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From Diazonium Salts to Optically Active 1-Arylpropan-2-ols Through a Sequential Photobiocatalytic Approach

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Abstract: The photocatalytic Meerwein arylation between aromatic diazonium salts and isopropenyl acetate under blue LED light irradiation in aqueous medium has been deeply investigated. Optimization of the reaction conditions in terms of substrate concentration, ester equivalents, cosolvent type and amount, reaction time and photocatalyst source, has allowed the access to a variety of 1-arylpropan-2-ones with yields up to 95% using 9-mesityl-10-methylacridinium perchlorate ([Acr-Mes]ClO_4). Next, the design of a one-pot sequential photobiocatalytic linear approach was accomplished, by the combination of the Meerwein arylation with the bioreduction of the corresponding ketone intermediates. Thus, a total of 19 pairs of 1-arylpropan-2-ol enantiomers were obtained depending on the alcohol dehydrogenase stereopreference. Global yields up to 76% were attained with high to excellent stereoselectivity (90 to >99% *ee*). Also, it was possible to get access to both 1-phenylpropan-2-ol antipodes (51–53% yield) starting from aniline through a one-pot three-step sequential photobiocatalytic protocol.

Keywords: Bioreduction; Diazonium salts; Meerwein arylation; Multicatalytic cascades; Photocatalysis

Introduction

Photocatalysis has emerged during the last years as a powerful tool for organic chemists towards the synthesis of highly valuable (chiral) organic compounds. Among the possible pathways, single-electron transfer (SET), energy-transfer (EnT) or hydrogen atom transfer (HAT) processes provide significant advantages in terms of sustainability when compared with traditional synthetic approaches.[1] Currently, the development of carbon–carbon and carbon–heteroatom bond formation reactions are attracting great attention in this area.[2] All these photocatalytic transformations are highly dependent on the different reagents and reaction conditions, as well as the type of light irradiated on the reaction medium.

Diazonium salts constitute a versatile group of organic compounds due to their ability to easily generate active aryl radicals,[3] which are ideal reactants to create novel types of bonds.[4] For instance, their uses in the Sandmeyer reaction[5] and Meerwein arylation[6] have been extensively explored. Particularly, the Meerwein reaction is one of the most well-known arylation processes, consisting of the addition of a diazonium salt to an electronically poor alkene using a reducing promoter, typically a copper(I) salt as catalyst, affording the corresponding alkylated arene product.[6b] Since these photochemical transformations proceed through radical intermediates, the performance of organic arylations via SET pathways can be

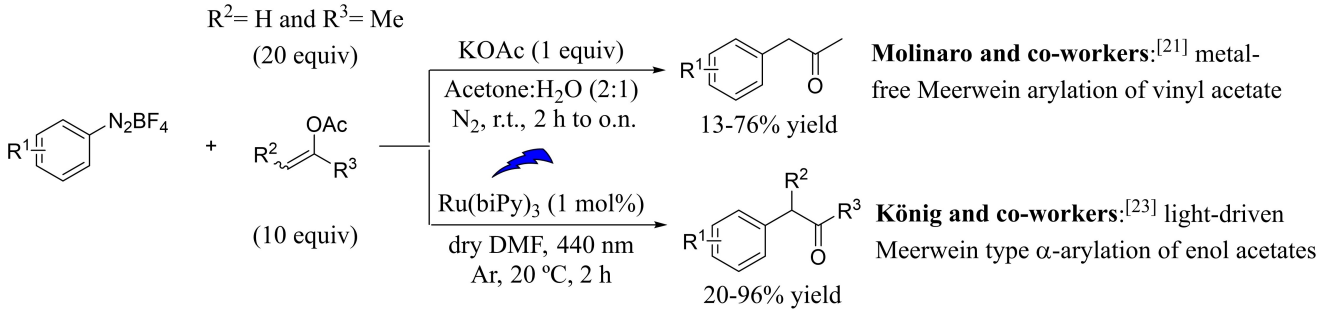
accomplished in a simple and efficient way,[7] including Meerwein reaction alternatives, avoiding the use of metal salts in stoichiometric amounts.[7b,8]

The design of multistep cascades through the combination of photochemical techniques with different catalysts (metals, enzymes and/or organocatalysts), simplifies synthetic routes without requiring the isolation of sometimes unstable intermediates.[9] In this context, light-driven chemical transformations can be easily combined with the use of enzymes, giving rise to photobiocatalytic processes that have already been applied for multiple linear cascades as well as for nicotinamide cofactor recycling purposes.[10] This emerging field provides a series of advantages including the use of mild reaction conditions in different media such as aqueous environments that are ideal for biotransformations.[11]

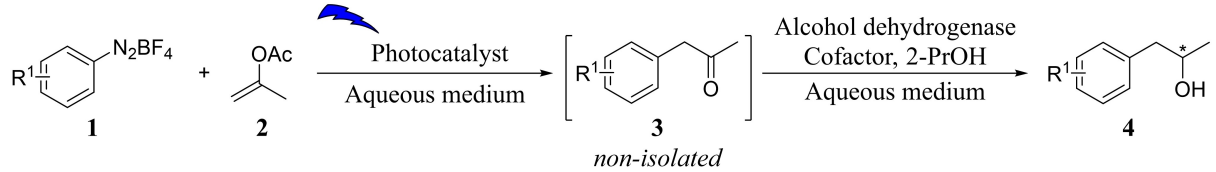
Optically active 1-arylpropan-2-ols are valuable intermediates for the synthesis of various organic compounds with remarkable biological activities including chiral 1-arylpropan-2-amines, also known as amphetamines.[12] The syntheses of this alcohol family have been accomplished through different single transformations such as non-enzymatic ones including asymmetrizations or kinetic resolutions (KRs),[13] and alternatively through asymmetric bioreduction of 1-arylpropan-2-ones using alcohol dehydrogenases (ADHs).[14] More interestingly, multicatalytic approaches have given access to chiral 1-arylpropan-2-ols via deracemization processes,[15] dynamic kinetic resolutions (DKRs)[16] and other linear cascades using several enzyme classes,[17] but also through the combination of organocatalysts or metals with biocatalysts.[18]

As already mentioned, 1-arylpropan-2-ones are ideal precursors of optically active 1-arylpropan-2-ols, carbonyl compounds that can be directly obtained from aryl diazonium salts and vinyl esters through Meerwein arylation approximations.[19,20] For instance, Molinaro and co-workers reported a transition-metal free system using potassium acetate under mild conditions in a partially aqueous medium (acetone and water, Scheme 1a, top).[21] Later, Maulide and co-workers described another metal-free methodology using 4-aminomorpholine as catalyst.[22] Interestingly, König and co-workers exploited the light-driven Meerwein-type α-arylation between aryl diazonium salts and enol acetates using a ruthenium photocatalyst in organic medium after short reaction times at 20 °C (Scheme 1a, bottom).[23] Also, de Oliveira and co-workers described a photocatalyzed protocol using porphyrins as catalysts under flow conditions.[24] Based on these precedents and our previous experience in the photobiocatalytic synthesis of optically active 1-arylpropan-2-ols, consisting of a Wacker-Tsuji oxidation of allylarenes followed by bioreduction of the resulting ketones,[18b] herein we propose to integrate a Meerwein arylation under light conditions with the subsequent action of stereocomplementary carbonyl reductases, to isolate valuable enantiopure 1-arylpropan-2-ols (**4**) from simple and easily accessible aryl diazonium salts (**1**) and isopropenyl acetate (**2**, Scheme 1b).

a) Previous Meerwin (type) arylation using aryl diazonium salts to produce 1-arylpropan-2-ones

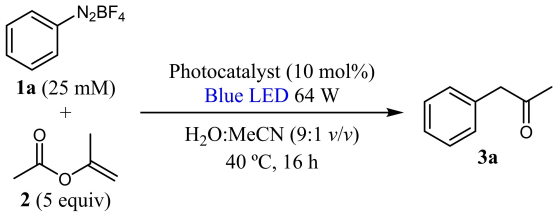


b) **This contribution**: Synthesis of enantiopure 1-arylpropan-2-ols from aryl diazonium salts via photobiocatalytic cascade



Scheme 1. Metal-free (a, top) and light-driven (a, bottom) Meerwein arylations to transform aryl diazonium salts into 1-arylpropan-2-ones, which could be used to develop a photobiocatalytic strategy towards optically active 1-arylpropan-2-ols (aim of this contribution, b).

Table 1. Screening of photocatalysts for the Meerwin arylation between **1a** and **2** under blue LED irradiation.



Entry	Photocatalyst [10 mol%]	**3a** [%][a]
1	–	9 ± 4
2	Rose Bengal	14 ± 2
3	Eosin-Y	35 ± 2
4	$Ir(ppy)_3$	40 ± 5
5	$Ru(bpy)_3Cl_2$	43 ± 4
6	SAS	54 ± 4
7	Riboflavin	56 ± 2
8	[Acr-Mes]ClO_4	65 ± 4
9[b]	[Acr-Mes]ClO_4	< 1

[a] Product percentages measured by GC analyses (see SI for further details). Experiments performed by triplicate.
[b] Under dark conditions.

Table 2. Optimization of the photocatalytic Meerwein arylation between **1a** and **2** under blue light irradiation (64 W).

Entry	**1a** [mM]	**2** [equiv.]	[Acr-Mes]-ClO_4 [mol%]	Cosolvent [% *v/v*]	time [h]	**3a** [%][a]
1	12.5	5	10	MeCN (10)	16	54
2	**25**	**5**	**10**	**MeCN (10)**	**16**	**63**
3	50	5	10	MeCN (10)	16	59
4	25	2	10	MeCN (10)	16	25
5	25	10	10	MeCN (10)	16	60
6	**25**	**15**	**10**	**MeCN (10)**	**16**	**74**
7	**25**	**15**	**2.5**	**MeCN (10)**	**16**	**76**
8	25	15	5	MeCN (10)	16	51
9	25	15	7.5	MeCN (10)	16	66
10	25	15	2.5	MeCN (5)	2	65
11	25	15	2.5	MeCN (5)	8	68
12	**25**	**15**	**2.5**	**MeCN (5)**	**16**	**75**
13	25	15	2.5	MeCN (2.5)	16	67
14	25	15	2.5	MeCN (7.5)	16	70
15	25	15	2.5	MeCN (12.5)	16	71

[a] Product percentages measured by GC analyses (see SI for further details). For clarity, the best results for each individual study are highlighted in bold font. A more comprehensive study using wider ranges can be found in Table S1 of the SI.

Results and Discussion

Photocatalytic Meerwein Arylation of Aryl Diazonium Salts. Optimization and Scope

In order to develop a suitable Meerwein arylation, benzenediazonium tetrafluoroborate (**1a**) was selected as the model substrate, and it was reacted with **2** to obtain 1-phenylpropan-2-one (**3a**). Firstly, various photocatalysts (10 mol%) were tested under blue light irradiation (64 W LED) in an aqueous medium (10% *v/v* of MeCN for solubilization reasons, Table 1). After 16 h at 40 °C, the best results for the light-driven Meerwein arylation were obtained when 9-mesityl-10-methylacridinium perchlorate ([Acr-Mes]ClO_4) photocatalyst was employed (entry 8, Table 1). Interestingly, no reaction was observed with this photosensitizer in the absence of light irradiation (entry 9, Table 1).

Once selected [Acr-Mes]ClO_4 as a suitable photocatalyst, a comprehensive analysis of the light-driven Meerwin arylation between **1a** and **2** was performed (Table S1). The most relevant results are highlighted in Table 2, studying the influence of the substrate **1a** concentration (12.5–100 mM), amount of vinyl ester **2** (2–20 equiv.) and photosensitizer (2.5–10 mol%), reaction time (2–16 h), percentage of MeCN (2.5–12.5% *v/v*) and the use of other cosolvents (2-PrOH, DMF, DMSO, and THF). After a comprehensive optimization study, it was concluded that the best results were achieved under the reaction conditions depicted in entries 7 and 12 of Table 2. Hence, 25 mM substrate concentration, 15 equivalents of **2**, 2.5 mol% of the photosensitizer [Acr-Mes]ClO_4 in an aqueous medium containing a 5–10% *v/v* of MeCN as cosolvent, and irradiation of the reaction mixture for 16 h at 40 °C with blue LEDs, allowed the formation of **3a** in 75–76% yield.

Once the photocatalytic Meerwein arylation was optimized, the protocol was applied to a series of aryl diazonium salts, bearing different pattern substitutions in the aromatic ring. The synthesis of these compounds was accomplished following general protocols previously described in the literature.[23] Having in mind the development of a one-pot sequential protocol, the use of 5% *v/v* of MeCN was considered as the most suitable conditions for the ADH action when coupling the bioreduction step. Thus, a collection of nineteen 1-arylpropan-2-ones **3a–s** containing various *para*-, *ortho*- and *meta*- substituents were obtained with variable yields (15–95%, Table 3). As in previous photocatalytic approaches,[23,24] unclear correlations were found between these values and the substituents at the aromatic ring, although in general better results were attained for substrates containing electron-withdrawing moieties, in most cases obtaining the desired ketones with moderate to good results. It is important to remark that no other by-products were detected in

Table 3. Substrate scope of the Meerwein arylation using aryl diazonium salts **1a-s** (25 mM), **2** (15 equiv.), [Acr-Mes]ClO_4 (2.5 mol%), H_2O-MeCN (95:5% *v/v*), and blue LED (64 W) for 16 h at 40 °C.

Entry	R	**3a–s** [%][a]
1	**1a** (H)	75
2	**1b** (4-F)	63
3	**1c** (4-Cl)	58
4	**1d** (4-Br)	60
5	**1e** (4-NO_2)	55
6	**1f** (4-OMe)	51
7	**1g** (4-Me)	47
8	**1h** (4-CF_3)	60
9	**1i** (2-F)	65
10	**1j** (2-Me)	78
11	**1k** (2-Br)	63
12	**1l** (2-NO_2)	36
13	**1m** (2-OMe)	49
14	**1n** (3-F)	55
15	**1o** (3-OMe)	28
16	**1p** (3-Me)	95
17	**1q** (3-NO_2)	77
18	**1r** (3,4-$(OMe)_2$)	22
19	**1s** (C3-CH_2OCH_2-C4)	15

[a] Product percentages were measured by GC analyses (see SI for further details).

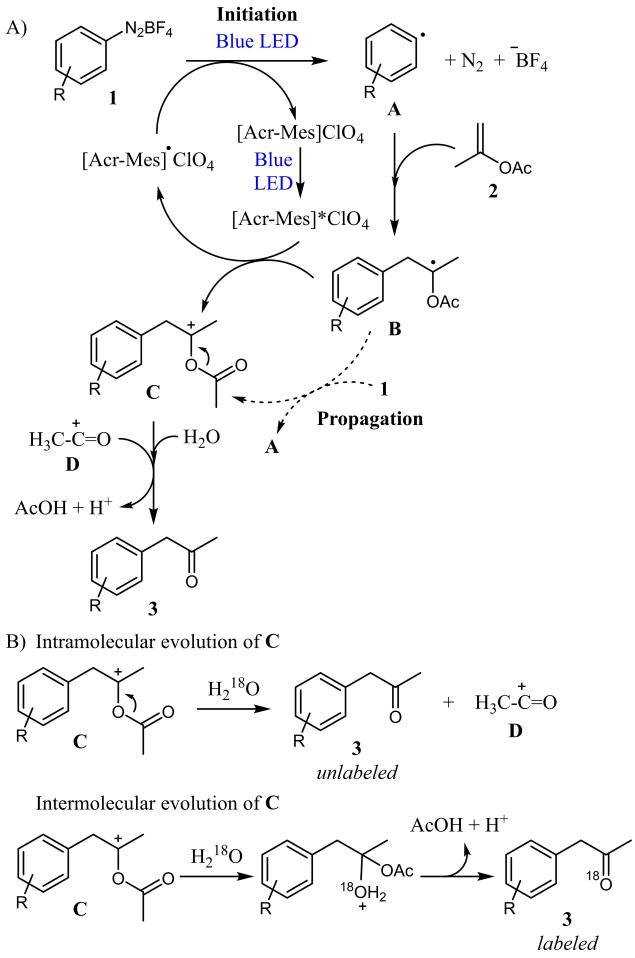
the reaction mixture except small quantities of phenol derivatives (< 3%).

Control experiments were performed to check the stability of the diazonium salt **1a**, isopropenyl acetate (**2**) and the photosensitizer, finding that: (i) the activated ester remained mostly stable during the time, even at acidic pH (see Figure S4 in SI); (ii) the compound **1a** was highly unstable at short reaction times (Figures S5 and S6 in SI); and (iii) [Acr-Mes]-ClO_4 remained mostly stable after light irradiation for several hours (Figure S7 in SI). Undoubtedly, the reaction outcome can be affected due to the diazonium salt **1a–s** that would explain the variable results observed in each case.

Mechanistic Considerations

The mechanism of the Meerwein arylation reaction is very well-known,[6] and it starts with the reduction of the aryl diazonium salt by a reductant to provide the aryl radical, which later reacts with an electrophile, in this case, isopropenyl acetate (**2**). The reductant can be a metal species,[6,20a] an electrode,[20b] an organic compound,[22] or a photocatalyst.[23,24] In our case, it was therefore surprising that [Acr-Mes]ClO_4, a powerful oxidant from the acridinium family,[25] was the best candidate to catalyze this transformation. From Tables 1 and 2, it was obvious its beneficial role even at just 2.5 mol%. However, it was noticeable that even in the absence of photocatalyst (entry 1, Table 1), a small quantity of ketone **3a** was detected, while under dark conditions, no conversion was observed (entry 9, Table 1). With these findings, we propose that the formation of the aryl radical must be accelerated directly by the light (Scheme 2A). In fact, previous reports have already described that arenediazonium salts can be activated using white[26] or blue[27] LED in the absence of photocatalysts.

Once initiated, the aryl radical **A** will attack **2** to afford radical **B**, which can propagate the reaction by direct reduction of **1** or can be oxidized by excited [Acr-Mes]ClO_4 in order to provide the cationic species **C** and the reduced photocatalyst, which now will be able to further react with the aryl diazonium salt giving radical **A** that will enter in a new catalytic cycle. On the other hand, cation **C** could evolve towards ketone **3** *via* intramolecular electron movement, also forming

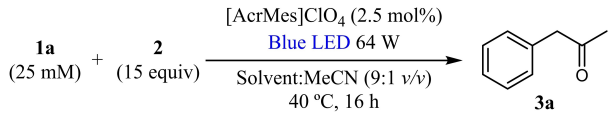


Scheme 2. A) Proposed mechanism for the light-driven formation of 1-arylpropan-2-ones from aryl diazonium salts catalyzed by [Acr-Mes]ClO_4. B) Possible evolution pathways of cation **C** to provide final ketone **3**.

acyl cation **D**,[20b,23] or since the reaction proceeds in aqueous medium, **C** will be attacked by a molecule of water, which after release of a molecule of acetic acid and a proton will finally deliver ketone **3**, as suggested by previous research groups.[24,28] To answer this question, we obtained ketone **3 a** from **1 a** although in labeled-^{18}O water. Thus, if the oxygen would come from the nucleophilic attack of water, labeled-^{18}O ketone **3 a** should be the product detected, differently from the intramolecular evolution of **C**, which would render unlabeled compound **3 a** (Scheme 2B). Surprisingly, we observed by MS a mixture of ^{18}O-**3 a**:^{16}O-**3 a** in a ratio 35:65. However, when we incubated ^{16}O-**3 a** in labeled-^{18}O water at pH 2, which is the final pH in our regular experiments (entry 1, Table 4), we attained a ^{18}O-**3 a**:^{16}O-**3 a** mixture of 47:53. The explanation for this fact must be that the addition of water to carbonyl compounds forming the hydrate form is known to be catalyzed in acidic media. Since in our experiment starting from **1 a** we did not have a low pH during the first hours, this can explain the lower amount of ^{18}O-**3 a** detected in that case. With these data in hand, we postulate that the main reaction pathway from **C** to **3**, even in water, should be the intramolecular one.

It was confirmed that the reaction was proceeding through radical intermediates since the addition of 3 equiv. of TEMPO diminished dramatically the product yield (10%). Since [Acr-Mes]ClO_4 is known as an oxygen activator,[29] the reaction was made in a deoxygenated medium under nitrogen, but the product formation was not affected (68%), therefore ruling out the possibility that oxygen could be involved in the mechanism. Also, when we used alcohol **4 a** as starting material, the formation of ketone **3 a** under the optimized conditions was not detected, discarding **4 a** as possible intermediate of this reaction.

Table 4. Study of the reaction medium to perform the Meerwein arylation and bioreduction cascade.



Entry	Solvent	Final pH	**3 a** [%][a]
1	H_2O	2	75
2	Tris·HCl (100 mM, pH 8.5)	3–4	61
3	Tris·HCl (100 mM, pH 9)	4	56
4	Tris·HCl (200 mM, pH 8)	3–4	69
5	Tris·HCl (200 mM, pH 8.5)	4-5	54
6	Tris·HCl (200 mM, pH 9)	8	<1
7	Tris·HCl (300 mM, pH 7)	2–3	68
8	Tris·HCl (300 mM, pH 7.5)	4	54
9	Tris·HCl (300 mM, pH 9)	8	<1
10	KPi (100 mM, pH 7.5)	4	69
11	Triazine (100 mM, pH 7.5)	2	69
12	MES (100 mM, pH 7.5)	2	53
13	MOPS (100 mM, pH 7.5)	3-4	60
14	$NaHCO_3$ aq. sat. solution	6–7	45

[a] Product yields were calculated by GC analyses using naphthalene as external standard (see SI for further details).

Reaction Medium Study to Set the Photoenzymatic Cascade

After the optimization of the photocatalytic Meerwein arylation of diazonium salts, the next aim was the development of a multicatalytic approach towards chiral 1-arylpropan-2-ols. This strategy consists of the coupling of the ketone synthesis already studied with the stereoselective bioreduction using complementary ADHs to obtain both alcohol enantiomers depending on the enzyme of choice. With this purpose, first the light-driven step was studied in different aqueous buffers, which are preferred by the enzymes (Table 4).

The reaction optimization was developed using MeCN (10% *v/v*) as cosolvent comparing the results with the reaction conditions previously optimized, which led to ketone **3 a** in 75% yield (entry 1). However, the pH of the resulting solution was measured at the final stage finding a highly acidic pH that would make unpractical the subsequent bioreduction. At this point, the use of a Tris·HCl buffer was selected because is one of the most common media for ADH-catalyzed bioreductions. The search for buffers that would afford at the end of the transformation neutral pHs was attempted by varying their concentrations (100–300 mM) and initial pH values (7–9, entries 2–9), although in all cases the formation of a significant amount of the ketone **3 a** led invariably to an acidic pH (2–4). The use of other buffer sources (KPi, triazine, MES and MOPS) at pH 7.5 did not provide significant improvements (entries 10–13). However, the use of a saturated $NaHCO_3$ aqueous solution allowed to reach a 45% yield while a neutral pH was maintained (entry 14), serving as a promising starting point for further optimizations.

Bioreduction of 1-Arylpropan-2-ones

The enzymatic reductions of most of the 1-arylpropan-2-ones here considered have already been reported in the literature,[18b] while the ADH screening for ketones **3 l**,**m**,**o**,**r** was performed. The results can be found in Tables S3–S7 in SI, enabling the access to both enantiomers of the corresponding alcohols (>99% *ee*). Remarkably, suitable ADHs were found to prepare all the 1-arylpropan-2-ols **4 a**–**s** enantiomers, so next the design of a concurrent or a sequential approach was studied.

Sequential vs Concurrent Approach for the Meerwin Arylation-Bioreduction Process

After stablishing both steps of the cascade approach, the first attempt was to develop a one-pot photobiocatalytic concurrent cascade. Thus, diazonium salt **1 a** was selected as benchmark substrate to obtain (*R*)-**4 a** or (*S*)-**4 a** depending on the enzyme of choice. Unfortunately, both steps were not fully compatible even in an aqueous $NaHCO_3$ saturated solution in the presence of MeCN (5% *v*/*v*) and 2-PrOH (5% *v*/*v*), attaining poor yields in the global reaction: 14–18% with evo.1.1.200 depending on the amount of **2** (15–25 equiv.) and just 16% with *E. coli*/ADH-A and 15 equiv. of **2** (see Table S8 in SI).

Therefore, the sequential linear approach was studied. After the light-driven transformation of **1 a** (25 mM) to obtain **3 a** under the optimized conditions (entry 12, Table 1), the final pH of the reaction medium was highly acidic. So, in order to obtain a pH medium compatible with the action of the enzyme, an aqueous $NaHCO_3$ saturated solution was added, affording a final pH around 8. Then, the corresponding ADH and reagents were added to the reaction medium, making feasible the synthesis of both **4 a** enantiomers.

Although some bioreduction experiments also afforded good results using commercial enzymes from Codexis Inc. (see, for instance, Tables S3, S5 and S6 in SI), the sequential approach was developed using the well-known (*S*)-selective ADH-A and (*R*)-selective evo.1.1.200 to demonstrate the generality of the system starting from diazonium salts **1 a**–**s**. Thus, both antipodes of alcohols **4 a**–**s** were obtained in most cases with >99% *ee* and 14–76% overall yield (Figure 1 and Table S9 in SI). These results agreed with

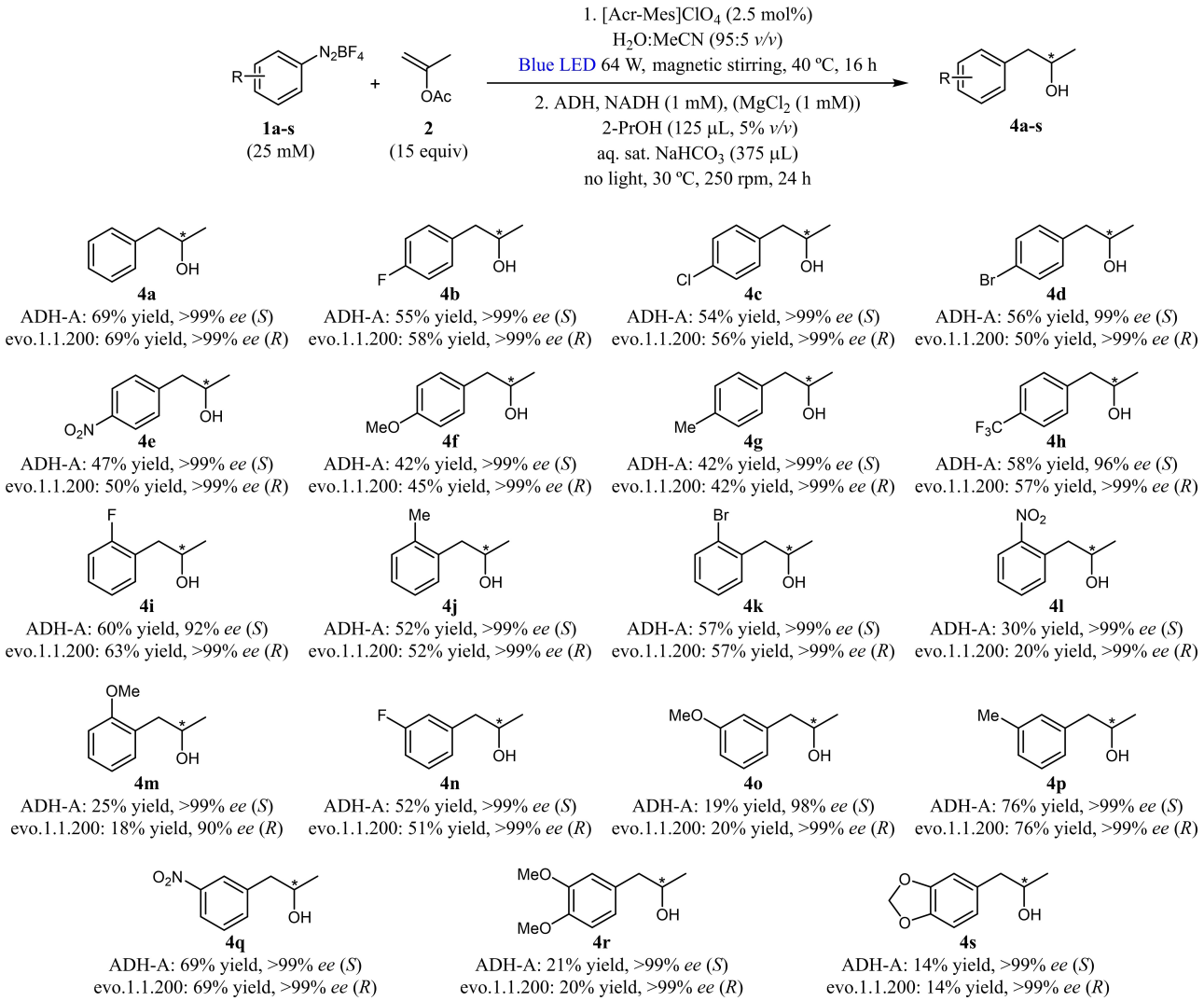


Figure 1. Substrate scope of the photocatalytic Meerwein arylation between diazonium salts **1 a**–**s** and isopropenyl acetate followed by sequential bioreduction of ketones **3 a**–**s** using stereocomplementary ADHs under optimized reaction conditions.

the ones attained for the intermediate ketones **3 a–s** previously described in Table 3.

Finally, the photobiocatalytic sequential process was scaled-up (100 mg, 25 mM) for some of the diazonium salts (**1 a**,**l**,**o–r**), bearing different pattern substitutions at the aromatic ring. Enantiopure alcohols (*R*)- and (*S*)-**4 a** and (*S*)-**4 l**,**o–r** were obtained in 17 to 70% isolated yield after liquid-liquid extraction and chromatography purification on silica gel (see Table S10 in SI).

One-Pot Three-Step Synthesis of Enantiopure 4 a from Aniline (5 a)

The reaction between aromatic amines and enol acetates has also been reported for the synthesis of α-aryl ketones under mild conditions in organic[20b] and aqueous medium,[28] after formation of aryl radicals from *in situ* generated aryl diazonium salts by reaction of the aniline derivatives with ^{t}BuONO. Particularly interesting are the examples described by Cai[30] and Wang[31] groups, that showed photocatalytic approaches to synthesize the desired 1-arylpropan-2-ones from aromatic amines using Eosin B in the presence of Triton X-100 as surfactant,[30] or a semiconductor composite[31] in aqueous media. Taking into account these precedents, we tried to adapt our previously described system to obtain enantiopure (*R*)- and (*S*)-**4 a** from aniline (**5 a**, 25 mM), without isolation of the aryl diazonium salt **1 a** and ketone **3 a** intermediates.

In Scheme 3 is detailed the formation of optically active **4 a** with a 51–53% yield after the one-pot three-step photobiocatalytic protocol, using the ADHs previously selected (see Figure 1). In our case, the addition of $NaNO_2$ first, and after 5 min, of [Acr-Mes]ClO_4, were the optima conditions to form **3 a**. While overall yields were moderate, this system is a remarkable example of the direct transformation of aniline into a valuable enantiopure molecule, opening the door for further applications.

Conclusions

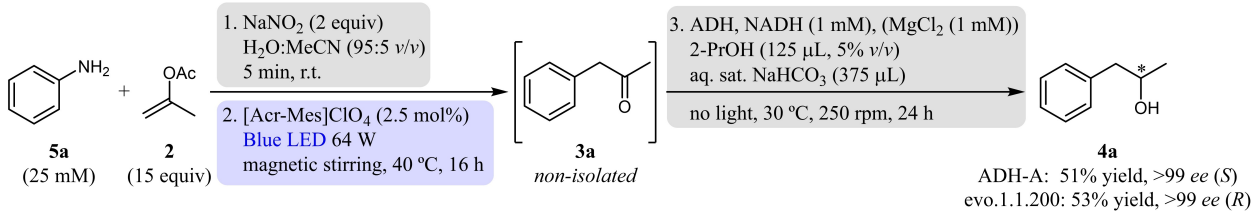
The performance of organic synthetic transformations under mild reaction conditions and in a straightforward manner is currently a need. In addition, the combination of sustainable methodologies to produce valuable (chiral) products offer multiple advantages to traditional syntheses. Herein, the combination of light-driven and biocatalyzed reactions has been investigated. Firstly, a photocatalytic Meerwein arylation has been studied towards the preparation of a series of 1-arylpropan-2-ones, in an aqueous solution together with [Acr-Mes]ClO_4, an organic photosensitizer. After light-induced formation of an aryl radical coming from the diazonium salt, an oxygenated radical intermediate was oxidized by the excited acridinium photocatalyst, which after intramolecular electron movement rendered the final products with variable yields (15–95%). Taking advantage of the mild conditions applied in this step, a biocatalytic process was coupled, consisting of the reduction of the ketone intermediates using stereocomplementary alcohol dehydrogenases. Screening of different ADHs for the enzymatic carbonyl reduction, and optimization of the reaction conditions to accomplish the sequential photobiocatalytic linear approach, led to a variety of valuable 1-arylpropan-2-ols with low to good overall yields (14–76%) and excellent stereoselectivity (90 to >99% *ee*). Some examples were scaled-up to 100 mg of substrate to demonstrate the applicability of this sequential transformation. As a final demonstration, a one-pot three-step sequential photobiocatalytic protocol was designed to obtain enantiopure (*R*)- or (*S*)-**4 a** starting from aniline.

Experimental Section

General information regarding the reagents and enzyme sources, and analytical techniques used for the monitorization and reaction analyses has been added in the Supporting Information.

Typical Procedure for the Light-Driven Meerwein Arylation of Diazonium Salts

Diazonium salt **1 a–s** (0.05 mmol) and [Acr-Mes]ClO_4 (1.25 µmol, 0.5 mg) were placed in a glass vial. Then, isopropenyl acetate (**2**, 15 equiv., 83 µL) was added in combination with dry MeCN (100 µL) and distilled water (1.9 mL). The vial was correctly placed in the set-up being irradiated with blue LED light (64 W) under magnetic stirring for 16 h reaching a temperature of around 40 °C (Figure S2 in SI). Afterwards,



Scheme 3. One-pot three-step sequential photobiocatalytic synthesis of optically active (*R*)- or (*S*)-**4 a** from aniline **5 a** without isolation of the aryl diazonium salt and ketone **3 a** intermediates.

naphthalene (0.05 mmol, 6.4 mg) was added into the reaction medium as external standard. The mixture was extracted with EtOAc (200 µL) 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 200 µL of the organic phase were transferred to a GC glass vial and diluted with EtOAc (until 1 mL total volume) for analysis of the percentage of products by GC analysis (see Section VIII in SI).

Typical Procedure for the Photobiocatalytic One-Pot Two-Step Meerwein Arylation-Bioreduction Sequence

Diazonium salt **1a–s** (0.05 mmol) and [Acr-Mes]ClO_4 (1.25 µmol, 0.5 mg) were placed in a glass vial. Then, isopropenyl acetate (**2**, 15 equiv., 83 µL) was added in combination with dry MeCN (100 µL) and distilled water (1.9 mL). The vial was correctly placed in the set-up and was irradiated with blue LED light (64 W) under magnetic stirring for 16 h reaching a temperature of around 40 °C. After that, 2-PrOH (5% *v/v*, 125 µL), 375–800 µL of an aqueous $NaHCO_3$ saturated solution containing $MgCl_2$ (1 mM for evo.1.1.200), and NADH (1 mM for both *E. coli*/ADH-A and evo.1.1.200) were added. Finally, *E. coli*/ADH-A (10 mg) or evo.1.1.200 (1 mg) was added, and the reaction was shaken at 250 rpm for 24 h at 30 °C. The mixture was extracted with EtOAc (500 µL) and the organic layer separated by centrifugation (2 min, 11,350 *g*). This extraction and centrifugation protocol was repeated once, and the organic layers were combined, dried over Na_2SO_4 and filtered. Percentage of products and enantiomeric excess (as acetylated derivatives) were determined by GC or HPLC analyses (see Section VIII in SI). Derivatization of the crude alcohols was performed dissolving the reaction crude in EtOAc (1 mL) and adding 4-dimethylaminopyridine (DMAP, 10 mg) and acetic anhydride (5 drops). The mixture was shaken at 30 °C and 900 rpm for 4 h. After that time, a 10 M NaOH aqueous solution (500 µL) was added, and the organic layer was separated by centrifugation (2 min, 11,350 *g*), dried over Na_2SO_4, filtered, and transferred to a glass vial for GC analysis.

Scale-Up Procedure for the Photobiocatalytic One-Pot Two-Step Meerwein Arylation-Bioreduction Sequence

The corresponding diazonium salt **1a**,**l**,**o–r** (100 mg) and [Acr-Mes]ClO_4 (0.025 equiv.) were placed into a sealed tube. Then, isopropenyl acetate (**2**, 15 equiv.) was added in combination with dry MeCN (1.6–2.0 mL), and the reaction volume was brought to 16–20 mL with distilled water. The reaction was irradiated during 16 h with blue LED light (64 W) under magnetic stirring at 40 °C. After that, 2-PrOH (5% *v/v*, 1.00–1.25 mL), 15–19 mL of a $NaHCO_3$ aqueous saturated solution containing $MgCl_2$ (1 mM for evo.1.1.200), and NADH (1 mM for both *E. coli*/ADH-A and evo.1.1.200) were added. Finally, *E. coli*/ADH-A (78 mg) or evo.1.1.200 (16 mg) was added, and the reaction was transferred to an orbital shaker to be shaken for 24 h at 30 °C and 250 rpm (see Table S10 in SI). Afterwards, the mixture was extracted with EtOAc (2 × 20 mL), the organic layers were combined, dried over Na_2SO_4 and filtered. The evaporated reaction crude was purified by column chromatography, affording the desired alcohols with 17 to 70% isolated yield.

One-Pot Three-Step Procedure for the Photobiocatalytic Synthesis of (*R*)- or (*S*)-4a Starting from 5a

Aniline **5a** (0.05 mmol, 4.7 mg), isopropenyl acetate (**2**, 15 equiv., 83 µL), MeCN (100 µL) and distilled water (1.9 mL) were mixed in a glass vial. Then, a solution of $NaNO_2$ (0.10 mmol, 6.9 mg) in water (100 µL) was added dropwise with continuous reaction stirring. After 5 min, the reaction turned into yellow, and [Acr-Mes]ClO_4 (1.25 µmol, 0.5 mg) was added. The reaction vial was placed inside the photocatalytic set-up being irradiated with blue LED light (64 W) under magnetic stirring at 40 °C during 16 h. After that, 2-PrOH (5% *v/v*, 125 µL), an aqueous $NaHCO_3$ saturated solution (375 µL) containing $MgCl_2$ (1 mM for evo.1.1.200), and NADH (1 mM for both *E. coli*/ADH-A and evo.1.1.200) were added. Finally, *E. coli*/ADH-A (10 mg) or evo.1.1.200 (1 mg) was added, and the reaction was transferred to an orbital shaker to be shaken for 24 h at 30 °C and 250 rpm. The mixture was extracted with EtOAc (500 µL) and the organic layer separated by centrifugation (2 min, 11,350 *g*). The extraction protocol was performed again with EtOAc (500 µL), and the resulting organic layers were combined, dried over Na_2SO_4 and filtered. Percentage of products and enantiomeric excess (as acetylated derivatives) were determined by GC analyses (see Section VIII in SI).

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