A project report entitled

CARBOXYLATION OF UNSATURATED COMPOUNDS USING TRANSITION METALS

Dissertation submitted to Goa University in partial fulfilment of the requirement for the degree of

MASTER OF SCIENCE

IN

CHEMISTRY

By

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Organic chemistry

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STATEMENT

I hereby declare that the matter represented in this dissertation certified ***"Carboxylation of unsaturated compounds using transition metals"*** *is the result of investigation carried out by me, under the supervision of Assistant Professor Dr. Sandesh Bughde and for the award of degree.*

Ms. Pallavi M. Ghatekari

CH-20-34

Certificate

This is to certify that dissertation entitled ***"Carboxylation of unsaturated compounds using transition metals"*** *is bonified work carried out by Ms. Pallavi M. Ghatekari under my supervision in partial fulfilment of the requirements for the award of Master of Science in Chemistry at the school of science, Goa University.*

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Assistant Professor

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14/05/2022

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It gives me an immense pleasure to present my dissertation topic ***"Carboxylation of unsaturated compounds using transition metals."***

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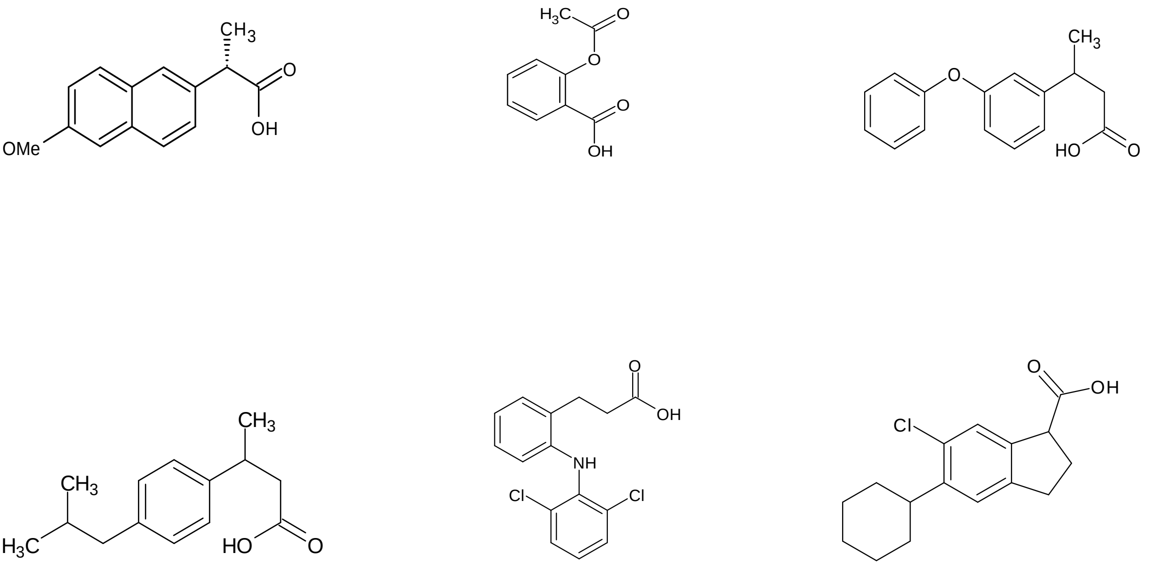
Last but the least, I wish to thank my parents for their moral support and financial assistance without whom I would have not been able to pursue my studies.

INTRODUCTION

Carboxylation is a chemical reaction in which a carboxylic acid is produced by treating a substrate with carbon dioxide. Carboxylic acids are one of the most important types of compounds. Although there are various well-developed protocols for the synthesis of carboxylic acids, direct carboxylation of carbon-based nucleophiles utilizing CO_2 as an electrophile is a straightforward method to fulfil the synthesis needs.

$$\text{R-H} + \text{O=C=O} \longrightarrow \text{R-COOH}$$

Synthesis of carboxylic acids with CO_2 through CAC bond formation is highly attractive, (1) because carboxylic acids widely exist in myriad natural products, agrochemicals and pharmaceuticals (scheme1) (2). Furthermore, carboxylic acids can serve as useful building blocks in chemical industry to manufacture cosmetics, detergents, rubbers, dyes, plastics and so on (3). The catalytic carboxylation reactions with CO_2 have been accomplished by several kinds of transition metals, such as Ni, Cu, Pd, Au, Rh, and so on. For catalytic carboxylation of unsaturated substrates, Ni and Cu are most widely investigated (4).



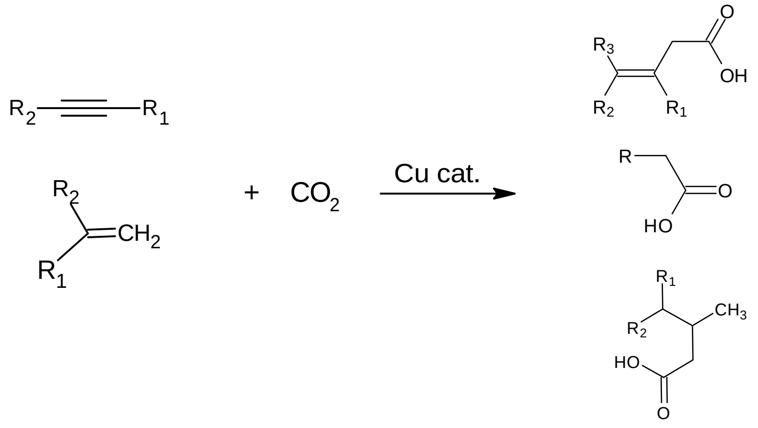
Scheme1. Examples of natural products

Carbon dioxide (CO_2) is one of the most important materials as renewable feedstock. However, the thermodynamic and kinetic stability of CO_2 sometimes limits its utility. Classically, harsh reaction conditions such as high temperature and high pressure of CO_2 were required. To overcome these problems, the use of transition-metal catalysts has been considered as a fundamental and reliable method.

Direct carboxylation of organometallic reagents with CO_2 has been well-studied and applied in organic synthesis. The advantages of this protocol include avoiding harsh reaction conditions and using CO_2 as a green and sustainable source.

Highly reactive organometallic reagents, such as organolithium and Grignard reagents, are the historical, yet still typical starting materials for nucleophilic carboxylation, since they are reactive enough to overcome the inherent thermodynamic stability of CO_2. For example reactions of organolithium or Grignard with CO_2 have been well-developed, however, the poor functional group compatibility limits their use. As a result, to obtain carboxylic acids more efficiently, attention was focused on transition-metal-catalysed carboxylation of milder organometallic reagents under more facile reaction conditions (5). And meanwhile catalytic systems for the synthesis of carboxylic acids by direct carboxylation of unsaturated organic compounds with CO_2 have been also developed through well-known oxidative cycloaddition. (6)

Among the metal catalysts, copper reagents are abundant, environmentally friendly, and inexpensive. Many copper-mediated reactions have been reported. , various copper-catalysed carboxylation reactions have been thoroughly studied in recent years (7). Generally, the copper-catalysed carboxylation reaction has three key steps: (i) generation of C–Cu species from the substrate; (ii) insertion of CO_2 into the C–Cu bond to afford the copper carboxylate; and (iii) release of carboxylate and copper catalysts. (Scheme2)



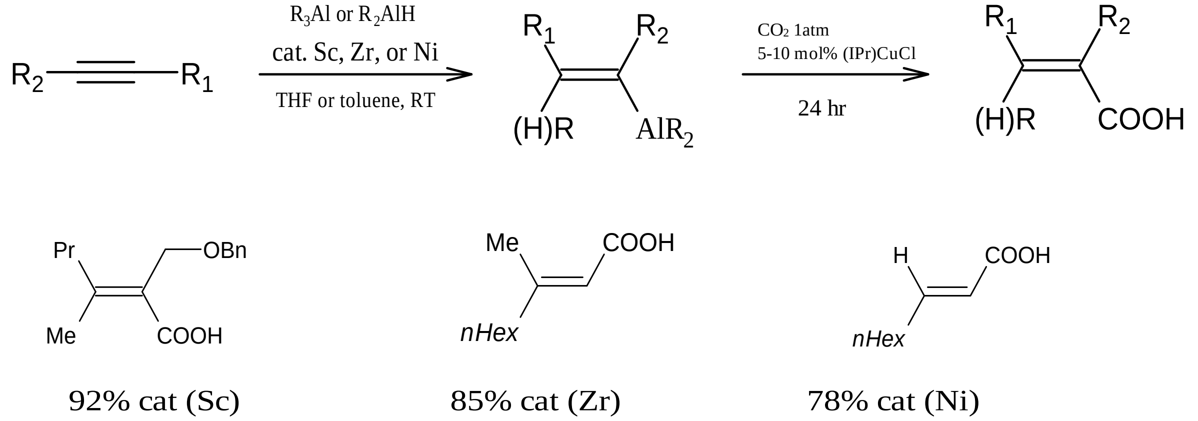
Scheme 2. Copper-catalyzed carboxylation of available substrates

LITERATURE REVIEW

Copper-catalysed carboxylation of organometallic reagents

Organoalumination reagent

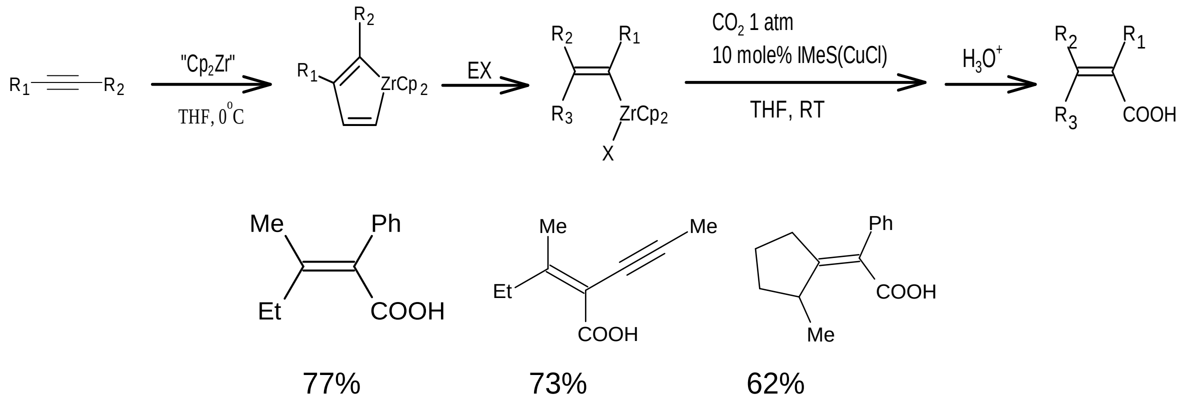
Hou and co-workers developed copper catalysed carboxylation of aluminium species utilizing CO_2. It has been reported that the hydroalumination and carboalumination of alkynes or alkenes can be achieved in a regio and stereospecific fashion to afford organoaluminum species, which provided a potential method for carboxylation with CO_2. Methylative and hydrogenative alumination of alkynes were conducted with excellent stereo- and regioselectivity assisted by a catalytic amount of Sc, Zr and Ni complexes to yield the corresponding alkenylaluminum, which underwent carboxylation with CO_2 in the presence of a catalytic amount of (IPr) CuCl to afford the target carboxylic acids in high yields with the retention of scaffold (Scheme 3) (8).



Scheme 3. One-pot carboxylation of alkynes by methylalumination

Organozirconium reagent

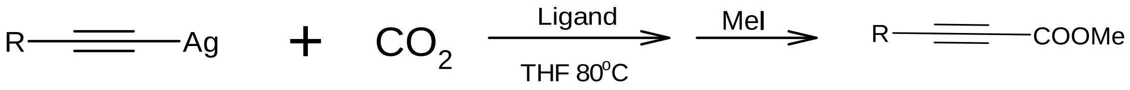
This paper reported, Carboxylation of alkenylzirconocene species with CO_2 was synthesized from tri-substituted α, β-unsaturated carboxylic acids, using (IMes) CuCl as a catalyst (Scheme 4) (9). The alkenylzirconocene species were easily generated in situ by carbozirconation of various alkynes through zirconacycles. It was found out that 10 mol% (IMes) CuCl displayed the best catalytic efficiency for carboxylation of a range of alkenylzirconocene species in THF at room temperature to yield the corresponding α, β-unsaturated carboxylic acids. (10)



Scheme 4. (IMes)CuCl-catalyzed carboxylation of alkenylzirconocenes.

Silver catalysed Carboxylation of terminal alkynes

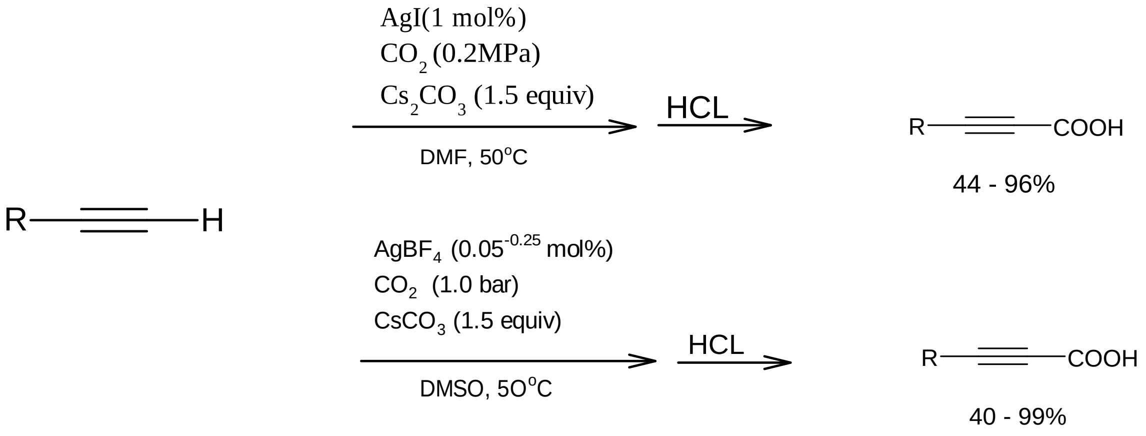
The study of carboxylation of terminal alkyne was reported by Saegusa's group. In this paper it was found that silver acetylide 30 reacted with carbon dioxide using the appropriate ligand, $^nBu_3P$ to produce the corresponding propiolic acid methyl ester 31 after methylation (Scheme 5) (11).



Scheme 5. Reaction of silver acetylide and carbon dioxide

Further Lu and co-workers also reported the silver-catalysed carboxylation of terminal alkynes using Cs_2CO_3 under 0.2 MPa of carbon dioxide in DMF to afford the corresponding propiolic acids (Scheme 6) (12). In addition, Gooßen and co-workers found that the same reaction proceeded at the lower catalyst loading of $AgBF_4$ (0.05–0.25 mol%) in DMSO (Scheme 6) (13).

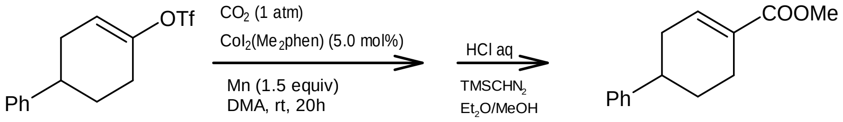
A highly efficient and reusable N-heterocyclic carbene polymer-supported silver nanoparticle catalyst was developed by Zhang's group (poly-NHC–Ag). They found that the carboxylation of terminal alkynes was effectively promoted using 0.3 mol% of poly-NHC–Ag and 1.2 equiv. of Cs_2CO_3 in DMSO even under 1 atm of carbon dioxide. (14) (15)



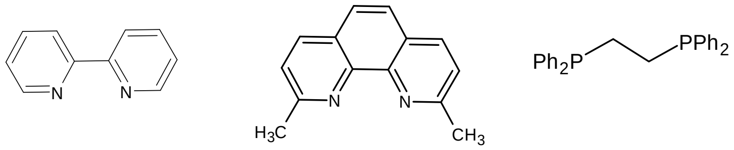
Scheme 6. Silver-catalyzed carboxylation of terminal alkynes

Cobalt catalysed carboxylation of alkenyl and aryl triflates

This paper reported the Co-catalysed carboxylation of alkenyl and aryl trifluoromethanesulfonates (triflates) as substrates (16). As a model reaction (Scheme 7), the carboxylation of 3a (alkenyl triflate) was performed using Mn powder (1.5 equiv) as the reductant in DMA as the solvent under an atmospheric pressure of CO_2 at room temperature. After esterification 4a-Me was obtained in 86% yield when CoI_2 (Me2phen) (Me2phen = 2, 9-dimethyl-1, 10-phenanthroline) as catalyst was employed. Other bidentate ligands such as bpy, phen, and dppe were not suitable for this reaction. Control experiments revealed that both the Co catalyst and the Mn reductant were indispensable to the reaction.



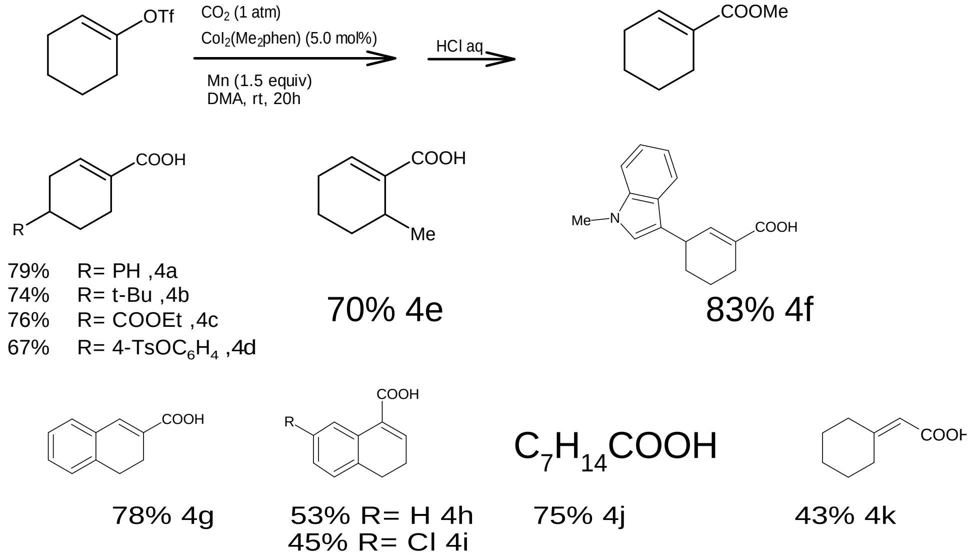
Under optimal reaction conditions:	Yield %
without Co catalyst	0
without Mn powder	0
$CoI_2(Me_2phen)$ as catalyst	76
CoI_2(bpy) as catalyst	23
CoI_2(dppe) as catalyst	0



phen bpy dppe

Scheme 7. Co-catalyzed carboxylation

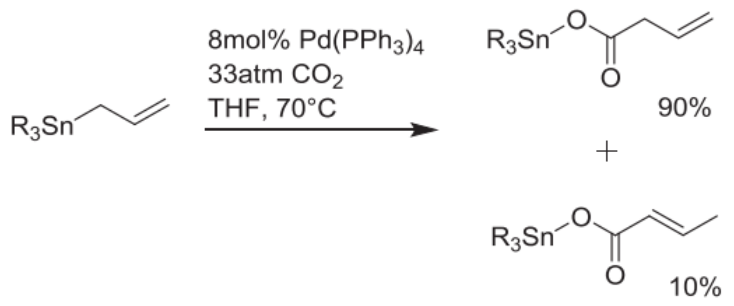
The carboxylation of diverse alkenyl triflates was also examined. As a result, the desired carboxylic acids 4a-k was obtained in good-to-high yield, as shown in (Scheme 8). The ester and p-toluenesulfonate functionalities in 4c and 4d, respectively, were tolerated. An indole-functionalized substrate 3f was converted into its corresponding carboxylic acid 4f. Conjugated alkenyl triflates 3g-i were also subjected to the reaction, and the desired carboxylation acids 4g-i were obtained in moderate-to-high yields. Furthermore, the seven membered cyclic substrate 3j afforded 75% yield of conjugated carboxylic acid 4j. Moderate yield of corresponding product 4k was obtained from alkenyl triflate 3k which was prepared from aldehyde that was carboxylated. (17)

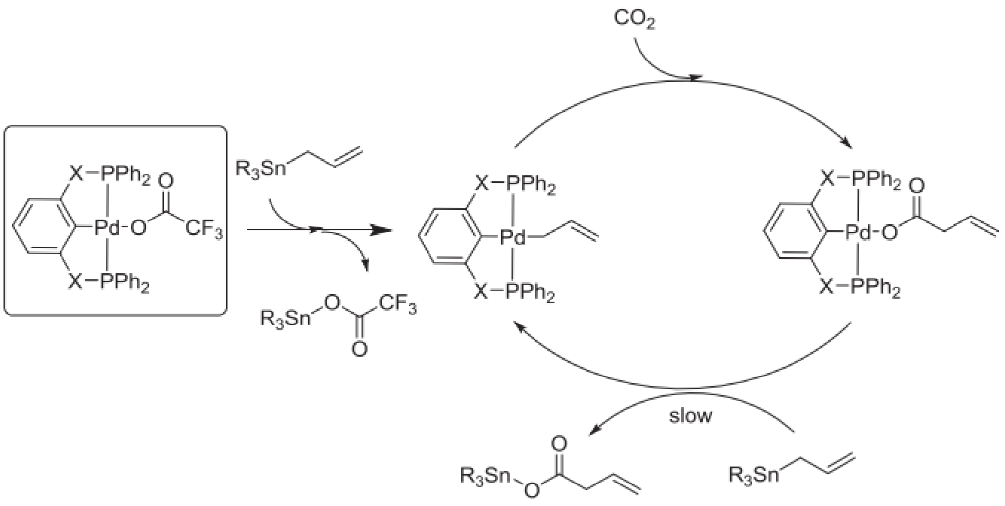


Scheme 8. Co-catalyzed carboxylation of vinyl triflates

Ni-Pd-catalysed carboxylation of R M (M = Sn, Zn) reagents with CO2

This paper discussed by Nicholas group in 1997 the first transition metal catalysed CO_2 insertion into less polarized metal (tin)-carbon bonds to form carboxylic acids. At high pressure CO_2 insertion into allyl stannanes was catalysed by palladium or platinum with phosphine ligands at high pressure (33 atm). Further developments were reported in 2006, where pincer-type palladium compounds were responsible for the high selectivity of the terminal alkene product (Scheme 9). (18)

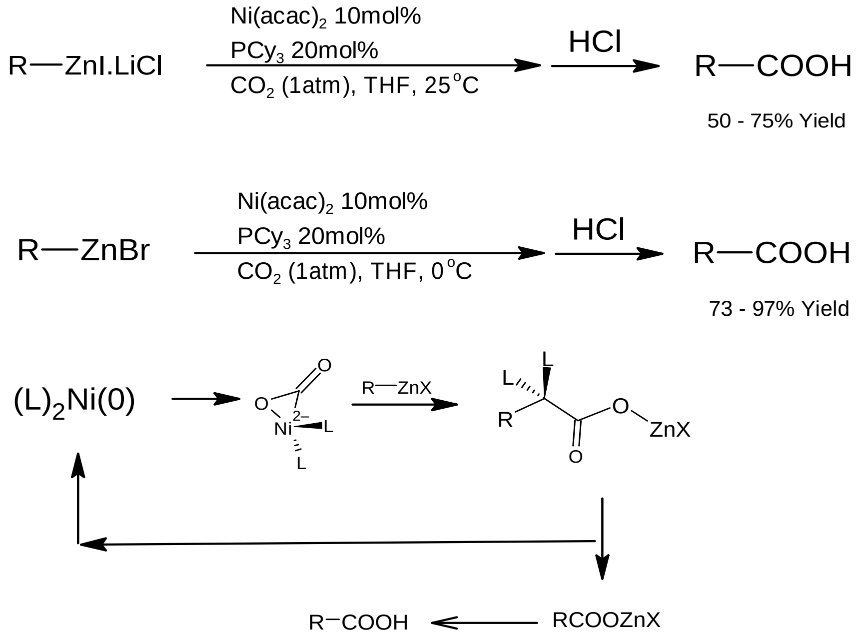




Scheme 9. Wendt's pincer-type Pd ligand complex for carboxylation of allyl stannanes

The reaction mechanism involved palladium transmetallation with allyl stannanes, followed by CO_2 insertion into Pd C bond to form carboxylates.

Nickel–catalysed coupling reactions of organozinc with CO_2 at room temperature have been reported (19), where Aresta's complex of Ni (2-CO_2) $(PCy_3)_2$ (Scheme 10) was a key intermediate. Electron rich phosphine's are essential for the oxidative addition of the metal to CO_2. The palladium catalysts gave higher yield for aryl-ZnBr while nickel catalyst works for both aromatic and alkyl organozinc reagents. Lithium chloride is essential for the carboxylation process, where a minimal yield of less than 5% was achieved without it. The reaction was applicable to secondary alkyl zinc reagents and tolerant to a wide range of functionalities, which widens its opportunities for carboxylation.

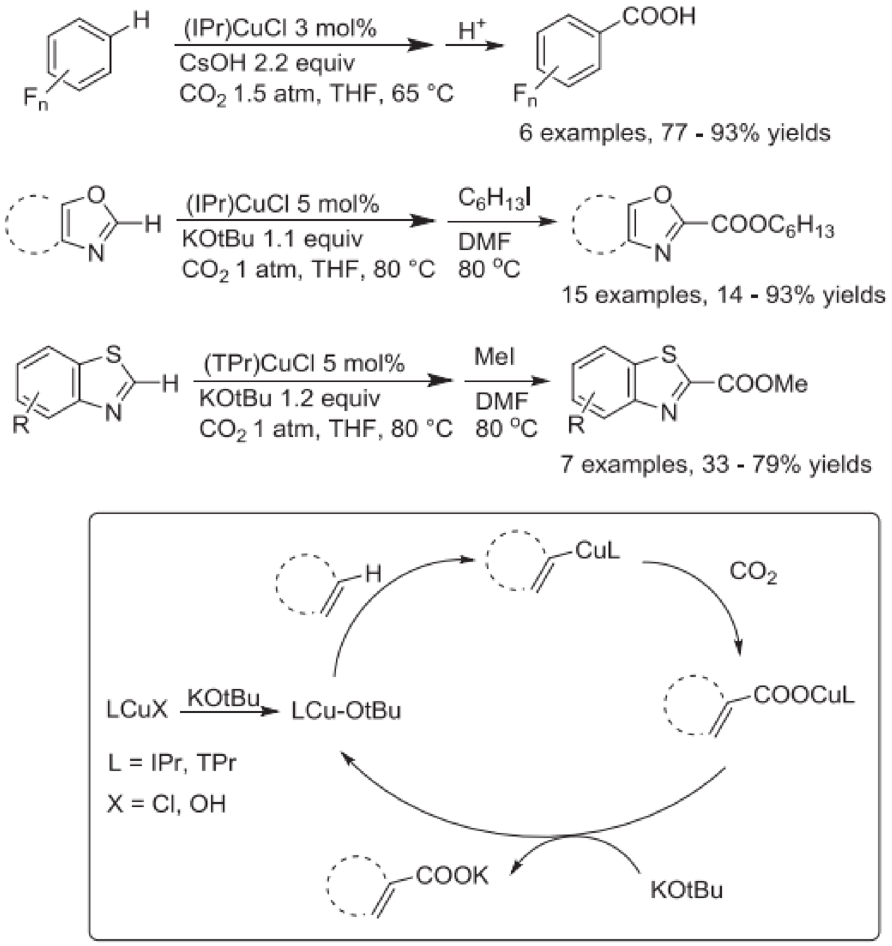


Scheme 10. Nickel(0)-catalyzed carboxylation of organozinc reagents

Cu- and Au-catalysed carboxylation of sp2 C H bonds with CO2

This paper discusses that Nolan et al. first described the copper [Cu(IPr)X] (X= OH, Cl) complex catalysed carboxylation of oxazole and multisubstituted fluorobenzenes in good yield (20). Copper complexes with various ligands for the benzoxazoles carboxylation have been systematically studied and [(IPr) CuCl] can be served as an efficient catalyst for the direct carboxylation of aromatic heterocyclic C H bonds with KOtBu to give corresponding esters after esterification with alkyl iodides (21). Copper complexes with phosphine or nitrogen-based ligands are less active, thus the reaction highly relies on the acidity of the C H bonds. The same system works well for benzoxazoles (pKa = 24.8), but not active to less acidic benzofuran (pKa = 33.2) and benzothiazole (pKa = 27.3).

Thereafter, the same group reported that the NHC–Cu complex with 1,2,3-triazol-5-ylidene ligand demonstrated high activities for this reaction (22). Benzothiazoles were converted to carboxylic esters with CO_2 (1bar) in presence of new NHC-Cu catalyst at 80 ◦C. The proposed mechanism was straight forward where the key step is C H activation to form Cu C bonds and subsequent CO_2 insertion to form copper carboxylates. (Scheme 11).



Scheme 11. Cu-catalyzed carboxylation of sp2 C H bonds with CO2

Palladium-catalysed carbomethoxylation reaction of olefins

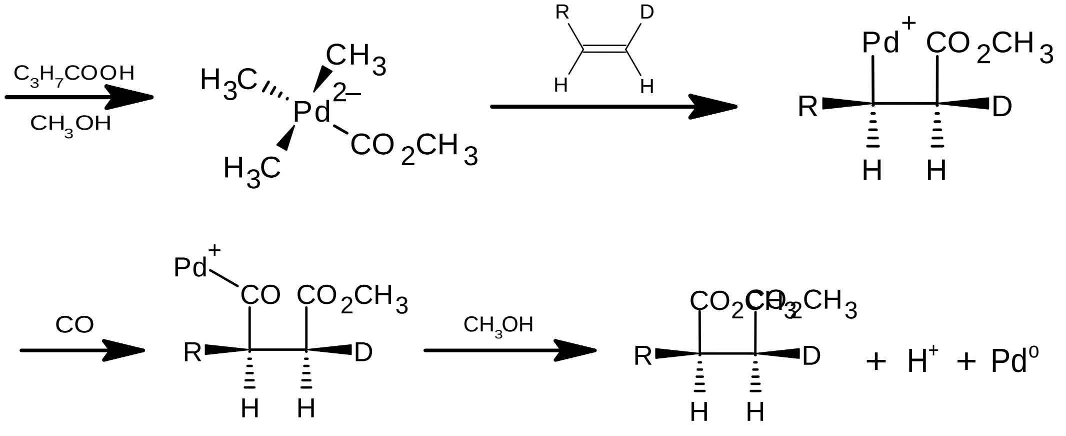
Palladium(II) chloride based was found to be effective reaction of olefins with CO in scheme I methanol to form esters (eq l).

$$PdCl_2 + RCH{=}CH_2 + 2CO + 2CH_3OH \xrightarrow{C_3H_7CO_2Na} R(CO_2CH_3)CHCH_2CO_2CH_3 + Pd^0 + 2HC1 \quad (1)$$

$$PdO + 2CuC1, - PdCl_2 + 2CuC1 \quad (2)$$

When a weak base such as sodium butyrate is present, a diester is formed under mild conditions (25 ^{O}C, 3 atm of CO). With respect to palladium chloride the reaction can be made catalytic using stoichiometric amounts of re-oxidant(cupric chloride). Palladium to an olefinic carbon atom proceeds in a regiospecific anti-Markownikoff direction 2s3 (Scheme 12).

Pd +2 + $C_3H_7COO^-$ + Co

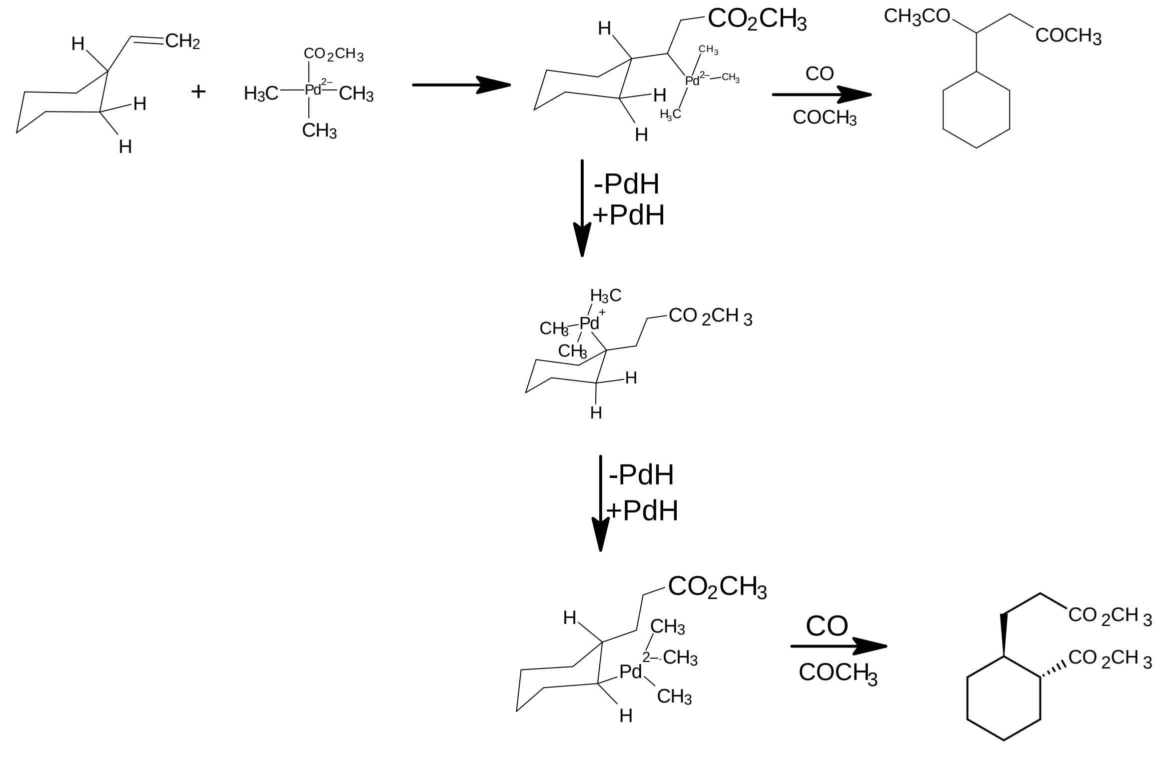


Scheme 12.

In this paper they have studied the carboxylation of representative monoolefins to determine the versatility of this reaction.

Carboxylation of Monoolefins.

In presence of base, catalytic amounts of palladium (II) chloride, and stoichiometric amounts of cupric chloride as a re-oxidant afforded dimethyl succinate and dimethyl α-methylsuccinate respectively in reaction of ethylene and propylene, with CO in methanol. The catalytic carboxylation of vinylcyclo-hexane gave two esters, 1 and 2, in 32 and 67% yields, respectively, as a result of a P-hydride elimination read-dition mechanism2 (Scheme 13).



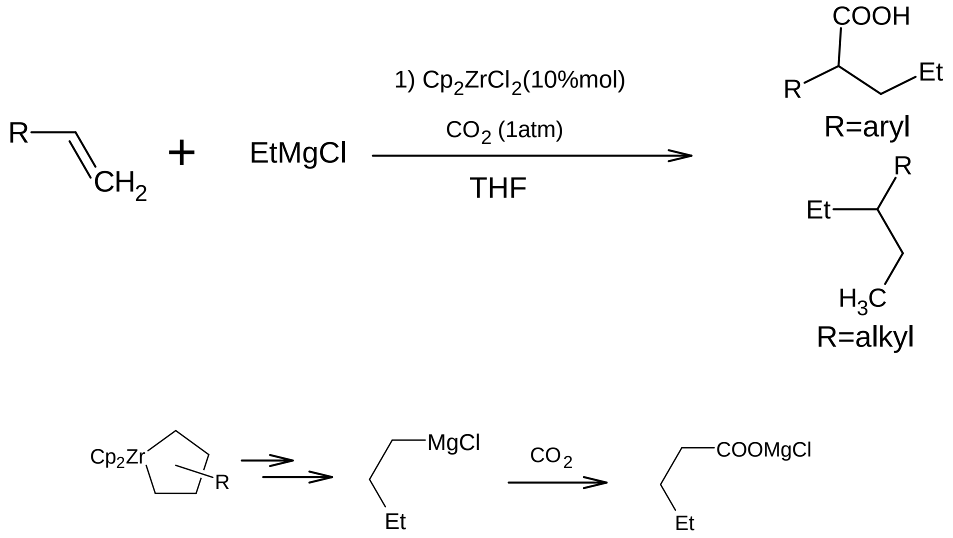
Scheme 13.

Carboxylation of 3-phenylpropene gave both diimethyl2-benzylsuccinate (4) (70%) and the β-methoxy ester 5 (30%) (23)

Carboxylation of unsaturated substrates with CO2

Carbocarboxylation of alkenes

This paper discusses, the Xi group developed a zirconocene-catalysed sequential ethyl carboxylation of alkenes using ethyl magnesium chloride and CO_2 in 2015(Scheme 14) (24). Further it reported a-aryl carboxylic acids and alkanoic acids could be formed regioselectively with styrene derivatives or alkyl-substituted alkenes. The authors proposed that an ethylmagnesiated intermediate might be generated from zirconacyclopentane reacting with EtMgCl, transmetallation and b-H abstraction process. Finally this ethylmagnesiated intermediate reacted with CO_2 to give the desired carboxylate products. (25)

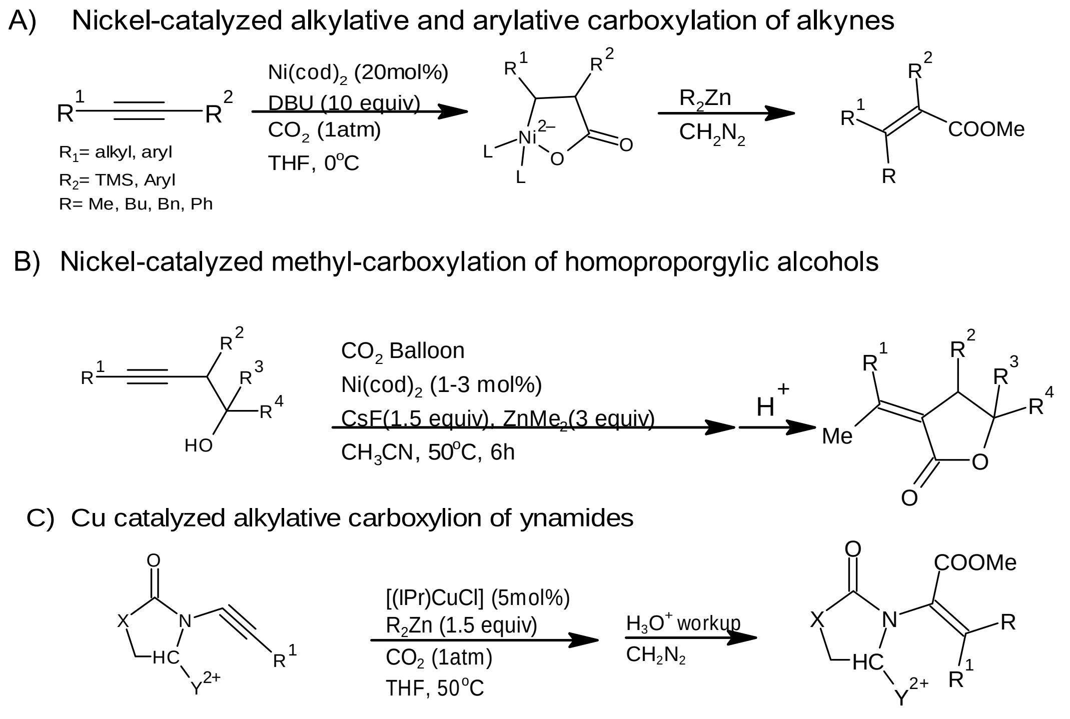


Scheme 14. Zirconocene-catalyzed sequential ethylcarboxylation of alkenes.

Carbocarboxylation of alkynes

α,β-Unsaturated carboxylic acids (acrylic acids) and derivatives are important substructure motifs, which widely exist in biologically active natural products, medicines (26) and play a vital role in organic synthesis (27) as useful building blocks. One of the most straightforward route to synthesize acrylic acids is the carboxylation of alkynes.

In 2005 Mori and Sato group reported first transition metal catalyst carboxylation of alkynes with CO_2 in the presence of Ni(cod)$_2$, an organozinc reagent and an excess amount of DBU via a cyclometallation mechanism.(Scheme 15A). In 2011 Ma group developed the first practical with the same Ni(0)-catalyst, Ni(0)-catalysed methyl carboxylation of homopropargylic alcohols employing $ZnMe_2$ and CO_2 for the efficient synthesis of α-alkylidene-γ-butyrolactones (Scheme 15B) (28). With the similar dialkylzinc reagents, Hou group realized (NHC)-copper catalysed carboxylation of ynamides with CO_2 and dialkylzinc reagents (Scheme 15C) (4)

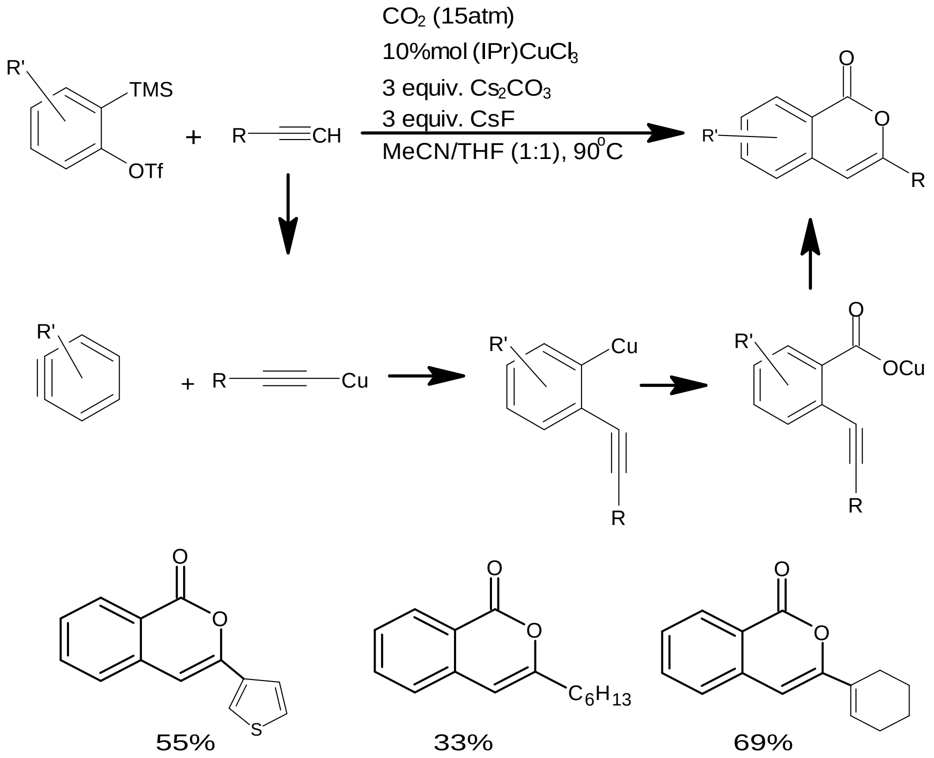


Scheme 15. Carbocarboxylation of alkynes

Carboxylation of benzynes

This paper discusses about benzynes. Benzyne is an active intermediate with high energy, which enabled a facile synthesis of 1, 2 disubstituted arenes. As 2- (trimethylsilyl) phenyl triflate could release benzyne in the presence of CsF, it is regarded as appropriate substrate to multicomponent reaction employing CO_2.

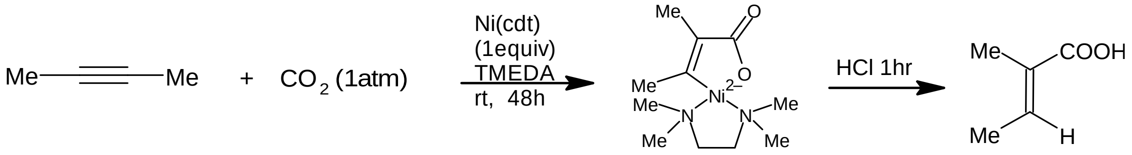
In 2014, Kobayashi reported a copper-catalysed three-component reaction involving CO_2, benzyne and terminal alkyne. Isocourmarins were synthesized at 90°C under 15 atm of CO_2 in presence of 3 equivalent Cs_2CO3 in moderate yield (Scheme 23) (29). When unsymmetrical aryne precursors were used and a mixture of products was obtained in moderate yield demonstrating poor regioselectivity of the reaction (10).



Scheme 16. IPr)CuCl-catalyzed synthesis of isocoumarins.

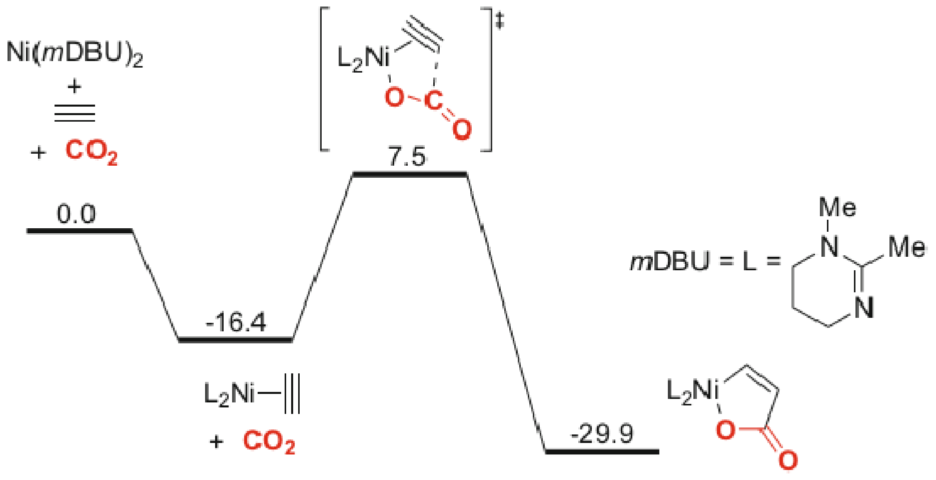
Nickel mediated Carboxylation of Alkynes

Inoue worked on Ni-catalysed oxidative cyclization for preparing 2-pyrones using CO_2 as coupling partner (30), Burkhart and Hoberg reported the isolation of an oxanickelacyclopentene (nickelalactone) from the coupling of 2-butyne and CO_2 with Ni(cdt) (cdt = 1,5,6-cyclododecatriene) and N,N,N',N'-tetramethylethylenediamine (TMEDA). The authors also highlighted that α, β-unsaturated carboxylic acid can be easily within reach upon simple protonolysis (Scheme 17).



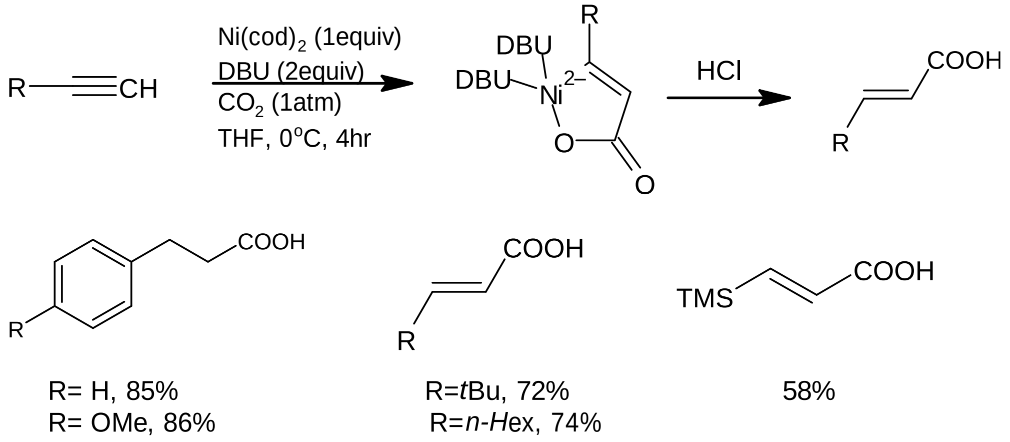
Scheme 17. Synthesis of acrylic acids via the intermediacy of nickelalactones

In 2008 Buntine and co-worker's modelled the reaction with acetylene and CO_2, selecting mDBU as a model ligand to mimic the behaviour of DBU (DBU = diazabicyclo [5.4.0] undec-7-ene). The authors found that the reaction proceeds through an associative mechanism, first involving the η^2 - coordination of the alkyne to the nickel (0) complex followed by a direct insertion of CO_2 (Scheme 18).



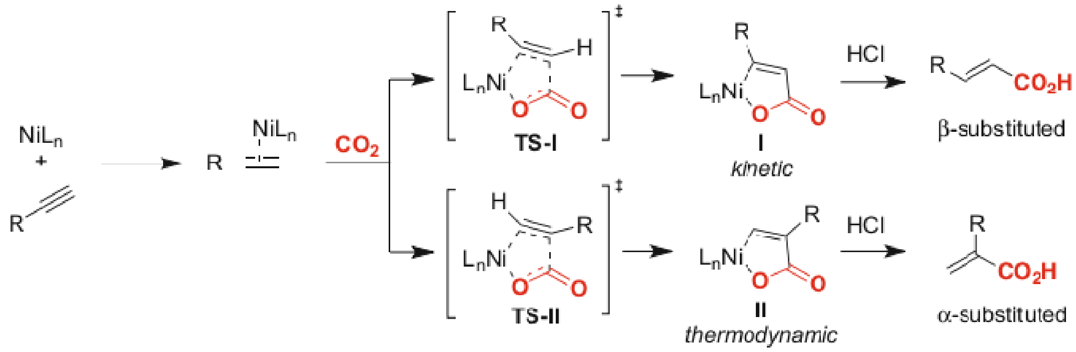
Scheme 18. Gibbs free energies (kcal/mol) for the coupling of CO2 with acetylene

The reaction turned out to be thermodynamically favoured, with an activation barrier of 23.9 kcal/mol for the key oxidative cyclization event without going through an Aresta-type complex. 15 years later Yamamoto and saito reported the preparation of nickelalactones with terminal alkynes (31). Rapid formation of b-substituted carboxylic acids with high levels of chemo- and regioselectivity was obtained under stoichiometric carboxylation of terminal alkynes in presence of $Ni(DBU)_2$. Were also reported by authors (Scheme 19).



Scheme 19. Nickel(0)-mediated carboxylation of terminal alkynes

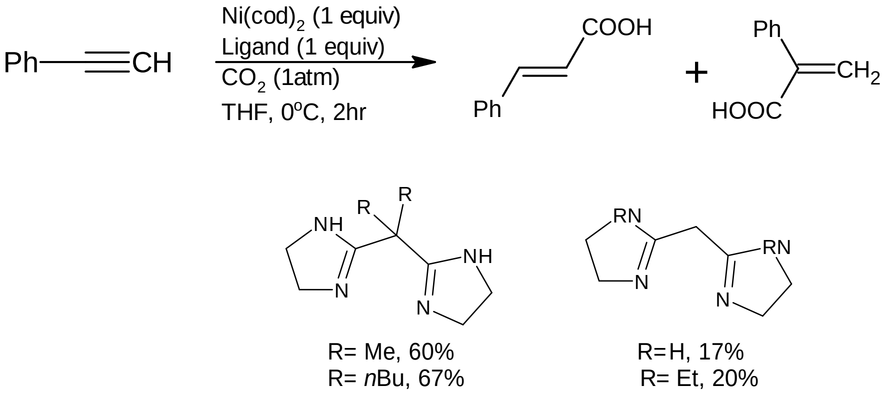
This reaction was applied for different substituted alkynes bearing aromatic, aliphatic or silyl groups with equal ease. The regioselectivity observed in the oxidative cyclization of monosubstituted alkynes with CO_2 was theoretically rationalized by Buntine (Scheme 20) (30). The authors observed a markedly different energetic preference for the two possible transition states (TS-I and TS-II), with a lower energy barrier for TS-I leading to I, in which CO_2 insertion takes place distal to the substituent on the alkyne motif.



Scheme 20. Regioselectivity profile in the cycloaddition of terminal alkynes with CO_2

However, nickelalactone II turned out to be thermodynamically favoured due to the avoidance of a steric clash of the substituent on the alkyne terminus with the Ni centre. Further it was investigated DBU leading to lower activation energies when compared to 2,2'-bipyridine (bpy). And also find out that polar solvents such as DMF lowered down all activation barriers due to the stabilizing effect of DMF on the transition states when compared with commonly employed tetrahydrofuran (THF).

Further this paper also discussed that in 2004, the group of Iwasawa reported a similar study for the stoichiometric carboxylation of terminal and unsymmetrical alkynes using a series of bis(amidine) ligands. The nature of the ligand dictated the regioselectivity pattern; while ligands bearing substituents at the methylene carbon generated predominantly cinnamic acids in good yields, less substituted bis(amidine) ligands resulted in a switch of selectivity, leading preferentially to a substituted carboxylic acids, albeit in lower yields (Scheme 21) (32).

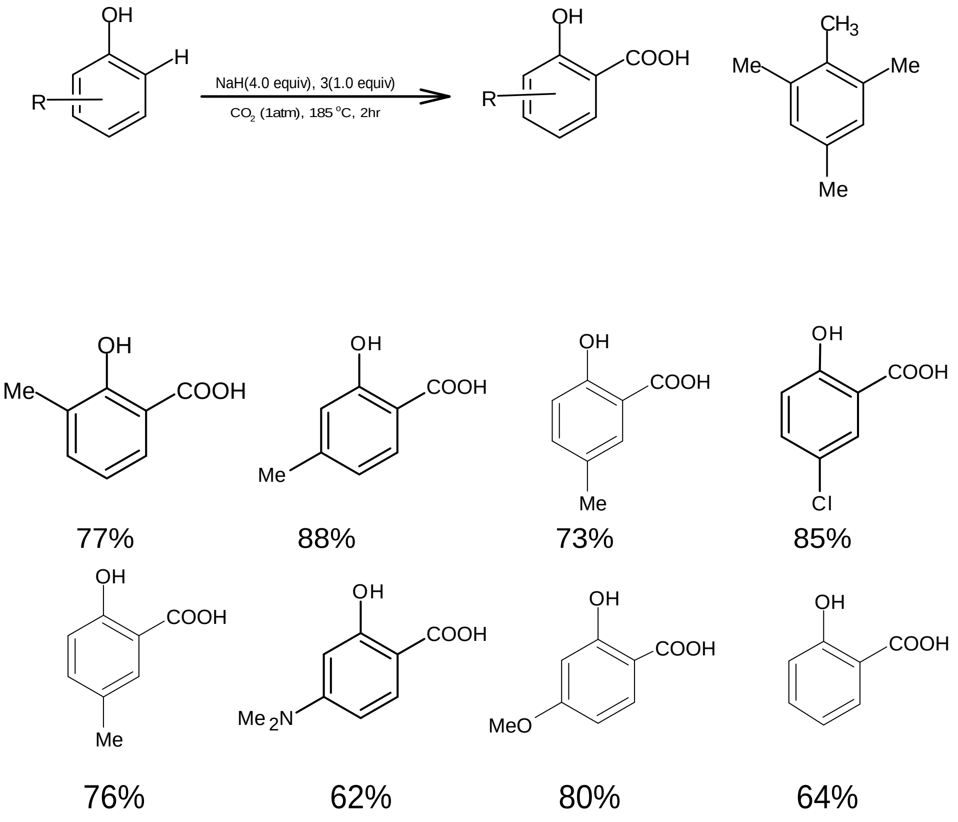


Scheme 21. Bis(amidine)ligands in Ni-mediated synthesis of acrylic acids

Base-mediated carboxylation

The first example of a C−H carboxylation of aromatic compounds was developed by Kolbe and Schmitt during the 1860′s and it is still widely used in industry today. The Kolbe–Schmitt reaction is most notable for the synthesis of Aspirin. It is one of the most important and well-known carboxylation reactions, providing direct access to salicylic acids through the ortho C−H carboxylation of phenoxides with CO_2. However, this process generally requires high CO_2 pressure (20–100 atm; 1 atm=0.101325 MPa) and temperature (130–280 °C) to achieve good conversion. It is generally accepted that in the Kolbe–Schmitt reaction, CO_2 could be captured by a metal phenolate through weak coordination between the alkali metal and CO_2. Water molecules present in the reaction vessel could strongly chelate with the alkali metal phenoxides, consequently preventing the initial addition of CO_2. The hydrolysis of the alkali metal phenoxides to the phenols may also occur. (33)

In 2016, the Larrosa group developed the first protocol for Kolbe–Schmitt-type carboxylation's that occur efficiently under an atmospheric pressure of CO_2 (34). The reaction proceeded in a one-pot process without isolation of the phenoxide precursor in presence of NaH as it avoided the undesired formation of H_2O. More importantly, the authors reported that using 2,4,6-trimethylphenol (TMP) as a recyclable additive significantly increased the carboxylation rate allowing the process to be carried out under 1 atm of CO_2. The reaction was compatible with both electron-donating and halogen substituents, and simple phenol (Scheme 22). However, substrates containing strongly electron-withdrawing nitro groups were not reactive under these conditions (Scheme 22).



Scheme 22. Examples of phenol carboxylation

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Acid mediated carboxylation

Friedel and crafts found that benzoic acid was obtained in minor amount when CO_2 was bubbled through a mixture of aluminium chloride and benzene which gave generation of small amount of hydrogen chloride when heated to its boiling point. They also reported that this process may involve an initial complex between benzene and Al2Cl6, with subsequent formation of phenyl aluminium dichloride intermediates ($PhAl_2Cl_5$). The organoaluminum species then reacted with CO_2 to obtain the benzoic acid after aqueous workup (Scheme 23).

$$C_6H_6 + Al_2Cl_6 \longrightarrow C_6H_5Al_2Cl_5 + HCl$$

$$C_6H_5Al_2Cl_5 + CO_2 \longrightarrow C_6H_5COOAl_2Cl_5$$

$$C_6H_5COOAl_2Cl_5 + H_2O \longrightarrow C_6H_5COOH + Al_2Cl_5OH$$

Scheme 23. Pathway for Lewis acid-promote carboxylation of benzene

However, due to the low electrophilicity of CO_2 and the side reactions caused by the strong Lewis acidity of aluminium-based compounds, the carboxylic acids are generally obtained in poor yields when using this procedure. (35) (36)

CONCLUSION

In this review various kinds of catalytic carboxylation reactions of unsaturated compounds such as alkynes, organometallic reagents, alkenes, olefins with CO_2 have been well achieved with different kinds of transition metals as catalysts such as Ni, Cu, Pd, Au, Rh, and so on have been carried out. The metal catalysed carboxylation reactions shows region and stereoselectivity and formation of a carboxylic acid is facilitated by the insertion of CO_2 into a carbon-metal bond which is generated through insertion of the unsaturated bond into a metal-Nu species.

In carboxylation of alkenes it was found that zirconocene-catalyzed ethyl carboxylation of alkenes was carried out using ethylmagnesism chloride and CO_2. It was noted that an aryl carbolic acids and alkanoic acids could be formed regioselectivity with styrene derivatives or alkyl-substituted alkenes.

The carboxylation of alkynes such as of terminal alkynes using Cs_2CO_3 was catalysed using AgI. The same reaction proceeded at the lower catalyst loading of $AgBF_4$ in DMSO which gave corresponding propiolic acids. It was found that the carboxylation of terminal alkynes was effectively promoted using 0.3 mol% of poly-NHC–Ag and 1.2 equiv. of Cs2CO3 in DMSO even under 1 atm of carbon dioxide.

In alkyne carboxylation, the reaction was most feasible with Nickel catalyst. Ni mediated carboxylation with different terminal alkynes. The reactions was found out to be thermodynamically favoured, with an activation barrier of 23.9 kcal/mol for the key oxidative cyclization. It was also found out that in preparation of nickelalactones with terminal alkynes, there was rapid formation of b-substituted carboxylic acids with high levels of chemo-and regioselectivity. This reaction could be applied differently to substituted alkynes bearing aromatic, aliphatic or silyl groups with equal ease. Further the stoichiometric carboxylation of terminal and unsymmetrical alkynes using a series of bis(amidine) ligands were studied. Ligands bearing substituents generated predominantly cinnamic acids in good yields were reported.

Moderate yield of products were obtained showing poor regioselectivity of the reaction, when unsymmetrical aryne precursors was used in synthesis of copper catalysed carboxylation of benzynes.

Base and acid mediated carboxylation were also reported. The classic strategies for C–H carboxylation with CO_2 are based on the use of base or Lewis acid mediators. In base-mediated C–H carboxylation usually requires a strong base to deprotonate the most acidic proton to form a strong nucleophilic carbon atom thus enabling attack to the weakly electrophilic CO_2. However, this base-mediated C–H carboxylation generally requires relatively high reaction temperatures.

The strategy of Lewis-acid-mediated C-H carboxylation, on the other hand, relies on the activation of CO_2 via coordination with the Lewis acid. The aromatic compounds can therefore react with the activated CO_2. This strategy allows for C-H carboxylation at relatively low reaction temperatures. However, it usually requires high CO_2 pressure and the regioselectivity is often poor. It is still desirable to develop new methodologies for carboxylation to proceed in simple, mild and generally applicable conditions using readily available starting materials.

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