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## 20.2.10.2 Arenecarboxylic Acids (Update 2024)

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## 20.2.10\_ Product Subclass 10: Arenecarboxylic Acids

*X. Franck and M. Durandetti*

### ***General Introduction***

This update describes published methods for the synthesis of arenecarboxylic acids reported between 2007 and 2022. Publications on this product subclass that appeared prior to 2007 are included in the previous version compiled by Jacobsen in 2007 (Section 20.2.10). Recently, new methodologies based on photochemical or electrochemical synthesis have emerged.

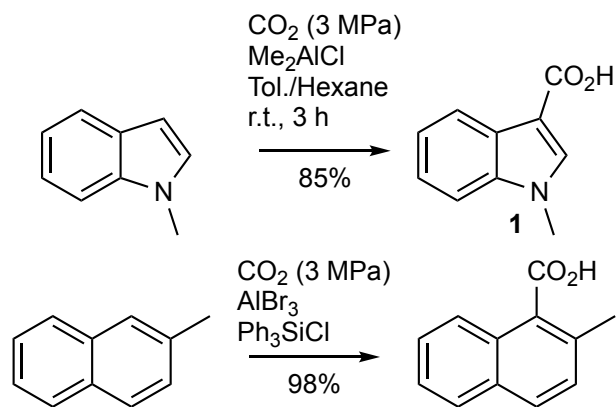
### **20.2.10.1.1 Method 1: Electrophilic Aromatic Substitution**

#### **20.2.10.1.1.1 Variation 1: Friedel–Crafts Carboxylation**

##### ***Introductory Text***

Since the pioneering work of Friedel and Crafts for the direct carboxylation of arenes,<sup>[1]</sup> many groups have increased the efficiency of the reaction by using various Lewis acid. The carboxylation of 1-substituted indoles and pyrroles can be accomplished regioselectively using an equimolar amount of Me<sub>2</sub>AlCl instead of aluminum trihalides under CO<sub>2</sub> pressure (3.0 MPa) at room temperature, as illustrated in the synthesis of 1-methylindole-3-carboxylic acid (**1**) (Scheme 1).<sup>[2]</sup> The combination of AlBr<sub>3</sub> and Ph<sub>3</sub>SiCl in neat substrates under CO<sub>2</sub> pressure (3.0 MPa) at room temperature also allows the carboxylation of polycyclic arenes.<sup>[3]</sup>

**<Scheme 1> Synthesis of Arenes Carboxylic Acids by Friedel-Crafts Reactions<sup>[2,3]</sup>**



1-methylindole-3-carboxylic acid (**1**)

**CAUTION:** Dimethylaluminium chloride solution and aluminium trichloride are severe irritants and react violently with water.

**CAUTION:** Chlorotriphenylsilane causes severe skin burns and eye damage.

A solution of 1-methylindole (131 mg, 1.00 mmol) and  $\text{Me}_2\text{AlCl}$  (1.0 M solution in hexane, 1 mL) in toluene (1 mL) were placed in a 50 cm<sup>3</sup> autoclave equipped with a glass inner tube and a magnetic stirring bar, under nitrogen and the apparatus was purged with  $\text{CO}_2$ , the final pressure being adjusted to 3.0 MPa. The mixture was stirred at room temperature for 3 h, then the reactor was depressurized and the mixture was quenched with 2 M HCl and extracted with chloroform. The organic layer was extracted with 0.5 M  $\text{Na}_2\text{CO}_3$  and acidified with conc. HCl. The carboxylic acid was extracted with chloroform, dried over  $\text{MgSO}_4$ , and evaporated. TLC purification with diethyl ether–hexane (1:1) give 1-methylindole-3-carboxylic acid (**1**). Yield: 149 mg (85%)

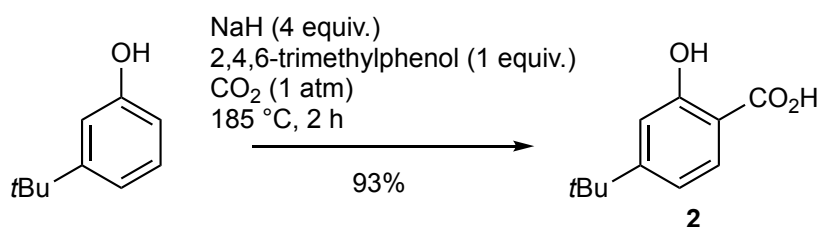
### 20.2.10.1.1.2 Variation 2: Kolbe-Schmitt Reaction

#### *Introductory Text*

The Kolbe-Schmitt reaction is one of the most important and well-known carboxylation reactions, providing *ortho* C–H carboxylation of phenol in basic conditions. The use of

2,4,6-trimethylphenol as additive appears as the key to perform efficiently the ortho-carboxylation of phenol under atmospheric CO<sub>2</sub> pressure, instead of high pressure generally required for the Kolbe-Schmitt reaction (Scheme 2).<sup>[4]</sup> The reaction proceeds at 185 °C in neat conditions with 4 equiv. of sodium hydride. The reaction can be carried out on gram scale, and 4-(*tert*-butyl)-2-hydroxybenzoic acid (**2**) is obtained in 93% isolated yields.

<Scheme 2> *Kolbe-Schmitt Carboxylation of Phenols*<sup>[4]</sup>



4-(*tert*-butyl)-2-hydroxybenzoic acid (**2**)

**CAUTION:** Sodium hydride is highly corrosive, reacts violently with water and is flammable in air.

**CAUTION:** 2,4,6-trimethylphenol causes skin irritation and serious eye damage.

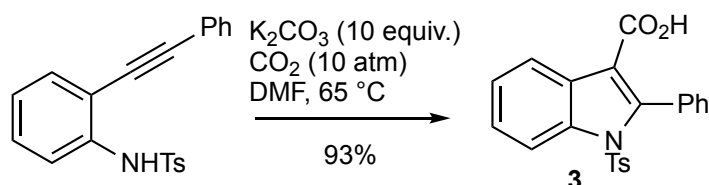
In a glovebox, NaH (60% dispersion in mineral oil, 1.12 g, 28.0 mmol) was added to a vial containing 3-(*tert*-butyl)phenol (1.050 g, 7.0 mmol) and 2,4,6-trimethylphenol (952 mg, 7 mmol), and the mixture was heated to 100 °C. After 5 min., the flask was cooled to room temperature, to reduce the mixture to powder. The vial was purged with CO<sub>2</sub> in an ice bath, and the mixture is reacted with a balloon filled with CO<sub>2</sub> at 185 °C for 2 h. After cooling to room temperature, the mixture was hydrolyzed carefully with 50 mL of H<sub>2</sub>O, and acidified with HCl 1 M to pH 4, then extracted with EtOAc. After drying over MgSO<sub>4</sub>, the solvent was evaporated to dryness and the crude was purified by column chromatography to give 4-(*tert*-butyl)-2-hydroxybenzoic acid (**2**). Yield: 1.26 g (93%)

### 20.2.10.1.1.3 Variation 3: Base promoted Carboxylation

#### *Introductory Text*

A tandem cyclisation of 2-ethynylphenols and subsequent CO<sub>2</sub> carboxylation allows the formation of 3-carboxylated benzofurans in good yields.<sup>[5]</sup> Extension of the process to indoles gives for example *N*-Tosyl-2-phenylindole-3-carboxylic acid (**3**) in 93% yield (Scheme 2). The carboxylation of electron-deficient azaarenes, such as benzoxazoles or benzothiazoles, is efficiently performed in the presence of Cs<sub>2</sub>CO<sub>3</sub><sup>[6]</sup> or KO-*t*Bu.<sup>[7]</sup> On the contrary, the carboxylation of electron rich heteroarenes can be promoted by LiO-*t*Bu in the presence of CsF and [18]crown-6.<sup>[8]</sup>

#### <Scheme 3> *Synthesis of Carboxylated Indoles or Benzofuranes through a Tandem Cyclisation-Carboxylation process*<sup>[5]</sup>



#### *N*-Tosyl-2-phenylindole-3-carboxylic acid (**3**)

K<sub>2</sub>CO<sub>3</sub> (0.35 g, 2.5 mmol) was added to a solution of *N*-[2-(phenylethynyl)phenyl]-4-toluene sulfonamide (0.087 g, 0.25 mmol) in DMF (3 mL) and the solution was stirred at 65 °C during 24 h under 10 atm of CO<sub>2</sub>. 2 M HCl was added to quench the reaction and the product was extracted with AcOEt. The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel), allowing *N*-Tosyl-2-phenylindole-3-carboxylic acid (**3**).  
Yield: 0.091 g (93%)

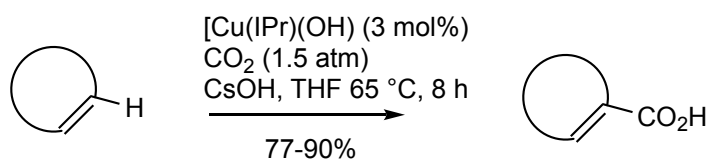
## 20.2.10.1.2 Method 2: C–H Activation for Carboxylation or Carbonylation



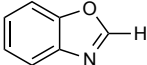
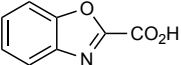
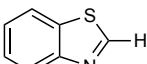
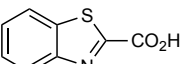
### 20.2.10.1.2.1 Variation 1: Copper-Catalyzed directed C(sp<sup>2</sup>)–H Carboxylation


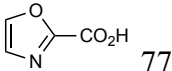
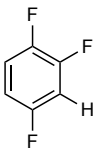
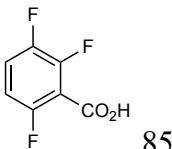
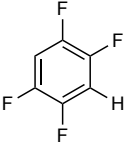
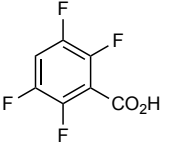
#### *Introductory Text*

NHC copper(I) hydroxide appears to be a highly reactive catalyst for performing direct C(sp<sup>2</sup>)–H carboxylation of a significant range of heteroaromatic rings containing acidic protons (C–H bond that have a pK<sub>a</sub> < 27.7).<sup>[9]</sup> The reaction must be carried out at 65 °C to obtain quantitative yields of carboxylic acid, and is selective for the most acidic proton, as shown by 2-benzoxazolecarboxylic acid (**4**) which is obtained in 90% isolated yield. C–H carboxylation of unactivated arenes was developed using IPrCuI, which reacts with an organoborate generated in situ after Ir-catalyzed C–H borylation.<sup>[10]</sup>

#### <Scheme 4> C–H carboxylation of aromatic substrates with [Cu(IPr)(OH)]<sup>[9]</sup>



	 Yield (%)	Ref
	 <b>4</b> 90	[9]
	 82	[9]

	 77	[9]
	 85	[9]
	 93	[9]

#### 2-benzoxazolecarboxylic acid (**4**)

A solution of [Cu(IPr)(OH)] (14 mg, 0.03 mmol) was added to CsOH (164.9 mg, 1.1 mmol) in THF (1.7 mL) under 1.5 bar of CO<sub>2</sub> and the solution was incubated at 65 °C with a vigorous stirring of 1450 rpm. After 15 minutes, a solution of benzoxazole (1 mmol) in THF (0.3 mL) was added via a CO<sub>2</sub>-flushed syringe, and stirred for 12 h at 65 °C. 1 mmol HCl was added to quench the reaction. The solvent was removed under reduced pressure, and the product was extracted with AcOEt, washed with 3 times with 4 mL of 15 % aqueous NaCl. The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent was removed under reduced pressure, giving 2-benzoxazolecarboxylic acid (**4**). Yield: 90%

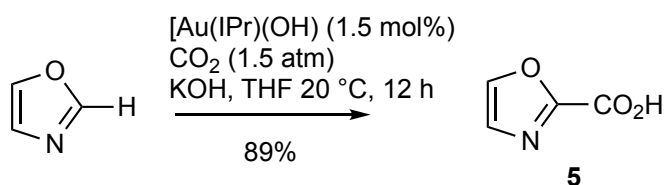
### 20.2.10.1.2.2 Variation 2: Gold- or Rhodium Catalyzed C(sp<sup>2</sup>)-H Carboxylation

#### *Introductory Text*

Au(I) allows the activation of C–H bonds of aromatic substrates. [Au(IPr)(OH)] appears as a Brønsted base for acidic C–H bond, and the organogold intermediate performs a nucleophilic addition on CO<sub>2</sub>. Under these conditions, oxazole-2-carboxylic acid (**5**) is

obtained in 89% yield.<sup>[11]</sup> The activation can be extended to less acidic protons, by increasing the  $\sigma$ -donor ability of the NHC ligand. Finally various (hetero)arenes were carboxylated in good to excellent yields, with high regioselectivity, with the exception of positions with protons of comparable pK<sub>a</sub>s. Direct carboxylation of unactivated arenes under atmospheric CO<sub>2</sub> pressure is achieved by rhodium-catalyzed C–H bond activation with good regioselectivities, in the presence of a nitrogen-directing group. The process is effective with various arenepyridines.<sup>[12]</sup> The necessity of a directing group, which cannot be removed, appears to be a limitation.<sup>[13]</sup>

**<Scheme 5> C–H carboxylation of aromatic substrates with [Au(IPr)(OH)]<sup>[11]</sup>**



oxazole-2-carboxylic acid (**5**)

A solution of [Au(IPr)(OH)] (9 mg, 0.015 mmol) was added to KOH (58.9 mg, 1.05 mmol) in THF (1.2 mL) under 1.5 bar of CO<sub>2</sub> and the solution was incubated at 20 °C with a vigorous stirring of 1450 rpm. After 15 minutes, a solution of oxazole (1 mmol) in THF (0.3 mL) was added via a CO<sub>2</sub>-flushed syringe, and stirred for 12 h at 20 °C. 1 mmol HCl was added to quench the reaction. The product was extracted with 3 times with 3 mL of AcOEt, and the organic layers were washed with 4 mL of 15 % aqueous NaCl. The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent was removed under reduced pressure. Purification by flash chromatography (hexane/AcOEt 5/1) gives oxazole-2-carboxylic acid (**5**). Yield: 89%

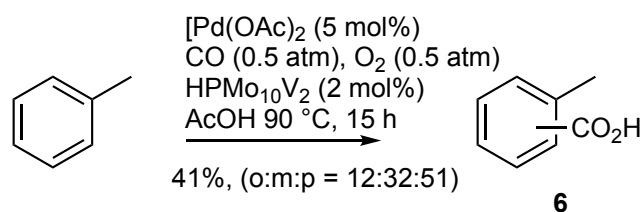
### 20.2.10.1.2.3 Variation 3: Palladium-Catalyzed C(sp<sup>2</sup>)–H Carboxylation or carbonylation



## Introductory Text

Palladium(II) acetate promotes the CO<sub>2</sub> insertion into various arenes with moderate to good selectivity using a concerted-metalation-deprotonation (CMD) type reaction in the presence of LiOtBu, and has been applied to the gram-scale synthesis of veratric acid.<sup>[14]</sup> Carbonylation of CO was achieved by combining Pd(OAc)<sub>2</sub> with H<sub>5</sub>PMo<sub>10</sub>V<sub>2</sub>O<sub>40</sub>,nH<sub>2</sub>O (HPMo<sub>10</sub>V<sub>2</sub>), in the presence of O<sub>2</sub>. The proposed mechanism is based on hydrogen substitution on the arene ring to form a σ-arylpalladium which reacts with CO to form an aroyl palladium species. Carboxylic acids are obtained after reductive elimination, in moderate yields. The regioselectivity is modest, and appears to be dominated by steric factor.<sup>[15]</sup>

### <Scheme 6> C–H carboxylation of aromatic substrates with Pd(OAc)<sub>2</sub><sup>[15]</sup>



Toluic acid (**6**)

**CAUTION:** Carbon monoxide is extremely flammable and exposure to higher concentrations can quickly lead to a coma.

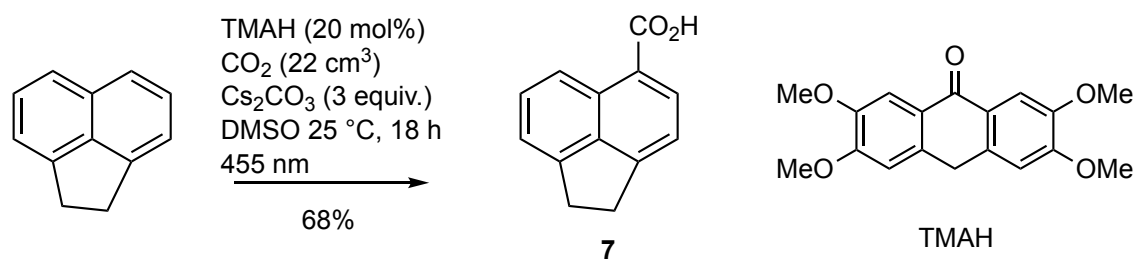
A solution of Pd(OAc)<sub>2</sub> (0.1 mmol) and HPMo<sub>10</sub>V<sub>2</sub> (0.04 mmol) was added to toluene (2 mmol) in AcOH (5 mL). Then the reaction was stirred under 0.5 atm of CO and 0.5 atm of O<sub>2</sub> at 90 °C during 15 h. The solvent was removed under reduced pressure, and the residue was extracted with 1 M NaOH (8 mL) and isopropyl ether (5 mL). The aqueous layer was acidified by H<sub>2</sub>SO<sub>4</sub> and then extracted with isopropyl ether. Toluic acid (**6**) can be isolated or engaged in an esterification process. Yield: 41%

## 20.2.10.1.2.4 Variation 4: Photocatalytic C(sp<sup>2</sup>)-H Carboxylation

### *Introductory Text*

Photocatalysis has re-emerged recently, and allows the insertion of CO<sub>2</sub> into C(sp<sup>2</sup>)-H, using blue LED light. The formation of the anthrolate anion as a photocatalyst, under blue-light excitation, allows the reduction of aromatic compounds into their corresponding radical anions, which react with CO<sub>2</sub>.<sup>[16]</sup> This approach presents an atom-economy alternative, with a wide range of substrates. Acenaphthene was selectively carboxylated in 68% yield under blue LED irradiation with TMAH as photosensitizer, Cs<sub>2</sub>CO<sub>3</sub> as the base, under CO<sub>2</sub> pressure.

### *<Scheme 7> C-H carboxylation of aromatic substrates with TMAH as photosensitizer<sup>[16]</sup>*



### 5-Acenaphthenecarboxylic acid (7)

A solution of acenaphthene (0.1 mmol) was added to TMAH as photocatalyst (6.3 mg, 0.02 mmol, 20 mol%) in a dry flat-bottomed crimp vial (5 mL). Cs<sub>2</sub>CO<sub>3</sub> (98 mg, 3 equiv.) was quickly added and the vial was sealed with a Supelco aluminium crimp seal with septum (PTFE/butyl). The vial was then evacuated and refilled with CO<sub>2</sub> (5 times) via syringe needle. The reaction mixture was dissolved in DMSO (1 mL, dry and degassed by bubbling with N<sub>2</sub>) The vial was sealed with two layers of Parafilm® and then gaseous CO<sub>2</sub> was added via a Luer Lock Monoject™ (22 cm<sup>3</sup>) syringe, into the head space. The

vial was stirred and irradiated at 455 nm at 25 °C (constant temperature was maintained via a cooling circuit connect to a thermostat). After 18 hours, the reaction was transferred with aq. NaOH (0.1M) into a centrifuge tube and was washed with 2 times with Et<sub>2</sub>O. The aqueous layer was acidified by adding aq. HCl (2M) and was extracted 3 times with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent was removed under reduced pressure. Purification by flash chromatography (hexane/AcOEt with 0.5% HOAc) gives 5-Acenaphthenecarboxylic acid (**7**). Yield: 68%

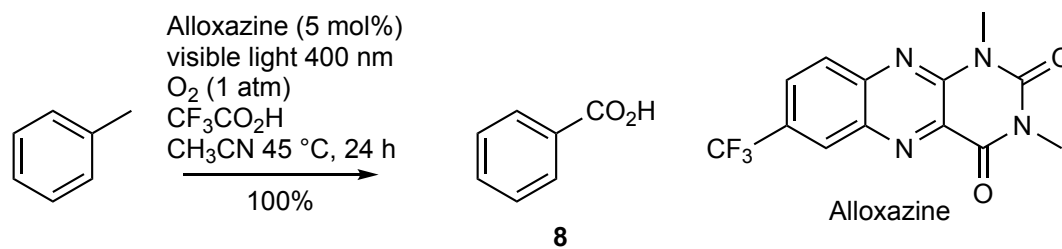
### 20.2.10.1.3 Method 3: Oxydative Method

#### 20.2.10.1.3.1 Variation 1: Oxidation of Alkyl Substituents

##### *Introductory Text*

The alkyl side chains of substituted benzene derivatives can be oxidized to carboxylic acid groups using flavine-based photocatalyst. The excited ethylene-bridged flavinium salt is an extremely strong oxidizing agent, capable of oxidating toluene derivatives.<sup>[17]</sup> By modulating the flavine core, the oxidation reaction can evolve into either aldehyde or carboxylic acid, and finally, benzoic acid (**8**) was selectively obtained from toluene under acidic conditions using alloxazine.<sup>[18]</sup>

##### *<Scheme 8> Oxidation of toluene derivatives with flavinium salt as oxydant<sup>[18]</sup>*



Benzoic acid (**8**)

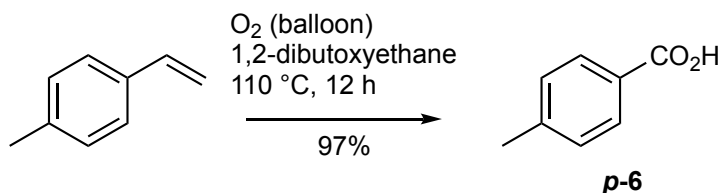
A solution of toluene (1 mmol), Alloxazine (0.05 mmol, 5 mol%) CF<sub>3</sub>CO<sub>2</sub>H (1 mmol) and activated MS 4 Å (150 mg) in CH<sub>3</sub>CN (2 mL) was bubbled with O<sub>2</sub> (2 min). The reaction mixture was stirred and irradiated with a LED Engine (400 nm, 1030 mW) diodes under O<sub>2</sub> atmosphere (balloon) at 45 °C. After 24 hours, the solid was filtered off, and the solvent was removed under reduced pressure. Purification by flash chromatography yields benzoic acid (**8**). Yield: 100%

### 20.2.10.1.3.2 Variation 2: Oxidative cleavage of Olefins

#### *Introductory Text*

Benzoic acids can be obtained by oxidative cleavage of styrene using various oxidizing agents such as I<sub>2</sub>/NaOH/TBHP,<sup>[19]</sup> FeCl<sub>3</sub>/TBHP,<sup>[20]</sup> NiBr<sub>2</sub>/O<sub>2</sub>.<sup>[21]</sup> Recently, 1,2-dibutoxyethane, as solvent, in combination with oxygen enables oxidative cleavage of various styrene derivatives into benzoic acids under very mild conditions, avoiding the use of an external catalyst or additive, as exemplified with *p*-toullic acid (*p*-**6**).<sup>[22]</sup> Moreover, in terms of environmental friendliness, more than 5 cycles can be carried out without any loss of chemical yields.

#### *<Scheme 9> Conversion of styrene derivatives into benzoic acids by oxidative cleavage<sup>[22]</sup>*



#### *p*-Toluic acid (*p*-**6**)

A solution of *p*-methyl styrene (0.6 mmol), and 1,2-dibutoxyethane (0.50 mL, 2.4 mmol) was added to a 5 mL round-bottom flask with O<sub>2</sub> balloon at room temperature. The

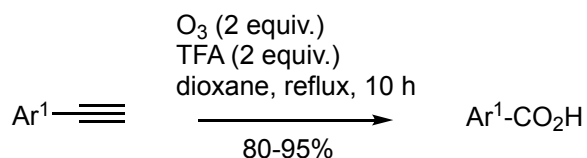
reaction mixture was stirred and heated in an oil bath at 110 °C. After 12 hours, the reaction mixture was cooled down to room temperature. Purification by flash chromatography yields *p*-methyl benzoic acid (**p-6**). Yield: 97%

### 20.2.10.1.3.3 Variation 3: Oxidative cleavage of Alkynes

#### *Introductory Text*

In addition to olefin oxidation, the FeCl<sub>3</sub>/TBHP,<sup>[20]</sup> system also cleaves aromatic alkynes to benzoic acids, with good chemical compatibility. The carboxylic acids were purified by simple filtration. The mixture of ozone and trifluoroacetic acid also enables arylalkynes to be oxidized under green and easy-to-use conditions, as in the synthesis of benzoic acid (**8**) from phenylacetylene.<sup>[23]</sup>

*<Scheme 10> Formation of benzoic acid from phenylacetylene by oxidation using trifluoroacetic acid and ozone mixture<sup>[23]</sup>*



Ar <sup>1</sup>	Yield (%)	Ref
Ph	<b>8</b> 95	[23]
4-Tol	90	[23]
4-Br-C <sub>6</sub> H <sub>4</sub>	89	[23]
4-Ph-C <sub>6</sub> H <sub>4</sub>	87	[23]
4-MeO-C <sub>6</sub> H <sub>4</sub>	91	[23]

Benzoic acid (**8**)

To a solution of phenylacetylene (1 equiv.) in dioxane (5 mL), oxone (2 equiv.) and TFA (2 equiv.) were added. The reaction mixture was stirred and heated to reflux. After 10 hours, the reaction mixture was cooled down to room temperature. H<sub>2</sub>O (10 mL) was added to quench the reaction. The product was extracted twice with 20 mL of EtOAc, and the organic layers were washed with sat. NaHCO<sub>3</sub> solution. The aqueous layers were poured onto crushed ice and treated with 2 M HCl, allowing the formation of a colorless solid. After filtration, the precipitate was dried in vacuo and after column chromatography (hexane/AcOEt 9:1) benzoic acid (**8**) was obtained as a white crystalline solid. Yield: 0.096 g, 95%.

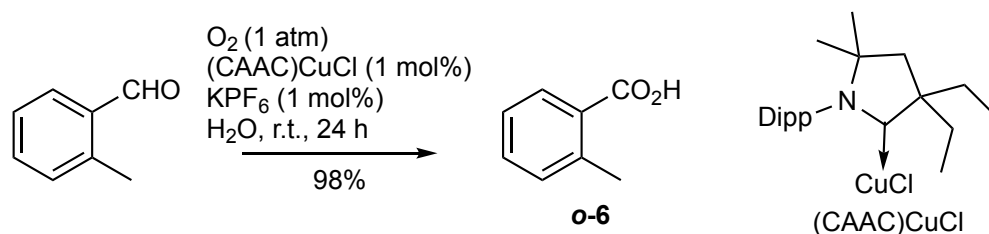
#### **20.2.10.1.3.4 Variation 4: Oxidation of Benzyl alcohol or benzaldehydes**

##### *Introductory Text*

The oxidation of alcohols and aldehydes is a fundamental process for accessing carboxylic acids. The Ru<sup>II</sup> catalyst or Ru<sup>II</sup>-supported catalyst on Dowex catalyzes the oxidation of benzyl alcohol or styrene in the presence of Ce<sup>IV</sup> in water. Cerium can be replaced by NaIO<sub>4</sub>, with a longer reaction time and lower yield. In the case of benzyl alcohol, 96% conversion is obtained.<sup>[24]</sup> Cobalt(II) phthalocyanine sulfonate supported on reduced graphene oxide, under sunlight and visible-light irradiation, enables photooxygenation of the aryl aldehyde to the corresponding carboxylic acid, with excellent conversions and selectivities.<sup>[25]</sup> H<sub>2</sub>O<sub>2</sub> has been widely used for aldehydes oxidation in the presence of molybdenum(VI) oxide hybrids<sup>[26-27]</sup>, solid heteropolyacids<sup>[28]</sup> or titanium-polyoxomolibdate.<sup>[29]</sup> O<sub>2</sub> was also used as an oxidant in combination with NHC and a photocatalyst to convert *o*-aryl salicyl aldehydes into *o*-aryl salicylic acid.<sup>[30]</sup> The Zn(OAc)<sub>2</sub>/I<sup>-</sup> mixture oxidizes nitrobenzyl compounds to the corresponding benzoic acids.<sup>[31]</sup> Recently, the aerobic oxidation of various aldehydes to their corresponding carboxylic acids has been carried out in water under neutral conditions using 1 atm O<sub>2</sub> as oxidant, and cyclic (alkyl)(amino)carbene copper as catalyst. *o*-Toluic acid (*o*-**6**) was thus obtained in 98% yield, and a mechanism was

proposed, based on activation of the C–H bond of the aldehyde by CAAC-Cu dioxygen complexes (Scheme 11).<sup>[32]</sup>

**<Scheme 11> (CAAC)CuCl/KPF<sub>6</sub> catalyzed the oxidation of arylaldehyde<sup>[32]</sup>**



*O*-Toluic acid (**o-6**)

To a solution of *o*-tolualdehyde (1 equiv.) containing 1 mol% of (CAAC)CuCl and 1 mol % of KPF<sub>6</sub> in water (5 mL), oxygen was flushed (1 atm.) in a closed reaction vessel. The reaction mixture was stirred for 24 h at 25 ° C. After reaction, sodium hydroxide was added to offer a homogeneous solution. The unreacted aldehyde was extract 3 times with 2 mL of DCM. Diluted HCl was added in the aqueous solution until pH value was 2. Then, the product was isolated by extraction into ethyl ether followed by the removal of solvent under reduced pressure at RT allowing *o*-toluic acid (**o-6**). Yield: 98%

### 20.2.10.1.3.5 Variation 5: Oxidation of Aryl Ketones

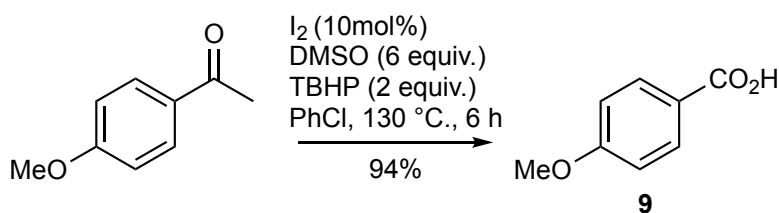
#### *Introductory Text*

Aryl alkyl ketones are stable and a readily available class of compounds, making their oxidative cleavage attractive. The acyl side chain of arenes can be oxidized to carboxylic acid under mild conditions. A number of transition metals catalyze C–C bond cleavage of aryl alkyl ketones, such as copper,<sup>[33-35]</sup> tungsten,<sup>[36]</sup> or ruthenium on carbonyl.<sup>[37]</sup>

Following work on oxidative cleavage of arylalkynes (see section 20.2.10.1.3.3), the mixture of ozone and trifluoroacetic acid can also be used to oxidize aryl alkyl ketones

under environmentally-friendly conditions.<sup>[23]</sup> A metal-free and one-pot two step synthesis of arylcarboxylic acids from aryl alkyl ketone has also been reported, with iodine as catalyst and DMSO and *tert*-butyl hydroperoxide as oxidants. The process was applied to various aryl methyl ketones, bearing electron-withdrawing as well as electron-donating substituent in *ortho*, *meta* or *para* positions, and finally, from 4-methoxyacetophenone, the corresponding carboxylic acid (**9**) was obtained in 94% yield (Scheme 12).<sup>[38]</sup> The methyl ketone in acetophenone can be replaced by several alkyl chains of different lengths with the same high yields.

**<Scheme 12> Synthesis of aryl carboxylic acids via oxidative C–C bond cleavage<sup>[38]</sup>**



**4-methoxy-benzoic acid (**9**)**

A solution of 4-methoxyacetophenone (1 mmol) containing DMSO (47 mg, 6 mmol) and iodine (25 mg, 0.1 mmol) in chlorobenzene (2 mL) was stirred for 3 h at 130 °C (4-methoxyacetophenone disappeared completely). After being cooled at room temperature, TBHP (0.26 mL, 2 mmol) was added to the above reaction mixture, and the reaction was stirred for another 3 h at 130 °C. The reaction was quenched with water, and pH was adjusted to 11 with NaOH. The aqueous phase was extracted 3 times with 3 mL of Et<sub>2</sub>O. 0.1 M HCl was added in the aqueous solution until pH value reached 2. Then, the product was isolated by extraction into ethyl ether followed by the removal of solvent under reduced pressure. Purification by column chromatography on silica gel with ethyl acetate/petroleum ether as the eluant afford 4-methoxybenzoic acid (**9**). Yields: 94%

**20.2.10.1.4 Method 4: Carboxylation of Arylmetal Species**



## *Introductory Text*

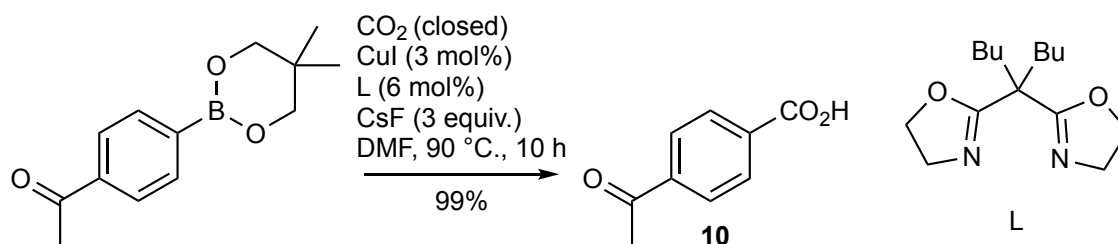
One of the simplest methods for synthesis of aromatic carboxylic acids involves the addition of a nucleophilic aryl organometallic species to carbon dioxide.<sup>[39]</sup> Typical organometallic species are organolithium or Grignard reagent. To overcome some chemical incompatibilities, other organometallic reagents have been used, usually in presence of a transition-metal catalyst.

### **20.2.10.1.4.1 Variation 1: Carboxylation of arylboronic acids or esters**

#### *Introductory Text*

Boronic acid esters are fairly stable and easy to handle, which is why they have been used in carboxylation reaction. Bisoxazoline-CuI complexes catalyze the carboxylation of a wide range of aryl boronic esters under CO<sub>2</sub>, in the presence of 3 equivalent of CsF. The crucial role of CsF is to generate the arylcopper species by transmetalation of the corresponding fluoroborate with Cu(I) salt, followed by a carboxylation step. Arylboronic esters, substituted by an acetyl group, gave the corresponding benzoic acid (**10**) in a high yield of 99%, without affecting the acetyl functionality (Scheme 13).<sup>[40]</sup> Based on this protocol, the process was adapted to prepare a radiotracer from labelled <sup>11</sup>CO<sub>2</sub>.<sup>[41]</sup>

#### *<Scheme 13> Cu(I)-catalyzed carboxylation reaction of arylboronic esters<sup>[40]</sup>*



#### 4-acetyl-benzoic acid (**10**)

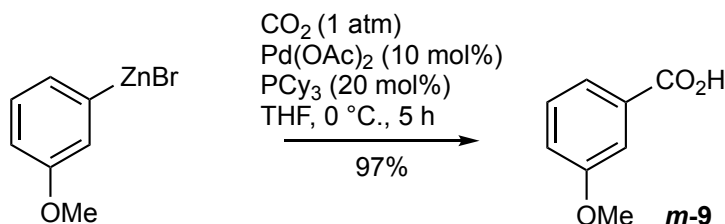
A DMF suspension (2.5 mL) of CuI (1.9 mg, 0.01 mmol), bisoxazoline ligand L (2.9 mg, 0.01 mmol), arylboronic ester (0.2 mmol) and CSF (91 mg, 0.6 mmol) was stirred in a glass tube under atmospheric pressure of CO<sub>2</sub>, and the system was closed. The system was heated for 10 h at 90 ° C. The reaction was quenched with 1 M HCl aq., and then the aqueous layer was extracted 4 times with Et<sub>2</sub>O. The combined organic layers were dried over MgSO<sub>4</sub>, followed by the removal of solvent under reduced pressure. Purification by column chromatography on silica gel with hexane/CH<sub>2</sub>Cl<sub>2</sub> as the eluant affords 4-acetyl-benzoic acid (**10**). Yields: 99%

### 20.2.10.1.4.2 Variation 2: Carboxylation of arylzinc intermediates

#### *Introductory Text*

Carboxylation of arylzinc reagents can be achieved by palladium (Pd(OAc)<sub>2</sub>/PCy<sub>3</sub>) or nickel ([Ni(PCy<sub>3</sub>)<sub>2</sub>]<sub>2</sub>(N<sub>2</sub>)) catalysis, with mild tolerance to functional groups, using a simple CO<sub>2</sub>-filled balloon (Scheme 14).<sup>[42]</sup> The process is efficient with many electron-rich or electron-poor substituents, providing the corresponding carboxylic acid, e.g. 3-methoxy-benzoic acid (**m-9**).

#### <Scheme 14> Pd-catalyzed carboxylation reaction of arylzinc<sup>[42]</sup>



3-methoxy-benzoic acid (**m-9**)

A Schlenk flask was charged with Pd(OAc)<sub>2</sub> (26.0 mg, 0.116 mmol), PCy<sub>3</sub> (65.0 mg, 0.232 mmol), in 2 mL of THF in a glovebox. After cooling to 0 °C, the suspension was subjected to CO<sub>2</sub> (15 psi). 3-methoxyphenylzinc bromide (2 mL, 1.160 mmol) was added by syringe. The reaction vessel remained open to CO<sub>2</sub> for 1 h, and the system was sealed. After 5 h, EtOAc was added, followed by the removal of solvents under reduced pressure. The reaction was quenched with 1 M HCl aq. (5 mL), and then the aqueous layer was extracted with EtOAc (4x5 mL). The combined organic layers were filtered, followed by the removal of solvent under reduced pressure. The resulting solid was re-dissolved in 5 mL of Et<sub>2</sub>O and extracted with 1 M NaOH (4x5 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, followed by the removal of solvent under reduced pressure to afford 3-methoxy-benzoic acid (*m-9*). Yields: 171.2 mg, 1.125 mmol, 97%.

## 20.2.10.1.5 Method 5: Substitution of Halogen

### 20.2.10.1.5.1 Variation 1: Metal-Catalyzed carboxylation of Haloarenes

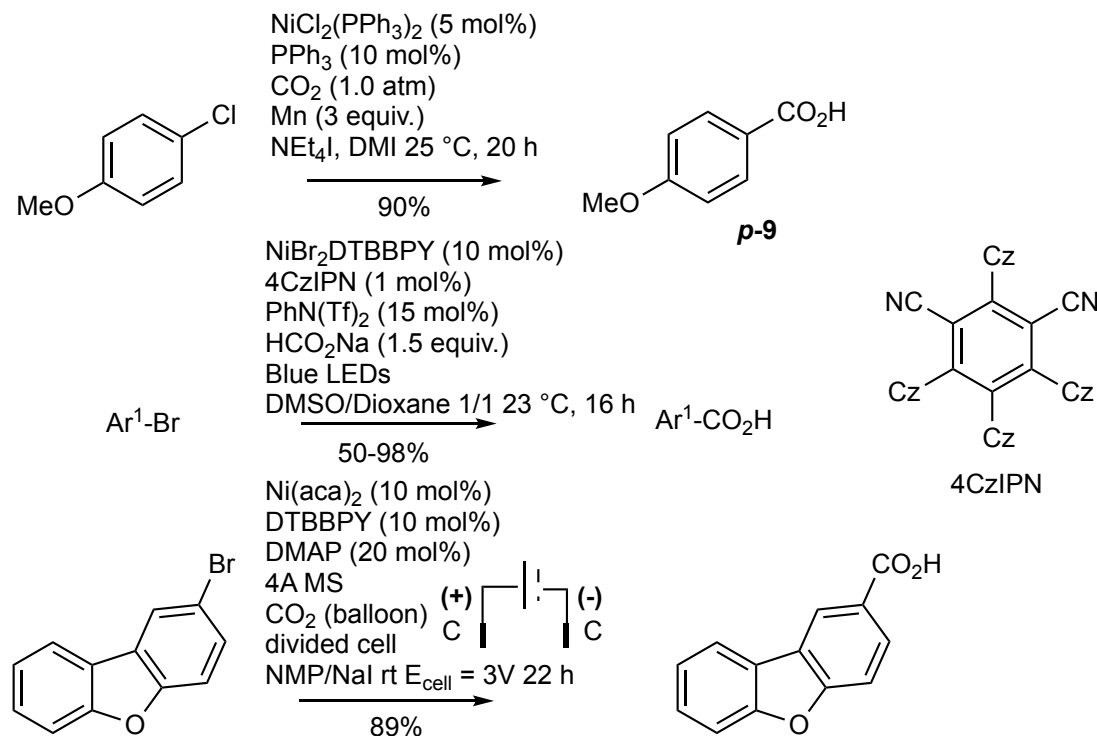
#### *Introductory Text*

Even if carboxylation reaction of organometallics is well developed, these techniques require stoichiometric amounts of organometallic reagents, often prepared from the corresponding organic halides by conventional metalation techniques. Direct carboxylation of aryl halides in the presence of transition metals (Ni, Pd, Co, Mo, Cu) has become an attractive method, and a number of research groups have developed processes following thermo-, photo- and electrochemical strategies.<sup>[43]</sup>

a – Nickel Catalysis: Nickel catalysis was used for the carboxylation of various aryl chlorides in good to high yields, using 1 atm of CO<sub>2</sub> at room temperature. Manganese metal was used to reduce Ni(II) to Ni(0), which was the effective catalyst (Scheme 15, top).<sup>[44]</sup> In recent years, visible-light photoredox catalysis combined with nickel catalysis has emerged as an innovative strategy for carrying out cross-coupling reactions, avoiding

the need for a reducing metal. 4CzIPN combined with NiBr<sub>2</sub>DTBBPY enabled the carboxylation of aryl bromide in good yield, except for *ortho*-substituted compounds, using sodium formate as carboxylating agent (Scheme 15, middle).<sup>[45]</sup> The use of <sup>13</sup>C-labeled sodium formate enables the formation of <sup>13</sup>C-labeled drug intermediates in moderate yields.<sup>[46]</sup> Similar results can be obtained using CO<sub>2</sub> balloon instead of sodium formate.<sup>[47]</sup> Selective carboxylation of non-activated aryl halide can be achieved by electrocatalysis. This sustainable and economical strategy with the electron as its own reductant features mild conditions, an inexpensive catalyst, safe and cheap electrodes and good functional group tolerance. The method uses Ni(II) salt combined with DTBBPY to form the pre-catalyst, which is reduced in situ to generate the Ni(0) catalyst. The process can be implemented in an undivided cell, using a zinc sacrificial anode, or in a divided cell, with a non-sacrificial carbone anode (Scheme 15, bottom).<sup>[48]</sup>

<Scheme 15> Nickel-catalyzed carboxylation of aryl halides<sup>[44-45, 48]</sup>



Ar <sup>1</sup>	Yield (%)	Ref

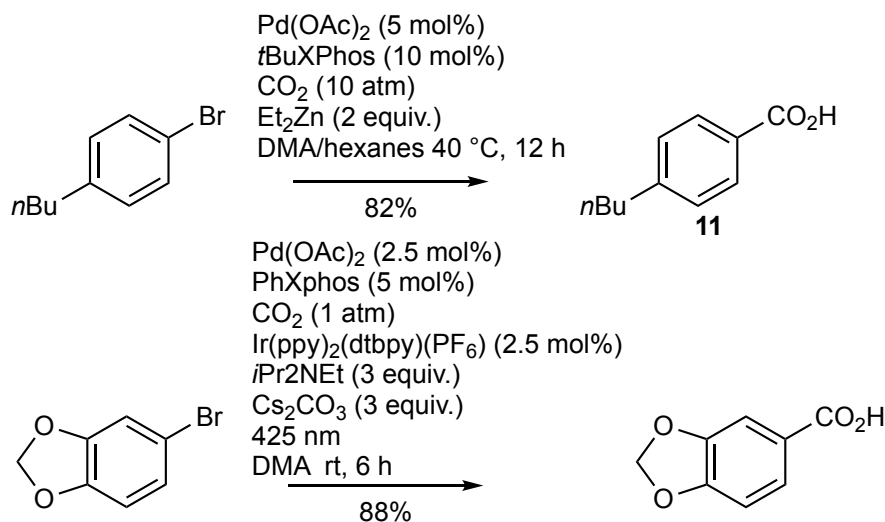
Ph	86	[45]
4-Tol	91	[45]
4-CN-C <sub>6</sub> H <sub>4</sub>	98	[45]
4-MeO-C <sub>6</sub> H <sub>4</sub>	52	[45]
3-(HOCH <sub>2</sub> )-C <sub>6</sub> H <sub>4</sub>	51	[45]

#### 4-methoxy-benzoic acid (**p-9**)

A Schlenk flask, dried with a heating-gun under vacuum, was charged with NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (66.4 mg, 0.025 mmol), PPh<sub>3</sub> (13.1 mg, 0.0502 mmol), Mn powder (82.4 mg, 1.5 mmol) and NEt<sub>4</sub>I (12.9 mg, 0.050 mmol). The Schlenk was evacuated and refilled with CO<sub>2</sub> (5 times), then DMI (0,75 mL) and *p*-chloroanisole (0.5 mmol) were added via air-tight syringes, and the resulting mixture was stirred at 25 °C for 20 h. After reaction, 6N HCl aq. (3 mL) and Et<sub>2</sub>O was added, and stirred at room temperature for 10 min. The aqueous layer was extracted 5 times with EtOAc (5x5 mL). The combined organic layers were dried over MgSO<sub>4</sub>, followed by the removal of solvent under reduced pressure. The residue was purified by silica gel chromatography with hexane/EtOAc (5/1, v/v) then EtOAc as the eluant to afford 4-methoxy-benzoic acid (**p-9**). Yields: 90%

b – Palladium Catalysis: Pioneering work on the electroreduction of aryl halides with CO<sub>2</sub> using Pd(II) catalysis, reduced to Pd(0) by 2 electrons, was reported in the 1990s.<sup>[49]</sup> Subsequently, palladium acetate could be reduced by diethylzinc in the presence of *t*BuXPhos as ligand to achieve carboxylation of the non-activated aryl bromide and thus provides compound (**11**) in 82% on a 1.5 mmol scale (Scheme 16, top).<sup>[50]</sup> A few years later, the use of reducing metals could be avoided by the use of a dual photochemical process, using a combination of Pd(OAc)<sub>2</sub> as catalyst and Ir(ppy)<sub>2</sub>(dtbpy)(PF<sub>6</sub>) as photocatalyst under visible light, under 1 atm of CO<sub>2</sub>. The presence of the amine *i*Pr<sub>2</sub>NEt as electron donor avoids the use of metallic reductants (Scheme 16, bottom).<sup>[51]</sup> The process proved effective for the carboxylation of highly sterically hindered aryl bromides.

<Scheme 16> Palladium-catalyzed carboxylation of aryl halides<sup>[50-51]</sup>



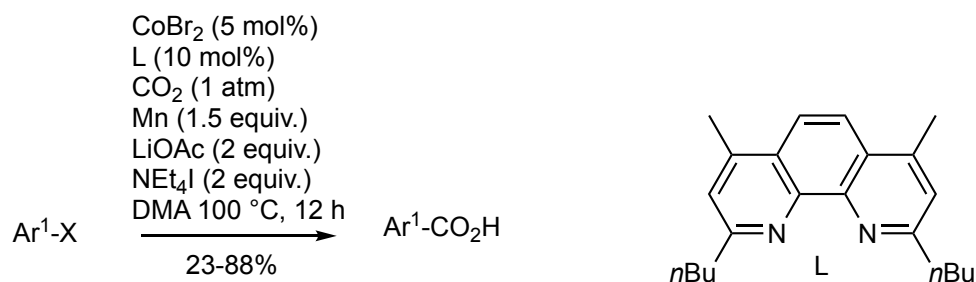
4-butyl-benzoic acid (**11**)

A reactor, containing a stirring bar, was charged with Pd(OAc)<sub>2</sub> (16.5 mg, 5 mol%), *t*BuXPhos (63.6 mg, 10 mol%). The Schlenk was placed in a parallel pressure synthesizer and evacuated and refilled with CO<sub>2</sub> (2-4 atm 2 times), then DMA (6 mL) and *p*-butylbromobenzene (273  $\mu$ L, 1.5 mmol) and Et<sub>2</sub>Zn (1.0 M in hexanes, 3 mL) were subsequently added by syringe. The reactor was then pressurized to 10 atm, warmed up to 40° C and stirred overnight (1000 rpm). After reaction, the reactor was allowed to cool down to room temperature and the mixture was carefully quenched with 5% aq. HCl and AcOEt was added. The aqueous layer was extracted with EtOAc. The combined organic layers were basified to pH = 14 with NaOH 2M. The side products were eliminated and the residual basic aqueous phase was acidified again to pH = 1 and extracted several times with AcOEt, then dried over MgSO<sub>4</sub>, followed by the removal of solvent under reduced pressure to afford 4-butyl-benzoic acid (**11**). Yields: 82%

c – Cobalt Catalysis: The carboxylation of aryl bromides has recently been reported using cobalt-catalysis. The reaction takes place under 1 atm of CO<sub>2</sub>, using CoI<sub>2</sub>bipyridine as ligand and zinc dust as reducing metal. Numerous aryl bromides could be converted into the corresponding carboxylic acids in medium to high yields.<sup>[52]</sup> In parallel, aryl chlorides

have been converted into carboxylic acids under mild conditions, using CoBr<sub>2</sub> associated to 2 equivalents of 2,9-dibutyl-4,7-dimethyl-1,10-phenantroline, reduced by manganese metal in the presence of lithium acetate as base and NEt<sub>4</sub>I as additive. In these conditions, 3,5-dimethylbenzoic acid (**12**) was obtained in isolated yields of 84% isolated yields (78% in the case of a 5 mmol scale) (Scheme 17).<sup>[53]</sup>

**<Scheme 17> Cobalt-catalyzed carboxylation of aryl halides<sup>[53]</sup>**



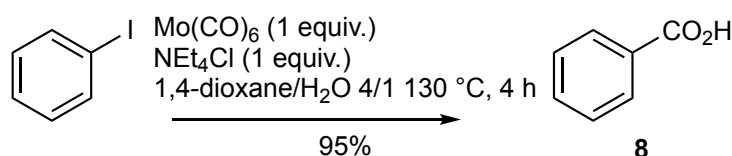
Ar <sup>1</sup>	Yield (%)	Ref
4-MeO-C <sub>6</sub> H <sub>4</sub>	X = Cl 71	[53]
	X = Br 75	
3-Tol	X = Cl 63	[53]
	X = Br 88	
3,5-diMe-C <sub>6</sub> H <sub>3</sub>	X = Cl <b>12</b> 84	[53]
	X = Br <b>12</b> 83	
3-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	X = Cl 66	[53]
	X = Br 66	
2-thiophene	X = Cl 35	[53]
	X = Br 23	

3,5-dimethylbenzoic acid (**12**)

An oven-dried 50 mL Schlenk tube containing a stirring bar was charged with CoBr<sub>2</sub> (5.5 mg, 5 mol%), 2,9-dibutyl-4,7-dimethyl-1,10-phenanthroline (16.0 mg, 10 mol%), Mn powder (41.2 mg, 0.75 mmol, 1.5 equiv.), Et<sub>4</sub>NI (257 mg, 2.0 equiv.) and LiOAc (1.0 mmol, 66 mg, 2.0 equiv.). The Schlenk was evacuated and refilled with CO<sub>2</sub> flow (3 times), then anhydrous DMA (1 mL) and 1-chloro-3,5-dimethylbenzen (0.5 mmol, 1.0 equiv.) were subsequently added under CO<sub>2</sub> flow. The mixture was warmed up to 100° C and stirred for 12h. After reaction, the mixture was allowed to room temperature and was carefully quenched with 4M HCl (in 1,4-dioxane) and stirred for 10 minutes. The crude material was purified by flash chromatography with acetic acid/EtOAc/petroleum ether (0/1/20 to 0.001/1/4/v) to afford 3,5-dimethylbenzoic acid (**12**). Yields: 63 mg, 84%

d – Molybdene Catalysis: Efficient carbonylation of aryl halides was developed under microwave irradiation using molybdenum-carbonyl complexes as catalyst. The use of *t*butyl alcohol or water as nucleophiles leads to benzoic acid (**8**) in 75% and 95% yield respectively (Scheme 18).<sup>[54]</sup> The catalyst Mo(CO)<sub>5</sub>Cl.NEt<sub>4</sub> is generated *in situ* by heating Mo(CO)<sub>6</sub> and NEt<sub>4</sub>Cl in 1,4-dioxane at 140° C for 2 minutes.

**<Scheme 18> Molybdene-catalyzed carboxylation of aryl halides<sup>[54]</sup>**



benzoic acid (**8**)

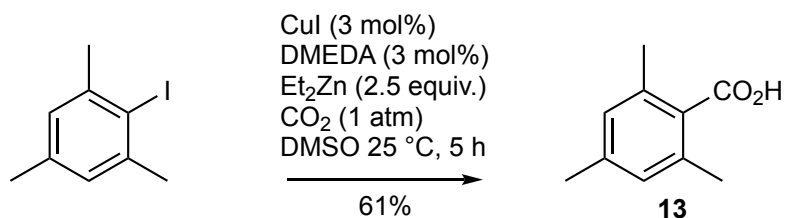
A 10 mL microwave tube with stirrer bar was charged with Mo(CO)<sub>6</sub> (1 mmol), NEt<sub>4</sub>Cl (1 mmol). 1,4-dioxane (0.8 mL) was added and the vial sealed. The tube was microwave heated to 140° C and stirred for 2 minutes. After reaction, the mixture was allowed to cool down to room temperature and phenyl iodide (1 mmol) and water (0.2 mL) was added. The microwave tube was resealed and heated to 130° C for 4 hours. Then the reaction mixture was cooled, quenched with water, extracted with ethyl acetate and the



solvent was removed *in vacuo*. The crude material was purified by silica gel flash chromatography with EtOAc/hexane to afford benzoic acid (**8**). Yields: 95%

e – Copper Catalysis: Aryl iodides can be carboxylated by copper catalysis. The process requires CuI as copper salt, TMEDA or DMEDA as ligand depending on the aryl iodide, 1 atm of CO<sub>2</sub> and DMSO or DMA as solvent. Good functional group tolerance was observed, with the aryl moiety able to carry either electro-withdrawing substituent (DMA solvent in these cases) or an electro-donating substituent. Hindered aryl iodides, such as iodo-mesitylene, can be converted in good yields, leading to 2,4,6-trimethylbenzoic acid (**13**) in 61% isolated yield (Scheme 19).<sup>[55]</sup>

<Scheme 19> Copper-catalyzed carboxylation of aryl iodides<sup>[55]</sup>



2,4,6-trimethylbenzoic acid (**13**)

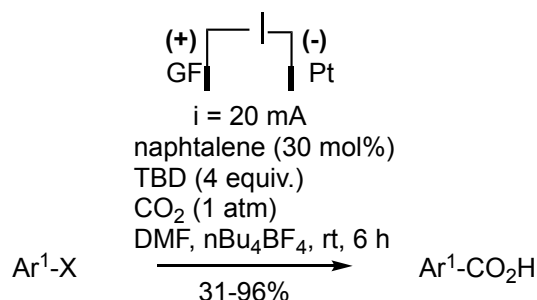
Outside the glovebox, a 20 mL 4-dram vial with stirrer bar was charged with DMEDA (2.7 mg, 0.03 mmol), CuI (6.3 mg, 0.03 mmol) and iodo-mesitylene (246 mg, 1 mmol). The vial was flushed with nitrogen, capped and placed inside glovebox. Then Et<sub>2</sub>Zn (309 mg, 2.5 mmol) was first added, followed by DMSO (4 mL). The vial was then taken out of the glovebox and dry CO<sub>2</sub> was introduced via a needle for 30s then stirred at room temperature for 5 hours. After reaction, the mixture was quenched with aqueous HCl (2 N) until pH = 1, following by addition of brine (3 mL). The reaction mixture was extract with ethyl acetate (4x20 mL), dried over MgSO<sub>4</sub> and the solvent was removed *in vacuo*. After addition of toluene (3 mL), the crude product was purified by flash silica gel chromatography with hexanes and EtOAc/hexanes (1/9 to 6/4) to afford 2,4,6-trimethylbenzoic acid (**13**). Yields: 100 mg, 61%

## 20.2.10.1.5.2 Variation 2: Free-metal carboxylation of Haloarenes

### *Introductory Text*

Although transition-metal catalysis is effective in carrying out the carboxylation reaction of aryl halides, the release of trace amounts of metal can limit their subsequent application. The development of metal-free methods is however rarely reported. Disilabenzocyclobutene appears to be an efficient mediator for the carboxylation of aryl iodides or bromides under transition-metal-free conditions.<sup>[56]</sup> The electroreductive carboxylation of aryl halides mediated by naphthalene was then reported, under CO<sub>2</sub> atmospheric pressure.<sup>[57]</sup> The process is efficient with aryl bromides or chlorides, bearing electron-donating as well as electron-withdrawing substituents, under constant current. TBD was used as a sacrificial amine for the oxidative process, thus avoiding the use of consumable anode. The reaction takes place at room temperature, using a graphite felt as anode and platinum plate as cathode, for 6 hours, ultimately involving 22 F/mol of substrate. Under these conditions, 4-Phenoxybenzoic acid (**14**) is obtained in 93% yield (Scheme 20), while direct electroreduction without naphthalene mediator yields only 5% of the desired product.

### <Scheme 20> *Naphtalene-mediated carboxylation of aryl bromides*<sup>[57]</sup>



Ar <sup>1</sup>	Yield (%)	Ref

Ph	X= Br 64	[57]
4-Tol	X= Br 60	[57]
4-PhO-C <sub>6</sub> H <sub>4</sub>	X= Br <b>14</b> 93	[57]
4-CN-C <sub>6</sub> H <sub>4</sub>	X= Cl 39	[57]
2,6-diMe-C <sub>6</sub> H <sub>3</sub>	X= Cl 31	[57]

#### 4-Phenoxybenzoic acid (**14**)

The electrocatalysis was carried out in an undivided cell with a graphite felt anode and a Pt cathode. To a 15 mL oven-dried undivided electrochemical cell equipped with a magnetic bar was added 4-phenoxy-1-iododobenzene (0.2 mmol, 1 equiv.), naphthalene (7.7 mg, 0.06 mmol, 30 mol%), TBD (111.4 mg, 0.8 mmol, 4 equiv.), and *n*Bu<sub>4</sub>BF<sub>4</sub> (65.9 mg, 0.2 mmol, 1 equiv.). Then the tube was evacuated and back-filled under CO<sub>2</sub> flow (3 times) and anhydrous DMF (4 mL) was introduced via a needle. The electrosynthesis was run at room temperature under a constant current of 20 mA for 6 h. After reaction, the mixture was quenched with aqueous HCl (2 N). The reaction mixture was extract with ethyl acetate (5x10 mL), and the combined organic phase were washed with sat. NH<sub>4</sub>Cl, dried over MgSO<sub>4</sub> and the solvent was removed *in vacuo*. The crude product was purified by flash silica gel chromatography with petroleum ether/EtOAc/AcOH (20:1:0 to 4:1:0.0025) to afford 4-Phenoxybenzoic acid (**14**). Yields: 39.8 mg, 93%

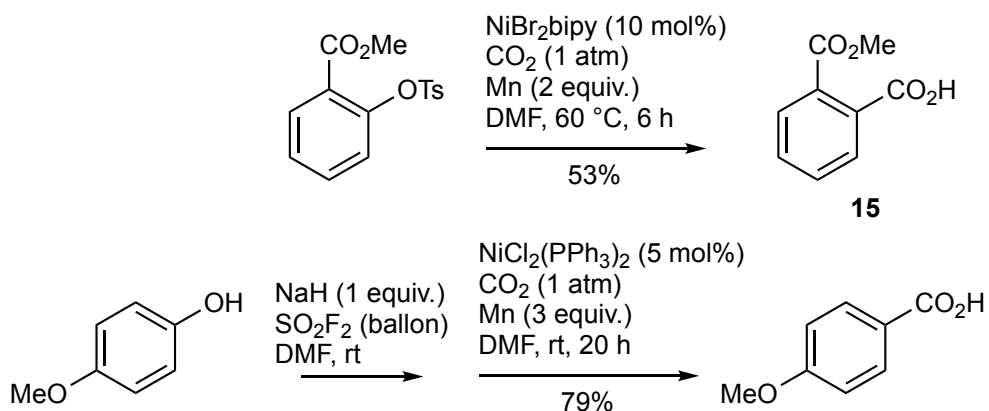
### 20.2.10.1.6 Method 6: Substitution of another group than a halogen

#### 20.2.10.1.6.1 Variation 1: Carboxylation of pseudo-halides

##### *Introductory Text*

A limitation to carboxylation of aryl halides is the access to substituted aryl halides, which can sometimes prove difficult. Alternative strategies can be proposed using pseudohalides, such as tosylates or triflates, easily accessible from the corresponding alcohols and phenols. Sterically hindered aryl triflates were converted into benzoic acids using cobalt or nickel catalysis, reduced by manganese metal at 40°C in 20 h.<sup>[58]</sup> In parallel, a NiCl<sub>2</sub>(dppf)-catalyzed carboxylation of naphthyl pivalates in DMA was developed.<sup>[59]</sup> The process, which takes place at 80°C for 48h, is limited to naphthyl derivatives, since other aryl pivalates lead only to traces amounts of benzoic acids. Subsequently, the reactivity of aryl tosylates was studied, in the presence of a Ni<sup>0</sup> catalyst generated *in situ*, to achieve the direct carboxylation of  $\sigma$ -arylnickels by CO<sub>2</sub>.<sup>[60]</sup> Aryl tosylates are efficiently converted at 60°C under one atmosphere of CO<sub>2</sub>, to the expected acids under uniform conditions regardless of the substituent. The method converts aryl tosylates in moderate to good isolated chemical yields, even for substrates with electron-donating or withdrawing substituents. The versatility of the process has been demonstrated using phenyl tosylates bearing sensitive functions such as nitrile, ester or ketone, and is compatible with ortho-substituted aromatics. In these cases, lower yields are obtained, probably due to steric effects, as seen with 2-(methoxycarbonyl)benzoic acid (**15**), which is isolated at 53% (Scheme 21, top). Aryl fluorosulfates and pyridinyl fluorosulfates also afford aryl and pyridyl carboxylic acids in good to excellent yields using NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as catalyst. In addition, a one-pot phenol fluorosulfation/carboxylation has been developed as an efficient method for synthesizing aryl carboxylic acids (Scheme 21, bottom).<sup>[61]</sup> Aryl triflates can also be carboxylated using dual catalysis, combining palladium and a photoredox Ir(III) catalyst, under blue LED irradiation, at room temperature for 36 h. In this case, the stoichiometric metal reductant is replaced by a sacrificial amine. Here again, a one-pot two-step synthesis of benzoic acids can be achieved directly from phenol, in the presence of 1.5 equivalents of triflic anhydride.<sup>[62]</sup>

**<Scheme 21> Nickel-catalyzed synthesis of carboxylic acid from aryl tosylates or fluorosulfates<sup>[60-61]</sup>**



### 2-(methoxycarbonyl)benzoic acid (**15**)

To a solution of methyl 2-(tosyloxy)benzoate (1 mmol, 1 equiv.) in anhydrous DMF (5 mL) under a  $\text{CO}_2$  atmosphere (dried on  $\text{P}_2\text{O}_5$ ) at  $60^\circ\text{C}$  was added manganese (110 mg, 2 mmol, 2 equiv.) followed by  $\text{NiBr}_2\text{bipy}$  (37 mg, 0.1 mmol, 0.1 equiv.). The medium was vigorously stirred for 6 h. After reaction, the resulting solution was then cooled to room temperature and was diluted with  $\text{Et}_2\text{O}$  (5.0 mL), then 4N HCl aq. (5.0 mL) was added. The reaction mixture was extract with ethyl acetate (3x10 mL), and the combined organic phase were washed with water (3x5 mL), dried over anhydrous  $\text{MgSO}_4$  and the solvent was removed *in vacuo*. Purification was obtained by acidic/basic extraction technique: the crude product was solubilized in 5 mL of  $\text{Et}_2\text{O}$ , then the organic solution was basified with 5 mL NaOH 1N. The aqueous phase was acidified again with HCl 1N until  $\text{pH} = 1$ , leading to the precipitation of the carboxylic acid, which was finally extracted with  $\text{Et}_2\text{O}$ , and afford 2-(methoxycarbonyl)benzoic acid (**15**). Yields: 53%

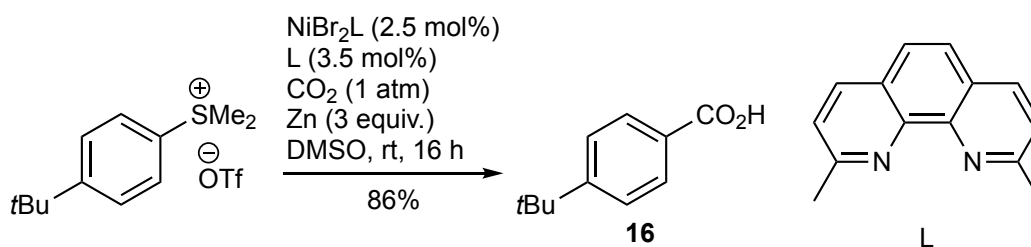
## 20.2.10.1.6.2 Variation 2: Carboxylation of arylsulfonium salts

### *Introductory Text*

Arylsulfonium salts have been proposed as an interesting alternative for nickel-catalyzed carboxylation.<sup>[63]</sup> The carboxylation of (4-*tert*-Butylphenyl)dimethylsulfonium trifluoromethanesulfonate in DMSO, using nickel(II) catalyst reduced by Zn metal, led to 4-*tert*-Butylbenzoic acid (**16**) in 86% yield after 16 h at room temperature (Scheme 22).

The reaction can be carried out in a one-pot procedure by preparing the sulfonium salts *in situ*, without isolation, directly from the parent aryl sulfide by treatment with MeOTf, after simply removing volatiles at the end of the reaction. In this case, a limitation arises with pyridyl sulfide, which cannot be converted to sulfonium salts, due to preferential *N*-methylation.

**<Scheme 22> Nickel-catalyzed synthesis of carboxylic acid from arylsulfonium salts<sup>[63]</sup>**



**4-(*tert*-butyl)-benzoic acid (**16**)**

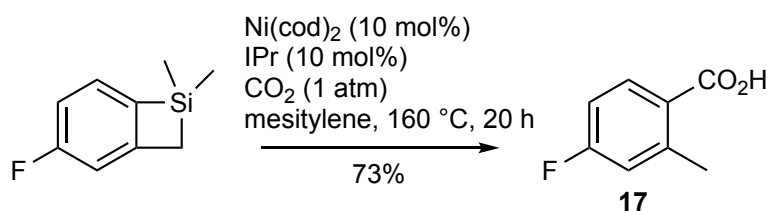
To a solution of (4-*tert*-Butylphenyl)dimethylsulfonium trifluoromethanesulfonate (103 mg, 0.30 mmol, 1 equiv.) in DMSO (1.5 mL) at room temperature was added Zn powder (60 mg, 0.90 mmol, 3 equiv.) followed by NiBr<sub>2</sub>L (3.2 mg, 7.5 μmol, 0.025 equiv.) and L (2.2 mg, 11 μmol, 0.035 equiv.). The tube was evacuated and refilled with CO<sub>2</sub> gas (3 times). The resulting mixture was vigorously stirred for 16 h. After reaction, the resulting solution was quenched with 3 M HCl aq. (2.0 mL). The reaction mixture was extract with Et<sub>2</sub>O (3x2 mL), and the combined organic phase were passed through pads of Na<sub>2</sub>SO<sub>4</sub> and silica gel, and the solvent was removed *in vacuo*. The crude product was purified by flash silica gel chromatography with hexane/EtOAc (5:1) + 3% of AcOH to afford 4-(*tert*-butyl)-benzoic acid (**16**). Yields: 46 mg, 86%

**20.2.10.1.6.3 Variation 3: Carboxylation of benzosilacyclobutenes**

## Introductory Text

Benzosilacyclobutenes were converted to benzoic acid by reaction with CO<sub>2</sub> in the presence of Ni(cod)<sub>2</sub> and IPr as NHC ligand.<sup>[64]</sup> Oxidative addition of Ni(0) associated with CO<sub>2</sub> in the C(sp<sup>2</sup>)-Si bond leads to a nickelacycle, yielding silalactone as key intermediate. Benzoic acid derivatives are then obtained after reductive elimination and desilylation at 160 °C in mesitylene as solvent, with a reaction time of 20 h. 4-Fluoro-2-methylbenzoic acid (**17**) was thus obtained in 73% yield (Scheme 23).

### <Scheme 23> Nickel-catalyzed synthesis of carboxylic acid from benzosilacyclobutenes<sup>[64]</sup>



#### 4-Fluoro-2-methylbenzoic acid (**17**)

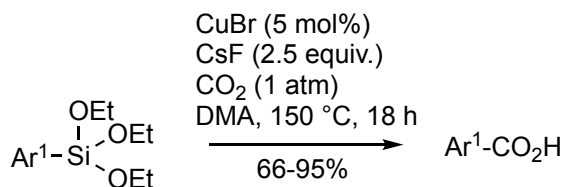
Ni(cod)<sub>2</sub> (2.7 mg, 0.01 mmol) and IPr (3.8 mg, 0.01 mmol) were placed in a Schlenk tube and the tube was filled with CO<sub>2</sub> using a balloon. Mesitylene (3 mL) was then added and the reaction mixture was stirred at room temperature for 10 minutes. Then, benzosilacyclobutene derivative (0.10 mmol) was added using a syringe through a rubber septum. The resulting mixture was then heated at 160 °C and vigorously stirred for 20 h. After reaction, the resulting solution was cooled to room temperature and quenched with saturated NaHCO<sub>3</sub>. The reaction mixture was extracted with saturated NaHCO<sub>3</sub> aq. (3 times). The combined aqueous layer was next acidified with 2M HCl aq. The organic components were extracted with Et<sub>2</sub>O (3 times), and the combined organic phase were washed with water and brine, and dried over MgSO<sub>4</sub>, and the solvent was removed *in vacuo* to afford 4-Fluoro-2-methylbenzoic acid (**17**). Yields: 0.073 mmol, 73%.

## 20.2.10.1.6.4 Variation 4: Carboxylation of aryltrialkoxysilanes

### *Introductory Text*

Aryltrialkoxysilanes undergo carboxylation with carbon dioxide in the presence of CuBr as a catalyst and CsF as activator, to afford carboxylic acids in good to high yields.<sup>[65]</sup> [1,1'-Biphenyl]-4-carboxylic acid (**18**) was thus obtained in 86% isolated yield under atmospheric pressure of CO<sub>2</sub> (Scheme 24). Activation of trialkoxysilane by the fluoride anion gives a pentavalent silicate intermediate, which evolves into a carboxylic acid in the presence of CO<sub>2</sub>.

### *<Scheme 24> Copper-catalyzed synthesis of carboxylic acid from aryltrialkoxysilanes<sup>[65]</sup>*



Ar <sup>1</sup>	Yield (%)	Ref
Ph	95	[65]
3-Tol	66	[65]
4-PhOC <sub>6</sub> H <sub>4</sub>	<b>18</b> 86	[65]
4-tBu-C <sub>6</sub> H <sub>4</sub>	76	[65]
3,4-diF-C <sub>6</sub> H <sub>3</sub>	75	[65]

[1,1'-Biphenyl]-4-carboxylic acid (**18**)



CuBr (3.5 mg, 0.025 mmol) and CsF (0.19 g, 1.25 mmol) were placed in a flame-dried 30 mL two-neck tube, in an argon filled glove box. The tube was removed from the glove box and attached to a vacuum line and a CO<sub>2</sub> balloon using a three-way stopcock. After three evacuation-CO<sub>2</sub> refill cycles, DMA (1 mL) and [1,1'-biphenyl]-4-yltriethoxysilane (0.135 g, 0.5 mmol) were added via syringes, and the reaction mixture was stirred at 150 °C for 18 hours. After reaction, the resulting solution was cooled to room temperature and quenched with H<sub>2</sub>O (10 mL), and 1N NaOH (20 mL), and then washed with DCM (3 x 20 mL). The aqueous solution was acidified with 6N HCl until pH~1 was reached and then extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with H<sub>2</sub>O (3 x 30 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. Then, the solvent was removed *in vacuo* to afford [1,1'-Biphenyl]-4-carboxylic acid (**18**). Yields: 85 mg, 0.43 mmol, 86%.

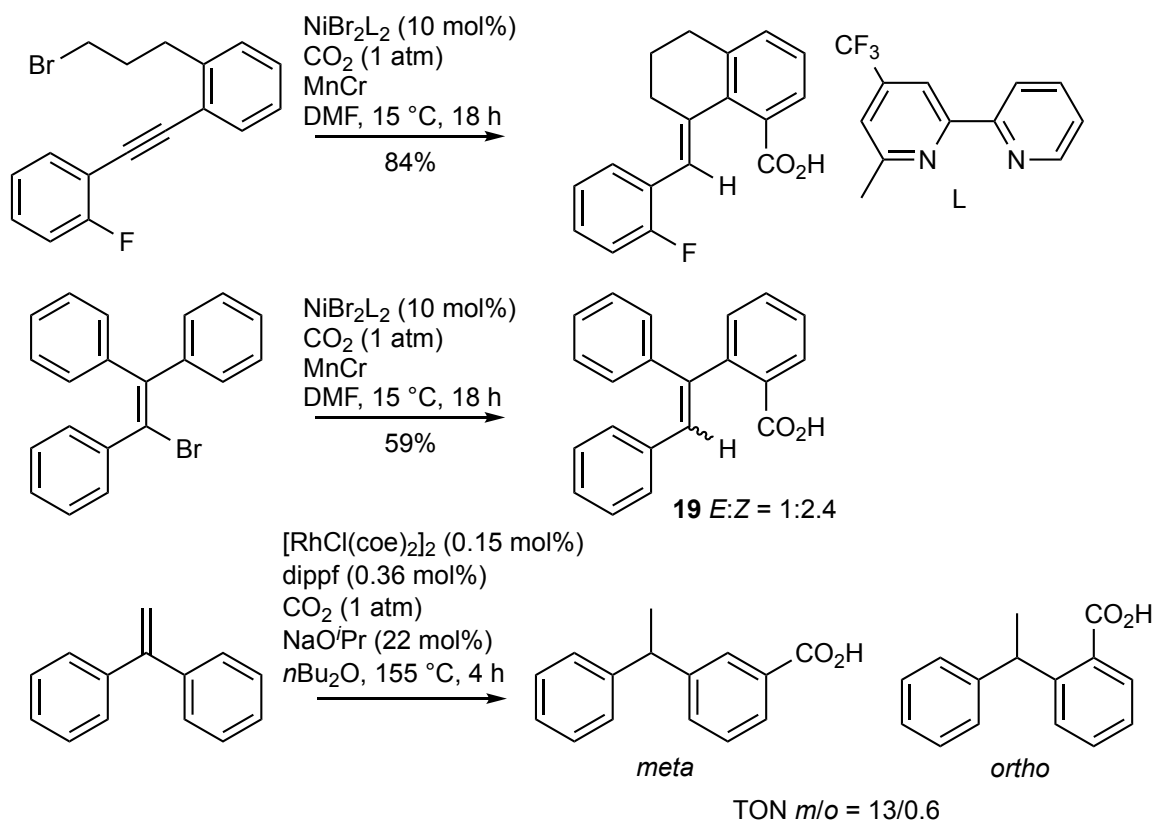
### 20.2.10.1.7 Method 7: Metal-migration carboxylation of C(sp<sup>2</sup>)-H

#### *Introductory Text*

A carbometalation reaction of unactivated alkyl bromides, bearing an aryl moiety, led after a domino carbonickelation/1,4-Ni-migration/carboxylation process to tetrahydronaphthalene-1-carboxylic acid.<sup>[66]</sup> The process is general, and a wide range of unactivated compounds enables this cascade process to be carried out efficiently. (*E*)-8-(2-fluorobenzylidene)-5,6,7,8-tetrahydronaphthalene-1-carboxylic acid is thus obtained in 84% yield in mixture with the non-transposed vinyl carboxylic acid in a 9:1 ratio (Scheme 25, top). In the same way, the process is extended to vinyl bromides, which provides a 1,4-Ni migration scenario, leading to 2-(1,2-diphenylvinyl)benzoic acid (**19**) in a *Z:E* ratio of 2.4:1, and with an average yield of 59% (Scheme 25, middle). Rhodium catalysis can also perform a *meta*-selective C(sp<sup>2</sup>)-H carboxylation reaction of 1,1-diarylethylene derivatives with CO<sub>2</sub>, in the presence of isopropoxide as reductant.<sup>[67]</sup> The process follows a cascade based on a hydro-rhodation step, followed by a 1,4-Rh shift and another 1,2-Rh shift, when the catalyst is [RhCl(coe)<sub>2</sub>]<sub>2</sub> in the presence of, 2.5 equivalents of 1,1'-bis(diisopropylphosphino)ferrocene (dippf) as ligand (Scheme 25,

bottom). Replacing dippf with 1,2-bis(dicyclohexylphosphino)ethane (dcype) results in orthobenzoic acid as the main product, minimizing the second 1,2-Rh shift.

**<Scheme 25> Nickel catalyzed C(sp<sup>2</sup>)-H carboxylation of alkyl and vinyl bromides via a 1,4-Ni migration process<sup>[66-67]</sup>**



**2-(1,2-diphenylvinyl)benzoic acid (**19**)**

An oven-dried Schlenk tube containing a stirring bar was charged with MnCr alloy (20.4 mg, 0.37 mmol, 1.25 equiv) and  $\text{NiBr}_2\text{L}_2$  (10 mol%, 20.8 mg, 0.03 mmol, 0.1 equiv). The schlenk tube was evacuated and back-filled under  $\text{CO}_2$  flow for at least 3 times. After this, 1-bromo-1,2,2-triphenylethylene (0.3 mmol) and DMA (0.2 M, 1.5 mL) were added, the Schlenk tube was closed at atmospheric pressure of  $\text{CO}_2$ , and the reaction mixture was stirred at 15 °C for 18 hours. After reaction, the resulting solution was cooled to room temperature and quenched with 2M HCl (2 mL) to hydrolyze the resulting

carboxylate and extracted 3 times with AcOEt. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The products were purified by flash chromatography on silica gel (hexanes/AcOEt 10/1 followed by hexanes/AcOEt 3/1 alternatively hexanes/AcOEt 7/1 with 1 % formic acid can be used). Yields: 53 mg, 59% (*Z:E*=2.4:1).

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