DMF or DMSO] did not show any improvement (see Table S2 in the Supporting Information).

In order to gain insight into the mechanism of this oxidative transformation, several experiments were performed (Scheme 2 and Table S2 in the Supporting Information). Hence, blank reactions were carried out in the absence of light, oxygen or catalysts (Scheme 2a). From these tests, it became clear that light irradiation and the Pd catalyst were essential. In the absence of light, 21% of the isomerized compound **6a** was detected along with just a 22% of **2a**. In the absence of $PdCl_2(MeCN)_2$, **3a** (26%) was detected as the main product, and **2a** was not formed at any extent. Surprisingly, the absence of the photocatalyst did not strongly affect the formation of the desired ketone **2a**, but a higher amount of by-products was observed, especially for aldehyde **3a** (15%). Finally, it was remarkable to find out that even under oxygen-free conditions – degasification of the reaction medium using the freeze-pump-thaw method and under argon atmosphere –, a high conversion into **2a** (72%) was still afforded (Table S2 in the Supporting Information).

To detect possible radical intermediates, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical (TEMPO, 1 equiv.) was added into the reaction mixture, but an analogous product distribution was detected (Scheme 2b).



Scheme 2. Transformations to investigate the reaction mechanism: a) Blank experiments. b) In the presence of TEMPO. c) Using compounds **4a** and **6a** as substrates in the presence (or not) of the palladium catalyst. d) Recycling the Pd particles precipitated after a first transformation under optimized oxidative conditions.

As cinnamaldehyde was usually attained as the main by-product, different reactions were performed using alcohol **4a** or alkene **6a** as possible precursors (Scheme 2c), studying in particular the effect of $PdCl_2(MeCN)_2$. Hence, when using cinnamyl alcohol as substrate, a mixture of compounds **1a** and **3a** was observed in the presence of both catalysts or adding only $[Acr\text{-}Mes]ClO_4$. However, using derivative **6a** as substrate, a different picture was noticed. A mixture of products **1a**, **2a** and **5a** was obtained using both catalysts, but mainly allylbenzene just in the presence of the photosensitizer.

At this point, it must be pointed out that the precipitation of Pd(0) black particles was observed during the performance of the oxidative transformation under optimized conditions. Once we carefully filtered the solid, it was reused as the palladium source for a new oxidative transformation (Scheme 2d), attaining noticeable conversions of 1-phenylpropan-2-one (39%) and aldehyde **3a** (18%, Table S2 in the Supporting Information).

The formation of these by-products in Wacker oxidations under other conditions is known as well as the involved reaction mechanisms. Palladium catalysts have provided excellent results in the isomerization of allylarenes into the more thermodynamically stable internal alkenes (e.g. compound **6a**),[42] which after water addition can provide the corresponding ketones (e.g. derivative **5a**).[2] On the other hand, the allylic functionalization of terminal alkenes via π-allyl Pd(II) complexes is also widely applied to obtain allylic alcohols (e.g. compound **4a**).[43] Under aerobic conditions, they can be oxidized into the corresponding α,β-unsaturated aldehydes (e.g. derivative **3a**).[43a,b,44]

With the exception of the isomerization reaction, these transformations reduce catalytically active Pd(II) into Pd(0), which obviously needs to get reoxidized. In our particular case, it was envisaged that $[Acr\text{-}Mes]ClO_4$ under blue light, in a similar approach than the one described by Fabry *et al.*,[25] could catalyze the recovery of the Pd(II) species. However, it was noticed that the photosensitizer was not strictly necessary, as the Wacker-Tsuji oxidation also proceeded, just affecting to the product selectivity. Therefore, under our conditions oxygen was able to recycle palladium(II). We believe that the formation of palladium nanoparticles is the key for the successful development of this method.

Various experimental results and observations pointed out that Pd NPs were indeed formed during the reaction course. As mentioned in the introduction, Pd nanoparticles derived from soluble complexes are able to mediate Wacker oxidative reactions,[16] and under the irradiation of light, they are able to promote reactions such as water splitting.[21] Herein, we have shown that the oxidative transformation also proceeded even under the absence of molecular oxygen (entry 6, Table S2 in the SI). Thus, the formation of oxygen (and hydrogen) from water mediated by the irradiated NPs can allow the reoxidation of Pd(0) into the catalytically active Pd(II) species. In fact, traces of propylbenzene (**7a**) were detected in this experiment, which must be obtained after hydrogenation of substrate **1a**, thus demonstrating the generation of hydrogen.

A time-study of the optimized reaction under aerobic conditions was achieved (Table S5 in the SI), observing that a mixture of desired product **2a** and isomerized alkene **6a** was quickly formed. However, this mixture slowly progressed into compound **2a** along the first 3 hours, and after that time the reaction proceeded faster, reaching a conversion around 80% after 16 h. This lag time is usually related to the conversion of soluble complex precursors into catalytically active nanoparticles.[10c] Finally, the deposit of metallic particles after the oxidative transformation and the fact that they demonstrated to be catalytically active, as shown in Scheme 2d, is probably the most relevant evidence that Pd NPs are involved in this transformation.

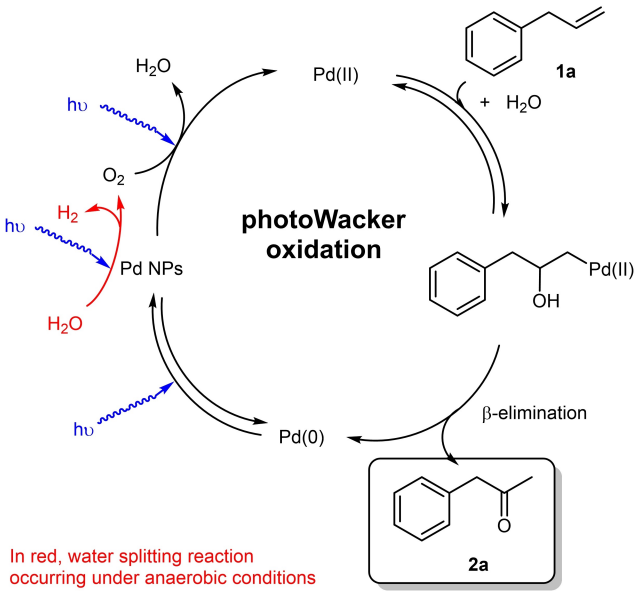
The role of the visible light irradiation could be related to the excitation of soluble Pd complex intermediates,[19,20] but these single-electron transfer procedures usually follow radical mechanisms. In our

case, the addition in the reaction mixture of a radical scavenger such as TEMPO (Scheme 2b) did not significantly modify the product conversion, thus ruling out the intervention of these reactive species in the formation of **2a**. We believe that blue light can favor the transient formation of Pd NPs involved in the catalysis and/or can facilitate the reoxidation into the active Pd(II) species. The direct interaction of oxygen with Pd(0)-hydride species releases hydrogen peroxide,[9,45] which later decomposes into water and oxygen, or enters in the metal-oxidative catalytic cycle as the oxidant, also providing water as final product.[4,46] To check the possible formation of H_2O_2 in our system, aliquots were taken at different reaction times and submitted to a highly selective colorimetric assay to detect hydrogen peroxide [titanium(IV) oxysulfate, $TiOSO_4$].[47] However, a conclusive positive result was not observed (see Section IV.2 in the SI). If H_2O_2 was transiently formed, it was continuously consumed in the reaction.

As mentioned before, the addition of the photocatalyst was not compulsory to obtain ketone **2a** at high extent, but it favored the process selectivity, as a higher amount of the desired ketone at expenses of a lower quantity of aldehyde **3a** was noticed (around 10%). A possible explanation can be drawn looking at the experiments done in Scheme 2c. Cinnamaldehyde (**3a**) can be obtained via Pd[43a,b,44] or [Acr-Mes]ClO_4 mediated oxidation[48] of cinnamyl alcohol (**4a**), or by photooxygenation of *trans*-β-methylstyrene (**6a**).[39a] In our case it was observed that **3a** was formed from alcohol **4a** in the presence of both catalysts, and also when [Acr-Mes]ClO_4 was just added to the reaction mixture (Scheme 2c and Table S3 in the Supporting Information). These results are in agreement with those reported in the bibliography,[43a,b,44,48] but remarkably allylbenzene **1a** was also obtained at significant extent (23%). Similar transfer hydrogenolysis transformations of allylic alcohols under photocatalytic conditions can be found in the literature in the presence of Pd NPs.[49]

When alkene **6a** was used as the substrate, isomerization into **1a** was expected due to the action of the Pd catalyst.[42] Interestingly, the simple addition of the photosensitizer also catalyzed the same transformation (see Scheme 2c and Table S4 in the Supporting Information). With these results, we think that [Acr-Mes]ClO_4 can promote the oxidation of cinnamyl alcohol to **3a**, but it has also an important role in our photocatalytic process isomerizing back *trans*-β-methylstyrene to provide again allylbenzene, which can enter in the main Wacker-type oxidative cycle, overall, affording a better product selectivity. With all these findings, we have summarized the proposed mechanism of the photoWacker-Tsuji oxidation in Scheme 3.

Once optimized the oxidation of **1a**, a series of allyl(hetero)arenes **1b–n** were purchased or chemically synthesized following previously described procedures



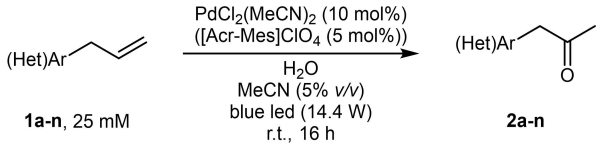
Scheme 3. Proposed mechanism for the photoWacker-Tsuji oxidation of allylbenzene (**1a**). For the whole scheme including the secondary transformations, see Scheme S1 in the Supporting Information.

(see additional information in the Supporting Information),[50] and subsequently submitted to light-driven Wacker-Tsuji conditions to selectively obtain the corresponding ketones **2b–n** (Table 2, right).

As can be observed, this combined photo-metal-catalyzed protocol was successfully applied to most of the arene derivatives independently of their substitution pattern and electronic character. Thus, *ortho*-substituted compounds **1b–e** (entries 2–5) afforded conversions around 80% towards the corresponding ketones with excellent selectivity (>91%), and *meta*- and/or *para*-substituted derivatives **1f–k** (entries 6–11) also formed the desired carbonyl compounds at high extent (70–85%) with similar selectivity values (>89%). Just for the substrate bearing a strongly deactivating nitro group (entry 8), a negative effect in the conversion towards ketone **2h** (43%) was observed, although the selectivity remained excellent. Finally, three heteroaromatic compounds containing thiophene and furan rings (**1l–n**, entries 12–14) were tested under optimized conditions, providing ketones **2l–n** in low to moderate conversions (30–56%) and selectivities (59–70%). These results clearly demonstrated the broad applicability of this catalytic methodology under very simple reaction conditions.

The effect of the photosensitizer was reevaluated by performing the same oxidations in its absence (Table 2, left). As occurred for the model substrate **1a**, conversions slightly decay and worse selectivities into the ketone products were attained. These effects were especially noticeable for derivatives **1h**, **j**, **k** (entries 8,

Table 2. Aerobic photoWacker-Tsuji oxidation of allyl(hetero)arenes **1 a–n** under optimized conditions.[a]



Entry	Substrate	Without $[Acr\text{-}Mes]ClO_4$			With $[Acr\text{-}Mes]ClO_4$		
		c [%][b]	**2 a–n** [%][b]	Selectivity [%][c]	*c* [%][b]	**2 a–n** [%][b]	Selectivity [%][c]
1	**1 a** (R=C_6H_5)	89	70	79	90	79	88
2	**1 b** (R = 2-CH_3–C_6H_4)	79	73	92	83	78	94
3	**1 c** (R = 2-OCH_3–C_6H_4)	77	66	86	85	77	91
4	**1 d** (R = 2-Br–C_6H_4)	78	70	90	80	76	95
5	**1 e** (R = 2-F–C_6H_4)	84	78	93	86	81	94
6	**1 f** (R = 3-F-C_6H_4)	79	71	90	84	80	95
7	**1 g** (R = 4-F–C_6H_4)	85	72	85	95	85	89
8	**1 h** (R = 4-NO_2–C_6H_4)	22	11	50	45	43	96
9	**1 i** (R = 4-CH_3–C_6H_4)	87	69	79	86	82	95
10	**1 j** (R = 4-OCH_3–C_6H_4)	76	49	64	76	70	92
11	**1 k** (R = 3,4-OCH_2O–C_6H_3)	64	55	86	85	76	89
12	**1 l** (R = 2-thienyl)	54	32	59	74	44	59
13	**1 m** (R = 3-thienyl)	63	41	65	86	56	65
14	**1 n** (R = 2-furyl)	39	26	67	43	30	70

[a] Reaction conditions: Pd catalyst (10 mol%) and photocatalyst (5 mol%) were placed into a glass vial (3.5 × 2.4 cm) and dissolved in MeCN (5% *v/v*, 150 µL). Next, allyl(hetero)arene **1 a–n** (0.075 mmol, 25 mM) and H_2O (2.85 mL) were added to the mixture. The reaction was magnetically stirred under blue led light (14.4 W) for 16 h at room temperature.
[b] Conversion and percentage of product values were measured by GC analysis.
[c] Selectivity = **2 a–n** percentage divided by the total conversion.

10, and 11). These findings demonstrate that the addition of $[Acr\text{-}Mes]ClO_4$ was beneficial in our system.

Since this transformation can be performed in aqueous medium and at room temperature, we envisaged the possibility to couple an enzymatic transformation to get access to high added value compounds. Due to the presence of a carbonyl moiety, readily available amine transaminases[27,28] or alcohol dehydrogenases[27] could directly afford, respectively, the corresponding enantioenriched 1-(hetero)arylpro-pan-2-amines (**8 a–m**) and 1-(hetero)arylpropan-2-ols (**9 a–m**),[51] privileged biologically active derivatives and intermediates of highly interesting drugs.[52] The overall processes can be foreseen as formal stereoselective hydration or hydroamination of allyl(hetero)arenes (Scheme 1c).

However, it became soon clear that a sequential design might be selected, since the addition of different essential components in the biotransformations [phosphate buffer, propan-2-amine (2-$PrNH_2$), propan-2-ol (2-PrOH), pyridoxal 5'-phosphate (PLP), or the enzymatic preparation], negatively affected to the photocatalyzed Wacker-Tsuji oxidation of model substrate **1 a** (Table S6 in the Supporting Information). Especially noticeable was the negative effect in the presence of the buffer (< 5% conversion). These results hampered the development of a concurrent cascade protocol.

Therefore, biotransamination and bioreduction screenings were performed on ketones **2 a–m** to find the best enzyme candidates. For substrates **2 a–c**, **i–k**, we already knew the best ATAs from a previous study in our group,[8d] and consequently, we focused our attention on the bioamination of ketones **2 d–h**, **l**, **m** (Tables S7–S13 in the Supporting Information) and the bioreduction of compounds **2 a–m** (Tables S14–S15 in the Supporting Information). For each substrate we tried to find stereocomplementary biocatalysts, thus accessing to both product antipodes.

Regarding the amine transaminases, we selected various enzymes obtained from a commercial source, while in the case of the alcohol dehydrogenases, lyophilized cells of *E. coli* overexpressing *S*-selective ADH from *Rhodococcus ruber* (*E. coli*/ADH-A)[53] or *Thermoanaerobacter sp.* (*E. coli*/ADH-T),[54] and commercially available *R*-selective evo-1.1.200 were chosen. Because both families of enzymes require a cofactor to remain active [PLP for ATAs and NAD(P)H for ADHs], a sacrificial co-substrate – propan-2-amine to obtain the chiral amines[27,28] and propan-2-ol to get access to the enantioenriched alcohols[27] – was chosen as cofactor recycling method in the so-called coupled-substrate approach. By this way, satisfactory conversions (> 90%) and excellent stereoselectivities (> 99%) were obtained for all the substrates.

After making the selection, we had to face one of the main issues when developing two reactions in a one-pot sequential fashion, since these enzymes work best in slightly basic (7.5–8.5) pHs, and after the first metal-photocatalytic step it resulted clearly acid (approx. 3–4). To overcome this problem, in the case of ATAs, a mixture of propan-2-ammonium phosphate and propan-2-amine in water was added to the medium, rising the pH up to approx. 8.5, while for ADHs, a NaOH aqueous solution was supplemented, attaining a final pH value of approx. 7.5. After these pH adjustments and once provided the biocatalyst, the cofactor and the co-substrate, target enantiopure amines **8a–m** and alcohols **9a–m** were synthesized in usually high isolated yields (>70%) and *ee* values (>99%) after additional 24 h, with the exception of substrates **1h,l,m** due to lower conversions achieved in the metal-photocatalytic transformation (Figure 1 and Tables S16-S17 in the Supporting Information).

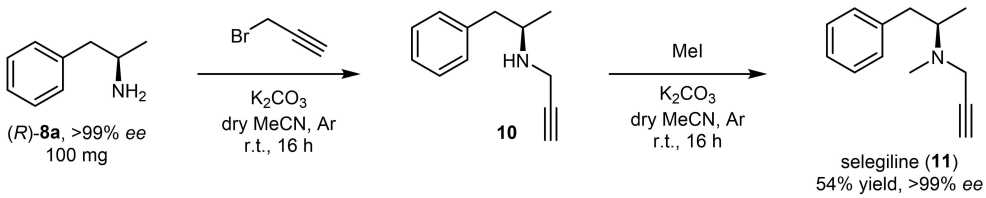
To demonstrate the applicability of this protocol, preparative sequential experiments at 1 mmol scale were performed with substrate **1a**, synthesizing (*R*)-**8a** using TA-P2-B01 (81%, >99% *ee*) and (*S*)-**9a** with *E. coli*/ADH-A as catalyst (80%, >99% *ee*). Moreover, starting from optically active amine (*R*)-**8a** and following a modified procedure to the one described by MacGregor and co-workers (Scheme 4),[55] we could get access to selegiline (**11**), an important anti-Parkinson drug, in 54% overall yield and in enantiopure form.

Conclusions

The transformation of alkenes into ketone derivatives is probably one of the most studied reactions in organic chemistry. The availability of the starting material and the synthetic possibilities that the carbonyl products offer, has risen the interest of researchers from different disciplines. In this field, the Wacker-Tsuji oxidation of C–C double bonds facilitates the preparation of the corresponding ketones via Markovnikov addition of water, appearing as a synthetically useful strategy that has been widely implemented at industrial level. The combination of a palladium(II) precursor in the presence of a chelating ligand and a co-oxidant such as a copper(II) salt in an organic solvent has provided impressive results at moderate to high temperatures. However, recent environmental concerns have prompted scientists, and in particular chemists, to explore novel sustainable alternatives that keep the outstanding results attained in the traditional chemical methods, and can also be performed under mild and safe reaction conditions.

Here, a promising approach to achieve the aerobic Wacker-Tsuji oxidation of allyl(hetero)arenes is presented. This approach consists in the use of a Pd(II) complex in aqueous medium, room temperature and under visible light. The key of this transformation is the transient formation of palladium nanoparticles that can activate molecular oxygen under light conditions, recovering back the Pd(II) species necessary for the Wacker-type oxidation. Whereas the use of blue led irradiation was mandatory to reach high conversions, the addition of a photosensitizer such as $[Acr\text{-}Mes]ClO_4$ improved the selectivity of the process, due its reactivity with some of the by-products attained in this process, forming back the starting material which entered in the main catalytic cycle. This light-driven Wacker-Tsuji oxidative protocol was successfully applied to a series of allyl(hetero)arenes which rendered the (hetero)arylacetone derivatives typically in high yields and very high selectivities. Taking advantage of the use of an aqueous medium under mild conditions for this transformation, a second enzymatic reaction was coupled in a sequential manner towards the formation of a wide panel of chiral amines and alcohols. Thus, selecting the proper biocatalyst – an amine transaminase or an alcohol dehydrogenase –, highly valuable enantiopure 1-(hetero)arylpropan-2-amines or 1-(hetero)arylpropan-2-ols were recovered in good isolated yields, up to 83%, following a one-pot two-step procedure.

This photo-metal-biocatalytic sequence could be easily performed at preparative scale, and one of the synthesized amines was employed as precursor of selegiline, a drug which is used in the treatment of Parkinson's disease and major depressive disorders, among others. We believe that the combination of palladium and light-induced transformations shown in this contribution can open the door for further valuable synthetic applications under sustainable conditions.



Scheme 4. Synthesis of selegiline starting from (*R*)-**8a** obtained through the light-driven Wacker-Tsuji oxidation-biotransamination sequential protocol at preparative scale.

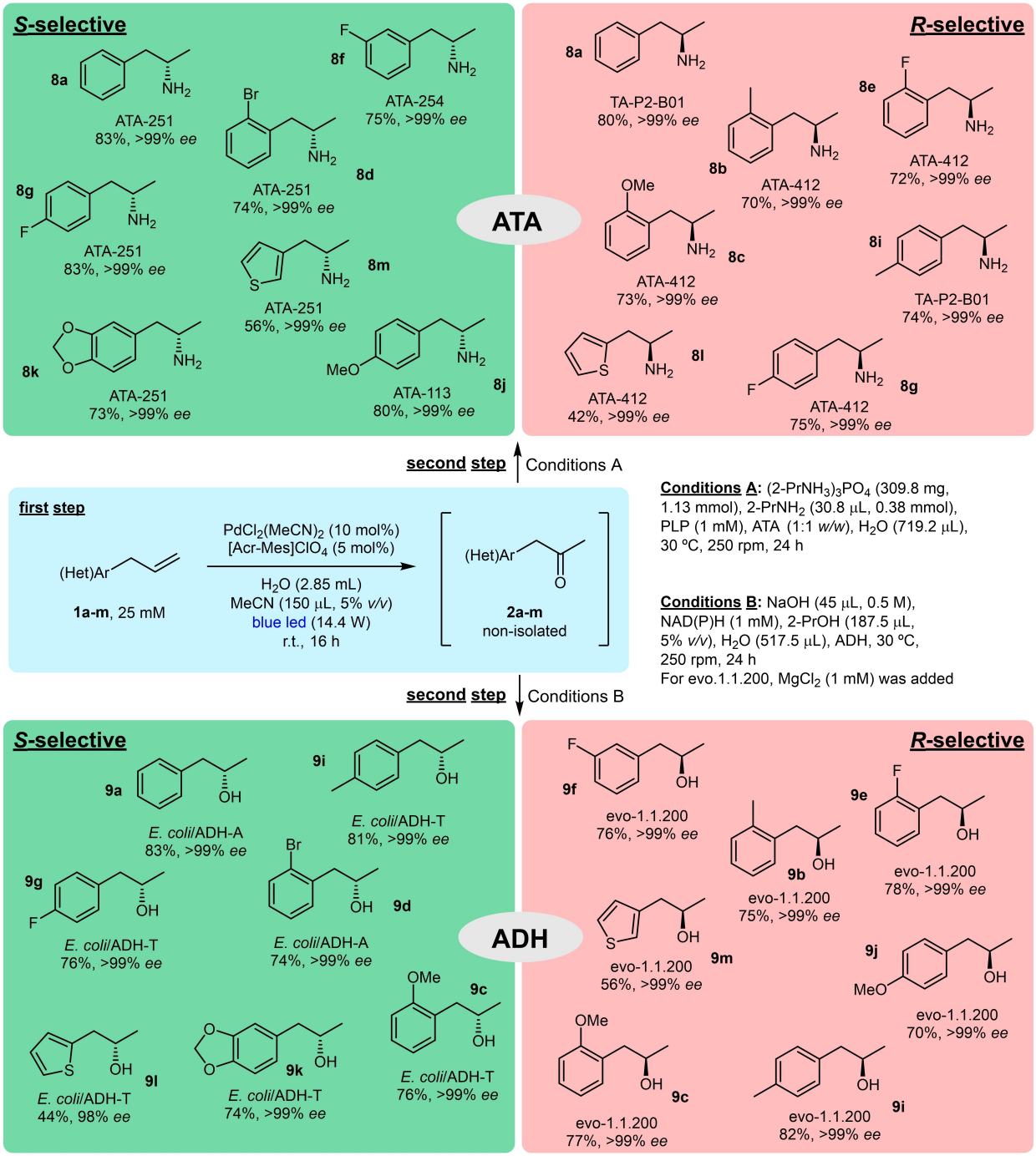


Figure 1. Synthesis of enantiopure 1-(hetero)arylpropan-2-amines and 1-(hetero)arylpropan-2-ols following a one-pot two-step photo-metal-biocatalytic sequential protocol. Isolated yields after chromatographic purification and enantiomeric excess values are indicated, and the whole set of data appears in Tables S16 and S17 of the Supporting Information.

Experimental Section

General Procedure for the Photocatalyzed Wacker-Tsuji Transformation at Analytical Scale

$PdCl_2(MeCN)_2$ (2.0 mg, 10 mol%) and $[Acr\text{-}Mes]ClO_4$ (1.6 mg, 5 mol%) were placed into a glass vial (3.5×2.4 cm) and dissolved in MeCN (150 μL). Next, allyl(hetero)arene **1a–n** (0.075 mmol, 25 mM) and H_2O (2.85 mL) were added to the mixture. The reaction was magnetically stirred under blue led light (14.4 W) for 16 h at room temperature. After that time, the mixture was extracted with EtOAc (1 mL) and the organic layer was separated by centrifugation (3 min, 4,300 *g*). This extraction and centrifugation protocol was repeated once and, finally, the organic phases were combined, dried over Na_2SO_4, filtered,

and transferred to a GC glass vial for analysis of the conversion degree and product distribution.

Photo-Metal-Biocatalytic Sequential Process towards Enantioenriched Amines

$PdCl_2(MeCN)_2$ (2.0 mg, 10 mol%) and [Acr-Mes]ClO_4 (1.6 mg, 5 mol%) were added and dissolved in MeCN (150 µL) inside a glass vial (3.5×2.4 cm). Next, allyl(hetero)arene **1a–m** (0.075 mmol, 25 mM) was dissolved in the mixture and H_2O (2.85 mL) was added. Then, the reaction mixture was stirred under blue led light (14.4 W) for 16 h at room temperature.

To the resulting reaction crude containing the ketone intermediate **2a–m**, $(2\text{-PrNH}_2)_3PO_4$ (309.8 mg, 1.13 mmol), 2-$PrNH_2$ (30.8 µL, 0.38 mmol), and H_2O (719.2 µL) were added, leading to approximately concentrations of 20 mM for the ketone and 1 M for 2-$PrNH_2$. These additions increased the pH from an initial value of 3 to approximately 8.5, optimum for the biotransamination step. After that, PLP (0.9 mg, 1 mM) and the corresponding amine transaminase (1:1 *w/w*) were added to the reaction medium. Finally, the vial was covered with aluminum foil and shaken in an orbital shaker at 30 °C and 250 rpm for 24 h. After that time, the reaction was stopped by the addition of a NaOH aqueous solution (1 mL, 10 M). The mixture was extracted with EtOAc (5 mL) and the organic layer separated by centrifugation (3 min, 4,300 *g*). This extraction and centrifugation protocol was performed three times and, finally, the organic layers were combined and dried over Na_2SO_4. The product distribution was measured by GC analysis and the enantiomeric excess values were determined by HPLC as acetamide derivatives, after derivatization of enantioenriched amines **8a–m** with acetic anhydride and potassium carbonate. The reaction crude was purified through column chromatography (eluent: 5% NH_3/MeOH), affording the amines **8a–m** in 31–83% yield (see Table S16 in the Supporting Information).

Photo-Metal-Biocatalytic Sequential Process towards Enantioenriched Alcohols

$PdCl_2(MeCN)_2$ (2.0 mg, 10 mol%) and [Acr-Mes]ClO_4 (1.6 mg, 5 mol%) were added and dissolved in MeCN (150 µL) inside a glass vial (3.5×2.4 cm). Next, allylarene **1a–m** (0.075 mmol, 25 mM) was dissolved in the mixture and H_2O (2.85 mL) was added. Then, the reaction mixture was magnetically stirred under blue led light (14.4 W) for 16 h at room temperature.

To the resulting reaction crude containing the ketone intermediate **2a–m**, an aqueous NaOH solution (45 µL, 0.5 M), H_2O (517.5 µL), and 2-PrOH (187.5 µL, 5% *v/v*) were added, leading to approximately a concentration of 20 mM for the substrate and increasing the pH from an initial value of 3 to approximately 7.5, optimum for the bioreduction step. Other additives were added depending on the biocatalyst used in the second step.

In the case of evo-1.1.200-catalyzed reactions, NADH (2.7 mg, 1 mM) was added to the reaction mixture and, instead of 517.5 µL of H_2O in the second step, 375 µL of a $MgCl_2$ 10 mM aqueous solution and 142.5 µL of H_2O were added, leading to a final concentration of 1 mM of $MgCl_2$. In the case of *E. coli*/ADH-T-catalyzed reactions, NADPH (3.1 mg, 1 mM) was added to the reaction mixture. In the case of *E. coli*/ADH-A-catalyzed reactions, NADH (2.7 mg, 1 mM) was added to the reaction mixture.

Finally, the corresponding biocatalyst (3 mg in the case of evo-1.1.200 or 30 mg in the case of lyophilized *E. coli* cells overexpressing an alcohol dehydrogenase) was added, and the vial was covered with aluminum foil and shaken in an orbital shaker at 30 °C and 250 rpm for 24 h. After that time, the reaction was stopped and the mixture extracted with EtOAc (5 mL), separating the organic layer by centrifugation (3 min, 4,300 *g*). This extraction and centrifugation protocol was performed three times and, finally, the organic layers were combined and dried over Na_2SO_4. The product distribution was measured by GC analysis and enantiomeric excess values were determined by chiral GC as acetylated derivatives, after derivatization of the enantioenriched alcohols **9a**,**b**,**d–m** with acetic anhydride in the presence of 4-dimethylaminopyridine. Enantiomeric excess of the alcohol **9c** was determined by chiral HPLC without derivatization. The reaction crude was purified through column chromatography (eluent: 25% EtOAc/Hexane), affording the alcohols **9a–m** in 34–83% yield (see Table S17 in the Supporting Information).

Photo-Metal-Biocatalytic Sequential Process towards Amine (*R*)-8a at Preparative Scale

$PdCl_2(MeCN)_2$ (25.9 mg, 10 mol%) and [Acr-Mes]ClO_4 (20.6 mg, 5 mol%) were added and dissolved in MeCN (2 mL) in a 100 mL Schlenk tube. Next, allylbenzene (**1a**, 118 mg, 1 mmol, 25 mM) was dissolved in the mixture and H_2O (38 mL) was added. Then, the reaction mixture was magnetically stirred under blue led light (14.4 W) for 16 h at room temperature.

To the resulting reaction crude containing the ketone intermediate **2a**, $(2\text{-PrNH}_2)_3PO_4$ (4.09 g, 14.85 mmol), 2-$PrNH_2$ (410 µL, 5.0 mmol), and H_2O (9.59 mL) were added, leading to approximately concentrations of 20 mM for the substrate and 1 M for 2-$PrNH_2$, and increasing the pH from an initial value of 3 to approximately 8.5, optimum for the biotransamination step. After that, PLP (12.4 mg, 1 mM) and TA-P2-B01 transaminase (118 mg, 1:1 *w/w*) were added to the reaction medium. Finally, the vial was shaken in the dark (using aluminum foil) at 30 °C and 250 rpm for 24 h. After that time, the reaction was stopped by the addition of an aqueous NaOH solution (5 mL, 10 M). The mixture was extracted with EtOAc (20 mL) and the organic layer separated by centrifugation (3 min, 4,300 *g*). This extraction and centrifugation protocol was performed three times and, finally, the organic layers were combined and dried over Na_2SO_4. The organic layer was filtered and the solvent removed under reduced pressure. The reaction crude containing (*R*)-**8a** was purified by column chromatography on silica gel (5% NH_3/MeOH), yielding the corresponding enantiopure amine in 81% yield (109.3 mg).

Photo-Metal-Biocatalytic Sequential Process towards Alcohol (*S*)-9a at Preparative Scale

$PdCl_2(MeCN)_2$ (25.9 mg, 10 mol%) and [Acr-Mes]ClO_4 (20.6 mg, 5 mol%) were added and dissolved in MeCN (2 mL)

in a 100 mL Schlenk tube. Next, allylbenzene (**1a**, 118 mg, 1 mmol, 25 mM) was dissolved in the mixture and H_2O (38 mL) was added. Then, the reaction mixture was magnetically stirred under blue led light (14.4 W) for 16 h at room temperature.

To the resulting reaction crude containing the ketone intermediate **2a**, an aqueous NaOH solution (600 µL, 0.5 M), H_2O (6.9 mL), and 2-PrOH (2.5 mL, 5% *v/v*) were added, leading to approximately a concentration of 20 mM for the substrate and increasing the pH from an initial value of 3 to approximately 7.5, optimum for the bioreduction step. After that, NADH (36 mg, 1 mM) and *E. coli*/ADH-A (400 mg) were added to the reaction medium. Finally, the vial was shaken in the dark (using aluminum foil) at 30 °C and 250 rpm for 24 h. After that time, the reaction was stopped and the mixture extracted with EtOAc (20 mL), separating the organic layer by centrifugation (3 min, 4,300 *g*). This extraction and centrifugation protocol was performed three times and, finally, the organic layers were combined and dried over Na_2SO_4. The organic layer was filtered and the solvent removed under reduced pressure. The reaction crude containing (*S*)-**9a** was purified by column chromatography on silica gel (25% EtOAc/Hexane), yielding the corresponding enantiopure alcohol in 80% yield (108.8 mg).

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UPDATES

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