

Carboxylation of Aryl Triflates with CO₂ Merging Palladium and Visible-Light-Photoredox Catalysts

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S Supporting Information

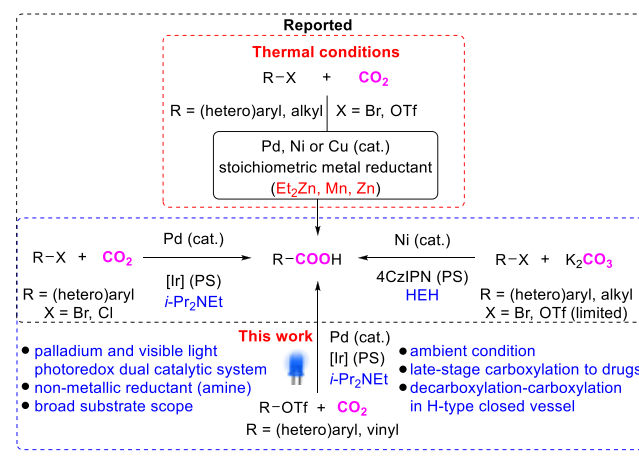
ABSTRACT: We report herein a visible-light-promoted, highly practical carboxylation of readily accessible aryl triflates at ambient temperature and a balloon pressure of CO₂ by the combined use of palladium and photoredox Ir(III) catalysts. Strikingly, the stoichiometric metallic reductant is replaced by a nonmetallic amine reductant providing an environmentally benign carboxylation process. In addition, one-pot synthesis of a carboxylic acid directly from phenol and modification of estrone and concise synthesis of pharmaceutical drugs adapalene and bexarotene have been accomplished via late-stage carboxylation reaction. Furthermore, a parallel decarboxylation–carboxylation reaction has been demonstrated in an H-type closed vessel that is an interesting concept for the strategic sector. Spectroscopic and spectroelectrochemical studies indicated electron transfer from the Ir(III)/DIPEA combination to generate aryl carboxylate and Pd(0) for catalytic turnover.



Due to stringent regulation by the Environmental Protection Agency (EPA), petrochemical industries are being forced to utilize CO₂ that is produced during the processing of fossil fuel.¹ Moreover, carboxylic acids and their derivatives are ubiquitously found in natural products, biologically active compounds, and polymeric materials.² Hence, there is an urgent call for the development of synthetic methods using CO₂ as an abundant, inexpensive, and nontoxic C1 building block.³ An impressive array of transition metal-catalyzed (Pd, Ni, and Cu) carboxylations of aryl, alkyl, alkenyl halides, triflates, or (pseudo)halides has been developed in the past few decades with CO₂.⁴ However, due to the inherent thermodynamic stability of CO₂, most of the transformations require high temperatures, high pressures of CO₂, and stoichiometric amounts of organometallic reductants like Et₂Zn, AlEt₃, Zn or Mn powder, etc. (Scheme 1), which leads to accidental and environmental hazards.⁴ Therefore, to explore the full potential of carboxylation reactions, the development of a mild and practical catalytic protocol without any stoichiometric metal additive is in high demand.

Previously, the group of Nielsen and Jutand reported palladium-catalyzed electrosynthesis of aromatic and α,β -unsaturated carboxylic acids from the corresponding triflates with CO₂.⁵ Deleterious homocoupling, hydrolysis to phenol, and reduced product formation at elevated temperatures lead to the carboxylation products in moderate yields. However, their mechanistic studies are intriguing for the development of transition metal and photoredox dual catalysis.⁶ In recent years, activation of inert CO₂ for the synthesis of carboxylic acids is emerging.⁷ In this vein, the group of Martin and Iwasawa developed an elegant methodology for the carboxylation of aryl bromides and chlorides combining palladium and visible-light-photoredox iridium catalysts.⁸ Subsequently, the group of König reported a nickel and organic photosensitizer dual catalytic approach for the carboxylation of aryl and alkyl bromides and a few aryl triflates using K₂CO₃ as a CO₂ source (Scheme 1).⁹ Thus, we were motivated to develop a general method for carboxylation of aryl triflates using CO₂ directly.

Scheme 1. Carboxylation Reaction with CO₂



In 2015, Murakami and co-workers proposed the carboxylation of *o*-alkylphenyl ketones with CO₂ under ultraviolet-

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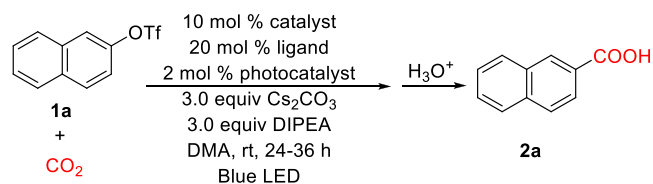
light or solar-light irradiation.^{7a} Jamison and co-workers reported the α -carboxylation of inert amine in a continuous flow via single-electron activation of CO₂ under ultraviolet-light irradiation.^{7c} In 2015, Tsuji and co-workers published cobalt- and nickel-catalyzed carboxylation of alkenyl and sterically hindered aryl triflates utilizing CO₂ with a metallic reductant at elevated temperatures.^{3j} Very recently, Mei and co-workers published nickel-catalyzed carboxylation of aryl and heteroaryl fluorosulfates by CO₂ where 3.0 equiv of manganese has been used as a reducing agent.¹⁰

We report herein a mild and general protocol for the carboxylation of aryl or (hetero)aryl triflates with a balloon pressure of CO₂ combining Pd(OAc)₂ and an iridium(III) photocatalyst and *i*-Pr₂NEt as the nonmetallic reducing agent at room temperature (Scheme 1).

Our initial trials with 2-naphthyl triflate using nickel and photoredox dual catalysts were not effective. Gratifyingly, palladium complexes in combination with electron-rich ligands such as xantphos and photocatalyst **1** provided 25% of the desired carboxylation product in DMA (entry 1, Table 1). The yield was further improved to 45% when photocatalyst Ir(4-F-ppy)₂(dtbpy)(PF₆) **2** was used (entry 2, Table 1). The yield was drastically improved to 82% by using Xphos ligand (entry 7, Table 1), and further screening reveals that 2.0 equiv of *i*-Pr₂NEt and Cs₂CO₃ are optimal reducing agents and bases, respectively. The optimal yield of 89% was obtained with davephos ligand and photocatalyst **3** (entry 12, Table 1). Other organic dyes such as 4CzIPN, 5CzBN, and 3DPAFIPN were found to be inferior compared to Ir catalyst **3**. Our control experiments reveal that all reagents are essential for furnishing the desired product (for details, see the Supporting Information).

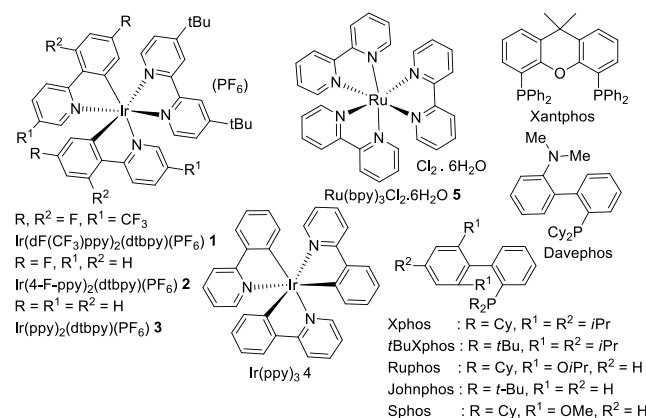
Next, we examined the generality of the reaction with a variety of *ortho*-, *meta*-, and *para*-substituted aryl triflates furnishing corresponding carboxylic acids in excellent to moderate yields (Scheme 2). As shown in Scheme 2, aryl triflates with various functional groups such as cyano (**2j**), trifluoromethoxy (**2k**), fluoro (**2l**), trifluoromethyl (**2m**), ether (**2b**, **2f**, **2h**, **2q**, **2w**, **2ab**, and **2ac**), esters (**2x**), ketone (**2z**), or NBoc or NHBoc (**2y** and **2aa**) groups were well-tolerated under the reaction conditions. This carboxylation reaction took place selectively at the triflate group, leaving chloro (**2g** and **2ac**) and bromo (**2c**) intact for further manipulations, which is a remarkable contrast from Martin's work.⁸ However, DMSO solvent was found to be optimal for **2c**, which may act as a ligand to tune the electronic nature of the palladium complex for selective oxidative addition.¹¹ Gratifyingly, 4-allyl (**2q**)- and 2-allyl (**2r**)-substituted aryl triflates also provided moderate to excellent yields. The sterically demanding substrate also delivered the desired product in good to moderate yields (**2i**, **2n**, **2p**, and **2v**). Overall, electron-rich substrates undergo carboxylation faster than electro-deficient arenes. Interestingly, heterocyclic triflates such as thiophene, indole, and carbazole provided the corresponding carboxylic acids (**2x**, **2y**, and **2ad**) in moderate yields. However, pyridine-3-triflate proved to be unsuccessful for this transformation. Notably, triflate of (+)- δ -tocopherol afforded the corresponding carboxylic acid (**2ae**) in 20% yield with 75% substrate recovery. The carboxylation of a vinyl triflate derived from β -tetralone provided the corresponding carboxylic acid in a 45% yield (**2af**) along with the formation of the homocoupling product. Unfortunately, other -OH derivatives of 2-naphthol such as tosylate, mesylate, nonaflate, and benzylic and allylic triflates provided a very low

Table 1. Optimization of the Reaction Conditions^a



entry	catalyst	ligand	photocatalyst	yield (%)
1	Pd(OAc) ₂	xantphos	1	25
2	Pd(OAc) ₂	xantphos	2	45
3	Pd(OAc) ₂	xantphos	4	not determined
4	Pd(OAc) ₂	xantphos	5	35
5	Pd(OAc) ₂	xantphos	3	50
6	Pd(PPh ₃) ₄	—	2	20
7	Pd(OAc) ₂	xphos	3	82
8	Pd(OAc) ₂	johnphos	3	50
9	Pd(OAc) ₂	ruphos	3	76
10	Pd(OAc) ₂	sphos	3	72
11	Pd(OAc) ₂	<i>t</i> -buxphos	3	50
12	Pd(OAc) ₂	davephos	3	91, 89 ^b
13	Pd(OAc) ₂	davephos	3	80 ^c
14	Pd(OAc) ₂	davephos	3	0, ^d 15 ^e

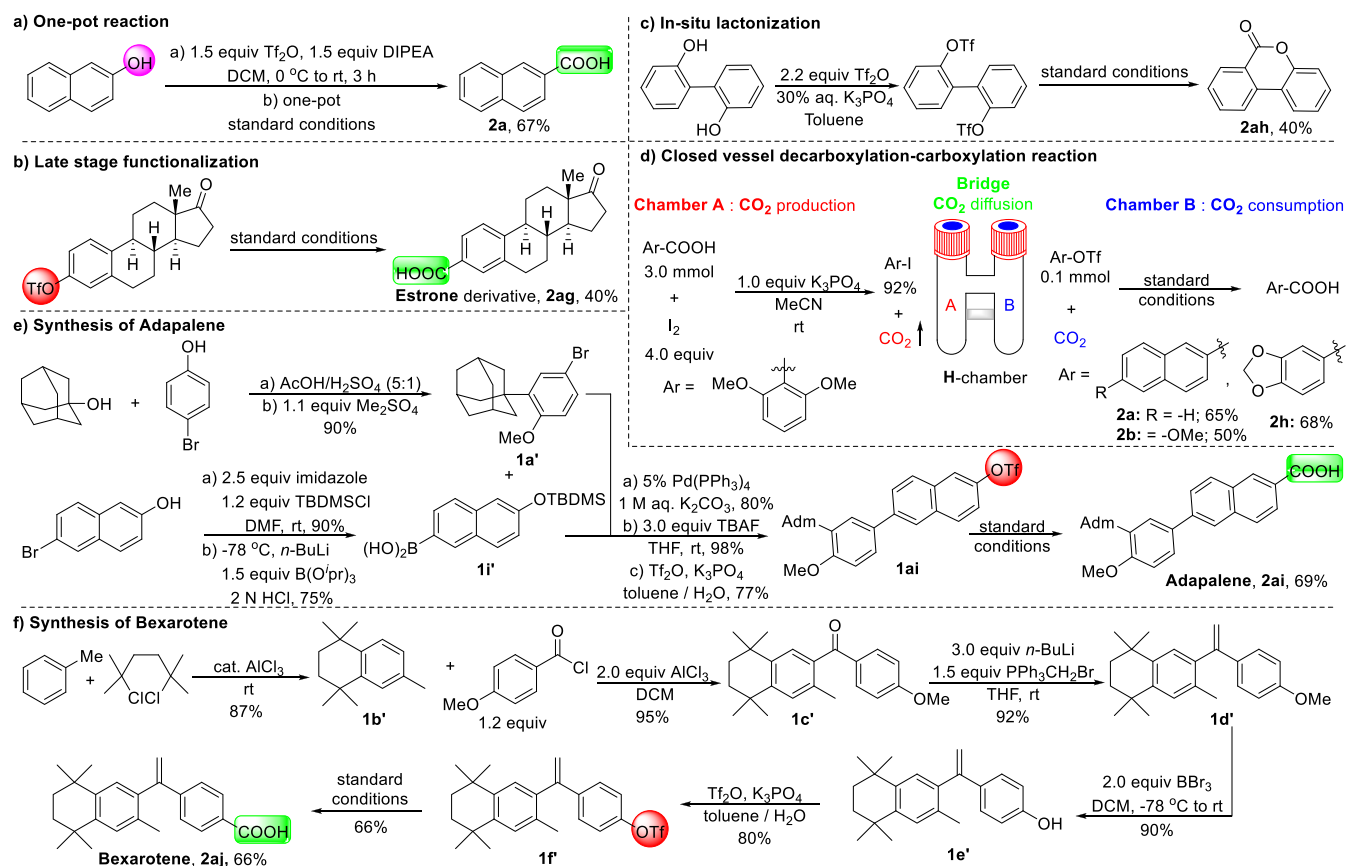
^aReactions were carried out with naphthyl triflate (0.1 mmol), a catalyst (0.01 mmol), a ligand (0.02 mmol), a photocatalyst (0.002 mmol), Cs₂CO₃ (0.3 mmol), and *i*-Pr₂NEt (0.3 mmol) under a CO₂ atmosphere in 2.0 mL of DMA, followed by irradiation with blue light-emitting diodes at room temperature for 24–36 h. Yields are overall isolated yields. ^bTwo equivalents of Cs₂CO₃ and *i*-Pr₂NEt were used for 36 h. ^cDMSO was used. ^dAny reagent absent from the optimized reaction conditions. ^eWithout Cs₂CO₃.



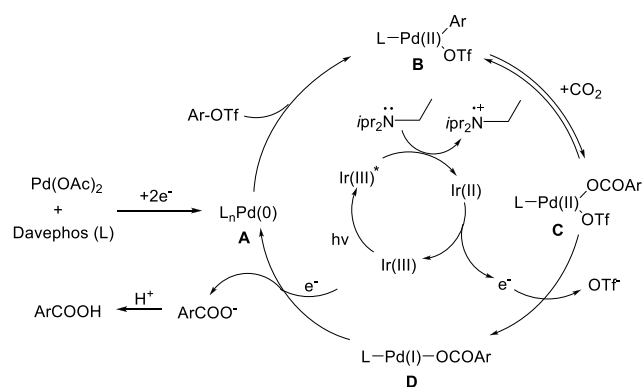
yield (<10%) of the carboxylation product under the optimized reaction conditions.

To demonstrate the practical utility of this methodology, one-pot carboxylation reaction starting from phenol was performed to provide the desired product in good yield (Scheme 3a). This methodology was applied for the late-stage modification of estrone to provide the corresponding carboxylated estrone in a 40% yield (**2ag**) (Scheme 3b). Interestingly, bis-triflate of the corresponding 2,2'-biphenol provided a lactone product directly through selective monocarboxylation and subsequent lactonization **2ah** (Scheme 3c).¹² The late-stage carboxylation was also applied for an expedient synthesis of adapalene **2ai** (Scheme 3e), a Food and Drug Administration-approved drug for acne treatment.¹³ Inexpensive 6-bromo-2-naphthol was used in this protocol instead of expensive 6-bromo-2-naphthoic acid in earlier methods.¹⁴ Furthermore, an improved synthesis of anticancer

Scheme 3. Practical Applications of the Dual Catalytic Carboxylation Reaction



Scheme 4. Plausible Catalytic Cycle



closed vessel that is a novel concept for the strategic sectors in chemical industries for sustainable development.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01532.

Experimental procedures, spectroscopic data, and ^1H , ^{13}C , and ^{19}F NMR spectra of all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(24) For an alternative mechanistic possibility, see the [Supporting Information \(Schemes S1 and S2\)](#).