Development of New Methods for the Synthesis of Aldehydes, Arenes and Trifluoromethylated Compounds

vom Fachbereich Chemie der Technischen Universität Kaiserslautern zur Verleihung des akademischen Grades “Doktor der Naturwissenschaften“ genehmigte Dissertation

D 386

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Kaiserslautern, 2012

Die vorliegende Arbeit wurde in der Zeit von September 2008 bis March 2012 in der Arbeitsgruppe von Prof. Dr. Lukas J. Gooßen an der Technischen Universität Kaiserslautern angefertigt.

Prüfungskommission

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Tag der mündlichen Prüfung: 30-03-2012

Eidesstattliche Erklärung

Hiermit versichere ich, dass ich die vorliegende Arbeit eigenständig verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel verwendet, sowie Literaturzitate kenntlich gemacht habe. Kooperationsprojekte sind ausdrücklich als solche gekennzeichnet. Ich erkläre außerdem, dass diese Arbeit weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

Kaiserslautern, den 25.07.2012

Bilal Ahmad Khan

Acknowledgement

First and foremost, I would like to express my sincere gratitude to Prof. Dr. Lukas J. Gooßen for giving me the opportunity to carry out my Ph.D. work under his supervision. Appreciation goes to him for all his contribution of time, ideas, and funding to make my Ph.D. experience productive and stimulating. I am also thankful to Mrs. Gooßen for all the help in finalizing my manuscripts.

I would like to thank Prof. Dr. Stefan Kubik and Prof. Dr. Helmut Sitzmann for being in my examination committee.

HEC Pakistan and the University of Azad Jammu and Kashmir are gratefully acknowledged for providing me with financial support to complete my Ph. D. I also appreciate Abdul Qayyum Tahir for his timely efforts in the extension of my fellowship.

I am grateful to ISGS for all the support during my stay in Kaiserslautern and nominating me for the DAAD fellowship to write my Ph.D. thesis.

I am especially thankful to N. Rodríguez, C. Linder, F. Costa, T. Fett, T. Knauber, A. Buba, P. Lange, A. Fromm, M. Blanchot, C. Oppel, D. Ohlmann, K. Salih, P. Mamone, R. Bauer, M. Rudzki, M. Arndt, M. Grünberg, B. Song, S. Bhadra, F. Collet, W. Dzik and S. Baader for providing me with an outstanding experience in and outside labs.

Thanks to Dr. N. Rodríguez, F. Costa, T. Fett, Dr. T. Knauber and A. Buba for fruitful discussion during collaborative projects.

I am thankful to Dr. T. Knauber for reviewing my thesis.

I would like to thank Mrs. Müller and Mr. Kelm from NMR facility, Mrs. Biel, Mrs. Dusch, Mrs. Ellmer and Mrs. Bergsträsse from the analytical department and Mr. Napast, Mr. Rahm, and Mr. Schröer from the chemical storage facility.

In the end, I owe my deepest gratitude to my parents and family members. They stood by my side in every aspect of my life. Without their support and encouragement, I would have not earned this degree.

Publications

Parts of this work have been published in the following journals:

- B. A. Khan, A. E. Buba, L. J. Gooßen, *Chem. Eur. J.* **2012,** *18*, 1577-1581: *Oxidative Trifluoromethylation of Arylboronates with Shelf-Stable Potassium (trifluoromethyl)trimethoxyborate*.
- L. J. Gooßen, B. A. Khan, T. Fett, M. Treu, *Adv. Synth. Catal*. **2010**, *352*, 2166-2170: *Low-pressure Hydrogenation of Arenecarboxylic Acids to Aryl Aldehydes*.
- L. J. Gooßen, F. Manjolinho, B. A. Khan, N. Rodríguez, *J. Org. Chem.* **2009**, *74*, 2620-2623: *Microwave assisted Cu-catalyzed protodecarboxylation of aromatic carboxylic acids.*

Abbreviations

Ac	Acetyl
acac	Acetylacetonate
AcOH	Acetic acid
Ad.	Adamantyl
Ar	Aryl
AS&C	Advenced Synthesis and Catalysis
BINAP	Bis-(diphenylphosphino)-1,1'-binaphthaline
Bipy	2,2'-bipyridin
Bn	Benzyl
BOC	Di-*tert*-butylldicarbonate
Brett-Phos	2-(Dialkylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'biphenyl
Bz	Benzoyl
CEJ	Chemistry, A European Journal
COD	1,5-Cycloctadiene
Cy	Cyclohexyl
dba	Dibenzylidene acetone
DCE	1,2-Dichloroethane
DMA	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylforamide
DMPU	*N*,*N*-Dimethylpropyleneurea
DPE-Phos	Bis(2-diphenylphosphino)-ethane
Dppp	1,1-Bis(diphenylphosphino)-propane
DMSO	Dimethylsulfoxide
EI	Electron Ionization
Et	Ethyl
eq.	Equivalent
F-acac	Hexafluoroacetylacetonate
GC	Gas chromatography
HMPA	Hexamethylphosphoramide
IPr	1,3-bis(2,6-diisopropyl)-phenyl-imidazol-2-ylidene
IR	Infrared
JOC	Journal of Organic Chemistry
John-phos	2-(Biphenyl)dialkylphosphine

L	Ligand
M	Metal
MeCN	Acetonitrile
Me	Methyl
Mes	Mesityl
MS	Molecular sieves
^{n}Bu	*n*-Butyl
NHC	*N*-Heterocyclic carbine
NMP	*N*-Methyl-2-pyrrolidone
^{n}Pr	*n*-Propyl
Nu	Nucleophile
PCy_3	Tricyclohexyl phosphine
Ph	Phenyl
Phen.	1,10-Phenanthroline
Piv.	Pivalic anhydride
PivOH	Pivalic acid
ppm	Parts per million
RT	Room temperature
Ru-Phos	2-Dicyclohexylphosphino-2’,6’-di-isopropoxy-1,1’-biphenyl
SET	Single electron transfer
TASF	Tris(dimethylaminosulfonium) difluorotrimethylsilicate
TBAf	Tetrabutylammonium fluoride
^{t}Bu	Tertiary butyl
Tf	Trifluoromethansulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Tol.	Toluene
X	Halide or pseudo halide
X-phos	2-(Dicyclohexylphosphino)-2’,4’,6’-isopropylbiphenyl

Structure Numbering

The chemical structures of each chapter are numbered separately for fast and easy understanding of the reader. The term is composed of a second level chapter number followed by hyphen and a sequential number for each chemical structure. For example, 3.2-1 represents compound one in chapter 3.2. Identical chemical structures in different chapters are represented by different numbers.

In the experimental section, chemical structures reported in the publications are represented by the abbreviations of the journal followed by a hyphen and structure number of the molecule, such as AS&C-2a represents the compound 2a in the “Advanced Synthesis and Catalysis” paper.

Table of Contents

1 Introduction

The development of sustainable processes has become a great challenge in recent chemical research. It draws on the establishment of safe, single step, waste free and eco-friendly processes for the ideal synthsis of bulk as well as fine chemicals.[1]

Historically, the quality of a chemical reaction was only evaluated in terms of percentage yield. However, this approach does not provide any information on the extent to which by-products are formed. Atom economy is a useful tool to rapidly evaluate the amount of waste generated by different routes to a specific product.[2] It was introduced by Trost and it is defined as "conversion efficiency of a chemical process in terms of all atoms involved". In an ideal chemical reaction, all of the starting materials are converted into products (Schema 1).

$$\text{AE} = \frac{\text{Molecular weight of the desired product}}{\text{Molecular weight of all reactants}} \cdot 100$$

Schema 1. *Atom economy*

Another important concept in "Green Chemistry" is the environmental factor introduced by Sheldon,[3] which displays the ratio of the mass of waste per unit mass of product (Schema 2).

$$\text{E-Factor} = \frac{\text{Mass of the waste (KG)}}{\text{Mass of the product (KG)}}$$

Schema 2. *E-Factor*

Both E-Factor and atom-economy concepts play a major role in focusing the attention of the chemical industry, and particularly the pharmaceutical industry, on the problem of waste generation in synthesis of chemicals. It has provided a new way of thinking about chemistry and the impetus for developing cleaner and more sustainable processes.[4]

However, the most reliable and frequently used reactions often suffer from extremely low atom-economy and E-factor. Chemists often employ these trustworthy methods for the synthesis of fine chemicals and structurally complex molecules. The development of reliable and easy to perform sustainable procedures is of high interest from both an environmental and synthetic point of view.

1.1 Modern Technologies in Fine Chemical Production

Fine chemicals are produced in small scale and high purity for special applications. They can be categorized as active pharmaceutical ingredients and their intermediates, biocides and speciality chemicals. Traditionally, fine chemicals are produced by fundamental organic name reactions

that require the use of stoichiometric amounts of reagents and mediators and thus suffer from low atom-economy and E-factor. For example Friedal–Crafts acylation is an important industrial process for the formation of C-C bond on the aromatic ring. It uses acetyl chlorides in the presence of excess $AlCl_3$ to produce 4.5 Kg of waste per Kg of the desired product.[5]

However, the fine chemical industry is under great pressure to reduce the environmental impact of old-fashioned processes which stem from the last century. It is highly required to develop new processes that are efficient in both energy and raw material production, and produce minimal waste.

The use of modern technologies in the fine chemical production and pharmaceutical industry has not only helped to develop atom-economic processes but also decreased the energy consumption in chemical reactions. Catalytic methods have been used to develop clean and efficient processes, whereas the combination of catalysis with non–conventional technologies such as microwave radiations and continuous flow reactors is dramatically reducing energy requirement and reaction time in several organic syntheses and chemical transformations.

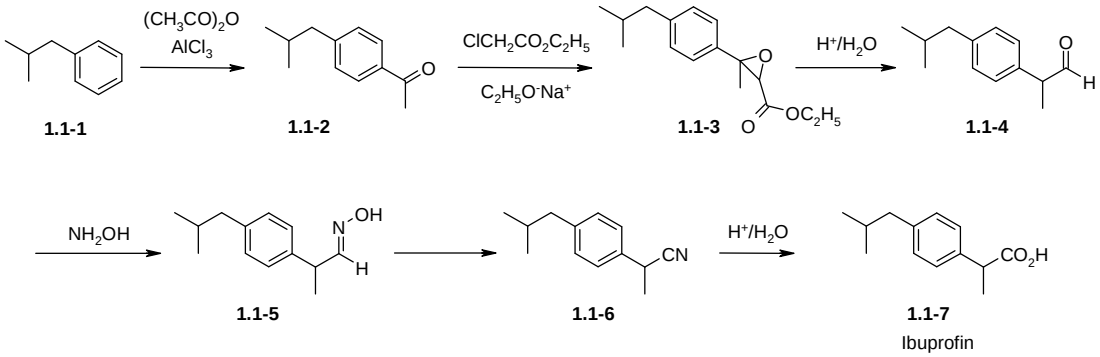
1.1.1 Catalysis

A catalyst provides an alternate low-energy route for a chemical reaction without changing the chemical equilibrium. It reduces the activation barrier of a chemical reaction by opening up an alternate reaction pathway. Thus cheaper, atom efficient and less reactive substrates can be connected in a catalytic reaction. As the catalyst is not consumed in the chemical reaction, so it takes part in many subsequent catalytic cycles. The catalyst activity is the substrate to catalyst ratio, and is expressed by the turnover number (TON) and turn over frequency (TOF). TON is the number of moles of the substrates converted into product by a catalyst before becoming inactive, whereas, TOF is the TON per unit time.

Catalysts range from protons (H^+), Lewis acids and bases, organo-metallic reagents, organic and inorganic polymers and enzymes. Catalysts are divided into three main categories: homogeneous catalysts, heterogeneous catalysts and biocatalysts. The last two catagories are not in the focus of the thesis and will not be discussed.

During the last century, transition metal catalysts were extensively studied and successfully applied for the development of mild and environmentally benign processes for the synthesis of valuable products.[6] As a result, transition metal catalyzed processes have replaced some environmentally unacceptable processes with cleaner and atom-efficient alternatives. For example, Hoechst-Celanese process for ibuprofen synthesis is an example of a highly atom-efficient process. Ibuprofin is primarily used for pain,[7] rheumatoid arthritis[8] and pericarditis.[9]

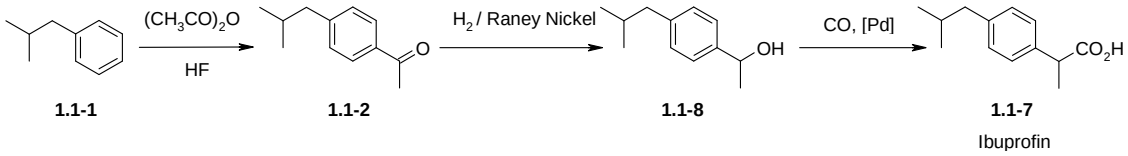
Traditionally, it was synthesized by Boots process[10] which involved waste intensive six steps (Schema 3).



Schema 3. *Traditional Boots process for Ibuprofin synthesis*

Friedal-Crafts acylation of isobutylbenzene (**1.1-1**) followed by treatment with ethyl chloroacetate produces α,β-epoxy ester (**1.1-3**), which was hydrolyzed and decarbonylated to the aldehyde (**1.1-4**). This aldehyde is converted into oxime (**1.1-5**) by treatment with hydroxylamine and then to nitrile (**1.1-6**). The hydrolysis of the nitrile gives the desired acid (**1.1-7**).

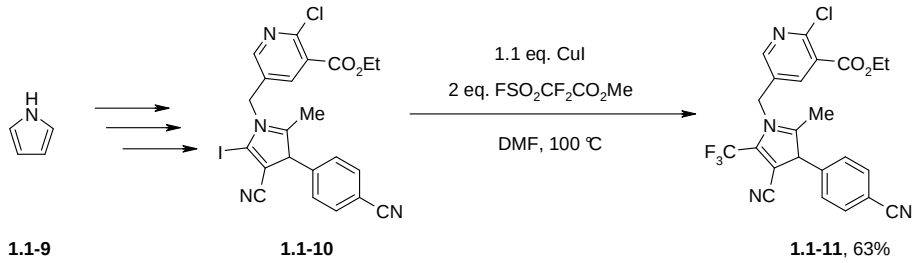
An improved and atom-efficient Hoechst-Celanese process takes only 3 steps involving a Friedal-Craft acylation, hydrogenation over Raney nickel and a palladium catalyzed carbonylation reaction (Schema 4).[11] Hydrofluoric acid is used as solvent and the Lewis acid for the Friedal-Crafts acylation. It is recycled at the end of the reaction.



Schema 4. *Hoechst-Celanese process for ibuprofen synthesis*

Although HF functions as Lewis acid as well as a solvent, a true catalyst is required for the Friedal-Crafts acylations such as a solid acid or an ionic liquid, which is the first step of Hoechst-Celanese ibuprofen synthesis. Besides, hydrogenaton (2nd step) and carbonylation (3rd step) are 100% atom-economic.

In addition to cleaner and atom-economic processes, catalysis often provides mild reaction conditions enabling the chemists to incorporate functional groups in the later stage of a synthetic sequence rather than using pre-functionalized building blocks. For example, N-substituted pyrrole (**1.1-10**) was heated with $FSO_2CF_2CO_2Me$ and copper(I) iodide in DMF at 80 °C to give the desired trifluoromethylated product (**1.1-11**) in 63 % yield (Schema 5).[12]



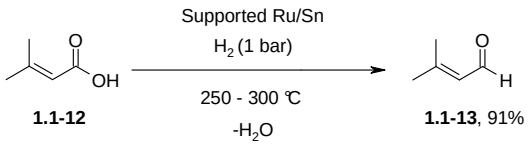
Schema 5. *Late stage introduction of CF_3 group*

Over the last century, a vast majority of catalytic processes were developed to replace the stoichiometric use of reagents with catalytic amounts of transition metals.[13] These include catalytic oxidation reactions, catalytic reduction reactions and catalytic acylations and many more. Among them catalytic hydrogenation is persistently used for industrial processes as well as in academia for research purposes.[14]

1.1.1.1 Hydrogenation Reactions

Hydrogenation reactions are arguably one of the most frequently employed catalytic reactions in the production of fine chemicals. A large number of functional groups can be hydrogenated, often with a high degree of chemo -, regio -, and stereoselectivity.[14]

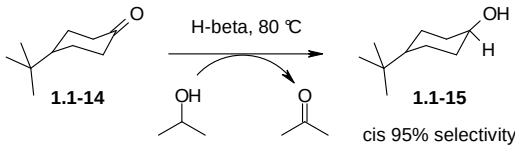
However, selective hydrogenation of carboxylic acids is a notoriously challenging transformation due to the high reactivity of resulting aldehydes towards reduction. Alcohols are produced as the main product in such reactions. Nevertheless, partial hydrogenation of aliphatic and aromatic carboxylic acids has been performed in the vapor phase over a ruthenium/tin alloy catalyst at 300 °C and ambient hydrogen pressures.[15] 1-Dodecanoic acid and trifluoroacetic acid were converted into 1-dodecanal and trifluoroacetaldehyde (fluoral), respectively. α,β-unsaturated acid (**1.1-12**) undergoes a chemoselective reduction to the corresponding α,β-unsaturated aldehyde (**1.1-13**) in high yield (Schema 6).



Schema 6. *Hydrogenation of α, β-unsaturated carboxylic acid to α, β-unsaturated aldehyde over a Ru / Sn catalyst*

The reduction of aldehydes and ketones is generally performed with the Meerwein-Ponndorf-Verley reduction method which involves the reaction of the substrate with a hydrogen donor in the presence of stoichiometric amounts of aluminum alkoxide. Such reactions give only trans product along with stoichiometric quantities of waste. Recently, zeolite beta has been reported to

catalyze Meerwein-Ponndorf-Verley reduction (Schema 7).[16] The catalyst can be readily separated via filtration and recycled. It also offers the selective formation of cis-alcohol (**1.1-15**) form 4-tert-butylcyclohexanone (**1.1-14**) which is an important fragrance chemical intermediate.



Schema 7. *Zeolite beta catalyzed selective MPV reduction*

1.1.2 Unconventional Process Techniques

The development and improvement of synthetic methods in organic chemistry is an integral part of the research in academia and industry. In the last decade, process technology was significantly improved by the introduction of the unconventional process techniques.[17] In particular, reaction under microwave irradiation and flow through process has improved classical organic transformations. The reaction times can be minimized by enhancing the reaction rate through efficient heating provided by microwaves whereas, flow-through processes provide a safe entry to particularly reactive compounds as only small quantities of the substrates are reacted at a time. Unconventional process techniques, which are also termed as enabling techniques by Kirschning *et al*., are the techniques that speed up a chemical reaction and simplify the purification and isolation of the products. On the basis of this definition, Kirschning *et al*. have classified enabling techniques as traditional and new techniques.[18] Traditional techniques are described as catalysis, solid-phase synthesis, electrochemistry and high-pressure synthesis whereas unconventional techniques include non-classical solvents, microwave radiation, continuous flow and microreactors. It is merely a chorological division as many techniques are closely linked. However, many applications of these novel technologies in organic synthesis are under development and their potential has not been fully explored yet.

1.1.2.1 Microwave-Assisted Synthesis

Acceleration of chemical reactions by microwave radiation was detected by Gedye and Giguere/Majetich as early as 1986,[19] and since the mid-1990s, numerous publications based on these non-conventional heating systems have demonstrated the great advantages of this technology in organic synthesis. Microwave-assisted chemical transformations generally occur in much shorter reaction times (days and hours to minutes and seconds) and often offer better yields and selectivities.[20] Thus, an impressive number of results can be obtained in a short time. Results of unknown reactions can be evaluated in a very short time. This led to speculation about indefinable microwave effects which has been debated vigorously in the literature.[21]

Physical effects produced in the microwave-assisted reactions play a crucial role in accelerating the reactions and can be classified into three categories:[22]

1: Thermal or Kinetic effects are produced as a result of the high reaction temperature that can rapidly be obtained when irradiating polar materials/reaction mixture in a closed vessel.

2: Specific effects have been claimed when the outcome of a synthesis performed under microwave conditions was different from the conventionally heated counterpart at the same measured reaction temperature.

3: Non-Thermal microwave effects which result from a proposed direct interaction of the electric field with specific molecules in the reaction medium that is not related to a macroscopic temperature effect.

The irradiation of polar compounds in a microwave field has a unique heating profile (Abbildung 1). The difference in the temperature profile of a reaction vessel under microwave radiation (left) and in an oil bath (right).

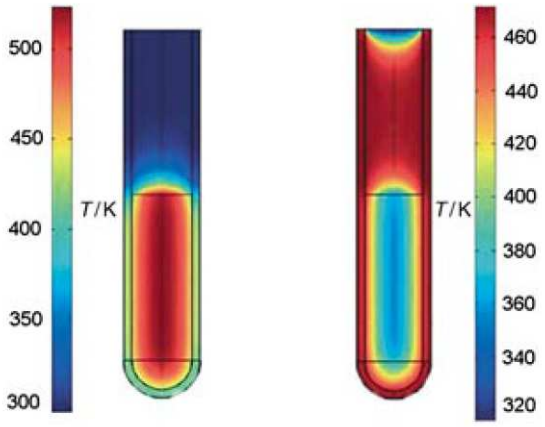


Abbildung 1. *Temperature profile of a reaction vessel under microwave radiation and oil bath*

Microwave radiation increases the temperature of the entire volume of the solvent and the vessel wall is colder than the reaction solution. In contrast, the oil bath heat is transferred through the vessel walls into the reaction mixture. Mechanism of heat generation and transfer is responsible for this effect. In classical solutions, heat is distributed by stirring and convection between the particles and the heated vessel wall, whereas microwaves generate heat by dielectric heating. Here, the ability of polar molecules to absorb microwave radiation and to convert it into heat is utilized. This is done by an oscillating electromagnetic field (frequency f=2.45 GHz, wavelength λ=12.24 cm), align the dipoles of the polar molecules. Thus, heat is generated very effectively by resulting molecular friction directly in the reaction medium. Due to the uniqueness of dielectric heating, thermal effects continue to suppress specific effects such as over-heating of solutions at ambient pressure, selective heating of strongly microwave absorbing heterogeneous catalyst or

reagents in a less polar reaction medium and the elimination of wall effects caused by inverted temperature gradients. As a result of all these specific effects, reactions proceed at a much faster rate. Still, many of the underlying effects are poorly understood and highly dependent on the reaction parameters. Nevertheless, microwave radiation has become an efficient method for laboratory scale reactions. Traditional heating could be replaced by microwave-heating in future.

1.1.2.2 Continuous Flow-Through Technology

The example of laboratory microwave shows that not only the development of a reaction is important, but also the evolution of the devices for its implementation is useful. The equipment used in organic synthesis is essentially the same as it was used 150 years ago. Glassware such as flasks and reflux condenser are used to carry out the stepwise syntheses. The bulk chemicals are produced in industrial scale in flow-through reactors as the continuous flow of molecules always offer an improved space-time-yield. In the last decade, small scale instruments have been developed which enable the chemists to perform organic transformations in continuous flow-through reactors.

The reaction scale in the batch reactor is a function of reactor volume, while being in the flow reactor is a function of time. By a continuous reactor, material flow per hour can be managed so that the reaction scale can be arbitrarily increased in the same reactor model. Production rate can be increased by parallel operation of the flow reactors.

The efficient heat and mass transport, caused by a larger surface to volume ratio provides improvements in the reaction time, yield and selectivity. An unusual mixing of the reaction mixtrure is achieved within seconds. Further advantages such as security by a closed system, reproducibility, purification, isolation and low labor cost are extremely attractive. Automatic isolation and purification of products can take place continuously (Abbildung 2).

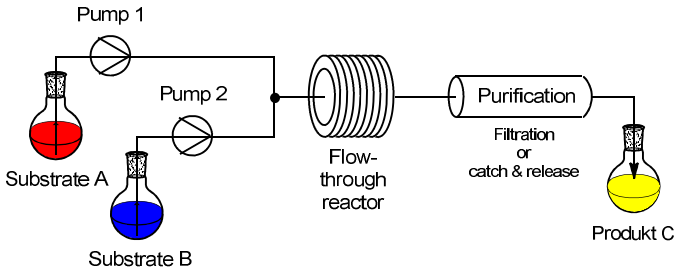


Abbildung 2. *Automatic product isolation in flow-through reactor*

Furthermore, the scale up of laboratory reactions to industrial scale in the flow reactor is safe and straightforward. The batch reactor operation is often tedious and usually requires drastic changes in the millimolar approach. Factors, such as an exothermic reaction behavior, accumulation of hazardous substances or their exposure to humans must be re-evaluated for larger reaction

mixtures. These factors are eliminated by the development of a reaction in the laboratory scale in a correspondingly small flow reactor. The reactor is a closed system, which keeps the reaction solution in constant flux. Thus, there are no potential risks of batch reactors, the associated additional development steps and costs.

The combination of new synthetic approaches using non-conventional technology therefore, opens up a wealth of unexplored opportunities with the potential for the effective development of the chemical field in the 21 century.

1.2 Carboxylic Acids as Substrates in Catalytic Transformations

The carboxylic acid group is one of the most common functional groups in organic molecules. They are readily availabe from natural and synthetic sources at low cost which makes them promising raw material for organic synthesis.

The reactivity of carboxylic acids is determined by two vicinal oxygen atoms, carbonyl oxygen atom and acidic hydroxyl group. The acidic properties of the hydroxyl proton are caused by the resonance stabilization and can be substituted by derivatization or by activation in the presence of a catalyst. Resonance stabilized carboxylate is formed under basic conditions which shows weak carbonyl reactivity to nucleophilic attack. Under such conditions, nucleophilic substitution *via* addition-elimination mechanism is only possible when the hydroxy group is replaced by a leaving group; for example, dehydration to anhydrides or conversion into acid chlorides or active esters. The hydroxyl group is activated in the presence of acid catalysts to form substituted products such as esters. Transition metal catalyzed reactions of the carboxylic acids and their derivatives also follow the same principles.[23]

Carboxylic acids have been used as versatile starting points for the construction of carbon frameworks, because of the high reactivity of their derivatives towards a large variety of reactions. In recent years, several catalytic transformations have been discovered in which carboxylic acids are used as the synthetic equivalent for acyl, aryl or alkyl halides and organometallic reagents without an additional activation step. A large number of different product classes have been accessed due to the unique reactivity of the single functional group.[24]

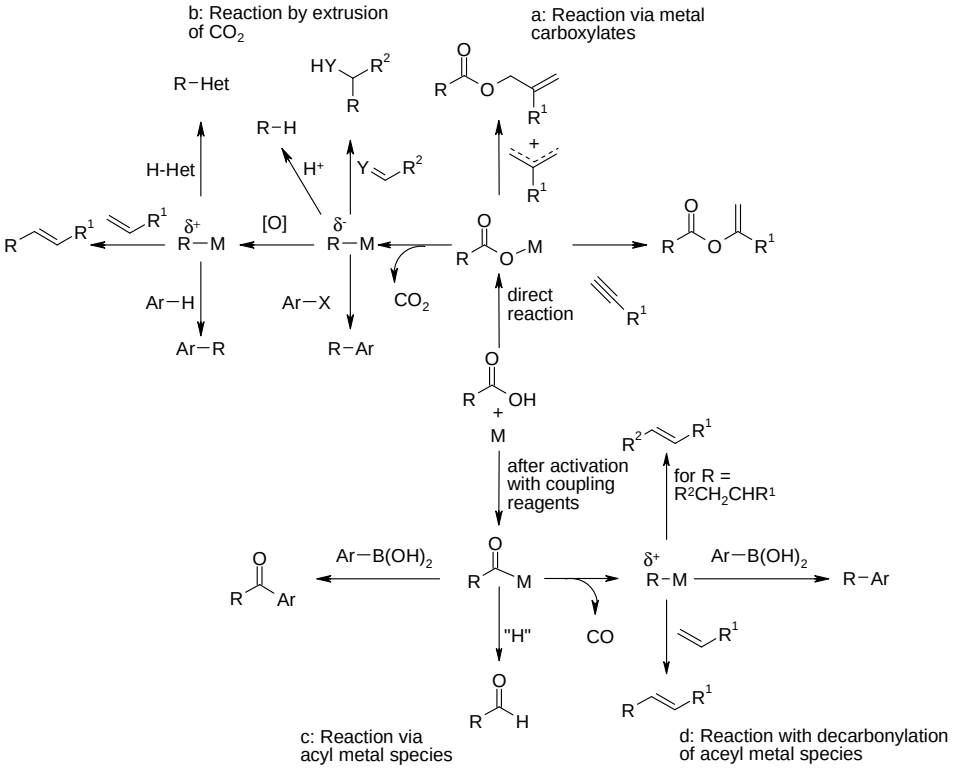
Carboxylic acids can either be employed directly in catalytic transformations or first be activated with a coupling reagent and then further used for the synthesis of a broad range of compounds. The catalytic transformation of carboxylic acids can be divided into four modes of reactivity on the basis of the position and polarity of the reactive bond (Schema 8).

a: reaction via metal carboxylates

b: reaction by extrusion of CO_2

c: reaction via acyl metal species

d: reaction via decarbonylation of acyl metal species



Schema 8. *Overview of catalytic transformation of carboxylic acids*

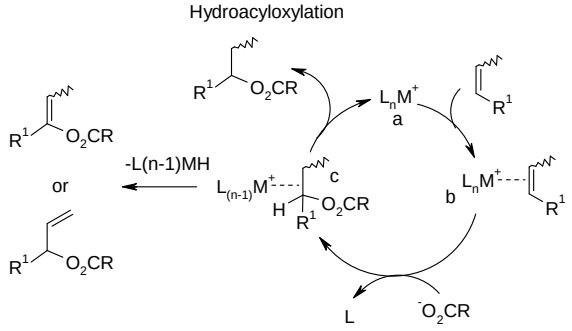
The reactions of carboxylic acids have been recently reviewed,[25] and will be briefly discussed here.

1.2.1 Direct Reactions of Carboxylic Acids

1.2.1.1 Reactions via Metal Carboxylates

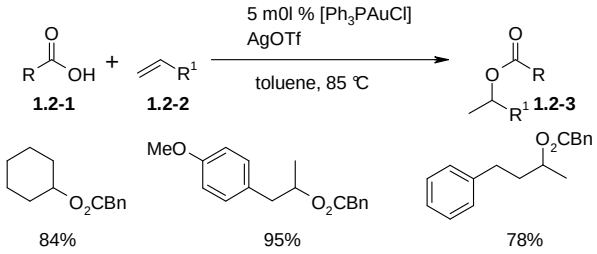
Carboxylic acids can be directly employed in catalytic reactions if the O–H bond is cleaved and caboxylate residue is attached to a metal species.

Under acidic conditions, carboxylic acids insert into olefinic double bonds with the formation of Markovnikov products.[26] The catalysts based on coinage metals and platinum metals offer the improved selectivity of these addition reactions under milder conditions. The major challenge associated with the transition metal catalyzed hydroacyloxylation is that many of their alkyl complexes undergo β-hydride elimination and the catalytic cycle is diverted towards the oxidative process (Schema 9).[27]



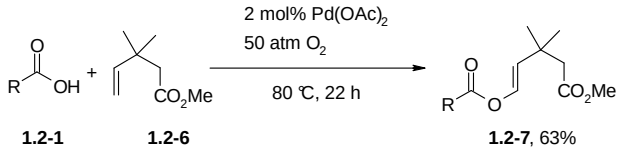
Schema 9. *Mechanism of the transition metal catalyzed hydroacyloxylation of olefins*

This unwanted β-hydride elimination was overcome by using transition metal catalyst systems such as [(Cp*$RuCl_2$)$_2$] in presence of dppb or PPh_3 and AgOTf,[28] $Cu(OTf)_2$/AgOTf[29] and $FeCl_3$/AgOTf.[30] The most successful results were obtained with [Ph_3PAuCl]/AgOTf because of the low tendency of the gold towards β-hydride elimination (Schema 10).[31]



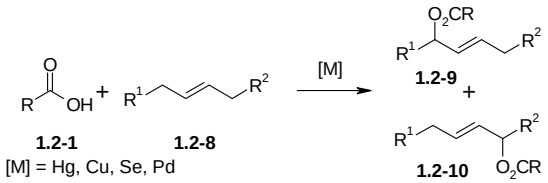
Schema 10. *Au-catalyzed hydroacyloxylation of olefins*

Under oxidative reaction conditions, carboxylic acids (**1.2-1**) react with alkenes (**1.2-6**) to form vinyl acetates (**1.2-7**) (Schema 11). Transition metal catalysts such as $PdCl_2$/$CuCl_2$[32] and $Pd(OAc)_2$[33] were used for the reaction of carboxylic acid with alkens to give vinyl acetates.



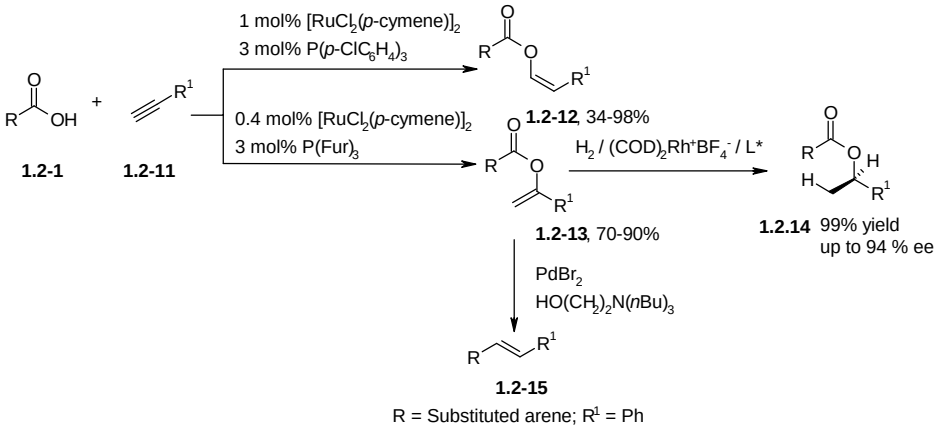
Schema 11. *Oxidative acyloxylation*

In the presence of allyl hydrogen atom, allylic acyloxylation takes place selectively in oxidative acyloxylation reactions (Schema 12). Stoichiometric quantities of Hg,[34] Se,[35] Cu[36] and Pd[37] salts were employed for allylic acyloxylation reaction before the catalytic variants were developed in the presence of oxygen or other oxidizing agents.[38] Copper and palladium based catalysts proved to be the catalyst of choice.[39] Enantioselective variant of allylic acyloxylation was developed in recent years.[40]



Schema 12. *Preparation of allylic carboxylates from alkenes*

The addition of carboxylic acids (**1.2-1**) to triple bonds ((**1.2-11**) with the formation of vinyl acetates [(**1.2-12**) and (**1.2-13**)] is a synthetic alternative to condensation reactions which requires harsh reaction conditions and produces a mixture of isomers. After the introduction of the first ruthenium catalyst for the formation of vinyl esters by Rotem and Shvo,[41] a range of ruthenium catalysts have been developed by Mitsudo,[42] Dixneuf[43] and Gooßen[44] for the synthesis of selective Markovnikov and anti-Markovnikov products. The Markovnikov products were further used for the Pd-catalyzed asymmetric hydrogenation[45] and decarbonylative Heck reaction to vinyl arenes (**1.2-15**) (Schema 13).[46]



Schema 13. *Addition of carboxylic acids to terminal alkynes*

In addition to ruthenium, numerous other transition metals such as rhodium,[47] iridium[48] and rhenium[49] have been used for the addition of carboxylic acids to terminal alkynes.

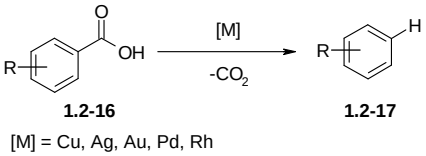
1.2.1.2 Reactions by Extrusion of CO_2

In this mode of reactivity, carboxylic acids release CO_2 in the presence of transition metals to give organometalllic species. As decarboxylation of carboxylic acid is highly endothermic, the extrusion of CO_2 takes place at elevated temperature in the presence of a catalyst. Theoretical investigation by Cohen *et al*. demonstrated that decarboxylation of metal carboxylates results in the formation of aryl metal species *in situ* which are subsequently protonolyzed to the corresponding arenes.[52e]

Nilsson showed already that unsymmetrical biaryl is formed by trapping the aryl copper intermediated generated as a result of decarboxylation with aryl iodides.[50] However, harsh

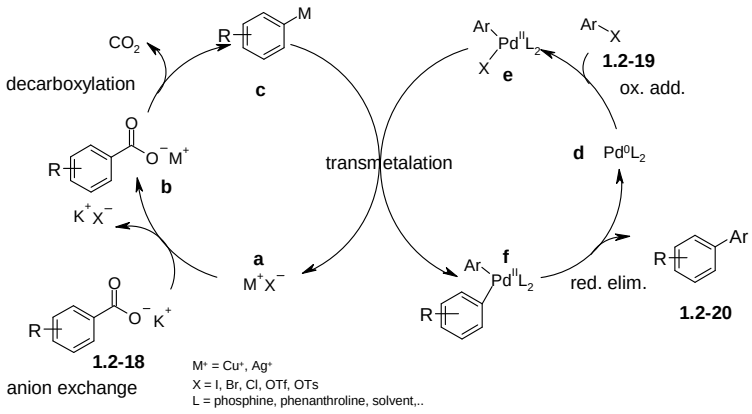
reaction conditions and general limitations of cross-Ulmann coupling prevented the development of preparative useful synthesis of unsymmetrical biaryls.

Several transition metal catalysts such as copper,[51] silver[52] or mercury[53] have been developed for decarboxylation of arenecarboxylic acids (**1.2-16**) at mild conditions. This is the key step for all decarboxylative coupling reactions of aromatic carboxylic acids. (Schema 14).



Schema 14. *Metal mediated protodecarboxylations of aromatic carboxylic acids*

The first practical decarboxylative coupling of aromatic carboxylic acids (**1.2-16**) with aryl halides (**1.2-19**) was developed with a bimetallic catalyst system.[54] This bimetallic catalyst system consists of a decarboxylation catalyst such as copper or silver and a cross-coupling catalyst based on palladium. Decarboxylative activity of palladium is only limited for a few particularly activated carboxylates.[55] The mechanism of action of the bimetallic catalyst system is illustrated below (Schema 15).

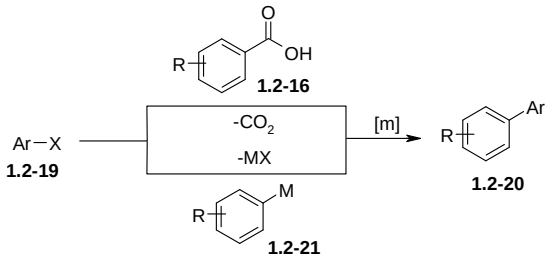


Schema 15. *Decarboxylative cross-coupling*

The reaction starts with the extrusion of CO_2 from a metal carboxylate (**1.2-18**) (b), generated by salt exchange from a potassium carboxylate and a copper or silver salt (a). The resulting arylcopper species (c) transfers its aryl group to an arylpalladium(II) complex (e) generated by the oxidative addition of an aryl halide or pseudo halide (**1.2-19**) to a palladium co-catalyst (d), giving rise to a diarylpalladium species (f). The catalytic cycle for the palladium is closed by reductive elimination of the biaryls (**1.2-20**) and the regeneration of the initial palladium(0) species.

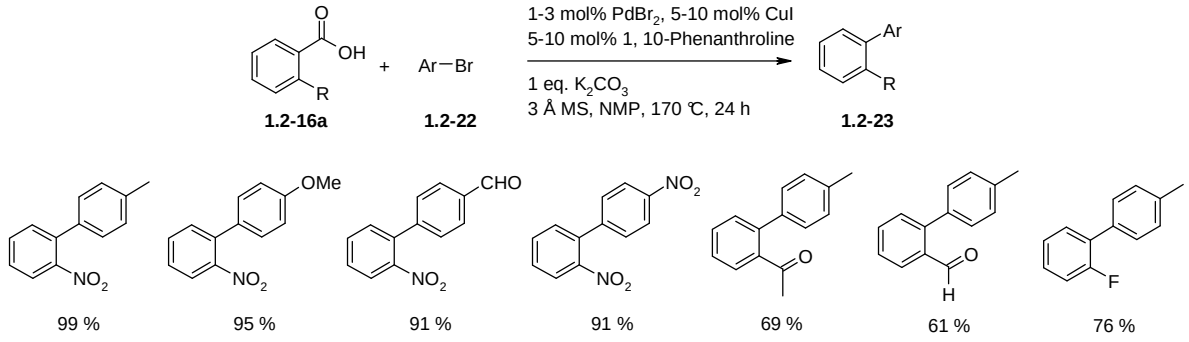
Although modern coupling reactions (Suzuki,[56] Stille,[57] Negishi,[58] Heyama,[59] Kumada coupling[60]) are very effective for selectivity, functional group tolerance and yield. They require

stoichiometric amounts of organometallic reagents (**1.2-21**) which are pregenerated in a separate reaction step and produce stoichimometric amounts of waste. The cheap and readily available aromatic carboxylic acids (**1.2-16**) are directly used without pre-synthesis of organometallic reagents and principally only CO_2 is produced as a waste product (Schema 16).



Schema 16. *Cross-coupling of organometallic compounds and carboxylic acids with aryl halides*

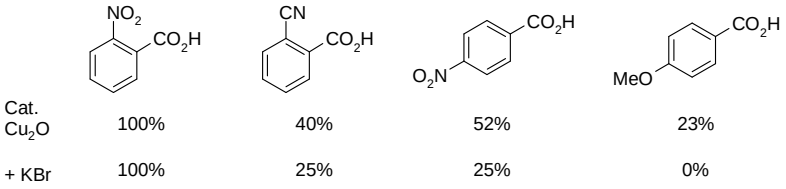
The decarboxylation reactions have been continuously improved over the last 5 years. In the initial report, stoichiometric and catalytic amounts of copper and palladium salts were used for the decarboxylative cross-coupling of the 2-nitrobenzoic acid (**1.2-21**) with a number of aryl halides (**1.2-19**).[54] In the second catalytic variant *o*-substituted benzoic acids (**1.2-16a**) were coupled with iodo, bromo and chloroarenes to produce corresponding biaryls (**1.2-23**)[61] (Schema 17). The catalyst system was generated *in situ* from $Cu^{I}I$, 1, 10 phenanthroline and $PdBr_2$. Notoriously stable aryl chlorides were introduced as substrates for decarboxylative cross-coupling reactions by the addition of sterically demanding electron rich phosphine ligands.[62]



Schema 17. *Cu/Pd-catalyzed biaryl synthesis*

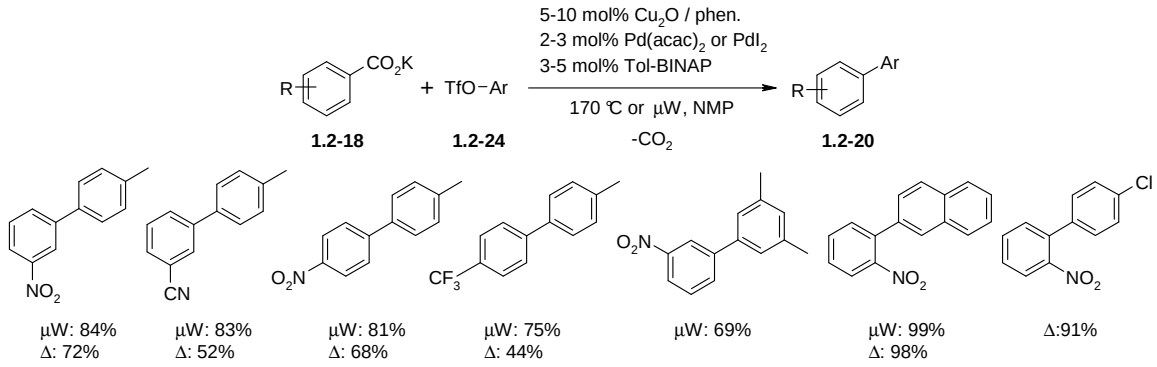
However, these protocols are limited to *ortho*-substituted benzoic acids, cinnamic acids and few heterocyclic carboxylic acids due to the limited efficiency of salt metathesis step. This was due to high the affinity of the copper catalyst towards the halide ions released in the cross-coupling step. This makes the salt metathesis unfavorable for carboxylates which have a non-coordinating atom at the *ortho*-position of the carboxylate group. Protodecarboxylation of non-*ortho*-

substituted carboxylic acids is completely suppressed by small amounts of bromide salts, whereas it has no influence on the protodcarboxylation of *ortho*-nitrobenzoic acids (Schema 18).



Schema 18. *Halides effect on protodecarboxylation*

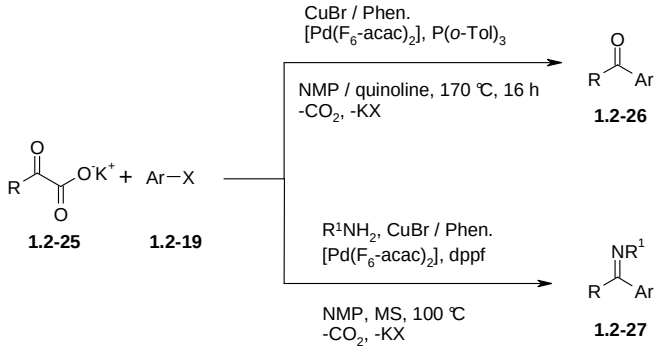
This limitation was overcome by replacing aryl halides with aryl triflates as weakly coordinating triflate salts are released instead of halide salts which do not affect the decarboxylation step (Schema 19). In the presence of $Pd(acac)_2$/tol-BINAP and Cu_2O/1, 10-phenanthroline, aryl triflates were coupled with a range of aryl carboxylic acids including *meta*-and *para*-substituted derivatives. In the context of these experiments, the beneficial effect of pressure on the decarboxylative cross-coupling reactions in the microwave has been observed for the first time. The reaction was performed by using both conventional (160 °C, 16 h) as well as microwave heating (190 °C, 5-10 min). However, microwave protocol afforded higher yields for deactivated carboxylates due to less thermal stress.[63]



Schema 19. *Decarboxylative coupling of aryl triflates*

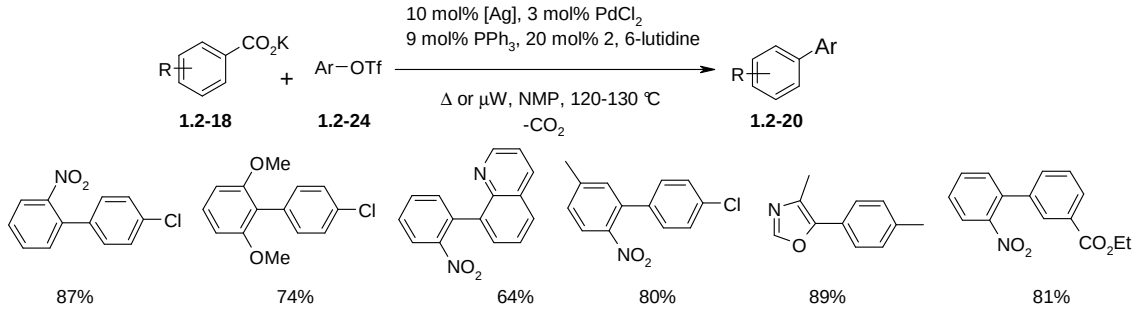
The scope of the decarboxylative coupling reaction was further extended to inexpensive and hard to activate aryl tosylates by improving the palladium catalyst and reaction conditions. $Pd(acac)_2$ stabilized by XPhos gave best results under microwave heating (190 °C, 150W/5min).[64]

In the presence of Cu/Pd catalyst system, α-oxocarboxylic acids (**1.2-25**) could be successfully coupled with aryl halides (**1.2-19**) to give the corresponding ketones (**1.2-26**).[65] This reaction is of particularly high interest; as formally electrophilic acyl groups undergo an "umpolung" for acyl nucleohiles by decarboxylations. Imines (**1.2-27**) are synthesized by decarboxylative coupling of α-oxocarboxylic acids (**1.2-25**) with aryl halides (**1.2-19**) in the presence of amine[66] (Schema 20).



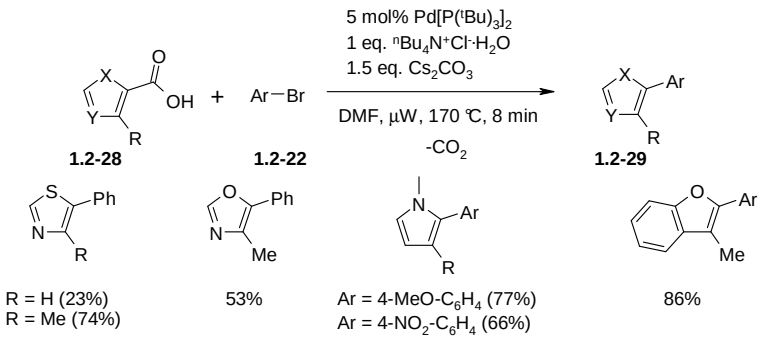
Schema 20. *Decarboxylative ketone and imine synthesis*

Similarly, analogues to Cu/Pd system, Ag/Pd catalyst systems were also used for decarboxylative biaryl synthesis.[67] Silver based systems allowed the lowering of the decarboxylation temperature from 170 °C to 120 °C. A more efficient catalyst system generated form Ag/Pd allowed the cross-coupling of aryl triflates (**1.2-24**) with arenecarboxylates (**1.2-18**) at 120 °C (Schema 21).[68]



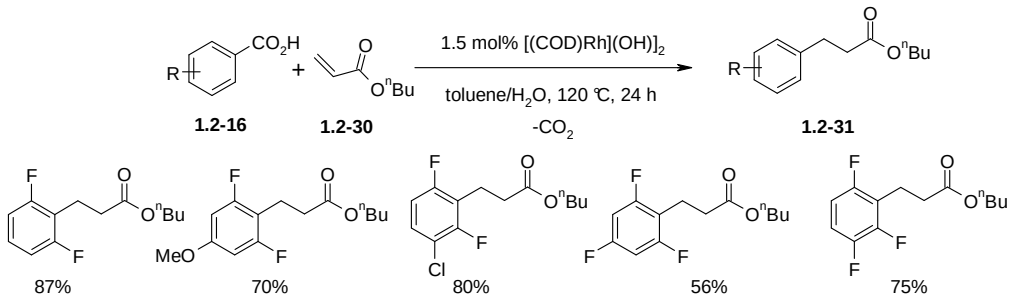
Schema 21. *Ag-catalyzed decarboxylative coupling of arene carboxylates with aryl triflates*

In parallel to our work, decarboxylative reactions have been extensively improved. Some particularly activated carboxylates can also be coupled with monometallic catalysts.[69] Steglich[69c] and Bilodeau, and Forgione[69a,b] reported coupling of five-membered heteroarenes bearing carboxylate groups in the 2-position (**1.2-28**) with various aryl bromides (**1.2-22**) under extrusion of CO_2 (Schema 22). Whereas, Miura reported the decarboxylative arylation of indole-3-carboxylic acids while 2-position of the indole was substituted already.[69d]



Schema 22. *Arylation of heteroarenecarboxylates*

Decarboxylative 1,4-addition to acrylic esters (**1.2-30**)[70,71] proceeds in the presence of 1 mol% of $[(cod)Rh(OH)]_2$ at moderate temperatures with mostly *ortho, ortho*-disubstituted benzoates (Schema 23), whereas decarboxylive 1,2-addition to carbonyl compounds in the presence of 10 mol% $PdCl_2$ and 20 mol% AgOTf gives the corresponding alcohols.[72]

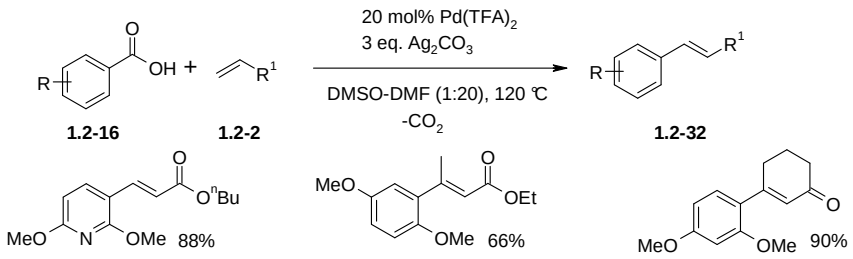


Schema 23. *Decarboxylative 1,4-addition reactions*

Decarboxylative allylation is another strategy for the synthesis of organic compounds from carboxylic acids and was recently reviewed by Tunge *et al*.[73] This strategy is beyond the scope of this thesis.

In the presence of stoichiometric quantities of an oxidant, the reactivity of organometallic species generated via decarboxylation can be reversed so that carboxylic acids may also undergo decarboxylative coupling reactions with nucleophiles. Decarboxylative Heck reactions or the coupling of carboxylic acids with arenes under C-H functionalization are the examples where carboxylic acids serve as a source of electrophilic coupling partners.

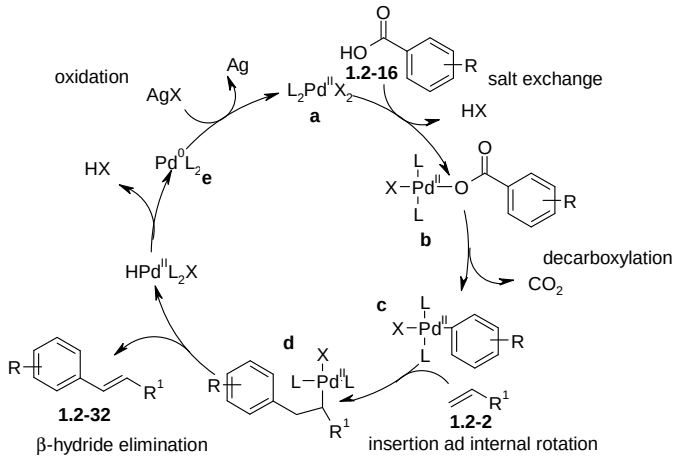
In 2002, Myers *et al*. reported the development of the first novel decarboxylative Heck reaction in which carboxylic acids (**1.2-16**) serve as substitutes for aryl chlorides.[74] In this transformation, carboxylic acids (**1.2-16**) provide aryl electrophiles in the presence of palladium catalyst and stoichiometric amount of silver carbonate (Schema 24).



Schema 24. *Decarboxylative Heck reaction*

The reaction mechanism is outlined below (Schema 25). The salt exchange between a Pd^{II} (a) precursor and benzoic acid (**1.2-16**) results in the formation of palladium benzoate (b) that generates an aryl palladium (II) species (c) on extrusion of CO_2. The alkene (**1.2-2**) insertion to the aryl palladium species and the internal rotation leads to the formation of species (d) which

produces Pd^0 (e) and vinyl arene (**1.2-32**) via β-hydride elimination. Pd^{II}(a) is regenerated by the oxidation of Pd^0 (e) to restart the catalytic cycle.

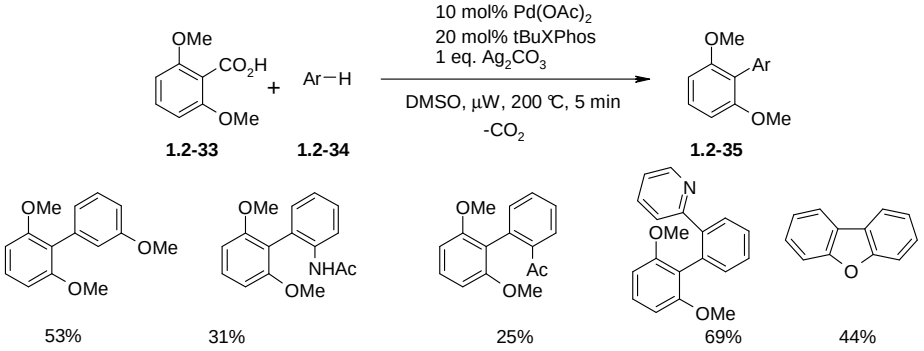


Schema 25. *Mechanism of the decarboxylative Heck reaction*

Further developments include the use of *p*-benzoquinone[75] and copper fluoride[76] as oxidants with $Pd(TFA)_2$ and $Pd(OAc)_2$, respectively. In the former development, only activated substrates were coupled which are decarboxylated by palladium. Whereas, later development showes the coupling of 2-nitrobenzoates with alkenes via decarboxylation.

The decarboxylative Heck-olefination can be seen as the prototype for all oxidative decarboxylation reactions in which aryl carboxylates serve formally as electrophilic coupling partners. This reaction has been intensively explored in the last three years.

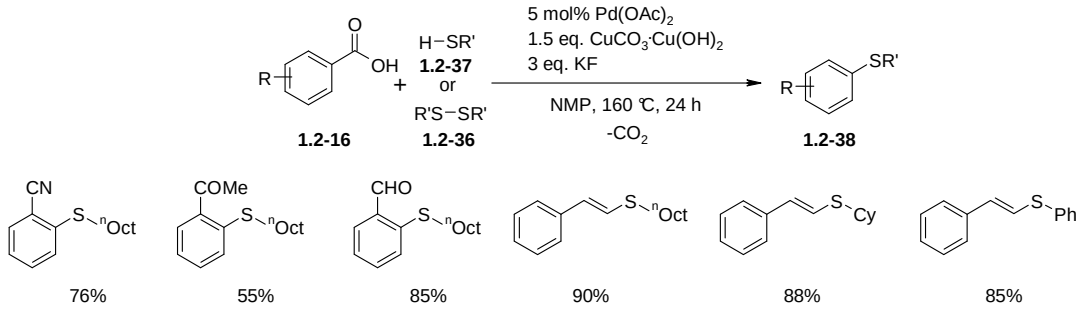
Crabtree *et al*. combined the oxidative decarboxylative coupling with C-H activation in their decarboxylative biaryl synthesis. The coupling of arene (**1.2-34**) with *o*,*o*-disubstituted carboxylic acids (**1.2-33**) was conducted in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% ^{t}BuXPhos and excess Ag_2CO_3[77] (Schema 26).



Schema 26. *Decarboxylative coupling under C-H activation*

The application was further utilized by Glorious *et al*.,[78] Larossa *et al*.[79] and Greaney *et al*.[80] for the synthesis of dibenzofurans, arylation of the indoles at the 3-position and the intermolecular decarboxylative C-H cross-coupling between oxazoles and thiazoles, respectively.

Oxidative decarboxylative couplings could also be extended to C-heteroatom bond formation reactions. Decarboxylative coupling of arenecarboxylic acids (**1.2-16**) with thiols (**1.2-37**) or disulfides (**1.2-36**) in the presence of 5 mol% $Pd(OAc)_2$ and super stoichiometric amount of $CuCO_3{\cdot}Cu(OH)_2$ gives aryl sulfides(**1.2-38**) [81] (Schema 27).



Schema 27. *Decarboxylative C-S coupling*

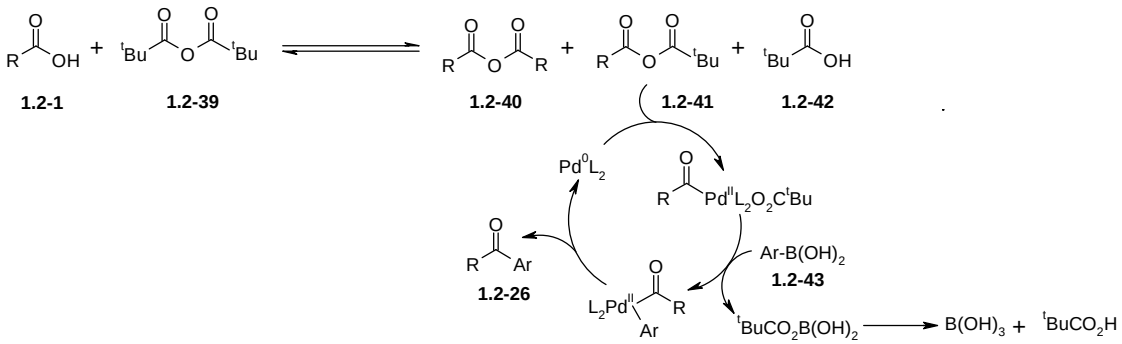
1.2.2 Reactions of in situ Activated Carboxylic Acids

As in classical reactions of carboxylic acids, nucleophilic attack at the carbonyl carbon followed by C (O)-O bond cleavage is only possible for activated carboxylic acids. Here the acid function is activated by substitution of the hydroxyl group, such as acid chlorides, anhydrides, esters, amides and thioesters. Few of them react with transition metal catalysts by oxidative addition to form acyl metal complexes and are thus available for further catalytic transformations.[6]

1.2.2.1 Reaction via Acyl Metal Species

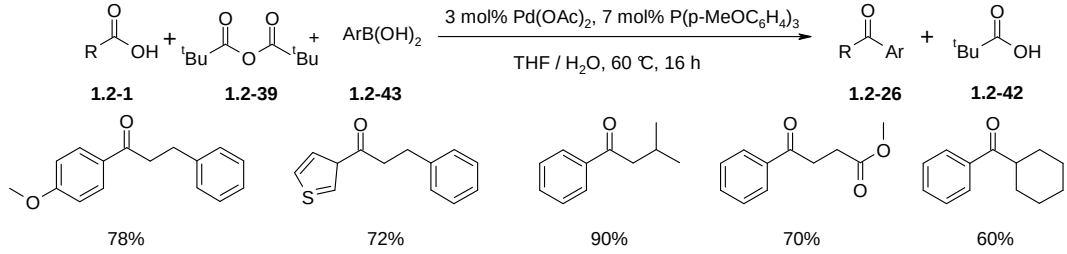
The activation of carboxylic acids can be achieved by their conversion into anhydrides or *N*-hydroxysuccinates which allows the insertion of transition-metal catalysts into acyl-oxygen bond. The resulting acyl-metal species are either hydrogenated or coupled with aryl boronic acids.

The aryl ketones (**1.2-26**) are formed by the coupling of carboxylic acids (**1.2-1**) with aryl boronic acids (**1.2-43**) in the presence of pivalic anhydride (**1.2-39**).[82] The catalyst system consists of $Pd(OAc)_2$ and P(*p*-$MeOC_6H_4$). In this process an equilibrium mixture of carboxylic acid anhydrides is formed by the reaction of carboxylic acids (**1.2-1**) and pivalic acid anhydride (**1.2-39**). The Pd(0) selectively inserts into the C(O)-O bond of the less shielded side of the mixed anhydride to form acyl palladium complex. Transmetallation and reductive elimination result in the formation of the desired ketones (**1.2-26**) (Schema 28).



Schema 28. *Mechanism of ketone synthesis from carboxylic acids and boronic acids*

Under the optimized reaction conditions, electron-rich and electron-deficient aryl boronic acids are coupled with carboxylic acids (**1.2-1**) to yield the corresponding ketones (**1.2-26**). However, pivalic acid (**1.2-42**) is produed as a by-product which complicates the isolation of the product (**1.2-26**) (Schema 29). [82]



Schema 29. *Coupling of carboxylic acids with boronic acids*

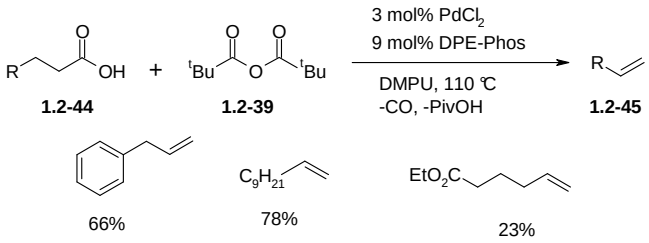
Improved protocols were developed by using dimethyldicarbonate[83] and disuccinimidyl carbonate[84] as activators which produce methanol, CO_2 and CO as volatile and *N*-hydroxysuccinimide as water soluble by-product, offering improved isolation of products.

1.2.2.2 Reactions via Decarbonylation

The initial step in many catalytic transformations is the formation of organometallic species which can also be created by a sequence of oxidative addition and decarbonylation of activated carboxylic acid derivative on metal catalysts. Hence, there are many opportunities for catalytic transformations. Acyl transition metal complexes are prone to decarbonylation reaction generating organometallic species that can be utilized as an electrophilic partner.

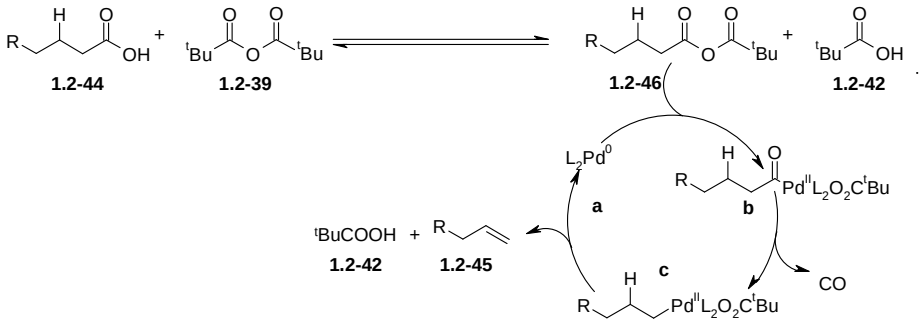
The alkyl metal complexes containing a β-hydrogen atom to carbonyl function undergo subsequent β-hydride elimination to the corresponding terminal alkenes. Miller *et al*. distilled off terminal alkene at 250 °C by heating a mixture of long-chain fatty acids and acetic anhydride in the presence of Pd-phosphine catalyst.[85] High reaction temperature, elaborate lay-out and double bond isomerization limit the synthetic usefulness of this reaction.

A more efficient catalyst system had been developed which allowed the selective synthesis of terminal alkenes (**1.2-45**) from carboxylic acids (**1.2-44**) in the presence of pivalic anhydride (**1.2-39**) at a low temperature. Both linear and branched carboxylic acids were successfully converted into the corresponding terminal alkenes (**1.2-45**) in the presence of $PdCl_2$ and DPE-Phos at 120 °C without double bond isomerization (Schema 30).[86]



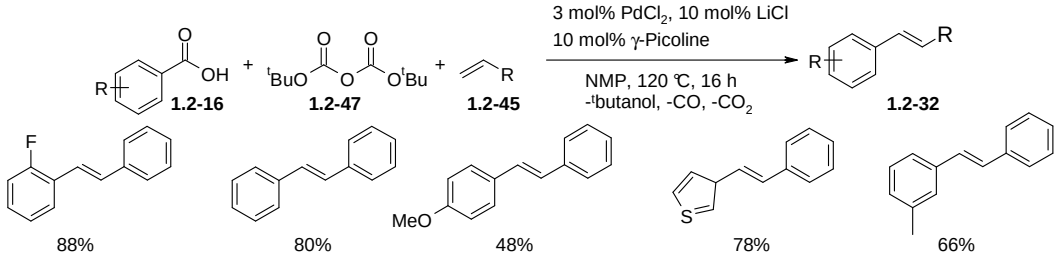
Schema 30. *Synthesis of terminal alkenes from carboxylic acids*

Aliphatic carboxylic acids (**1.2-44**) containing a β-hydrogen atom to the carbonyl function react with pivalic anhydride (**1.2-39**) to generate mixed anhydride which oxidatively adds palladium(a) to result in the formation of acyl palladium complex (b). At an elevated temperature, acyl palladium complex releases carbon monoxide to produce alkyl palladium complex (c) that liberates terminal alkene (**1.2-45**) via β-hydride elimination and palladium(0) to start the catalytic cycle again (Schema 31).



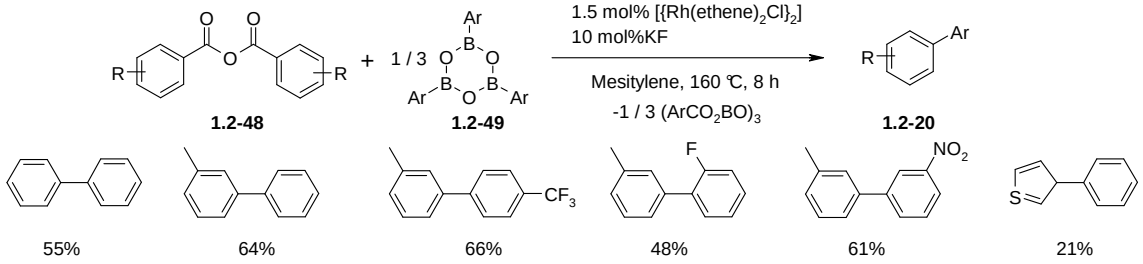
Schema 31. *Mechanism of the decarbonylative alkene synthesis*

Decarbonylative Heck-type reaction was introduced by Miura *et al.*[87] and De veries *et al.*[88] in which acid chlorides were coupled with olefins. Heck reaction was improved by activating the carboxylic acid (**1.2-16**) *in situ* with di-*tert*-butyl dicarbonate (**1.2-47**) and coupling with olefins (**1.2-45**) to give the corresponding vinyl arenes (**1.2-32**).[89] CO, CO_2 and *tert*-butanol are produced as byproducts (Schema 32).



Schema 32.*Decarbonylative Heck reaction of carboxylic acids*

Decarbonylative biaryl synthsis was achieved by using less reactive aryl boroxines (**1.2-49**) and more active rhodium catalyst in non-polar solvent. Aryl anhydrides (**1.2-48**) were coupled with aryl boroxines (**1.2-49**) in the presence of 1.5 mol% of [{Rh(ethene)$_2$Cl}$_2$] catalyst and 10 mol% of KF to form a variety of biaryls via decarbonylation (Schema 33).[90]



Schema 33. *Decarbonylative biaryl synthesis*

Over the last 5 years, catalytic transformations of inexpensive carboxylic acids have been optimized to an impressive level. However, the potential of the carboxylic acids in organic chemistry has not been fully explored yet.

2 Aims of the Research

The focus of this research work is to use carboxylic acids as substrates in homogeneous catalysis. This thesis is divided into two main parts:

The objective of the first part is to improve the methods that involve the conversion of carboxylic acids to valuable intermediates and organic compounds. This work consists of the following subprojects:

The 1st project involeves the development of a mild and efficient method for the conversion of carboxylic acids to aldehydes based on the pioneering work of our group on the selective reduction of carboxylic acids to aldehydes.

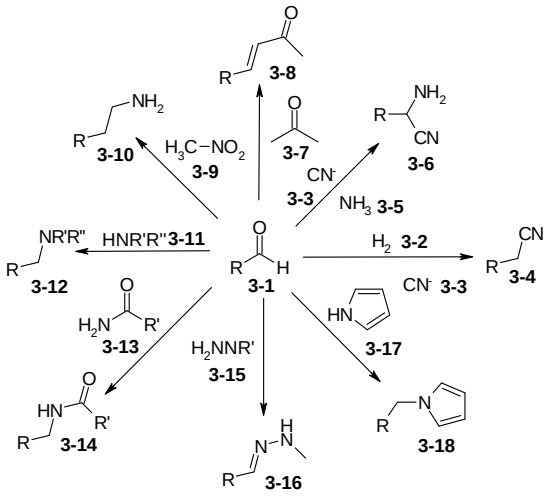
The 2nd project is aimed to study the role of microwaves on the copper catalyzed protodecarboxylation of arenecarboxylic acids which is the key step in decarboxylative coupling reactions and was initially developed by our group.

The objective of the second part is to set a stage for the development of decarboxylative trifluoromethylation reactions. In this context, my aim of the 3rd project is to develope a catalytic process for the conversion of arylboronic acid derivatives as carboxylic acids analogues into benzotrifluorides by using $K^+[CF_3B(OMe)_3]^-$ as trilfuoroemthylating reagent.

The 4th project involves the development of a straightforward method for the conversion of carbonyl compounds into the corresponding trifluoromethylated alcohols by using $K^+[CF_3B(OMe)_3]^-$. This work was also independently developed under similar reaction conditions by Dilmann *et al*.[206]

3 Synthesis of Aldehydes from Carboxylic Acids

The aldehyde function is an important moiety in organic chemistry. Due to the high reactivity of the formyl group, it serves as an excellent substrate for the formation of C-C, C-N and C-S bond and thus plays a major role in the synthesis of useful compound. The synthetic applications of aldehydes are summarized below (Schema 34).[91]



Schema 34. *Synthetic applications of aldehydes*

Naturally occurring aldehydes include cinnamaldehyde (**3-19**),[92] vanillin (**3-20**),[93] pyridoxal (**3-21**)[94] and retinal (**3-22**)[95] (Abbildung 3). Cinnamaldehyde (**3-19**) and vanilline (**3-20**) are extracted from the bark of the cinnamon trees[92a] and vanilla beans,[93a] respectively. Both are used as flavouring agents in food,[92b, 93b] in agrochemicals[92c, 93c] and pharmaceuticals.[92d, 93d] Pyridoxal (**3-21**) is the natural form of vitamin B_6 which is obtained from green plants. Similarly, retinal (**3-22**) is a form of vitamin A which is obtained from meat and plants.[95]

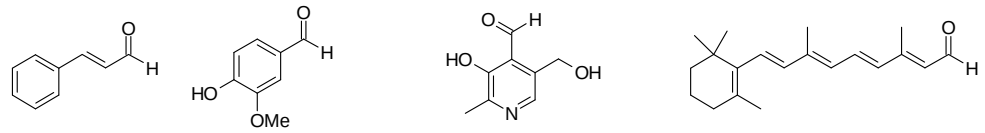


Abbildung 3. *Examples of naturally occurring aldehydes*

Hence, aldehydes are synthetically and naturally useful compounds. The developments of simple, sustainable and general methods for the synthesis of aldehydes are still in the process of improvement.

3.1 State of the Art Aldehyde Synthesis

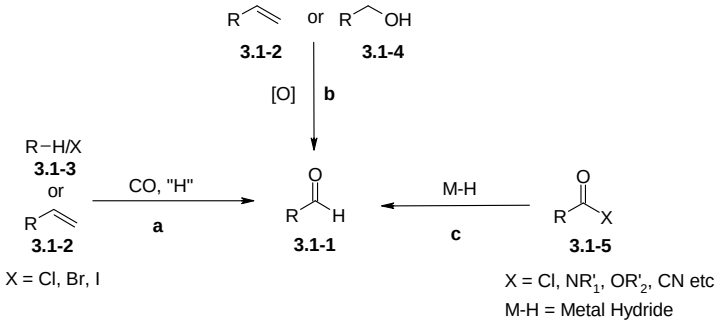
Despite the large number of methods for the synthesis of aldehydes, convenient and economical routes are still rare. However, these methods can be classified in three major catagories:

a: Aldehyde synthesis via carbonylation reactions

b: Aldehyde synthesis via oxidation reactions

c: Aldehyde synthesis via reduction reactions

the first two catagories will be briefly discussed whereas the third category will be discussed in detail.



Schema 35. *Stratergies for aldehyde synthesis*

3.1.1 Aldehyde Synthesis via Carbonylation Reactions

The first category involves the synthesis of aldehydes by using carbon monoxide and a reducing agent in the presence of a Lewis acid or a transition metal catalyst (Schema 35, a). It includes Gattermann Koch[96] reaction in which CO is used under Friedal-Craft conditions to produce aldehydes from arenes C-H bond. Besides regioselective issues, the reaction requires different reaction conditions and additives for the hydroformylation of activated, non activated and deactivated arenes and the scope of the transformation is limited to only aromatic aldehydes.

The famous industrial oxo synthesis process also represents carbonylative aldehyde synthesis.[97] It is used for the synthesis of aliphatic aldehydes from alkenes, carbon monoxide and hydrogen. Cobalt and rhodium based catalysts had been developed for obtaining the better selectives for linear and branched aldehydes at mild reaction conditions.[98] However, the process is limited to only aliphatic aldehydes.

Palladium catalyzed reductive carbonylation of aryl (pseudo) halides to aldehydes is another example of carbonylative aldehyde synthesis which was first developed by Heck and Shoenberg in 1974.[99] In the course of development, different reducing agents such as metal hydrides and formate salts were used to synthesize aldehydes from aryl halide and carbon monoxide.[100] Recently, palladium catalyzed reductive carbonylation of aromatic, heteroaromatic and vinyl bromides have been reported under low pressure of carbon monoxide and hydrogen.[101]

Although carbonylative aldehyde synthesis is an important class employing cheap and environmentally benign source of formyl group, but these reactions are limited to either aromatic aldehydes or aliphatic aldehydes. Until now, no general protocol is available which can be applied for the synthesis of aromatic, heteroaromatic as well as aliphatic aldehydes using carbon monoxide and hydrogen. The use of toxic CO as a reagent is not very practical in academia for the optimization of reaction protocol. These reactions are only useful for the industrial scale applications where the proper reaction setup is used for the handling of toxic gases.

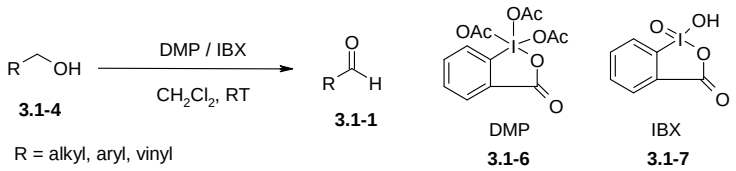
3.1.2 Aldehyde Synthesis via Oxidation Reactions

Selective oxidation of olefins (**3.1-2**) and primary alcohols (**3.1-4**) represents the second catagory of aldehyde synthesis (Schema 35, b). Oxidative cleavage of the alkene (**3.1-2**) has been traditionally performed by ozonolysis.[102] Catalytic variants have been developed by utilizing high valent oxometals,[103] such as RuO_4 and OsO_4. Recent developments include the use of palladium catalyst for the oxidation of olefins (**3.1-2**) to aldehydes (**3.1-1**) in the presence of oxygen.[104] Aromatic and aliphatic alkenes were converted into aldehydes.

Among the oxidative methods, the partial oxidation of primary alcohols (**3.1-4**) to aldehydes (**3.1-1**) is a widely used oxidation reaction in organic synthesis. Several classical reagents such as chromium,[105] managanese oxide,[106] activated DMSO methods (Swern oxidation),[107] and hypervalent iodine reagents (Dess-Martin oxidation),[108] pyridine·SO_3[109] and NaOCl/TEMPO[110] are frequently employed in the laboratory as well as large-scale applications. Among them, the Swern and the Dess-Martin oxidation are the most frequently used for the synthesis of aldehydes (**3.1-1**) from the primary alcohols (**3.1-4**).

However, the Swern oxidation is not a user friendly protocol because it applies toxic reagents such as oxalyl chloride. From an environmental point of view, quantitative amounts of waste are produced in addition to toxic gases such as CO and CS_2 and CO_2.[107]

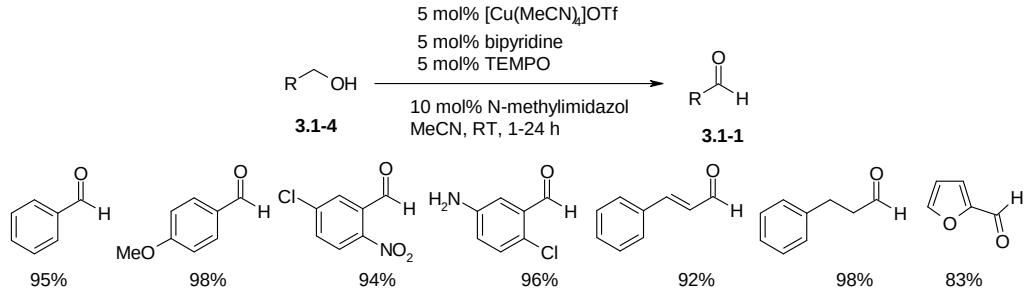
The Dess-Martin oxidation has several advantages over Swern oxidation such as milder reaction conditions, shorter reaction times, higher yields, simplified workups, high chemoselectivity and tolerance of sensitive functional groups (Schema 36). 1-hydroxy-1,2-benziodoxol-3(1H)–one1-oxide (IBX) (**3.1-7**) was initially used and later on replaced by Dess-Martin Periodinane (DMP) (**3.1-6**) that is solid, more stable and soluble in organic solvents.[111]



Schema 36. *Dess-Martin oxidation*

Although the Dess-Martin oxidation is considered as a state of the art method for aldehyde synthesis by oxidative methods, the use of expensive and waste producing oxidizing reagent encourages the development of atom-economic transition metal catalyzed oxidation of alcohols to aldehydes in the presence of air as oxidant.

Considerable progress has been made in the aerobic oxidation of primary alcohols (**3.1-4**).[112] These oxidation reactions include transition metal[113] based complexes which oxidize a variety of allylic, benzylic and aliphatic substrates. Recently, Stahl and Hoover reported a highly active (bpy)Cu^{I}/TEMPO catalyst system that allows the partial aerobic oxidation of primary alcohols (**3.1-4**) to the corresponding aldehydes (**3.1-1**) (Schema 37).[114] This reaction protocol was published a year after our work.



Schema 37. *Cu^{I}-catalyzed aerobic oxidation of primary alcohols*

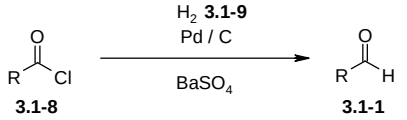
Although the reaction gives high yields, broad functional-group tolerance and mild reaction conditions, over oxidation to carboxylic acids is still a challenge in this protocol. In addition, the environmental factor of the reaction is increased by the use of a large number of additives which not only complicate the reaction setup but also produce waste.

3.1.3 Aldehyde Synthesis via Reduction Reactions

The selective reduction of carboxylic acid derivatives to aldehydes represents the third category of aldehyde synthesis (Schema 35, c). It is a highly used stratergy for the synthesis of aldehydes from carboxylic acid derivatives. Over the last decades, substantial research has been diverted towards the development of simple and general methods which utilize carboxylic acids and derivatives as substrates. As a result, more reactive derivatives such as acid chlorides,[115] amides, esters, anhydrides and nitriles were selectively converted into aldehydes.

Rosenmund reduction is one of the oldest transformations in this field in which acid chlorides (**3.1-8**) are hydrogenated in the presence of Pd/C (Schema 38).[115a-c] However, the reaction is sensitive to acide labile functional groups. The palladium catalyst is very reactive and thus overreduction is often observed and the corresponding alcohols are obtained in considerable quantities. This side reaction is controlled by applying an elaborate reaction setup in combination

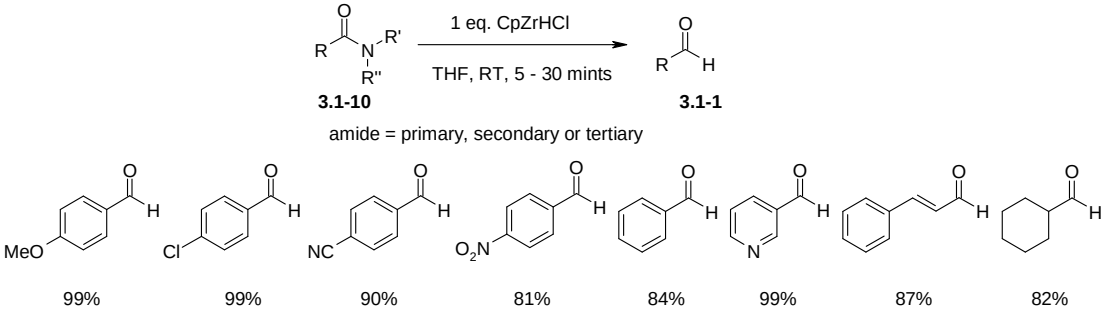
with catalyst poison such as barium sulfate. Hydrogen chloride is produced as a corrosive by-product which is trapped by the base. As a result, a considerable amount of waste is produced.



Schema 38. *Rosenmund reduction*

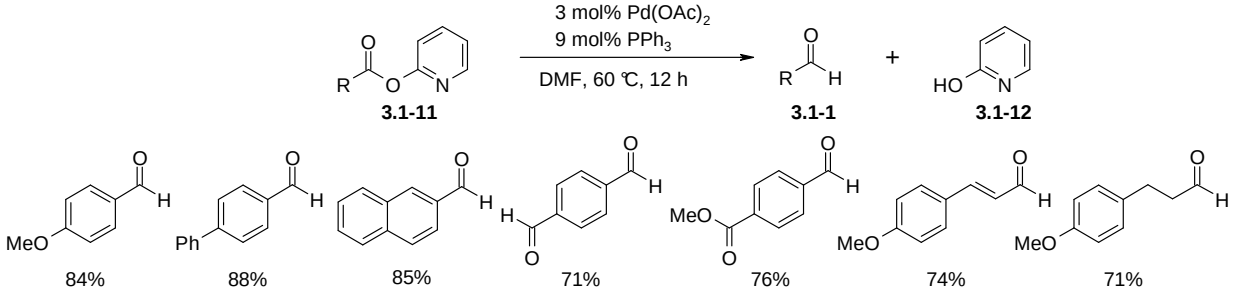
Besides palladium catalysts, various metal hydrides have been established for the selective reduction of acid chlorides to aldehydes. These include aluminum,[115d-f] boron,[115g-h] silicon and stannous hydrides. Borohydrides are used with pyridine which captures the borane and avoids overreduction. Whereas, organo silicons[115i-m] and organo stannous[115l] are used in the presence of palladium, rhodium and indium based catalysts. In addition, anionic transition metal reductants such as $HFe(CO)^{-1}$, $CpV(CO)_3H^-$, and $HCr(CO)_5^-$ function under relatively mild conditions and offer high yields.[115m-p] However, all these protocols require the use of stoichiometric quantities of metal based reagents which generate large quantities of waste.

The reduction of carboxylic acid amides (**3.1-10**) to aldehydes (**3.1-1**) can be performed by employing stoichiometric quantities of samarium iodide with H_3PO_4,[116]aluminum[117] and boron hydrides.[118] The success of all these methods is highly dependent on the nature of the amide group. Overreduction of the corresponding aldehydes is often observed. Best results were obtained by employing *N*,*N*-dimethyl and *N*,*N*-diethyl amides in combination with $LiAlH_4$. In 1996, Buchwald *et al*. reported the reduction of a broad range of tertiary amides to aldehydes by using stoichiometric amounts of Ph_2SiH_2 and $Ti(O^iPr)$ at room temperature.[119] In addition to the use of stoichiometric quantities of hydrosilane and a titanium reagent, this reaction has the limitation of using α-enolizable tertiary amides as only substrates. Very recently, George *et al*. utilized Schwartz's reagent to convert primary, secondary and tertiary amides to the corresponding aldehydes (**3.1-1**) at room temperature (Schema 39).[120] Although the reaction offers mild conditions and shorter reaction time, the use of stoichiometric quantities of zirconium reagent limits the atom-efficiency of the reaction mode.



Schema 39. *Selective reduction of carboxylic acid amides with Schwartz reagent*

The selective reduction of carboxylic acid esters to aldehydes is performed with aluminum hydride reducing agents.[121] Fukuyama reported Pd/C catalyzed reduction of thioesters to aldehydes with broad scope under mild reaction conditions.[122] In 2006, Chatani *et al*. reported the palladium catalyzed reduction of 2-pyridinyl esters (**3.1-11**) with hydrosilanes to aldehydes (**3.1-1**) (Schema 40).[123] Aliphatic, aromatic, and α,β-unsaturated aldehydes were prepared in moderate yields. The reaction conditions are compatible with various functional groups, such as fluoro, methoxy, aldehyde, acetal, and ester.

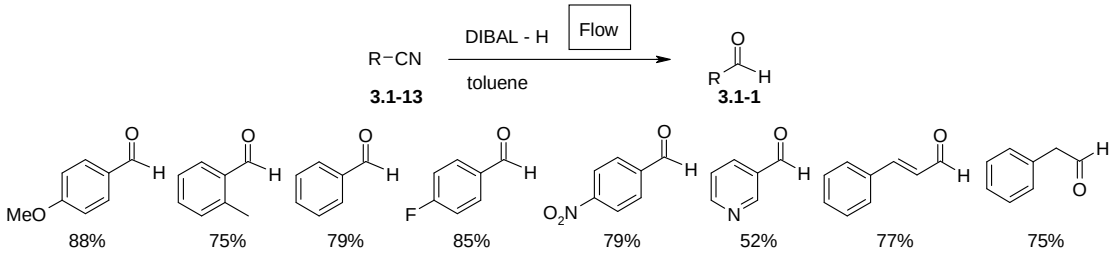


Schema 40. *Reduction of 2-pyridinylesters with hydrosilane*

The conversion of carboxylic acid anhydrides to aldehydes is not synthetically useful because of the harsh reaction conditions and lower yields.[124]

In comparison to the aforementioned methods, various protocols have been established for the partial reduction of nitriles followed by hydrolysis of the resulting imides.[125] Aluminum, silicon and boron based reducing agents have been successfully employed for the reduction of various aliphatic and aromatic nitriles.[126] In addition to these reducing agents, waste free and inexpensive hydrogen was also used for the reduction of nitriles to aldehydes.[127]

Recently, the reduction of nitriles (**3.1-13**) to aldehydes (**3.1-1**) was performed by using a continuous flow technology as an alternate to batch processes (Schema 41). High yields have been reported for aromatic, heteroarmatic and aliphatic aldehydes by using DIBAL-H as reducing agent.



Schema 41. *Reduction of nitriles to aldehydes in Flow*

A broad variety of reducing agents have been developed for the selective reduction of carboxylic acid derivatives to aldehydes. These reactions require an additional waste-producing step for the synthesis of carboxylic acid derivatives along with stoichiometric amounts of hygroscopic and

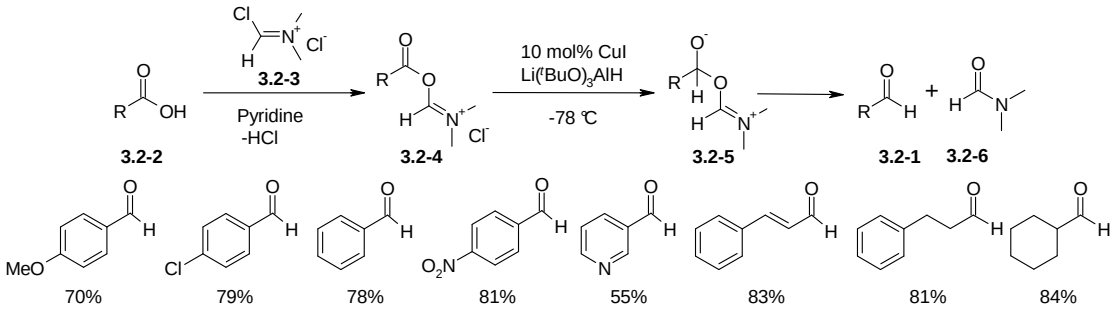
corrosive metal hydrides which are also associated with a large amount of waste production. Low temperatures are particularly required to avoid over-reduction of aldehydes to alcohols and reduction of other functional groups. Efficient methods for transition metal catalyzed selective reduction of carboxylic acid to aldehydes are rare. The development of new catalytic methods for the direct reduction of carboxylic acids to aldehydes by using atomic-economic and environmental friendly hydrogen gas as a reducing agent is a highly desirable transformation in organic synthetic chemistry.

3.2 Direct Reduction of Carboxylic Acids to Aldehydes

As mentioned before, the selective reduction of cheap and easily available carboxylic acids to aldehydes is a method of choice. However, these methods employ stoichiometric quantities of waste intensive reducing agents.

Initial reports on the direct reduction of carboxylic acids to aldehydes utilize lithium in amine solution[128] and sodium diisobutylaluminum hydride.[129] These reactions are restricted to aliphatic carboxylic acids and require a very low temperature. The reactions of both aliphatic and aromatic carboxylic acids with thexylborane produced high yields at a high temperature and required three equivalents of the reagent.[130] The reduction of carboxylic acids with borane dimethylsulfide followed by the oxidation of the resultant trialkoxyboroxine with pyridinium chlorochromate in dichloromethane provides a broadly applicable methodology.[131]

Fujisawa *et al*. proposed a simple and chemoselective method in which *N,N*-dimethylchloromethylenium chloride (**3.2-3**) and lithium tri-^{t}butoxyaluminum hydride were used respectively for the activation and the reduction of carboxylic acids (**3.2-2**) (Schema 42).[132]



Schema 42. *Fujisawa reduction of carboxylic acids to aldehydes*

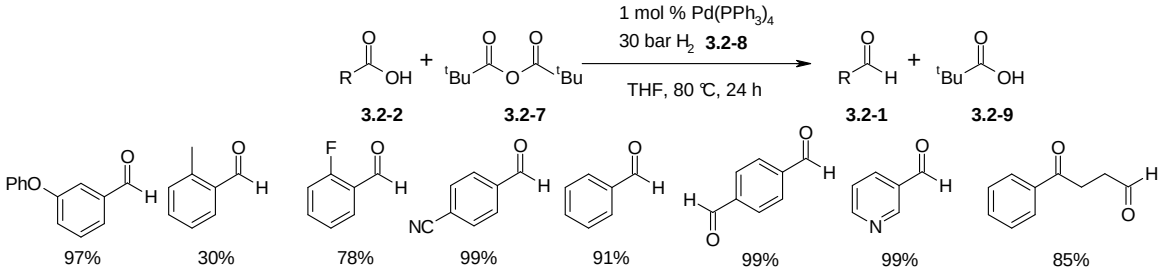
This method demonstrates that the activation of carboxylic acids can be achieved *in situ* for the partial reduction with other reducing agents.

3.2.1 Direct Hydrogenation of Carboxylic Acids to Aldehydes

The selective conversion of carboxylic acids to aldehydes with hydrogen is the most straight forward and sustainable transformation. However, the low reactivity of carboxylic acid function, harsh reaction conditions and overreduction of more reactive aldehydes is always problematic. Mitsubishi Chemicals selectively hydrogenated carboxylic acids to the corresponding aldehydes in the presence of chromia catalyst at 350 °C.[133] The reaction cannot be applied to thermally unstable aldehydes and laboratory scale synthesis due to high reaction temperature.

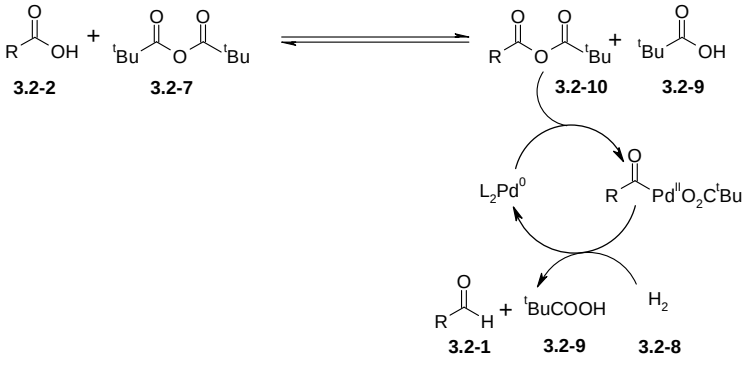
A major breakthrough in this field was achieved by Yamamoto *et al*. with the development of the first direct hydrogenation of carboxylic acids to aldehydes with molecular hydrogen under mild reaction conditions. The key to success of this reaction is the *in situ* activation of carboxylic acids with pivalic anhydride.

Aromatic, heteroromatic and aliphatic carboxylic acids (**3.2-2**) were successfully converted into the corresponding aldehydes (**3.2-1**) in the presence of pivalic anhydride (**3.2-7**) and 1 mol% $Pd(PPh_3)_4$ at 80 °C and 30 bar hydrogen pressure. Cyano, keto, ester, and alkene functional groups remain intact at the end of the reaction (Schema 43).



Schema 43. *Pd-catalyzed high pressure direct hydrogenation of carboxylic acids to aldehydes*

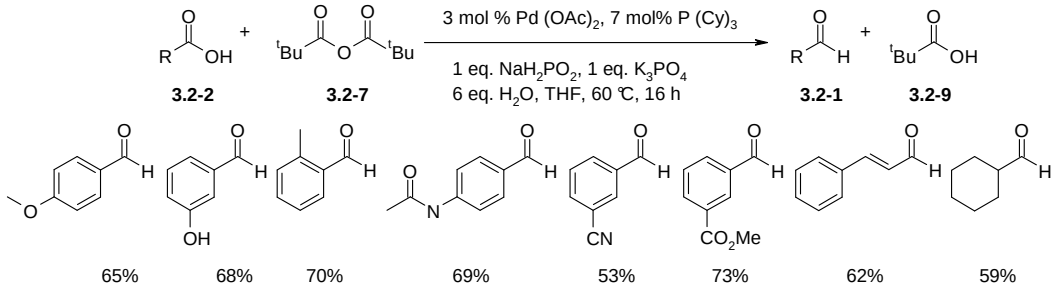
The reaction mechanism involves the oxidative addition of the Pd(0)(a) catalyst into the less hindered side of the mixed anhydrides to form acylpalladium (II) pivalate (b) due to the steric demand of the bulky *tert*-butyl group. The complex reacts with molecular hydrogen (**3.2-8**) to form aldehyde (**3.2-1**) and pivalic acid (**3.2-9**) (Schema 44).



Schema 44. *Proposed mechanism for Pd-catalyzed direct hydrogenation of carboxylic acids*

This elegant transformation could not gain the appropriate attention due to the moderate activity of the catalyst which requires high pressure of hydrogen for a good turnover. This transformation can only be performed in high pressure resistant equipment which is not very common in most preparative labs throughout academia and industry.

Palladium catalyzed direct reduction of carboxylic acids (**3.2-2**) to aldehydes (**3.2-1**) by using sodium hyophosphite as mild reducing agent is a pressure free alternate reported by Gooßen *et al*. In the presence of pivalic anhydride (**3.2-7**), 3 mol% $Pd(OAc)_2$, 7 mol% $P(Cy)_3$, 1 equivalent of NaH_2PO_2 and K_3PO_4, and 6 equivalent of H_2O, aromatic and aliphatic carboxylic acids were selectively reduced to aldehydes (**3.2-1**) at 60 °C in moderate yields (Schema 45).



Schema 45. *Reduction of carboxylic acids to aldehydes*

Although the alternate use of hypophosphite salts as mild reducing agents is more practical for lab-scale applications, the reaction is waste intensive and gives lower yields. Thus it is highly desirable to develop a new catalyst system that allows the direct hydrogenation of carboxylic acids to aldehydes under mild conditions and at or near ambient hydrogen-pressure.

3.3 Results and Discussions

3.3.1 Low-Pressure Hydrogenation of Arenecarboxylic Acids to Aryl Aldehydes

The development of a low pressure direct hydrogenation of arenecarboxylic acids to aryl aldehydes is described in the enclosed publication. It was a shared project between AK Gooßen and Boeringer Ingelheim, Austria. The work was performed in cooperation with Dipl. Chem. Thomas Fett who was an internee from Boeringer Ingelheim in our group for 3 months. The whole project was supervised by me.

The initial palladium catalyst system developed for the direct hydrogenation of carboxylic acids to aldehydes in the presence of pivalic anhydride requires high hydrogen pressure due to the moderate activity of the catalyst thus, limiting this protocol for only industrial scale applications. We addressed this problem by developing a 2nd generation of a highly effective palladium catalyst that allows the direct hydrogenation of carboxylic acids to aldehydes below 5 bar of

hydrogen pressure. Thus this transformation can be performed in both industrial hydrogenation reactors and laboratory scale glass autoclaves. The new catalyst system selectively transforms diversely functionalized carboxylic acids to corresponding aldehydes at 80 °C.

These results were published in 2010 in *Advanced Synthesis & Catalysis*, **2010**, *352*, 2166-2170. A copy of the manuscript is provided.

DOI: 10.1002/adsc.201000418

Low-Pressure Hydrogenation of Arenecarboxylic Acids to Aryl Aldehydes

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Received: May 28, 2010; Published online: September 7, 2010

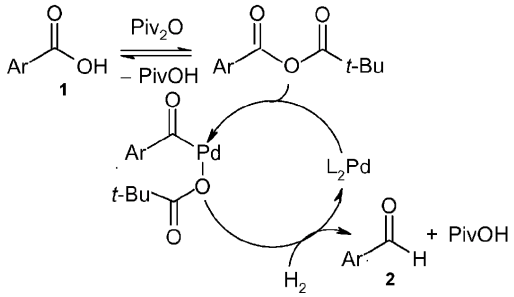
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000418.

Abstract: A highly effective palladium catalyst has been developed that allows the selective hydrogenation of arenecarboxylic acids to the aryl aldehydes in the presence of pivalic anhydride already at 5 bar hydrogen pressure. With the new catalyst, diversely functionalized aromatic and heteroaromatic aldehydes are conveniently accessible from the corresponding carboxylic acids in a single reaction step without any overreduction to the alcohols.

Keywords: aldehydes; carboxylic acids; catalysis; hydrogenation; palladium

The conversion of carboxylic acid derivatives into aldehydes is a frequently used transformation in organic synthesis.[1] It is usually performed using stoichiometric amounts of metal- or metal hydride-based reducing agents.[2,3,4] However, most protocols involve an additional reaction step for the preparation of activated carboxylic acid derivatives. Also, unwanted side reactions, such as the overreduction to alcohols and the reduction of other functional groups, are notoriously hard to suppress. The transition metal-catalyzed hydrogenation of acid chlorides (Rosenmund reduction)[5] is more atom-economic, but overreduction to the alcohols can be avoided only with elaborate flow-through reaction layouts, which are impractical for small-scale syntheses. This is why many chemists still prefer to first reduce the carboxylic acids all the way to the alcohols, and then to selectively reoxidize them to the aldehydes using Swern-type reactions.

A new concept for the direct reduction of carboxylic acids to aldehydes was introduced by Yamamoto et al.[6] In his single-step protocol the carboxylic acids are activated *in situ* by treatment with pivalic anhydride. The resulting equilibrium mixture of anhydrides undergoes a palladium-catalyzed hydrogenation to give the aldehydes along with pivalic acid (Scheme 1). The reaction mechanism involves an oxidative addition of the mixed anhydrides to the Pd(0) center.[7] The high steric demand of the *tert*-butyl group dictates the regiochemistry of this step, so that the acylpalladium(II) pivalate is almost exclusively formed. This complex reacts with molecular hydrogen to liberate the aldehyde along with pivalic acid.



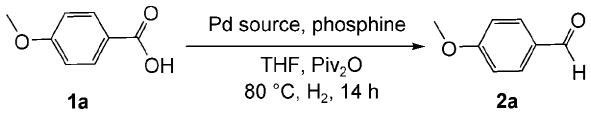
Scheme 1. Hydrogenation of arenecarboxylic acids.

In the original protocol, palladium complexes of PPh_3 and other triarylphosphines were employed as catalyst. However, they are only moderately active, so that high hydrogen pressures of at least 30 bar are necessary for good turnover. The Yamamoto aldehyde synthesis thus requires high-pressure equipment, which is unavailable in many preparative labs throughout industry and academia. This may be the main reason why this elegant transformation has so far found surprisingly little application in organic synthesis. The alternative use of hypophosphite salts as reducing agents is more practical for lab-scale applications, but waste-intensive and usually gives lower yields.[8]

There clearly remained a need for a new generation of more active Pd catalysts that would allow performance of the Yamamoto aldehyde synthesis below 10 bar hydrogen pressures which can be reached with laboratory-scale hydrogenation equipment and industrial-multi purpose reactors.

We began our search for a more active catalyst by studying the hydrogenation of 4-methoxybenzoic acid (**1a**) in the presence of pivalic anhydride and 1 mol% of various palladium catalysts in THF. The model system was chosen based on the fact that this electron-rich benzoic acid is of particularly low reactivity. Using Yamamoto's conditions [$Pd(OAc)_2$/PPh_3, 30 bar H_2], 4-methoxybenzaldehyde (**2a**) was formed only in low yield (Table 1, entry 1). At a reduced H_2 pressure of 15 bar, the activity of this catalyst was unsatisfactory. However, a systematic investigation of various phosphine ligands revealed that with a more electron-rich triarylphosphine, moderate yields are achieved even at this reduced pressure (entries 2 and 3). Sterically demanding, electron-rich trialkylphosphines such as PCy_3 and some of Buchwald's dicyclohexylbiarylphosphines gave even better results (entries 4–9). Full conversion of the carboxylic acid and high yields of the aldehyde were finally achieved with dicyclohexylphenylphosphine, a ligand seldom used in palladium catalysis (entry 10).

Table 1. Optimization of the catalyst system.[a]



Entry	Pd source	Phosphine	H_2 [bar]	**2a** [%]
1	$Pd(OAc)_2$	PPh_3	30	12
2	$Pd(OAc)_2$	P(*p*-MeOPh)$_3$	15	33
3	$Pd(OAc)_2$	P(*p*-tol)$_3$	15	52
4	$Pd(OAc)_2$	SPhos	15	57
5	$Pd(OAc)_2$	XPhos	15	70
6	$Pd(OAc)_2$	DavePhos	15	72
7	$Pd(OAc)_2$	JohnPhos	15	89
8	$Pd(OAc)_2$	PCy_3	15	90
9	$Pd(OAc)_2$	CyJohnPhos	15	93
10	$Pd(OAc)_2$	$PPhCy_2$	15	99
11	$Pd(OAc)_2$	$PPhCy_2$	5	89
12	$Pd(CN)_2$	$PPhCy_2$	5	0
13	$Pd(dba)_2$	$PPhCy_2$	5	64
14	$Pd(F_6\text{-acac})_2$	$PPhCy_2$	5	80
15	$Pd(TFA)_2$	$PPhCy_2$	5	80
16	$Pd(acac)_2$	$PPhCy_2$	5	91
17[b]	$Pd(acac)_2$	$PPhCy_2$	5	87
18[c]	$Pd(acac)_2$	$PPhCy_2$	5	92
19[d]	$Pd(acac)_2$	$PPhCy_2$	1	73

[a] *Reaction conditions:* 1.00 mmol **1a**, 3.00 mmol pivalic anhydride, 1 mol% Pd source, 5 mol% phosphine, 2 mL THF, 80 °C, 14 h. Yields determined by HPLC analysis using propiophenone as internal standard.
[b] 60 °C.
[c] Acetone as solvent.
[d] 3 mol% of $Pd(acac)_2$, 15 mol% of dicyclohexylphenylphosphine, DMF, 50 h.

With dicyclohexylphenylphosphine, the model reaction proceeded well even when reducing the hydrogen pressure to 5 bar. At this low pressure, several Pd precursors were tested (entries 12–16). The best yields were achieved with palladium acetylacetonate, but other Pd(II) salts or Pd(0) precursors can be used as well. A slightly lower conversion to **2a** was observed when reducing the reaction temperature to 60 °C (entry 17). Several other solvents were tested as a replacement for THF. We were pleased to find that not only DMF, but also non-toxic acetone (entry 18) and diethyl ketone were effective solvents. With toluene and acetonitrile, inferior results were obtained.

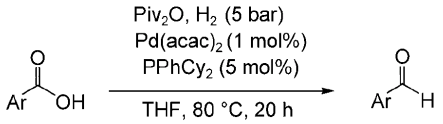
Under the optimal conditions, using 1 mol% of $Pd(acac)_2$, 5 mol% of dicyclohexylphenylphosphine, acetone (2 mL), pivalic anhydride (3 equiv.), 80 °C, 20 h, 4-methoxybenzoic acid was smoothly converted to the corresponding aldehyde in 92% yield at a hydrogen pressure of only 5 bar. In this screening, the catalyst and ligand, although expensive, were used in 1 and 5 mol% loadings, respectively, to ensure good conversion of a range of substrates. On these small scales, further reduction of the catalyst loading resulted in decreased yields.

The reactions can thus be carried out using a standard hydrogenation reactor, for example, a glass autoclave. Most industrial reactors are also certified for pressures of up to 5 bar. The new catalyst system is active even at ambient pressures: With an increased catalysts loading of 3 mol% and using DMF as a more high-boiling solvent, 73% yield was reached.

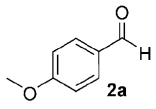
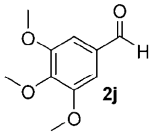
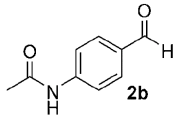
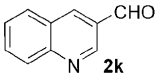
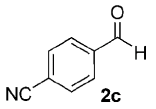
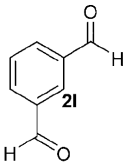
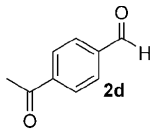
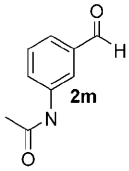
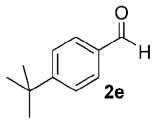
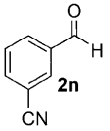
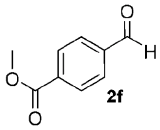
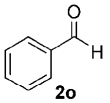
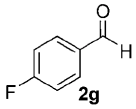
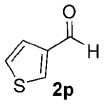
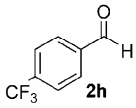
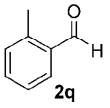
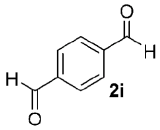
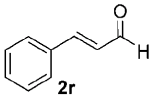
Having thus established a reliable low-pressure protocol for the Yamamoto aldehyde synthesis, we next tested its generality by applying it to the hydrogenation of various carboxylic acids. As can be seen from Table 2, the new catalyst allows the smooth conversion of aromatic and heteroaromatic carboxylic acids. In particular, *para*-, *meta*- and *ortho*-substituted benzoic acids reacted equally well. Five-ring heterocycles, quinolines and terephthalic acid were also hydrogenated in high yields. Many functional groups are tolerated: Carboxylic acids containing alkoxy, keto, cyano, protected amino, and even ester groups were successfully converted without competing reduction of double bonds or of functional groups.

In conclusion, the new catalyst system, generated *in situ* from $Pd(acac)_2$ and dicyclohexylphenylphosphine, allows the selective hydrogenation of arenecarboxylic acids to aryl aldehydes already at low hydrogen pressures. The new protocol is convenient for applications on both laboratory and industrial scales, and might convince organic chemists to add the Yamamoto aldehyde synthesis to their chemical toolbox.

Table 2. Hydrogenation of arenecarboxylic acids **1**.[a]



1a – r 2a – r

Product	Yield [%]	Product	Yield [%]
 2a	91	 2j	89
 2b	91	 2k	74
 2c	75	 2l	42
 2d	92	 2m	92
 2e	80	 2n	75
 2f	80	 2o	79
 2g	80	 2p	70
 2h	80	 2q	88
 2i	85	 2r	81[b]

[a] *Reaction conditions:* 1.00 mmol of benzoic acid **1**, 1 mol% $Pd(acac)_2$, 5 mol% dicyclohexylphenylphosphine, pivalic anhydride (3 equiv.), THF (2 mL), 80 °C, H_2 (5 bar), 20 h.

[b] HPLC yields.

Experimental Section

General Procedure for the Synthesis and Characterization of the Aldehydes (1a–r)

An oven-dried, argon-flushed 10-mL glass vessel with septum top was charged with benzoic acid **1a–r** (1.00 mmol), $Pd(acac)_2$ (3.05 mg, 0.01 mmol), and dicyclohexylphenylphosphine (13.7 mg, 0.05 mmol). Degassed THF (2 mL) and degassed pivalic anhydride (0.62 mL, 3.00 mmol) were added. The vessel was placed in a steel autoclave, which was then purged with hydrogen and then pressurized with 5 bar of hydrogen. The reaction mixture was stirred at 80 °C for 20 h, then cooled to room temperature. The autoclave pressure was released, the reaction mixture diluted with 10 mL saturated $NaHCO_3$ solution and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$, filtered, and the volatiles were removed under vacuum. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient) yielding the corresponding aldehydes.

The particularly volatile aldehydes **2a**, **e**, **g**, **h**, **o**, **p**, and **q** were isolated as bisulfite adducts: after releasing the pressue from the autoclaves, 38% sodium bisulfite solution (1.50 mL, 8.10 mmol) was added *via* syringe to the reaction vessel. The residue mixture was stirred at 50 °C for 4 h, then cooled to room temperature. The white crystalline adducts were filtered off and washed with chloroform (10 mL) and water (0.50 mL), dried under vacuum, and weighed to determine the yield. For the spectroscopic characterization, part of the aldehydes was then liberated by adding the adduct to saturated aqueous $NaHCO_3$ solution (2.0 mL), followed by extraction with $CDCL_3$ (2.0 mL). The NMR samples were then washed with water and brine, dried over $MgSO_4$ and filtered.

4-Methoxybenzaldehyde (2a): Compound **2a** was prepared from 4-methoxybenzoic acid (**1a**) (152 mg, 1.00 mmol) affording **2a** as a colorless oil; yield: 124.9 mg (90.8%). The spectroscopic data matched those reported in the literature for 4-methoxybenzaldehyde [CAS: 123-11-5].

4-Acetamidobenzaldehyde (2b): Compound **2b** was prepared from 4-acetamidobenzoic acid (**1b**) (179 mg, 1.00 mmol) affording **2b** as a colorless crystalline solid; yield: 149 mg (91%). The spectroscopic data (NMR) matched those reported in the literature for 4-acetamidobenzaldehyde [CAS: 122-85-0].

4-Cyanobenzaldehyde (2c): Compound **2c** was prepared from 4-cyanobenzoic acid (**1c**) (149 mg, 1.00 mmol) affording **2c** as a colorless crystalline solid; yield: 98.6 mg (75%). The spectroscopic data (NMR) matched those reported in the literature for 4-cyanobenzaldehyde [CAS: 105-07-7].

4-Acetylbenzaldehyde (2d): Compound **2d** was prepared from 4-acetylbenzoic acid (**1d**) (164 mg, 1.00 mmol) affording **2d** as a colorless crystalline solid; yield: 137 mg (92%). The spectroscopic data (NMR) matched those reported in the literature for 4-acetylbenzaldehyde [CAS: 3457-45-2].

4-*tert*-Butylbenzaldehyde (2e): Compound **2e** was prepared from 4-*tert*-butylbenzoic acid (**1e**) (180 mg, 1.00 mmol) affording **2e** as a colorless oil; yield: 123 mg (75.8%). The spectroscopic data (NMR) matched those reported in the literature for 4-*tert*-butylbenzaldehyde [CAS: 939-97-9].

4-Methoxycarbonylbenzaldehyde (2f): Compound **2f** was prepared from 4-methoxycarbonylbenzoic acid (**1f**) (180 mg, 1.00 mmol) affording **2f** as a colorless crystalline solid; yield: 132 mg (80%). The spectroscopic data (NMR) matched those reported in the literature for 4-methoxycarbonylbenzaldehyde [CAS: 1571-08-0].

4-Fluorobenzaldehyde (2g): Compound **2g** was prepared from 4-fluorobenzoic acid (**1g**) (143.0 mg, 1.00 mmol) affording **2g** as a colorless oil; yield: 90 mg (80%). The spectroscopic data (NMR) matched those reported in the literature for 4-fluorobenzaldehyde [CAS: 459-57-4].

4-(Trifluoromethyl)benzaldehyde (2h): Compound **2h** was prepared from 4-(trifluoromethyl)benzoic acid (**1h**) (190 mg, 1.00 mmol) affording **2h** as a colorless oil; yield: 139 mg (80%). The spectroscopic data (NMR) matched those reported in the literature for 4-(trifluoromethyl)benzaldehyde [CAS: 455-19-6].

1,4-Benzenedicarboxaldehyde (2i): Compound **2i** was prepared from 1,4-benzenedicarboxalic acid (**1i**) (166 mg, 1.00 mmol) affording **2i** as a colorless crystalline solid; yield: 114 mg (85%). The spectroscopic data (NMR) matched those reported in the literature for 1,4-benzenedicarboxaldehyde [CAS: 623-27-8].

3,4,5-Trimethoxybenzaldehyde (2j): Compound **2j** was prepared from 3,4,5-trimethoxybenzoic acid (**1j**) (212 mg, 1.00 mmol) affording **2j** as a colorless crystalline solid; yield: 174 mg (75.8%). The spectroscopic data (NMR) matched those reported in the literature for 3,4,5-trimethoxybenzaldehyde [CAS: 86-81-7].

3-Quinolinecarboxaldehyde (2k): Compound **2k** was prepared from 3-quinolinecarboxylic acid (**1k**) (177 mg, 1.00 mmol) affording **2k** as a colorless crystalline solid; yield: 102 mg (78%). The spectroscopic data (NMR) matched those reported in the literature for 3-quinolinecarboxaldehyde [CAS: 13669-42-6].

1,3-Benzenedicarboxaldehyde (2l): Compound **2l** was prepared from 1,3-benzenedicarboxylic acid (**1l**) (166 mg, 1.00 mmol) affording **2l** as colorless crystals; yield: 56.0 mg (42%). The spectroscopic data (NMR) matched those reported in the literature for 1,3-benzenedicarboxaldehyde [CAS: 626-19-7].

3-Acetamidobenzaldehyde (2m): Compound **2m** was prepared from 3-acetamidobenzoic acid (**1m**) (179 mg, 1.00 mmol) affording **2m** as a colorless crystalline solid; yield: 150 mg (92%). The spectroscopic data (NMR) matched those reported in the literature for 3-acetamidobenzaldehyde [CAS: 59755-25-8].

3-Cyanobenzaldehyde (2n): Compound **2n** was prepared from 3-cyanobenzoic acid (**1n**) (150 mg, 1.00 mmol) affording **2n** as colorless crystals; yield: 102 mg (78%). The spectroscopic data (NMR) matched those reported in the literature for 3-cyanobenzaldehyde [CAS: 24964-64-5].

Benzaldehyde (2o): Compound **2o** was prepared from benzoic acid (**1o**) (122 mg, 1.00 mmol) affording **2o** as colorless oil; yield: 84.0 mg (79%). The spectroscopic data (NMR) matched those reported in the literature for benzaldehyde [CAS: 100-52-7].

3-Thiophenecarboxaldehyde (2p): Compound **2p** was prepared from 3-thiophenecarboxylic acid (**1p**) (128 mg, 1.00 mmol) affording **2p** as a colorless oil; yield: 79.0 mg (70%). The spectroscopic data (NMR) matched those reported in the literature for 3-thiophenecarboxaldehyde [CAS: 498-62-4].

2-Methylbenzaldehyde (2q): Compound **2q** was prepared from 2-methylbenzoicacid (**1q**) (138 mg, 1.00 mmol) affording **2q** as a colorless oil; yield: 106.0 mg (88%). The spectroscopic data (NMR) matched those reported in the literature for 2-methylbenzaldehyde [CAS: 529-20-4].

(2*E*)-3-Phenylprop-2-enal (2r): Compound **2r** [CAS: 16939-04-1] was prepared from (*E*)-3-phenylprop-2-enoic acid (**1r**) (148 mg, 1.00 mmol). Unfortunately, the adduct formation did not take place. Therefore, the identity of the product **2r** was confirmed by GC-MS and the yield determined by quantative HPLC to be 81% based on a response factor obtained with commercial (2*E*)-3-phenylprop-2-enal (**2r**) [CAS: 104-55-2] using propiophenone (25 μL) as an internal HPLC standard.

Preparative-Scale Synthesis of 4-Acetamidobenzaldehyde: A 300-mL hydrogenation reactor was charged with 4-acetamidobenzoic acid (**1a**) (5.00 mmol, 896 mg), $Pd(acac)_2$ (15.2 mg, 0.05 mmol) and dicyclohexylphenylphosphine (72.2 mg, 0.25 mmol). THF (15.0 mL) and pivalic anhydride (3.0 mL, 15.0 mmol) were added *via* syringe. The autoclave was purged with hydrogen and then pressurized with 5 bar of hydrogen. The reaction was stirred at 80 °C for 20 h, then cooled to room temperature. The pressure was released, the reaction mixture diluted with saturated $NaHCO_3$ solution (25 mL) and extracted with ethyl acetate (3×25.0 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the volatiles were removed under vacuum. The residue was taken up in of diethyl ether (10 mL) causing the product 4-acetamidobenzaldehyde (**2b**) to precipitate in spectroscopically pure form; yield: 584 mg (71%).

Acknowledgements

We thank HEC Pakistan for a scholarship to B.A.K.

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3.4 Summary and Outlook

A second generation of palladium catalyst has been developed that allows the selective conversion of carboxylic acids to the corresponding aldehydes. The activation of the carboxylic acids is achieved *in situ* in the presence of pivalic anhydride and hydrogenated at 5 bar of hydrogen pressure with a catalyst system generated from $Pd(acac)_2$ and dicyclohexylphenylphosphine. Model substrate was also hydrogenated at 1 bar hydrogen pressure by using higher loading of the catalyst and high boiling solvent. Under the optimized reaction conditions, diversely functionalized aromatic, aliphatic and heterocyclic carboxylic acids were hydrogenated to the corresponding aldehydes in excellent yields. The reaction conditions are mild enough that various functional groups are tolerated such as amide, cyano, ester, keto and ether.

Hence, it is convenient for applications on both laboratory and industrial scale applications. The use of low hydrogen pressure might also convince organic chemists to add Yamamoto aldehyde synthesis to their chemical toolbox.

In future prospects, selective conversion of carboxylic acids to aldehydes by using continuous flow-through technology at ambient hydrogen pressure will be an excellent development in this area.

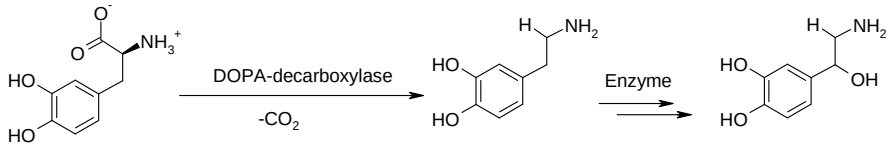
4 Synthesis of Arenes from Carboxylic Acids

4.1 Protodecarboxylations

Protodecarboxylations are important transformations in synthetic organic chemistry and biology.[134] They are used to remove groups that had been employed as directing groups in proceeding routes.[135] It is also the simplest case of catalytic surplus carboxylate activation of free carboxylic acids or their salts.

In nature, protodecarboxylations play an important role in many metabolic pathways and is often chosen to fascilitate a thermodynamically unfavoured transformation. The formal extrusion of CO_2 is catalyzed by enzymes. Some examples of biological protodecarboxylations are illustrated in the following paragraphs.

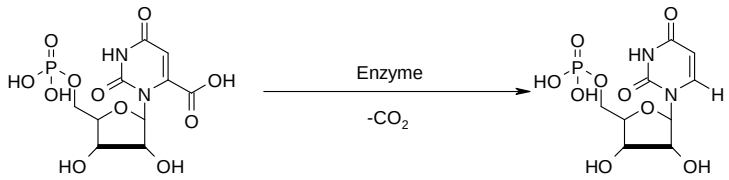
One example is the enzymatic decarboxylation of amino acid L-DOPA (**4.1-1**) in the living organisms to biogenic amines dopamine (**4.1-2**). In addition to their physiological effects as neurotransmitters, biogenic amines are often used as precursors for alkaloids such as adrenaline (**4.1-3**) and hormones (Schema 46). Furthermore, they also serve as building blocks for the synthesis of coenzymes and vitamins. [136]



4.1-1 **4.1-2** **4.1-3**

Schema 46. *Biosynthesis of adrenaline*

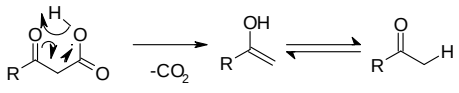
Another example occurring in all living organisms is the decarboxylation of orotidine 5'-monophosphate (OMP) (**4.1-4**) to uridine monophosphate (UMP) (**4.1-5**) with the help of enzyme orotidylate decarboxylase (Schema 47). The OMP is the last intermediate in the biosynthesis of pyrimidine.[137] Studies on the non-catalyzed decarboxylation of orotic acid in pressure vessels at elevated temperatures showed that the decarboxylation under physiological conditions proceeds extremely slowly with a half-life of 78 million years. The decarboxylation enzyme, OMP decarboxylase accelerates the reaction to complete within milliseconds.[137b]



OMP **4.1-4** UMP **4.1-5**

Schema 47. *Enzymetic decarboxylation of OMP*

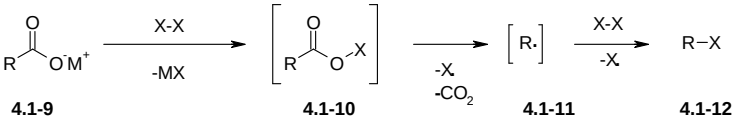
The success of the protodecarboxylations in organic chemistry is highly dependent on the reactivity of the carboxyl group. Some activated carboxylic acids (**4.1-6**) readily undergo thermal decarboxylation at moderate temperature for example, β-oxoacids and 1, 3-dicarboxylic acids decarboxylate via cyclic 6-membered transition state to enol-form (**4.1-7**) which readily tautomerize to more stable keto-form (**4.1–8**) (Schema 48).[138]



4.1-6 **4.1-7** **4.1-8**

Schema 48. *Thermal decarboxylation of β-oxocarboxylic acids*

Aliphatic carboxylic acids follow a radical mechanism or decarboxylate under oxidative conditions. Borodin and Hunsdieker developed various protocols that allow the radical decarboxylation of potassium, silver, mercury, thalium salts of aliphatic, vinylic and certain aromatic carboxylic acid salts (**4.1-9**) in the presence of dihalogens to give alkyl halides (**4.1-12**) (Schema 49).[139]

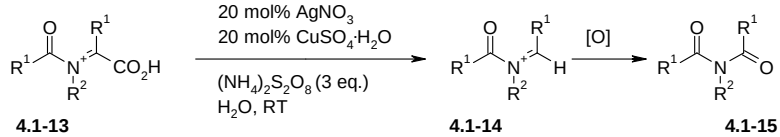


4.1-9 **4.1-10** **4.1-11** **4.1-12**

$M^+ = K^+, Ag^+, Hg^+, Tl^+$
X = Cl, Br, I
R = primary, secondary, tertiary alkyl
alkenyl, deactivated aryl

Schema 49. *The Hunsdieker-Borodin reaction*

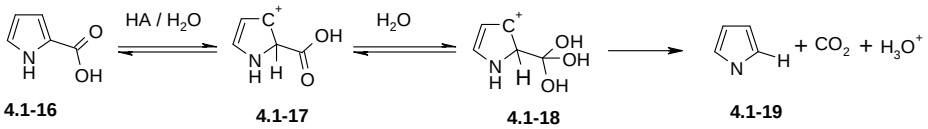
Oxidative decarboxylation of aliphatic carboxylic acids (**4.1-13**) takes place at lower temperature (60-90 °C) in the presence of peroxodisulfate.[140] Protected amino acids selectively decarboxylate under oxidative conditions to acylimines (**4.1-14**) which produce amides on further oxidation (**4.1-15**) (Schema 50).



4.1-13 **4.1-14** **4.1-15**

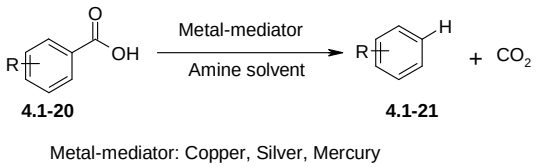
Schema 50. *Oxidative decarboxylation of amino acids*

Decarboxylation of aromatic carboxylic acids takes place in the presence of acids or metal catalysts. Acid catalyzed decarboxylation of five membered heteroaromatic carboxylic acids (**4.1-16**) occurs via an associative mechanism (Schema 51).[141] The downside of the metal-free protodecarboxylations is that they could not be used for coupling reactions as they do not proceed via organometallic intermediates.



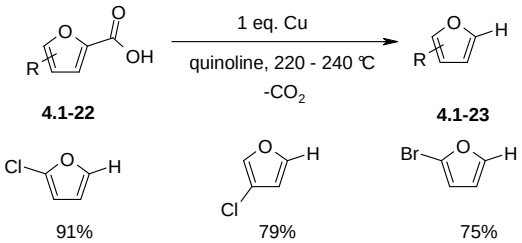
Schema 51. *Acid catalyzed decarboxylation of pyrrole-2-carboxylic acids*

The pioneering work of Shepard, Cohen and Nilsson demonstrates that aromatic carboxylic acids (**4.1-20**) liberate CO_2 in the presence of transition metal catalysts such as silver,[52] copper[51] or mercury[53] to form aryl metal species which is protonolyzed to the corresponding arenes (**4.1-21**) (Schema 52). The formation of nucleophilic aryl-metal intermediate makes this reaction highly valuable for employment of the organometallic species as C-nucleophile in catalytic C-C or C-heteroatom bond formation. Thus, the investigations on the nature of the decarboxylation reactions are of great importance for the development of novel, waste minimized catalytic processes.



Schema 52. *Metal-mediated protodecarboxylation of benzoic acids*

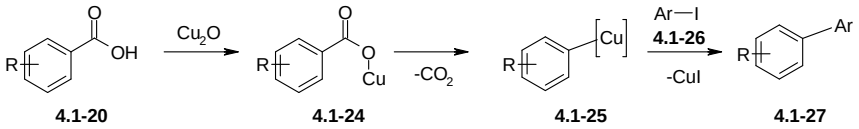
Shepard *et al*. discovered that halogenated furancarboxylic acids (**4.1-22**) decarboxylate in the presence of stoichiometric amounts of copper or copper salts at high temperature (Schema 53). The use of quinoline as a solvent and base is proved to be extremely beneficial for the trapping of HCl which is generated as a result of pyrolysis of the halogenated furan.[51a]



Schema 53. *Copper promoted decarboxylation of furan carboxylic acids*

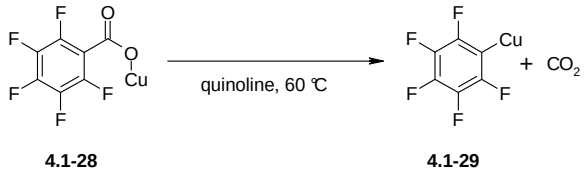
Nilsson *et al*. examined the protodecarboxylation of reactive, aromatic carboxylic acids (**4.1-20**) in the presence of 30-60 mol% copper(I) oxide in refluxing quinoline (Schema 54).[50, 142] *Ortho*-nitrobenzoic acid and heteroaromatic carboxylic acids such as furan and thiophene carboxylic

acids undergo fast decarboxylation. The authors were able to trap the intermediate from such reactions with aryl iodides.



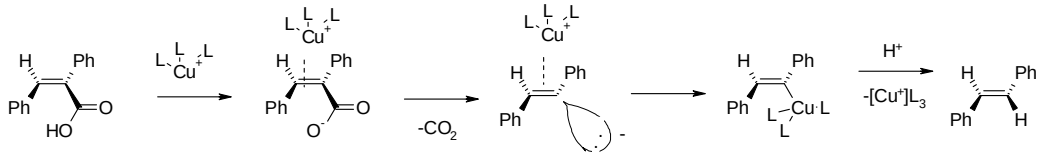
Schema 54. *First trapping of aryl copper intermediate*

Sheppard *et al*. confirmed this fact by isolating organometallic specie generated by decarboxylation of previously synthesized copper-carboxylate.[51d] It was described that copper pentafluorobenzoate (**4.1-28**) generates a relatively stable pentafluorophenylcopper complex (**4.1-29**) in quinoline at 60 °C via decarboxylation (Schema 55).



Schema 55. *Decarboxylation of copper carboxylate*

Cohen *et al*. investigated the mechanism of Cu^{I}-mediated decarboxylation of cis-or trans-2, 3-diphenylpropencarboxylic acid (**4.1-30**) by heating in the presence of Cu-salt. The products possessed the same configurations and thus demonstrate that the reaction proceeds via an aryl species (Schema 56).[51e,f] The authors suggest that the copper center first coordinates to the C-C double bond (a) and then intrudes into the C-C (O) bond under extrusion of carbon dioxide. The negative charge on the vinylic carbon (b) is stabilized by copper as in (c). The use of chelating nitrogen ligands for example, 1, 10-phenanthroline or 2, 2`-bipyridine led to further stabilization of π-complex and thus enhancing the rate of the decarboxylation.



Schema 56. *Cu-mediated decarboxylation of vinyl carboxylic acids*

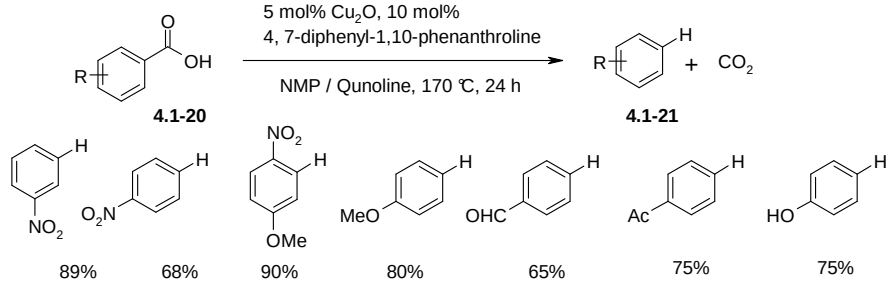
Transition metal-mediated protodecarboxylations were restricted to only activated derivatives such as benzoic acids with electron-withdrawing *ortho*-substituents, phenyl or diphenyl acetic acids and heteroarene carboxylic acids. Only highly activated carboxylic acid derivatives such as malonic acids were decarboxylated with catalytic amount of copper.[143] As the decarboxlative step plays a key role in decarboxylative coupling reactions, different transiton-metal based catalyst systems have been developed to expand the scope of carboxylic acids from activated carboxylic acids to all range of aromatic carboxylic acids at lower temperature.

Heterogeneous Pd/C catalyzed protodecarboxylation of some carboxylic acids under hydrothermal conditions (250 °C/4MPa) was used for the preparation of deuterium-labeled compounds.[144] Homogeneous palladium catalysts also promote the decarboxylation of some special electron-rich aromatic carboxylic acids such as *o, o*-disubstituted benzoic acids (**4.1-35**) at even lower temperature.[55] However, the protocol is limited to only *o, o*-disubstituted electron rich substrates in the presence of 20 mol% of $Pd(CF_3CO_2)_2$ and 10 equivalent of trifluoroacetic acid (Schema 57). Restricted scope and higher loadings of the expensive palladium catalyst limit the synthetic utility of this protocol.

4.1-35 **4.1-36**

Schema 57. *Pd-catalyzed protodecarboxylations*

The copper based catalyst system developed in our group possesses a vast substrate scope. Not only the *ortho* substituted but also *meta* and *para* substituted benzoic acids are protodecarboxylated in high yields. The highly effective catalyst system is generated from 5 mol% of Cu_2O and 10 mol% 4, 7-diphenyl-1,10-phenanthroline in a mixture of N-methyl pyrrolidone (NMP) and quinoline (Schema 58).[145] The limitations of this protocol include the use of expensive ligand, thermal stress for long reaction time (170 °C, 24 h) and loss of volatile arenes (**4.1-21**) with the release of CO_2.

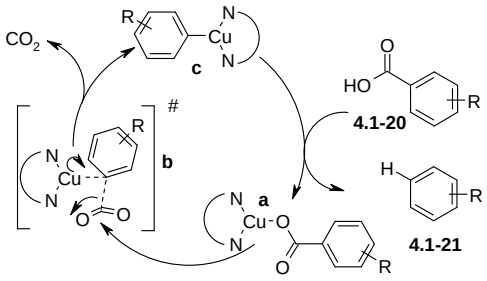


4.1-20 **4.1-21**

89% 68% 90% 80% 65% 75% 75%

Schema 58. *Cu-catalyzed protodecarboxylation*

The proposed mechanism for the copper catalyzed protodecarboxylations involes the formation of a copper carboxylate (a) by an acid-base reaction between aromatic carboxylic acid and ligand-stabilized copper(I) oxide. Decarboxylation via transition state (b) gives organometallic species (c) which produces desired protonated product after acidic work up (Schema 59). DFT calculations show that nitro and methoxy groups at *ortho* position inhance the decarboxylation by short-range inductive effects transmitted via the σ-backbone.



Schema 59. *Proposed mechanism for Cu-catalyzed protodecarboxylation*

Only two catalytic methods are known for the decarboxylation of arene carboxylic acids. Low temperature palladium catalyzed protocol is limited to only activated substrates. Whereas, the high temperature copper catalyzed protocol is more general and applicable in decarboxylative coupling reactions. However, the substituted benzoic acids are subjected to thermal stress for long reaction time and volatile products are carried off by the release of CO_2. In addition, the expensive ligand was employed.

4.2 Results and Discussions

4.2.1 Use of Modern Technology for Protodecarboxylations

The modern microwave technology is an appropriate tool for the development of the protodecarboxylations in a controlled fashion as it provides the opportunity to carry out the protodecarboxylation reactions in small, sealed vessels certified for pressure reactions. The CO_2 is kept within the reaction vessel until the end of the reaction and released slowly after cooling the reaction vessel to room temperature so that no volatile product is lost. Thus, the reactions are more reproducible than conventional method. The reaction progress can be monitored by the buildup of the carbon dioxide gas on the pressure sensor. The efficient heating provided by the microwaves increases the rate of the reaction at a slightly higher temperature so that the reaction is completed within 5-15 min.

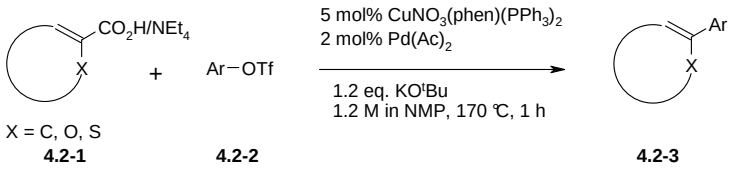
Hence, microwave radiation is a useful alternate to conventional heating for protodecarboxylation reactions as it provides high yields and more reproducibility in short reaction time.

4.2.2 Microwave-Assisted Cu-Catalyzed Protodecarboxylation of Arenecarboxylic Acids

In the enclosed publication, the development of a concise microwave assisted protodecarboxylation reaction is demonstrated in the presence of Cu^{I}/1,10-phenanthroline catalyst. Various bezoic acids and heterocyclic carboxylic acids have been converted into the corresponding arenes in high yields. The catalyst system is generated *in situ* from 1-5 mol%

Cu_2O and 2-10 mol% 1,10-phenanthroline in NMP/quinoline at 190 °C. The reaction is complete within only 5-15 min. The reaction temperature is achieved within only two mins due to the effective microwave radiation. Sealed tubes are used to avoid the loss of volatile products with the delayed and slow release of CO_2 at room temperature. The use of inexpensive 1,10-phenanthroline reduces the cost of the transformation.

This is a fundamental protocol for all the follow up microwave and flow through transformations of carboxylic acids.[63] Decarboxylative coupling of aryl carboxylates (**4.2-1**) with aryl triflates (**4.1-2**) in continuous flow represents an example demonstrated below (Schema 60).[146]



Schema 60. *Decarboxylative coupling in flow*

The project was performed in the supervision of Dr. Rodríguez. All screening experiments were performed together with Mr. Manjolinho. I isolated the scope compounds following method B, whereas Mr. Manjolinho isolated scope compounds following method A.

These results were published in 2009 in *Journal of Organic Chemistry*, **2009**, *74*, 2620-2623. A copy of the manuscript is provided. Reprinted (adapted) with permission from (*J. Org. Chem.* **2009**, *74*, 2620-2623). Copyright (2012) American Chemical Society.

JOC*Note*

Microwave-Assisted Cu-Catalyzed Protodecarboxylation of Aromatic Carboxylic Acids

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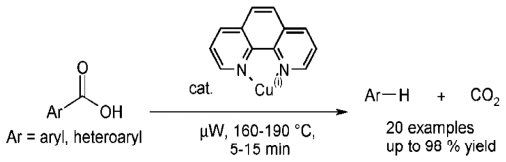
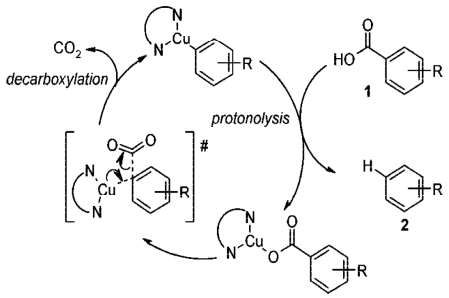
Received December 18, 2008



An effective protocol has been developed that allows the smooth protodecarboxylation of diversely functionalized aromatic carboxylic acids within 5−15 min. In the presence of at most 5 mol % of an inexpensive catalyst generated in situ from copper(I) oxide and 1,10-phenanthroline, even nonactivated benzoates were converted in high yields and with great preparative ease.

Decarboxylation reactions are useful for the removal of surplus carboxylate groups, which may arise from the use of highly functionalized natural product starting materials or may be left behind as a result of ring-closure reactions of oxocarboxylate intermediates.[1,2] While highly activated carboxylic acids, e.g., β-oxo acids, diphenylacetic acids, or polyfluorinated benzoic acids, decarboxylate reasonably easily even in the absence of a catalyst,[3] the release of CO_2 from simple aromatic carboxylic acids is much harder to accomplish. The use of copper as a stoichiometric mediator was disclosed already in 1930 by Shepard et al. for the decarboxylation of halogenated furancarboxylic acids at high temperatures.[4] Nilsson,[5] Shepard,[6] and Cohen[7] found that the copper source employed has little influence on the efficiency of protodecarboxylations but that the presence of bipyridine ligands at the copper and the use of aromatic amines as solvents is highly beneficial. Still, stoichiometric quantities of copper were required in virtually all published protocols, and the substrate scope was for a long time limited to aromatic carboxylates bearing electron-withdrawing groups such as nitro or halo in the ortho position as well as to certain heterocyclic carboxylates.

SCHEME 1. Proposed Mechanism for the Cu-Catalyzed Protodecarboxylation of Aromatic Carboxylates



We became interested in this transformation in the context of our research on decarboxylative cross-coupling reactions[8] when we optimized the copper cocatalyst that mediates the decarboxylation step by using protodecarboxylations as a model reaction.[9] This work led to the discovery that such protodecarboxylations can be made catalytic in copper and extended to the full range of benzoic acids, including even deactivated derivatives such as 4-methoxybenzoic acid, when 4,7-diphenyl-1,10-phenanthroline is employed as the ligand and a mixture of NMP and quinoline as the solvent. Based on mechanistic studies and DFT calculations, we proposed a reaction mechanism that involves a direct insertion of the copper catalyst into the aryl carboxylate bond without the previous formation of a π-coordinated intermediate (Scheme 1).[7a,9,10]

Whereas this protocol avoids stoichiometric amounts of heavy metals and thus represents major progress from an environmental standpoint, it has some practical disadvantages. The substrates are submitted to considerable thermal stress over the course of the reaction (170 °C for up to 24 h), volatile products are partially carried off by the CO_2 gas released, and the high cost of the ligand can become prohibitive for preparative applications.

We herein present an alternative protodecarboxylation protocol which involves performing the reactions in a laboratory microwave that combines efficient heating with the possibility to use small, contained vessels certified for pressure reactions.[11,12] This protocol allows for a dramatic reduction of the reaction times and leads to higher yields, even at lower loadings of a

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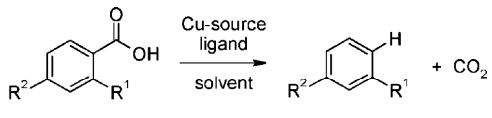
10.1021/jo802628z CCC: $40.75 © 2009 American Chemical Society
Published on Web 02/24/2009

TABLE 1. Optimization of the Catalyst System[a]



1a: R^1 = H, R^2 = OMe
1b: R^1 = NO_2, R^2 = H

2a / 2b

no.	substrate	Cu source	ligand	solvent	*T* (°C)	**2** (%)
1[b]	**1a**	Cu_2O	**3a**	NMP/quin	170	9
2[b]	**1a**	Cu_2O	**3a**	NMP/quin	180	6
3[b]	**1a**	Cu_2O	**3a**	NMP/quin	190	43
4[b]	**1a**	Cu_2O	**3a**	NMP/quin	200	17
5[b,c]	**1a**	Cu_2O	**3a**	NMP/quin	190	88
6	**1a**	Cu_2O	**3a**	NMP	190	32
7	**1a**	Cu_2O	**3a**	quinoline	190	18
8[b]	**1a**	Cu_2O	**3a**	mesit/quin	190	9
9[b]	**1a**	Cu_2O	**3a**	DMF/quin	190	26
10[b]	**1a**	Cu_2O	**3a**	DMSO/quin	190	0
11[b]	**1a**	CuOAc	**3a**	NMP/quin	190	27
12[b]	**1a**	CuBr	**3a**	NMP/quin	190	0
13[b,d]	**1a**	CuBr	**3a**	NMP/quin	190	15
14[b]	**1a**	Cu_2O	**3b**	NMP/quin	190	97
15[b]	**1a**	Cu_2O	**3c**	NMP/quin	190	24
16[b]	**1a**	Cu_2O	**3d**	NMP/quin	190	10
17[b]	**1a**	Cu_2O	**4a**	NMP/quin	190	20
18[b]	**1a**	Cu_2O	**4b**	NMP/quin	190	21
19[b]	**1a**	Cu_2O	**5a**	NMP/quin	190	7
20[b]	**1a**	Cu_2O	**5b**	NMP/quin	190	13
21[b]	**1a**	Cu_2O	**6a**	NMP/quin	190	7
22[b]	**1a**	Cu_2O	**6b**	NMP/quin	190	5
23[b]	**1b**	Cu_2O	**3a**	NMP/quin	160	98
24[b,e]	**1b**	Cu_2O	**3a**	NMP/quin	160	95

[a] Reaction conditions: 1.0 mmol of carboxylic acid, 10 mol % of Cu source (5 mol % for Cu_2O), 10 mol % of ligand, 2 mL of degassed solvent, 5 min, 190 °C/150 W. Conversions were determined by GC analysis using *n*-tetradecane as the internal standard; quin = quinoline, mesit = mesitylene. [b] 3:1 mixture of solvents. [c] 15 min. [d] 15 mol % of K_2CO_3. [e] 1 mol % of Cu_2O, 2 mol % of 1,10-phenanthroline.

less expensive catalyst. The loss of volatile products is avoided, as the release of CO_2 gas can be delayed until the end of the reaction, after the reaction mixture has reached room temperature.

We based the search for a microwave-assisted decarboxylation protocol on 4-methoxybenzoic acid (**1a**) as a test substrate because this electron-rich benzoic acid is of particularly low reactivity. In thermal decarboxylations, it gave only 82% yield after 24 h at 170 °C in the presence of 10 mol % of a customized copper(I)/4,7-diphenyl-1,10-phenanthroline complex and an unsatisfactory 35% yield with simple 1,10-phenanthroline.[9]

In contrast, when **1a** was heated in the presence of only 5 mol % of a copper(I) oxide/1,10-phenanthroline catalyst in a mixture of NMP and quinoline at 170 °C using a maximum of 150 W microwave irradiation, traces of product were detected after only 5 min (Table 1, entry 1). Increases in the reaction temperature resulted in a steady improvement of the yields until a turnaround point was reached at 190 °C, above which the yield dropped again (entries 3 and 4). Further test reactions performed at this temperature but at incomplete conversion (5 min) revealed that the protodecarboxylation is very sensitive

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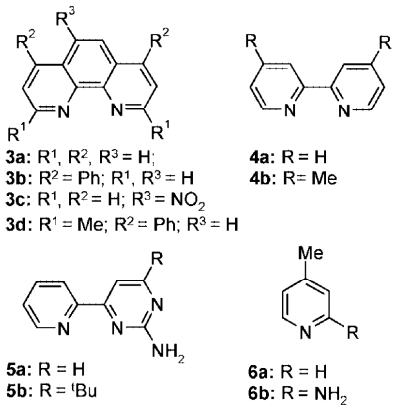


FIGURE 1. Cu ligands evaluated in the protodecarboxylation reaction.

to the solvent employed. Best results were obtained with a 3:1 mixture of NMP and quinoline, which was superior to either solvent alone or any other solvent combination tested (entries 3 and 6−10). The chosen solvent mixture strongly absorbs microwave radiation, causing a rapid increase in temperature and pressure during the first few seconds. Copper(I) oxide proved to be the copper source of choice, other copper(I) or copper(II) salts were less effective (entries 11−13).

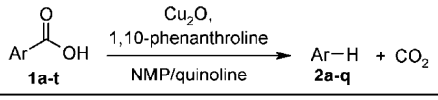
When extending the reaction time to 15 min at optimum reaction conditions, the yields could finally be improved up to an excellent 88% when using simple 1,10-phenanthroline (entry 5). Again, we found 4,7-diphenyl-1,10-phenanthroline to be even more effective, leading to almost quantitative formation of anisole (**2a**) after only 5 min (entry 14). Besides phenanthrolines, other ligands (Figure 1) can also be employed, but none of them was of similar effectiveness to the phenanthrolines (entries 14−22).

A second test reaction with 2-nitrobenzoic acid (**1b**) revealed that for such highly reactive substrates the decarboxylation proceeds in high yields even when the reaction temperature is reduced to 160 °C and the catalyst loading to 2 mol % (entries 23 and 24).

Encouraged by the results obtained with these two rather extreme model substrates, we set out to systematically explore the generality of the catalytic protocol using various aromatic and heteroaromatic carboxylic acids. Due to its easy availability and low price, we used Cu_2O/1,10-phenanthroline as the catalyst. We were pleased to find that even with this simple system, all substrates tested smoothly decarboxylated within 5−15 min. Usually, the yields were significantly in excess of those obtained after 16−24 h of conventional heating using the expensive 4,7-diphenyl-1,10-phenanthroline ligand. Selected results are summarized in Table 2.

The reactions are very easy to perform by irradiating a suspension of the carboxylic acid (**1a**−**t**), Cu_2O, and 1,10-phenanthroline in NMP/quinoline (3:1) at 190 °C for 5−15 min under inert conditions in a sealed crimp-top glass tube. After air-jet cooling, the pressure is carefully released, and the product is isolated by simple aqueous workup and removal of the solvents by fractional distillation. The conditions are sufficiently mild to be tolerated by a number of functionalities including ether, ester, formyl, nitro, cyano, and hydroxyl groups. The selectivity is high throughout, with at most traces of side products arising from homocoupling or substitution reactions. Lower yields were due only to incomplete conversion. All

TABLE 2. Scope of the Transformation[a]



	Ar-COOH	method	Ar-H	yield (GC) (%)
1a	4-MeO-C_6H_4-COOH	A	**2a**	77 (88)
1b	2-NO_2-C_6H_4-COOH	B	**2b**	85 (98)
1c	4-NO_2-C_6H_4-COOH	A	**2b**	86[b] (94)
1d	4-CN-C_6H_4-COOH	A	**2c**	81 (89)
1e	4-CHO-C_6H_4-COOH	A	**2d**	64 (77)
1f	4-MeC(O)-C_6H_4-COOH	A	**2e**	79 (87)
1g	4-Et-C_6H_4-COOH	A	**2f**	(80)
1h	4-CF_3-C_6H_4-COOH	A	**2g**	(22)
1i	4-Cl-C_6H_4-COOH	A	**2h**	(90)
1j	4-HO-C_6H_4-COOH	A	**2i**	(64)
1k	3-Me-C_6H_4-COOH	A	**2b**	(96)
1l	3-NO_2-C_6H_4-COOH	B	**2j**	(99)
1m	2-PhNH-C_6H_4-COOH	B	**2k**	63 (88)
1n	2-MeC(O)-C_6H_4-COOH	B	**2e**	84 (91)
1o	2-MeS$(O)_2$-C_6H_4-COOH	B	**2l**	70 (82)
1p	2-*i*PrOC(O)-C_6H_4-COOH	B	**2m**	85 (94)
1q	2-thienyl-COOH	B[c]	**2n**	(62)
1r	2-furyl-COOH	B[c]	**2o**	(99)
1s	1-naphthyl-COOH	B	**2p**	38 (56)
1t	2-NO_2-5-Me-C_6H_3-COOH	B	**2q**	80 (94)

[a] Reaction conditions. Method A: 1.0 mmol of carboxylic acid, 5 mol % of Cu_2O, 10 mol % of 1,10-phenanthroline, 1.5 mL of NMP, 0.5 mL of quinoline, 190 °C, 150 W, 15 min; isolated yields. Method B: 1.0 mmol of carboxylic acid, 1 mol % of Cu_2O, 2 mol % of 1,10-phenanthroline, 1.50 mL of NMP, 0.50 mL of quinoline, 190 °C, 150 W, 5 min; isolated yields. GC yields were determined using *n*-tetradecane as the internal standard and calibrated for each product. [b] a yield of 80% was isolated on 3 mmol scale [c] 160 °C.

reactions were performed on a 1 mmol scale in 10 mL vessels. When using these standard microwave vials, the reactions can be scaled up to a maximum of 3 mmol with comparable yields as shown for compound **2b**. Larger scales should also be possible but require additional equipment.

In conclusion, an efficient microwave-based protocol has been developed for Cu-catalyzed decarboxylations of arenecarboxylates. It is ideally suited for the demands of parallel synthesis as commonly used, for example, in drug discovery. Because test reactions can now be completed within a few minutes rather than an entire day, it will also serve to expedite the development of more effective catalyst systems.

Experimental Section

Protodecarboxylation of Aromatic Carboxylic Acids. Method A (Table 2). An oven-dried 10 mL microwave vial was charged with the carboxylic acid (**1a,c−k**) (1.0 mmol), Cu_2O (7.2 mg, 0.05 mmol), and 1,10-phenanthroline (18 mg, 0.10 mmol). After the reaction mixture was made inert, a mixture of NMP (1.5 mL) and quinoline (0.5 mL) was added via syringe. The resulting mixture was submitted to microwave irradiation at 190 °C for 15 min at a maximum power of 150 W and subsequently air-jet cooled to room temperature. The maximum pressure detected during the reaction was 5.5 bar. The mixture was then diluted with aqueous HCl (5N, 10 mL) and extracted repeatedly with diethyl ether (2 mL portions). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and filtered. The corresponding arene **2** was obtained in pure form after removal of the solvents by distillation over a Vigreux column.

Method B (Table 2). Method B is analogous to method A but with a lower loading of the copper/phenanthroline catalyst and microwave irradiation at 190 °C for 5 min at a maximum power of 150 W. The following amounts were used: carboxylic acid (**1b, l−t**) (1.0 mmol), Cu_2O (1.5 mg, 0.01 mmol), and 1,10-phenanthroline (3.6 mg, 0.02 mmol).

Anisole (2a). Synthesized from 4-methoxybenzoic acid (**1a**) (152 mg, 1.00 mmol) following method A and obtained as a colorless liquid (84 mg, 77%). The spectroscopic data (NMR, GC−MS) matched those reported in the literature [CAS no. 100-66-3].

Nitrobenzene (2b). Synthesized from 2-nitrobenzoic acid (**1b**) (167 mg, 1.00 mmol) following method B (105 mg, 85%), from 3-nitrobenzoic acid (**1l**) (167 mg, 1.00 mmol) following method B (107 mg, 87%), and from 4-nitrobenzoic acid (**1c**) (167 mg, 1.00 mmol) following method A (105 mg, 86%), obtained each time as a yellow liquid. The spectroscopic data (NMR, GC−MS) all matched those reported in the literature [CAS no. 98-95-3]. A larger scale reaction starting from 4-nitrobenzoic acid (**1c**) (501 mg, 3 mmol) in 6 mL of NMP gave **2b** in 80% yield (293 mg).

Benzonitrile (2c). Synthesized from 4-cyanobenzoic acid (**1d**) (147 mg, 1.00 mmol) following method A and obtained as a colorless liquid (84 mg, 81%). The spectroscopic data (NMR, GC−MS) matched those reported in the literature [CAS no. 100-47-0].

Benzaldehyde (2d). Synthesized from 4-formylbenzoic acid (**1e**) (150 mg, 1.00 mmol) following method A and obtained as a yellow liquid (68 mg, 64%). The spectroscopic data (NMR, GC−MS) matched those reported in the literature [CAS no. 100-52-7].

Acetophenone (2e). Synthesized from 4-acetylbenzoic acid (**1f**) (164 mg, 1.00 mmol) following method A (95 mg, 79%) and from 2-acetylbenzoic acid (**1n**) (164 mg, 1.00 mmol) following method B (101 mg, 84%), both times obtained as a yellow liquid. The spectroscopic data (NMR, GC−MS) all matched those reported in the literature [CAS no. 98-86-2].

Ethylbenzene (2f). Synthesized from 4-ethylbenzoic acid (**1g**) (150 mg, 1.00 mmol) following method B. The identity of the product **2f** was confirmed by GC−MS and the yield determined by quantitative GC to be 80% based on a response factor obtained with commercial ethylbenzene [CAS no. 100-41-4] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Trifluoromethylbenzene (2g). Synthesized from 4-(trifluoromethyl)benzoic acid (**1h**) (190 mg, 1.00 mmol) following method B. The identity of the product **2g** was confirmed by GC−MS and the yield determined by quantitative GC to be 22%, based on a response factor obtained with commercial trifluoromethylbenzene [CAS no. 98-08-8] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Chlorobenzene (2h). Synthesized from 4-chlorobenzoic acid (**1i**) (156 mg, 1.00 mmol) following method A. The identity of the product **2h** was confirmed by GC−MS and the yield determined by quantitative GC to be 90% based on a response factor obtained with commercial chlorobenzene [CAS no. 108-90-7] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Phenol (2i). Synthesized from 4-hydroxybenzoic acid (**1j**) (138 mg, 1.00 mmol) following method A. The identity of the product **2i** was confirmed by GC−MS and the yield determined by quantitative GC to be 64%, based on a response factor obtained with commercial phenol [CAS no. 108-95-2] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Toluene (2j). Synthesized from 3-methylbenzoic acid (**1k**) (136 mg, 1.00 mmol) following method A. The identity of the product **2j** was confirmed by GC−MS and the yield determined by quantitative GC to be 99%, based on a response factor obtained with commercial toluene [CAS no. 108-88-3] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Diphenylamine (2k). Synthesized from 2-(phenylamino)benzoic acid (**1m**) (213 mg, 1.00 mmol) following method B and obtained as a white solid (107 mg, 63%): mp 49−51 °C. The spectroscopic data (NMR, GC−MS) matched those reported in the literature for diphenylamine [CAS no. 122-39-4].

Methyl Phenyl Sulfone (2l). Synthesized from 2-(methylsulfonyl)benzoic acid (**1o**) (200 mg, 1.00 mmol) following method B and obtained as a white solid (109 mg, 70%): mp. 85−87 °C. The

spectroscopic data (NMR, GC−MS) matched those reported in the literature for methyl phenyl sulfone [CAS no. 3112-85-4].

Isopropyl Benzoate (2m). Synthesized from 2-(isopropyloxycarbonyl)benzoic acid (**1p**) (208 mg, 1.00 mmol) following method B and obtained as a yellow liquid (139 mg, 85%). The spectroscopic data (NMR, GC−MS) matched those reported in the literature for isopropyl benzoate [CAS no. 939-48-0].

Thiophene (2n). Synthesized from thiophene-2-carboxylic acid (**1q**) (128 mg, 1.00 mmol) following method B but at 160 °C reaction temperature. The identity of the product **2n** was confirmed by GC−MS and the yield determined by quantitative GC to be 62%, based on a response factor obtained with commercial thiophene [CAS no. 110-02-1] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Furan (2o). Synthesized from furan-2-carboxylic acid (**1r**) (112 mg, 1.00 mmol) following method B but at 160 °C reaction temperature. The identity of the product **2o** was confirmed by GC−MS and the yield determined by quantitative GC to be 99% based on a response factor obtained with commercial furan [CAS no. 110-00-9] using *n*-tetradecane (50 μL) as an internal gas chromatographic standard.

Naphthalene (2p). Synthesized from 1-naphthoic acid (**1s**) (172 mg, 1.00 mmol) following method B and obtained as a white solid (49 mg, 38%): mp.78−80 °C. The spectroscopic data (NMR, GC−MS) matched those reported in the literature for naphthalene [CAS no. 91-20-3].

4-Nitrotoluene (2q). Synthesized from 5-methyl-2-nitrobenzoic acid (**1t**) (197 mg, 1.00 mmol) following method B and obtained as a colorless liquid (109 mg, 80%). The spectroscopic data (NMR, GC−MS) matched those reported in the literature for 4-nitrotoluene [CAS no. 99-99-0].

Acknowledgment. We thank Prof. Jens Hartung for giving us access to his microwave equipment. We also thank the DFG, the Saltigo GmbH, and NanoKat for funding, Umicore AG for the generous donation of catalysts, the A. v. Humboldt Foundation for a scholarship to N.R., and the HEC Pakistan for a scholarship to B.A.K.

Supporting Information Available: NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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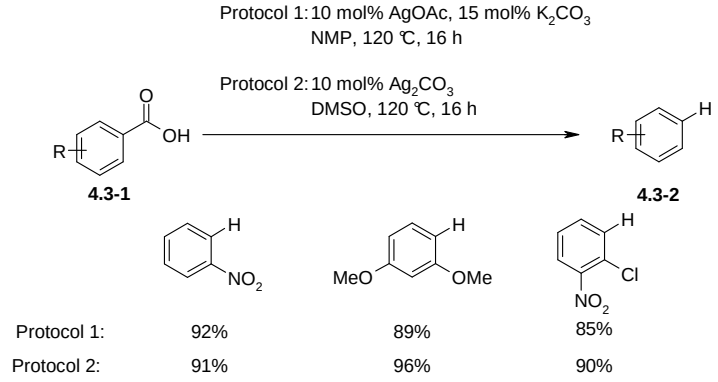
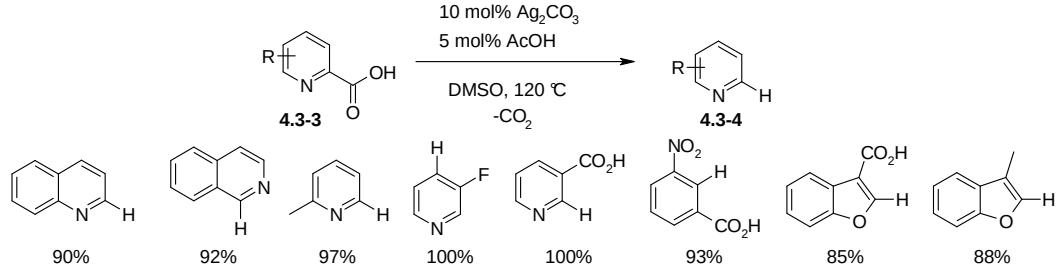
4.3 Recent Advances in the Protodecarboxylations

Shortly after this publication, major advancements in this field were achieved by the development of new catalysts. It was demonstrated that the ligand has little influence on the catalytic activity whereas central metal has a profound effect on protodecarboxylations. Based on DFT calculations, silver based catalyst systems were developed and tested for protodecarboxylation reactions. A catalyst system generated from 10 mol% of AgOAc, 15 mol% K_2CO_3 in NMP smoothly decarboxylated aromatic carboxylic acids (**4.3-1**) at 120 °C (Schema 61).[147] A similar catalyst system generated from 10 mol% of Ag_2CO_3 in DMSO gave compareable results.[148] Catalytic amounts of silver carbonate also decarboxylated the deactivated coumarin carboxylic acids to coumarins at 100 °C.[149] Silver-based catalyst systems have certain advantages for special substrate class such as *ortho*-halo benzoic acid and a temperature which is 50 °C lower than copper-based system.



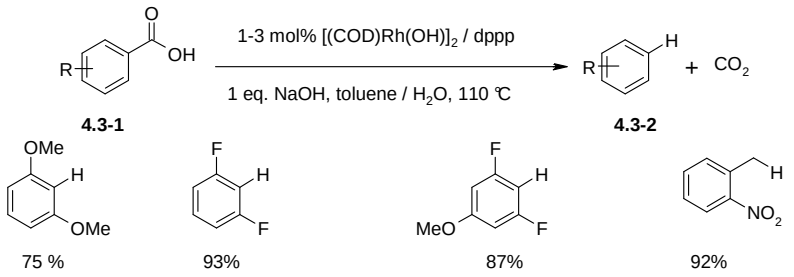
Schema 61. *Ag-catlyzed protodecarboxylation of arenecarboxylic acids*

Protodecarboxylation of particularly 6 membered heteroaromatic carboxylic acids (**4.3-3**) was also successfully achieved by using a silver catalyst. In the presence of catalytic amounts of silver carbonate, five and six membered heteroaromatic carboxylic acids were converted into the heteroarenes (**4.3-4**) at comparatively mild reaction conditions. Aromatic as well as heteroaromatic dicarboxylic acids containing an electron withdrawing functional group were selectively mono decarboxylated (Schema 62).



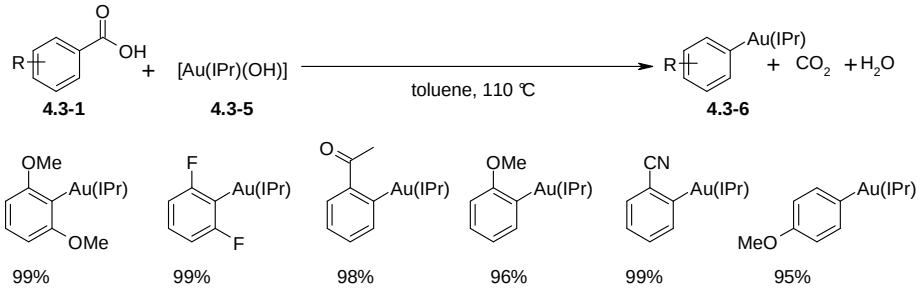
Schema 62. *Protodecarboxylation of heteroaromatic carboxylic acids*

In parallel, rhodium-mediated protodecarboxylations were developed for *ortho*, *ortho*-disubstituted, 2 and 4 dinitrophenylacetic acid, and indole-3-carboxylic acids at mild conditions (Schema 63).[150]



Schema 63. *Rhodium mediated protodecarboxylations*

Nolan *et al*. recently utilized an isolated gold(I) complex [Au(IPr)OH] (**4.3-5**) to prepare a broad range of highly stable gold(I)-aryl complexes (**4.3-6**) via decarboxylation of the corresponding aromatic carboxylic acids (**4.3-1**) without the use of silver co-catalyst. No protodemetallation was observed under mild conditions (Schema 64).[151] This reaction has the advantage over all other decarboxylation reactions because it tolerates a variety of functional groups including methoxy, acetoxy, formyl, nitro, cyano and fluoro. In addition aromatic heterocyclic compounds were also smoothly converted into gold complexes at mild temperatures. However, stoichiometric quantities of expensive gold complex are required for this transformation.



Schema 64. *Preparation of gold(1)-aryl coplexes*

4.4 Outlook

An effective microwave-assisted protocol has been developed for the Cu-catalyzed protodecarboxylation of arenecarboxylic acids. The new catalyst system is composed of Cu_2O and economical 1, 10-phenanthroline that marginally reduces the cost of the transformation. The use of microwave radiation has considerably improved this transformation thus equally suitable for both volatile and non volatile products. Short reaction times make it highly acceptable for parallel synthesis. The applicability of the protocol for a wide range of functional groups enhances the quality of the transformation. Now, the requirement of high temperature is the only limitation left with Cu-catalyzed protodecarboxylation of aromatic carboxylic acids.

Later on, the use of silver, rhodium and gold catalysts has allowed this reaction to take place at lower temperature for particularly activated substrates. Although copper based catalyst systems require higher temperature, they are generally more effectively applied than other catalyst systems.

Based on the beneficial role of microwaves on protodecarboxylation reactions, decarboxylative biaryl synthesis was also performed under microwave conditions. Microwave assisted coupling of aryl triflates and tosylates with aryl bromides afforded higher yields due to less thermal stress particularly for deactivated carboxylates in 15 mins.[63]

5 Synthesis of Trifluoromethylated Compounds

5.1 Properties Trifluoromethylated Compounds

Fluorine is a pale yellow gas with an electronic configuration of [($1s^2$)($2s^2$)($2p^5$)]. It is the most reactive element of the periodic table with an electronegativity value of 3.98 (Pauling scale). It even reacts with noble gases, for example it reacts with Xe to form XeF_2..[152] Due to high reactivity, it is always found in the form of different compounds in nature, such as fluorite (CaF_2), cryolite (Na_3AlF_6) and fluorapatite $Ca_5(PO_4)_3F$. These are the most common fluoride-containing minerals. In contrast to other halogens,[153] few examples of fluorine containing natural products are known.[154]

Due to the steric and electronic properties, fluorine has the ability to modify the physical and chemical properties of molecules such as bioavailability, lipophilicity, and metabolic stability. It is of great significance in drugs, functional materials and reagents. New reactions have been developed in the last few decades for regio-and stereoselective introduction of fluorine into organic molecules. The progress in the field of fluorination has been summarized in numerous review articles[155] and is far beyond the scope of this work.

The trifluoromethyl substituent is particularly valuable due to its exceptional physical and chemical properties.[156] The CF_3-group possesses high electronegativity of 3.44 (Pauling scale),[157] low polarizeability and high inertness [E(C–F)=116 kcal / mol)]. These properties are highly beneficial in many functional molecules spanning from pharmaceuticals[158] and agrochemicals[159] to high performance polymeric materials.[160] Some of the numerous examples of commercially meaningful trifluoromethyl arenes are depicted in Abbildung 4.

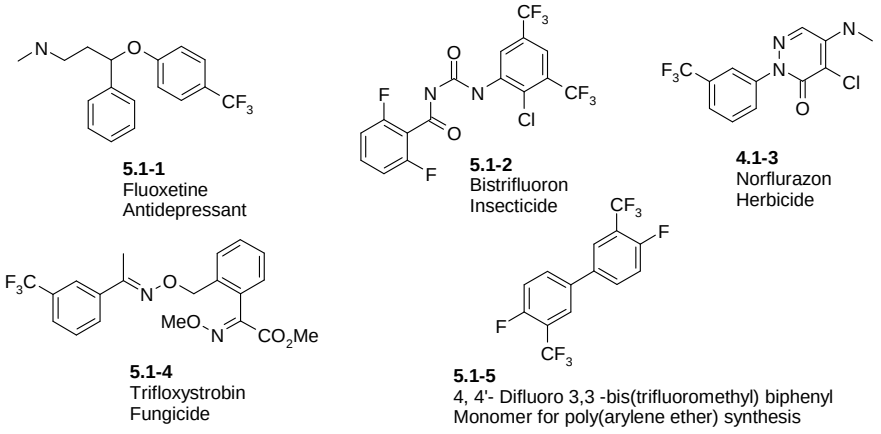


Abbildung 4. *Examples of trifluoromethylated arenes in medicinal, agrochemical and polymer chemistry*

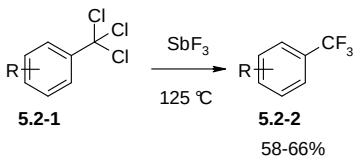
Fluoxetine (**5.1-1**), the active component of the drug Prozac, is a well known antidepressant.[161] This compound selectively inhibits the uptake of serotonin with a six-fold increase of activity over its non-fluorinated parent compound. Besides trifluoromethylated pharmaceuticals, other biologically relevant compounds containing the trifluoromethyl group are extensively used in crop protection. The introduction of electron-withdrawing groups often extend the pesticidal spectrum of inhibitors of chitin formation based on *N*-benzoyl-*N'*-phenylureas (e.g. Bistrifluoron)[162] (**5.1-2**). The 3-trifluoromethylphenyl moiety is also an essential building block for inhibitors of carotenoid synthesis (e.g Norfluazon)[163] (**5.1-3**) or fungicides like Trifloxystrobin[164] (tradename Flint) (**5.1-4**) which has an outstanding activity. Trifluoromethylated compounds have also found wide applications in material science.[160] The introduction of a CF_3 group usually increases solubility, thermal stability, optical transparency, flame resistance, and decreases the dielectric constant along with the ability of the polymers to crystalize (**5.1-5**).[160] Moreover, the trifluoromethyl group activates fluoro and nitro groups for nucleophilic aromatic substitution thus facilitating the formation of poly(arylene)ethers.

5.2 Trifluoromethylation Reactions

The interesting properties of the trifluoromethyl group have spurred synthetic efforts for selective and direct introduction of this CF_3-group.[165] Conventional strategies have relied on two approaches: one involves C-F bond formation via substitutuion of a functional group by fluoride, such as Swarts reaction.[166] Intense research efforts in recent decades led to the development of the second category that involves C-C bond formation from commercially available CF_3-substituted compounds.[167] This category has been further divided into three classes; radical, electrophilic and nucleophilic trifluoromethylations. Progress in this field has been summarized in many review articles,[168] and the major developments in this area will be highlighted in the following sections.

5.2.1 Swarts Reaction: Nucleophilic Substitution with Fluoride

The substitution of a chlorine atom by a fluorine atom in an organic molecule with antimony trifluoride was first described by Swarts in 1892, and the reaction is known as Swarts reaction.[169] (Schema 65)



5.2-1 **5.2-2**

58-66%

Schema 65. *Swarts reaction*

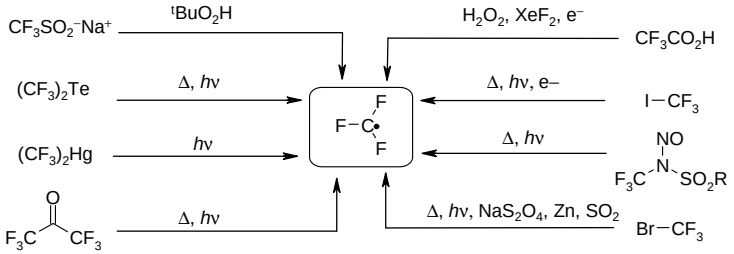
Since its discovery, the Swarts reaction has still been used in industrial processes to access simple trifluoromethylated building blocks. The benzotrichlorides (**5.2-1**) used as starting compounds for the Swarts reaction are easily accessed by free radical chlorination or by Friedal-Craft alkylations.[170] Instead of toxic antimonytrifluoride, a mixture of $AlCl_3/FCCl_3$[171] or hydrogen fluoride[172] is frequently used as a fluoride source.

In addition to benzotrichlorides, carboxylic acid derivatives could also serve as a starting material to synthesize trifluoromethylated compounds with specially designed reagents such as SF_4,[173] and XeF_2.[174]

However, the Swarts reaction is neither atom-economic nor environmentally friendly. Each equivalent of the CF_3-group is incorporated at the cost of six equivalents of hydrogen chloride. Furthermore, the scope of the Swart reaction is limited to robust functional groups due to the harsh reaction conditions. Still, the development of efficient methods for late stage trifluoromethylation of organic molecules is of high interest for synthetic and large scale industrial applications.

5.2.2 Radical Trifluoromethylation Reactions

CF_3-radicals can be generated under various reaction conditions including photochemical, electrochemical or thermal. Various CF_3-precursors such as trifluoromethyl iodide,[175] trifluoromethyl bromide,[176] bis (trifluoromethyl) mercury[177] silver trifluoroacetate,[178] the combination of sodium trifluoromethyl sulfinate with tertiary butyl hydroperoxide,[179] and bis trifluoroacetyl peroxide[180] had been successfully employed for the trifluoromethylation of organic molecules[168a] but none of these procedures is generally applicable (Schema 66).[181]



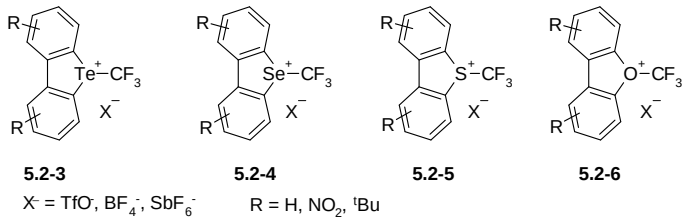
Schema 66. *Sources of trifluoromethyl radicals*

The advances in the field of radical trifluoromethylation have been reviewed[168a] and a detailed discussion is beyond the scope of this thesis.

5.2.3 Electrophilic Trifluoromethylation Reactions

The high energy trifluoromethyl cation is difficult to generate in a chemical reaction.[182] Under ordinary reaction conditions, all classical methods failed to trifluoromethylate the nucleophiles due to high electronegativity of the CF_3-carbon atom.

Based on the successful discovery of the first electrophilic perfluoroalkylation reagents by Yagupolskii *et al.*,[183] two major classes of electrophilic trifluoromethylation reagents have been developed. The first one is the class of trifluoromethyl chalcogenium salts developed by Umemoto *et al*. (Schema 67).[184]



5.2-3 **5.2-4** **5.2-5** **5.2-6**

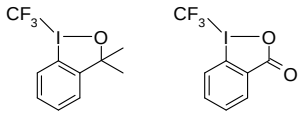
X^- = TfO^-, BF_4^-, SbF_6^- R = H, NO_2, ^{t}Bu

Schema 67. *Dibenzochalcogenium salts*

The great success of these reagents is due to their ability to modify the reactivity by the installation of electron–withdrawing and electron–donating substituent in benzene ring or by varying the chalcogen atom. The trifluoromethylating power increases from tellurium to selenium to sulfur. In addition, electron-withdrawing groups such as NO_2-or SO_3-groups also enhance the reactivity of these reagents.[184] The most reactive isolable reagent is 3,7-dinitro-S-(trifluoromethyl)dibenzothiopheniumtriflate. However, only *C*- and *S*- nucleophiles can be trifluoromethyalted by using these reagents. Whereas, the *O*-(trifluoromethyl)dibenzofuranium salts (**5.2-6**) can be generated *in situ* to transfer CF_3-group to *N*-and *O*-centered nucleophiles.[185]

During the last two decades, syntheses of (trifluoromethyl)dibenzochalconium salts have been steadily developed[186] and the reaction conditions for trifluoromethylation reactions have been optimized.[187] Also the acyclic *S*-(trifluoromethyl)diarylsulfoniumsalts were further developed by the groups of Shreeve,[188] Magnier[189] and Yagupolskii,[190] so that the new derivatives are now approaching the performance of Umemoto's dibenzochalconium compounds. However, their multistep synthesis is still based on the use of highly expensive and reactive reagents such as trifluoromethyl sulfuric anhydride.

The second class of electrophilic trilfluoromethylation reagents is the class of neutral hypervalent iodine reagents reported by Togni *et al*. in 2006 (Schema 68).[191] 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (**5.2-7**) and 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (**5.2-8**) are found to be one of the most effective reagent for the trifluoromethylation of *C*[192]-, *S*[192]-, *P*[193]-and *O*[194]-nucleophiles at mild reaction conditions.



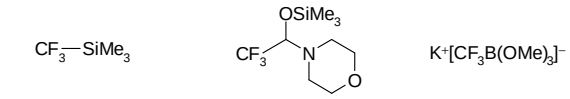
5.2-7 **5.2-8**

Schema 68. *Togni's trifluoromethylation reagent*

The synthesis of these reagents also involves the use of highly expensive iodide precursors. Only the CF_3-group is transferred to the products generating a large amount of waste in the reaction.

5.2.4 Nucleophilic Trifluoromethylation Reactions

The reactions of CF_3-anion with carbon electrophiles represent the most frequently used strategy for the introduction of CF_3-group into organic molecules. These reactions are not trivial as CF_3-anion is extremely unstable and gives rise to difluorocarbene via α-elimination.[195] CF_3-anion has been stabilized by a covalent bond with a semi-metal such as tin,[196] silicon[197] or boron[198] or with a transition metal. The transition metal stabilized reactions will be discussed in section 5.3. The toxic tin reagents have been rarely used for trifluoroemthylation reactions. Trifluoromethylsilicons are widely used reagents for the synthesis of trifluoromethylated compounds, whereas boron reagents have been recently introduced as beneficial CF_3-sources for the trifluoroemthylation reactions. The most representative examples of nucleophilic trifluoroemthylation reagents are described below (Schema 69).



Ruppert's reagent Langlois reagent

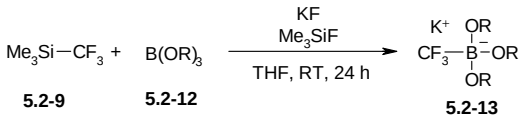
5.2-9 **5.2-10** **5.2-11**

Schema 69. *Examples of nucleophilic trifluoromethylation reagents*

In 1984, Ruppert reported the first synthesis of trifluoromethylsilane (**5.2-9**) meanwhile known as Ruppert's reagent.[199] However, its chemical and physical properties complicate the handling of this reagent. It is a colorless and highly volatile liquid that decomposes within a few days in air or moisture. The key to nucleophilic trifluoromethylations with Ruppert's reagent (**5.2-9**) is the presence of catalytic amounts of fluoride base which activates the CF_3-Si bond. It was utilized by Prakash and Olah in 1989 for the first nucleophilic trifluoromethylation of carbon electrophiles.[200] Since the first report, Ruppert's reagent has become an extremely powerful and widely applicable reagent for the nucleophilic trifluoromethylation of electrophiles. By using Ruppert's reagent and a suitable activator, many carbon electrophiles such as aldehydes, ketones and Micheal systems,[200, 201] lactoles and lactones,[202] reactive carbonyl chlorides,[200] carboxylic

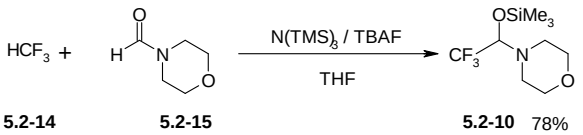
acid methyl esters,[201] unreactive amides,[201] N-aryl nitrones[203] and azirines[204] were converted into the corresponding trilfuoromethylated compounds.

In 2003, Röschenthaler *et al.*[205] utilized Ruppert's reagent (**5.2-9**) with trialkoxyborate and a fluoride base to synthesize (trifluoromethyl)trialkoxyborate salts (**5.2-13**) in excellent yields (Schema 70). The respective Me_3SiCF_3 (**5.2-9**) can be activated under mild reaction conditions with a fluoride source and the trifluoromethyl group is absorbed by the Lewis acids to form borate salts. Moisture and air-stable, and crystaline potassium (trifluoromethyl)trialkoxyborates are used as single component trifluoromethyalting reagents. Potassium (trifluoromethyl)trimethoxyborate (**5.2-11**) was used by Dilman *et al*. to synthesize trifluoromethylated alcohols and amines from carbonyl compounds and imines, respectively.[206] Meanwhile, we have also independently developed one component trifluoromethylation of carbonyl compounds by using $K^+[CF_3B(OMe)_3]^-$.



Schema 70. *Röschenthaler synthesis of (trifluoromethyl)trialkoxyborate salts*

However, nucleophilic trifluoromethylation reactions still suffer from the limited availability of inexpensive and low weight CF_3-sources. The group of Langlois[207] and Normant[208] demonstrated that fluoroform can be employed as the most simple nucleophilic trifluoromethylation source by forming an adduct with electrophiles such as DMF.[209] The Langlois reagent is synthesized by deprotonation of fluoroform (**5.2-14**) with $N(TMS)_3/F^-$ in the presence of TBAF followed by trapping of the CF_3-anion by N-formylmorpholine (**5.2-15**) (Schema 71). This adduct was further employed for the trifluoromethylation of carbonyl compounds in the presence of catalytic amounts of fluoride source.[210] However, these reagents are less reactive than Ruppert's reagent and thus seldom used in organic synthesis.[211]



Schema 71. *Synthesis of Langlois reagent*

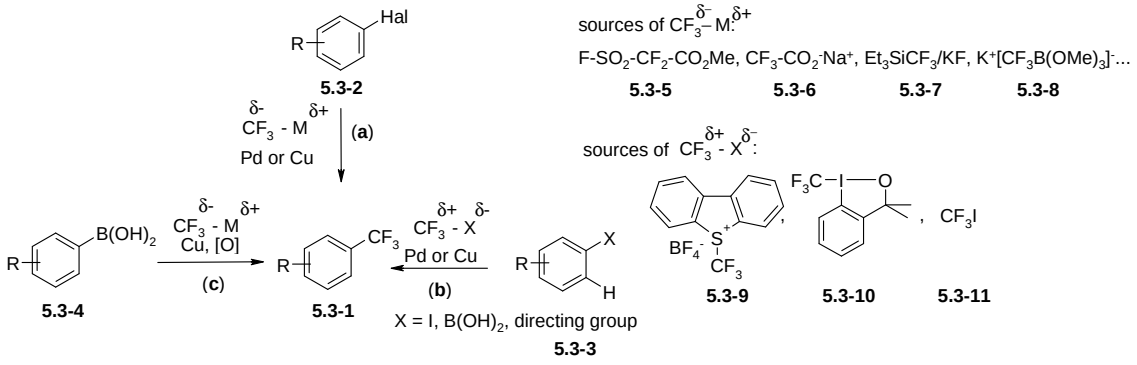
The great success of nucleophilic trifluoromethylation reaction is based to a large extent on the use of Ruppert's reagent (**5.2-9**) for the transfer of trifluoromethyl group. Solid and moisture-stable reagents have been developed and tested as trifluoromethylating reagents. Potassium (trifluoromethyl)trimethoxyborate (**5.2-11**) is emerging as a solid, one component and

moisture stable trifluoromethylating reagent. However, its potential as a nucleophilic trifluoromethylating source has not been fully explored yet.

5.3 Transition Metal Mediated Trifluoromethylation Reactions

Successful strategies for stabilizing CF_3-anion involve the complexation to a transition metal such as Hg, Cu, Pd and Ni. The substantial progress achieved in transition metal mediated trifluoromethylation reactions has been extensively reviewed[212] and the major achievements in this field will be discussed in this work. The role of transition metal for incorporation of trifluoromethyl group into organic molecule is a subject of intense research. Copper is vastly employed in metal promoted aromatic trifluoromethylation reactions, whereas C-CF_3 bond formation at Pd ad Ni metals has been reported only in the last few years.

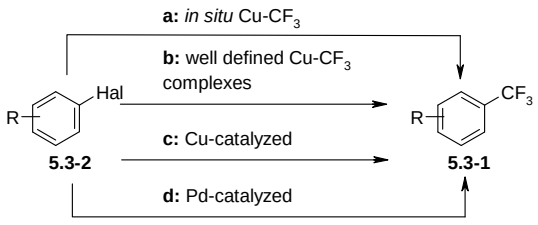
Based on pioneering work by McLoughlin, Yagupolskii, Burton, Kondo, Chambers, Grushin and others,[213] on Cu- and Pd-perfluoroalkyl complexes, three types of processes have been devised as illustrated below (Schema 72).



Schema 72. *Stratergies for the introduction of trifluoromethyl group*

5.3.1 Transition Metal Mediated Coupling with Nucleophilic CF_3-Reagents

The coupling of aryl halides with nucleophilic trifluoromethylation reagents in the presence of copper or palladium is among the most studied trifluoromethylation reactions (Schema 72, a). These reactions can be further divided into four categories on the basis of the type of nucleophilic reagents and transition metal (Schema 73).

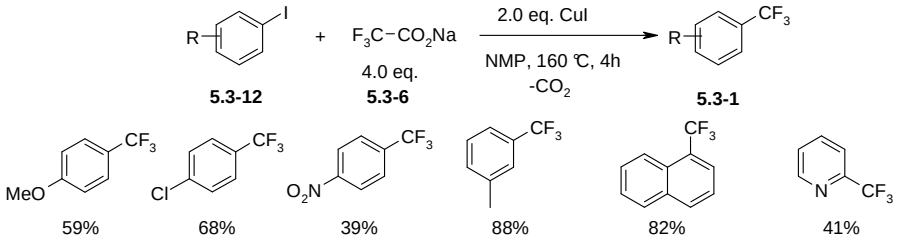


Schema 73. *Transition metal mediated coupling with nucleophilic CF_3-reagents*

The first category involves the generation of copper–CF_3 species *in situ* by transmetallation of preformed orgnometallic reagents or by decarboxylation of trifluoroacetates or Ruppert's reagent with copper salts (Schema 73, a).

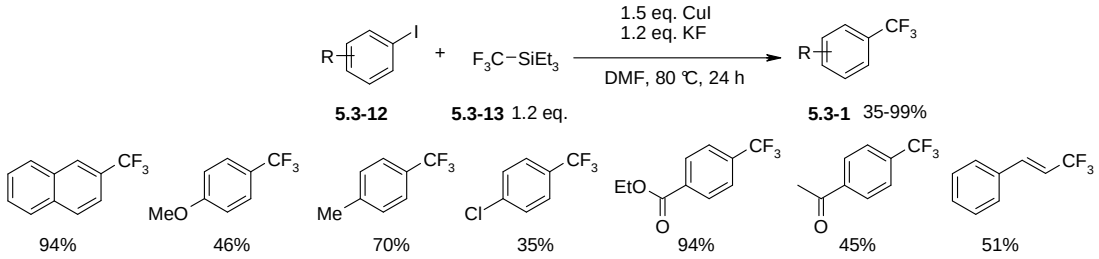
The transmetallation of CF_3-group was first employed by Yagupolskii[213b] in 1980 who prepared reactive Cu-CF_3 species by treating $Hg(CF_3)_2$ or $Hg(CF_3)I$ with copper powder and used it for the trifluoromethylation of iodoarenes. Later on, Burton and Weimer[213d] showed that transmetallation of Cd(II) and Zn(II) trifluoromethyl reagents with copper halides takes place in DMF at lower temperatures. These reagents can be synthesized from the respective elements and CF_2Br_2, CF_2Cl_2, and CF_2BrCl involving radical and carbene intermediates. This group also succeeded in characterizing different Cu-CF_3 species formed at low temperature by NMR experiments. However, preformed organometallic trifluoromethylating reagents have limited applications due to their high toxicity (Hg, Cd) and low reactivity (Zn).

In 1981, Kondo[213c] introduced inexpensive and shelf-stable sodium trifluoroacetate (**5.3-6**) as trifluoromethylating reagent for aryl iodides (**5.3-12**). Aromatic and heteroaromatic halides were trifluoromethylated in the presence of an excess amount of CuI at 160 °C in NMP (Schema 74). The decarboxylation of $FSO_2(CF_2)_2OCF_2CO_2Me$,[214] $BrCF_2CO_2K$,[215] and XCF_2CO_2Me (X=Cl,Br)[216] takes place at mild conditions to generate difluorocarbene and fluoride anion which reacts with copper to give Cu-CF_3 species. This Cu-CF_3 species further reacts with iodoarenes to give the trifluoromethylated arenes.



Schema 74. *Cu-mediated decarboxylative trifluoromethylation of aryl iodides*

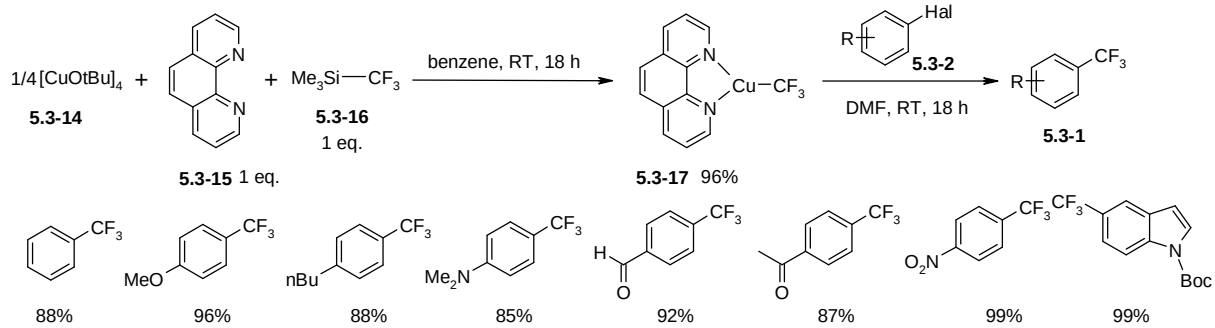
In 1991, Urata and Fuchikami[217] successfully applied the ethyl analogue of Ruppert's reagent for the synthesis of benzotrifluorides (**5.3-1**) from aryl iodides (**5.3-12**). Under mild reaction conditions, iodoarenes (**5.3-12**) were trifluoromethylated in the presence of 1.5 equivalent of CuI, 1.2 equivalent of each of activator and Et_3SiCF_3 (**5.3-13**) in DMF at 80 °C (Schema 75). It was the first successful report in which Et_3SiCF_3 was employed to generate Cu-CF_3 species *in situ* for the trifluoromethylation of aromatic compounds.



Schema 75. *Cu-mediated trifluoromethlation of iodoarenes with Et_3SiCF_3.*

The generation of Cu-CF_3 species *in situ* via transmetallation requires toxic metals whereas, cheap and easily available decarboxylation method demands for the excess of copper salts and harsh reaction conditions which are not suitable for particular substrates. The use of Et_3SiCF_3 is advantageous with regard to reaction conditions but the cost of the reagent and the requirement of extra base for its activation are major drawbacks in addition to excess of copper salt.

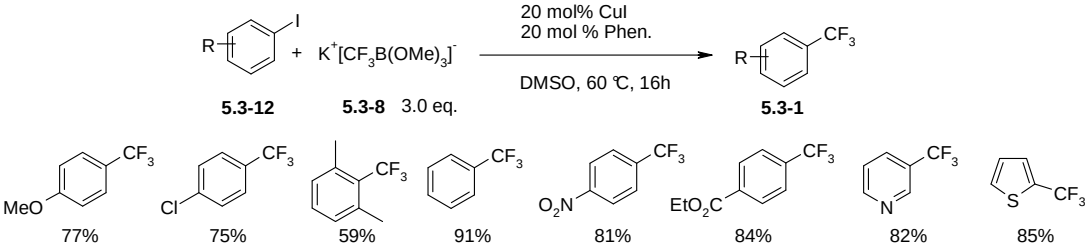
The use of easy to handle and thermally stable well-defined copper-CF_3 complexes[218] for the trifluoroemthyaltion of aryl halides represents the second category (Schema 73, b). These NHC,[218a-c] 1,10 phenanthroline[218e] and triphenylphosphine[218d] stabilized Cu-CF_3 complexes were synthesized from Ruppert's reagent. Among all of the well defined Cu-CF_3 complexes, 1, 10 phenanthrolins Cu-CF_3 complexes (**5.3-17**) are highly active for the transfer of trifluoromethyl group to aryl halides (**5.3-2**) and bromides under mild reaction conditions (Schema 76). Electron-rich and electron-deficient iodoarenes as well as sterically-hindered iodoarenes react in high yields. A broad range of functional groups are tolerated. Aryl halides containing carbonyl functions which are highly sensitive to the nucleophilic addition of trifluoromethyl group, are selectively trifluoromethylated on the aromatic ring.



Schema 76. *(1,10-Phen)$CuCF_3$ as trifluoromethylating reagent*

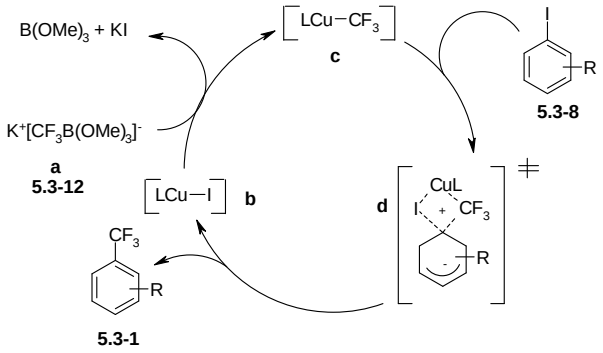
The third category had been estabilished with the development of the first copper catalyzed trifluoromethylation reaction (Schema 73, c). However, these reactions are still rare. The first copper catalyzed trifluoromethylation reaction was reported by Chen and Wu in 1989.[219] Aryl, alkenyl and alkyl halide were treated with methyl fluorosulfonyldifluoroacetate in the presence of a catalytic amount of copper iodide. The reaction is characterized by different reaction

conditions for different compounds. Twenty years later, Amii *et al.*[220] developed a copper catalyzed trifluoromethylation of aryl iodides (**5.3-12**) in the presence of $Cu^{I}I$/1,10-phenanthroline catalyst by using the combination of expensive Et_3SiCF_3 (**5.3-13**)and highly hygroscopic KF as trifluoromethylating reagent. The reaction is limited to electron poor aryl iodides. Two years later, the first generally applicable Cu-catalyzed trifluoromethylation of aryl iodides was developed by Gooßen *et al*. The key to success lies in the use of shelf-stable, moisture-stable and single component potassium (trifluoromethyl)trimethoxyborate (**5.3-8**) (Schema 77).[221] In the presence of 20 mol % $Cu^{I}I$/1,10-phenanthroline, electron-rich, electron-poor, heterocyclic and sterically demanding iodoarenes (**5.3-12**) were smoothly converted into the corresponding benzotrifluorides (**5.3-1**) at 60 °C in DMSO.



Schema 77. *Cu-catalyzed trifluoroemthylation of aryl iodides*

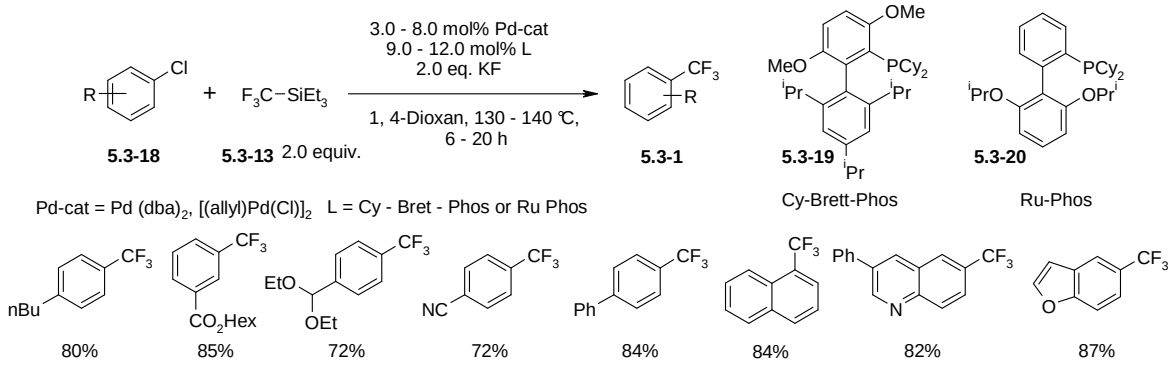
The reaction of potassium (trifluoromethyl)trimethoxyborate (a) with ligand-stabilized copper halide complex (b) leads to the formation of a trifluoromethylcopper complex (c). The CF_3 group would then be transferred from the copper to the aryl iodide via transition state (d), resulting in the formation of benzotrifluoride and initial copper halide complex (b) (Schema 78).



Schema 78. *Cu-catalyzed trifluoromethylation of aryl iodides with $K^{+}[CF_3B(OMe)_3]$*

Based on the pioneering work of Grushin[222] and Sanford[223], the fourth category of palladium catalyzed trifluoromethylation was developed by Buchwald,[224] who employed cheap and widely available aryl chlorides (**5.3-18**) with Et_3SiCF_3 (**5.3-13**) (Schema 73, d). The catalyst system was generated *in situ* from [(allyl) PdCl]$_2$ and Cy-Brett-Phos (**5.3-19**) in dioxane at 120-140 °C which successfully allowed the conversion of diversely functionalized aryl chlorides to the

corresponding benzotrifluorides (**5.3-1**) in good yields (Schema 79). The use of highly electron rich and bulky Brett-phos ligand is the key of this reaction. KF was used to activate the Si-CF_3 bond.



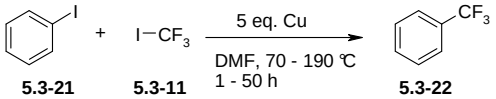
Schema 79. *Palladium catalyzed trifluoromethylation of aryl chlorides*

Buchwald protocol represents the state of the art method for the synthesis of benzotrifluorides by using widely available and cheap aryl chlorides. However, the use of expensive Et_3SiCF_3 limits the application of this method.

5.3.2 Transition Metal Mediated Coupling with Electrophilic CF_3-Reagents

The transition metal mediated couplings with electrophilic trifluoromethylating reagents include the initial reports of McLouglin[213a] and Kitazume[225] on copper mediated and palladium catalyzed coupling of perfluoroalkyl iodides with aryl halides, respectively.

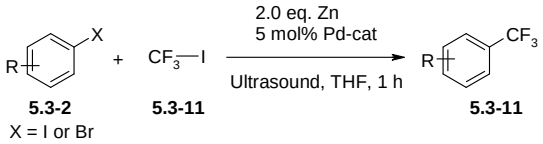
In 1969, McLouglin and Thrower[213a] introduced the first synthetic strategy for the regioselective introduction of the perfluoroalkyl group to the aromatic iodides by using elemental copper. Benzotrifluoride (**5.3-22**) was the only trifluoromethylated product formed in this protocol in 45% yield (Schema 80). Kobayashi and Kumadaki[226] further developed this process by employing a 3–12-fold excess of both CF_3I (**5.3-11**) and freshly precipitated Cu-powder. Electron-deficient chloro-and bromosubstituted arenes, quinolines and isoquinolines gave moderate yields of trifluoromethylated products. Attempts were made to substitute expensive CF_3I with CF_3Br, CF_2Br_2 and the cheapest HCF_3 but none of them was as successful as CF_3I.



Schema 80. *Cu-promoted trifluoromethylation of aryl iodides*

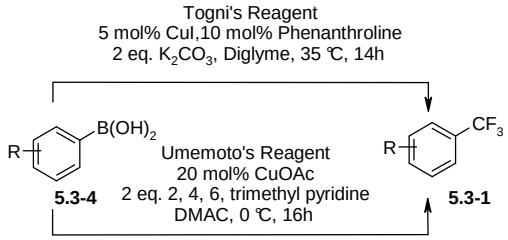
In 1982, Kitazume and Ishikawa[225] reported the first Pd catalyzed cross-coupling of aromatic, vinylic and allylic halides (**5.3-2**) with CF_3I (**5.3-11**) or perfluoroalkyl iodide in the presence of

2 equivalent of Zinc. It was the first palladium catalyzed protocol for the synthesis of benzotrifluorides (Schema 81).



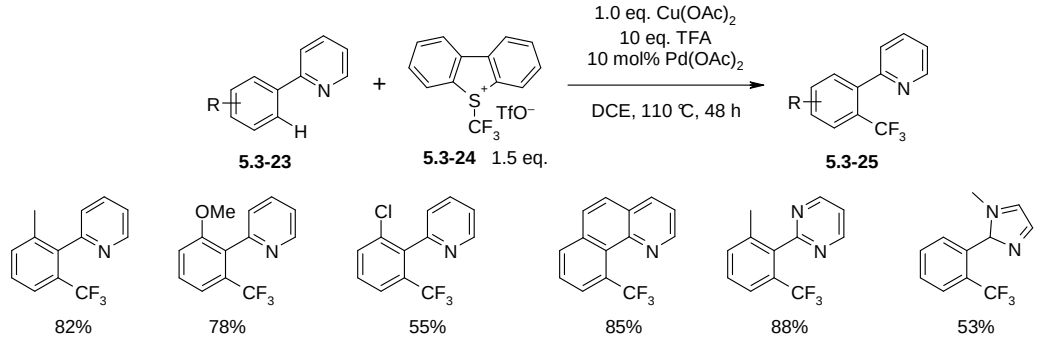
Schema 81. *First Pd catalyzed trifluoromethylation of organic halides*

Shen *et al.*[227] and Liu *et al.* [228] disclosed copper-catalyzed trifluoromethylation of aryl boronic acids (**5.3-4**) with electrophilic Togni's and Umemoto's reagent, respectively (Schema 82). Both protocols give access to benzotrifluorides (**5.3-1**) in good yields for mostly electron rich and heterocyclic boronic acids whereas, comparatively lower yields were reported for electron poor substrates.



Schema 82. *Trifluoromethylation of aryl boronic acids with electrophilic CF_3-reagent*

Yu *et al.*[229] reported Pd-catalyzed *ortho*-trifluoromethylation of donor-substituted arenes (**5.3-23**) with Umemoto's reagent (**5.3-24**) in the presence of 10 mol% $Pd(OAc)_2$ and one equivalent of the Cu $(OAc)_2$ in 1,2-dichloroethane at 110 °C (Schema 83). The sterically less hindered *ortho*-CH bonds were selectively functionalized so that the mono-trifluoromethylated compounds were obtained in consistent yields. Based on mechanistic studies by Sanford,[230] Pd(II)/Pd(IV) catalytic cycle is the plausible mechanism for this transformation.



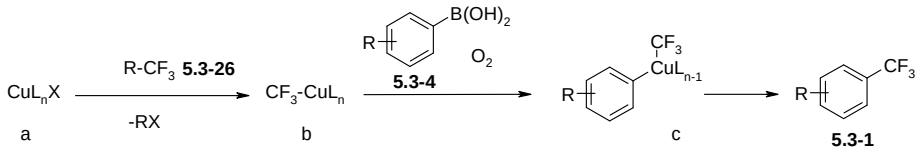
Schema 83. *Pd–catalyzed ortho–trifluoromethylation of Arylptridines*

This protocol is not synthetically efficient as neither Pd^{II} nor Pd^{IV} has the ability to activate cheap, widely available and sustainable aryl chlorides for trifluoromethylation reactions. Furthermore, the use of expensive and waste intensive Umemoto's reagent also limits the

synthetic applicability. However, it is an important transformation from the academic stand point.

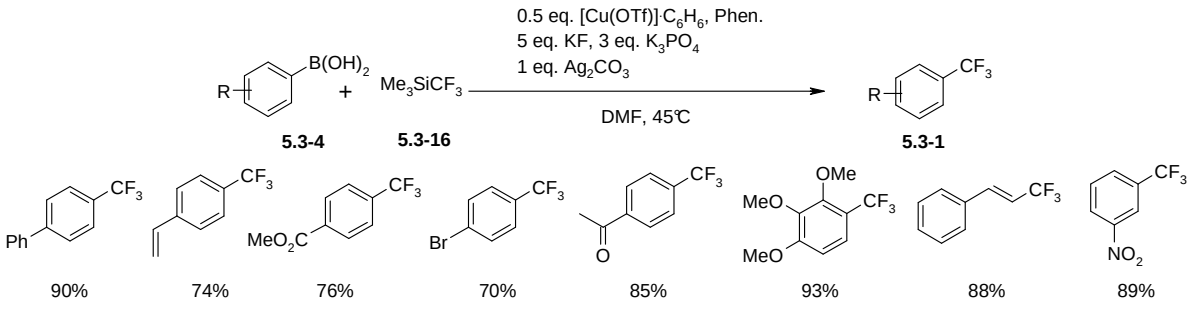
5.3.3 Transition Metal Mediated Oxidative Trifluoromethylation Reactions

The oxidative coupling of arylboronic acids with nucleophilic Ruppert's reagent in the presence of copper represents the third type of trifluoromethylation reactions. Until now only two reports are available which utilize the coupling of arylboronic acids with a nucleophilic trifluoromethylating reagent in the presence of a copper mediator under oxidative conditions. These oxidative trifluoromethylation reactions follow the reaction mechanism as depicted below (Schema 84).[231] The reactive Cu-CF_3 (b) species is formed by the reaction of copper salt (a) and trifluoromethylating reagent (**5.3-26**) which undergoes transmetallation with arylboronic acids (**5.3-4**) to generate aryl-Cu-CF_3-species (c). Benzotrifluoride (**5.3-1**) is liberated via reductive elimination. The role of oxidant is to aid in the reductive elimination.



Schema 84. *Reaction mechanism of oxidative trifluoromethylation reactions*

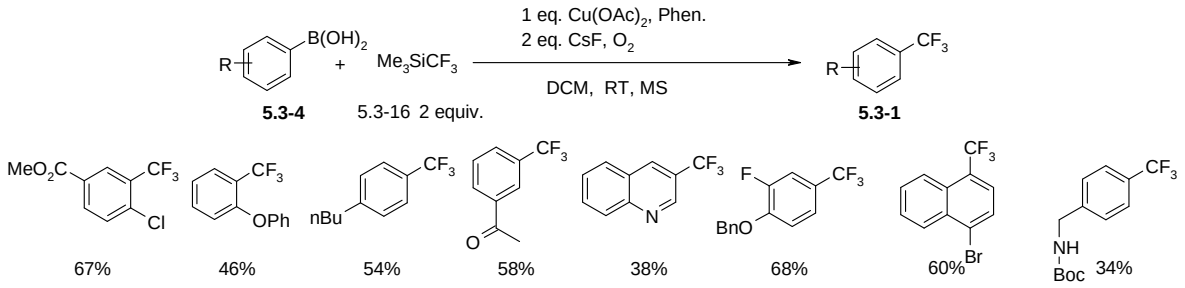
Qing *et al*.[231] reported the copper mediated oxidative coupling of arylboronic acids (**5.3-4**) with Ruppert's reagent (**5.3-16**) in the presence of [Cu(OTf)]·C_6H_6, Ag_2CO_3, K_3PO_4 and molecular sieves at 45 °C (Schema 85). Under the optimized reaction conditions, electron rich, electron poor and heterocyclic aromatic boronic acids were successfully trifluoromethylated. However, the reaction suffers from some serious drawbacks such as the use of expensive and hygroscopic copper-catalyst, expensive silver oxidant and 5 fold excess of highly volatile Ruppert's reagent and often stoichiometric amount of waste generation.



Schema 85. *Oxidative trifluoromethylation of arylboronic acids with Rupperts reagent*

Recently, Buchwald[232] group developed a room temperature oxidative trifluoromethylation of aromatic boronic acids (**5.3-4**) with Ruppert's reagent (**5.3-16**) (Schema 86).[233] Although the

reaction has certain advantages over Qing's protocol in use of cheap and moisture stable $Cu(OAc)_2$, only 2 equivallent of Me_3SiCF_3, and molecular oxygen as oxidant, but complex reaction set up with molecular sieves, use of 2 equivalent of hygroscopic base, and lower yields are the limitations of the Buchwald method.

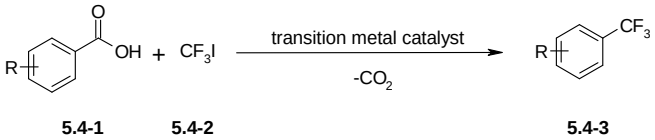


Schema 86. *RT oxidative trifluoromethylation of aryl boronic acids with Rupert's reagent*

This oxidative strategy appears to possess a high potential for late stage trifluoromethylation of complex molecules due to mild reaction conditions. However, the limitations of these reactions can be addressed by using air-and moisture-stable trifluoromethylating partner which does not require any additional activating agent and also avoids molecular sieves.

5.4 Dream Reaction: Decarboxylative Trifluoromethylation of Arenecarboxylic Acids.

Based on the pioneering work in the field of decarboxylative coupling reactions by our group, development of decarboxylative trifluoromethylation reaction is one of our future dream projects. A graphical sketch of this reaction is shown below (Schema 87).



Schema 87. *Dream reaction: decarboxylative trifluoromethylation of arene carboxylic acids*

In order to achieve this goal, our first aim was to develop a one component trifluoromethylating reagent and to study its coupling reactions with aryl halides. This aim was achieved by the development of potassium (trifluoroemthyl)trimethoxyborate as single component and user friendly trifluoromethyalting reagent. The coupling of this reagent with aryl iodides was successfully achieved in the presence of a copper catalyst.[221]

Having established that, our next step will be to apply arylboronic acid derivatives which are easy to activate at lower temperatures and serve as analogus to arenecarboxylic acids, for the synthesis of benzotrifluorides by using the potassium (trifluoroemthyl)trimethoxyborate in the presence of a transition metal.

5.5 Results and Discussions

5.5.1 Oxidative Trifluoromethylation of Arylboronates with Shelf-Stable Potassium (trifluoromethyl)trimethoxyborate

In the enclosed publication, the development of a user friendly protocol for the synthesis of benzotrifluorides from arylboronates is described. This protocol can be useful for late stage introduction of CF_3-group into complex molecules due to mild reaction conditions and easy generation of the arylboronates by Ir-catalyzed C-H functionalization of arenes.[234] Under the optimized reaction conditions, diversely substituted aryl boronic acid pinacol esters are smoothly coupled with commercially available and easy to handle potassium (trifluoromethyl)trimethoxyborate in the presence of 1 equivalent of $Cu(OAc)_2$ and molecular oxygen in DMSO at 60 °C. The use of arylboronates avoids the protodeborylation which is the main side reaction of preceeding protocols. Hygroscopic bases, molecular sieves and 1, 10-phenanthroline ligand are no longer required in this protocol.

The reaction protocol is simplified to a great extent under mild reaction conditions with good yields. This work was done in close cooperation with Dipl. Chem. Annette E. Buba. I performed screening of ligands, catalyst and oxidant, whereas solvents and trifluoromethylation reagent screening was performed by Miss Buba. In addition to the interpretation of all the analytic data, I have also isolated 16 scope compounds out of 20 which are CEJ (**2a-c**, **2e**, **2g-l**, **2n**, **2o**, **2q-t)**.

These results were published in "*Chemistry; A European Journal* **2012**, *18*, 1577-1581." A copy of the manuscript has been attatched. (Oxidative Trifluoromethylation of Arylboronates with Shelf-Stable Potassium (trifluoromethyl)trimethoxyborate, Bilal A. Khan, Annette E. Buba, and Lukas J. Gooßen, Chemistry, A European journal 18/6 Copyright © [2012] Wiley-VCH Verlag GmbH & Co. KGaA).

DOI: 10.1002/chem.201102652

Oxidative Trifluoromethylation of Arylboronates with Shelf-Stable Potassium (Trifluoromethyl)trimethoxyborate

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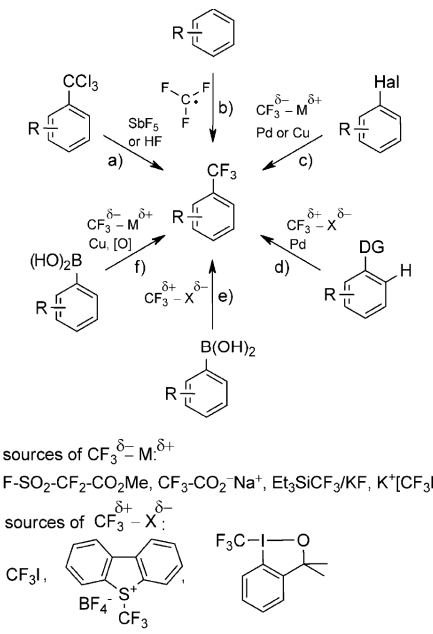
Trifluoromethyl-substituted (hetero)arenes are structural motifs often encountered in pharmaceuticals, agrochemicals, and organic materials, as the CF_3 substituent profoundly affects their chemical and physical properties.[1] In medicinal chemistry, trifluoromethyl groups are widely employed to impart higher metabolic stability, increased lipophilicity, and stronger dipole moments to druglike molecules.[1a–d] Examples for top-selling products featuring trifluoromethyl groups are the pharmaceuticals celecoxib, dutasteride, fluoxetine, and sitagliptin, as well as the agrochemicals beflubutamid, diflufenican, and norfluazon.[1]

Traditional methods to access benzotrifluorides typically require harsh conditions and display a low substrate scope, so that the introduction of a trifluoromethyl group is usually confined to the beginning of a synthetic sequence. Examples of trifluoromethylation strategies are the Swarts reaction of benzotrichlorides using HF or SbF_5, the fluorination of carboxylic acid derivatives with SF_4, and the radical trifluoromethylation of arenes with bis(trifluoroacetyl)peroxide or Langlois' reagent (Scheme 1, a and b).[2] In recent years, substantial research has been devoted to the development of trifluoromethylation reactions that allow the selective introduction of CF_3 groups into functionalized, late-stage synthetic intermediates.[3]

Based on pioneering work on Cu– and Pd–perfluoroalkyl complexes by McLoughlin, Yagupolskii, Burton, Kondo, Chambers, Grushin, and others,[4] four types of processes have been devised (Scheme 1, c–f). Most studied are coupling reactions of aryl halides with nucleophilic CF_3 reagents (Scheme 1, c), most of which involve the use of stoichiometric amounts of copper–CF_3 complexes.[4b,d] These may also be generated in situ from copper salts and Ruppert's reagent (CF_3SiMe_3)[5] or by decarboxylation of copper trifluoroacetates.[6] Chen and Wu reported the use of fluorosulfonyldifluoroacetic acid for the transformation using catalytic amounts of copper.[7] The groups of Amii[8] and Gooßen[9] reported copper-catalyzed processes, which allowed the coupling of aryl iodides with trifluoromethyl silanes or borates. Grushin[10] and Sanford[11] disclosed stoichiometric transformations of Pd–CF_3 complexes, and Buchwald developed the first Pd-catalyzed coupling of aryl chlorides with triethyl(trifluoromethyl)silane.[12]



Scheme 1. Strategies for the introduction of trifluoromethyl groups.

Palladium complexes were also found to catalyze regiospecific C–H functionalizations of arenes with electrophilic trifluoromethylating reagents (Scheme 1, d). Thus, Yu reported the *ortho*-trifluoromethylation of donor-substituted arenes with Umemoto's reagent,[13] and Sanford described a Pd-catalyzed coupling of arenes with perfluoroalkyl iodides.[14] The reaction of arylboronic acids with Togni's and Umemoto's reagent by Shen and Liu, respectively, are examples of coupling reactions of aryl nucleophiles with electrophilic CF_3 sources (Scheme 1, e).[15] Oxidative couplings of aryl nucleophiles with nucleophilic CF_3 reagents (Scheme 1, f) were first reported by Qing, who developed a Chan–Lam–type coupling[16] of arylboronic acids with Ruppert's reagent.[17] The authors proposed a mechanism (Scheme 2) involving the formation of reactive Cu–CF_3 species (**B**) that undergo transmetallation with aryl borates, generating aryl–Cu–CF_3 species (**C**). The benzotrifluoride products are liberated by reductive elimination.

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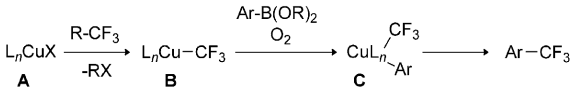
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201102652.

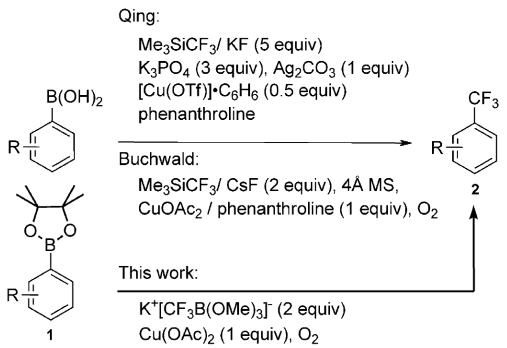


Scheme 2. Tentative mechanism of the oxidative trifluoromethylation.

This last strategy appears to possess a high potential for late-stage functionalizations of complex molecules, as the coupling proceeds close to room temperature and works well for a broad range of substrates. However, the prototype protocol makes use of a $[Cu(OTf)]\cdot C_6H_6$ catalyst that has to be handled in a glove-box, requires Ag_2CO_3 as the oxidant, and involves the slow addition of the boronic acid to a five-fold excess of Ruppert's reagent. Buchwald disclosed an improved protocol, in which many of these initial shortcomings were overcome.[18] Nevertheless, they also used Ruppert's reagent, which acts as a source of CF_3^- in combination with a hygroscopic fluoride salt. It is less expensive than most electrophilic CF_3 reagents, but volatile (b.p. = 45 °C), sensitive to moisture, and prone to decomposition with formation of difluorocarbene and fluorosilicon compounds.

As an alternative one-component trifluoromethylation reagent, Röschenthaler and our group have recently introduced the bench-stable, crystalline potassium (trifluoromethyl)trimethoxyborate.[9,19] It smoothly transfers trifluoromethyl anions to copper catalysts and thus allows the synthesis of benzotrifluorides from aryl iodides. Recently, this meanwhile commercially available reagent has also been used to transfer CF_3 groups to carbonyl compounds.[20]

Herein, we report a straightforward, user-friendly protocol for the conversion of arylboronic acid derivatives into the corresponding benzotrifluorides, based on potassium (trifluoromethyl)trimethoxyborate as the CF_3 source (Scheme 3).

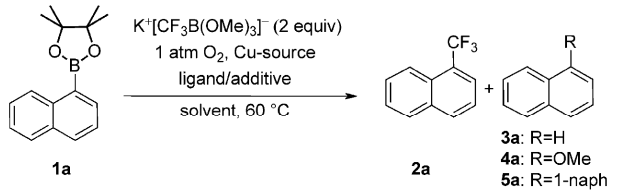


Scheme 3. Oxidative trifluoromethylations of arylboronic acid derivatives.

Both Qing and Buchwald found protodeborylation to be the main side reaction in the Cu-mediated oxidative trifluoromethylation of arylboronic acids with a combination of Ruppert's reagent and CsF as a CF_3 source. Thus, all reagents and additives have to be dried carefully. However, moisture and protons are inevitably introduced with the boronic acid substrate, making the addition of an excess of base or molecular sieves unavoidable. We envisioned that replacing the boronic acids with the corresponding pinacol esters should effectively suppress the protodeborylation, and that the use of $K^+[CF_3B(OMe)_3]^-$ as a one-component trifluoromethylating reagent might allow the development of a simplified and more effective trifluoromethylation method. Pinacol borates are commonly used synthons for the late-stage functionalization of complex molecules, because they can be generated under mild conditions by Pd-catalyzed cross-coupling of the corresponding aryl halides with bis(pinacolato)-diboron,[21] by Ir-catalyzed C–H functionalization of arenes,[22] or by briefly heating the corresponding boronic acids with pinacol.[23] Besides, many of them are commercially available.

We selected 1-naphthylboronic acid pinacol ester (**1a**) as a model substrate for catalyst development, knowing from our investigations on other couplings of boronic acid derivatives that 1-naphthyl boronates are particularly susceptible to protodeborylation.[24] With this model substrate, all products and potential side products, including protodeborylation product **3b**, homocoupling product **5b**, methoxylation product **4b**, and halogenation products, would be detectable by gas chromatography. In analogy to the Buchwald system, we initially used a copper(II)/1,10-phenanthroline catalyst, dichloroethane as the solvent and molecular oxygen as the oxidant, but employed $K^+[CF_3B(OMe)_3]^-$ as the CF_3 source (Table 1).

Table 1. Development of the catalyst system.[a]



	Cu source	Oxidant	Add.	Solvent	Yield [%]			
					2a	**3a**	**4a**	**5a**
1	$Cu(OAc)_2$	O_2	phen	$C_2H_4Cl_2$	17	52	22	8
2	$Cu(OAc)_2$	O_2	CsF	$C_2H_4Cl_2$	12	23	39	16
3	$Cu(OAc)_2$	O_2	MS	$C_2H_4Cl_2$	13	–	60	24
4	$Cu(OAc)_2$	O_2	–	$C_2H_4Cl_2$	20	–	45	33
5	$Cu(OAc)_2$	O_2	–	THF	25[b]	–	29	–
6	$Cu(OAc)_2$	O_2	–	CH_3CN	50[b]	–	26	23
7	$Cu(OAc)_2$	O_2	–	NMP	58	–	36	–
8	$Cu(OAc)_2$	O_2	–	DMSO	79	–	21	–
9	$Cu(acac)_2$	O_2	–	DMSO	21	–	45	32
10	CuOAc	O_2	–	DMSO	25	–	70	–
11	CuF_2	O_2	–	DMSO	15	–	37	42
12	$Cu(OAc)_2$	BQ	–	DMSO	0	–	–	–
13	$Cu(OAc)_2$	DDQ	–	DMSO	0	–	–	–
14	$Cu(OAc)_2$	Ag_2CO_3	–	DMSO	50	–	30	18
15	$Cu(OAc)_2$	$K_2S_2O_8$	–	DMSO	0	–	–	–
16[b]	$Cu(OAc)_2$	O_2	–	DMSO	80	–	20	–

[a] Reaction conditions: **1a** (0.50 mmol), Cu source (1 equiv), additive (1 equiv), solvent (2.5 mL), 80 °C, 1.5 h. Yields were determined by GC analysis using *n*-tetradecane as the internal standard. Add. = Additive, BQ = *p*-benzoquinone, phen = 1,10-phenanthroline, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, MS = 4 Å molecular sieves. NMP = *N*-methylpyrrolidone. [b] Reaction at 60 °C for 3 h.

The desired product was formed in detectable quantities, along with large amounts of by-products resulting from protodeborylation, methoxylation, and homocoupling (Table 1, entry 1). We did not observe any halogenation by-products. Control experiments soon revealed that neither the phenanthroline ligand nor the presence of molecular sieves or fluoride salts had a beneficial influence on the reaction outcome (entries 2–4). In contrast, the choice of solvent was crucial to minimize protodeborylation, as well as homocoupling (entries 4–8). In low polarity solvents, such as dichloroethane and THF, the yields of trifluoromethylated product remained low and the rates of side reactions remained almost unaffected (Table 1, entries 4 and 5). Better results were obtained in aprotic polar solvents, such as acetonitrile and NMP (Table 1, entries 6 and 7). The best results were achieved when using DMSO, in which 1-trifluoromethyl naphthalene was formed in 79% yield (Table 1, entry 8). Under these conditions, neither homocoupling nor protodeborylation was observed. The only by-product was 1-methoxynaphthalene (**4a**, 21%), which results from the transfer of a methoxy group rather than a trifluoromethyl group from $K^+[CF_3B(OMe)_3]^-$. This side reaction could not be further reduced by employing other CF_3 salts, such as $K^+[CF_3B(OEt)_3]^-$. With this reagent, only 37% of the benzotrifluoride **2a** was obtained, along with 58% 1-ethoxynaphthalene. However, we hope that in the future this side reaction can be suppressed by using chelating substituents at the boron.

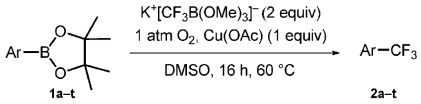
Among the copper salts tested, copper acetate gave the best results (entries 8–11). Beside molecular oxygen, silver carbonate could also be used as the oxidant, whereas other oxidants were ineffective (entries 12–15). A reaction temperature of 60°C proved optimal (entry 16). At lower temperatures, incomplete conversion was observed, while at temperatures higher than 80°C the trifluoromethylating reagent started to decompose.

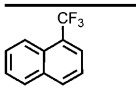
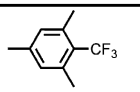
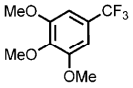
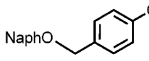
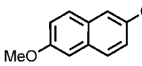
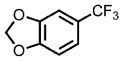
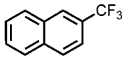
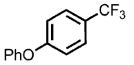
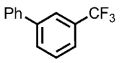
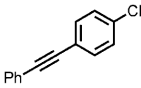
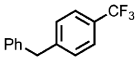
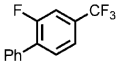
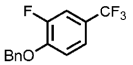
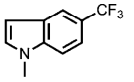
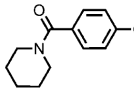
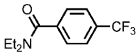
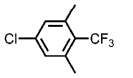
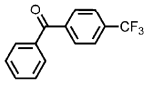
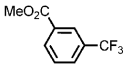
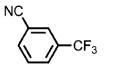
The protocol is very easy to perform. The stable solids aryl pinacol borate, copper(II) acetate, and potassium (trifluoromethyl)trimethoxyborate were dissolved in DMSO and the reaction mixture was briefly purged with oxygen and stirred at 60°C at ambient oxygen pressure for three hours. Then, it was diluted with diethyl ether, washed with aqueous sodium bicarbonate, and the crude product was separated from the by-products by column chromatography.

The optimized protocol allowed the selective synthesis of a wide range of products in moderate to good yields, and many functional groups, such as ether, amide, fluoride, ketone, ester, cyano, and alkynyl groups were tolerated (Table 2). Throughout, the scope of this protocol is comparable with those reported for the related oxidative trifluoromethylation procedures of boronic acids with Ruppert's reagent.[17,18] Particularly electron-rich substrates, such as compounds **2c**–**2h**, were converted in good yields. These compounds are only accessible by treating the boronic acid with expensive electrophilic trifluoromethylation reagents[15] or from the corresponding aryl iodides under harsh reaction conditions.[25] The indole derivative **2n**, an electron-rich heterocycle, was converted in moderate yield, which is in the same order as with the previously reported procedures. Moderately electron-deficient substrates, such as compounds **2l**, **2o**, **2p**, and **2s**, were converted smoothly. In contrast to the other oxidative trifluoromethylation methods, sterically hindered *ortho*,*ortho*-disubstituted boronates, such as **2b** and **2q**, were successfully trifluoromethylated. The optimized reaction conditions were mild enough to be tolerated by electrophilic carbonyl groups. Compound **2r** was obtained in good yield, along with only 10% of the corresponding trifluoromethylated alcohol, which originates from nucleophilic addition of the CF_3 group to the carbonyl group. This represents a frequently observed side reaction common to most nucleophilic trifluoromethylations of carbonyl-group-containing substrates.

In conclusion, the use of the crystalline, shelf-stable, and easy-to-handle potassium (trifluoromethyl)trimethoxyborate as a source of CF_3 nucleophiles in combination with copper acetate as the mediator, molecular oxygen as the oxidant,

Table 2. Scope of the Cu-mediated trifluoromethylation.[a]



Product		Yield [%][b]	Product		Yield [%][b]
	**2a**	73		**2b**	49
	**2c**	63		**2d**	99
	**2e**	70		**2f**	68
	**2g**	63		**2h**	84
	**2i**	71		**2j**	71
	**2k**	59		**2l**	63
	**2m**	44		**2n**	49
	**2o**	67		**2p**	71
	**2q**	46		**2r**	63
	**2s**	40		**2t**	36

[a] Reaction conditions: Potassium (trifluoromethyl)trimethoxyborate (216 mg, 1.00 mmol), $Cu(OAc)_2$ (90.9 mg, 0.50 mmol), arylboronic acid pinacol ester **1** (0.50 mmol), DMSO (2.5 mL), 60°C, 16 h. Naph = 1-naphthyl. [b] Isolated yields.

and DMSO as the solvent led to a user-friendly protocol that allows the smooth conversion of arylboronic acid pinacol esters into the corresponding benzotrifluorides. All yields obtained were comparable to those reported in related oxidative trifluoromethylations or even higher. Protodeborylation, a side reaction in related protocols, was not observed. The main side reaction in our transformation was a substitution of the boronate by methoxy groups originating from the CF_3 source, and in future this side reaction may be controlled by appropriate modification of the CF_3 reagent.

Experimental Section

Representative synthetic procedure—preparation of 1-[{4-(trifluoromethyl)-naphthoxy}methyl]benzene (2d): A 20 mL reaction vessel was charged with 4-[(1-naphthyloxy)methyl]phenylboronic acid pinacol ester (**1d**, 360 mg, 1.00 mmol), copper(II) acetate (90.9 mg, 0.50 mmol), and potassium (trifluoromethyl) trimethoxylborate (216 mg, 1.00 mmol). Anhydrous DMSO (2.5 mL) was added, the reaction vessel was briefly purged with oxygen, and the resulting mixture was stirred at 60°C for 16 h at ambient oxygen pressure. After cooling to room temperature, the reaction mixture was diluted with diethyl ether (20 mL) and washed with saturated aqueous sodium bicarbonate (20 mL). The aqueous layer was extracted with diethyl ether (3×20 mL), and the organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuum. The residue was purified by column chromatography (silica gel, *n*-hexane) to yield **2d** (298 mg, 99%) as a colorless solid. M.p. 80°C; ^{1}H NMR (400 MHz, $CDCl_3$,): δ = 8.33–8.39 (m, 1H; Ar-H), 7.82–7.86 (m, 1H; Ar-H), 7.70 (d, ^3J(H,H) = 8.2 Hz, 2H; Ar-H), 7.67 (d, ^3J-(H,H) = 8.2 Hz, 2H; Ar-H), 7.53 (m, 2H; Ar-H), 7.49 (d, ^3J(H,H) = 8.2 Hz, 1H; Ar-H), 7.39 (t, ^3J(H,H) = 7.9 Hz, 1H; Ar-H), 6.87 (d, ^3J-(H,H) = 7.3 Hz, 1H; Ar-H), 5.33 ppm (s, 2H; $ArCH_2O$); ^{13}C NMR (101 MHz, $CDCl_3$,): δ = 154.1, 141.2, 134.6, 130.1 (q, ^2J(C,F) = 31.9 Hz) 127.5, 127.3, 126.6, 125.7 125.6 (q, ^3J(C,F) = 4.2 Hz) 125.4, 122.0, 124.2 (q, ^1J(C,F) = 271.9 Hz) 120.9, 105.2, 69.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −62.49 ppm (s); IR (KBr): $\tilde{\nu}$ = 3073 (Ar-H), 3052 (Ar-H), 1737, 1598, 1462, 1323, 1264, 1238, 1167, 1112, 1095, 1065, 1017, 825, 769 cm^{-1} (C−F) ; MS (70 eV): *m/z* (%): 303 (16), 302 (77) $[M]^+$, 159 (100), 143 (39), 115 (54), 109 (21), 89 (11); GC/HRMS (EI): *m/z* calcd for $C_{18}H_{13}F_3O$: 302.0918 $[M]^+$; found: 302.0908; elemental analysis calcd (%) for $C_{18}H_{13}F_3O$: C 71.52, H 4.33; found: C 71.39, H 4.45.

Acknowledgements

We thank T. Knauber and G.-V. Röschenthaler for helpful discussions, NanoKat and the DFG (SFB-TRR 88 "3MET") for financial support, and the HEC Pakistan (B.A.K.) and Landesgraduiertenstiftung (A.B.) for fellowships.

Keywords: benzotrifluorides · boronic acids · C−C coupling · copper · trifluoromethylation

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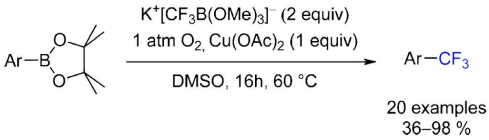
Received: August 25, 2011
Published online: ■■ ▮▮, 2012

Trifluoromethylation



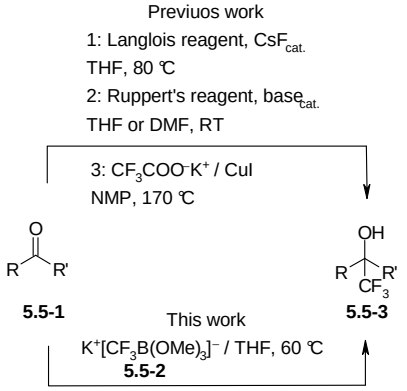
Oxidative Trifluoromethylation of Arylboronates with Shelf-Stable Potassium (Trifluoromethyl)trimethoxyborate

Introducing CF_3: Arylboronic acid pinacol esters are converted into the corresponding benzotrifluorides with the easy-to-use one-component trifluoromethylating reagent potassium (trifluoromethyl)trimethoxyborate, mediated by copper acetate under an oxygen atmosphere (see scheme).

5.5.2 Trifluoromethylation of Carbonyl Compounds with Shelf-Stable Potassium (trifluoromethyl)trimethoxyborate

In this section, synthesis of α-trifluoromethylated alcohols from carbonyl compounds by using single component, easy to handle and commercially available potassium (trifluoromethyl)trimethoxyborate (**5.5-2**) is described. The project was carried out in close collaboration with Dipl. Chem. Annette. E. Buba and Dr. T. Knauber. The project was developed by Mr. Knauber, whereas I and Miss. Buba divided the scope compounds in a way that I isolated compounds **5.5-3a**-**5.5-3m** and she isolated compounds **5.5-3n**-**5.5-3z**.

These α-trifluoromethylated (**5.5-3**) alcohols are usually prepared by treating the corresponding carbonyl compounds (**5.5-1**) with trifluoromethylating reagents such as Ruppert's reagent,[200] Langlois reagent[210] and potassium trifluoromethyl acetates.[235] However, all these procedures are linked with the use of either hygroscopic bases[236] such as CsF or TBAF, or stoichiometric quantities of copper salts at high reaction temperatures[235] (Schema 88).



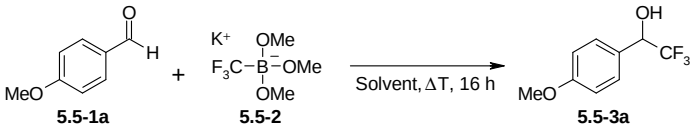
Schema 88. *Synthesis of α-trifluoromethylated alcohols from carbonyl compounds*

Herein, we present a broadly applicable and user-friendly nucleophilic addition of trifluoromethyl group to aldehydes and ketones by using potassium (trifluoromethyl)trimethoxyborate that has already been successfully used for the trifluoromethylation of aryl iodedes.[221]

We selected electron rich and less reactive 4-anisaldehyde (**5.5-1a**) as a test substrate for nucleophilic addition reactions. In a first set of test reactions 4-anisaldehyde (**5.5-1a**) was heated with 1 equiv. of potassium (trifluoromethyl)trimethoxyborate (**5.5-2**) at 60 °C in DMSO (entry 1). The desired product (**5.5-3a**) was detected in 70% yield along with 28% of unreacted substrate (**5.5-1a**). A systematic variation of the solvents showed that the reactivity of potassium (trifluoromethyl)trimethoxyborate (**5.5-2**) is highly dependent on its solubility (entries 2-7). No reaction occured in non polar toluene due to complete insolubility of the salt in toluene, and the aldehyde was fully recovered at the end of the reaction (entry 2). Lower yields were

detected in the 1, 4-dioxane (entry 4) and diglyme (entry 5). In aprotic polar NMP (entry 7), the decomposition of the solvent was observed under the reaction conditions, and a dark brown reaction mixture was formed. The best yields of 86% and 87% were obtained in THF (entry 3) and DMF (entry 6) respectively, in which the salt (**5.5-2**) is completely soluble. The following experiments were carried out in THF, because of its less toxicity in comparison to DMF.

Table 1. *Optimization of the reaction conditions*



5.5-1a **5.5-2** **5.5-3a**

#	Solvent	**5.5-2** [1.25]	T [°C]	**5.5-3a** [%][a]	**5.5-1a** [%][a]
1	DMSO	1.0	60	70	28
2	Toluene	"	"	-	> 99
3	THF	"	"	86	14
4	1,4-Dioxane	"	"	79	19
5	Diglyme	"	"	70	30
6	DMF	"	"	87	12
7	NMP	"	"	-	-
8	THF	"	45	70	30
9	"	"	RT	27	73
10	"	"	80	76	24
11	"	1.25	60	99	-

Reaction conditions: 4-Anisaldehyde (**5.5-1a**, 68.1 mg, 0.50 mmol), $K^+[CF_3B(OMe)_3]^-$ (**5.5-2**), solvent (2.0 mL), 16 h. a) Yields were determined by GC analysis using tetradecane as an internal standard.

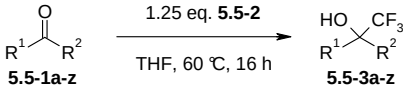
The optimum reaction temperature is 60 °C (entries 8-10). Below this temperature, the reactions were quite slow and much lower yields of (**5.5-3a**) were observed (entries 8 and 9). A decomposition of the salt to volatile fluorocarbons appeared at 80 °C (entry 10).

The aldehyde (**5.5-1a**) was completely converted into the corresponding trifluoromethylated alcohol (**5.5-3a**) by using 1.25 equivalents of CF_3 source (**5.5-2)**, in THF at 60 °C (entry 11).

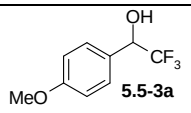
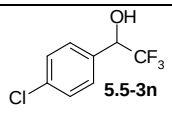
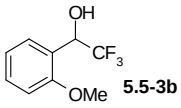
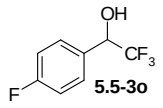
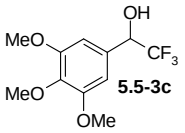
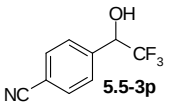
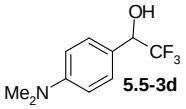
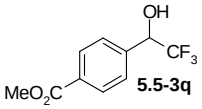
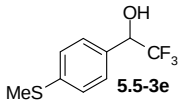
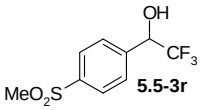
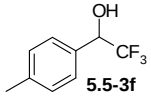
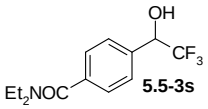
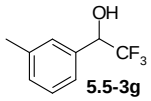
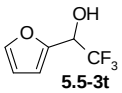
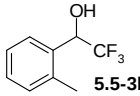
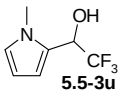
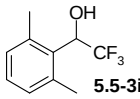
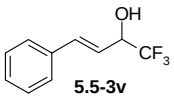
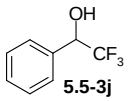
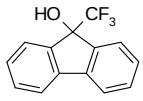
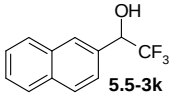
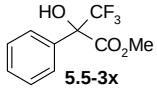
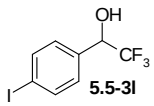
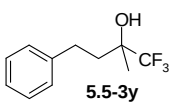
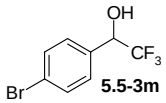
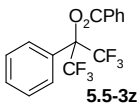
The trifluoromethylation reaction of carbonyl compounds with potassium (trifluoromethyl)trimethoxyborate (**5.5-2)** is very simple to perform. A reaction vessel is charged with potassium (trifluoromethyl)trimethoxyborate (**5.5-2**) and purged with nitrogen to avoid oxidation of sensitive aldehydes. The solvent and the corresponding carbonyl compound (**5.5-1a**) were added and stirred at reaction temperature overnight.

Under the optimized reaction conditions, substituted aromatic, heteroaromatic and aliphatic carbonyl compouds were smoothly converted into the corresponding trifluoromethylated alcohols with potassium (trifluoromethyl)trimethoxyborate (table 2).

Table 2. *Scope of the transformation*



5.5-1a-z → **5.5-3a-z**

Product	yield [%][a]	Product	yield [%]
 **5.5-3a**	85	 **5.5-3n**	74
 **5.5-3b**	79	 **5.5-3o**	59
 **5.5-3c**	84	 **5.5-3p**	75
 **5.5-3d**	83	 **5.5-3q**	92
 **5.5-3e**	78	 **5.5-3r**	77
 **5.5-3f**	75	 **5.5-3s**	83
 **5.5-3g**	87	 **5.5-3t**	49
 **5.5-3h**	80	 **5.5-3u**	53
 **5.5-3i**	79	 **5.5-3v**	77
 **5.5-3j**	92	 **5.5-3w**	79
 **5.5-3k**	91	 **5.5-3x**	30
 **5.5-3l**	87	 **5.5-3y**	37
 **5.5-3m**	70	 **5.5-3z**	49

Reaction conditions: 1 mmol carbonyl compound (**5.5-1a-z**), 1.25 mmol of $K^+[CF_3B(OMe)_3]^-$ (**5.5-2**), 4.0 mL THF, 60 °C, 16 h.

Electron-rich and electron-poor benzaldehydes (**5.5-3a**-**s**) were trifluoromethylated in good yields and even less reactive derivatives such as 3,4,5-trimethoxy-(**5.5-3c**) or bulky 2,6-dimethylbenzaldehydes (**5.5-3i**) were also successfully converted. Many functional groups are tolerated such as amines, thioethers, halides, methylsulfonyl, amides and esters. Slightly lower yields of the volatile products were obtained such as 1-(4-fluorophenyl)-2,2,2-trifluoroethanol (**5.5-3o**), and heterocyclic compounds (**5.5-3t**) and (**5.5-3u**).

Trifluoromethyliton of the Michael systems with potassium (trifluoromethyl)trimethoxyborate (**5.5-2**) regioselectively took place at the carbonyl carbon. The test compound *E*-cinnamaldehyde (**5.5-3v**) was functionalized in a good yield only at the carbonyl group. Under the optimized reaction conditions, ketones (**5.5-3w-y**) were also trifluoromethylated with potassium (trifluoromethyl)trimethoxyborate (**5.5-2**). The best results were obtained with the cyclic diaryl ketones such as fluorenone (**5.5-3w**), for which the corresponding alcohol in 79% yield was isolated.

Low yields were observed for enolizable ketones (**5.5-3y**). In addition to the trifluoromethylated alcohols, large amounts of aldol-reaction products were detected along with gaseous compounds in the reaction mixtures. We concluded that the α-CH-acidic carbonyl compounds are enolized by Lewis acid and borate to react with another molecule of aldehyde or ketone. CF_3-anion is protonated to form fluoroform by the released proton.

As expected, highly reactive carbonyl compounds such as benzoyl chloride (**5.5-3z**) underwent double addition of CF_3-group.[237] The intermediate α,α,α-trifluoroacetophenone reacts with another molecule of borate salt, and the resulting bis-(trifluoromethyl) phenylmethanol (**5.5-3a**) is esterified with benzoyl chloride.

Potassium (trifluoromethyl)trimethoxyborate was used as a single component and user friendly CF_3 reagent. Under the optimized reaction conditions, electron rich, electron-deficient aromatic and heterocyclic carbonyl compounds were selectively trifluoromethylated with only 1.25 equivalents of potassium (trifluoromethyl)trimethoxyborate in THF at 60 °C in good yields. The method has excellent compatibility with functional groups and is characterized by its simple preparative feasibility. Shortly before completion of the manuscript for publication, Dilman *et al*. reported a comparable process with similar results.[206]

5.6 Outlook

Crystalline and shelf-stable potassium (trifluoromethyl)trimethoxyborate has been established as highly versatile CF_3-source in nucleophilic trifluoromethylation reactions. These new protocols

are characterized by their user-friendliness and broad applicability under mild conditions, thus they are beneficial for late stage introduction of CF_3-group into organic molecules.

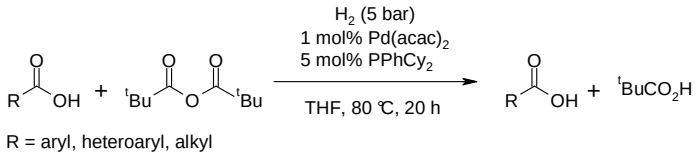
In the first project, potassium (trifluoromethyl)trimethoxyborate was successfully applied for the synthesis of trifluoromethylated arenes under oxidative conditions. In the presence of $Cu(OAc)_2$, and molecular oxygen, arylboronates were coupled with $K^+[CF_3B(OMe)_3]$ in DMSO at 60 °C. Under the optimized reaction conditions, a variety of benzotriflurides are synthesized in good yields. Efficiency of the reagent can be improved by appropriate modifications of the CF_3-reagent.

These optimized protocols for the oxidative trifluoromethylation of arylboronates are developed as the basis for the development of decarboxylative trifluoromethylation reaction of arenecarboxylic acids.

The second project discloses the simple synthesis of trifluormethylated alcohols by nucleophilic addition of potassium (trifluoromethyl)trimethoxyborate to carbonyl compounds. In the presence of $K^+[CF_3B(OMe)_3]$ in THF at 60 °C, diversely functionalized aldehydes and ketones were successfully converted into the corresponding alcohols.

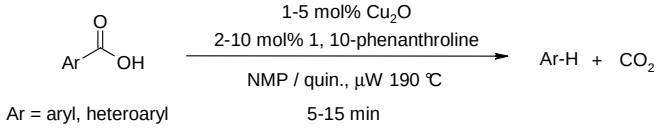
6 Summary of the Thesis

In the 1st project, successful development of 2nd generation of a palladium catalyst for the selective hydrogenation of carboxylic acids to aldehydes was accomplished (Schema 89). This project was done in cooperation with Dipl. Chem. Thomas Fett from Boeringer Ingelheim, Austria. The new catalyst is highly effective for the conversion of diversely functionalized aromatic, heteroaromatic and aliphatic carboxylic acids to the corresponding aldehydes in the presence of pivalic anhydride at 5 bar hydrogen pressure, which was otherwise achieved either at 30 bar of hydrogen pressure or by using waste intensive hypophosphite bases as reducing agent. Our method has increased the synthetic importance of this valuable transformation. Selective hydrogenation of carboxylic acids to the corresponding aldehydes is now possible with industrial hydrogenation equipment as well as laboratory scale glass autoclaves. It might also convince the synthetic organic chemists to use this transformation for routine aldehyde synthesis in the laboratories.



Schema 89. *Low pressure hydrogenation of carboxylic acids to aldehydes*

In the 2nd project, a microwave assisted Cu-catalyzed protodecarboxylation of arenecarboxylic acids to arenes is achieved (Schema 90). This work was done in collaboration with Dipl. Chem. Filipe Manjolinho under the supervision of Dr. Nuria Rodríguez. In the presence of 1-5 mol% of inexpensive Cu^{I}/1,10-phenanthroline catalyst generated *in situ* under microwave radiations, diversely functionalized arenes and heteroarene carboxylic acids have been decarboxylated to the corresponding arenes in good yields at 190 °C in 5-15 min. The loss of volatile arenes with the release of CO_2 is controled by the use of sealed high pressure resistant microwave vessels. These reactions are highly beneficial for parallel synthesis in drug discovery due to their short reaction time. Microwave technology will also help in the future to develop more effective catalysts for protodecarboxylation rections.

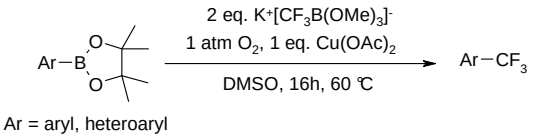


Schema 90. *Microwave-assisted Cu-catalyzed protodecarboxylation of arenecarbocylic acids*

Based on the microwave assisted protodecarboxylation strategy, decarboxylative coupling of arenecarboxylic acids with aryl triflates and tosylates was also conducted under microwave

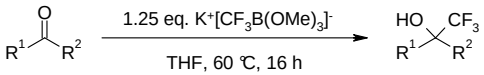
radiation which provided higher yields of the corresponding biphenyls from deactivated substrates in short reaction time compared to the conventional heating.

In the 3rd project, crystalline, potassium (trifluoromethyl)trimethoxyborate was successfully applied for the synthesis of benzotrifluorides under the oxidative conditions (Schema 91). This project was done in cooperation with Dipl. Chem. Annette Buba. In the presence of $Cu(OAc)_2$ and molecular oxygen, arylboronates were coupled with $K^+[CF_3B(OMe)_3]^-$ in DMSO at 60 °C. A variety of benzotriflurides was synthesized in good yields under the optimized reaction conditions. This protocol for the oxidative trifluoromethylation of arylboronates is the base for the development of decarboxylative trifluoromethylation reaction of arenecarboxylic acids.



Schema 91. *Synthesis of benzotrifluorides*

The 4th project discloses the simple and straightforward synthesis of trifluoromethylated alcohols by nucleophilic addition of potassium (trifluoromethyl)trimethoxyborate to carbonyl compounds (Schema 92). This project was done in cooperation with Dr. Thomas Knauber and Dipl. Chem. Annette Buba. In the presence of $K^+[CF_3B(OMe)_3]^-$ in THF at 60 °C, diversely functionalized aldehydes and ketones were successfully converted into the corresponding trifluoromethylated alcohols.



Schema 92. *Synthesis of α-trifluoromethylated alcohols*

The 3rd and 4th projects demonstrate the successful establishment of crystalline and shelf stable potassium (trifluoromethyl)trimethoxyborate as highly versatile CF_3-source in nucleophilic trifluoromethylation reactions. These new protocols are characterized by their user-friendliness and broad applicability under mild reaction conditions, thus they are beneficial for late stage introduction of CF_3-group into organic molecules.

7 Experimental Section

7.1 General Techniques

7.1.1 Chemicals and Solvents

All commercially available chemicals were used without any further purification. Air and moisture sensitive chemical were stored under nitrogen or argon. Reaction vessels were usually charged with solid starting materials and reagents, evacuated (oil pump $\leq 10^{-3}$mbar) to remove oxygen and moisture and backfilled with nitrogen. Solvents and liquid reagents were added under an atmosphere of nitrogen. Solvents were purified with standard literature techniques and stored over 3Å molecular sieves. Inorganic salts such as KF, K_2CO_3, or K_3PO_4 were dried under vacuum at 120°C for 3 hours and stored under nitrogen. Copper salts were dried under vacuum at 60°C for 1 hour.

7.2 Analytical Methods

7.2.1 Thin Layer Chromatography

TLC was performed using analytical silica gel plates 60 F_{254} and analytical neutral alumina plates by Polygram Alox N/UV_{254} by Merk and Macherey-Nagel. The silica gel (230-400 mesh, 60 Å) used for column chromatography was purchased from Aldrich.

7.2.2 Gas Chromatography

For GC-analysis a Hewlett Packard 6980 chromatograph was used. The gas carrier was nitrogen with a flow rate of 149mL/min (0.5 bar pressure). The temperature of the injector was 220 °C. The split-ratio was 1:100. For separation an Agilent HP-5-column with 5% phenyl-methyl-siloxane (30 x 320 μm x 1.0 μm, 100/ 2.3-30-300/ 3) was used. The following temperature program was implemented: starting temperature 60 °C (2min), linear temperature increase (30 °C min^{-1}) to 300 °C, end temperature 300 °C (13min).

7.2.3 Mass Spectroscopy

Mass spectrometry was performed with a GC-MS Varian Saturn 2100 T. The ionization was done by EI AGC. The intensities of the signals are relative to the highest peak. For fragments with isotopes only the more intensive peak of the isotope is given.
High Resolution Mass Spectrum was taken on a GCT premier (Waters).

7.2.4 High-Performance Liquid Chromatography

HPLC analysis was carried out using a Shimadzu HPLC equipped with a Merck KGaA reversed phase column LiChroCart©PAH C 18 with a particle diameter of 5 µm, was operated at a constant temperature of 60°C and a pressure of 200 bars. Acetonitrile and water were used as eluents with a flow rate of 2 mL/mint. Gradient: 15% acetonitrile for 3 min linear increase to 85% within 7 min, hold for 1 min, decrease to 15% within 1 min. and hold for 50 seconds. 5 µL of probe were injected as standard amount into the Rheodyne. This amount can be varied manually through the Shimadzu sequence program Class-VP.

7.2.5 Infrared Spectroscopy

Infrared spectra were recorded with a Perkin-Elmer Fourier Transform Infrared Spectrometer FT/IR. Solids were thoroughly ground and mixed with potassium bromide and pressed into a pellet. Liquids were measured as a thin film in between sodium chloride plates. Absorbance bands are shown in wave numbers (cm^{-1}). Intensities are abbreviated: s (strong), m (medium) and b (broad).

7.2.6 Nuclear Magnetic Resonance Spectroscopy

Proton-, Fluorine- and decoupled carbon-NMR spectra were recorded with a Bruker FT-NMR DPX 200, DPX 400 and a Bruker Avance 600. The frequency and solvent used are described separately for each substance. Chemical shifts are given in units of the δ-scale in ppm. Shifts for ^{1}H-spectra are given respectively to the proton signal of the solvent used (chloroform: 7.25 ppm, dimethyl sulfoxide: 2.50 ppm, methanol: 3.35 ppm, water: 4.75 ppm), for ^{13}C-spectra respectively to the deuterated solvent (chloroform: 77.0 ppm, dimethyl sulfoxide: 37.7 ppm, methanol: 49.3 ppm). *The atom numbering within products is not according to the IUPAC rules*. The multiplicity of the signals is abbreviated by the following letters: Coupling constants are given in Hertz (Hz). Processing and interpretation were performed with ACD- labs 7.0 and ACD- labs 12.0 (Advanced Chemistry Development Inc.)

Signals are abbreviated as s (singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), td (triplet of doublet), q (quartet), quin: (quintet), m: (multiplet), br: (broad).

7.2.7 Elemental Analysis

CHN-elemental analysis was performed with a Perkin-Elmer Elemental Analyzer EA 2400 CHN.

7.2.8 Melting Point

Melting points were measured in a glass cappilary tube with an automatic measuring apparatus Mettler FP61.

7.3 High-throughput Experiments

In order to perform a vast number of experiments a specially manufactured setup was used. All reactions were carried out in 20 mL headspace vials that were closed and clamped shut with aluminum caps fitted with a Teflon-coated butyl rubber septum (both commercially available at Macherey & Nagel).

In 8 cm high round aluminum block, which fit the hot plate of a regular laboratory heater in diameter, 10 of the thus equipped 20 mL headspace vials can be tempered between 25°C and 180 °C. An 11th smaller hole drilled in the middle of the case creates room to hold the thermometer of the heater. A similar setup was used for reactions in autoclave except a 4 cm aluminum block containing 8 holes for head space vials and a small hole for holding the thermameter. This aluminum block is designed to fit inside the autoclave. 10 mL head space vials were used for reactions in autoclave. Figure 1 shows a magnetic stirrer, aluminum block and vacuum distributer (spider) (Abbildung 5).

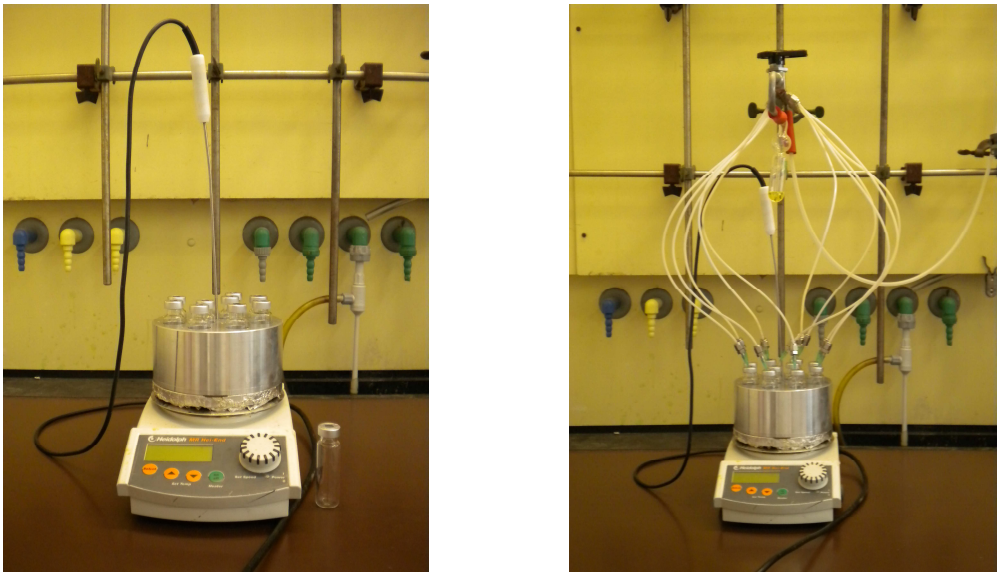


Abbildung 5. *Aluminum block, magnetic stirrer and vacuum distributer*

To correctly evacuate and refill 10 reaction vessels with inert gas at the same time, special vacuum distributors were manufactured to be connected to the Schlenck-line.

A steel tubing is linked to ten 3 mm Teflon tubes, which are equipped on the opposite end with adaptors for Luer-Lock syringe needles. The steel tubing can be connected to the Schlenck-line just like any other laboratory equipment by a steel olive and vacuum tubing. To perform 10 or

more reactions in parallel the following protocol was used. All solid substances were weighed in the reaction vessels, an oven-dried, hot 20 mm stir bar added and each vessel closed with a separate cap using flanging pliars. All 10 vessels were transferred to one of the aforementioned aluminum cases and evacuated using syringe needles connected to the vacuum steel tubing.

The reaction vessels were evacuated and refilled with nitrogen. Using standard sterile and Hamilton syringes all liquid reagents, stock solutions of reagents and solvents were added and the vessels were evacuated and refilled with nitrogen 3 times. After removal of the needles, the aluminum case was tempered to the desired temperature. Every temperature description is the case temperature, which only differs by maximum 2°C from the actual reaction media temperature.

At the end of the reaction time and after cooling to room temperature, pressure was released with a needle and the standard (n-tetradecane) was added with a Hamilton syringe. The reaction vials were opened carefully. 2 mL of ethyl acetate were added to dilute the reaction mixture and with a disposable pipette mixed thoroughly to ensure a homogenous mixture. A 0.25 mL sample was withdrawn and extracted with 2 mL of ethyl acetate and 2 mL of aqueous HCl solution (acidic work up) or saturated potassium bicarbonate solution (basic work up). The organic layer was filtered through a pipette filled with a cotton plug and $NaHCO_3$ /magnesium sulfate(in case of acidic work up) or only $MgSO_4$ into a GC-vial.

After evaluating the contents on the GC and if necessary GC-MS, the contents of all work-up and analysis vials were recombined and the product isolated using standard procedures, deposed on silica-gel and purified by flash chromatography using a Combi Flash Companion-Chromatography apparatus from Ico-Systems.

The developed experimental setups and an electronic laboratory journal allowed a substantial amount of reactions to be performed during the course of this work. Approximately 2500 reactions would have consumed a much longer time using standard laboratory techniques. Preparative reactions were performed mostly in standard laboratory oven-dried glass ware. The following experimental section describes all reactions performed, that are mentioned in the theoretical section above. Yields are isolated yields if nothing else is mentioned. All known compounds were analysed by at least ^{1}H-NMR, ^{13}C-NMR and GC-MS whereas unknown compounds were analyzed by ^{1}H-NMR, ^{13}C-NMR, IR spectroscopy, GC-MS and HR-MS or elemental analysis, melting point (for solids) and ^{19}F-NMR for trifluoromethylated compounds.

7.4 Reactions under Pressure

All hydrogenation reactions were performed in 10 mL headspace vials which were sealed with aluminum crimp caps Teflon-coated butyl rubber septa. The septa of closed reaction vessels were pierced with spiral needles to uniformely distribute the reaction gas inside the vials. These pressurized reactions were carried out in a specially designed autoclave which has a volume of 100 mL and a diameter of 8.2 cm, equipped with a 7 cm deep hole for receiving a temperature sensor. It contains an inner block which can hold upto 8 reaction vials. The pressurization of the autoclave was done through a quick fit with the respective gas. After reaching the desired pressure, it was closed by a needle valve.

7.5 Reactions under Microwave-Irradiation

All microwave radiation experiments were carried out in a CEM-Discover® LabMate mono-mode microwave apparatus equipped with an IntelliVent™ pressure control system and a vertically-focused IR temperature sensor. The reaction was monitored with CEM's ChemDriverTM software. After the irradiation period, the reaction vessel was cooled rapidly (60-120 sec) to ambient temperature by air jet cooling.

7.6 Low Pressure Hydrogenation of Carboxylic Acids to Aldehydes

7.6.1 General Methods for the Synthesis of Aldehydes

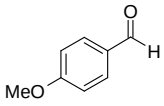
An oven-dried, argon-flushed 10-mL glass vessel with septum top was charged with benzoic acid 1a–r (1.00 mmol), $Pd(acac)_2$ (3.05 mg, 0.01 mmol), and dicyclohexylphenylphosphine (13.7 mg, 0.05 mmol). Degassed THF (2 mL) and degassed pivalic anhydride (0.62 mL, 3.00 mmol) were added. The vessel was placed in a steel autoclave, which was then purged with hydrogen and then pressurized with 5 bar of hydrogen. The reaction mixture was stirred at 80°C for 20 h, then cooled to room temperature. The autoclave pressure was released, the reaction mixture diluted with 10 mL saturated $NaHCO_3$ solution and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$, filtered, and the volatiles were removed under vacuum. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient) affording corresponding aldehydes.

The particularly volatile aldehydes AS&C–(2a, e, g, h, o, p, and q) were isolated as bisulfite adducts: after releasing the pressue from the autoclaves, 38% sodium bisulfite solution (1.50 mL, 8.10 mmol) was added via syringe to the reaction vessel. The residue mixture was stirred at 50 °C for 4 h, and then cooled to room temperature. The white crystalline adducts were filtered off

and washed with chloroform (10 mL) and water (0.50 mL), dried under vacuum, and weighed to determine the yield. For the spectroscopic characterization, part of the aldehydes was then liberated by adding the adduct to saturated aqueous $NaHCO_3$ solution (2.0 mL), followed by extraction with $CDCl_3$ (2.0 mL). The NMR samples were then washed with water and brine, dried over $MgSO_4$ and filtered. NMR samples were evaporated to get pure products.

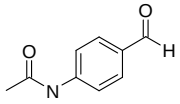
7.6.2 Synthesis of Aldehydes

4-Methoxybenzaldehyde (AS&C-2a) CAS: [123-11-5]



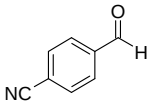
Compound (AS&C-2a) was prepared from 4-methoxybenzoic acid (AS&C-1a) (152 mg, 1.00 mmol) affording (AS&C-2a) as colorless oil; yield: 124.9 mg (90.8%). The spectroscopic data matched those reported in the literature for (AS&C-2a). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.83 (s, 1H), 7.78 (d, *J* = 8.6Hz, 2H), 6.95 (d, *J* = 8.6Hz, 2H), 3.83 (s, 3H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 91.0, 164.8, 132.1, 130.1, 114.5, 55.7 ppm; MS (EI): m/z (%) = 136 (53) [M^+], 135 (100), 107 (27), 77 (60), 63 (23), 50 (20), 40 (46); IR (NaCl) = 3010 (w), 2970 (w), 2938 (w), 2840 (w), 2739 (w), 1679 (s), 1594 (m), 1576 (m), 1509 (m), 1255 (m), 1156 (s), 1021 (m), 829 (s) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_8H_8O_2$: calc. mass: 136.0520; found: 136.0524.

4-Acetamidobenzaldehyde (AS&C-2b) CAS: [122-85-0]



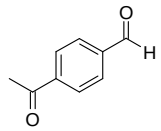
Compound (AS&C-2b) was prepared from 4-acetamidobenzoic acid (AS&C-1b) (179 mg, 1.00 mmol) affording (AS&C-2b) as a colorless crystalline solid; yield: 149 mg (91%). The spectroscopic data matched those reported in the literature for (AS&C-2b). m.p. 149 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.91 (s, 1H), 7.84 (d, *J* = 8.6, Hz, 2H), 7.70 (d, *J* = 8.6Hz, 3H), 2.22 (s, 3H) ppm;^{13}C-NMR (101 MHz, $CDCl_3$) δ = 190.6, 168.2, 143.1, 132.0, 130.8, 118.8, 24.5; MS (EI): m/z (%) = 163 (42) [M^+], 121 (61), 120 (100), 92 (23), 65 (29), 43 (40); IR (KBr) = 3308 (w), 3262 (w), 3193 (w), 3122 (w), 2816 (w), 2733 (w), 1687 (m), 1673 (m), 1597 (m), 1533 (m), 1372 (m), 1327 (m), 1268 (m), 1165 (m), 830 (m) cm^{-1}; Elemental analysis: Calcd: C, 66.25; H, 5.56; N, 8.58; Found: C, 66.01; H, 5.52; N, 8.55.

4-Cyanobenzaldehyde (AS&C-2c) CAS: [105-07-7]



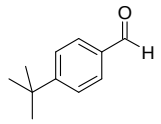
Compound (AS&C-2c) was prepared from 4-cyanobenzoic acid (AS&C-1c) (149 mg, 1.00 mmol) affording (AS&C-2c) as a colorless crystalline solid; yield: 98.6 mg (75%). The spectroscopic data matched those reported in the literature for (AS&C-2c). m.p. 99 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 10.05 (s, 1H), 7.89-8.02 (m, 2H), 7.76-7.86 (m, 2H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 190.5, 138.6, 132.7, 129.7, 117.5, 117.3, ppm; MS (EI): m/z (%) = 132 (16), 131 (18) [M^+], 130 (100), 102 (37), 76 (14), 75 (11), 50 (13); IR (KBr) = 3093 (w), 3046 (w), 2855 (w), 2752 (w), 2229 (w), 1698 (s), 1606 (w), 1570 (w), 1296 (w), 1201 (m), 827 (s); Elemental analysis: Calcd: C, 73.27; H, 3.84; N, 10.68; Found: C, 73.27; H, 3.91; N, 10.61.

4-Acetylbenzaldehyde (AS&C-2d) CAS: [3457-45-2]



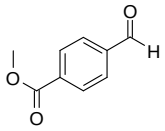
Compound (AS&C-2d) was prepared from 4-acetylbenzoic acid (AS&C-1d) (164 mg, 1.00 mmol) affording (AS&C-2d) as a colorless crystalline solid; yield: 137 mg (92%). The spectroscopic data matched those reported in the literature for 4-acetylbenzaldehyde (AS&C-2d). m.p. 34 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 10.01 (s, 1H), 8.01 (d, *J* = 8.6Hz, 2H), 7.88(d, *J* = 8.2Hz, 2H), 2.57 (s, 3H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 197.2, 191.4, 141.0, 138.8, 129.6, 128.6, 26.7 ppm; MS (EI): m/z (%) = 149 (13), 148 (4) [M^+], 133 (100), 105 (22), 104 (5), 77 (5), 43 (27); IR (KBr) = 3060 (w), 3006 (w), 2914 (w), 2846 (w), 2740 (w), 1697 (s), 1676 (s), 1500 (m), 1258 (s), 1203 (s), 823 (s); GC/HRMS-EI m/z [M^+] calcd. for $C_9H_8O_2$: Calcd 148.0528; found 148.0524.

4-*tert*-Butylbenzaldehyde (AS&C-2e) CAS: [939-97-9]



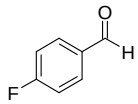
Compound (AS&C-2e) was prepared from 4-tert-butylbenzoic acid (AS&C-1e) (180 mg, 1.00 mmol) affording (AS&C-2e) as colorless oil; yield: 123 mg (76%). The spectroscopic data matched those reported in the literature for 4-*tert*-butylbenzaldehyde (AS&C-2e). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.97 (s, 1H), 7.80 (d, *J* = 8.2Hz, 2H), 7.54 (d, *J* = 8.2Hz, 2H), 1.34 (s, 9H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 192.3, 158.7, 134.3, 130.0, 126.3, 35.6, 31.3; MS: (EI): m/z (%) = 163 (18), 162 (5), 147 (100), 119 (39), 115 (8), 91 (69), 77 (9).

4-Methoxycarbonylbenzaldehyde (AS&C-2f) CAS: [1571-08-0]



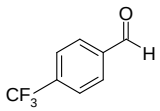
Compound (AS&C-2f) was prepared from 4-methoxycarbonylbenzoic acid (AS&C-1f) (180 mg, 1.00 mmol) affording (AS&C-2f) as a colorless crystalline solid; yield: 132 mg (80%). The spectroscopic data matched those reported in the literature for 4-methoxycarbonylbenzaldehyde (AS&C-2f). m.p.: 61 °C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 10.08 (s, 1H), 8.18 (d *J* = 8.2Hz, 2H), 7.94 (d, *J* = 8.6 Hz, 2H), 3.94 (s, 3H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 191.9, 166.3, 139.4, 135.4, 130.5, 129.9, 129.8, 52.9 ppm; MS (EI): m/z (%) = 164 (53) [M^+], 163 (27), 133 (100), 105 (45), 77 (43), 51 (29), 50 (27); IR (KBr) = 2963 (w), 2887 (w), 1721 (s), 1682 (m), 1576 (m), 1434 (m), 1279 (s), 1105 (s), 850 (s) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_9H_8O_3$: Calcd: 164.0471; found: 164.0473.

4-Fluorobenzaldehyde (AS&C-2g) CAS: 459-57-4



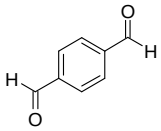
Compound (AS&C-2g) was prepared from 4-fluorobenzoic acid (AS&C-1g) (143.0 mg, 1.00 mmol) affording (AS&C-2g) as colorless oil; yield: 90 mg (80%). The spectroscopic data matched those reported in the literature for 4-fluorobenzaldehyde (AS&C-2g). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.96 (s, 1H), 7.90 (dd, *J* = 8.6, 5.5Hz, 2H), 7.20 (t, *J* = 8.6Hz, 2H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 190.5, 167.4, 165.7, 133, 132.3, 116.4, 116.3 ppm; MS (EI): m/z (%) = 124 (33) [M^+], 123 (100), 96 (12), 95 (61), 75 (36), 74 (15), 50 (20); IR (NaCl) = 2827 (w), 2729 (w), 1701 (s), 1596 (s), 1506 (s), 1420 (w), 1388 (w), 1229 (s), 1149 (s), 1128 (s), 833 (m); GC/HRMS-EI m/z [M^+] calcd. for C_7H_5FO: 124.0314; found: 124.0324.

4-(Trifluoromethyl) benzaldehyde (AS&C-2h): CAS: [455-19-6]



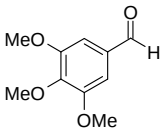
Compound (AS&C-2h) was prepared from 4-(trifluoromethyl)benzoic acid (AS&C-1h) (190 mg, 1.00 mmol) affording (AS&C-2h) as a colorless oil; yield: 139 mg (80%). The spectroscopic data matched those reported in the literature for 4-(trifluoromethyl) benzaldehyde (AS&C-2h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 10.09 (s, 1H), 8.0 (d, *J* = 8.2Hz, 2H), 7.80 (d, *J* = 7.8Hz, 2H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 191.1, 138.6, 135.8, 129.9, 126.1 (q, *J* = 3.7 Hz), 122.3 (q, *J* =272 Hz) ppm; MS: (EI): m/z (%) = 175 (12), 174 (15) [M^+], 173 (100), 145 (63), 127 (12), 75 (18), 50 (15).

1,4-Benzenedicarboxaldehyde (AS&C-2i) CAS: [623-27-8]



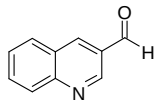
Compound (AS&C-2i) was prepared from 1,4-benzenedicarboxalic acid (AS&C-1i) (166 mg, 1.00 mmol) affording 2i as a colorless crystalline solid; yield: 114 mg (85%). The spectroscopic data matched those reported in the literature for 1,4-benzenedicarboxaldehyde (AS&C-2i). m.p.: 115 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 10.13 (s, 2H), 8.04 (s, 4H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 191.3, 139.8, 129.9 ppm; MS (EI): m/z (%) = 135 (19), 134 (24) [M^+], 133 (100), 105 (39), 77 (29), 51 (20), 50 (12); IR (KBr) = 3089 (w), 2865 (w), 2807 (w), 1686 (s), 1498 (m), 1367 (m), 1300 (m), 1195 (s), 769 (s) cm^{-1}; Elemental analysis: Calcd: C, 71.50; H, 4.51; Found: C, 71.50; H, 4.46.

3,4,5-Trimethoxybenzaldehyde (AS&C-2j) CAS: [86-81-7]



Compound (AS&C-2j) was prepared from 3,4,5-trimethoxybenzoic acid (AS&C-1j) (212 mg, 1.00 mmol) affording 2j as a colorless crystalline solid; yield: 174 mg (75.8%). The spectroscopic data (NMR) matched those reported in the literature for 3,4,5-trimethoxybenzaldehyde (AS&C-2j). m.p. 75 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.86 (s, 1H), 7.12 (s, 2H), 3.90-3.97 (m, 9H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 190.7, 143.3, 131.4, 106.4, 60.7, 56.0 ppm; MS (EI): m/z (%) = 197 (20), 196 (100) [M^+], 181 (48), 125 (31), 110 (28), 95 (17), 93 (17); IR (NaCl): = 3091 (w), 2987 (m), 2841 (m), 2753 (w), 1685 (s), 1585 (s), 1505 (s), 1457 (s), 1435 (s), 1423 (s), 1391 (s), 1332 (s), 1234 (s), 1146 (s), 1128 (s), 992 (s), 846 (s), 758 (s), 730 (s) cm^{-1}; Elemental analysis: Calcd: C, 61.22; H, 6.16; Found: C, 61.46; H, 6.26.

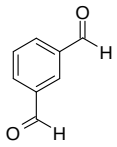
3-Quinolinecarboxaldehyde (AS&C-2k) CAS: [13669-42-6]



Commpound (AS&C-2k) was prepared from 3-quinolinecarboxylic acid (AS&C-1k) (177 mg, 1.00 mmol) affording (AS&C-2k) as a colorless crystalline solid; yield: 102 mg (78%). The spectroscopic data matched those reported in the literature for 3-quinolinecarboxaldehyde (AS&C-2k). m.p. 67 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 10.26 (s, 1H), 9.37 (d, *J* = 1.5Hz, 1H), 8.649 (s, 1H), 8.20 (d, *J* = 8.2Hz, 1H), 8.00 (d, *J* = 7.9Hz, 1H), 7.89 (t, *J* = 7.6Hz, 1H), 7.67(t, *J* = 7.5Hz, 1H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 190.5, 150.4, 148.9, 139.9, 132.5, 129.5,

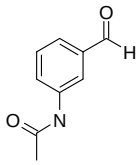
129.2, 128.4, 127.7, 126.8 ppm; MS (EI): m/z (%) = 157 (79) [M^+], 156 (83), 128 (100), 101 (35), 75 (36), 74 (19), 50 (25); IR = 3018 (w), 2843 (w), 2795 (w), 1685 (s) 1620 (w), 1574 (m), 1429 (m), 1218 (m), 1153 (m), 835 (s) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. $C_{10}H_7NO$: 157.0527; found: 157.0528.

1,3-Benzenedicarboxaldehyde (AS&C-2l) CAS: [626-19-7]



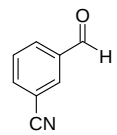
Compound (AS&C-2l) was prepared from 1,3-benzenedicarboxylic acid (AS&C-1l) (166 mg, 1.00 mmol) affording (AS&C-2l) as colorless crystals; yield: 56.0 mg (42%). The spectroscopic data matched those reported in the literature for 1,3-benzenedicarboxaldehyde (AS&C-2l). m.p. 88 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 10.11 (s, 2H), 8.38 (s, 1H), 8.15 (dd, *J* = 7.4, 1.6Hz, 2H), 7.73 (t, *J* = 7.6Hz, 1H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 191.3, 137.3, 134.9, 131.39, 130.2 ppm; MS (EI): m/z (%) = 135 (10), 134 (29) [M^+], 133 (100), 105 (49), 77 (43), 51 (30), 50 (22); Elemental Analysis; Calcd: C, 71.64; H, 4.51; Found: C, 71.15; H, 4.54.

3-Acetamidobenzaldehyde (AS&C-2m) CAS: [59755-25-8]



Compound (AS&C-2m) was prepared from 3-acetamidobenzoic acid (AS&C-1m) (179 mg, 1.00 mmol) affording (AS&C-2m) as a colorless crystalline solid; yield: 150 mg (92%). The spectroscopic data matched those reported in the literature for 3-acetamidobenzaldehyde (AS&C-2m). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.88 (s, 1H), 8.96 (s, 1H), 7.82 (d, *J* = 7.8Hz, 1H), 7.54 (d, *J* = 7.4Hz, 1H), 7.40 (t, *J* = 7.8Hz, 1H), 2.18(s, 3H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 192.3, 169.5, 139.1, 136.7, 129.5, 120.4, 24.2 ppm; MS (EI): m/z (%) = 163 (42) [M^+], 121 (100), 120 (83), 92 (24), 65 (27), 63 (16), 43 (36); Elemental Analysis: Calcd: C, 66.25; H, 5.56; N, 8.58; Found: C, 66.07; H, 5.79; N, 8.45.

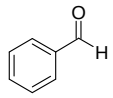
3-Cyanobenzaldehyde (AS&C-2n) CAS: [24964-64-5]



Compound (AS&C-2n) was prepared from 3-cyanobenzoic acid (AS&C-2n) (150 mg, 1.00 mmol) affording (AS&C-2n) as colorless crystals; yield: 102 mg (78%). The spectroscopic data matched those reported in the literature for 3-cyanobenzaldehyde (AS&C-2n). m.p. 78 °C;^{1}H-

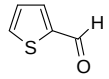
NMR (400 MHz, $CDCl_3$) δ = 10.04 (s, 1H), 8.16 (s, 1H), 8.12 (d, *J* = 7.8Hz, 1H), 7.91 (d, *J* = 7.8Hz, 1H), 7.69 (t, *J* = 7.6Hz, 1H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 189.6, 136.9, 136.5, 132.9, 132.8, 129.8, 117.2, 113.4 ppm; MS: (EI): m/z (%) = 132 (16), 131 (18) [M^+], 130 (100), 102 (37), 76 (14), 75 (11), 50 (13).

Benzaldehyde (AS&C-2o) CAS: [100-52-7]



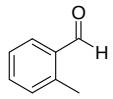
Compound (AS&C-2o) was prepared from benzoic acid (AS&C-1o) (122 mg, 1.00 mmol) affording (AS&C-2o) as colorless oil; yield: 84.0 mg (79%). The spectroscopic data matched those reported in the literature for benzaldehyde (AS&C-2o). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 10.01(s, 1H), 7.87(d, *J* = 7.0Hz, 2H), 7.62 (t, *J* = 7.2Hz, 1H), 7.52 (d, *J* = 7.5Hz, 2H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 192.7, 134.8, 130.1, 129.7, 129.0 ppm; MS (EI): m/z (%) = 106 (32) [M^+], 105 (100), 78 (14), 77 (91), 51 (49), 50 (41), 40 (21); IR (NaCl) = 3084 (w), 2818 (m), 2737 (m), 1701 (s), 1596 (s), 1583 (s), 1455 (s), 1390 (s), 1310 (s), 1203 (s), 1167 (s), 1234 (s), 1167 (s), 827 (s), 746 (s), 688 (s) cm^{-1}.

3-Thiophenecarboxaldehyde (AS&C-2p) CAS: [498-62-4]



Compound (AS&C-2p) was prepared from 3-thiophenecarboxylic acid (AS&C-1p) (128 mg, 1.00 mmol) affording (AS&C-2p) as colorless oil; yield: 79.0 mg (70%). The spectroscopic data matched those reported in the literature for 3-thiophenecarboxaldehyde (AS&C-2p). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.93 (s, 1H), 8.12 (dd, *J* = 2.9, 1.2Hz, 1H), 7.51-7.56 (m, 1H), 7.37 (dd, *J* = 4.4, 2.9Hz 1H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 185.1, 143.2, 136.9, 127.6, 125.6 ppm; MS (EI): m/z (%) = 113 (15), 112 (45) [M^+], 111 (100), 83 (20), 58 (11), 57 (8), 45 (21); IR (NaCl) = 3088 (m), 2820 (m), 2789 (m), 2760 (w), 1695, (s), 1519 (s), 1418 (s), 1391 (s), 1355 (m), 1234 (s), 1046 (s), 863 (s), 728 (s); Elemental Analysis: Calcd: C, 53.55; H, 3.59; S, 28.59; Found: C, 53.24; H, 3.75; S, 28.70.

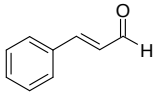
2-Methylbenzaldehyde (AS&C-2q) CAS: [529-20-4]



Compound (AS&C-2q)was prepared from 2-methylbenzoicacid (AS&C-1q) (138 mg, 1.00 mmol) affording (AS&C-2q) as colorless oil; yield: 106.0 mg (88%). The spectroscopic data matched those reported in the literature for 2-methylbenzaldehyde (AS&C-2q). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 10.28 (s, 1H), 7.88 (dd, *J* = 7.5, 1.3Hz, 1H), 7.47 (dd, *J* = 7.4, 1.6, 1H), 7.24-

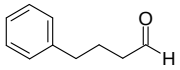
7.41 (m, 2H), 2.68 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 192.5, 140.3, 133.8, 133.3, 131.7, 131.4, 19.3 ppm; MS (EI): m/z (%) = 120 (53) [M^+], 119 (79), 92 (10), 91 (100), 89 (11), 65 (38), 63 (19); IR (NaCl) = 3067 (w), 2962 (w), 2926 (w), 2734 (w), 1701 (s), 1600 (s), 1573 (m), 1457 (w), 1438 (w), 1405 (w), 1284 (s), 1211 (s), 1194 (s), 862 (m), 833 (m), 754 (s); GC/HRMS-EI m/z [M^+] calcd. for C_8H_8O: 120.0572; found: 120.0575.

(2E)-3-Phenylprop-2-enal (AS&C-2r) CAS: [104-55-2]



Compound (AS&C-2r) was prepared from (E)-3-phenylprop-2-enoic acid (AS&C-1r) (148 mg, 1.00 mmol) affording (AS&C-2r) as colorless oil; yield: 90.0 mg (68%). The spectroscopic data matched those reported in the literature for (2E)-3-phenylprop-2-enal (AS&C-2r). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 7.8 Hz, 1 H), 7.58 (dd, *J* = 6.7, 2.7 Hz, 2 H), 7.49 (d, *J* = 16.0 Hz, 1 H), 7.41-7.47 (m, 3 H), 6.73 (dd, *J* = 16.0, 7.8 Hz, 1 H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 193.7, 152.7, 134.0, 131.2, 129.1, 128.6, 128.5; IR (NaCl) = 3060 (w), 3028 (w), 2814 (w), 2742 (w), 1700 (s), 1625 (s), 1450 (m), 1294 (m), 1124 (s), 973 (s), 748 (s), 688 (s); Elemental Analysis: Calcd: C, 81.79; H, 6.10.; Found: C, 81.43; H, 6.10.

4-Phenylbutyl aldehyde (3.3-2s): [18328-11-5]



Compound (3.3-2s) was prepared from 4–phenylbutyric acid (3.2-1s) (148 mg, 1.00 mmol) affording (3.2-2s) as colorless oil; yield: 121 mg (82%). The spectroscopic data matched those reported in the literature for 4-phenylbutylaldehyde (5.2-2s). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.78 (s, 1 H), 7.31-7.40 (m, 2 H), 7.20-7.28 (m, 3 H), 2.70 (t, *J* = 7.6 Hz, 2 H), 2.48 (t, *J* = 7.2 Hz, 2 H), 1.94-2.08 (m, 2 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 202.1, 141.1, 128.3, 128.3, 125.9, 42.9, 34.8, 23.5 ppm; MS (EI): m/z (%) = 148 (3) (M^+), 147 (1), 130 (57), 104 (100), 91 (38), 55 (15).

7.7 Microwave-Assisted Copper-Catalyzed Protodecarboxylation of Arenecarboxylic Acids

7.7.1 General ethods for the Synthesis of Arenes

Method A.

An oven-dried 10 mL microwave vial was charged with the carboxylic acid (1.0 mmol), Cu_2O (7.2 mg, 0.05 mmol), and 1,10-phenanthroline (18 mg, 0.10 mmol). After the reaction mixture was made inert, a mixture of NMP (1.5 mL) and quinoline (0.5 mL) was added via syringe. The

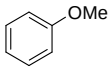
resulting mixture was submitted to microwave irradiation at 190 °C for 15 min at a maximum power of 150 W and subsequently air-jet cooled to room temperature. The maximum pressure detected during the reaction was 5.5 bar. The mixture was then diluted with aqueous HCl (5N, 10 mL) and extracted repeatedly with diethyl ether (2 mL portions). The combined organic layers were washed with water and brine, dried over MgSO4, and filtered. The corresponding arene was obtained in pure form after removal of the solvents by distillation over a Vigreux column.

Method B.

Method B is analogous to method A but with a lower loading of the copper/phenanthroline catalyst and microwave irradiation at 190 °C for 5 min at a maximum power of 150 W. The following amounts were used: carboxylic acid (1b, l-t) (1.0 mmol), Cu_2O (1.5 mg, 0.01 mmol), and 1,10-phenanthroline (3.6 mg, 0.02 mmol).

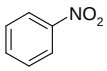
7.7.2 Synthesis of Arenes

Anisole (JOC-2a) CAS: [100-66-3]



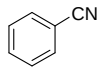
Synthesized from 4-methoxybenzoic acid (JOC-1a) (152 mg, 1.00 mmol) following method A and obtained as colorless liquid (84 mg, 77%). The spectroscopic data matched those reported in the literature. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.31-7.37 (m, 2H), 6.94-7.02 (m, 3H), 3.84 (s, 3H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 159.6, 129.4, 120.6, 113.9, 55.0 ppm; MS (EI) m/z (%) = 108 (100) [M^+], 78 (7), 65 (10), 63 (5); IR (NaCl) = 3031 (w), 3003 (w), 2945 (w), 1599 (m), 1587 (m), 1496 (s), 1243 (s), 1038 (s), 751 (s); Elemental analysis:Calcd: C, 77.75; H, 7.46; Found: C, 78.01; H, 7.35.

Nitrobenzene (JOC-2b) CAS: [98-95-3].



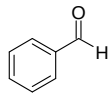
Synthesized from 2-nitrobenzoic acid (JOC-1b) (167 mg, 1.00 mmol) following method B (105 mg, 85%), from 3-nitrobenzoic acid (JOC-1l) (167 mg, 1.00 mmol) following method B (107 mg, 87%), and from 4-nitrobenzoic acid (JOC-1c) (167 mg, 1.00 mmol) following method A (105 mg, 86%), obtained each time as yellow liquid. The spectroscopic data all matched those reported in the literature. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.21 (ddd, *J* = 8.8, 1.8, 1.6 Hz, 2H), 7.66-7.71 (m, 1H), 7.50-7.56 (m, 2H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 148.3, 134.5, 129.2, 123.4 ppm; MS (EI): m/z (%) = 123 (88) [M^+], 107 (100), 93 (59), 91 (15), 77 (27), 65 (44), 51 (12); IR (NaCl) = 3076 (w), 3027 (w), 2970 (w), 2861 (w), 1518 (s), 1343 (s), 851 (s), 792 (s); Elemental analysis: Calcd: C, 66.25; H, 5.56; N, 8.58; Found: C, 66.01; H, 5.52; N, 8.55.

Benzonitrile (JOC-2c) CAS: [100-47-0]



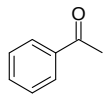
Synthesized from 4-cyanobenzoic acid (JOC-1d) (147 mg, 1.00 mmol) following method A and obtained as a colorless liquid (84 mg, 81%). The spectroscopic data matched those reported in the literature. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.55-7.64 (m, 3H), 7.44 (t, *J* = 7.8 Hz, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 132.6, 132.0, 129.0, 118.6, 112.5 ppm; MS (EI): m/z (%) = 103 (100) [M^+], 76 (41), 63 (3), 50 (21); IR (NaCl) = 3066 (w), 2228 (m), 1490 (m), 1447 (m), 755 (s), 686 (s); GC/HRMS-EI m/z [M^+] calcd. for C_7H_5N: 103.0422; found: 103.0422.

Benzaldehyde (JOC-2d) [CAS: 100-52-7]



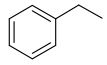
Synthesized from 4-formylbenzoic acid (JOC-1e) (150 mg, 1.00 mmol) following method A and obtained as a yellow liquid (68 mg, 64%). The spectroscopic data matched those reported in the literature. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.98 (s, 1H), 7.83-7.87 (m, 2H), 7.59 (tt, *J* = 7.4, 1.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H) ppm; ^{13}C-NMR: (101 MHz, $CDCl_3$): δ = 192.1, 136.5, 134.3, 129.6, 128.9 ppm; MS (EI): m/z (%) = 106 (17) [M^+], 105 (100), 77 (18), 51 (10).

Acetophenone (JOC-2e) [CAS: 98-86-2]



Synthesized from 4-acetylbenzoic acid (JOC-1f) (164 mg, 1.00 mmol) following method A (95 mg, 79%) and from 2-acetylbenzoic acid (JOC-1n) (164 mg, 1.00 mmol) following method B (101 mg, 84%), both times obtained as a yellow liquid. The spectroscopic data all matched those reported in the literature. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.93 (dd, *J* = 8.1, 0.9 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 2.58 (s, 3H) ppm; ^{13}C-NMR (151 MHz, $CDCl_3$): δ = 198.2, 137.0, 133.1, 128.5, 128.2, 26.5 ppm; MS (EI): m/z (%) = 120 (7) [M^+], 105 (100), 77 (78), 51 (35); IR = 3031 (w), 3003 (w), 2970 (w), 1738 (s), 1365 (m), 1217 (m), 1243 (s), 760 (s) cm^{-1}; Elemental analysis: Calcd: C, 79.97; H, 6.71; Found: C, 79.47; H, 6.50.

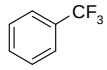
Ethylbenzene (JOC-2f) CAS: [100-41-4]



Synthesized from 4-ethylbenzoic acid (JOC-1g) (150 mg, 1.00 mmol) following method A. The identity of the product (JOC-2f) was confirmed by GC-MS and the yield determined by quantitative GC to be 80% based on a response factor obtained with commercial ethylbenzene

using ntetradecane (50 μL) as an internal gas chromatographic standard. MS (EI): m/z (%) = 107 (3), 106 (35) [M^+], 91 (100), 77 (9), 65 (14), 50(9).

Trifluoromethylbenzene (JOC-2g) CAS: [98-08-8]

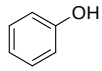


Synthesized from 4-(trifluoromethyl)benzoic acid (JOC-1h) (190 mg, 1.00 mmol) following method A. The identity of the product (JOC-2g) was confirmed by GC-MS and the yield determined by quantitative GC to be 22%, based on a response factor obtained with commercial trifluoromethylbenzene using n-tetradecane (50 μL) as an internal gas chromatographic standard. MS (EI): m/z (%) = 146 (100) [M^+], 145 (58), 127 (57), 96 (52), 77 (13), 51(21).

Chlorobenzene (JOC-2h) [CAS: 108-90-7]

Synthesized from 4-chlorobenzoic acid (JOC-1i) (156 mg, 1.00 mmol) following method A. The identity of the product (JOC-2h) was confirmed by GC-MS and the yield determined by quantitative GC to be 90% based on a response factor obtained with commercial chlorobenzene using ntetradecane (50 μL) as an internal gas chromatographic standard. MS (EI): m/z (%) = 112 (100) [M^+], 77 (57), 51 (23), 50 (22).

Phenol (JOC-2i) CAS: [108-95-2]

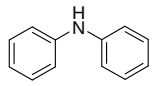


Synthesized from 4-hydroxybenzoic acid (JOC-1j) (138 mg, 1.00 mmol) following method A. The identity of the product (JOC – 2i) was confirmed by GC-MS and the yield determined by quantitative GC to be 64%, based on a response factor obtained with commercial phenol using n-tetradecane (50 μL) as an internal gas chromatographic standard. MS (EI): m/z (%) = 94 (100) [M^+], 66 (56), 65 (40).

Toluene (JOC-2j) [CAS: 108-88-3]

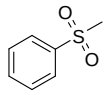
Synthesized from 3-methylbenzoic acid (JOC-1k) (136 mg, 1.00 mmol) following method A. The identity of the product (JOC-2j) was confirmed by GC-MS and the yield determined by quantitative GC to be 99%, based on a response factor obtained with commercial toluene using n-tetradecane (50 μL) as an internal gas chromatographic standard. MS (EI): m/z (%) = 92 (42) [M^+], 91 (100), 77 (1), 65 (15), 63 (8), 50 (6).

Diphenylamine (JOC-2k) [CAS: 122-39-4]



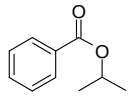
Synthesized from 2-(phenylamino) benzoic acid (JOC–1m) (213 mg, 1.00 mmol) following method B and obtained as a white solid (107 mg, 63%): mp 49-51 °C. The spectroscopic data matched those reported in the literature for diphenylamine (JOC – 2k). m.p. 52-56 °C; 1H-NMR (400 MHz, $CDCl_3$): δ = 7.27-7.35 (m, 4H), 7.11 (dd, *J* = 7.6, 0.8 Hz, 4H), 6.97 (td, *J* = 7.3, 1.0 Hz, 2H), 5.73 (s, 1H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 143.3, 129.3, 121.0, 117.9 ppm; MS: (EI): m/z (%) = 169 (100) [M^+], 168 (64), 141 (8), 84 (9), 77 (11), 65 (10), 51 (21); GC/HRMS-EI m/z [M^+] calcd. for $C_{12}H_{11}N$: 169.0890; found: 169.0891.

Methyl Phenyl Sulfone (JOC-2l) CAS: [3112-85-4]



Synthesized from 2-(methylsulfonyl)benzoic acid (JOC-1o) (200 mg, 1.00 mmol) following method B and obtained as a white solid (109 mg, 70%): mp. 85-87 °C. The spectroscopic data matched those reported in the literature for methyl phenyl sulfone (JOC – 2l). m.p.: 88 °C; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.87-7.92 (m, 2H), 7.58-7.64 (m, 1H), 7.50-7.56 (m, 2H), 3.01 (s, 3H) ppm; ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 140.5, 133.5, 129.2, 127.1, 44.3 ppm. MS (EI): m/z (%) = 156 (6) [M^+], 141 (33), 94 (72), 77 (100), 65 (14), 51, (43); IR (KBr) = 3010 (w), 3024 (w), 2928 (w), 1584 (w), 1447 (s), 1327 (s), 1293 (s), 1282 (s), 1143 (m), 1084 (m), 745 (s) cm^{-1}; Elemental analysis: Calcd: C 53.82; H 5.16, S 20.53; Found: C 53.70; H 5.13, S 20.31.

Isopropyl benzoate (JOC-2m) CAS: [939-48-0]



Synthesized from 2-(isopropyloxycarbonyl)benzoic acid (JOC-1p) (208 mg, 1.00 mmol) following method B and obtained as yellow liquid (139 mg, 85%). The spectroscopic data matched those reported in the literature for isopropyl benzoate (JOC-2m). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01-8.06 (m, 2H), 7.51 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.38-7.43 (m, 2H), 5.20-5.30 (m, 1H), 1.36 (d, *J* = 6.3 Hz, 6H) ppm; ^{13}C-NMR: (101 MHz, $CDCl_3$): δ = 165.9, 132.5, 130.9, 129.4, 128.1, 68.2, 21.8 ppm; MS (EI): m/z (%) = 164 (17) [M^+], 123 (26), 105 (100), 77 (21), 51 (12).

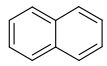
Thiophene (JOC-2n) [CAS: 110-02-1]

Synthesized from thiophene-2-carboxylic acid (JOC-1q) (128 mg, 1.00 mmol) following method B at 160 °C reaction temperature. The identity of the product 2n was confirmed by GC-MS and the yield determined by quantitative GC to be 62%, based on a response factor obtained with commercial thiophene using n-tetradecane (50 μL) as an internal gas chromatographic standard. MS (EI): m/z (%) = 84 (100) [M^+], 83 (6), 69 (4), 58 (9), 45 (14).

Furan (JOC-2o) [CAS: 110-00-9]

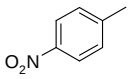
Synthesized from furan-2-carboxylic acid (JOC-1r) (112 mg, 1.00 mmol) following method B at 160 °C reaction temperature. The identity of the product 2o was confirmed by GC-MS and the yield determined by quantitative GC to be 99% based on a response factor obtained with commercial furan using n-tetradecane (50 μL) as an internal gas chromatographic standard. MS (EI): m/z (%) = 68 (100) [M^+], 67 (2), 45 (4), 40 (5).

Naphthalene (JOC-2p) CAS: [91-20-3]



Synthesized from 1-naphthoic acid (JOC-1s) (172 mg, 1.00 mmol) following method B and obtained as a white solid (49 mg, 38%). The spectroscopic data matched those reported in the literature for naphthalene (JOC-2p). m.p.: 81 °C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.84 (td, *J* = 6.2, 2.9 Hz, 4H), 7.48 (td, *J* = 6.3, 3.1 Hz, 4H) ppm; ^{13}C-NMR: (151 MHz, $CDCl_3$): δ = 133.4, 127.9, 125.8 ppm; MS (EI): m/z (%) = 128 (100) [M^+], 126 (8), 102 (14), 87 (2), 75 (6), 63 (7), 50 (7); IR (KBr) = 3085 (w), 3029 (w), 3049 (m), 1592 (w), 1503 (w), 1388 (s), 1210 (m), 1122 (m), 774 (s); Elemental analysis: Calcd: C, 93.71; H, 6.29; Found: C, 93.42; H, 6.13.

4-Nitrotoluene (JOC-2q) CAS: [99-99-0]



Synthesized from 5-methyl-2-nitrobenzoic acid (JOC-1t) (197 mg, 1.00 mmol) following method B and obtained as a colorless solid (109 mg, 80%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-nitrotoluene (JOC-2q). m.p. 51 °C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.5 Hz, 2 H) 7.31 (d, *J* = 8.2 Hz, 2 H) 2.46 (s, 3 H) ppm; ^{13}C-NMR (151 MHz, $CDCl_3$): δ = 145.9, 129.8, 123.5, 21.6 ppm; MS (EI): m/z (%) = 137 (100) [M^+], 136 (99), 107 (87), 91 (99), 77 (47), 65 (99), 63 (26); IR (KBr)= 3107 (w), 3082 (w), 2937

(w), 2842 (w), 1596 (m), 1509 (s), 1339 (s), 1106 (m), 835 (s), 735 (s) cm^{-1}; Elemental analysis: Calcd: C, 61.31; H, 5.14; Found: C, 60.87; H, 5.46.

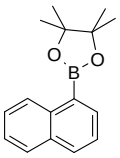
7.8 Oxidative Trifluoromethylation of Arylboronates with Shelf-Stable Potassium (trifluoromethyl)trimethoxyborate

7.8.1 General Methods for the Synthesis of Arylboronates

A 20 mL reaction vessel was charged with respective boronic acid (10.0 mmol) and 2,3-dimethyl-2,3-butandiol (pinacol) (1.19 g, 10.0 mmol). The resulting mixture was stirred at 150 °C. After 1 h, it was allowed to cool to room temperature. The reaction mixture was filtered through a plug of basic alox, rinsed with ethylacetate and the combined rinsings were filtered through compressed celite. After removing the solvent, the pinacol ester was purified by recrystalization (methanol). The identity and purity of the products were confirmed by ^{1}H- ^{13}C- and ^{11}B-NMR spectroscopy, mass spectroscopy, elemental analysis, infrared spectroscopy and, if a solid product was obtained, the melting points were determined.

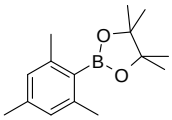
7.8.2 Synthesis of Arylboronates

1-Naphthaleneboronic acid pinacol ester (CEJ–1a**)** CAS: [68716-52-9]



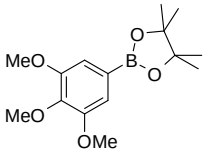
(CEJ–1a) was synthesized following the general procedure using 1-naphthaleneboronic acid (8.60 g, 50.0 mmol) and pinacol (5.97 g, 50.0 mmol) and purified by recrystalization (methanol), affording (CEJ–1a) as a colorless solid (9.50 g, 75 %). m.p.: 59.4 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.81 (d, *J* = 7.8 Hz, 1H), 8.12 (d, *J* = 6.3 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.54−7.60 (m, 1H), 7.51 (t, *J* = 7.4 Hz, 2H), 1.46 (s, 12H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 136.9, 135.6, 133.2, 131.6, 128.4, 128.3, 126.3, 125.4, 124.9, 83.7, 24.9 ppm; ^{11}B-NMR (128 MHz, $CDCl_3$) δ = 31.43 (s, 1 B) ppm; MS: (EI): m/z (%) = 254 (100) [M^+], 211 (14), 181 (16), 168 (19), 154 (19), 153 (13); IR = 3044 (w), 2994 (w), 2974 (w), 2453 (w), 1577 (w), 1508 (w), 1401 (m), 1355 (s), 1334 (vs), 1267 (m), 1141 (vs), 1088 (m), 990 (m), 771 (s) cm^{-1}; Elemental Analysis: Calcd: C, 75.62; H, 7.54; found: C, 75.53; H, 7.64.

2,4,6-Trimethylphenylboronic acid pinacol ester(CEJ–1b) CAS: [171364-84-4]



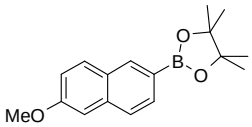
(CEJ–1b) was synthesized following the general procedure using 2,4,6-trimethylphenylboronic acid (820 mg, 5.00 mmol) and pinacol (597 mg, 5.00 mmol) and purified by recrystalization (methanol), affording (CEJ–1b) as a colorless solid (1.14 g, 93 %). m.p. 47.2 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.81 (s, 2H), 2.41 (s, 6H), 2.28 (s, 3H), 1.41 (s, 12H) ppm; ^{13}C-NMR 101 MHz, $CDCl_3$) δ = 142.1, 138.9, 127.4, 83.4, 24.9, 22.1, 21.2 ppm; ^{11}B-NMR (128 MHz, $CDCl_3$) δ = 32.31 (s, 1B) ppm; MS: (EI): m/z (%) = 246 (M^+, 100), 190 (28), 189 (65), 147 (48), 146 (48), 131 (28); IR (KBr) = 3026 (w), 2990 (w), 2977 (w), 2923 (w), 1738 (w), 1611 (w), 1445 (w), 1370 (m), 1330 (s), 1295 (vs), 1143 (s), 1064 (s), 848 (m), 682 (m) cm^{-1}; Elemental Analysis: Calcd: C, 73.19; H, 9.42. Found: C, 73.02; H, 9.64.

3,4,5-Trimethoxyphenylboronic acid pinacol ester (CEJ–1c) CAS: [214360-67-5]



(CEJ–1c) was synthesized following the general procedure using 3,4,5-trimethoxyphenylboronic acid (546 mg, 2.50 mmol) and pinacol (298 mg, 2.50 mmol) and purified by recrystalization (methanol), yielding colorless solid (654 mg, 89 %). m.p.: 103.6 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.05 (s, 2H), 3.91 (s, 6H), 3.88 (s, 3H), 1.35 (s, 12H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 152.8, 140.8, 111.2, 83.8, 60.7, 56.1, 24.8 ppm; ^{11}B-NMR (128 MHz, $CDCl_3$) δ = 30.57 (s, 1B) ppm; MS: (EI): m/z (%) = 294(100)[M^+], 280 (47), 279 (15), 252 (13), 195 (17), 194 (14); IR (KBr) = 3019 (w), 2989 (w), 2975 (w), 2940 (w), 2845 (w), 2822 (w), 1739 (w), 1578 (w), 1398 (m), 1238 (m), 1121 (vs), 1010 (m), 965 (m), 849 (s) cm^{-1}; Elemental Analysis: Calcd: C, 61.25; H, 7.88; Found: C, 61.09; H, 7.73.

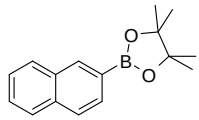
6-Methoxy-2-naphthaleneboronic acid pinacol ester (CEJ –1e) CAS: [269410-13-1]



(CEJ–1e) was synthesized following the general procedure using 6-methoxy-2-naphthaleneboronic acid (1.04 g, 5.00 mmol) and pinacol (597 mg, 5.00 mmol) and purified by recrystalization (methanol), affording (CEJ –1e) as a pale orange solid (1.21 g, 85 %). m.p. 100.1 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.33 (s, 1H), 7.78−7.89 (m, 2H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.11−7.19 (m, 2H), 3.93 (s, 3H), 1.41 (s, 12H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ =

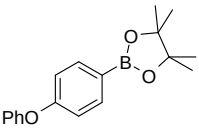
158.5, 136.4, 135.9, 131.1, 130.2, 128.3, 125.9, 118.6, 105.6, 83.7, 55.2, 24.9 ppm; ^{11}B-NMR (128 MHz, $CDCl_3$) δ = 30.94 (s, 1 B) ppm; MS: (EI): m/z (%) = 284 (100) [M^+], 270 (9), 200 (9), 199 (28), 186 (7), 185 (14); IR (KBr) = 2982 (w), 2939 (w), 2842 (w), 1625 (m), 1485 (s), 1380 (m), 1339 (vs), 1207 (vs), 1138 (vs), 1079 (s), 858 (vs), 833 (m), 813 (m), 693 (s) cm^{-1}; Elemental Analysis: Calcd: C, 71.86; H, 7.45; Found: C, 71.89; H, 7.46.

2-Naphthaleneboronic acid pinacol ester (CEJ–1g) [CAS: 256652-04-7]



(CEJ–1g) was synthesized following the general procedure using 2-naphthaleneboronic acid (860 mg, 5.00 mmol) and pinacol (597 mg, 5.00 mmol) and purified by recrystalization (methanol), affording (CEJ–1g) as a colorless solid (1.11 g, 87 %). m.p. 104.2 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.40 (s, 1H), 7.75−8.03 (m, 4H), 7.42−7.62 (m, 2H), 1.42 (s, 12H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 136.2, 135.0, 132.8, 130.4, 128.6, 127.7, 127.0, 125.8, 83.9, 24.9 ppm; ^{11}B-NMR (128 MHz, $CDCl_3$) δ = 31.11 (s, 1 B) ppm; MS: (EI): m/z (%) = 254 (100) [M^+], 253 (34), 211 (19), 169 (21), 168 (83), 155 (19), 154 (41).; IR (KBr) = 3053 (w), 2993 (w), 2980 (w), 2971 (w), 1629 (w), 1598 (w), 1477 (m), 1370 (s), 1351 (vs), 1338 (vs), 1297 (s), 1132 (vs), 1078 (m), 963 (m), 849 (s), 824 (s), 748 (vs), 688 (vs) cm^{-1}; Elemental Analysis: Calcd: C, 75.62; H, 7.54; Found: C, 75.67; H, 7.41.

1-Phenoxyphenylboronic acid pinacol ester (CEJ–1h) CAS: [269410-26-6]



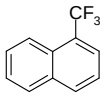
(CEJ–1h) was synthesized following the general procedure using 1-phenoxyphenylboronicacid (2.14 g, 10.0 mmol) and pinacol (1.19 g, 10.0 mmol) and purified by recrystalization (methanol), affording the (CEJ–1h) as a colorless solid (2.21 g, 74 %). m.p. 54.1 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.84 (d, *J* = 8.6 Hz, 2H), 7.34−7.42 (m, 2H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.06−7.10 (m, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 1.38 (s, 12H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 160.1, 156.5, 136.6, 129.7, 123.6, 119.4, 117.6, 83.6, 24.8 ppm; ^{11}B-NMR (128 MHz, $CDCl_3$) δ = 30.78 (s, 1 B) ppm; MS: (EI): m/z (%) = 296(100) [M^+], 282 (33), 211 (11), 210 (9), 197 (20), 77 (8); IR (KBr) = 2994 (m), 2980 (m), 1605 (w), 1585 (s), 1572 (w), 1488 (m), 1393 (m), 1355 (vs), 1234 (vs), 1141 (vs), 1090 (s), 857 (m), 838 (m), 831 (m) cm^{-1}; Elemental Analysis: Calcd: C, 73.00; H, 7.15; Found: C, 73.03; H, 7.18.

7.8.3 General Methods for the Synthesis of Benzotrifluorides

A 20 mL reaction vessel was charged with respective boronic acid pinacol ester (CEJ 1a-s), (0.50 mmol), copper(II) acetate (90.9 mg, 0.50 mmol) and potassium (trifluoromethyl)trimethoxyborate (216 mg, 1.00 mmol). Dry DMSO (2.5 mL) was added, the reaction vessel was briefly purged with oxygen, and the resulting mixture was stirred at 60 °C for 16 h at ambient oxygen pressure. After cooling to room temperature, the reaction mixture was diluted with diethyl ether (20 mL) and washed with saturated aqueous sodium bicarbonate (20 mL) solution. The aqueous layer was extracted with diethyl ether (3×20 ml), and the organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (SiO_2, *n*-hexane) to yield products (CEJ 2a-s). The identity and purity of the known compounds was confirmed by ^{1}H- ^{13}C- and ^{19}F-NMR spectroscopy, mass spectroscopy, IR spectroscopy and HR-MS whereas melting points were also reported for solid compounds.

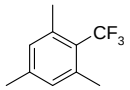
7.8.4 Synthesis of Benzotrifluorides

1-Trifluoromethylnaphthalene (CEJ-2a) [CAS: 26458-04-8]



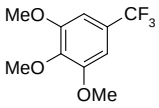
(CEJ-2a) was synthesized following the general procedure using 1-naphthylboronic acid pinacol ester (CEJ-1a) (268 mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, n-pentane), affording (CEJ-2a) (144 mg, 73.4 %) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 7.8 Hz, 1 H), 8.04 (d, *J* = 8.2 Hz, 1 H), 7.94 (d, *J* = 7.8 Hz, 1 H), 7.89 (d, *J* = 7.4 Hz, 1 H), 7.57-7.69 (m, 2 H), 7.52 (t, *J* = 7.6 Hz, 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 133.9, 132.7, 128.9 , 128.7, 127.6, 126.4-126.8 (m), 126.2 (q, *J* = 30.2Hz), 124.7 (q, *J* = 273.7Hz), 124.3 (q, *J* = 2.7Hz) 124.7 (q, *J* = 6.5Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -59.71 (s) ppm; MS (EI): m/z (%) = 197 (13), 196 (100) [M^+], 195 (7), 177 (15), 176 (7), 146 (9), 126 (7); IR (NaCl) = 1645 (w), 1635 (w), 1627 (w), 1585 (w), 1513 (w), 1465 (w), 1449 (w), 1353 (w), 1316 (m), 1262 (m), 1134 (m), 1118 (m), 1068 (w), 1026 (w), 976 (w), 922 (w), 864 (w), 804 (w), 774 (w), 732 (w), 450 (vs) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_{11}H_7F_3$: 196.0500; found: 196.0506.

1,3,5-Trimethyl-2-(trifluoromethyl)-benzene (CEJ-2b) [CAS: 3360-56-3]



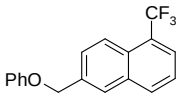
(CEJ–2b) was synthesized following the general procedure using 2,4,6-trimethylphenylboronic acid pinacol ester (CEJ–1b) (260 mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, n-pentane), affording (CEJ–2b) (92 mg, 49 %) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.91 (s, 2 H), 2.46 (q, *J* = 3.2 Hz, 6 H), 2.31 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 140.8, 137.3 (q, *J* = 4.2Hz) 130.8, 124.8 (q, *J* = 276Hz), 124.9 (q, *J* = 29.1Hz) 120.0, 21.3 (q, *J* = 4.2Hz), 20.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -53.69 (s) ppm; MS (EI): m/z (%) = 188 (89) [M^+], 187 (18), 173 (80), 133 (14), 119 (100), 91 (20), 40 (24); IR (NaCl) = 2979 (s), 2933 (s), 1733 (w), 1717 (w), 1611 (m), 1579 (w), 1457 (m), 1433 (s), 1294 (s), 1150 (s), 1110 (vs), 1040 (s), 854 (m), 754 (w), 744 (w), 590 (w), 562 (w), 450 (s) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_{10}H_{11}F_3$: 188.0813; found: 188.0819.

1,2,3–Trimethoxy-5-(trifluoromethyl)-benzene (CEJ-2c)



(CEJ-2c) was synthesized following the general procedure using 3,4,5-trimethoxyphenylboronic acid pinacol ester (CEJ-1c) (147 mg, 0.50 mmol), copper(II) acetate (90.9 mg, 0.50 mmol) and potassium (trifluoromethyl)trimethoxyborate (216 mg, 1.00 mmol) and purified by column chromatography (SiO_2, n-hexane), affording (CEJ-2c) (74 mg, 62.7 %) as a colorless solid. m.p. 66.7 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.83 (s, 2 H), 3.90 (s, 6 H),3.88 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 153.4, 140.6, 125.6 (q, *J* = 32.4Hz) 123.6 (q, *J* = 271.9Hz), 102.5 (q, *J* = 3.7Hz) 91.6, 60.8, 56.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.12 (s) ppm; MS (EI): m/z (%) = 236 (100) [M^+], 221 (79), 193 (42), 178 (47), 163 (36), 161 (32), 40 (23); IR (KBr) = 3014 (w), 2978 (w), 2949 (w), 2933 (w), 2850 (w), 2837 (w), 2716 (w), 1738 (w), 1595 (m), 1509 (w), 1469 (m), 1458 (w), 1418 (m), 1353 (m), 1273 (w), 1244 (m), 1227 (m), 1165 (m), 1103 (vs), 1066 (m), 992 (s), 951 (w), 894 (m), 842 (m), 833 (m), 815 (w), 780 (m), 705 (m), 673 (m) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_{10}H_{11}F_3O_3$: 236.0660; found: 236.0650.

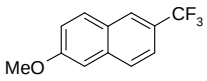
1-[4-(Trifluoromethyl)phenoxy]methyl]-naphthalene (CEJ-2d) CAS: [785789-59-5]



(CEJ-2d) was synthesized following the general procedure using 4-[(1-naphthyloxy)methyl]phenylboronic acid pinacol ester (CEJ-1d) (360 mg, 1.00 mmol), copper(II)

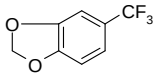
acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol). and purified by column chromatography (SiO_2, n-hexane), affording (CEJ-2d) (298 mg, 98.6 %) as a colorless solid. m.p. 79.5 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.33-8.39 (m, 1 H), 7.82-7.86 (m, 1 H), 7.70 (m, *J* = 8.2 Hz, 2 H), 7.67 (m, *J* = 8.2 Hz, 2 H), 7.53 (ddd, *J* = 7.5, 5.1, 1.8 Hz, 2 H), 7.49 (d, *J* = 8.2 Hz, 1 H), 7.39 (t, *J* = 7.9 Hz, 1 H), 6.87 (d, *J* = 7.3 Hz, 1 H), 5.33 (s, 2 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 154.1, 141.2, 134.6, 130.1 (q, *J* = 31.9Hz) 127.5, 127.3, 126.6, 125.7, 125.6 (q, J = 4.2Hz) 125.4, 122.0, 124.2 (q, *J* = 271.9Hz), 120.9, 105.2, 69.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.49 (s) ppm; MS (EI): m/z (%) = 303 (16), 302 (77) [M^+], 159 (100), 143 (39), 115 (54), 109 (21), 89 (11); IR (KBr) = 3073 (w), 3052 (w), 2186 (w), 2162 (w), 2051 (w), 1936 (w), 1925 (w), 1846 (w), 1812 (w), 1737 (w), 1622 (w), 1598 (w), 1579 (w), 1507 (w), 1462 (w), 1418 (w), 1406 (w), 1398 (w), 1323 (m), 1264 (m), 1238 (m), 1228 (w), 1214 (w), 1167 (m), 1112 (s), 1095 (s), 1065 (s), 1017 (m), 971 (w), 956 (w), 884 (w), 855 (w), 825 (m), 795 (s), 769 (vs) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_{18}H_{13}F_3O$: 302.0918; found: 302.0908.

2-Methoxy-6-(trifluoromethyl)-naphthalene (CEJ-2e) [CAS: 39499-17-7]



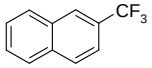
(CEJ-2e) was synthesized following the general procedure using 6-methoxy-2-naphthoylboronic acid pinacol ester (CEJ-1e) (142 mg, 0.50 mmol), copper(II) acetate (90.9 mg, 0.50 mmol) and potassium (trifluoromethyl)trimethoxyborate (216 mg, 1.00 mmol) and purified by column chromatography (SiO_2, n-hexane), affording (CEJ-2e) (80.2 mg, 70.7 %) as a colorless solid. m.p. 74.9 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.08 (s, 1 H), 7.82 (dd, *J* = 8.6, 3.1 Hz, 2 H), 7.59-7.64 (m, 1 H), 7.25 (dd, *J* = 9.0, 2.3 Hz, 1 H), 7.18 (d, *J* = 2.3 Hz, 1 H), 3.96 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 159.2, 136.1, 130.2, 127.6, 127.5, 125.4 (q, *J* = 4.6Hz) 125.5 (q, *J* = 32.4) 122.0 (q, *J* = 3.7Hz) 124.6 (q, *J* = 271.9) 120.1, 105.7, 55.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -61.85 (s) ppm; MS: (EI): m/z (%) = 227 (13), 226 (100) [M^+], 207 (8), 184 (6), 183 (14), 164 (6), 133 (12); IR (KBr) = 3034 (w), 2974 (w), 2948 (w), 2853 (w), 2187 (w), 2163 (w), 2052 (w), 2036 (w), 1927 (w), 1773 (w), 1739 (w), 1717 (w), 1630 (w), 1615 (w), 1586 (w), 1493 (m), 1460 (w), 1440 (w), 1385 (w), 1316 (m), 1276 (m), 1209 (m), 1194 (m), 1172 (s), 1164 (s), 1145 (s), 1130 (m), 1109 (vs), 1066 (s), 1029 (s), 958 (w), 909 (s), 856 (vs), 824 (s), 754 (w), 707 (w), 683 (m) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_{11}H_9F_3O$: 226.0605; found: 226.0614.

5-(Trifluoromethyl)-1,3-benzodioxole (CEJ-2f) CAS: [1254164-46-9]



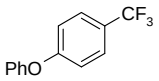
(CEJ-2f) was synthesized following the general procedure using 1,3-benzodioxol-5-ylboronic acid pinacol ester (CEJ-1f) (248mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, n-pentane), affording (CEJ-2f) (129 mg, 68 %) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.14-7.17 (m, 1 H), 7.05 (d, *J* = 1.8 Hz, 1 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 6.05 (s, 2 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 150.3, 147.9, 124.3 (q, *J* = 33.3Hz), 124.0 (q, *J* = 270.5Hz), 119.8 (q, *J* = 4.2Hz), 108.2, 105.8 (q, *J* = 2.77Hz), 101.9 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -61.50 (s) ppm; MS (EI): m/z (%) = 191 (6), 190 (57) [M^+], 189 (100), 188 (4), 171 (12), 141 (3), 63 (11); IR (KBr) = 3073 (w), 3052 (w), 2186 (w), 2162 (w), 2051 (w), 1936 (w), 1925 (w), 1846 (w), 1812 (w), 1737 (w), 1622 (w), 1598 (w), 1579 (w), 1507 (w), 1462 (w), 1418 (w), 1406 (w), 1398 (w), 1323 (m), 1264 (m), 1238 (m), 1228 (w), 1214 (w), 1167 (m), 1112 (s), 1095 (s), 1065 (s), 1017 (m), 971 (w), 956 (w), 884 (w), 855 (w), 825 (m), 795 (s), 769 (vs) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_8H_5F_3O$: 190.0242; found: 190.0246.

2-(Trifluoromethyl)-naphthalene (CEJ-2g) CAS: [581-90-8]



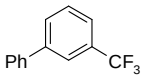
(CEJ-2g) was synthesized following the general procedure using 2-naphthylboronic acid pinacol ester (CEJ-1g) (127 mg, 0.50 mmol), copper(II) acetate (90.9 mg, 0.50 mmol) and potassium (trifluoromethyl)trimethoxyborate (216 mg, 1.00 mmol) and purified by column chromatography (SiO_2, n-hexane), affording (CEJ–2g) (62.0 mg, 63.2 %) as a colorless solid. m.p. 65.3 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.18 (s, 1 H), 7.87-8.01 (m, 3 H), 7.54-7.71 (m, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 134.5, 132.2, 129.0, 128.8, 128.0, 127.8, 127.7 (q, *J* =32.4 Hz), 127.1 (s) 125.7 (q, *J* = 4.6 Hz), 121.4 (q, *J* = 3.7Hz), 124.9 (q, *J* = 271.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.23 (s) ppm; MS: (EI): m/z (%) = 197 (11), 196 (100) [M^+], 195 (23), 177 (18), 147 (29), 146 (10), 126 (7); IR (KBr) = 3068 (w), 2924 (w), 2851 (w), 2189 (w), 2178 (w), 2167 (w), 2051 (w), 1974 (w), 1947 (w), 1931 (w), 1854 (w), 1828 (w), 1815 (w), 1786 (w), 1739 (w), 1635 (w), 1606 (w), 1513 (w), 1475 (w), 1461 (w), 1389 (w), 1363 (w), 1314 (m), 1201 (m), 1173 (m), 1144 (s), 1132 (m), 1106 (vs), 1064 (vs), 960 (w), 944 (w), 911 (m), 872 (m), 861 (w), 826 (s), 753 (s), 737 (m), 670 (w) cm^{-1}; MS (EI, 70 eV): m/z (%):); GC/HRMS-EI m/z [M^+] calcd. for $C_{11}H_7F_3$: 196.0500; found: 196.0509.

1-Phenoxy-4-(trifluoromethyl)-benzene (CEJ-2h) CAS: [2367-02-4]



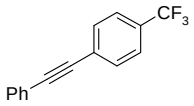
(CEJ–2h) was synthesized following the general procedure using 4-phenoxyphenylboronic acid pinacol ester (CEJ–1h) (148 mg, 0.50 mmol), copper(II) acetate (90.9 mg, 0.50 mmol) and potassium (trifluoromethyl)trimethoxyborate (216 mg, 1.00 mmol) and purified by column chromatography (SiO_2, n-hexane), affording (CEJ–2h) (100 mg, 84 %) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 8.6 Hz, 2H), 7.37−7.44 (m, 2H), 7.18−7.24 (m, 1H), 7.07 (t, *J* = 7.8 Hz, 4H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 160.5, 155.7, 130.1, 127.1 (q, *J* = 3.7 Hz), 124.9 (q, *J* = 32.4 Hz), 124.3 (q, *J* = 271.9 Hz), 119.9, 117.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -61.72 (s) ppm; MS: (EI): m/z (%) = 238 (100) [M^+], 169 (14), 141 (31), 77 (14), 51 (13), 50 (7); IR (KBr) = 3902 (vs), 3852 (vs), 3838 (vs), 3820 (vs), 3750 (vs), 3734 (vs), 3710 (s), 3688 (s), 3674 (vs), 3648 (vs), 3628 (s), 1923 (w), 1909 (w), 1869 (w), 1773 (w), 1733 (w), 1717 (w), 1699 (w), 1683 (w), 1669 (w), 1663 (w), 1617 (m), 1589 (m), 1513 (m), 1489 (s), 1473 (w), 1326 (s), 1246 (s), 1168 (m), 1124 (s), 1106 (m), 1066 (s), 1014 (w), 872 (w), 842 (w), 802 (w), 770 (w), 740 (w), 694 (w), 596 (w) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd for $C_{13}H_9F_3O$: 238.0605; found: 238.0614.

3-(Trifluoromethyl)-1,1-biphenyl (CEJ-2i) CAS: [366-04-1]



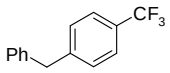
(CEJ-2i) was synthesized following the general procedure using 3-biphenylboronic acid pinacol ester (CEJ-1i) (140 mg, 0.50 mmol), copper(II) acetate (90.9 mg, 0.50 mmol) and potassium (trifluoromethyl)trimethoxyborate (216 mg, 1.00 mmol) and purified by column chromatography (SiO_2, n-hexane), affording (CEJ-2i) (79.3mg, 71.4 %) as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.89 (s, 1 H), 7.80 (d, *J* = 7.8 Hz, 1 H), 7.61-7.69 (m, 3 H) 7.55-7.61, (m, 1 H), 7.51 (t, *J* = 7.4 Hz, 2 H), 7.39-7.47 (m, 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 142.0, 139.7, 131.1 (q, *J* = 31.4Hz), 130.4 (q, *J* = 1.85Hz), 129.2, 129.0, 128.0, 127.2, 123.9 (q, *J* = 2.77Hz), 125.6 (q, *J* = 271.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.56 (s) ppm; MS: (EI): m/z (%) = 223(14), 222 (100) [M^+], 202 (10), 153 (12), 152 (5), 69 (5), 50 (6); IR (KBr) = 3063 (s), 3035 (s), 1715 (w), 1683 (w), 1653 (w), 1609 (w), 1593 (w), 1577 (w), 1483 (m), 1455 (m), 1423 (m), 1334 (vs), 1262 (s), 1166 (s), 1126 (vs), 1098 (s), 1076 (s), 1046 (m), 1022 (w), 900 (w), 820 (w), 806 (w), 758 (s), 732 (w), 702 (m), 660 (m), 450 (s) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_{13}H_9F_3$: 222.0656; found: 222.0653.

1-(2-Phenylethynyl)-4-(trifluoromethyl)-benzene (CEJ-2j) CAS: [370-99-0]



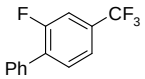
(CEJ-2j) was synthesized following the general procedure using 4-(phenylethynyl)phenylboronic acid pinacol ester (CEJ-1j) (360 mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, 25% n-hexane/ethylacetate), affording (CEJ-2j) (175 mg, 71 %) as a colorless solid. m.p. 105.3 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = = 7.60-7.68 (m, 4 H), 7.58 (dt, *J* = 4.0, 2.7 Hz, 2 H), 7.34-7.44 (m, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 131.8, 131.7, 130.1 (q, *J* = 32.4Hz), 128.8, 128.4, 127.1 (q, *J* = 1.9Hz), 125.3 (q, *J* = 3.7), 122.6, 119.9 (q, *J* = 272.8Hz), 91.7, 88.0 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.75 (s) ppm; MS: (EI): m/z (%) = 247 (71), 246 (100) [M^+], 228 (35), 226 (16), 197 (31), 176 (8), 50 (8); IR (KBr) = 2221 (w), 2187 (w), 2163 (w), 1979 (w), 1935 (w), 1907 (w), 1890 (w), 1814 (w), 1745 (w), 1739 (w), 1609 (w), 1572 (w), 1520 (w), 1487 (w), 1442 (w), 1406 (w), 1322 (m), 1288 (w), 1165 (m), 1154 (m), 1128 (m), 1103 (vs), 1065 (s), 972 (w), 965 (w), 920 (w), 841 (vs), 757 (s), 700 (w), 689 (s) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for C15H9F3: 246.0656; found: 246.0643.

1-(Phenylmethyl)-4-(trifluoromethyl)-benzene (CEJ-2k) [CAS: 34239-04-8]



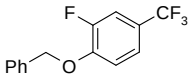
(CEJ-2k) was synthesized following the general procedure using 4-benzylphenylboronic acid pinacol ester (CEJ-1k) (147 mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, n-hexane), affording (CEJ-2k) (140 mg, 59.3 %) as colorless oil ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.48 (d, *J* = 8.0 Hz, 2 H), 7.21-7.28 (m, 4 H), 7.14-7.20 (m, 1 H), 7.10-7.14 (m, 2 H), 3.97 (s, 2 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 145.2 (q, *J* = 1.5Hz) 140.0, 129.2, 128.9, 128.7, 128.4 (q, *J* = 32.3Hz) 126.5, 124.1 (q, *J* = 272.2Hz), 41.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.27 (s) ppm; MS: (EI): m/z (%) = 237 (14), 236 (100) [M^+], 217 (13), 168 (18), 167 (71), 166 (24), 91 (18); IR (KBr) = 3902 (vs), 3852 (vs), 3838 (vs), 3820 (vs), 3750 (vs), 3734 (s), 3710 (s), 3688 (s), 3674 (vs), 3648 (vs), 3628 (s), 3029 (m), 2923 (m), 2343 (w), 1923 (w), 1793 (w), 1773 (w), 1751 (w), 1733 (w), 1717 (w), 1699 (w), 1685 (w), 1669 (w), 1663 (w), 1653 (w), 1647 (w), 1635 (w), 1617 (m), 1603 (w), 1559 (w), 1495 (w), 1453 (w), 1437 (w), 1417 (m), 1326 (vs), 1164 (m), 1124 (s), 1108 (s), 1068 (s), 1030 (w), 1020 (m), 854 (w), 800 (w), 734 (m), 698 (w), 594 (w) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_{14}H_{11}F_3$: 236.0813; found: 236.0817;

2-Fluoro-4-(trifluoromethyl)-1,1'-biphenyl (CEJ-2l) CAS: [1214369-54-6]



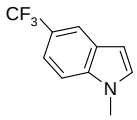
(CEJ-2l) was synthesized following the general procedure using 2-Fluoro-4-biphenylylboronic acid pinacol ester (CEJ-1l) (298 mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, n-hexane), affording (CEJ-2l) (152 mg, 63.2 %) as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.58-7.64 (m, 3 H), 7.51-7.57 (m, 3 H), 7.49-7.51 (m, 1 H), 7.47-7.47 (m, 1 H), 7.48 (s, 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 160.6 (d, *J* = 250Hz) 134.3, 132.8 (d, *J* = 13.2Hz), 131.4 (d, *J* = 4.4Hz), 130.8 (qd, *J* = 33.4Hz, 8.1Hz), 129.0 (d, *J* = 2.9Hz), 128.7, 128.5, 121.2 (quin, *J* = 3.7Hz), 124.0 (q, *J* = 272.2Hz, 2.9Hz) 113.6 (dq, *J* = 25.6Hz, 3.7Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.61 (s) ppm; MS: (EI): m/z (%) = 241 (15), 240 (100) [M^+], 221 (7), 220 (5), 172 (3), 171 (12), 170 (13); IR (KBr) = 2221 (w), 2187 (w), 2163 (w), 1979 (w), 1935 (w), 1907 (w), 1890 (w), 1814 (w), 1745 (w), 1739 (w), 1609 (w), 1572 (w), 1520 (w), 1487 (w), 1442 (w), 1406 (w), 1322 (m), 1288 (w), 1165 (m), 1154 (m), 1128 (m), 1103 (vs), 1065 (s), 972 (w), 965 (w), 920 (w), 841 (vs), 757 (s), 700 (w), 689 (s)cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_{13}H_8F_4$: 240.0562; found: 240.0558.

2-Fluoro-1-(phenylmethoxy)-4-(trifluoromethyl)-benzene (CEJ-2m) CAS: [1044067-80-2].



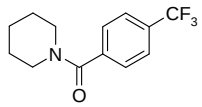
(CEJ-2m) was synthesized following the general procedure using 4-(benzyloxy)-3-fluorophenylboronic acid pinacol ester (CEJ-1m) (328mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, n-hexane), affording (CEJ-2m) (118 mg, 43.7 %) as a colorless solid. m.p. 65.3 °C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.28-7.53 (m, 7 H), 7.00-7.16 (m, 1 H), 5.21 (s, 2 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 153.4, 150.9, 149.3-149.7 (m), 135.6, 128.7, 128.4, 127.4, 123.4 (qd, *J* = 33.7Hz, 3.6Hz), 123.5 (qd, *J* = 271.4Hz, 2.9Hz), 121.7 (quin *J* = 3.7Hz), 114.9 (d, *J* = 2.2Hz) 113.8 (dq, *J* = 21.3Hz, 3.6Hz) 71.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -61.76 (s) -131.68 (s) ppm; MS: (EI): m/z (%) = 151 (4), 101 (6), 92 (8), 91 (100), 89 (3), 65 (12), 63 (4); IR (KCl) = 2950 (w), 2187 (w), 2051 (w), 2044 (w), 2037 (w), 1984 (w), 1968 (w), 1912 (w), 1898 (w), 1869 (w), 1741 (w), 1620 (w), 1529 (w), 1520 (w), 1455 (w), 1438 (m), 1334 (m), 1323 (m), 1280 (m), 1201 (m), 1168 (m), 1102 (vs), 1068 (m), 1012 (m), 998 (m), 907 (m), 872 (m), 849 (w), 810 (s), 790 (w), 748 (s), 741 (s), 724 (w), 698 (m) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_{14}H_{10}F_4O$: 270.0668; found: 270.0666.

1-Methyl-5-(trifluoromethyl)-1H-indole (CEJ-2n) CAS: [1264670-41-8]



(CEJ-2n) was synthesized following the general procedure using 1-methylindole-5-boronic acid pinacol ester (CEJ-1n) (265 mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, 25% n-hexane/ethylacetate), affording (CEJ-2n) (103 mg, 52 %).as a colorless solid. m.p. 74.1 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.96 (s, 1 H), 7.48 (d, *J* = 8.6 Hz, 1 H), 7.39 (d, *J* = 8.6 Hz, 1 H), 7.16 (d, *J* = 2.7 Hz, 1 H), 6.60 (d, *J* = 2.7 Hz, 1 H), 3.83 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 137.9, 130.5, 127.7, 125.5 (q, *J*(C,F)=271.9Hz) 121.7 (q, *J* = 31.4Hz), 118.6 (q, *J* = 3.7Hz), 118.2 (q, *J* = 3.7Hz), 109.4, 102.0, 32.9 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -60.10 (s) ppm; MS: (EI): m/z (%) = 200 (12), 199 (99) [M^+], 198 (100), 180 (13), 178 (11), 151 (7), 69 (6); IR (KCl) = 3075 (w), 3033 (w), 2951 (w), 2945 (w), 2850 (w), 2833 (w), 2428 (w), 2186 (w), 2177 (w), 2163 (w), 2051 (w), 2043 (w), 1994 (w), 1980 (w), 1959 (w), 1915 (w), 1903 (w), 1888 (w), 1743 (w), 1740 (w), 1728 (w), 1613 (m), 1589 (w), 1519 (w), 1494 (w), 1456 (w), 1425 (w), 1325 (m), 1310 (m), 1246 (m), 1231 (m), 1165 (s), 1094 (vs), 1060 (s), 1004 (s), 974 (w), 945 (w), 912 (w), 903 (w), 856 (w), 845 (m), 820 (m), 740 (s), 695 (s) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_{10}H_8F_3N$: 199.0609; found: 199.061.

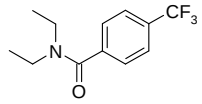
1-Piperidinyl[4-(trifluoromethyl)phenyl]-methanone (CEJ-2o) CAS: [411209-38-6]



(CEJ-2o) was synthesized following the general procedure using 4-(piperidine-1-carbonyl)phenylboronic acid pinacol ester (CEJ-1o) (315 mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, 25% n-hexane/ethylacetate), affording (CEJ-2o) (173 mg, 67.2 %) as a colorless solid. m.p. 98.2 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 8.0 Hz, 2 H), 7.46 (d, *J* = 7.8 Hz, 2 H), 3.68 (s, 2 H), 3.25 (s, 2 H), 1.64 (s, 4 H), 1.47 (s, 2 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 168.8, 140.0 (q, *J* = 1.5Hz) 131.3 (q, *J* = 33.0Hz) 127.1, 125.5 (q, *J* = 3.7Hz), 123.7 (q, *J* = 272.2Hz), 48.5-48.8 (m), 42.9-43.2 (m), 26.3-26.6 (m), 25.4-25.6 (m), 24.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.86 (s) ppm; MS: (EI): m/z (%) = 257 (32) [M^+], 256 (100), 173 (77), 145 (48); IR (KCl) = 3044 (w), 3008 (w), 2995 (w), 2953 (w), 2931 (w), 2918 (w), 2858 (w), 1739 (w), 1728 (w), 1622 (m), 1616 (m), 1575 (w), 1468 (w), 1459 (w), 1441 (m), 1407 (w), 1322 (m), 1277 (m), 1235 (w), 1168 (m), 1158 (m), 1106 (vs), 1063 (s),

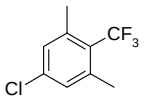
1003 (m), 953 (w), 888 (w), 854 (m), 828 (w), 768 (w), 728 (w), 702 (w) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_{13}H_{14}F_3NO$: 257.1027; found: 257.1015.

***N,N*-Diethyl-4-(trifluoromethyl)-benzamide** (CEJ-2p) [CAS: 95725-04-5]



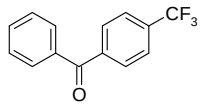
(CEJ-2p) was synthesized following the general procedure using 3-(N,N-diethylaminocarbonyl)phenylboronic acid pinacol ester (CEJ-1p) (303 mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, 25% n-hexane/ethylacetate), affording (CEJ-2p) (173 mg, 71 %) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 8.0 Hz, 2 H), 7.46 (d, *J* = 7.8 Hz, 2 H), 3.68 (s, 2 H), 3.25 (s, 2 H), 1.64 (s, 4 H), 1.47 (s, 2 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 169.6, 137.9, 130.8 (q, *J* = 32.3Hz), 129.5 (q, *J* = 1.5Hz), 129.0, 125.8 (q, *J* = 3.7Hz), 123.2 (q, *J* = 3.9Hz), 123.6 (q, *J* = 272.2Hz), 43.3 (br. s.), 39.4 (br. s.), 14.0 (br. s.), 12.7 (br. s.) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.83 (s) ppm; MS: (EI): m/z (%) = 245 (13) [M^+], 244 (27), 173 (100), 145 (37); IR (KCl) = 3902 (vs), 3852 (vs), 3838 (vs), 3820 (vs), 3750 (vs), 3734 (vs), 3710 (vs), 3688 (vs), 3674 (vs), 3648 (vs), 3628 (s), 2977 (s), 2345 (w), 1923 (w), 1869 (w), 1845 (w), 1751 (w), 1733 (w), 1717 (w), 1701 (w), 1685 (w), 1635 (vs), 1475 (m), 1457 (m), 1425 (m), 1334 (vs), 1314 (m), 1276 (s), 1168 (s), 1128 (s), 1072 (m), 944 (w), 910 (w), 890 (w), 816 (w), 800 (w), 752 (w), 716 (w), 702 (w), 664 (w) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_{12}H_{14}F_3NO$: 245.1027; found: 245.1025.

5-Chloro-1,3-dimethyl-2-(trifluoromethyl)-benzene (CEJ-2q)



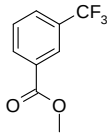
(CEJ-2q) was synthesized following the general procedure using 4-chloro-2,6-dimethylphenylboronic acid pinacol ester (CEJ-1q) (260 mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, n-pentane), affording (CEJ-2q) (92 mg, 49 %) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.10 (s, 2 H), 2.46 (q, J = 3.2 Hz, 6 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 139.4 (q, *J* = 1.82Hz), 136.5 (br. s), 129.9, 128.1, 126.2 (q, *J* = 29.1Hz), 125.5 (q, *J* = 276.1Hz), 21.3 (q, *J* = 4.5Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -54.14 (s) ppm; MS: (EI): m/z (%) = 210 (34), 208 (100) [M^+], 188 (23), 173 (93), 139 (57), 103 (23), 43 (50); IR (KCl) = 2361 (w), 1585 (s), 1475 (m), 1457 (w), 1429 (m), 1415 (m), 1292 (vs), 1254 (w), 1240 (w), 1154 (vs), 1118 (vs), 1040 (s), 878 (w), 862 (m), 744 (w), 668 (w), 566 (w) cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_9H_8ClF_3$: 208.0276; found: 208.0250.

Phenyl[4-(trifluoromethyl)phenyl]-methanone (CEJ-2r) CAS: [728-86-9]



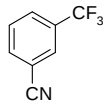
(CEJ-2r) was synthesized following the general procedure using 4-benzoylphenylboronic acid pinacol ester (CEJ-1r) (308 mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, 25% n-hexane/ethylacetate), affording (CEJ-2r) (157 mg, 63 %) as a colorless solid. m.p. 113 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.87-7.94 (m, 2 H), 7.79-7.85 (m, 2 H), 7.77 (d, *J* = 8.0 Hz, 2 H), 7.60-7.68 (m, 1 H), 7.47-7.56 (m, 2 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 195.5, 140.7, 136.7, 133.7 (q, *J* = 33.3Hz) 133.1, 130.1, 130,1, 128.5, 125.3 (q, *J* = 4.16Hz) 123.6 (q, *J* = 273.3Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.96 (s) ppm; MS: (EI): m/z (%) = 251 (13), 250 (31) [M^+], 231(15), 181 (14), 173 (44), 145 (19), 105 (100); GC/HRMS-EI m/z [M^+] calcd. for $C_{14}H_9F_3O$: 250.0605; found: 250.0599.

Methyl-3-(trifluoromethyl)benzoate (CEJ-2s) CAS: [2557-13-3]



(CEJ-2s) was synthesized following the general procedure using 3-(methoxycarbonyl)phenylboronic acid pinacol ester (CEJ-1s) (262 mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, 25% n-pentane/diethyl ether), affording (CEJ-2s) (82 mg, 40 %) as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.32 (s, 1 H), 8.24 (d, *J* = 7.6 Hz, 1 H), 7.82 (d, *J* = 7.6 Hz, 1 H), 7.56-7.64 (m, 1 H), 3.97 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 165.8, 132.8, 131.0, 131.0 (q, *J* = 33.3Hz), 129.4 (q, *J* = 2.77Hz) 129.0, 126.5 (q, *J* = 4.16Hz), 123.6 (q, *J* = 273.3Hz) 52.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.82 (s) ppm; MS: (EI): m/z (%) = 204 (9) [M^+], 203 (20), 185 (11), 174 (9), 173 (100), 145 (39), 95 (8); IR (KCl) = 2955 (s), 2359 (w), 1731 (s), 1617 (m), 1597 (w), 1435 (s), 1338 (vs), 1260 (vs), 1170 (s), 1132 (s), 1090 (s), 1074 (s), 976 (m), 922 (w), 850 (w), 822 (w), 776 (w), 758 (s), 714 (w), 694 (s), 650 (w), 450 cm^{-1}; GC/HRMS-EI m/z [M^+] calcd. for $C_9H_7F_3O_2$: 204.0398; found: 204.0395.

3-Trifluoromethylbenzonitril (CEJ-2t) [CAS: 368-77-4]



(CEJ-2t) was synthesized following the general procedure from 3-cyanophenylboronic acid pinacol ester (CEJ-1t) (229 mg, 1.00 mmol), copper(II) acetate (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (432 mg, 2.00 mmol) and purified by column chromatography (SiO_2, 60% n-pentane/diethyl ether), affording (CEJ-2t) (69 mg, 40 %) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.94 (s, 1 H), 7.88 (t, *J* = 7.8 Hz, 2 H), 7.67 (t, *J* = 7.9 Hz, 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 135.3 (br. s), 132.1 (q, *J* = 33.6Hz), 130.0, 129.5 (q, *J* = 3.6Hz), 129.1 (q, *J* = 3.6Hz), 122.9 (q, *J* =272.5Hz), 117.3, 113.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = - 63.19 (s) ppm; MS: (EI): m/z (%) = 171 (100), 170 (29) [M^+], 152 (37), 121 (48), 75 (16), 50 (15), 43 (30); GC/HRMS-EI m/z [M^+] calcd. for $C_8H_4F_3N$: 171.0296; found: 171.0293.

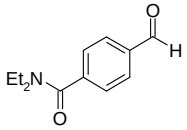
7.9 Trifluoromethylation of Carbonyl Compounds with Shelf-Stable Potassium (trifluoromethyl)trimethoxyborate

7.9.1 General Methods for the Synthesis of α-Trifluoromethylated Alcohols

A 20 mL reaction vessel was charged with potassium (trifluormethyl)trimethoxyborate (265 mg, 1.25 mmol) and solid carbonyl compound (1.0 mmol). The reaction vessel was purged three times with nitrogen. Under an inert atmosphere, dry and degassed THF was added. Liquid carbonyl compounds (1.0 mmol) were added after addition of THF. The reaction mixture was stirred at 60 °C for 16 hours. After cooling to room temperature, it was neutrilized with aqueous HCl (1 N, 50 mL), and extracted with ethyl acetate (3 × 20 mL). Organic phases were washed with water (30mL) and brine. Combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude product was purified with column chromatography (SiO_2, n-hexane/ethylacetate).

7.9.2 Sythesis of Starting Materials

N,*N*-**Diethylbenzamide-4-carboxaldehyde** (5.5-1s) CAS: [58287-77-7]

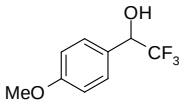


The reaction was performed according to a modified literature procedure:[238] A 100 mL round bottom flask, equipped with a condenser and a dropping funnel, was charged with 4-

carboxybenzaldehyde (1.50 g, 10 mmol) and dichloromethane (40 mL) was added. After drop wise addition of oxalyl chloride (6.48 g, 50.0 mmol, 4.85 mL), DMF (20 µL) was added. The reaction mixture was stirred at 55 °C. After the gas evolution was over, volatiles were removed under vacuum. The remaining brownish solid was dissolved in dichloromethane (20 mL) and diethylamine (2.19 mg, 30.0 mmol, 3.10 mL) was added. After stirring at room temperature for 30 min, reaction mixture was washed with saturated $NaHCO_3$ (500 mL), and the aqueous washing was re-extracted with dichloromethane (2 × 20 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The product (5.5-1s) (1.60 g, 78%) was received as yellow oil in the form of two different rotamers. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.97 (s, 1 H), 7.85 (d, *J* = 7.8 Hz, 2 H), 7.46 (d, *J* = 7.8 Hz, 2 H), 3.49 (q, *J* = 6.3 Hz, 2 H), 3.15 (d, *J* = 6.7 Hz, 2 H), 1.19 (t, *J* = 6.7 Hz, 3 H), 1.04 (t, *J* = 6.8 Hz, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ =191.4, 169.6, 142.8, 136.3, 129.7, 126.7, 43.1, 39.2, 14.0, 12.7 ppm; MS (EI): m/z (%) = 207 (16), 206 (100), 205 (34) [M^+], 204 (12), 134 (9), 133 (93), 105 (25); Elemental analysis: Calcd: C, 70.22, H, 7.37; N, 6.82; Found: C, 70.26; H, 7.15; N, 6.96.

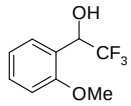
7.9.3 Synthesis of α- Trifluoromethylalcohols

1-(4-Methoxyphenyl)-2,2,2-trifluoroethanol (5.5-3a) CAS: [1737-25-5]



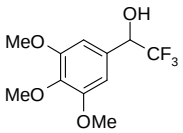
Compound (5.5-3a) was prepared from 4-methoxybenzaldehyde (5.5-1a) (136 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate(5.5-2) (265 mg, 1.25 mmol) affording (5.5-3a) as a colorless oil; yield: 176 mg (85 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.37 (d, *J* = 8.5 Hz, 2 H), 6.89-6.92 (m, 2 H), 4.91 (dd, *J* = 6.6 Hz, J = 3.4 Hz, 1 H), 3.80 (s, 3 H), 3.14 (d, *J* = 3.8 Hz, 1 H) ppm. 6.83 (s, 2 H), 3.90 (s, 6 H),3.88 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 160.4, 128.8, 126.1, 124.3 (q, *J* = 282.1 Hz), 114.0, 72.4 (q, *J* = 32.4 Hz), 55.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -78.51 (d, *J* = 6.9 Hz) ppm; MS: (EI): m/z (%) = 206 [M^+] (32), 138 (9), 137 (100), 109 (44), 94 (28), 77 (22), 69 (8); IR (NaCl) = 3300 (br, s), 2939 (m), 2913 (m), 1897 (w), 1613 (s), 1587 (w), 1517 (s), 1465 (m), 1443 (w), 1254 (s), 1174 (s), 1128 (s), 1074 (m), 1032 (m), 872 (w), 820 (m), 778 (w), 730 (w), 694 (w) cm^{-1}; Elemental analysis: Calcd: C, 52.52; H, 4.40; Found: C, 52.52; H, 4.54.

1-(2-Methoxyphenyl)-2,2,2-trifluoroethanol (5.5-3b) CAS: [26902-84-1]



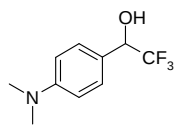
Compound (5.5-3b) was prepared from 2-methoxybenzaldehyde (5.5-1b) (136 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate ((5.5-2) (265 mg, 1.25 mmol) affording (5.5-3b) as a colorless oil; yield: 163 mg (79 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.33-7.45 (m, 2 H), 6.98-7.08 (m, 1 H), 6.95 (d, *J* = 8.2 Hz, 1 H), 5.29 (quin., *J* = 7.1 Hz, 1 H), 3.91 (d, *J* = 7.8 Hz, 1 H), 3.86 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 157.5, 130.5, 129.2, 123.6 (q, *J* = 282.9 Hz), 122.1, 121.0, 111.2, 69.5 (q, *J* = 32.4 Hz), 55.6 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -78.06 (d, *J* = 6.9 Hz) ppm; MS: (EI): m/z (%) = 206 (45)[M^+], 189 (25), 138 (9), 137 (100), 121 (18), 109 (11), 107 (74); IR (NaCl) = 3300 (br, s), 2945 (s), 2843 (m), 1703 (w), 1603 (s), 1591 (s), 1493 (s), 1467 (s), 1274 (s), 1258 (s), 1252 (s), 1064 (s), 1050 (s), 1028 (s), 872 (m), 758 (m) cm^{-1}; Elemental analysis: Calcd: C, 52.52; H, 4.40; Found: C, 52.61; H, 4.46.

1-(3,4,5-Trimethoxyphenyl)-2,2,2-trifluoroethanol (5.5-3c) CAS: [207502-47-4]



Compound (5.5-3c) was prepared from 3,4,5-trimethoxybenzaldehyde (5.5-1c) (200 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3c) as a colorless solid; yield: 163 mg (79 %). m.p. 96 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.64 (s, 2 H), 4.93 (q, *J* = 6.7 Hz, 1 H), 3.85 (s, 6 H), 3.83 (s, 3 H), 3.31 (br. s, 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 153.1, 138.3, 129.9, 125.6 (q, *J* = 282.0 Hz), 104.5, 72.7, (q, *J* = 31.4 Hz) 60.8, 56.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -78.18 (d, *J* = 6.9 Hz) ppm; MS: (EI): m/z (%) = 267 (16) [M^+], 266 (100), 251 (10), 197 (36), 169 (49), 154 (10), 138 (16); IR (KBr) = 3406 (br, s), 3005 (m), 2940 (m), 2840 (m), 1598 (s), 1507 (s), 1463 (s), 1414 (s), 1329(s), 1236 (s), 1128 (s), 998 (s), 820 (m), 683 (m) cm^{-1}; Elemental analysis: Calcd: C, 49.63; H, 4.92; Found: C, 49.74; H, 5.01.

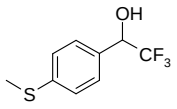
1-(4-Dimethylaminophenyl)-2,2,2-trifluorethanol (5.5-3d) CAS: [58822-13-8]



Compound (5.5-3d) was prepared from 4-dimethylaminobenzaldehyde (5.5-1d) (149 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3d) as a yellow solid; yield: 180 mg (82 %). m.p. 100 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.33 (d, *J* = 8.6 Hz, 2 H), 6.73 (d, *J* = 8.6 Hz, 2 H),4.92 (q, *J* = 6.9 Hz, 1 H), 2.99 (s,

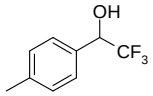
6 H), 2.43 (br. s., 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 151.2, 128.4, 121.4, 124.4 (q, *J* = 282.1 Hz), 112.1, 72.8 (q, *J* = 32.4 Hz), 40.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -78.42 (d, *J* = 6.9 Hz) ppm; MS: (EI): m/z (%) = 220 (67) [M^+], 219 (100), 218 (15), 150 (94), 122 (34), 120 (39), 107 (19); IR (KBr) = 3366 (br, s), 2899 (w), 1621 (s), 1533 (s), 1447 (w), 1365 (m), 1349 (m), 1260 (s), 1234 (m), 1192 (s), 1166 (s), 1118 (s), 1064 (s), 946 (w), 804 (s), 692 (m) cm^{-1}; Elemental analysis: Calcd: C, 54.79; H, 6.39; Found: C, 55.20; H, 6.45.

1-(4-Methylthio)phenyl)-2,2,2-trifluorethanol (5.5-3e) CAS: [122035-81-8]



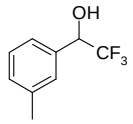
Compound (5.5-3e) was prepared from 4-methylthiobenzaldehyde (5.5-1e) (152 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3e) as a yellow solid; yield: 172 mg (78 %). m.p. 40 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 4.92-5.08 (m, 1 H), 3.08 (d, *J* = 4.7 Hz, 1 H), 2.56 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 140.4, 130.4, 127.8, 126.1, 124.14 (q, *J* = 282.1 Hz), 72.15 (q, *J* = 31.4 Hz), 15.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -78.38 (d, *J* = 6.9 Hz) ppm; MS: (EI): m/z (%) = 223 (20), 222 (100) [M^+], 221 (7), 154 (8), 153 (55), 125 (10), 109 (15); IR (KBr) = 3339 (br, s), 2925 (m), 1751 (w), 1602 (m), 1497 (m) 1438 (m), 1266 (s), 1168 (s), 1126 (s), 958 (w), 871 (m), 811 (s), 678 (s) cm^{-1}; Elemental analysis: Calcd: C, 48.64; H, 4.08; S 14.43; Found: C, 48.78; H, 3.77; S, 14.41.

1-(4-Methylphenyl)-2,2,2-trifluorethanol (5.5-3f) CAS: [446-65-1]



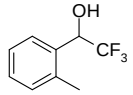
Compound (5.5-3f) was prepared from 4-methylbenzaldehyde (5.5-1f) (120 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3f) as a colorless oil; yield: 143 mg (75 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 7.8 Hz, 2 H), 7.24 (d, *J* = 7.8 Hz, 2 H), 4.77-5.01 (m, 1 H), 3.02 (d, *J* = 4.7 Hz, 1 H), 2.40 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 139.5, 131.0, 129.3, 127.3, 124.0 (q, *J* = 282.1 Hz), 72.6 (q, *J* = 31.4 Hz), 21.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -78.35 (d, *J* = 6.9 Hz) ppm; MS: (EI): m/z (%) = 190 (21) [M^+], 173 (15), 121 (100), 93 (67), 91 (79), 77 (16), 65 (14); IR (NaCl) = 3330 (br, s), 2927 (m), 1685 (w), 1517 (w), 1457 (w), 1381 (w), 1270 (s), 1170 (s), 1128 (s), 1074 (m), 872 (w), 848 (w), 806 (m), 778 (w) cm^{-1}; Elemental analysis: Calcd: C, 56.84; H, 4.77; Found: C, 56.74; H, 4.89.

1-(3-Methylphenyl)-2,2,2-trifluorethanol (5.5-3g) CAS: [1737-23-1]



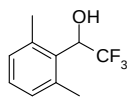
Compound (5.5-3g) was prepared from 4-methylbenzaldehyde (5.5-1g) (120 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3f) as colorless oil; yield: 165 mg (87 %)^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.08-7.34 (m, 4 H), 4.90 (q, *J* = 6.3 Hz, 1 H), 2.83 (br. s, 1 H), 2.35 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 138.4, 133.9, 130.3, 128.5, 128.0, 124.5, 125.1 (q, *J* = 282.1 Hz), 72.8 (q, *J* = 32.4 Hz), 21.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -78.24 (d, *J* =6.9 Hz) ppm; MS: (EI): m/z (%) = 190 (21) [M^+], 173 (15), 121 (100), 93 (67), 91 (79), 77 (16), 65 (14); IR (NaCl) = 3330 (br, s), 2925 (m), 1705 (m), 1653 (w), 1593 (w), 1457 (w), 1266 (s), 1162 (s), 1128 (s), 1074 (m), 712 (m) cm^{-1}; Elemental analysis: Calcd: C, 56.84; H, 4.77; Found: C, 57.04; H, 4.91.

1-(2-Methylphenyl)-2,2,2-trifluorethanol (5.5-3h) CAS: [438-24-4]



Compound (5.5-3h) was prepared from 2-methylbenzaldehyde (5.5-1h) (120 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3h) as a colorless oil; yield: 153 mg (80 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 7.1 Hz, 1 H), 7.28-7.35 (m, 2 H), 7.18-7.26 (m, 1 H), 5.33 (q, *J* = 6.3 Hz, 1 H), 2.63 (br. s., 1 H), 2.40 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 136.5, 132.5, 130.6, 129.3, 126.9 (d, *J* = 1.8 Hz), 126.4, 124.4 (q, *J* = 283.0 Hz), 68.8 (q, *J* = 32.4 Hz), 19.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -77.73 (d, *J* = 6.9 Hz) ppm; MS: (EI): m/z (%) = 190 (22) [M^+], 173 (31), 172 (73), 171 (15), 121 (100), 93 (56), 91 (100), 65 (19); IR (NaCl) = 3330 (br, s), 3015 (w), 2860 (w), 1709 (w), 1607 (w), 1493 (m), 1463 (m), 1445 (w), 1383 (w), 1268 (s), 1172 (s), 1134 (s), 1114 (s), 1062 (m), 1052 (m), 866 (m), 836 (m), 760 (m), 728 (m) cm^{-1}; Elemental analysis: Calcd: C, 56.84; H, 4.77; Found: C, 57.06; H, 4.84.

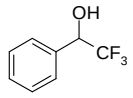
1-(2,6-Dimethylphenyl)-2,2,2-trifluorethanol (5.5-3i)



Compound (5.5-3i) was prepared from 2,6-dimethylbenzaldehyde (5.5-1i) (132 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate(5.5-2) (265 mg, 1.25 mmol) affording (5.5-3i) as a yellow oil; yield: 160 mg (79 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.01-7.08 (m, 1 H), 6.94 (d, *J* = 7.4 Hz, 2 H), 5.44 (m, 1 H), 2.62 (d, *J* = 5.1 Hz, 1 H), 2.35 (br., s., 6 H) ppm; ^{13}C-NMR

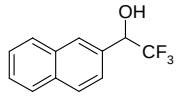
(101 MHz, $CDCl_3$) δ = 138.2 (br., s), 129.7, 128.9, 124.8 (q, *J* = 283.9 Hz), 70.5 (q, *J* = 32.4 Hz), 20.9 (q, *J* = 2.8 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -75.31 (d, *J* = 8.0 Hz) ppm; MS: (EI): m/z (%) = 204 (11) [M^+], 187 (33), 186 (91), 135 (100), 133 (18), 107 (94), 105 (45), 91 (44); IR (NaCl) = 3330 (br, s), 3015 (w), 2850 (w), 1705 (w), 1593 (w), 1587 (w), 1467 (m), 1383 (w), 1268 (s), 1164 (s), 1126 (s), 1076 (m), 1026 (w), 922 (w), 866 (w), 820 (w), 774 (m), 690 (m) cm^{-1}; Elemental analysis: Calcd: C, 58.82; H, 5.43; Found: C, 58.21; H, 5.57.

1-Phenyl-2,2,2-trifluorethanol (5.5-3j) CAS: [340-05-6]



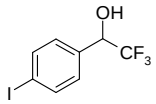
Compound (5.5-3j) was prepared from benzaldehyde (5.5-1j) (106 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3j) as a colorless oil; yield: 161 mg (92 %). ^1H-NMR (400 MHz, $CDCl_3$) δ = 7.39-7.53 (m, 5 H), 4.95-5.12 (m, 1 H), 2.69 (d, *J* = 3.5 Hz, 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 133.9, 129.6, 128.7, 127.5, 124.1 (q, *J* = 282.1 Hz), 72.9 (q, *J* = 31.4 Hz) ppm;^{19}F NMR (376 MHz, $CDCl_3$): δ = -78.35 (d, *J* = 6.9 Hz) ppm; MS: (EI): m/z (%) = 175 (1) [M^+], 159 (18), 137 (5), 109 (12), 107 (100), 79 (26), 77 (14); IR (NaCl) = 3330 (br, s), 3037 (w), 1707 (w), 1457 (m), 1268 (s), 1172 (s), 1128 (s), 1064 (m), 1030 (w), 866 (w), 834 (w), 706 (s) cm^{-1}.Elemental analysis: Calcd: C, 54.55; H, 4.01; Found: C, 54.19; H, 3.94.

1-(2-Naphthyl)-2,2,2-trifluorethanol (5.5-3k) CAS: [1645-50-7]



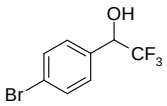
Compound (5.5-3k) was prepared from 2-naphthylaldehyde (5.5-1k) (160 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-32a) (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3k)as a colorless solid; yield: 207 mg (91 %). m.p. 84 °C; ^1H-NMR (400 MHz, $CDCl_3$) δ = 7.79-8.01 (m, 4 H), 7.48-7.67 (m, 3 H), 5.14 (q, *J* = 6.4 Hz, 1 H), 3.31 (br. s., 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 133.7, 132.8, 131.2, 128.5, 128.2, 127.7, 127.3, 126.8, 126.5, 124.2, 123.8 (q, *J* = 282.1 Hz), 72.9 (q, *J* = 32.4 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -77.81 (d, J = 6.9 Hz) ppm; MS: (EI): m/z (%) = 227 (13), 226 (100) [M^+], 209 (15), 157 (55), 129 (43), 128 (25), 127 (9); IR (KBr) = 3367 (br, s), 3065 (w), 2905 (w), 1601 (w), 1508 (m), 1429 (w), 166 (m), 1342 (m), 1262 (s), 1247 (s), 1196 (s), 1124 (s), 1084 (m), 969 (w), 822 (s), 751 (m), 701 (s) cm^{-1}; Elemental analysis: Calcd: C, 63.73; H, 4.01; Found: C, 63.75; H, 3.91.

1-(4-Iodophenyl)-2,2,2-trifluorethanol (5.5-3l) CAS: [857521-44-9]



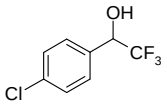
Compound (5.5-3l) was prepared from 4-iodobenzaldehyde (5.5-1l) (234 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3l) as a colorless solid; yield: 265 mg (87 %). m.p. 67 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 8.2 Hz, 2 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 4.95 (m, 1 H), 2.85 (d, *J* = 4.3 Hz, 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 137.7, 133.4, 129.2, 123.9 (q, *J* = 283.0 Hz), 95.6, 72.3 (q, *J* = 32.4 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -78.42 (d, *J* = 5.7 Hz) ppm; MS: (EI): m/z (%) = 302 (5) [M^+], 282 (8), 235 (4), 234 (14), 233 (100), 232 (4), 106 (4), 105 (10), 78 (5); IR (KBr) = 3304 (br, s), 3015 (w), 1910 (m), 1792 (w), 1626 (w), 1592 (s), 1567 (w), 1488 (s), 1399 (s), 1353 (s), 1256 (s), 1116 (s), 1006 (s), 949 (m), 863 (s), 792 (s), 725 (s), 683 (m), 663 (m) cm^{-1}; Elemental analysis: Calcd: C, 31.81; H, 2.00; Found: C, 31.76; H, 1.88.

1-(4-Bromophenl)-2,2,2-trifluorethanol (5.5-3m) CAS: [76911-73-4]



Compound (5.5-3m) was prepared from 4-bromobenzaldehyde (5.5-1m) (185 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3m)as a colorless solid; yield: 179 mg (70 %). m.p. 53 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 4.95 (q, *J* =6.5 Hz, 1 H), 3.02 (s, 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 132.7; 131.8. 129.0. 123.8. 123.7 (q, *J* = 282.1 Hz), 72.2 (q, J = 32.4 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -78.46 (d, *J* = 6.9 Hz) ppm; MS: (EI): m/z (%) = 256 (18) [M^+], 254 (22), 239 (18), 237 (18), 187 (100), 185 (97), 157 (14); IR (KBr) = 3368 (br, s), 2940 (w), 1908 (w), 1594 (w), 1493 (s), 1404 (w), 1356 (m), 1258 (s), 1175 (s), 1126 (s), 1076 (s), 1011 (s), 949 (w), 864 (m), 798 (s), 728 (m), 686 (m), 671 (m) cm^{-1}; Elemental analysis: Calcd: C, 37.68; H, 2.37; Found: C, 38.17; H, 2.40.

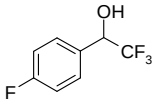
1-(4-Chlorophenyl)-2,2,2-trifluorethanol (5.5-3n) CAS: [446-66-2]



Compound (5.5-3n) was prepared from 4-chlorobenzaldehyde (5.5-1n) (146 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3n) as colorless oil; yield: 155 mg (74 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.31-7.45 (m, 4 H), 4.99 (m, 1 H), 2.79 (d, *J* = 3.1 Hz, 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 135.6, 132.2, 128.8, 128.8, 124.0 (q, *J* = 282.1 Hz), 72.1 (q, *J* = 32.4 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -

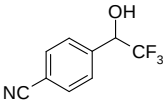
78.53 (d, J = 6.9 Hz) ppm; MS: (EI): m/z (%) = 210 (11) [M^+], 193 (18), 143 (42), 142 (11), 141 (100), 113 (26), 77 (25); IR (KBr) = 3330 (br. S), 2923 (w), 1717 (w), 1599 (m), 1581 (w), 1495 (s), 1411 (m), 1268 (s), 1074 (s), 1016 (s), 872 (m), 848 (m), 810 (s), 732 (s) cm^{-1}; Elemental analysis: Calcd: C, 45.63; H, 2.87; Found: C, 45.49; H, 2.87.

1-(4-Fluorophenyl)-2,2,2-trifluorethanol (5.5-3o) CAS: [50562-19-1]



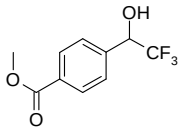
Compound (5.5-3o) was prepared from 4-fluorobenzaldehyde (5.5-1o) (124 mg, 1.00 mmol, 108 µL) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3o) as colorless oil; yield: 114 mg (59 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.45 (m, 2 H), 7.09 (m, 2 H), 5.00 (m, 1 H), 2.72 (d, *J* = 4.3 Hz, 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 163.4 (d, *J* = 248.8 Hz), 129.7 (d, *J* = 1.9 Hz), 129.3 (d, *J* = 9.3 Hz), 124.1 (q, *J* = 283.0 Hz), 115.7 (d, *J* = 22.2 Hz), 72.2 (q, *J* = 32.4 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -111.96--111.69 (m, 1 F), -78.67 (d, *J* = 6.9 Hz, 3 F) ppm; MS: (EI): m/z (%) = 194 (7) [M^+], 177 (20), 127 (14), 126 (7), 125 (100), 123 (11), 97 (37), 77 (15); IR (NaCl) = = 3330 (br, s), 2860 (w), 1705 (w), 1609 (m), 1513 (s), 1419 (w), 1272 (s), 1232 (s), 1176 (s), 1130 (s), 1072 (m), 1016 (w), 874 (m), 856 (m), 822 (s), 794 (w) cm^{-1}; Elemental analysis: Calcd: C, 49.50; H, 3.12 Found: C, 49.10; H, 3.13.

1-(4-Cyanophenyl)-2,2,2-trifluorethanol (5.5-3p) CAS: [107018-37-1]



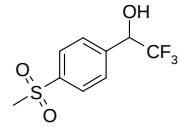
Compound (5.5-3p) was prepared from 4-cyanobenzaldehyde (5.5-1p) (131 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3p) as a colorless solid; yield: 150 mg (75%). m.p. 99 °C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.67-7.77 (m, 2 H), 7.56-7.67 (m, 2 H), 5.12 (m, 1 H), 3.28 (d, *J* = 3.1 Hz, 1 H) ppm; ^{13}C-NMR (101 MHz, CDCl3) δ = 139.0, 132.3, 128.2, 125.2 (q, *J* = 283.0 Hz), 118.2, 113.1, 71.8 (q, *J* = 32.4 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -78.18 (d, *J* = 6.9 Hz) ppm; MS: (EI): m/z (%) =202 (10) [M^+], 202 (100), 134 (8), 132 (37), 104 (53), 102 (6), 77 (10); IR (KBr): = 3391 (br, s), 3015 (w), 2244 (s), 1734 (w), 1718 (w), 1654 (w), 1610 (m), 1560 (w), 1508 (w), 1412 (m), 1349 (m), 1267 (s), 1204 (m), 1156 (s), 1128 (s), 1089 (m), 858 (m), 817 (s), 691 (s) cm^{-1}; Elemental analysis: Calcd: C, 53.74; H, 3.01; N, 6.96; Found: C, 54.16; H, 2.93; N, 7.01.

Methyl-4-(2,2,2-trifluoro-1-hydroxyethyl)benzoate(5.5-3q) CAS: [1086836-85-2]



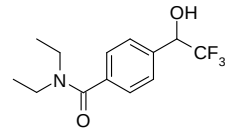
Compound (5.5-3p) was prepared from 4-formylbenzoic acid methyl ester (5.5-3q) (172 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3q) as a colorless solid; yield: 215 mg (92 %). m.p. 54 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.94 (d, *J* = 8.6 Hz, 2 H), 7.47 (d, *J* = 8.2 Hz, 2 H), 4.95-5.07 (m, 1 H), 3.82 (s, 3 H), 3.60 (d, *J* = 4.7 Hz, 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 167.0, 139.0, 130.9, 129.7, 127.5, 124.0 (q, *J* = 283.0 Hz), 72.3 (q, *J* = 32.4 Hz), 52.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -78.14 (d, *J* = 5.5 Hz) ppm; MS: (EI): m/z (%) =202 (10) [M^+], 202 (100), 134 (8), 132 (37), 104 (53), 102 (6), 77 (10); IR (KBr): = 3392 (br., m), 3023 (w), 2967 (w), 2855 (w), 1699 (s), 1441 (m), 1417 (m), 1330 (s), 1300 (s), 1248 (s), 1178 (s), 1116 (s), 1078 (m), 1022 (w), 724 (s) cm^{-1}; Elemental analysis: Calcd: C, 51.29; H, 3.87; Found: C, 51.29; H, 3.96.

4-Methylsulfonyl-2,2,2-trifluoroethanol (5.5-3r)



Compound (5.5-3r) was prepared from 4-methylsulfonylbenzaldehyde (5.5-1r) (194 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3r) as a colorless solid; yield: 165 mg (77 %). m.p. 116 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 8.6 Hz, 2 H), 7.68 (d, *J* = 8.2 Hz, 2 H), 5.15 (m, 1 H), 3.14 (s, 1 H), 3.05 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 141.4, 141.2, 128.6, 127.0, 124.6 (q, *J* = 283.0 Hz), 69.6 (q, *J* = 30.5 Hz), 43.4 ppm; ^{19}F NMR (376 MHz, CDCl3): δ = -78.12 (d, *J* = 6.9 Hz) ppm; MS: (EI): m/z (%) = 254 (1) [M^+], 207 (3), 185 (22), 139 (10), 138 (100), 121 (57), 76 (10), 50 (16); Elemental analysis: Calcd: C, 42.52; H, 3.57; S, 12.61; Found: C, 42.93; H, 3.62; S, 12.86.

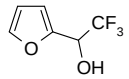
4-(2,2,2-Trifluor-1-hydroxyethyl)-benzoic acid diethylamide (5.5-3s)



Compound (5.5-3s) was prepared from 4-formyl-benzoic acid diethylamide (5.5-1s) (205 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3s) as a colorless solid; yield: 209 mg (76 %). Product was a mixture of two colorless solid, m.p. 141 °C; ^{1}H-NMR (400 MHz, DMSO-D_6) δ = 7.56 (d, *J* = 7.8 Hz, 2 H), 7.38

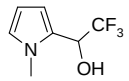
(d, *J* = 8.1 Hz, 2 H), 6.93 (d, *J* = 5.5 Hz, 1 H), 5.23 (m, 1 H), 3.35-3.48 (m, 2 H), 3.16 (br. s., 2 H), 1.14 (br. s., 3 H), 1.04 (br. s., 3 H) ppm; ^{13}C-NMR (101 MHz, DMSO-D_6) δ = 169.6, 137.8, 136.6, 127.7, 126.0, 124.9 (q, *J* = 283.2 Hz), 70.2 (q, *J* = 30.1 Hz), 42.8 (br), 38.7 (br), 14.0 (br), 12.8 (br) ppm; ^{19}F NMR (376 MHz, DMSO-D_6): δ = -76.80 (s) ppm; MS: (EI): m/z (%) = 276 [M^+] (11), 275 (16), 274 (63), 204 (12), 203 (100), 127 (10), 105 (11); IR (KBr): = 3186 (br, s), 2988 (s), 2938 (s), 2877 (s), 2800 (w), 1923 (w), 1602 (s), 1521 (w), 1479 (s), 1460 (s), 1448 (s), 1384 (w), 1362 (m), 1348 (m), 1254 (s), 1167 (s), 1125 (s), 1100 (s), 1020 (m), 944 (m), 864 (m), 811 (s) cm^{-1}; Elemental analysis: Calcd: C, 56.72; H, 5.86; N, 5.09; Found: C, 56.76; H, 5.85; N, 5.13.

1-(2-Furyl)-2,2,2-trifluoroethanol (5.5-3t) CAS: [70783-48-1]



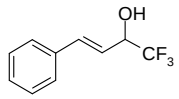
Compound (5.5-3t) was prepared from 2-furaldehyde (5.5-1t) (96 mg, 1.00 mmol, 83.0 µL) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3t) as a colorless oil; yield: 81.6 mg (49 %).^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.48 (m, 1 H), 6.54 (m, 1 H), 6.44 (m, 1 H), 5.06 (q, *J* = 5.9 Hz, 1 H), 2.80 (br. s., 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 147.1 (q, *J* = 1.9 Hz), 143.7, 123.4 (q, *J* = 281.1 Hz), 110.8, 110.2, 67.3 (q, *J* = 34.2 Hz) ppm; ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -77.98 (d, *J* = 5.7 Hz) ppm; MS: (EI): m/z (%) = 166 (30) [M^+], 149 (7), 127 (12), 101 (9), 99 (13), 97 (100), 69 (50), 50 (13); Elemental analysis: Calcd: C, 43.39; H, 3.03 Found: C, 43.67; H, 2.78.

1-(1-Methyl-2-pyrrolyl)-2,2,2-trifluoroethanol (5.5-3u) CAS: [70783-51-6]



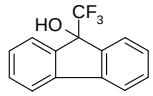
Compound (5.5-3u) was prepared from N-methyl-2-formylpyrrol (5.5-1u) (109 mg, 1.00 mmol, 108 µL) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3u) as a colorless solid; yield: 96 mg (54 %). m.p. 46 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.67 (s, 1 H), 6.33 (s, 1 H), 6.10-6.13 (m, 1 H), 5.01 (q, *J* = 6.7 Hz, 1 H), 3.67 (s, 3 H), 2.42 (br. s, 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 125.6, 124.8, 124.1 (q, *J* = 282.1 Hz), 109.3, 107.5, 66.3 (q, *J* = 33.3 Hz), 34.2 ppm; ^{19}F NMR (376 MHz, CDCl3): δ = –76.97 (d, *J* = 6.9 Hz) ppm; MS: (EI): m/z (%) = 179 (88) [M^+], 162 (36), 112 (19), 110 (100), 82 (95), 80 (30), 67 (32); IR (KBr): = 3525 (br, s), 2929 (w), 1653 (m), 1559 (m), 1497 (w) 1387 (w), 1260 (m), 1168 (s), 1182 (s), 1108 (m), 1064 (w), 862 (m), 740 (s) cm^{-1}; Elemental analysis: Calcd: C, 46.93; H, 4.50; N, 7.82; Found: C, 46.81; H, 4.47; N, 7.82.

(*E*)-1,1,1-Trifluor-4-phenyl-3-buten-2-ol (5.5-3v) CAS: [89524-18-5]



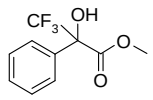
Compound (5.5-3v) was prepared from (*E*)- cinnamaldehyde (5.5-1v) (132 mg, 1.00 mmol, 126 µL) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3v) as a colorless solid; yield: 156 mg (77 %). m.p. 45 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.39-7.44 (m, 2 H), 7.34 (m, 3 H), 6.85 (d, *J* = 16.0 Hz, 1 H), 6.21 (dd, *J* = 16.0 Hz, *J* = 6.7 Hz, 1 H), 4.63 (m, 1 H), 2.68 (d, *J* = 4.3 Hz, 1 H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 136.4, 135.4, 128.8, 128.8, 126.9, 120.6, (q, *J* = 1.9 Hz), 124.3 (q, *J* = 282.1 Hz), 71.7 (q, *J* = 32.4 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –78.99 (d, J_F = 6.9 Hz) ppm; MS: (EI): m/z (%) = 202 (52) [M^+], 185 (16), 133 (100), 115 (35), 105 (15), 103 (18), 55 (19); IR (KBr): = 3306 (br, s), 2850 (w), 1961 (w), 1734 (w), 1654 (m), 1579 (w), 1477 (m), 1452 (m), 1370 (m), 1269 (s), 1172 (s), 1129 (s), 1049 (s), 971 (s), 885 (m), 814 (m), 753 (s) cm^{-1}; Elemental analysis: Calcd: C, 59.41; H, 4.49; Found: C,59.14; H, 4.48.

9-Trifluoromethyl fluoren-9-ol (5.5-3w) CAS: [120747-41-3]



Compound (5.5-3w) was prepared from 9-fluorenone (5.5-3w) (182 mg, 1.00 mmol) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3w) as a colorless solid; yield: 182 mg (79 %). m.p. 80 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.50 (m, 4 H), 7.30 (t, *J* = 7.4 Hz, 2 H), 7.18 (t, *J* = 7.4 Hz, 2 H), 2.83 (s, 1 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 141.1, 141.0, 130.9, 128.5, 125.2, (q, *J* = 1.9 Hz), 125.1 (q, *J* = 283.9 Hz), 120.4, 81.4 (q, *J* = 31.4 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –78.51 (s) ppm; MS: (EI): m/z (%) = 251 (8) [M^+], 250 (51), 233 (7), 182 (15), 181 (100), 153 (18), 152 (21); IR (KBr): = 3413 (br, s), 3068 (w), 1707 (s), 1609 (s), 178 (m), 1453 (s), 1376 (m), 1261 (s), 1154 (s), 1110 (s), 1059 (s), 959 (m), 935 (m), 770 (m) cm^{-1}; Elemental analysis: Calcd: C, 67.20; H, 3.79; Found: C, 66.73; H, 3.79.

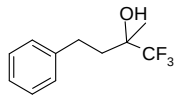
2-Hydroxy-2-phenyl-3,3,3-trifluoro-2-propanoic acid methyl ester (5.5-3x) CAS: [20445-36-7]



Compound (5.5-3x) was prepared from benzoyl-formic acid methyl ester (5.5-1x) (66 mg, 1.00 mmol, 144 µL) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3x) as a colorless oil; yield: 70.0 mg (30 %). ^{1}H-NMR (400 MHz,

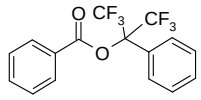
$CDCl_3$) δ = 7.76-7.84 (m, 2 H), 7.39-7.46 (m, 3 H), 4.35 (s, 1 H), 3.98 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 169.4, 129.6, 128.9, 128.4, 131.2 (q, *J* = 267.3 Hz), 126.70 (m), 78.0 (q, *J* = 30.5 Hz), 54.6 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –76.35 (s) ppm; MS: (EI): m/z (%) = 232 (9), 231 (74), 230 (7), 175 (19), 106 (8), 105 (100), 77 (9); IR (KBr): = 2860 (br., s), 1697 (s), 1581 (s), 1559 (s), 1487 (s), 1449 (s), 1413 (s), 1385 (s), 1336 (s), 1276 (s), 1240 (s), 1200 (s), 1166 (s), 1114 (s), 1028 (s), 1002 (s), 922 (s), 854 (m), 808 (m), 776 (s), 726 (s) cm^{-1}; Elemental analysis: Calcd: C, 51.29; H, 3.87; Found: C, 50.91; H, 4.05.

2-Trifluoromethyl-4-phenylbutan-2-ol (5.5-3y) CAS: [120714-66-1]



Compound (5.5-3y) was prepared from 4-phenyl-butan-2-one (5.5-1y) (148 mg, 1.00 mmol, 150 µL) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3y) as a colorless oil; yield: 80.0 mg (37 %); ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.31-7.38 (m, 2 H), 7.21-7.29 (m, 3 H), 2.74-2.87 (m, 2 H), 2.19 (s, 1 H), 2.03 (ddd, *J* = 15.6 Hz, *J* = 11.2 Hz, *J* = 5.7 Hz, 2 H), 1.48 (s, 3 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 141.2, 128.6, 128.3, 126.2, 126.4 (q, *J* = 285.8 Hz), 73.6 (q, *J* = 27.7 Hz), 36.9, 28.9, 20.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –82.92 (s) ppm; MS: (EI): m/z (%) = 218 (10) [M^+], 200 (44), 132 (12), 131 (100), 105 (27), 91 (45), 65 (11), 43 (12); IR (NaCl): = 3330 (br, s), 3027 (s), 2871 (m), 1705 (w), 1653 (w), 1603 (w), 1497 (m), 1455 (m), 1385 (m), 1318 (m), 1266 (m), 1168 (s), 1102 (s), 1068 (m), 1030 (w), 980 (w), 910 (w), 876 (w), 762 (w) cm^{-1}; Elemental analysis: Calcd: C, 60.55; H, 6.00; Found: C, 60.69; H, 6.20.

α,α-Di-(trifluormethyl)-benzyl-benzoate (5.5-3z) CAS: [40999-26-6]



Compound (5.5-3z) was prepared from 4-phenyl-butan-2-one (5.5-3z) (148 mg, 1.00 mmol, 150 µL) and potassium (trifluoromethyl)trimethoxyborate (5.5-2) (265 mg, 1.25 mmol) affording (5.5-3z) as a colorless oil; yield: 80.0 mg (37 %).^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.15 (m, 2 H), 7.65-7.72 (m, 1 H), 7.54 (t, *J* = 7.9 Hz, 2 H), 7.40-7.50 (m, 5 H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 161.9, 134.4, 130.3, 130.2, 128.9, 128.6, 128.1, 127.1, 126.7, 121.9 (q, *J* = 289.8 Hz) 83.6 (quint., *J* = 30.7 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.16 (s) ppm; MS: (EI): m/z (%) = 348 (7) [M^+], 331 (12), 227 (6), 106 (8), 105 (100), 77 (19), 51 (9); IR (NaCl): = 3071 (w), 2959 (w), 2855 (w), 1757 (s), 1599 (w), 1453 (m), 1270 (s), 1240 (s), 1226 (s), 1192 (s), 1180 (s), 1104 (s), 1096 (s), 1082 (s), 1070 (s), 992 (s), 948 (s), 722 (s), 700 (s) cm^{-1}; Elemental analysis: Calcd: C, 55.18; H, 2.89; Found: C, 54.83; H, 3.14.

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Author: Lukas J. Goossen et al.

Publication: The Journal of Organic Chemistry

Publisher: American Chemical Society

Date: Mar 1, 2009

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