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# Electrochemical α-Arylation of Ketones via Anodic Oxidation of In Situ Generated Silyl Enol Ethers

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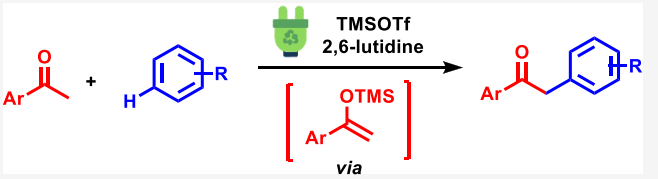
**ABSTRACT:** An electrochemical procedure for the α-arylation of ketones has been developed. The method is based on the generation and one-pot anodic oxidation of silyl enol ethers in the presence of the arene. This strategy avoids isolation of the silyl enol intermediate and the utilization of external supporting electrolytes. Intermolecular arylations, which had not been reported so far, are possible when electron-rich arenes are utilized as coupling partners. The method has been demonstrated for a wide variety of aryl ketones and activated arenes, with moderate to good yields (up to 69%) obtained. Mechanistic insights and a theoretical rationale that explains the ketone α-arylation versus dimerization selectivity are also presented.






## INTRODUCTION

The α-arylation of ketones constitutes a useful and powerful class of C−C bond-forming reactions. Many α-aryl carbonyl-containing compounds feature interesting pharmacological and biological properties, including several approved active pharmaceutical ingredients such as fluindione or anisindione. Over the past two decades, metal-catalyzed α-arylations using aryl halides have been extensively investigated and utilized,[1] stemming from the pioneering work of Buchwald,[2] Hartwig,[3] and Miura.[4] More recently, novel methodologies that circumvent the need for aryl halides have been developed, based on the activation of either the carbonyl α-position or the arene.[5] In this context, oxidative umpolung of silyl enol ethers and enolates, typically using hypervalent iodine reagents, has emerged as an interesting methodology.[6] In such umpolung strategies, electron-rich nucleophilic enol ethers and enolates are transformed into electrophiles, thus promoting the coupling with the electron-rich aromatic ring. Not surprisingly, electrochemical umpolung of silyl enol ethers to achieve carbonyl α-arylation has also been described (Figure 1a).[7−11] For instance, Moeller and co-workers reported electrochemical procedures for the intramolecular coupling of silyl enol ethers and furans, as intermediate steps in the synthesis of Alliacol A and the Arteannuin skeleton.[7,8] An analogous procedure, also involving oxidative coupling of enol ethers and furans, was described by the group of Trauner for the generation of the guanacastepene core.[9] Intramolecular coupling of silyl enol ethers with substituted electron-rich phenyl derivatives has also been demonstrated by Sperry and White (Figure 1a, bottom).[11] These examples illustrate organic electrochemistry as a powerful strategy for the generation of reactivity via umpolung of functional groups,[12] in addition to an enabling potentially sustainable method of organic synthesis.[13]

In all anodic arylation methods cited above, the silyl enol ether was prepared, isolated, and utilized in the electrochemical step in a pure form. An external supporting electrolyte ($LiClO_4$ was utilized in all cases[7−11]) was added to aid the electrolysis by increasing the conductivity of the solution. Moreover, not surprisingly, all examples of electrochemical coupling of silyl enol ethers with arenes published to date comprised intramolecular reactions (Figure 1a).[14] Intermolecular couplings are likely tampered by the expected dimerization of the carbonyl species, which can readily take place by a reaction of the radical cation resulting from anodic oxidation of the silyl enol ether with another unreacted molecule of the enol intermediate.[15]

We envisioned that one-pot electrolysis of a ketone silylation reaction mixture, which includes a silylating agent and a base as reagents, would not require the addition of external supporting electrolytes to confer conductivity to the solution (Figure 1b). Such a strategy would avoid purification of the silyl enol ether and the use of additional salts for the electrochemical step, rendering a more convenient and sustainable methodology. Moreover, we wondered whether intermolecular electrochemical couplings of silyl enol ether and arenes, not reported thus far, were also possible and questioned what accounts for the reaction selectivity in this type of electrochemically induced C−C coupling reaction.

Herein, we describe an electrochemical procedure for the α-arylation of ketones based on the in situ generation and anodic

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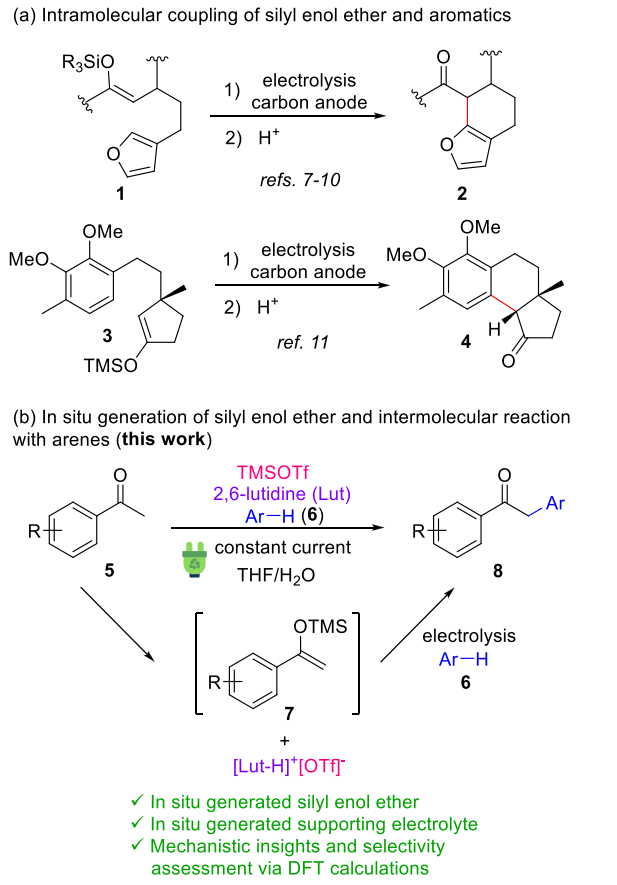


**Figure 1.** (a) Previous examples of the synthesis of $\alpha$-aryl ketones via electrochemical oxidation of silyl enol ethers and intramolecular cyclization and (b) proposed one-pot strategy for intramolecular electrochemical ketone $\alpha$-arylation.

oxidation of silyl enol ethers. Intermolecular couplings have been achieved in the presence of electro-rich aromatic compounds. Mechanistic insights and a theoretical rationale that interprets the intermolecular reaction selectivity are also presented.

## RESULTS AND DISCUSSION

Anodic oxidation of silyl enol ethers **7** (Figure 2) generates the corresponding cation radical. In principle, this reactive species can be trapped by a nucleophile, such as an arene (**6**), providing

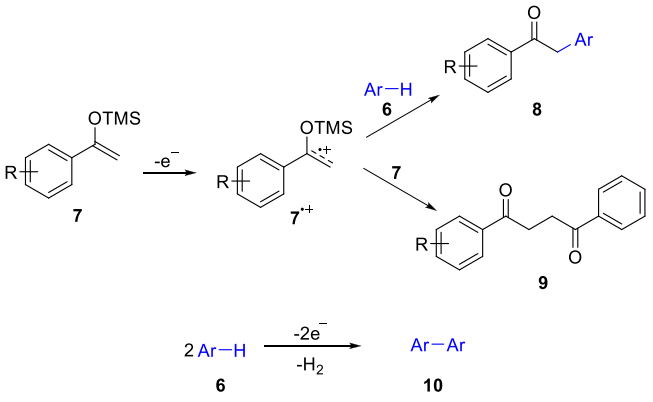


**Figure 2.** Expected reactivity from the anodic oxidation of silyl enol ethers in the presence of arenes.

a convenient strategy for the preparation of $\alpha$-aryl ketones **8**. However, unreacted **7**, with also a marked nucleophilic character, can readily react with the cation radical, providing dimer **9**. A potential strategy to selectively form the target compound **8**, apart from performing the arylation in an intramolecular fashion,[7−11] would be the utilization of electron-rich arenes. Activated aromatics could be able to trap the cation radical, selectively avoiding the formation of **9**. However, electron-rich aromatics can also be oxidized, typically producing the corresponding biaryls **10**.[16] To test this hypothesis, the coupling of acetophenone (**5a**) with 1,3,5-trimethoxybenzene (TMB) (**6a**) was initially evaluated as a model reaction (Table 1). First, the conditions for the in situ generation of the corresponding silyl enol ether **7a** were screened (see Experimental Section). A combination of trimethylsilyl triflate (TMSOTf) as a silylating agent and 2,6-lutidine as a base in THF as solvent provided satisfactory results. Importantly, 2,6-lutidine is sufficiently stable to anodic oxidation and can withstand the electrolysis of the silyl enol ether. Other organic bases typically used for silylation, such as $i$Pr$_2$EtN or Et$_3$N, are oxidatively labile and were therefore not considered. Generation of silyl enol ethers **7** using this system produces 2,6-lutidinium triflate as a byproduct. This salt, which is also relatively electrochemically inert, served as a supporting electrolyte for the subsequent electrolysis.

Electrochemical $\alpha$-arylation experiments were carried out using an IKA ElectraSyn 2.0 reactor in an undivided 5 mL cell. In a typical experiment, acetophenone (**5a**), TMB (**6a**), and 2,6-lutidine were placed into the vial. Then, TMSOTf was added under stirring, and the cell was capped with the vial head equipped with the electrodes. The mixture was stirred for 30 min at room temperature to permit silyl enol ether generation, and then a protic cosolvent was added. The electrolysis under constant current was then initiated. Optimal reaction conditions (Table 1, entry 1) included a 0.5 M concentration of substrate **5a**, 2 equiv of arene **6a**, and a current of 10 mA (6.7 mA/cm$^2$). The reaction outcome was monitored by $^1$H NMR using trichloroethylene as an internal standard. Gratifyingly, NMR analysis of the crude mixture revealed the formation of the target $\alpha$-aryl ketone **8a** and confirmed the generation of a ketone dimer as the main side product of the reaction (see Figure S1). Impervious graphite was found to be an excellent material for this transformation, superior to standard graphite (Table 1, entry 1 vs entry 2). This is probably due to the fact that impervious graphite is nonporous, and therefore it does not absorb reaction solution (graphite was thoroughly washed with THF in an attempt to recover all the material). Other electrode material combinations, including stainless steel and platinum as the cathode material or platinum as the anode, did not improve the results (entries 3−6). A combination of glassy carbon and nickel (entry 7) provided a similar yield as impervious graphite/nickel. However, the latter was selected as optimal material due to its lower cost. Several protic solvents were evaluated as additives to facilitate proton reduction at the cathode. Water (entry 1) performed significantly better than alcohols such as MeOH, $i$PrOH, or hexafluoroisopropanol (HFIP) (entries 8−10). The amount of water also played an important role in the reaction efficiency. Thus, excessive amounts of water (entry 11 vs 12) reduced the yield by more than 20%. Notably, the current efficiency of the anodic oxidation proved to be relatively high, as high conversion and 70% yield was obtained with 2 F/mol, which corresponds to the theoretical amount of charge needed (entry 13). An analogous yield was achieved with 2.2 F/mol,


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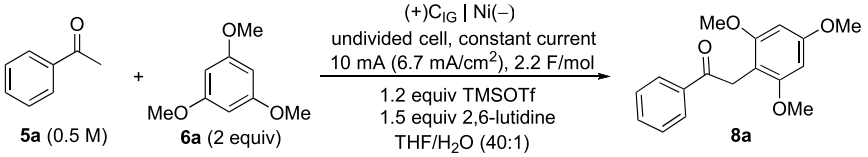
**Table 1. Optimization of the Electrochemical $\alpha$-Arylation of Ketones via In Situ Generated Silyl Enol Ethers**




| entry | variation from the above[a] | yield [%][b] |
|---|---|---|
| 1 | none | 69(62) |
| 2 | (+)graphite /(−)Ni | 46 |
| 3 | (+)graphite/(−)steel | 56 |
| 4 | (+)graphite /(−)Pt | 61 |
| 5 | (+)impervious graphite/(−)Pt | 47 |
| 6 | (+)Pt/(−)Pt | 23 |
| 7 | (+)glassy carbon/(−)Ni | 70 |
| 8 | MeOH instead of $H_2O$ | 44 |
| 9 | iPrOH instead of $H_2O$ | 39 |
| 10 | HFIP instead of $H_2O$ | 53 |
| 11 | THF/$H_2O$ 80:1 | 66 |
| 12 | THF/$H_2O$ 20:1 | 42 |
| 13 | 2 F/mol | 70 |
| 14 | 2.5 F/mol | 54 |
| 15 | 2 equiv base | 59 |
| 16 | 1.5 equiv base, 3 equiv **6a** | 62 |
| 17 | 1 M concentration of **5a** | 66 |

[a]Conditions: 1.5 mmol **5a**, 2 mL of solvent (the total volume of the reaction solution was ca. 3 mL); a 5 mL IKA ElectraSyn 2.0 vial was used. The reaction mixture was stirred at rt for 30 min and then electrolyzed under constant current. [b]Determined by $^1$H NMR using trichloroethylene as an internal standard. Isolated yield shown in parentheses. $C_{IG}$ = impervious graphite.

which was selected as optimal for the methodology to make it suitable for less reactive systems. Further increase of the charge (entry 14) led to product degradation. Variation of the excess amount of arene or 2,6-luditine did not improve the results (entries 15 and 16). Notably, the electrochemical procedure was also compatible with higher substrate concentration (1 M **5a**) (entry 17), although a slightly lower yield was achieved. Purification of the reaction mixture by column chromatography permitted isolation of **8a** (62%). Importantly, dimer **9a** (see Figure 2) could also be isolated and characterized, thus confirming the identity of the main side product of the reaction.

With the optimal reaction conditions in hand, the scope of the electrochemical $\alpha$-arylation was investigated (Figure 3). Both the suitability of a wide variety of aryl ketones (Figure 3a) and electron-rich arenes (Figure 3b) were evaluated. All reactions were carried out under the same conditions to provide a better understanding of the substituent effects. The presence of halogens (**8b**−**d**) in the acetophenone derivative did not have a significant effect on the reaction outcome. A stronger electron-withdrawing group such as a nitrile (**8e**) considerably reduced the yield. In this case, low conversion of the starting material was observed, along with a notable proportion of arene dimerization. This effect could be ascribed to a higher oxidation potential of the silyl enol ether due to the electron-withdrawing effect of the 4-CN group. Interestingly, an electron-rich acetophenone derivative also provided a relatively low yield (**8h**). In this case, aryl−aryl oligomerization may also occur with the activated aromatic ring of the silyl enol ether. Notably, the method was compatible with ketones bearing a sulfur-containing heterocycle (**8i**) but not a pyridine derivative (**8j**). An aliphatic ketone was also evaluated under the optimal electrolysis conditions. Cyclohexanone did not provide the corresponding $\alpha$-aryl derivative **8k**. Instead, partial $\alpha$-carbonyl desaturation most likely ensued.[17] It is expected that a similar effect would be observed for aryl ketones bearing hydrogens in $\beta$-position (e.g., aryl ethyl ketones).

We next turned our attention to the range of arenes that can be utilized for this transformation (Figure 3b). As anticipated, only electron-rich arenes were suitable for the anodic $\alpha$-arylation. Indeed, most examples contained one or two alkoxy substituents. Additional substituents such as alkyl (**8o**) and halogen (**8p**−**r**) were well tolerated. Coupling of the naphthalene ring was also successful (**8s**-**t**) as well as 2-methylthiophene (**8u**). Most compounds could be isolated in moderate yields by column chromatography. In some cases (**8l**, **8t**, and **8u**), purification was difficult, and only NMR yields are reported. As stated above, for the model reaction (**8a**), variable amounts of the dimer formation were observed in many examples and predominated in cases in which low yield was observed. For example, with compound **8l** (13% yield), a 24% NMR yield for the dimer was observed. 1,3-Dialkoxy arenes (**8m**−**8r**) typically resulted in notable amounts of silyl enol dimerization, amounting to 20−35% by $^1$H NMR analysis. Generation of $\alpha$-aryl ketone **8u** also proceeds with concomitant ketone dimerization (25%). It should be noted that many more arenes were evaluated under the optimal electrolysis conditions and failed to produce the $\alpha$-aryl ketones. It was expected that electron-poor aromatics would not be sufficiently reactive to trap the cation radical developed by anodic oxidation of the silyl enol ether **5**, in which case formation of the dimer **9** would ensue (see Figure 2). However, to our surprise, activated arenes such as 1,2,3-trimethoxybenzene or 1,2,4-trimethoxybenezene failed to react. NMR monitoring of the crude reaction mixtures revealed that some electron-rich arenes tended to dimerize, generating biaryl side products **10** while most of the acetophenone (**5a**) remained unreacted. On the other hand, ketone dimerization to **9** instead of $\alpha$-arylation was observed in some cases. We hypothesized that aromatic rings with a very high electron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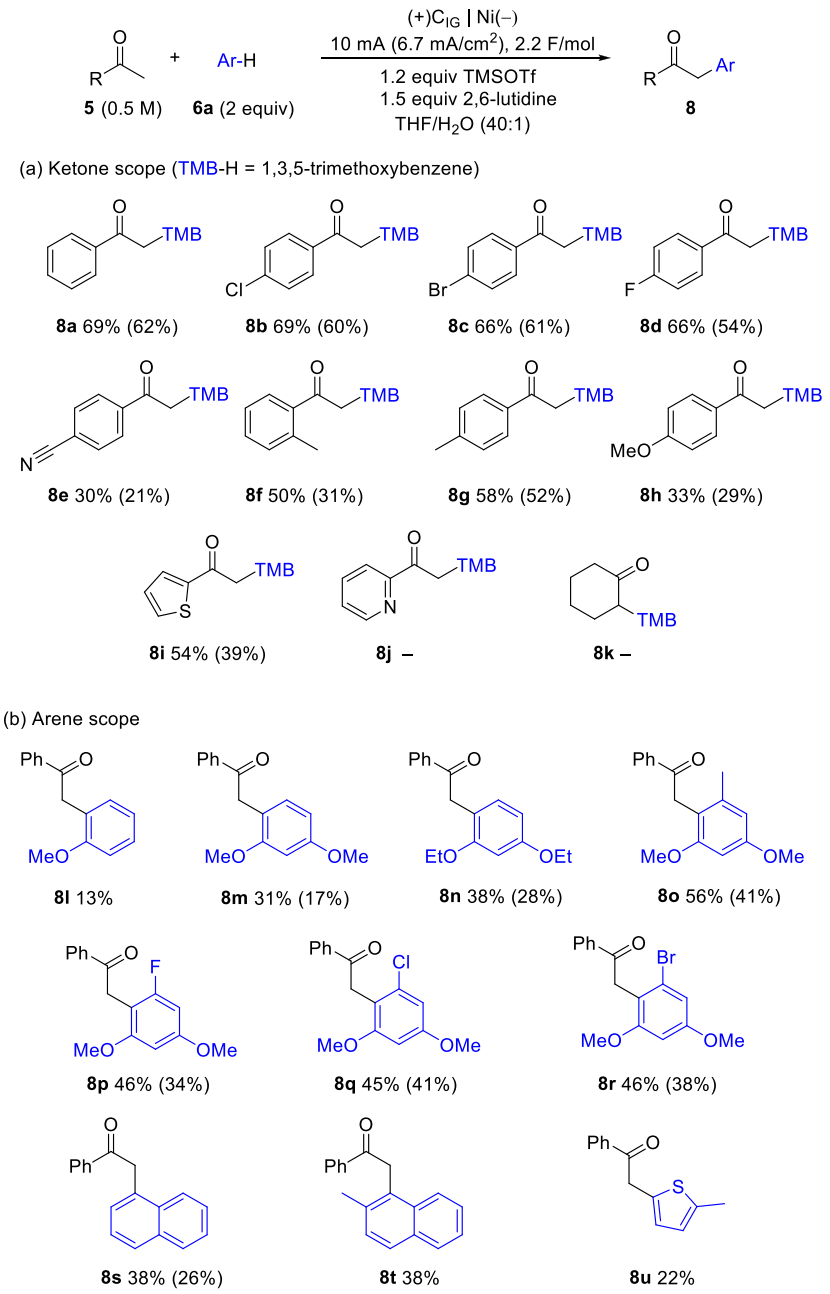


**Figure 3.** Scope of the electrochemical $\alpha$-arylation of ketones. (a) Scope of ketones. (b) Scope of arenes. $^1$H NMR yields using trichloroethylene as a standard, and isolated yields (in parentheses) are shown.

density could oxidize at a lower potential than the silyl enol ether group, thus forming biaryl dimers **10**, while arenes with insufficient electron density would lack sufficient nucleophilicity to trap the cation radical $7^{\bullet+}$.

To shed light into the observed reactivity and provide a theoretical rationale, the ionization potentials (IP) of all arenes tested for the reaction were calculated using density functional theory (DFT). The IP of a molecule is a measure of both its oxidation potential[18] and its nucleophilicity.[19] Moreover, the quadrupole moments of the arenes were also computed. The quadrupole moments of aromatics have classically been associated with their tendency of aggregate via $\pi$-stacking,[20] which may also influence their adsorption behavior in the presence of graphite material.[21] DFT calculations were carried out at the M06-2X/def2-TZVPP level (see Computational Details in the Experimental Section). This method has shown a good correlation between experimental and theoretical values for the ionization and redox potentials of arenes and heteroarenes in solution.[22] Interestingly, when the IP and the quadrupole moment of all arene molecules were plotted (Figure 4), all reactants which had worked followed a similar trend. Successful examples featured an IP in the range 140−147 kcal/mol and a quadrupole in the range from −9 DÅ to −15 DÅ. The IP value had a major impact on the observed arene reactivity. Indeed, all arenes with a value below 140 kcal/mol (Figure 4) had been experimentally observed to fail as $\alpha$-arylation coupling partners, typically giving low conversion of acetophenone **5a** and biaryls **10** as the main side product. This can therefore be ascribed to a lower oxidation potential for the arene compared to the silyl enol ether. On the other hand, arenes with a higher IP


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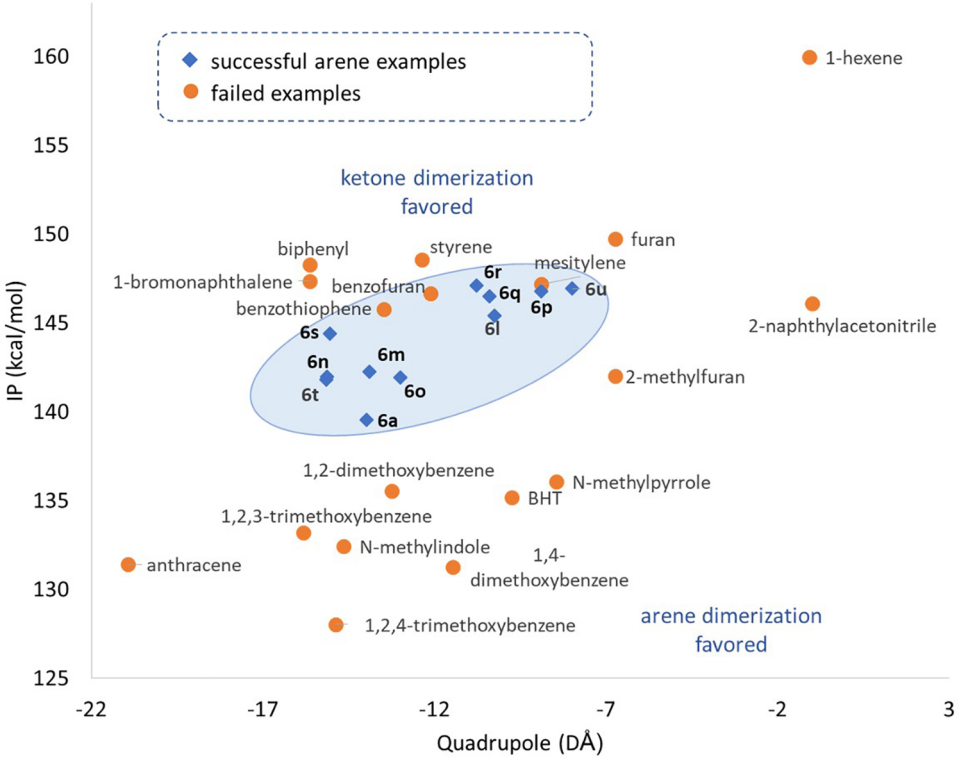


**Figure 4.** Graphic representation of ionization potentials (IP) and quadrupole moments of all arenes evaluated, and additionally 1-hexene, calculated at the M06-2X/def2-TZVPP level.

(e.g., biphenyl, 1-bromonathlene, etc.) failed to trap the cation radical $7^{\bullet+}$ resulting from the anodic oxidation of the enol ether, which thus ensued dimerization to **9**, due to the lack of nucleophilicity of the arene. In this context, an aliphatic alkene (1-hexene) was also tested with the same results.

The effect of the quadrupole moment proved to be more complex. Importantly, aromatic compounds that should have worked according to their IP value (2-methylfuran, 2-naphthylacetonitrile) failed to provide $\alpha$-aryl ketones. Their computed quadrupole moment was less negative, which may point to a lower tendency to aggregate in solution or adsorb on the anode surface. It should be emphasized that the computational data presented a very good fit with the experimental results. Thus, this computational methodology could serve as a predictive tool to evaluate whether a nucleophile is suitable for trapping anodically generated cation radical intermediates. Yet, the calculated molecular properties failed to explain why the ketone $\alpha$-arylation with mesitylene, benzofuran, and benzothiophene did not work.

Cyclic voltammetry of the reaction components (Figure 5) confirmed that acetophenone (**5a**) presents a relatively high oxidation potential, while upon transformation into the corresponding silyl enol ether **7a**, the molecule can be oxidized with ease ($E_{p/2}$ = +0.98 V vs Fc/Fc$^+$). To carry out this voltammogram, **7a** was generated in a separate vial from **5a**, TMSOTf, and 2,6-lutidine and then diluted into a cyclic voltammetry cell containing solvent and supporting electrolyte. 1,3,5-Trimethoxybenzene (**6a**) was oxidized at a higher oxidation potential ($E_{p/2}$ = +1.20 V vs Fc/Fc$^+$), thus explaining that, during the study of the model reaction, no arene oxidation was observed. Both reactants showed irreversible oxidation peaks, pointing to rapid chemical reactions of the cation radicals generated.

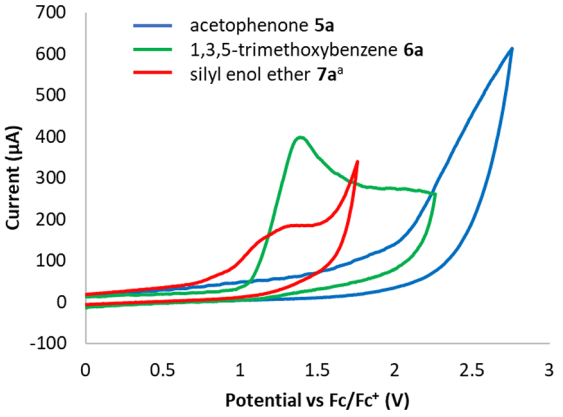


**Figure 5.** Cyclic voltammograms of acetophenone (**5a**), 1,3,5-trimethoxybenzene (**6a**), and intermediate **7a**. Footnote a represents **7a** was generated in situ from **5a**, TMSOTf, and 2,6-lutidine in a separate vial, and an aliquot of the reaction mixture was diluted in the voltammetry cell.

With this information in hand, a mechanism for the electrochemical $\alpha$-arylation of ketones from in situ generated silyl enol ether was proposed (Figure 6). Ketone **5** reacts with TMSOTf in the presence of 2,6-lutidine, generating oxidizable silyl enol ether **7** and 2,6-lutidinium triflate [(Lut-H)$^+$(OTf)$^-$] as a byproduct, thus also producing a salt that can act as a supporting electrolyte. One-electron anodic oxidation of **7** generates the corresponding cation radical $7^{\bullet+}$, which can be trapped either by the arene **6** or by another molecule of **7**. In the latter case, a second oxidation event and hydrolysis release dimer **9**. Trapping of $7^{\bullet+}$ by **6** generates radical intermediate **11**, which, upon a second 1-electron oxidation to **12** and hydrolysis with the release of protons, produces $\alpha$-aryl ketone **8**. Both the formation


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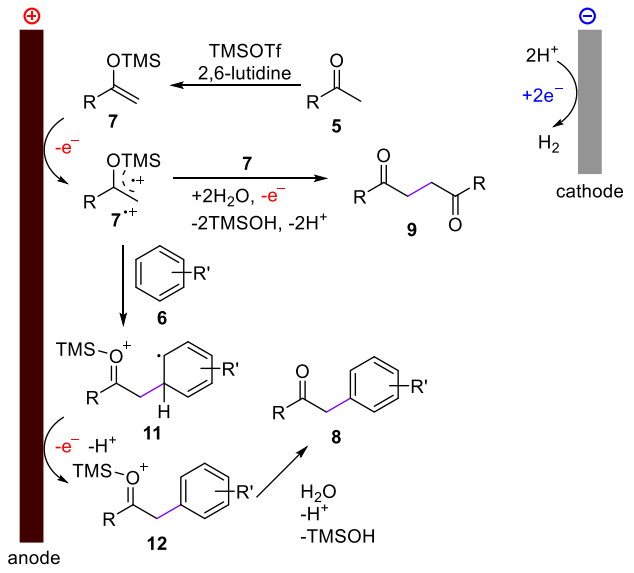


**Figure 6.** Proposed mechanism for the electrochemical $\alpha$-arylation of ketones via in situ generated silyl enol ethers.

of **8** and **9** involve the exchange of 2 electrons with the anode and the release of 2 protons. At the same time, 2 protons are reduced at the cathode producing $H_2$ gas as a byproduct. If an arene **6** with a low oxidation potential is present (lower than the oxidation potential of **7**), **6** is oxidized at the anode instead of **5**, resulting in the corresponding biaryl side product, or even more complex trimers or oligomers.[23] The mechanism of this type of aryl−aryl anodic coupling has been published elsewhere.[24] In an additional experiment, the electrochemical reaction was carried out under the optimal conditions but in the absence of arene **6**. $^1$H NMR analysis of the reaction mixture showed that ketone dimer **9a** had been formed in 53% yield.

## CONCLUSIONS

In summary, we have described an electrochemical procedure for the $\alpha$-arylation of ketones, based on the generation and anodic oxidation of silyl enol ethers in the presence of an arene. The one-pot strategy avoids isolation of the silyl enol intermediate and, importantly, exploits the formation of a salt byproduct during the silylation to increase the conductivity of the reaction mixture. Thus, the addition of supporting electrolytes could be avoided. Only intramolecular arylations based on the anodic oxidation of silyl enol ethers had been previously reported. Herein, intermolecular anodic arylation reactions have been shown to work when electron-rich arenes are utilized. The method simply consists of the addition of TMSOTf and 2,6-lutidine to a THF solution containing the ketone and the arene and, after a few minutes, to permit the formation of silyl enol ether, electrolysis under constant current in an undivided cell with inexpensive impervious graphite and nickel electrodes. Moderate to good yields have been obtained for a variety of aryl ketones. Only electron-rich arenes have been found to be suitable for this transformation. Less activated aromatics were not sufficiently nucleophilic to trap the cation radical intermediate, thus provoking ketone dimerization instead of $\alpha$-arylation. However, some electron-rich arenes also failed in the reaction due to the formation of biaryl side products. This effect has been ascribed to anodic oxidation of the arene instead of the target enol ether. To explain the reaction selectivity and provide a predictive computational tool, the ionization potentials (IP) and quadrupole moments of all arenes evaluated have been calculated using DFT methods. The calculations have shown a good fit with the experimental observations due to their close relation to important parameters such as oxidation potential or nucleophilicity, which play a key role in the arene reactivity.

## EXPERIMENTAL SECTION

**General.** $^1$H NMR spectra were recorded on a 300 MHz instrument. $^{13}$C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts ($\delta$) are expressed in ppm downfield from TMS as an internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. Flash chromatography purifications were carried out on an automated flash chromatography system using cartridges packed with KP-SIL, 60 Å (32−63 $\mu$m particle size). All chemicals, including ketones **5** and arenes **6**, were obtained from standard commercial vendors and were used without any further purification. All electrochemical reactions were carried out in an IKA ElectraSyn 2.0 using IKA Electra-Syn 2.0 undivided cells (5 mL vials) equipped with standard IKA ElectraSyn 2.0 electrodes, unless stated otherwise. All electrodes were polished with sandpaper (3000 frit) before each electrolysis experiment.

**Cyclic Voltammetry.** Cyclic voltammograms were recorded in a glass cell with a Rodeostat open source potentiostat (IO Rodeo Inc.). A glassy carbon disk (a 2 mm diameter rod with a PTFE shroud) was used as the working electrode and a platinum wire as the counter electrode. A silver wire was utilized as a quasi reference electrode, using ferrocene as a reference. The electrolyte consisted of 10 mM of analyte and 0.1 M $Et_4NBF_4$ in MeCN. Samples were degassed prior to analysis.

**Computational Details.** All calculations were carried out with the Gaussian 09 package.[25] The M06-2X density functional method[26] in conjunction with the def2-TZVP(-f) basis set was selected for all geometry optimizations and frequency analysis. The geometries were optimized with the inclusion of solvation effects. For this purpose, the SMD solvation method[27] was employed using tetrahydrofuran as a solvent. The def2-TZVPP basis set was used to obtain single point energies. Ground states were characterized by no imaginary frequency. All of the presented relative energies are free energies at 298.15 K. Ionization potentials were calculated as the difference between the neutral arenes and the corresponding cation radicals.

**Screening of Reaction Conditions for the Generation of the Silyl Enol Ether Intermediate 7a.** In situ generation of **7a** was evaluated using TMSCl or TMSOTf as a silylating agent, MeCN or THF as a solvent, and 2,6-lutidine pr $i$Pr$_2$EtN as the base. For this set of experiments, acetophenone (**5a**) (1 mmol) and the base (1.5 mmol) were placed in a vial and dissolved in the corresponding solvent (2 mL). Then, the silylating agent (1.2 mmol) was added under stirring. The reaction mixture was monitored by GC-FID. TMSCl failed to generate **7a** in the presence of the mild bases utilized at room temperature. In contrast, TMSOTf was successful in all cases. Conversion to **7a** was nearly quantitative in THF, both with 2,6-lutidine and $i$Pr$_2$EtN as the base (96% and 99%, respectively). 2,6-Lutidine was ultimately selected due to its higher stability to anodic oxidation.

**Optimization of the Electrochemical $\alpha$-Arylation of Ketones (Table 1).** To a 5 mL IKA ElectraSyn 2.0 vial were placed the corresponding amounts of 1,3,5-trimethoxybenzene (**6a**), 2 mL of THF, acetophenone (**5a**), and 2,6-lutidine. Then, trimethylsilyl triflate (TMSOTf) was added under stirring. The vial was capped, and the reaction solution was stirred at room temperature for an additional 30 min. The corresponding amount of the protic cosolvent was then added, and the electrolysis was initiated under constant current. After the desired amount of charge had been passed, 2 mL of MeOH was added, and the solution was gently warmed to quench any remaining silyl enol ether species. The solvent was evaporated under reduced pressure. Then, 1 equiv of trichloroethylene was added to the concentrated reaction mixture and analyzed by $^1$H NMR.

**General Procedure for the Electrochemical $\alpha$-Arylation of Ketones (Optimized Conditions).** All reactions were performed in an IKA ElectraSyn 2.0 using an IKA Ni electrode as a cathode and


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impervious graphite as an anode. A 5 mL IKA ElectraSyn 2.0 vial was equipped with a stir bar and charged with 2 mL of THF, 1 mmol of ketone **5**, 174 $\mu$L (1.5 equiv) of 2,6-lutidine, and 2 equiv of the corresponding arene. Then, 217 $\mu$L (1.2 equiv) of trimethylsilyl trifluoromethanesulfonate (TMSOTf) was added, and the reaction mixture was stirred at room temperature for 30 min. Then, 50 $\mu$L water was added, and the electrolysis was initiated with a constant current of 10 mA (ca. 6.7 mA/cm$^2$) and a 600 rpm stirring speed. After 2.2 F/mol of charge had been passed, the reaction mixture was evaporated under reduced pressure, and the residue was purified by flash column chromatography using petroleum ether/ethyl acetate as an eluent.

*1-Phenyl-2-(2,4,6-trimethoxyphenyl)ethan-1-one (**8a**).* Following the general procedure with acetophenone (**5a**) and 1,3,5-trimethoxybenzene (**6a**) as starting materials, the title compound was obtained as a white solid (177 mg, 62% yield): mp = 104−106 °C (lit.[28] 90−91 °C); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.09−7.99 (m, 2H), 7.59−7.49 (m, 1H), 7.49−7.41 (m, 2H), 6.16 (s, 2H), 4.25 (s, 2H), 3.82 (s, 3H), 3.74 (s, 6H). $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 198.5, 160.5, 159.0, 137.6, 132.6, 128.5, 128.3, 104.8, 90.8, 55.8, 55.5, 33.8; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{17}H_{19}O_4$ 287.1278, found 287.1275.

*1-(4-Chlorophenyl)-2-(2,4,6-trimethoxyphenyl)ethan-1-one (**8b**).* Following the general procedure with 4′-chloroacetophenone (**5b**) and 1,3,5-trimethoxybenzene (**6a**) as starting materials, the title compound was obtained as a white solid (192 mg, 60% yield): mp = 122−124 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.00−7.89 (m, 2H), 7.43−7.37 (m, 2H), 6.15 (s, 2H), 4.19 (s, 2H), 3.81 (s, 3H), 3.74 (s, 6H). $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 197.5, 160.6, 158.9, 138.9, 135.8, 129.7, 128.7, 104.4, 90.7, 55.8, 55.5, 33.8; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{17}H_{18}ClO_4$ 321.0888, found 321.0885.

*1-(4-Bromophenyl)-2-(2,4,6-trimethoxyphenyl)ethan-1-one (**8c**).* Following the general procedure with 4′-bromoacetophenone (**5c**) and 1,3,5-trimethoxybenzene (**6a**) as starting materials, the title compound was obtained as a white solid (226 mg, 61% yield): mp = 109−111 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.90−7.84 (m, 2H), 7.59−7.53 (m, 2H), 6.15 (s, 2H), 4.18 (s, 2H), 3.81 (s, 3H), 3.74 (s, 6H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 197.7, 160.6, 158.9, 136.2, 131.7, 129.9, 127.6, 104.4, 90.7, 55.8, 55.5, 33.8; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{17}H_{18}BrO_4$ 365.0383, found 365.0383.

*1-(4-Fluorophenyl)-2-(2,4,6-trimethoxyphenyl)ethan-1-one (**8d**).* Following the general procedure with 4′-fluoroacetophenone (**5d**) and 1,3,5-trimethoxybenzene (**6a**) as starting materials, the title compound was obtained as a white solid (163 mg, 54% yield): mp = 101−103 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.11−7.98 (m, 2H), 7.15−7.06 (m, 2H), 6.16 (s, 2H), 4.20 (s, 2H), 3.82 (s, 3H), 3.74 (s, 6H). $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 197.0, 165.5 (d, $J$ = 253.4 Hz), 160.5, 158.9, 133.9, 130.8, 115.5 (d, $J$ = 21.7 Hz), 104.5, 90.7, 55.8, 55.5, 33.7. $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −106.46 (ddd, $J$ = 14.0, 8.5, 5.5 Hz); HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{17}H_{18}FO_4$ 305.1184, found 305.1187.

*4-(2-(2,4,6-Trimethoxyphenyl)acetyl)benzonitrile (**8e**).* Following the general procedure with 2′,4′,6′-trimethoxyacetophenone (**5e**) and 1,3,5-trimethoxybenzene (**6a**) as starting materials, the title compound was obtained as a colorless oil (65 mg, 21% yield): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.08−8.03 (m, 2H), 7.74−7.70 (m, 2H), 6.14 (s, 2H), 4.20 (s, 2H), 3.81 (s, 3H), 3.74 (s, 6H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 197.7, 160.7, 158.8, 140.6, 132.4, 128.6, 118.3, 115.8, 103.8, 90.7, 55.8, 55.5, 34.3; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{18}H_{18}NO_4$ 312.1230, found 312.1231.

*1-(o-Tolyl)-2-(2,4,6-trimethoxyphenyl)ethan-1-one (**8f**).* Following the general procedure with 2′-methylacetophenone (**5f**) and 1,3,5-trimethoxybenzene (**6a**) as starting materials, the title compound was obtained as a colorless oil (93 mg, 31% yield): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.71 (dd, $J$ = 8.0, 1.5 Hz, 1H), 7.36−7.27 (m, 1H), 7.26−7.16 (m, 2H), 6.14 (s, 2H), 4.13 (s, 2H), 3.80 (s, 3H), 3.77 (s, 6H), 2.47 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 203.4, 160.4, 158.9, 139.0, 137.6, 131.6, 130.6, 128.1, 125.4, 105.0, 90.7, 55.8, 55.4, 36.7, 20.8; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{18}H_{21}O_4$ 301.1434, found 301.1435.

*1-(p-Tolyl)-2-(2,4,6-trimethoxyphenyl)ethan-1-one (**8g**).* Following the general procedure with 4′-methylacetophenone (**5g**) and 1,3,5-trimethoxybenzene (**6a**) as starting materials, the title compound was obtained as white solid (155 mg, 52% yield): mp = 103−105 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.96 (d, $J$ = 8.2 Hz, 2H), 7.27 (d, $J$ = 8.0 Hz, 2H), 6.18 (s, 2H), 4.25 (s, 2H), 3.84 (s, 3H), 3.76 (s, 6H), 2.43 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 198.1, 160.4, 159.0, 143.2, 135.0, 129.1, 128.4, 104.9, 90.7, 55.8, 55.5, 33.6, 21.7; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{18}H_{21}O_4$ 301.1434, found 301.1433.

*1-(4-Methoxyphenyl)-2-(2,4,6-trimethoxyphenyl)ethan-1-one (**8h**).* Following the general procedure with 4′-methoxyacetophenone (**5h**) and 1,3,5-trimethoxybenzene (**6a**) as starting materials, the title compound was obtained as a white solid (93 mg, 29% yield): mp = 132−134 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.06−7.99 (m, 2H), 7.00−6.87 (m, 2H), 6.16 (s, 2H), 4.20 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.74 (s, 6H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 197.0, 163.1, 160.4, 159.0, 130.5, 113.6, 105.0, 90.8, 55.8, 55.5, 55.5, 33.4; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{18}H_{21}O_5$ 317.1384, found 317.1384.

*1-(Thiophen-2-yl)-2-(2,4,6-trimethoxyphenyl)ethan-1-one (**8i**).* Following the general procedure with 2-acetylthiophene (**5i**) and 1,3,5-trimethoxybenzene (**6a**) as starting materials, the title compound was obtained as a white solid (114 mg, 39% yield): mp = 107−109 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.78 (dd, $J$ = 3.8, 1.1 Hz, 1H), 7.57 (dd, $J$ = 4.9, 1.2 Hz, 1H), 7.10 (dd, $J$ = 5.0, 3.8 Hz, 1H), 6.16 (s, 2H), 4.18 (s, 2H), 3.82 (s, 3H), 3.75 (s, 6H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 191.4, 160.6, 159.1, 144.4, 132.8, 131.7, 127.9, 104.4, 90.7, 55.9, 55.5, 34.4; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{15}H_{17}O_4S$ 293.0842, found 293.0843.

*2-(2,4-Dimethoxyphenyl)-1-phenylethan-1-one (**8m**).* Following the general procedure with acetophenone (**5a**) and 1,3-dimethoxybenzene (**6m**) as starting materials, the title compound was obtained as a colorless oil (43 mg, 17% yield): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.07−8.02 (m, 2H), 7.60−7.50 (m, 1H), 7.50−7.42 (m, 2H), 7.12−7.05 (m, 1H), 6.48−6.45 (m, 2H), 4.21 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 198.4, 160.2, 158.2, 137.1, 132.9, 131.3, 128.6, 128.5, 116.1, 104.4, 98.8, 55.5, 55.4, 39.4; MS-EI $m/z$ 256 (7%), 151 (100%), 121 (39%), 105 (25%), 91 (26%), 77 (58%). These data are in agreement with those reported previously in the literature.[30]

*2-(3,5-Diethoxyphenyl)-1-phenylethan-1-one (**8n**).* Following the general procedure with acetophenone (**5a**) and 1,3-diethoxybenzene (**6n**) as starting materials, the title compound was obtained as a colorless oil (79 mg, 28% yield): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.10−7.99 (m, 2H), 7.58−7.49 (m, 1H), 7.49−7.41 (m, 2H), 7.08 (d, $J$ = 8.7 Hz, 1H), 6.48−6.39 (m, 2H), 4.19 (s, 2H), 3.99 (dq, $J$ = 8.7, 7.0 Hz, 4H), 1.40 (t, $J$ = 7.0 Hz, 3H), 1.29 (t, $J$ = 7.0 Hz, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 198.8, 159.4, 157.4, 137.3, 132.9, 131.3, 128.6, 128.5, 116.3, 104.9, 100.0, 63.7, 63.6, 39.4, 15.0, 14.8; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{18}H_{21}O_3$ 285.1485; found 285.1487.

*2-(2,4-Dimethoxy-6-methylphenyl)-1-phenylethan-1-one (**8o**).* Following the general procedure with acetophenone (**5a**) and 1,3-dimethoxy-5-methylbenzene (**6o**) as starting materials the title compound was obtained as a white solid (111 mg, 41% yield): mp = 108−110 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.12−8.02 (m, 2H), 7.62−7.53 (m, 1H), 7.52−7.43 (m, 2H), 6.38 (dd, $J$ = 12.4, 2.3 Hz, 2H), 4.29 (s, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 2.22 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, chloroform-$d$) $\delta$ 198.1, 159.4, 158.5, 139.2, 137.4, 132.9, 128.6, 128.3, 115.0, 106.8, 96.3, 55.7, 55.4, 36.3, 20.4; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{17}H_{19}O_3$ 271.1329, found 271.1330.

*2-(2-Fluoro-4,6-dimethoxyphenyl)-1-phenylethan-1-one (Major) and 2-(4-Fluoro-2,6-dimethoxyphenyl)-1-phenylethan-1-one (Minor) (**8p**).* Following the general procedure with acetophenone (**5a**) and 1-fluoro-3,5-dimethoxybenzene (**6p**) as starting materials, the title compound was obtained as a white solid as a 10:1 mixture of isomers (94 mg, 34% yield, 75% purity according to NMR): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.08−8.01 (m, 2H), 7.62−7.53 (m, 1H), 7.52−7.43 (m, 2H), 6.35−6.22 (m, 2H), 4.25 (s, 2H), 3.79 (s, 3H), 3.74 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 196.8, 163.9, 160.7, 160.5, 160.3, 159.3, 159.1, 137.0, 133.0, 128.6, 128.3, 103.7, 103.5, 94.6, 94.5, 93.3, 92.9, 55.9, 55.6, 33.0, 33.0; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$


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−111.69 (t, $J$ = 10.8 Hz, minor), −115.14 (d, $J$ = 9.9 Hz, major); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{16}H_{16}FO_3$ 275.1078, found 275.1079.

*2-(2-Chloro-4,6-dimethoxyphenyl)-1-phenylethan-1-one (**8q**).* Following the general procedure with acetophenone (**5a**) and 1-chloro-3,5-dimethoxybenzene (**6q**) as starting materials, the title compound was obtained as a white solid (119 mg, 41% yield, 75% purity according to NMR): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.09−8.02 (m, 2H), 7.64−7.52 (m, 1H), 7.54−7.43 (m, 2H), 6.59 (d, $J$ = 2.4 Hz, 1H), 6.40 (d, $J$ = 2.4 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.73 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 196.8, 159.8, 159.2, 137.2, 135.8, 133.0, 128.7, 128.3, 115.2, 105.7, 97.7, 55.9, 55.7, 37.1; HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{16}H_{16}ClO_3$ $[M + H]^+$ 291.0782, found 291.0784.

*2-(2-Bromo-4,6-dimethoxyphenyl)-1-phenylethan-1-one (**8r**).* Following the general procedure with acetophenone (**5a**) and 1-bromo-3,5-dimethoxybenzene (**6r**) as starting materials, the title compound was obtained as a white solid (129 mg, 38% yield, 73% purity according to NMR): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.10−8.01 (m, 2H), 7.63−7.54 (m, 1H), 7.54−7.43 (m, 2H), 6.76 (d, $J$ = 2.4 Hz, 1H), 6.43 (d, $J$ = 2.4 Hz, 1H), 4.46 (s, 2H), 3.80 (s, 3H), 3.72 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 196.7, 160.0, 159.1, 137.2, 133.1, 128.7, 128.3, 126.3, 117.1, 108.8, 98.3, 56.0, 55.7, 39.8; HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{16}H_{16}BrO_3$ 335.0277, found 335.0278.

*2-(Naphthalen-1-yl)-1-phenylethan-1-one (**8s**).* Following the general procedure with acetophenone (**5a**) and naphthalene (**6r**) as starting materials, the title compound was obtained as a white solid (65 mg, 26% yield): mp = 101−103 °C (lit.[29] 106−106 °C); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.14−8.03 (m, 2H), 7.93−7.86 (m, 2H), 7.81 (d, $J$ = 8.1 Hz, 1H), 7.64−7.56 (m, 1H), 7.54−7.46 (m, 4H), 7.45−7.41 (m, 1H), 7.37 (d, $J$ = 6.0 Hz, 1H), 4.75 (s, 2H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 197.7, 136.8, 134.0, 133.4, 132.4, 131.5, 128.9, 128.8, 128.6, 128.1, 128.0, 126.4, 125.9, 125.6, 124.0, 43.2; HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{18}H_{15}O$ 247.1117, found 247.1116.

**Confirmation of the Structure of Side Product 1,4-Diphenylbutane-1,4-dione 9a.** Following the general procedure for the electrochemical $\alpha$-arylation of ketones with acetophenone **5a** as the ketone and naphthalene **6s** as the arene, side product **9a** could be purified and isolated by column chromatography using petroleum ether/ethyl acetate as an eluent as a pale yellow oil (15 mg, 12% yield): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.08−8.01 (m, 4H), 7.63−7.53 (m, 2H), 7.54−7.42 (m, 4H), 3.47 (s, 4H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 198.8, 136.9, 133.3, 128.7, 128.3, 32.7; MS-EI $m/z$ 238 (5%), 133 (7%), 105 (100%), 77 (73%), 51 (29%). These data are in agreement with those reported previously in the literature.[15]

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01224.

Copies of $^1$H and $^{13}$C NMR spectra, Cartesian coordinates, and energies of all calculated structures (PDF)

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### Notes

The authors declare no competing financial interest.

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