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20.2.11.2 Alk-2-enoic Acids (Update 2024)

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20.2.11 **Product Subclass 11 : Alk-2-enoic acids**

M. Durandetti and X. Franck

General introduction

In the field of synthetic methods, the incorporation of the α,β -unsaturated carboxylic acid motif is particularly noteworthy for its versatility and usefulness in the construction of complex molecular architectures, from pharmaceuticals to natural products. The conjugated system within the motif can participate in a variety of reactions, offering synthetic chemists a vast toolbox for the creation of complex molecular structures.

This update describes published methods for the synthesis of arenecarboxylic acids reported between 2007 and 2023. Publications on this product subclass that appeared prior to 2007 are included in the previous version compiled by C. D. Vanderwal and E. N. Jacobsen in 2007 (Section 20.2.11). Emphasis will be on new synthetic methods that allow the introduction of the α,β -unsaturated carboxylic acid motif, and conventional methods such as ester saponification will not be mentioned.

20.2.11.1 Synthesis of Product Subclass 11

20.2.11.1.1 Method 1: Oxidation Reactions

20.2.11.1.1.1 Variation 1: Oxidation of Alcohols

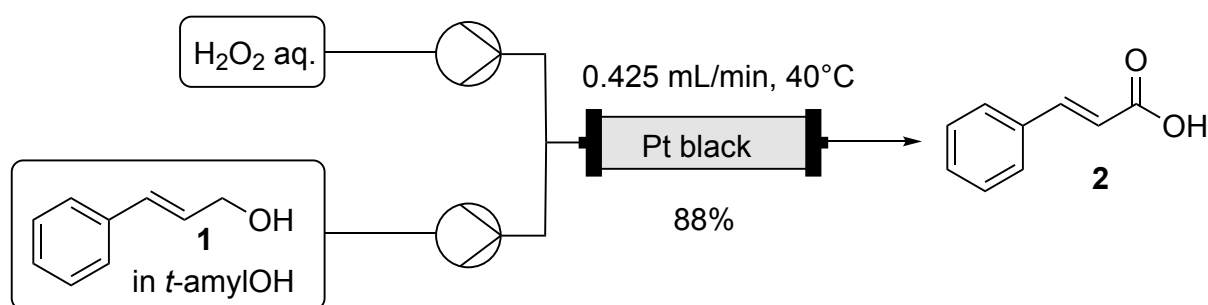
Introductory Text

While the direct oxidation of alcohols to carboxylic acids has been democratized by the use of toxic-metal based strong oxidants e.g. CrO_3 , KMnO_4 , PDC/DMF..., new methods using noble metals are currently being developed. In addition, metal-free oxidative cleavage of homoallylic alcohols can be done using strong base (tBuONa) in the presence of oxygen.^[1] Pt-catalyzed reactions in batch^[2] or in flow^[3] are well adapted to allylic alcohol oxidation. Use of Pt black with a 0.1 ml/min flow rate for cinnamyl alcohol **1** and a 15% H_2O_2 aqueous solution allows the production of cinnamic acid **2** in excellent yields (Scheme 1).^[4]

Additionally, oxidation of allylic alcohol can be performed with a catalytic amount of cobalt and KOH,^[5] or with palladium and rhodium.^[6]

Oxidative rearrangement of tertiary propargylic alcohols can also be performed with m-CPBA and trichloroacetic acid, giving rise to tetrasubstituted alkenoic acids in moderate yields, after a 1,2-aryl shift.^[7]

<Scheme 1> Platinum-catalyzed flow oxidation of cinnamyl alcohol into cinnamic acid^[4]



Experimental Procedure

Cinnamic acid (2):^[4]

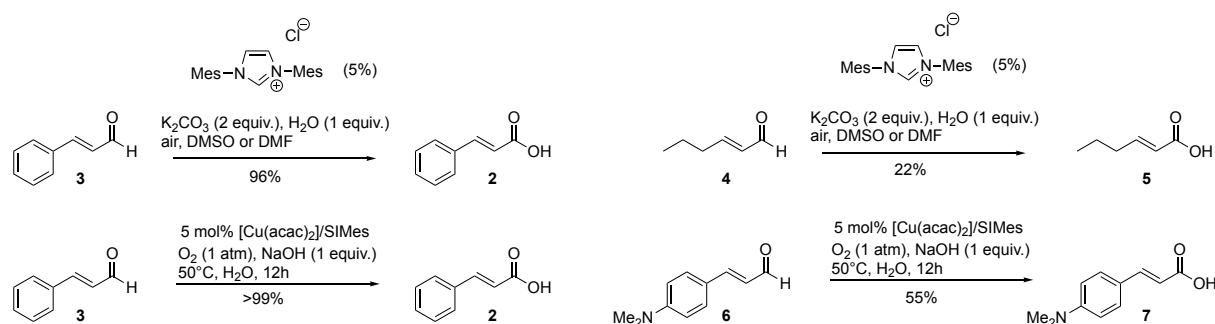
SiO₂ (820 mg) and Pt black (300 mg) were mixed and packed in a column reactor (length: 100 mm, inner diameter: 5 mm) equipped with double plunger pumps. The first plunger pump was used to pass **1** in *t*-amylOH solution (0.20 mol/L) and the other to pass 15% H₂O₂ aqueous solution. An air trap was utilized to maintain steady delivery of H₂O₂ aq. to the column reactor. A back pressure regulator was set at 1.5 MPa. The column was set to 40 °C to flow cinnamaldehyde and H₂O₂ at a 0.425 ml/min flow rate. The product solution for 1 hour reaction was collected, and the organic phase was separated from the water phase. Cinnamic acid was recovered as sodium cinnamate in the aqueous phase after washing the reaction organic solution with 1 M NaOH followed by phase separation. Cinnamic acid **1** was obtained from the treatment of the previous aqueous phase with 1 M HCl and AcOEt extraction followed concentration under reduced pressure, as a white solid. Yield: 0.15 g (88%).

20.2.11.1.1.2 Variation 2: Oxidation of Aldehydes

Introductory Text

Sodium hypochlorite, the oxidant used in the classical Pinnick oxidation of aldehyde into carboxylic acid can be replaced by oxygen as a greener option, with or without a metal catalyst. In combination with 5% N-Heterocyclic Carbenes (NHC), water (1 equiv.) and K_2CO_3 (2 equiv.), cinnamaldehyde **3** is cleanly oxidized under air atmosphere to cinnamic acid **2** in 96% yield. However, unsaturated aldehydes substituted by an aliphatic side chain such as in penten-2-al **4** give low yield in carboxylic acid such as penten-2-oic acid **5**.^[8] The same oxidation can be done with a copper catalysis, also in the presence of NHC and using NaOH as the base (scheme 2), allowing oxidation of cinnamaldehyde **3** or *p*-dimethylamino-cinnamaldehyde **6** into their corresponding acid **2** or **7**, respectively.^[9] The reactions work well also for α,β -unsaturated, aromatic or aliphatic aldehydes.

<Scheme 2> Oxidation of aldehydes into carboxylic acid^[8-9]



Experimental Procedure

Cinnamic acid (**2**):^[8]

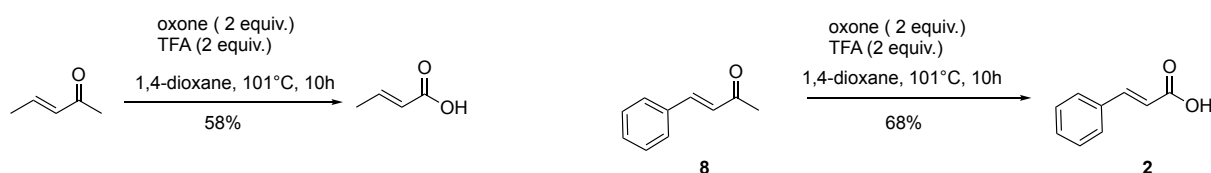
In a round bottom flask, IMesCl (8.5 mg, 25 μ mol, 5 mol %) and K_2CO_3 (138.2 mg, 1.0 mmol, 2 equiv) were dissolved in 5 mL of DMF. Cinnamaldehyde **3** (0.066g, 0.5 mmol) and H_2O (1.8 μ L, 0.5 mmol) were added to the solution before stirring at 25 $^\circ C$ for 16 h at the open air. The reaction was quenched with 1N HCl (25 mL) and extracted with EtOAc (3 \times 20 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. 10 mL of saturated aqueous $NaHCO_3$ was added to the residue, and the resulting solution was stirred at room temperature for 30 min. The mixture was washed with EtOAc (3 \times 20 mL) and the aqueous layer was acidified with concentrated HCl to pH = 1, followed by extraction with EtOAc (3 \times 25 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure affording cinnamic acid **2** as a white solid. Yield: 0.074g (99%)

20.2.11.1.1.3 Variation 3: Oxidation of ketones

Introductory Text

The most common transformation of ketones into carboxylic acids is the haloform reaction where the methyl ketone is converted into the tri-halogenated (F, Cl, Br, I) intermediate which is further converted into the carboxylic acid under basic conditions (OH⁻).^[10] Acidic conditions (TFA) can also be used in combination with an oxidant (oxone) to efficiently convert aliphatic, aromatic or α,β -unsaturated methyl-ketones into carboxylic acids (Scheme 3).^[11]

<Scheme 3> Oxidation of methylketones^[11]



Experimental Procedure

Cinnamic acid (**2**):^[11]

4-phenyl-3-buten-2-one **8** (0.1g, 1 equiv) was dissolved in dioxane (5 mL) and Oxone (2 equiv) and TFA (2 equiv) were added. The mixture was then heated to reflux for 10 h and then cooled to room temperature. The reaction mixture was hydrolyzed by addition of water (10 mL) and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with sat. NaHCO₃ and the aqueous layer was poured onto crushed ice and treated with 2 M HCl. The precipitate was filtered off and purified by column chromatography to give cinnamic acid **2** as a white crystalline solid; yield: 0.069 g (68%).

20.2.11.1.1.4 Variation 4: Oxidation of saturated carboxylic acids

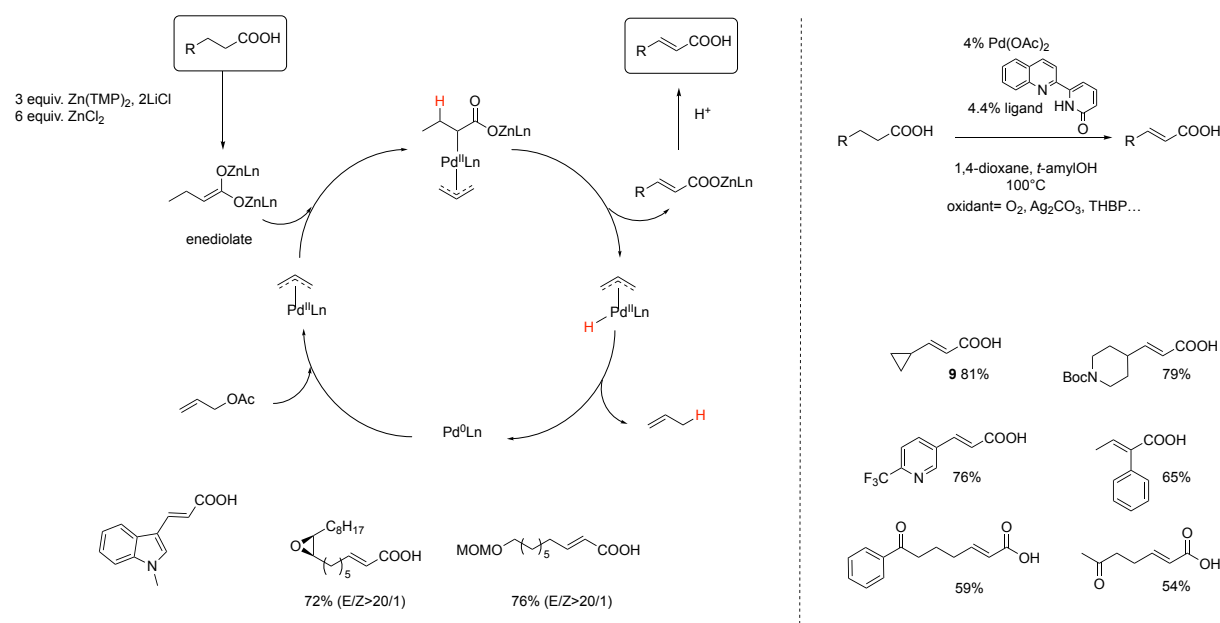
Introductory Text

The oxidative-dehydrogenation of carboxylic acids to produce the corresponding higher-value unsaturated acids remains an important challenge in organic chemistry. Although numerous

reaction deal with the oxidative-dehydrogenation of saturated acid derivatives, very few methods are compatible with the free carboxylic acid. Among the latter, the oxidation of the enediolate of the saturated carboxylic acid by trapping it with a palladium-allyl species to form a C-bound palladium enolate which can subsequently undergo β -hydride elimination is attractive. Although the reaction conditions may be difficult to apply to highly functionalized substrates, halogens, indoles and epoxides are tolerated (Scheme 4 left).^[12]

Another method uses a Pd(II)-catalyzed dehydrogenation reaction directed by a bidentate pyridine ligand in presence of various oxidants such as O_2 , Ag_2CO_3 or TBHP at $100^\circ C$ (scheme 4 right).^[13] Either method work well to prepare α,β -unsaturated carboxylic acid substituted by aliphatic as well as aromatic chain, which makes them very useful. Noteworthy, thanks to the carboxylic acid directed C-H insertion, there is preferential oxidative-dehydrogenation of carboxylic acid in the presence of a ketone.

<Scheme 4> Oxidative dehydrogenation of carboxylic acids^[12-13]



Experimental Procedure

(E)-3-cyclopropylacrylic acid (**9**):^[13]

3-cyclopropylpropanoic acid (11.4 mg, 0.10 mmol), Ag_2CO_3 (55.0 mg, 0.2 mmol), Li_2CO_3 (14.8 mg, 0.2 mmol) and NaOAc (4.1 mg, 0.05 mmol) were added in a sealed tube. A solution

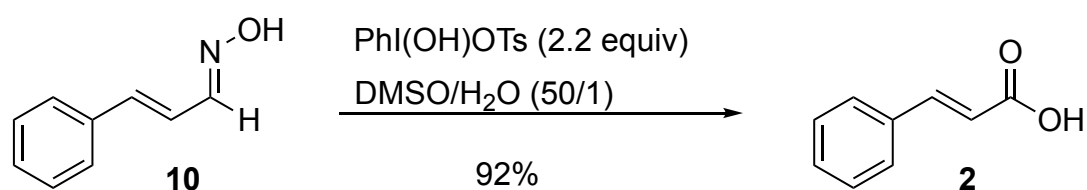
of Pd(OAc)₂ (0.9 mg, 4 mol%) and 6-(quinolin-2-yl)pyridin-2(1H)-one (1.0 mg, 4.4 mol%) in 1,4-dioxane (0.2 mL) was added to the tube. t-Amyl-OH (0.8 ml) was then added and the tube flushed with nitrogen. After closing the tube, the reaction mixture was then stirred at 100 °C for 16 h. After being cooled to room temperature, the mixture was acidified with 20 μL of formic acid and sonicated for 30 seconds. The mixture was filtered through a pad of Celite® with eluent (methanol: formic acid: DCM = 5:5:90). The filtrate was concentrated, and the crude mixture purified using reverse phase chromatography (H₂O: acetonitrile =10:1 to 1:4). Yield: 9.1 mg (81%).

20.2.11.1.1.5 Variation 5: Oxidation of aldoximes

Introductory Text

The oxidation of aldoximes can be done by hypervalent iodine reagents and either hydroxamic esters or acids are obtained when PhI(OAc)₂ in acetonitrile or PhI(OH)OTs in CHCl₃ is used, respectively. However, using PhI(OH)OTs in wet DMSO cleanly transformed aldoximes into the corresponding carboxylic acids (Scheme 5). The reaction works well for aromatic, aliphatic or α,β-unsaturated aldoximes.^[14]

<Scheme 5> Oxidation of aldoximes^[14]



Experimental Procedure

Cinnamic acid (**2**):^[14]

Cinnamaldehyde aldoxime **10** (0.029 g, 0.2 mmol) was dissolved in a DMSO/H₂O solution (50/1, 2 mL) and PhI(OH)OTs (0.082g, 0.21 mmol) was added. After 30 minutes, another amount of PhI(OH)OTs (0.082g, 0.21 mmol) is added. After completion of the reaction, the reaction mixture was poured into 10% aq. Na₂CO₃ and extracted with EtOAc. The organic layer

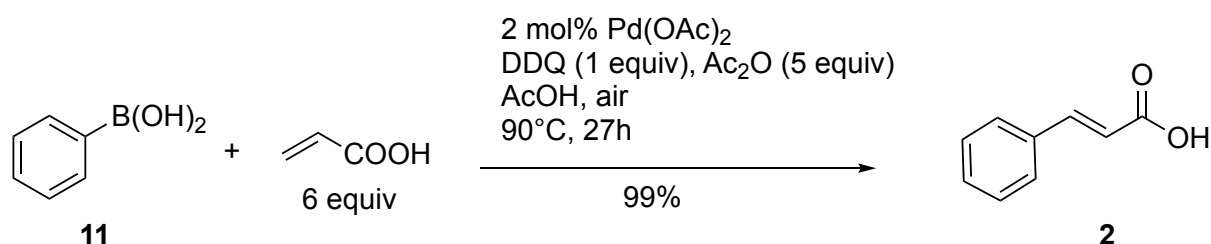
was extracted with 10% aq. Na₂CO₃ and the aqueous layer acidified by addition of aq. HCl, and then extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and then concentrated *in vacuo* to afford pure cinnamic acid **2**. Yield: 0.027g (92%).

20.2.11.1.1.6 Variation 6: Oxidative Heck reactions

Introductory Text

The Pd-catalyzed Heck-type oxidative couplings between arylboronic acids and acrylic acid affords the addition product with excellent yields. The method does not necessitate the use of ligand or base to be effective (Scheme 6), it works also well with acrylic esters to give the corresponding cinnamic esters.^[15]

<Scheme 6> Oxidative Heck reactions^[15]



Hypervalent iodine of ArI(OAc)₂ type reagents can also be used in such couplings, however it has been shown that under the reaction conditions used, aryl iodide is generated *in situ*, and is the reactive species that undergoes classical Heck reaction with acrylic acid derivatives.^[16]

Experimental Procedure

Cinnamic acid (**2**):^[15]

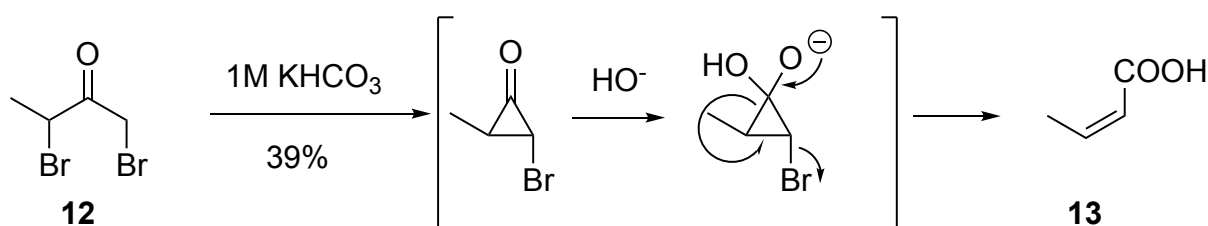
Phenylboronic acid **11** (61 mg, 0.5 mmol), acrylic acid (0.21ml, 3.0 mmol), Pd(OAc)₂ (0.22 mg, 2 mol %), DDQ (113 mg, 1 equiv.), Ac₂O (0.24 ml, 5 equiv) and AcOH (3 mL) were stirred under air atmosphere in a Schlenk tube at 90 °C for 27 hours. After cooling to room temperature, the mixture was poured into diethyl ether, was washed with water, extracted with ethyl acetate, dried over anhydrous Na₂SO₄, filtered and evaporated under vacuum. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate) to afford cinnamic acid **2**. Yield 0.074 g (99%).

20.2.11.1.2 Method 2: Elimination Reactions

Introductory Text

Z-crotonic acid **13** can be easily obtained by elimination of 1,3-dibromobutan-2-one **12** under basic aqueous conditions (KHCO₃). The mechanism involves a Favorskii rearrangement followed by β-elimination (Scheme 7).^[17]

<Scheme 7> Elimination of bromoketones^[17]



Experimental Procedure

Z-crotonic acid (**13**):^[17]

To a 1M KHCO₃ (12.01 g, 120 mmol, 2.4 equiv.) solution, 1,3- dibromobutan-2-one **12** (11 g, 51 mmol) was added and the solution was stirred at room temperature for 3.5 h. The reaction mixture was extracted with diethyl ether (2 × 40 mL) and the aqueous layer was acidified with hydrochloric acid (1 M, 50 mL) to pH 2 and extracted with Et₂O (6 × 50 mL). The combined organic layers were then dried over MgSO₄ and the solvent was removed under reduced pressure. Flash chromatography on silica gel (cyclohexane/EtOAc 5/1) yielded cis-crotonic acid **13** as a colorless liquid. Yield 1.71 g (39%).

20.2.11.1.3 Method 3: Carboxylation Reactions

20.2.11.1.3.1 Variation 1: From simple alkenes

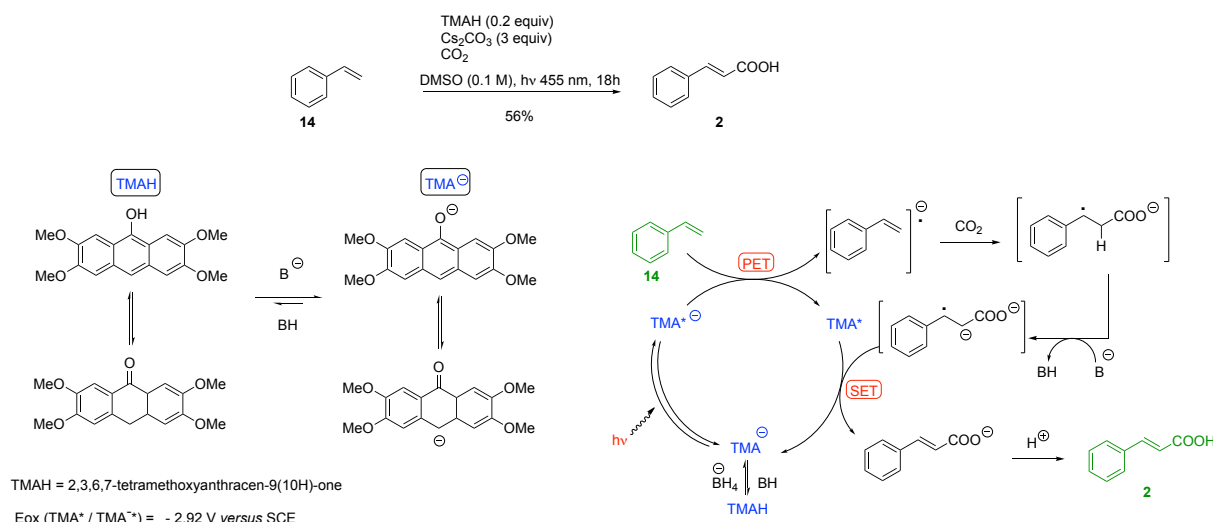
Introductory Text

The direct carboxylation of simple alkenes without preforming organometallic species is a highly challenging reaction due to the relative inertness of CO₂. A Lewis-acid mediated double bond activation has recently been used to perform carboxylation of alkenes, the key step being

the formation of a zwitterionic species by addition of the double bond on Et₂AlCl. The resulting organoaluminum reagent β-eliminates to give an alkenyl-aluminum reagent then can add onto CO₂ to yield the corresponding carboxylic acids.^[18] In the search for milder conditions to perform such reaction, the current rise of photochemistry represents a good opportunity for the efficient redox-neutral carboxylation of C(sp²)-H of alkenes. The photocatalytic approach involves the conversion of styrenes, arenes or heteroarenes into their radical anions by a photoinduced single-electron transfer (SET) from a visible-light excited anthrolate anion. The generated nucleophilic radical anions then react with CO₂ to provide the corresponding carboxylic acids (Scheme 8).^[19]

The mechanism starts by deprotonation of 2,3,6,7-tetramethoxyanthracen-9(10H)-one (TMAH) to form TMA⁻ which, upon irradiation with visible light (455 nm) gives rise to a strongly reducing excited anion TMA^{-*}. The latter is then quenched by the styrene **14** via PET to afford the electron-rich radical anion of the styrene which reacts with CO₂ to generate a radical carboxylate as an intermediate which is in turn rapidly deprotonated in the presence of base. The resulting radical dianion then reduces TMA^{*} via SET, leading to cinnamic acid **2** after acid hydrolysis.

<Scheme 8> Photocatalytic carboxylation of alkenes^[19]



Experimental Procedure

Cinnamic acid (**2**):^[19]

To a dry flat-bottomed crimp vial (5 mL) equipped with stirring bar, was added 2,3,6,7-tetramethoxyanthracen-9(10H)-one (6.3 mg, 0.02 mmol, 20 mol %) followed by Cs₂CO₃ (98 mg, 3 equiv) and the vial was sealed with a Supelco aluminium crimp seal with septum

(PTFE/butyl). The vial atmosphere was then purged with CO₂ (5×) via syringe needle before adding DMSO (1 mL, dry and degassed by bubbling with N₂) and styrene **13** (11.4 μL, 0.1 mmol). The vial was sealed with two layers of Parafilm® and then gaseous CO₂ was added *via* a Luer Lock Monoject™ syringe, into the head space. The vial was then irradiated from the bottom side with blue LED light and a constant reaction temperature (25°C) was maintained. After 18 hours of reaction the pressure was released. For product isolation, the reaction mixtures of 4 reactions run in parallel were combined and transferred with water and Et₂O into a separating funnel. The ether layer was extracted with water (3×) and the combined aqueous layers were acidified with aq. HCl (2M). The aqueous layer was extracted three times with EtOAc and the combined layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude material was purified by silica flash column chromatography using mixtures of hexanes and ethyl acetate with 0.5% AcOH (v/v) as eluents to yield cinnamic acid **2**. Yield 33.1 mg (56%).

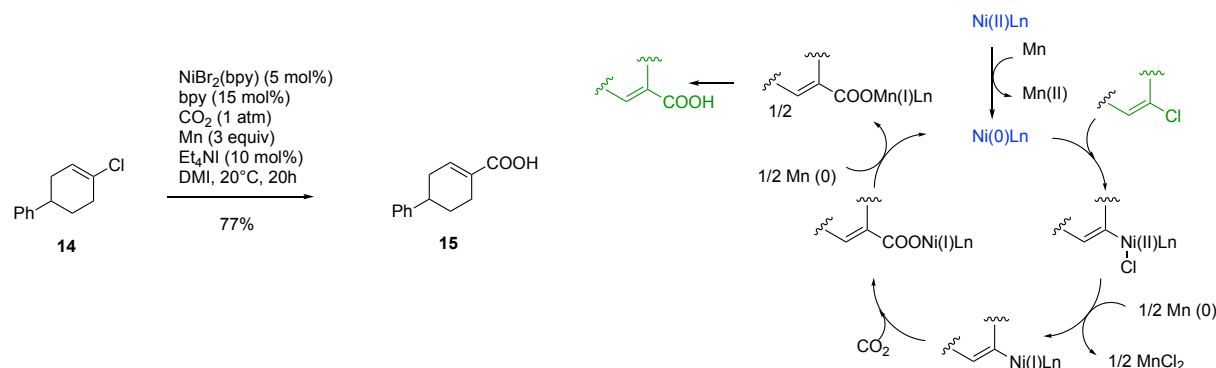
20.2.11.1.3.2 Variation 2: From halogenoalkenes

Introductory Text

Halogenoalkenes can be carboxylated easily by reaction with CO₂, provided that the corresponding organometallic species is prepared beforehand, such in the case of Grignard or organolithium reagents. However, this cannot be applied to sensitive substrates due to the high reactivity of these organometallic species. Silyloxycarbonylation of aryl and vinylbromides has been performed by using a tandem Cu/Pd catalysis in the presence of silane. The first step is reduction of CO₂ into CO by silane/Cu then Pd catalyst, after oxidative insertion into the C-Br bond, inserts into CO to generate the desired carboxylic acid.^[20] Nickel or cobalt catalyses have been recently developed and show high substrate compatibility due to lesser reactivity of organonickel or organocobalt intermediates that are generated *in situ* (Barbier conditions); for example, boronic esters or methyl esters are well tolerated. In addition, alkenyl iodides, bromides and even chlorides are suitable substrates. The Nickel catalysis is supposed to go through first reduction by Mn of Ni(II) onto Ni(0) that undergoes insertion into the C-X bond to yield an organonickel(II) reagent. The latter is then reduced to Ni(I) by Mn allowing addition of the organonickel reagent to CO₂, generating a Ni(I) carboxylate that is further reduced to Ni(0) by Mn again, closing the catalytic circle (Scheme 9).^[21] On the other hand, cobalt

catalyzed reactions uses Co(I) as the reactive species and goes through organo-Co(III) and -Co(II) intermediates.^[22]

<Scheme 9> Nickel catalyzed carboxylation of chloroalkenes^[21]



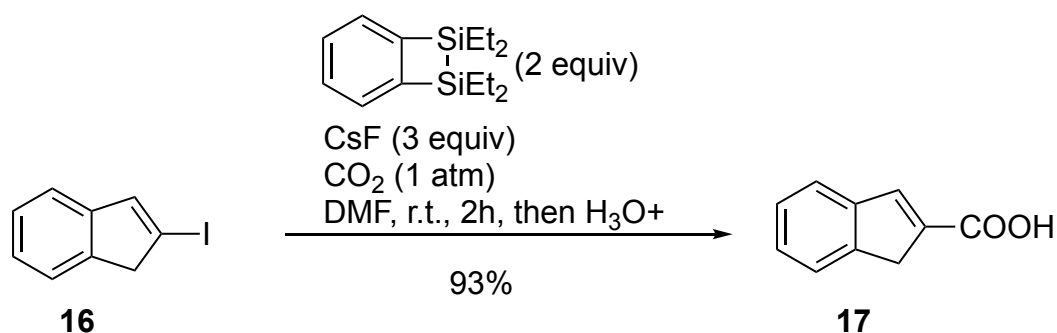
Experimental Procedure

4-Phenyl-1-cyclohexenoic acid (15**):^[21]**

A dry Schlenk tube was charged with NiBr₂(bpy) (9.4 mg, 0.025 mmol), 2,2'-bipyridine (11.7 mg, 0.075 mmol), Mn powder (82.4 mg, 1.5 mmol) and Et₄Ni (12.9 mg, 0.050 mmol). The tube was evacuated and refilled with CO₂ five times. DMI (0.75 mL) and 4-phenyl-1-cyclohexenylchloride **14** (96 mg, 0.50 mmol) were added via air-tight syringes, and the resulting mixture was stirred at 20°C for 20 h. After reaction, 6N HCl aq. (3 mL) and Et₂O (5 mL) were added, and stirred at room temperature for 10 min. The mixture was extracted with Et₂O (5 x 5 mL). The combined organic layers were dried over anhydrous MgSO₄, filtrated and concentrated under reduced pressure. The residue was purified by silica gel chromatography using first Hexane/EtOAc (5/1) and then EtOAc as an eluent to give 4-phenyl-1-cyclohexenoic acid **15**. Yield 77.4 mg (77%).

Transition-metal-free conditions have been developed by using a cyclic disilane in the presence of CsF to generate a reactive silyl anion that can promote the reaction of iodovinyl compound with CO₂ (Scheme 10).^[23] The mechanism goes through activation of the disilane by fluoride anion, leading to a nucleophilic silyl anion species. Its nucleophilic attack to the halide bond of the alkenyl halide generates a new vinylic anion which is then trapped by CO₂ to give the corresponding carboxylic acid.

<Scheme 10> Metal-free carboxylation of vinyl iodides^[23]



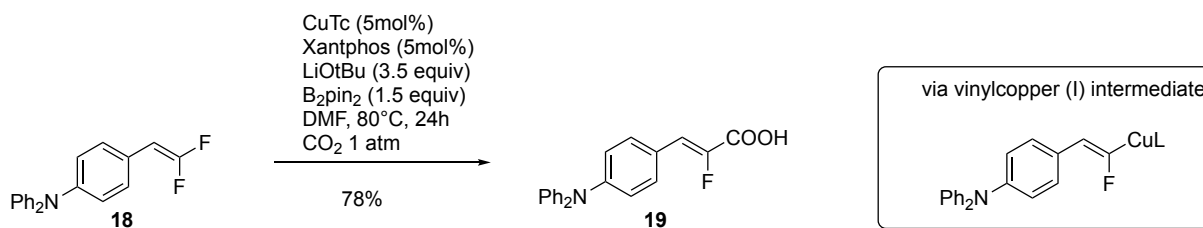
Experimental Procedure

1H-Indene-2-carboxylic acid (**17**):^[23]

CsF (91.1 mg, 0.6 mmol, 3 equiv) was placed to a 15 mL test tube and dried for 5 min by a heat gun under vacuum before use (<5 mmHg at ca. 400 °C), then the test tube was filled with CO₂ gas (1 atm: balloon) before adding 2-iodo-1H-indene **16** (48.4 mg, 0.2 mmol) and dry DMF (1.4 mL). The resultant mixture was vigorously stirred at 0°C, and 3,4-benzo-1,1,2,2-tetraethyl-1,2-dihydrocyclobutene (99.4 mg, 108 μL, 0.4 mmol, 2 equiv) was added in one portion. The mixture was warmed to room temperature and stirred for 2 h. After monitoring the reaction progress by TLC, H₂O (10 mL) and 1 M HCl aq. (3 mL) were added to the mixture and extracted with AcOEt (10 mL x3). The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure to afford the crude product which was then purified by silica-gel column chromatography (CH₂Cl₂/MeOH, 10:1) to afford **17**. Yield (29.8 mg) 93%.

Gem-difluorovinyl derivatives that are generally poorly reactive can be carboxylated by CO₂ via a copper catalysis and in the presence B₂pin₂ and LiOtBu. It is proposed that an intermediate vinyl-pinacolboronate obtained by insertion of a boryl-copper(I) species into a C-F bond transmetalates into the reactive vinylcopper (I) species (Scheme 11). Z-α-fluoroacrylic acids are thus obtained with good yields and the reaction can be performed on a gram scale.^[24-25] Alternatively, an iridium photoredox (iridium photocatalyst in combination with a palladium catalyst)^[26] or an electrochemical process (undivided cell, Pt and Nickel electrodes)^[27] can be used, giving the Z-α-fluoroacrylic acids as the major isomer.

<Scheme 11> Copper catalyzed carboxylation of vinyl fluorides^[24]



Ar	Yield (%)	Ref
2-naphthyl	82	[24]
1-naphthyl	66	[24]
3-benzothiophene	70	[24]
3-quinoline	52	[24]

Experimental Procedure

(Z)-3-(4-(diphenylamino)phenyl)-2-fluoroacrylic acid (**19**):^[24]

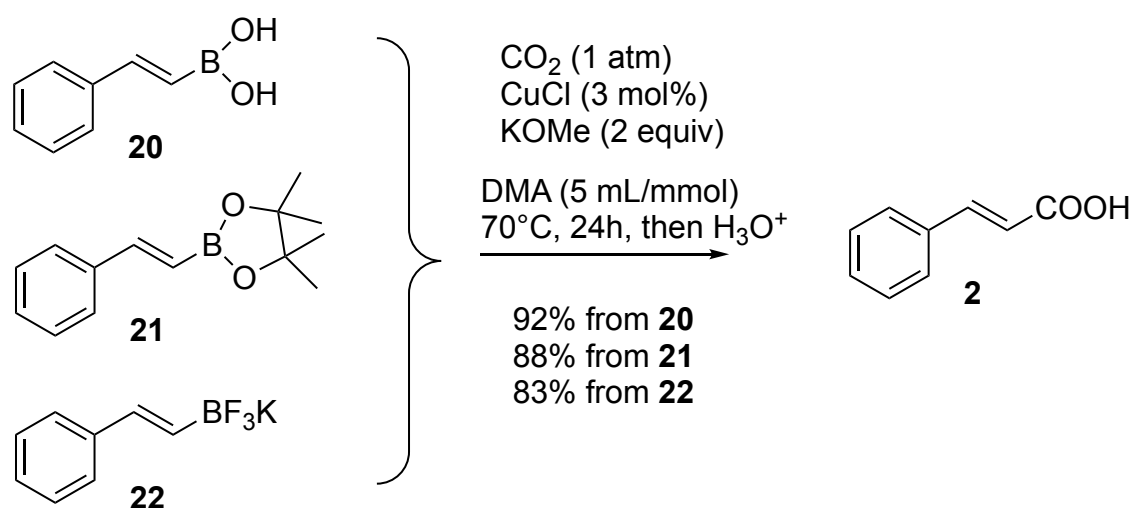
In a flame-dried Schlenk flask (250 mL) containing a stirring bar was added bis(pinacolato)diboron (1.52 g, 6 mmol, 1.5 equiv.) and 4-(diphenylamino)phenyl-1-(2,2-difluoroethenyl) **18** (1.23 g, 4 mmol, 1.0 equiv). The reaction tube was transferred to the glovebox and CuTc (38 mg, 0.2 mmol, 5 mol%), Xantphos (116 mg, 0.2 mmol, 5 mol%) and LiOtBu (1.12 g, 14 mmol, 3.5 equiv) were added. The reaction tube was moved out of the glovebox and the tube was then evacuated and back-filled with carbon dioxide for 3 times. Subsequently anhydrous DMF (20 mL) were added via syringe under CO₂ atmosphere. The Schlenk tube was then sealed at atmospheric pressure of CO₂ (1 atm) and the resulting mixture was stirred for 24 h at 80 °C. After cooling to room temperature, the resulting mixture was diluted with 20 mL EtOAc and 20 mL 2N HCl were added. The reaction mixture was extracted by EtOAc (3 x 50 mL) and the combined organic phases were concentrated in vacuo. The residue was purified by a silica gel flash column chromatography (petroleum ether/EtOAc 10/1, then 0.1% AcOH in petroleum ether/EtOAc 8/1 -> 5/1) to give (Z)-3-(4-(diphenylamino)phenyl)-2-fluoroacrylic acid **19** as a yellow solid. Yield 1.04 g (78%).

20.2.11.1.3.3 Variation 3: From alkenyl-boronic acids derivatives

Introductory Text

Organoboron reagents are stable organometallic intermediates well known for their use in palladium-catalyzed cross-couplings, mainly represented by the Suzuki reaction. Diverse alkenyl boronic acids, boronates or tetrafluoroborates can be carbonylated in the presence of various catalysts such as copper,^[28-30] nickel,^[31] silver^[32] or rhodium^[33] showing generally satisfactory functional group tolerance (Scheme 12). ¹¹C Labeled CO₂ can also be used leading to labeled carboxylic acids for PET imaging.^[34] Depending on the metal used, different mechanisms occur: either transmetalation of the organoboron followed by insertion of CO₂ into the C-Metal bond (Cu, Rh, Ag) or by activation of CO₂ (by zero-valent Ni) followed by transmetalation and reductive elimination.

<Scheme 12> Carboxylation of boronic acid derivatives^[28]



Experimental Procedure

Cinnamic acid (**2**):^[28]

Phenylvinylboronic acid **20** (148.0 mg, 1.0 mmol), KOMe (140.3 mg, 2.0 mmol), CuCl (3.0 mg, 0.03 mmol) and DMA were added in a Schlenk tube under N₂. The Schlenk tube was filled with carbon dioxide by applying five cycles of evacuation and filling with CO₂. The Schlenk tube was tightly sealed and stirred at 70 °C for 24 hours after which it was quenched by careful addition of 1.0 M HCl. The reaction mixture was diluted with water and extracted three times with EtOAc. The combined organic phases were washed with brine, dried over anhydrous

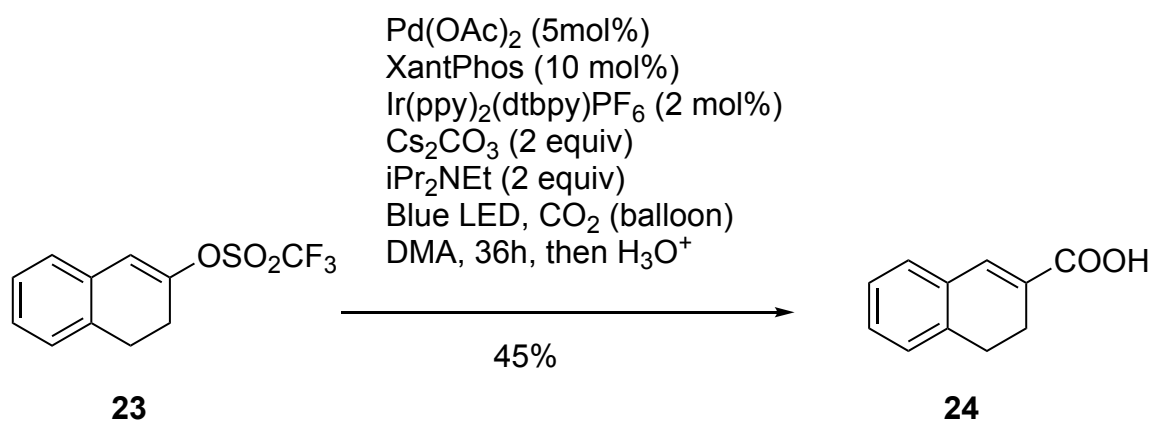
Na₂SO₄ and filtered before removing the solvent under vacuum. The crude product was purified by silica gel column chromatography (0–25 % EtOAc in petroleum ether) to obtain cinnamic acid **2**. Yield 136.2 mg (92 %).

20.2.11.1.3.4 Variation 4: From alkenyl triflate derivatives

Introductory Text

Alkenyl triflates are surrogates of halogenated alkenes and can be prepared from the corresponding ketones by basic treatment and trapping of the corresponding enolate with triflic anhydride. The reductive carboxylation of alkenyl triflates is effective when employing manganese powder as a reducing reagent in the presence of a cobalt catalyst (Scheme 13).^[35] As an alternative, photocatalysis may also be employed when combining Pd(OAc)₂, an iridium(III) photocatalyst and *i*-Pr₂NEt as a nonmetallic reducing agent, in the presence of CO₂. Sodium sulfinates may also be used in combination with a copper catalysis, although at high temperature.^[36]

<Scheme 13> Photocatalytic carboxylation of vinyl triflates^[35]



Experimental Procedure

3,4-dihydronaphthalene-2-carboxylic acid (**24**):^[35]

A DMA solution (8.0 mL) of 3,4-dihydronaphthalene-2-triflate **23** (276 mg, 1 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol, 5.0 mol %), XantPhos (57.8 mg, 0.1 mmol, 10.0 mol %), Ir(ppy)₂(dtbbpy)PF₆ (18 mg, 0.02 mmol, 2.0 mol %), Cs₂CO₃ (650 mg, 2 mmol, 2.0 equiv) and *i*-Pr₂NEt (350 μL, 2 mmol, 2.0 equiv) was prepared in a 15 mL screw cap glass vial under a

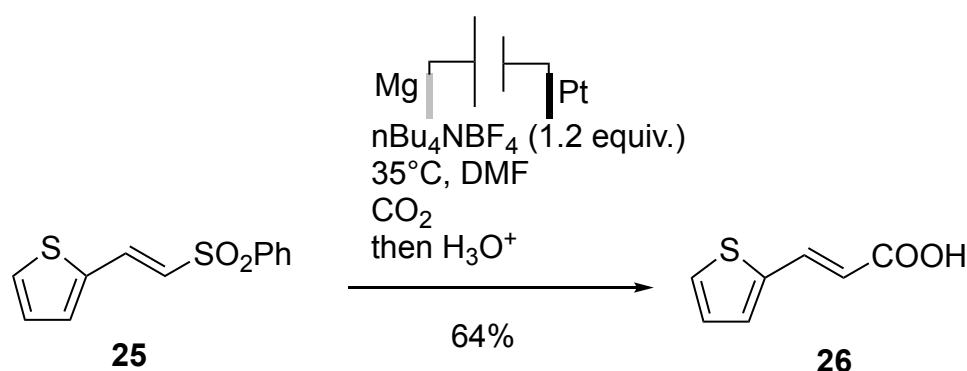
nitrogen atmosphere. Then the solution was bubbled with CO₂ through a needle for 15 min. Then the reaction vial was kept in a water bath which is placed at the middle of the customized blue LED strip chamber. The resulting mixture was irradiated under blue LED (48 W) light under balloon pressure of CO₂ for 36 h. After irradiation, the reaction mixture was quenched with H₂O and 2N HCl before extraction with EtOAc (3x). The combined organic layer was washed with H₂O and dried over Na₂SO₄. The solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography (hexane/ethyl acetate) to afford 4-dihydronaphthalene-2-carboxylic acid. Yield 15.7 mg (45%).

20.2.11.1.3.5 Variation 5: From alkenyl-sulfone derivatives

Introductory Text

Alkenylsulfones are versatile substrates easily obtained by numerous methods from carbonyl compounds, alkenes, alkynes... In addition, their desulfonylative transformation has been largely described, involving transition-metal catalysts, photocatalysts, organocatalysts or radical conditions.^[37] The electrochemical desulfonylative reaction of α,β -unsaturated sulfones can be performed with a Mg anode and a Pt cathode under a CO₂ atmosphere (1 atm) in an undivided cell to give the corresponding α,β -unsaturated carboxylic acids with moderate to excellent yields.^[38]

<Scheme 14> Electrochemical carboxylation of vinyl sulfones^[38]



Experimental Procedure

3-(thiophen-2-yl)acrylic acid (**26**):^[38]

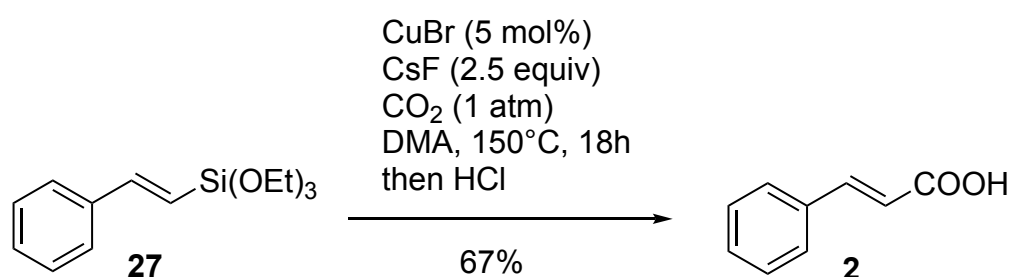
To an undivided cell equipped with a magnesium anode (1.5*1.5 cm²), a platinum cathode (1.5*1.5 cm²) and a stirring bar, *n*Bu₄NBF₄ (99mg, 0.3 mmol) and 2-(2-(phenylsulfonyl)vinyl)thiophen **25** (75 mg, 0.3 mmol) were dissolved in 7.5 mL of DMF/CH₃CN under CO₂ atmosphere. The reaction was saturated with CO₂ by bubbling (20 mL/min) for 5 min. Then 15 mA of constant current was applied to the electrolysis for the indicated time. During the electrolysis CO₂ was supplied by constant bubbling (10 mL/min). After electrolysis the reaction mixture was acidified by 20 mL of 1 M HCl and extracted by 30 mL of EtOAc. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 2/1) to afford 3-(thiophen-2-yl)acrylic acid **26** as pale yellow solid. Yield 30.9 mg (64%).

20.2.11.1.3.6 Variation 6: From alkenyl-silane derivatives

Introductory Text

Aryl- or heteroaryl-silanes have been reported to undergo carboxylation provided that there is a heteroatom at the ortho-position to the silicon group by using either cesium fluoride or tetrabutylammonium difluorotriphenylsilicate (TBAT) as additives. Alkenyl-triethylsilane bearing a nitrogen atom at the β-position can also react under these conditions.^[39-40] These limitations have been overcome by the use of alkenyl-trialkoxysilanes in the presence of cesium fluoride and a copper catalysis (Scheme 15). The reaction mechanism involves transmetalation from silicon to copper, leading to an alkenyl-copper reactive intermediate that adds onto CO₂, delivering the α,β-unsaturated carboxylic acid.^[41]

<Scheme 15> Copper catalyzed carboxylation of vinyl-silanes^[41]



Experimental Procedure

Cinnamic acid (**2**):^[41]

In an argon filled glove box, CuBr (3.5 mg, 0.025 mmol) and CsF (0.19 g, 1.25 mmol) were added to a flame-dried 30 mL two-neck tube. The tube was removed from the glove box and attached to a vacuum line and a CO₂ balloon using a three-way stopcock. After three evacuation-CO₂ refill cycles, DMA (1 mL) and ®-triethoxy(styryl)silane (0.135 g, 0.5 mmol) **27** was added via syringe, and the reaction was stirred at 1°C for 18 h. After being cooled to room temperature, the reaction mixture was diluted with H₂O (10 mL) and a NaOH solution (1M, 20 mL), and then washed with CH₂Cl₂ (3x20 mL). The aqueous solution was then acidified with 6M HCl until pH=1 and then was extracted with EtOAc (3x20 mL). The combined organic solution was washed with H₂O (3x30 mL) and dried over Na₂SO₄. The organic solvent was removed under reduced pressure to afford the pure cinnamic acid **2**. Yield 50mg (67%).

20.2.11.1.3.7 Variation 7: From terminal alkynes derivatives

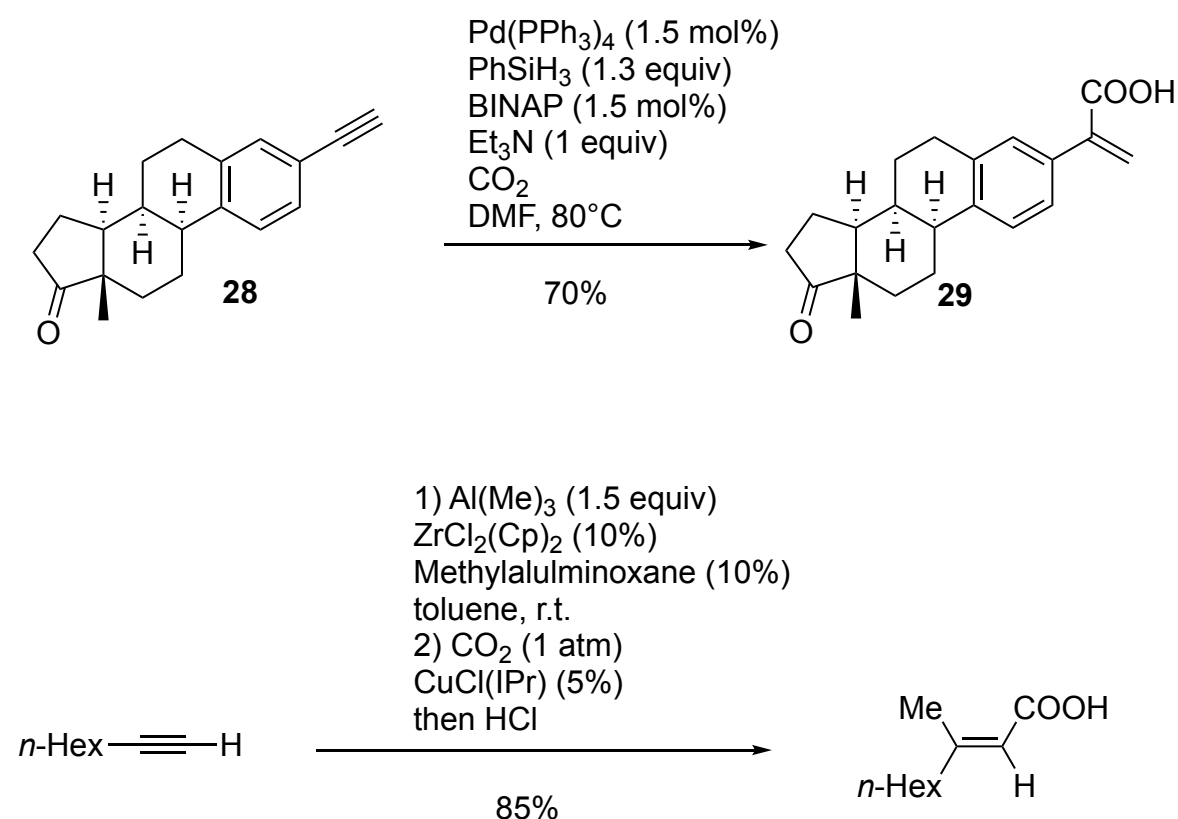
Introductory Text

Terminal alkynes are substrates of choice for the synthesis of unsaturated carboxylic acid, provided that they can be metalated and further reacted with CO₂. One of the difficulties arises from the presence of an acid proton in the terminal position of the alkyne, which prevents the use of strongly basic reagents. The regioselectivity of the carboxylation process can also be affected by the reaction conditions with the obtaining of α - and/or β -substituted acrylic acid derivatives. For example, the use of trialkylborane along with a copper catalysis leads regioselectively to the α - substituted acrylic acid derivative where one of the alkyl groups of BR₃ has been transferred. The reactive intermediate is a vinylic organoboron reagent that is transmetalated to copper before reacting with CO₂.^[42] A Cu(II)-Ni(II) combination is also effective in performing the regioselective hydrocarboxylation of terminal alkynes in the presence of CO₂, while polymethylhydrosiloxane provides the necessary hydride.^[43] A palladium catalysis can also be applied to obtain the α - substituted acrylic acid derivative, using PhSiH₃ as the hydride donor (Scheme 16 top). This methodology can also be applied to late-stage functionalization of complex biomolecules.^[44] Formal carboxylation can be achieved by using formic acid (precursor of carbon monoxide) and a nickel catalysis (Ni(acac)₂) with high selectivity,^[45-46] or by using a palladium catalysis.^[47]

In order to access β -substituted acrylic acid derivatives from terminal alkynes, different methods can be used. A formal methylative or hydrogenative carboxylation can be achieved regioselectively by first methyl-alumination (AlMe_3) or hydro-alumination (DIBAL-H) of the triple bond, catalyzed by Zirconium or Nickel salts, respectively. Then, the corresponding vinyl aluminum species at the terminal position is transmetalated to copper species which undergoes carboxylation with CO_2 , leading to the β -substituted acrylic acid derivatives (Scheme 16 bottom).^[48] Electrochemistry can also be used and reduction of CO_2 by electrons, mediated by a nickel complex, leads to the radical which adds onto the triple bond of phenylacetylene, leading to cinnamic acid.^[49]

Intramolecular nickel-catalyzed cycloisomerization of enynes followed by CO_2 trapping leads also to β,β -disubstituted acrylic acids.^[50]

<Scheme 16> Palladium catalyzed carboxylation of terminal alkynes^[44, 48]



R—C≡C—H	Yield (%)	Ref
PhCH ₂ CH ₂ -	100	[48]
TBDPSO-CH ₂ CH ₂ -	88	[48]

TBDPSO-CH ₂ CH ₂ -CH ₂ -	87	[48]
CH ₃ CH(OTBDPS)CH ₂ -	78	[48]

Experimental Procedure

2-((8*S*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]20arbazole201a-3 -yl)acrylic acid (**29**):^[44]

To a 15 mL oven-dried polytetrafluoroethylene (PTFE) reaction vessel equipped with a magnetic stirring bar, estrone **28** (162 mg, 0.6 mmol), Pd(PPh₃)₄ (0.009 mmol), Binap (0.009 mmol), Et₃N (0.6 mmol), anhydrous DMF (3 mL), and PhSiH₃ (0.78 mmol) were added successively. The vessel was fixed into a stainless-steel autoclave with a pressure-regulating system. Then the autoclave was sealed and CO₂ was introduced from a cylinder. The reaction mixture was stirred at 80°C for 12 h. After the reaction was completed, it was cooled to room temperature and the pressure was released slowly to atmospheric pressure. The residual material was quenched with HCl (2 M) and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous MgSO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluting with petroleum ether /ethyl acetate = 5/1 to 1/1) to provide the carboxylic acid **29**. Yield 136.0 mg (70%).

20.2.11.1.3.8 Variation 8: From internal alkynes derivatives

Introductory Text

Internal alkynes can undergo carboxylation under various conditions depending on the nature of the substituent R that is added (in addition to CO₂). The regioselectivity of CO₂ insertion is usually high and either α- or β-arylated alkenyl carboxylic acids can be obtained, depending on the reaction conditions.

Hydrocarboxylation reactions (R=H) can be performed with isopropanol in combination with Ni(II) and Mn(0) catalysis (Scheme 17 top),^[51] silane in combination with copper^[52] or palladium catalyst,^[44] diethylzinc in combination with nickel salts,^[53-55] *i*-BuMgBr in combination with Cp₂TiCl₂,^[56] EtMgBr in combination with iron catalysis^[57] as hydrogen donors.

A greener approach that is formally a carboxylation, using CO instead of CO₂, uses H₂O as the hydrogen source in combination with a water-soluble palladium catalyst.^[58]

In addition to organometallic conditions, photocatalysis can also be used to hydrocarboxylate internal alkynes, using CO₂ in the presence of Ir(ppy)₂(dtbppy)PF₆, CoBr₂, dcype, iPr₂Net and ZnBr₂ under blue LED irradiation. Regioselectivity can be moderate in some cases but is good when alkyne substituents are sterically differentiated.^[59]

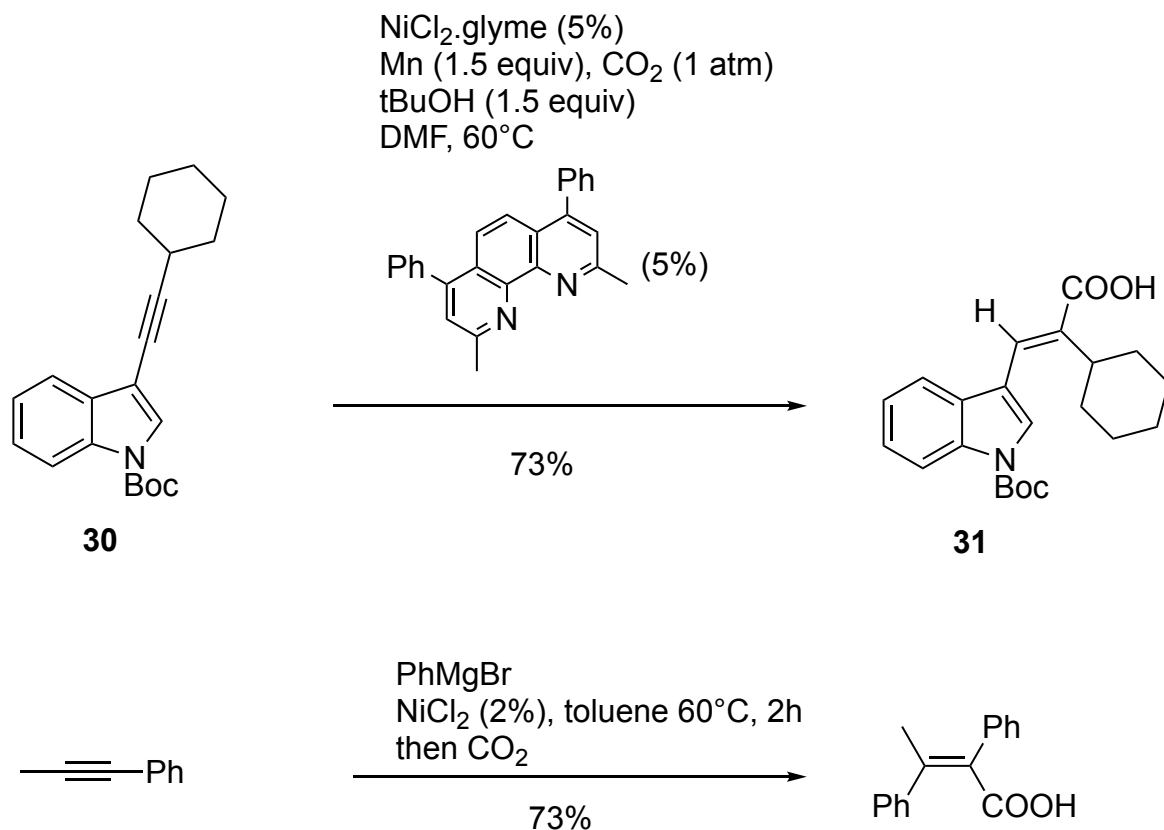
Carbo-carboxylation reactions (R=alkyl, aryl) on internal alkynes can also be performed but require the use of an organometallic species that first adds onto the alkyne to generate a vinyl-metal intermediate (carbometallation) that will further be trapped by CO₂ in a *syn* addition manner. The regioselectivity may be difficult to control if the nature of the two alkyne substituents is similar. One way to control the regioselectivity is to use an ether-tether group located at one end of the alkyne that will control the regioselectivity of the carbometallation through chelation and by forming a 5-membered 21arbazole211a.^[48] 5-membered 21arbazole211a can also be generated in the case of zirconometalation,^[60-61] they further react with CO₂ to give the corresponding carboxylic acid. Other metalacycles can be prepared, when metal and CO₂ are simultaneously added to the triple bond such as in the case of sila-carboxylation and the formed sila-lactones are good substrates for Hiyama cross-coupling reactions^[62] or boro-carboxylation where borolactones are formed and can be engaged in Suzuki couplings.^[63] In addition, cobaltacycles can be obtained after cobalt-catalyzed carboxyzincation of alkynes; further transmetalation and reduction by Zn(II) and Zn(0) provides an organozinc species that can react with various electrophiles or be engaged in palladium cross-couplings.^[64]

Carbometallation of alkyne followed by CO₂ addition can be catalyzed by nickel salts associated with Grignard reagents such as in the case of aryl- or methyl-magnesiations (Scheme 17 bottom).^[65-66]

Cyclizative carboxylation can be done on enynes with Et₂Zn and a Nickel catalysis followed by addition of CO₂,^[50, 67] on alkyl bromides and chlorides using a nickel (II)/Mn(0) catalysis^[68-69] or on alkyl iodides after iodine-magnesium exchange.^[70]

Ynamides can also be carboxylated after addition of dialkylzinc in the presence of Cu(acac)₂ and LiCl, followed by addition of CO₂. The regioselectivity of 21arbazole211ation and carboxylation is complete, introducing the carboxylic acid and alkyl group onto α- and β-carbons, respectively.^[71]

<Scheme 17> Nickel catalyzed carboxylation of internal alkynes^[51, 65]



Experimental Procedure

®-3-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)-2-cyclohexylacrylic acid (**3**):^[51]

A Schlenk tube was charged with alkyne **30** (161.5 mg, 0.50 mmol), 2,9-Dimethyl-4,7-diphenyl-1,10-phenanthroline (10.8 mg, 0.03 mmol), Mn powder (41.2 mg, 0.75 mmol) and NiCl₂.glyme (5.5 mg, 0.025 mmol). The tube was then flushed with CO₂ three times. T-BuOH (57.4 μL, 0.75 mmol) and DMF (2 mL) were then added by syringe under a CO₂ flow. The Schlenk tube was then closed at atmospheric pressure of CO₂ (1atm) and stirred for 36 h at 60°C. After this time, the reaction mixture was quenched with HCl (2M) and extracted with DCM. The combined organic layers were washed with brine and dried over anhydrous MgSO₄ and evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate 10/1 to 1/1) to give the carboxylic acid **31**. Yield 131.2 mg (73%).

20.2.11.1.4 Method 4: Carbonyl alkenylation

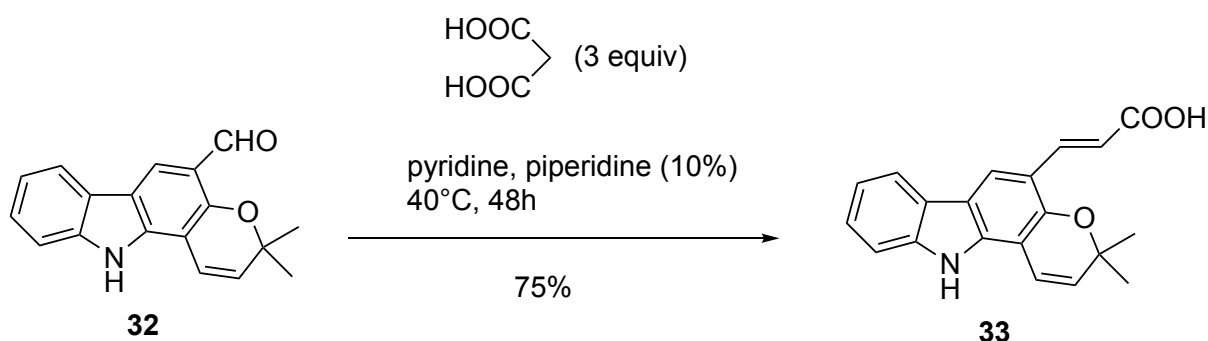
20.2.11.1.4.1 Variation 1: Doebner reaction

Introductory Text

The classic Doebner reaction is the condensation of malonic acid with aldehydes to form alkylidene malonic acids which then liberates the α -2-enoic acid after *in situ* decarboxylation (Scheme 18). This is a variant of the Knoevenagel reaction. This reaction is very general for aromatic, heteroaromatic aldehydes but can also be applied to aliphatic aldehydes.^[72-73] Typical conditions are the use of aminated base (piperidine or pyridine) at moderate to high temperatures.

Meldrum acid and cyanoacetic acid can also be used for such transformation, leading to α -cyano α,β -unsaturated acids for the latter.

<Scheme 18> Doebner condensation of aldehydes^[73]



Experimental Procedure

®-3-(8-Methoxy-3,3-dimethyl-3,11-dihydropyrano[3,2-a]23arbazole-5-yl)acrylic acid (**33**):^[73]

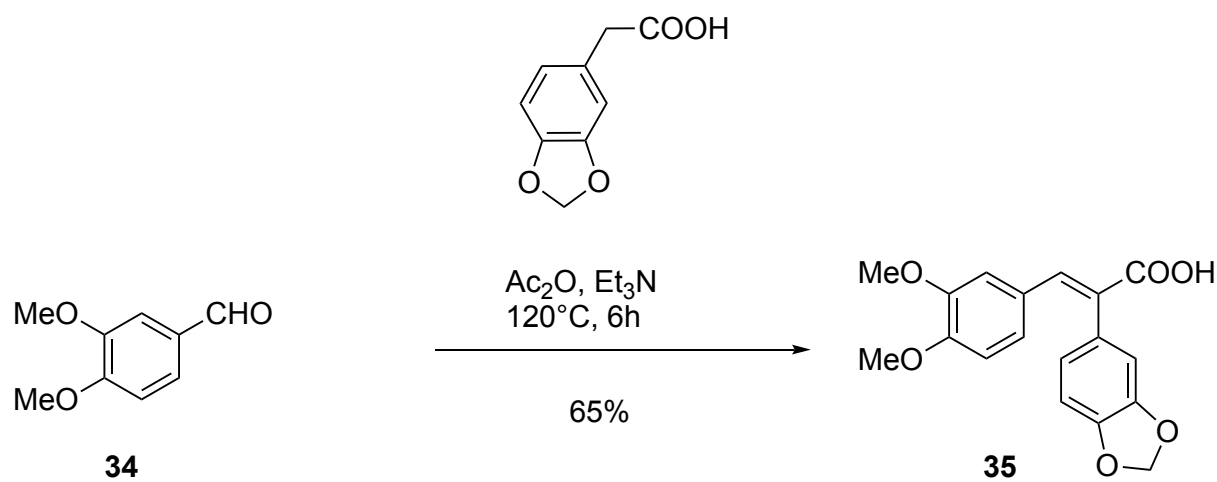
A solution of **32** (0.277g, 1 equiv) and malonic acid (3 equiv) in a mixture of pyridine (10 mL/mmol) and piperidine (0.01 equiv.) was maintained at 40°C for 48 h. The solution was concentrated by evaporation, the residue was diluted with 250 mL of water, and the pH was adjusted to 11.0 with 2 N NaOH. The solution was extracted with 200 mL of ethyl acetate (4 times) to remove bases and neutral impurities. The aqueous phase was treated with charcoal, and the filtrate was acidified to pH 1.8 by dropwise addition of 6 N hydrochloric acid with stirring at 5°C. The resulting yellow precipitate was washed with cold water to obtain **33**. Yield 0.239g (75%).

20.2.11.1.4.2 Variation 2: Perkin condensation

Introductory Text

Perkin condensation uses generally arylacetic acid derivatives, less stabilized carbanions than Doebner reaction, for their addition onto carbonyl derivatives. The reaction is performed at the reflux of acetic anhydride (Scheme 19).^[74]

<Scheme 19> Perkin condensation of aldehydes^[74]



Experimental Procedure

(αE)-α-[(3,4-Dimethoxyphenyl)methylene]-1,3-benzodioxole-5-acetic acid (**35**):^[74]

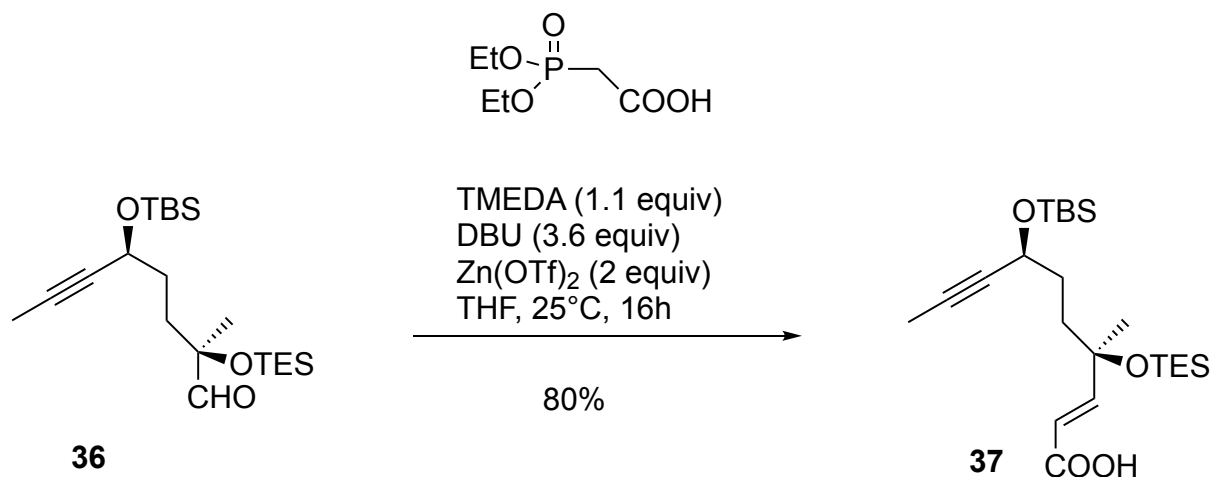
To a mixture of aldehyde **34** (4.98g, 30 mmol) and arylacetic acid (1.0 equiv) was sequentially added Ac₂O (1.5 equiv.) and Et₃N (36 mmol, 1.2 equiv.). The mixture was stirred at 120 °C for 6 h to complete the reaction. Then, H₂O (50 mL) was added, and the mixture was extracted with dichloromethane (3x150 mL). The combined organic phase was dried over Na₂SO₄ and concentrated in vacuo. The solid was triturated with MeOH for 6 h to afford **35**. Yield 6.4g (65%).

20.2.11.1.4.3 Variation 3: Wittig and Horner Wadsworth Emmons reaction

Introductory Text

Wittig reaction with phosphonium salts of acetic acid derivatives is not well documented contrary to the phosphonate variant (Horner Wadsworth Emmons reaction). The base of choice is butyllithium^[75] although milder conditions can be used such as a combination of DBU/TMEDA and Zn(OTf)₂ developed by Helquist^[76-77] to prepare the α,β -unsaturated acids with R -selectivity (Scheme 20).

<Scheme 20> Horner-Wadsworth-Emmons reaction^[77]



Experimental Procedure

(4*R*,7*S*,*E*)-7-((tert-Butyldimethylsilyl)oxy)-4-methyl-4-((triethylsilyl)oxy)dec-2-en-8-ynoic acid (**37**):^[77]

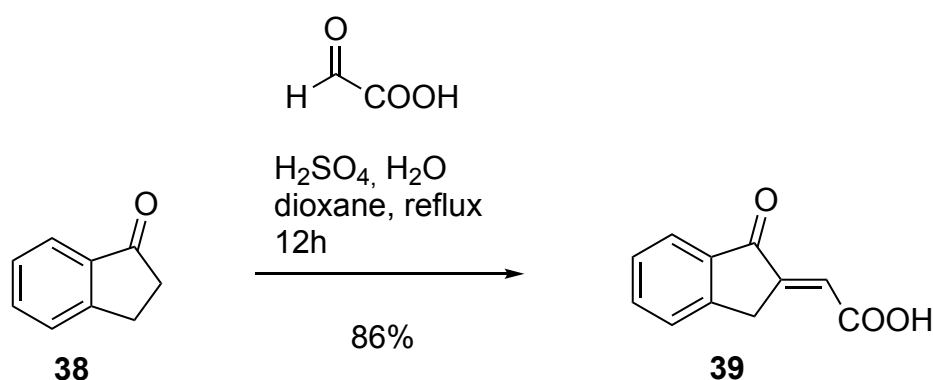
Diethylphosphonoacetic acid (1.48 mL, 9.2 mmol), TMEDA (1.50 mL, 10.0 mmol) and DBU (5.00 mL, 33.4 mmol) were added to a suspension of Zn(OTf)₂ (6.68 g, 18.4 mmol) in THF (25 mL) at 0 °C. Aldehyde **36** (3.31 g, 8.35 mmol) was introduced, the ice-bath was removed and the mixture stirred for 16 h at room temperature. The reaction was quenched with saturated aq. NH₄Cl and the aqueous layer extracted with CH₂Cl₂ (4 x). The combined extracts were washed with brine, which was re-extracted with CH₂Cl₂ (4 x). The combined extracts were dried over MgSO₄, the drying agent was filtered off and the solution was concentrated. Purification of the crude product by flash chromatography (hexanes/EtOAc, 5/1 to 1/1) afforded the acid **37** as a colorless oil. Yield 2.95g (80%).

20.2.11.1.4.4 Variation 4: Alkenation of α -oxo acids

Introductory Text

Reaction of activated α -oxo acids such as glyoxylic or pyruvic acid with ketones *via* an aldol process, leads to γ -oxo- α,β -unsaturated acid. The reaction conditions are usually acidic at high temperature, therefore not compatible with sensitive substrates (Scheme 21).^[78] Microwave conditions are useful to reduce the reaction time.^[79]

<Scheme 21> Alkenylation of glyoxylic acid^[78]



Experimental Procedure

®-2-(1-Oxo-1H-inden-2(3H)-ylidene)acetic acid (39):^[78]

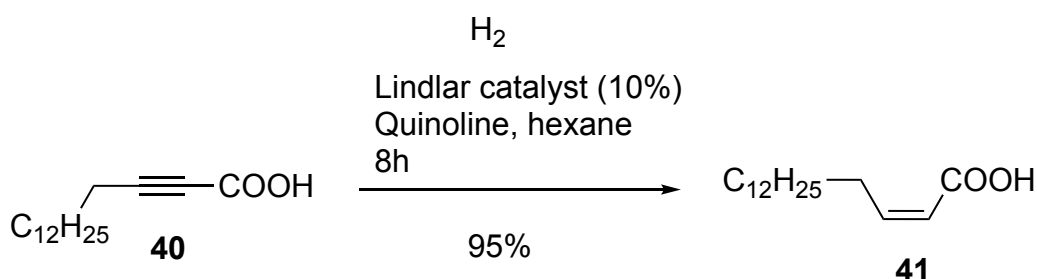
A mixture of 1-indanone, **38** (3 g, 22.7 mmol), glyoxylic acid (50% aqueous solution, 5.9 g, 54.5 mmol), and conc. H₂SO₄ (0.74 mL) in dioxane (5 mL) were stirred at refluxing temperature for 12 h. The mixture was cooled, the product filtered off, washed with water and dried to give the acid **39** as a white solid. Yield 3.68 g (86%).

20.2.11.1.5 Method 5: Reduction of alkynoic acids

Introductory Text

Semi-reduction of alkynes to (*Z*)-alkenes by hydrogenation is a common reaction that uses poisoned palladium catalysts to avoid over-reduction to the alkane. The same precaution applies with alkynoic acids, upon which the semi-reduction leads to (*Z*) α,β -unsaturated acids. Reductant is hydrogen gas coming from a cylinder^[80] (Scheme 22) or *in-situ* generated from formic acid.^[81]

<Scheme 22> *Semi reduction of alkynoic acids*^[80]



Experimental Procedure

(Z)-hexadec-2-enoic acid (**41**):^[80]

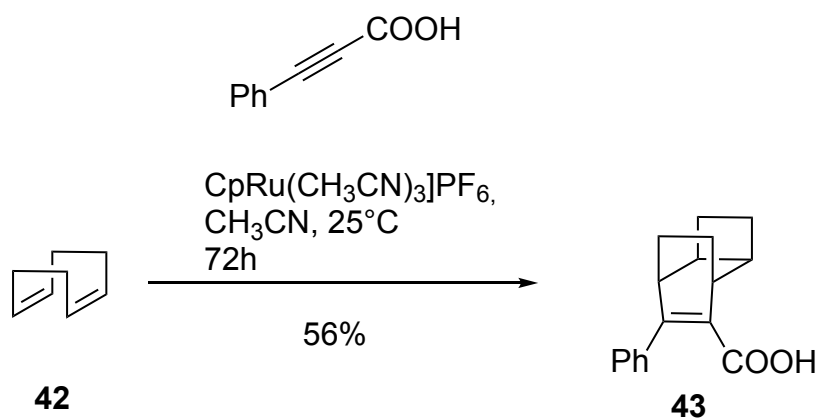
Hexadecyn-1-ynoic acid **40** (1.0 g, 4.0 mmol) was dissolved in hexane (20 mL), 50 μ L of quinoline followed by Lindlar catalyst (100 mg, 10 weight%) were added. The reaction mixture was purged with hydrogen gas for about 10 minutes and stirred for 8 h under a hydrogen balloon. The reaction mixture was filtered through Celite, concentrated under reduced pressure and purified by silica gel flash column chromatography eluting with EtOAc-hexane (1:4) to afford alkene acid **41** as a pale-yellow solid. Yield 950 mg (95%).

20.2.11.1.6 Method 6: cycloaddition of alkynoic acids

Introductory Text

Alkynoic acids react with 1,5-cyclooctadiene *via* a Bis-Homo-Diels-Alder [2+2+2] cycloaddition reactions. For this transformation, it has been reported that cationic ruthenium catalyst [CpRu(CH₃CN)₃]PF₆ is more effective than neutral ruthenium catalyst, allowing for the formation of cycloadducts in higher yields (Scheme 23).^[82]

<Scheme 23> *Cycloaddition of alkynoic acid*^[82]



Experimental Procedure

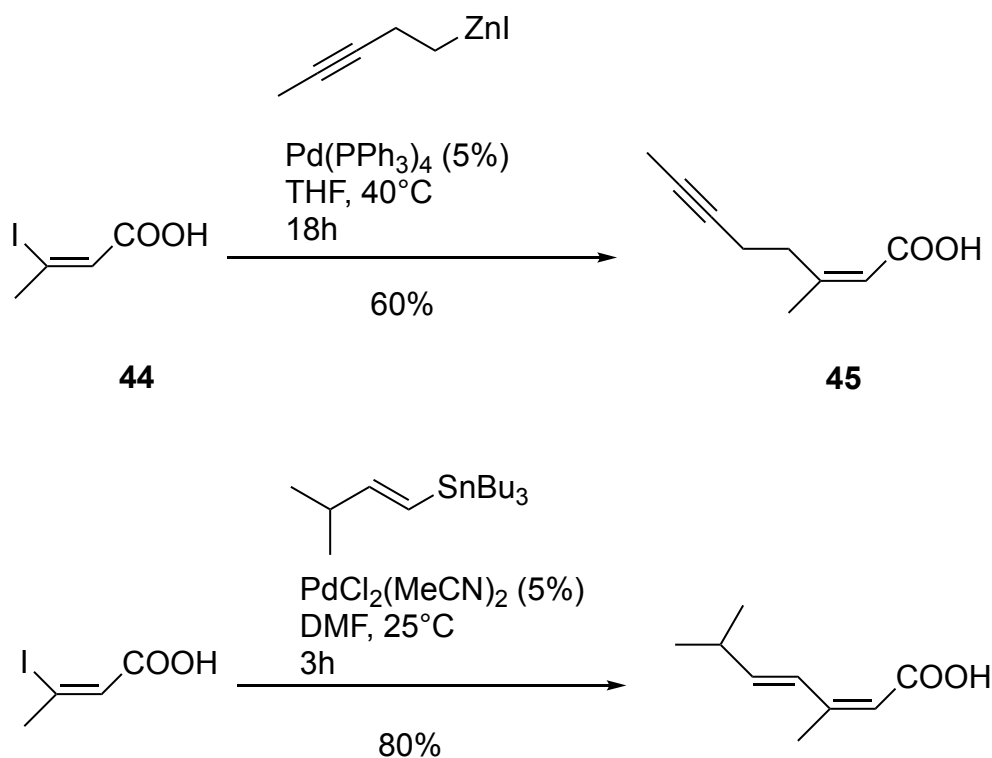
8-Phenyltricyclo[4.2.2.0^{2,5}]dec-7-ene-7-carboxylic acid (**43**):^[82]
 Phenylpropionic acid (0.24 mmol, 35 mg) and 1,5-cyclooctadiene **42** (1.3 equiv) were placed into oven-dried screwcap vials, purged with argon and imported into a glovebox. Within the glovebox, the alkyne, 1,5-cyclooctadiene, ruthenium catalyst (0.06 equiv) and dry acetonitrile (2.5 mL) were combined and mixed in a two-dram screw cap vial equipped with a small stir bar. The vials were then sealed and exported out of the glove box and allowed to react for 72 h at 25°C. The acid was isolated by flash chromatography using hexanes/ethyl acetate (19/1) as an eluent to give **43** as an orange solid. Yield 33.8 mg (56%).

20.2.11.1.6 Method 6: Palladium-Catalyzed Cross Coupling to β -Halogen-Substituted Alk-2-enoicAcids

Introductory Text

Cross coupling to β -halogeno-2-enoic acids has so far been limited to the iodo derivatives obtained by iodination of alkynoic acids. β -iodo-2-enoic acids are then engaged in palladium catalyzed reactions with organozinc^[83] or organotin^[84] species to give the coupling product with good yields and retention of the configuration of the double bond (Scheme 24). These reactions can usually be scale-up to multigram quantities without difficulties.

<Scheme 24> organozinc coupling on β -iodo-2-enoic acids^[83-84]



Experimental Procedure

(Z)-3-methyloct-2-en-6-ynoic acid (**45**):^[83]

A solution of the zincate derived from 5-iodopent-2-yne (21.7 mL, 3 equiv) was slowly added via syringe (control the exothermicity by slow rate of addition) into a solution containing **44** (13.7 g, 64.8 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (3.74 g, 3.24 mmol) in THF (65 ml) at 40°C . The mixture turned dark brown as the zincate solution was syringed in. The mixture was stirred at 40°C for 18 h. The reaction was quenched with 1M HCl and extracted with ether (3 x 50mL). The organic layer was back extracted with 1M NaOH (3 x 150 mL). The combined NaOH aqueous layers were washed with DCM (2x) then acidified with conc. Aq. HCl then extracted with EtOAc (3 x 150mL). The organic phase was dried with Na_2SO_4 , filtered, and concentrated in vacuo, yielding a crude liquid which was purified by flash-chromatography (Hex/EtOAc 80/20), yielding **45** as a white solid. Yield 5.93 g (60%).

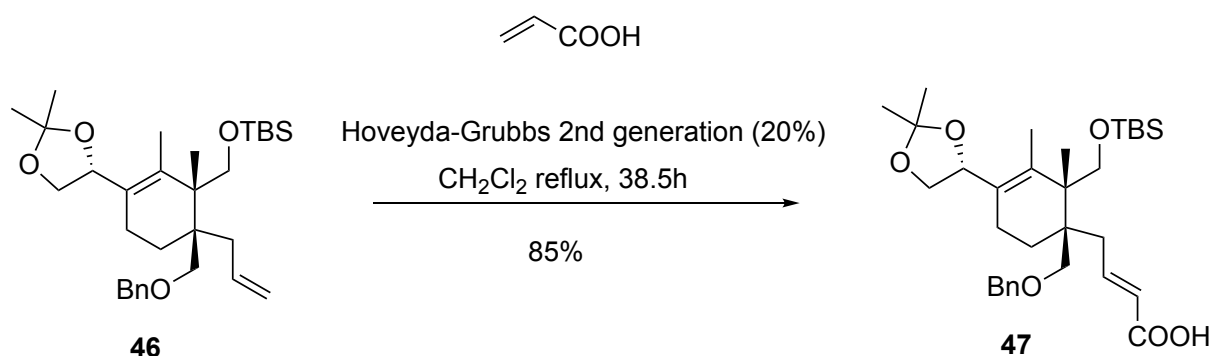
20.2.11.1.7 Method 7: Alkene metathesis

Introductory Text

Alkene metathesis reactions on alk-2-enoic acids generates valuable compounds from less functionalized starting materials and in very mild conditions. This ruthenium–carbene-

catalyzed reaction can be done intramolecularly (ring closing metathesis) or intermolecularly (cross-metathesis). Selectivity on different double bonds born by starting materials can be achieved, depending on steric or electronic factors (Scheme 25).^[85-86]

<Scheme 25> Cross metathesis on acrylic acid^[85]



Experimental Procedure

4-((1R,2S)-2-(tert-Butyldimethylsilyloxymethyl)-1-(benzyloxymethyl)-3-methyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl) cyclohex-3-enyl)-but-2-enoic acid (**47**).^[85]

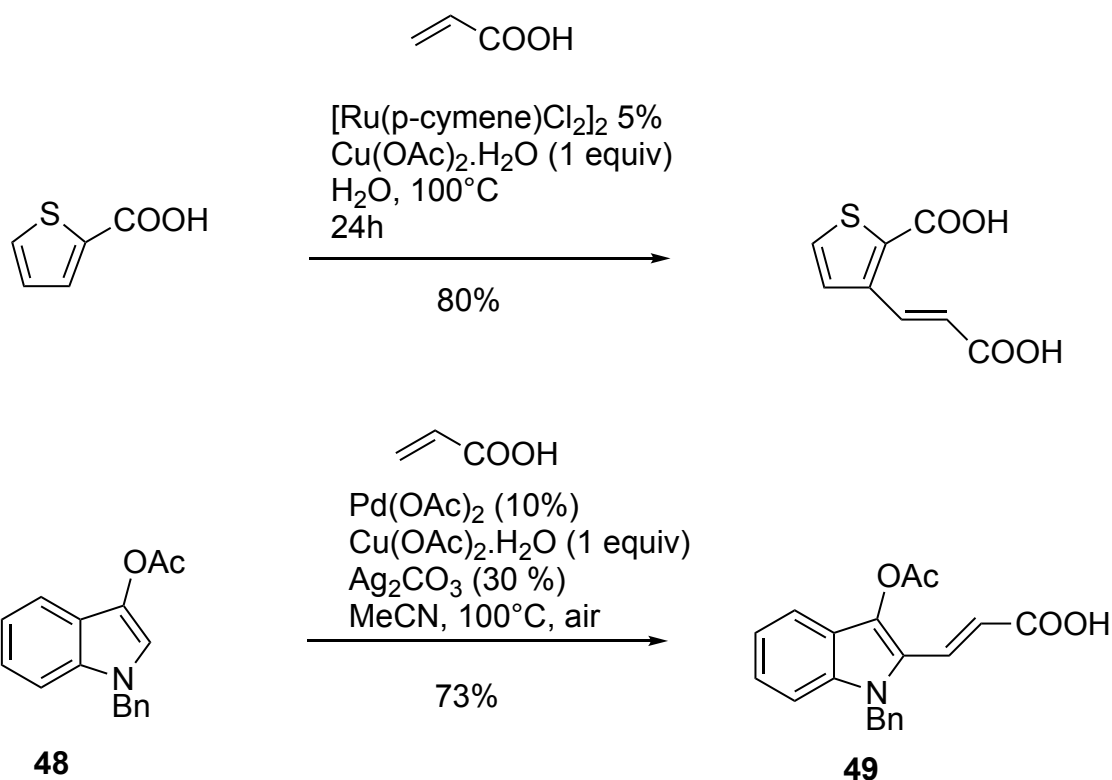
To a solution of alkene **46** (291 mg, 0.581 mmol) in degassed CH_2Cl_2 (29 mL) were added acrylic acid (0.399 mL, 5.81 mmol) and Hoveyda–Grubbs second generation catalyst (72.8 mg, 0.116 mmol) and the mixture was heated to reflux for 38.5 h. The mixture was allowed to cool to room temperature and stirring was continued for 30 min under air. The mixture was concentrated and the residue was purified by flash chromatography (hexanes/EtOAc, 15/1) to give the acid **47** as a colorless amorphous solid. Yield (268 mg) 85%.

20.2.11.1.8 Method 8: C-H activation

Direct functionalization of arene with alk-2-enoic acids by C-H activation is a powerful method to functionalize simple aromatic or heteroaromatic compounds. Regioselectivity can sometimes be an issue but it can be controlled by the use of a directing group (Scheme 26).^[87-88]

Electrochemical activation can also be applied, resulting in milder conditions as it can be done at room temperature.^[89]

<Scheme 26> C-H activation with acrylic acid^[87-88]



3-acetoxyindole	Yield (%)	Ref
N-methyl	79	[88]
N-allyl	64	[88]
7-methyl-N-benzyl	70	[88]
6-bromo-N-benzyl	73	[88]

Experimental Procedure

(*E*)-3-(3-Acetoxy-1-benzyl-1*H*-indol-2-yl)acrylic acid (**49**):^[88]

An oven-dried sealed tube equipped with a magnetic bar was charged with indole **48** (0.1 mmol, 0.026g), Pd(OAc)₂ (0.002g, 10.0 mol %), Cu(OAc)₂.H₂O (0.02g, 1.0 equiv), Ag₂CO₃ (0.008g, 30.0 mol %), and acrylic acid (2.0 equiv). 2.0 mL of MeCN was added to the reaction vessel, and the overall reaction mixture was stirred for 12 h at 100°C under open flask conditions. The crude mixture was diluted with ethyl acetate (10.0 mL) and filtered through a bed of Celite and rinsed with an excess of ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄ and concentrated to afford the residue which was subjected to flash column chromatography on silica gel using petroleum ether/EtOAc (3/1) as the eluent to obtain the pure acid **49**. Yield 0.024g (73%).

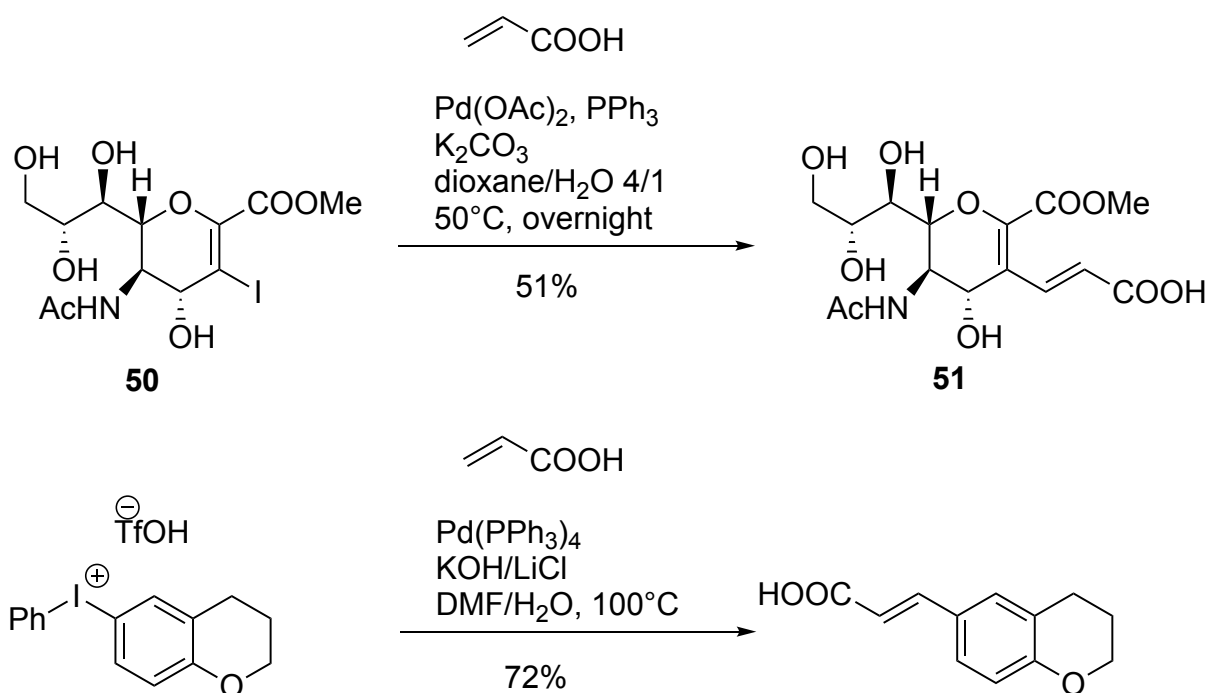
20.2.11.1.9 Method 9: Heck reactions

Introductory Text

The Heck reaction is a Pd-catalyzed carbon-carbon cross-coupling reaction that takes place between aryl halides or vinyl halides (mainly Br, I or Tf) and activated alkenes in the presence of a base. Recent developments in catalysts and reaction conditions have considerably extended the range of donors and acceptors suitable for the Heck reaction. Acrylic acid is a suitable substrate for this reaction and introduction of this moiety on complex molecules is made possible (Scheme 27 top).^[90-91]

In addition to halides, iodonium salts proved also reactive under palladium catalysis (Scheme 27 bottom).^[92]

<Scheme 27> Heck reaction with acrylic acid^[91-92]



Experimental Procedure

5-Acetamido-5-deoxy-3-[(E)-2-carboxyvinyl]- β -D-glycero-D-galacto-non-2-enonic acid (**51**):^[91]

Vinyl iodide **50** (10.4 mg, 0.025 mmol), acrylic acid (0.05 mmol), palladium acetate (0.6 mg, 0.0025 mmol), triphenylphosphine (1.3 mg, 0.005 mmol), and K₂CO₃ (8.6 mg, 0.0625 mmol) were mixed in dioxane and H₂O (v/v = 4/1, 1 mL, degassed by bubbling nitrogen for 0.5 h). The reaction mixture was flushed with nitrogen, heated to 50 °C and stirred overnight. NaOH solution (1 M, 0.5 mL) was added, and the resulting mixture was stirred at rt for another 0.5 h before being neutralized with Amberlyst® 15 resin. After filtration, the filtrate was collected and the solvent was removed under vacuum before purification by flash chromatography (20-35% MeOH/H₂O/AcOH 5/1/0.1 in Ethyl Acetate) to give the carboxylic acid **14**. Yield 4.6 mg (51%).

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