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Method development towards synthesis of carbapenemase inhibitors

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Abstract

Carbapenemases are enzymes able to hydrolyze the last resort β-lactam antibiotics (carbapenems), which are used for the treatment of infections caused by resistant bacteria. Carbapenemases are structurally and mechanistically classified into serine-β-lactamases (SBLs) and metallo-β-lactamases (MBLs). In order to combat the hydrolytic activity of these enzymes, combination therapy of β-lactam with β-lactamase inhibitor have been clinically successful. Nevertheless, clinically approved inhibitors for a number of important carbapenemases are still missing and resistance against some of the clinically successful combinations have been already reported.[1] Therefore, there is an urgent need to find new effective inhibitors that could potentially reach clinical use. The approach targeted in this thesis is to design new inhibitors against carbapenemases that could be used in the combination therapy with a carbapenem antibiotic to restore its effect.

The goal of my work was to develop synthetic methods for the synthesis of inhibitors targeting two clinically relevant carbapenemases - the serine-β-lactamase oxacillinase 48 (OXA-48) and the metallo-β-lactamase Verona integron-encoded metallo-β-lactamase (VIM-2). For the design and development of inhibitors, a fragment-based approach based on previously discovered inhibitory fragments and structural data of the fragments in complex with the target enzymes was choosen.

In this thesis I discuss the developed synthetic strategy towards unsymmetrical 3,5-disubstituted benzoic acids using selective Suzuki-Miyaura cross-coupling. Applying the developed method, I synthesized a small extended fragment library of both symmetrical and unsymmetrical 3,5-disubstituted benzoic acids targeting OXA-48. The aim of synthesizing these extended fragments was to target two directions in the binding pocket as suggested by overlaying structural data of smaller fragments in complex with OXA-48.

I also developed a synthetic strategy towards 2-aroylbenzoic acid analogues via carbonylative Suzuki coupling using CO in a safe fashion. 2-Aroylbenzoic acids were known to inhibit the carbapenemase VIM-2. Through my investigations about a general synthetic strategy towards 2-aroylbenzoic acid, I found some limitations about substrates with ionizable functional groups and sterically hindered substrates. I then extended my investigation to find

better reaction conditions for carbonylative coupling reactions. I also introduced sustainability to the project by using renewable solvents aiming for better reactivity in palladium-catalyzed C-C, C-O, C-N bond forming carbonylative couplings.

In summary, through the presented work a range of carbapenemase (OXA-48 and VIM-2) inhibitors have been synthesized. Additionally, the developed synthetic strategies are considered to be a starting point to build a general approach to synthesize a wide range of potent inhibitors against carbapenemases. The work resulted in three publications (Paper I, II, III).

Abbreviations

Ampc	Class C β-lactamase
aq	Aqueous
Arg	Arginine
Asn	Asparagine
Asp	Aspartic acid
BL	β-lactamase
Bp	Boiling point
CataCXiumA	Di(1-adamantyl)-*n*-butylphosphine
CC	Column chromatography
COgen	9- methylfluorene-9-carbonyl chloride
CphA	*Aeromonas* carbapenem-hydrolyzing β-lactamase
CTX-M	Ceftoximase-Munich
Cym	*p*-Cymene
Cyr	Cyrene
Da	Dalton
DBO	diazabicyclooctanone analogue
DCM	Dichloromethane
DEC	Diethylcarbonate
DIPEA	N,N-Diisopropylethylamine
DMAc	N,N-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMC	Dimethylcarbonate
DME	Dimethyl ether
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
EC	Ethylenecarbonate
EDTA	Ethylemediaminetetraacetic acid
Equiv	Equivalent

ESBL	Extended spectrum β-lactamase
FBDD	Fragment based drug design
FDA	Food and drug administration
GIM	German imipenemase metallo-β-lactamase
Gly	Glycerol
GVL	γ-valerolactone
His	Histidine
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
HTS	High throughput screening
IC_{50}	Half maximal inhibitory concentration
Ile	Isoleucine
IMP	Imipenemase
K_d	Dissociation constant
K_i	Inhibitory constant
KPC	*Klebsiella pneumoniae* carbapenemase
L.E.	Ligand efficiency
L1	*Stenotrophomonas maltophilia* L1 (β-lactamase 1)
LBDD	Ligand based drug design
Leu	Leucine
Lim	Limonene
MBL	Metallo-β-lactamase
MS	Mass spectrometry
MW	Micro waves
NDM	New Delhi metallo-β-lactamase
NHC	N-Heterocyclic carbine
Ni(COD)	Bis(cyclooctadiene)nickel(0)
NMP	N-Methyl-2-pyrrolidine
NMR	Nuclear magnetic resonance
Nu	Nucleophile
OTf	triflate
OXA	Oxacillinase
PAINS	Pan assay interreference compounds

PBP	Penicillin binding protein
PC	Propylenecarbonate
PCy_3	Tricyclohexylphosphine
$Pd(acac)_2$	Palladium(II) bis(acetylacetonate)
$Pd(TFA)_2$	Palladium(II) trifluoroacetate
$Pd(tmhd)_2$	Bis(2,2,6,6-tetramethyl-3,5-heptanedionato)palladium(II)
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd_2(dppf)Cl_2$	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PdCl(C3H5)(dppb)	Dichloro-1,4-bis(diphenylphosphino)butane-palladium(II)
$PdCl_2(dppp)$	Dichloro[1,3-bis(diphenylphosphino)propane]palladium(II)
Phe	Phenylalanine
R.T	Room temperature
RuPhos-Pd G_3	(2-Dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)
SAR	Structure activity relationship
SBDD	Structure based drug design
SBL	Serine-β-lactamase
Ser	Serine
SilaCOgen	Methyldiphenylsilacarboxylic acid
SMC	Suzuki-Miyaura coupling
SPhos	[2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl]
SPR	surface plasmon resonance
TEA	Triethylamine
THF	Tetrahydrofuran
Thr	Threonine
TLC	Thin layer chromatography
Trp	Tryptophan
Tyr	Tyrosine
UV	Ultraviolet
Val	Valine
VIM	Verona integron-encoded metallo-β-lactamase
X-Phos	[2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl]
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Acknowledgements

Table of Contents

Summary of publications and author contributions

Paper I   **A focused fragment library targeting the antibiotic resistance enzyme -
Oxacillinase-48: Synthesis, structural evaluation and inhibitor design**

Sundus Ahkter, Bjarte Aarmo Lund, **Aya Ismael**, Manuel Langer, Johan
Isaksson, Tony Christopeit, Hanna-Kirsti Schrøder Leiros, Annette Bayer.
European Journal of Medicinal Chemistry, 2018, *145*, 634–648.
DOI: 10.1016/j.ejmech.2017.12.085.

*I contributed with the development of a synthetic strategy towards
unsymmetrically disubstituted benzoic acids. Synthesis of fragment 36, 37, 38, in-
40, 40. I also contributed to data analysis and writing the experimental section
of the mentioned fragments.*

Paper II   **Carbonylative Suzuki–Miyaura couplings of sterically hindered aryl
halides: synthesis of 2-aroylbenzoate derivatives**

Aya Ismael, Troels Skrydstrup, and Annette Bayer.
Org. Biomol. Chem., 2020, 18, 175. DOI: 10.1039/d0ob00044b.

*I contributed to the planning and developing of the synthetic methodology. I
performed all the experiments and data analysis. I also contributed to the
manuscript writing.*

Paper III   **Renewable Solvents for Pd-Catalyzed Carbonylations**

Aya Ismael, Ashot Gevorgyan, Troels Skrydstrup, and Annette Bayer
Manuscript submitted to Organic Process Research & Development

*I contributed to the planning and developing of the synthetic methodology. I
performed all the experiments, data analysis and contributed to the manuscript
writing.*

Related publication not included in this thesis: **Structural studies of triazole inhibitors with
promising inhibitor effects against antibiotic resistance metallo-β-lactamases**
Zeeshan Muhammad, Susann Skagseth, Marc Boomgaren, SundusAkhter, Christopher
Fröhlich, **Aya Ismael**, Tony Christopeit, Annette Bayer, Hanna-Kirsti S. Leiros.
Bioorganic & Medicinal Chemistry 28 (2020) 1155983 DOI*:* 10.1016/j.bmc.2020.115598

1. Introduction

Antibiotic resistance is among the most challenging threats to the global health in the 21st century and soon will be one of the top public health challenges unless urgent actions are taken. Infections such as pneumonia, tuberculosis, gonorrhea and salmonellosis are becoming more challenging to treat as the bacteria are becoming more resistant to the current antibiotics.[2] Antibiotic resistance is mainly caused by their misuse in humans, animals and accelerating agricultural processes. The world needs urgent actions to find solutions for the spread of resistant bacteria not only by developing new medicines but also by changing the public behavior towards antibiotic consumption.[2]

β-Lactam antibiotics are one of the most widely used antibiotics and they include penicillins, cephalosporins, monobactams and carbapenems. All members of β-lactam antibiotics share the β-lactam ring as the common feature in their chemical structure.[3,4] The continuous evolution of bacteria containing β-lactam antibiotic-hydrolyzing enzymes is one of the main reasons behind the rise of antibiotic resistance. The enzymes hydrolyzing β-lactam antibiotics are called β-lactamases and they are divided into two main groups based on their hydrolyzing mechanism: serine-β-lactamases (SBLs) and metallo-β-lactamases (MBLs). The β-lactamases (BLs) with activity towards carbapenems are called carbapenemases and they are of high importance as they are threatening the most important groups of β-lactams, carbapenems, used for the treatment of serious bacterial infections. Carbapenemases can be serine-β-lactamases (SBLs) or metallo-β-lactamases (MBLs) that are active against the last resort antibiotics- carbapenems. In addition, carbapenemases not only can hydrolyze carbapenems but also nearly all groups of β-lactams.[5–9]

There are several approaches to combat the threat of the antibiotic resistance such as the continuous development of new antibiotic lines against the resistant bacteria or the development of inhibitors that could suppress or disturb the resistance mechanism of the bacteria. A very successful approach to overcome bacterial resistance caused by β-lactamases is the combination therapy using an antibiotic and a β-lactamase inhibitor. The role of the β-lactamase inhibitor is to block the hydrolyzing enzyme from reaching the antibiotic and thus preserving the antibiotic's activity against the bacterial infection.[1]

The combination therapy approach has proven to be a successful strategy regarding β-lactamases. Combination therapy using β-lactamase inhibitors such as tazobactam, clavulanic acid, sulbactam, etc. targeting SBLs that are not active against carbapenems have been available for clinical use.[1] There are several inhibitors against serine-β-lactamases, which are active against carbapenems that have recently been approved for clinical use or are in a late stage of the drug development process.[1] However, there are no MBL inhibitors that have reached clinical use so far. In addition, MBL carrying bacteria are spread globally. Therefore, the lack of MBL inhibitors can eventually lead to the world standing helpless against common bacterial infections that are caused by bacteria carrying MBLs. Thus, the global need for carbapenemase inhibitors restoring the potency of the last-line antibiotics is outstanding.[4,10,11]

1.1 Aim of the study

The long-term goal of our work is to develop carbapenemase inhibitors that could potentially block the resistance enzymes and restore the activity of the carbapenem. Our research group is especially interested in carbapenemases (e.g., VIM-2, NDM-1, GIM-1, TMB-1, KPC and OXA-48).[12–15] Over time, the group has obtained structural data from crystal structures of these enzymes in complex with a range of inhibitory fragments (small-sized compounds MW < 300) and inhibitors. The structural data gives us insight into the binding site and assists us with generating ideas for further development of active inhibitors by structure-based drug design (SBDD).

The overarching aim of my PhD work was to develop active inhibitors of two carbapenemases to restore the carbapenem antibiotic activity. I have mainly focused on two carbapenemases- the verona integron-encoded metallo-β-lactamase (VIM-2) and the serine-β-lactamase oxacillinase-48 (OXA-48).

In order to achieve the overall aim, the work in the thesis had several subgoals:

- Use the structural data from two carbapenemases (VIM-2 & OXA-48) in complex with inhibitory fragment complexes to develop fragment libraries (Figure 1). The crystal structures gave us insight into the binding site and helped identify possible interactions that we could target while designing the fragment library.
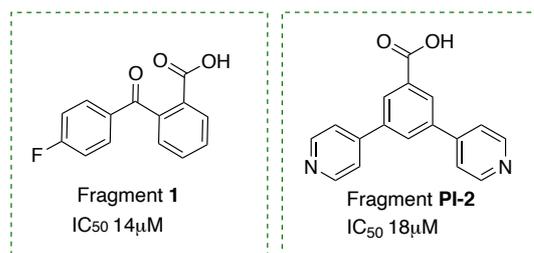
Figure 1. (left) Fragment 1 targeting VIM-2, (right) Fragment PI-2 targeting OXA-48.

- Develop efficient synthetic methods for the synthesis of fragment libraries.
- Synthesize analogues of the initial fragment and evaluate their inhibitory activity.

1.2 Outline

The thesis consists of 9 chapters. The first three chapters introduce the research question, the background and the existing knowledge. Chapter 4, 5 and 6 present the three papers resulting from the research described in the thesis. Chapter 7 presents the concluding remarks, while chapter 8 highlights open research question for future studies. A more detailed presentation of the content of the chapters follows:

Chapter 1 Introduces the aim of the study and places the study in a wider context.

Chapter 2 Discusses β-lactamase antibiotics including carbapenems and the antibiotic resistance assembled in carbapenemases. It also addresses the different carbapenemase enzymes and their mode of action. Furthermore, it discusses the combination therapy approach and the evolution of inhibitors used against carbapenemases. The chapter also includes a short introduction to fragment-based drug design.

Chapter3 Provides the chemical background for the reactions applied in this thesis. For each reaction an overview of the reaction mechanism is provided. In addition, some examples from literature are discussed to provide some knowledge about the reaction applications. Green solvents.

Chapter 4 Introduces the background for the research described in **paper I.** In addition, it illustrates the fragment design and important features that should be included in the structure to target both binding sites R^1 & R^2. The chapter also discusses a developed general synthetic strategy to synthesize a number of extended fragments against OXA-48 via the selective Suzuki-Miyaura coupling. Finally, the chapter addresses results presented in paper I.

Chapter 5   Introduces the background for the research described in **paper II.** The chapter illustrates the different possible synthetic routes to synthesize active fragments containing the 2-aroylbenzoic acid moiety against VIM-2. I highlight the best synthetic route in my hands towards the targeted VIM-2 fragments. The chapter also discusses reaction optimization for carbonylative Suzuki-Miyaura coupling and our efforts to suppress the competing normal Suzuki-Miyaura coupling required to synthesize a number of developed fragments against VIM-2. Finally, it addresses results presented in the paper together with some findings about the reaction limitations.

Chapter 6   Is a continuation of the work conducted in paper II. It discusses the extended optimization of carbonylative Suzuki-Miyaura coupling to find a better system and cover the reaction limitation addressed in paper II. In this chapter I introduce sustainability character to my research by using new renewable solvents and test them for better reactivity within Pd-catalyzed carbonylation reactions such as carbonylative Suzuki-Miyaura coupling (C-C), alkoxycarbonylation (C-O), aminocarbonylation (C-N). The chapter highlights that changing the common organic solvents to greener alternatives is a positive step towards sustainability without losing activity in the chemical reactions. A number of applications is mentioned to address the importance of the studied solvents in both academia and industry. Finally, it addresses some results presented in the paper.

Chapter 7   Conclusion.

Chapter 8   Future direction

Chapter 9   Appendix: this chapter includes experimental details and spectral data of fragments presented in Chapter 5.5, Table 8 (entry 1-7).

2. Relevant background for the thesis

2.1 Antibiotics & antibiotic resistance

An antibiotic is a substance that can kill or cause inhibition of the microbial growth. The name "antibiotic" was first introduced by Selman Waksman in 1942. Since their discovery, antibiotics have saved many lives and improved life quality.[16,17]

There are several classes of antibiotics such as β-lactams, macrolides, sulfonamides, aminoglycosides, quinolones etc. Each class of antibiotics affect the bacteria in different ways. For instance, β-lactams interfere with the cell-wall synthesis of the bacteria, thus killing it. While quinolones inhibit topoisomerases preventing the DNA replication and cause death of the bacteria.[18]

Due to the overuse of antibiotics and the resulting evolutionary pressure, bacteria have learnt to resist antibiotics. Bacteria identify antibiotics, and thus adapt and build immunity against them. Furthermore, the rapid generation time of bacteria makes it even quicker for the bacteria to evolve and build resistance against antibiotics in a short time.[19] The uncontrolled growth of bacterial resistance leads to the suppression of the antibiotics effect. Bacterial infection and associated diseases that could be treated by antibiotics earlier are becoming harder to treat.[2] This is a growing concern threatening the health and welfare of the population worldwide and thus needs an urgent resolution.

2.2 β-lactam antibiotics

β-Lactams are considered to be among the most used antibiotics, more than 65% of the antibacterial prescriptions include β-lactam antibiotics.[20] There are several β-lactam antibiotics on the market. The class of β-lactam antibiotics shares a common core structure, which is a four membered ring known as the β-lactam ring. The importance of this class of antibiotics lies in their broad-spectrum antibacterial activity as they are active against both gram-negative and gram-positive bacteria.[3] β-lactams are structurally classified into penicillins, cephalosporins, carbapenems and monobactams (Figure 2).[3,4]
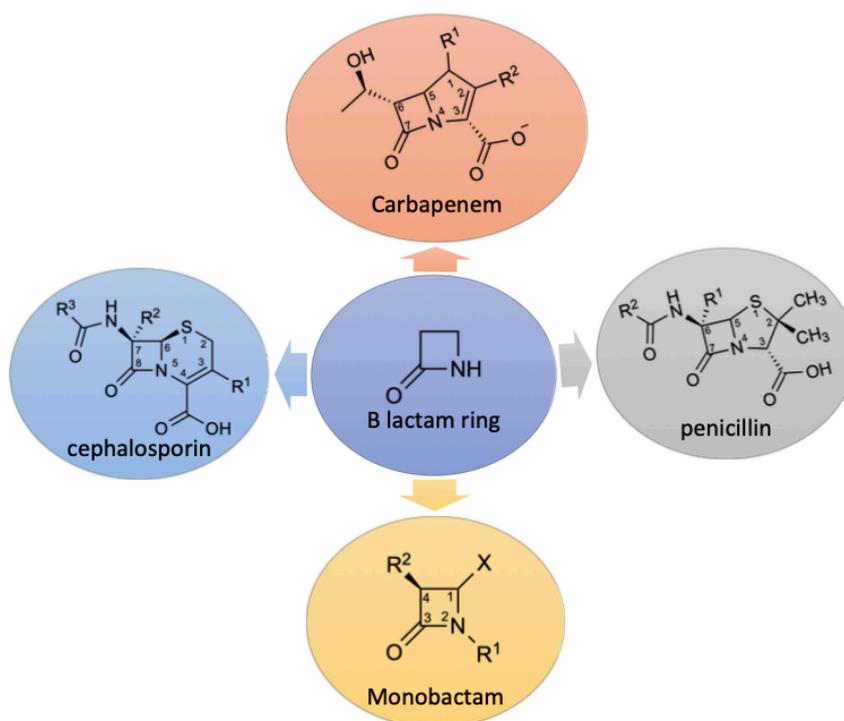
Figure 2. Chemical structure of β-lactam antibiotics with a common β-lactam ring. The R groups differs in various antibiotics. The X in the monobactam chemical structure represents α-methyl.

Penicillins: were the first developed β-lactam antibiotics and were used to treat a wide range of infections caused by bacteria such as *streptococcus*, *staphylococcus*. Penicillins have a five membered ring fused to the β-lactam ring and an amide moiety attached to the β-lactam ring. There are several penicillins available on market, all of which are β-lactam antibiotics and only differ in the side chain of the penicillin. Ampicillins, oxacillin and amoxicillin are examples of penicillins.[21,22]

Cephalosporins: have a six membered ring fused to the β-lactam ring and an amide moiety attached to the β-lactam ring as in penicillins. Cephalosporins cover a broader spectrum of both gram-negative and gram-positive bacteria than penicillins.[23–25] Cephalosporins are grouped into different generations based on the modified structure and the activity spectrum. For instance, the first generation was similar to the cephalosporine C, which was introduced in 1940s. Structural modification of the cephalosporine C by adding a methoxy group on the β-lactam ring resulted in the second generation of cephalosporines e.g. cefoxitin. The methoxy group added some steric hindrance to the β-lactam ring, which made it harder to hydrolyze by the BLs. Ceftazidime is an example of the third generation cephalosporines, they are characterized by the aminothiazole ring added to the side chain of the cephalosporine structure.[22,24] The new features of the aminothiazole ring made the antibiotics of this generation more active against

gram-negative bacteria and increased the potency against penicillin-binding proteins (PBPs). Cefepime belongs to the fourth generation, while ceftobiprole[26] and ceftaroline[27] belong to the fifth generation.[22] Cefiderocol is a recently US FDA-approved cephalosporin, which is used for the treatment of urinary tract infections. Moreover, cefiderocol is currently being tested in phase III against nosocomial pneumonia and infections resulted from carbapenem-resistant gram-negative bacteria.[28]

Monobactams: are the only β-lactam antibiotics that have no ring fused to the β-lactam ring. Monobactams are only active against gram-negative bacteria such as *Neisseria* and *pseudomonas.*[29] Tigemonam, nocradicin[30], taboxin and aztreonam are examples of monobactams.[22]

Carbapenems: have an unsaturated five membered ring fused to the β-lactam ring, they also have a chiral center with a hydroxyethyl side chain on the β-lactam ring. An example of a carbapenem is thienamycin, which has potency against both gram-positive and gram-negative bacteria but it is unstable for clinical applications.[31] Imipenem is also a carbapenem but it is hydrolyzed by dehydropeptidase (human enzyme). However, a dehydropeptidase inhibitor (cilastatin) could be used to prevent the human enzyme from hydrolyzing the imipenem and thus could be used as an antibiotic.[22] Meropenem, doripenem and ertapenem are more stable carbapenems than thienamycin and imipenem due to the bulkier substituents on the five membered ring. Carbapenems are known for their broad-spectrum activity against gram-negative bacteria, gram-positive bacteria and anaerobes.[31] Carbapenems are also used recently as last resort antibiotics against antibiotic-resistant bacteria. Tebipenem is one of the latest approved carbapenems for clinical use, but it is only available in Japan.[31,22]

Table 1. Examples of available β-lactam antibiotics.

penicillin	cephalosporine	monobactam	carbapenem
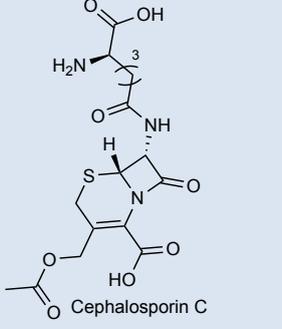
Ampicillin
  Amoxicillin
  Oxacillin
	Cephalosporin C
	  Ceftazidime
		Aztreonam
		  Tigemonam
		  Tabtoxin
			Meropenem
			  Imipenem
			  Ertapenem
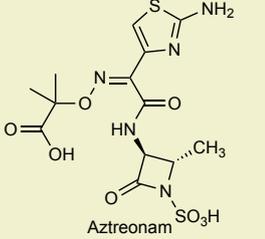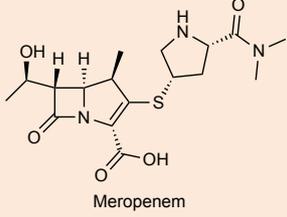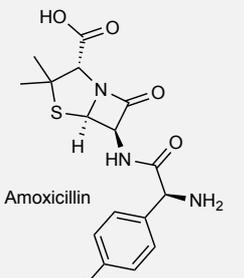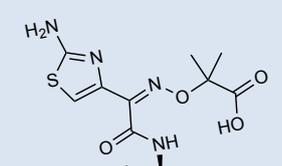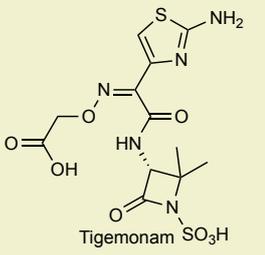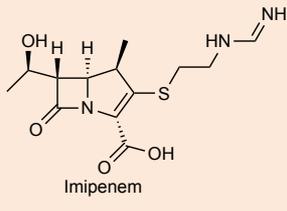
2.3 Antibiotic resistance: bacterial resistance modes against β-lactam antibiotics

Bacteria adapt to the known antibiotics by developing several mechanisms to gain resistance against antibiotics (Figure 3).[32] Bacteria can as well combine the different mechanisms and become multidrug resistant, which increases the severity of the problem.[17,33] Bacteria can obtain resistance to the antibiotic by reducing the permeability of the drug into its cell wall. Bacteria with no cell walls e.g. *mycoplasma-genus* are not affected by antibiotics targeting the cell wall and tend to express their resistance in another way. For instance, some other bacteria contain efflux pumps that transfer the antibiotics out of the cell directly after their entry before they reach the target.[34] Another resistance mechanism is based on structurally mutating the targeted enzyme so that the antibiotic is not be able to bind to its target.[35] An example of the mutating bacteria is *Staphylococcus aureus,* which rapidly gains resistance to linezolid (antibiotic targets

23S rRNA ribosomal subunit of gram-positive bacteria) via selection of mutated copies of the gene encoding the targeted subunit.[18] Bacteria can use other enzymes to modify the binding site itself and thus prevent the drug from recognizing it so that the drug would not bind to the active site and lose its activity. Macrolide erythromycin functions by binding to the bacterial ribosome. In this case, the bacteria produce an enzyme called erythromycin ribosome methylase, the enzyme methylates the binding site and prevents the antibiotic from binding. In addition, some gram-positive and gram-negative bacteria tend to produce specific enzymes to modify or inactivate the antibiotic itself and make it lose its activity. For instance, BLs enzymatically hydrolyze β-lactam antibiotics leaving them inactive.[36,37,18,32]
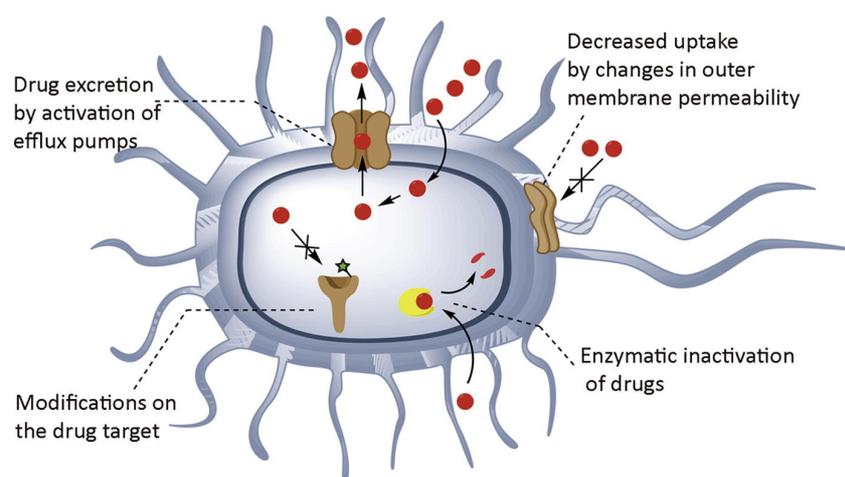
Figure 3. General presentation of the main bacterial resistance mechanism. Red represents the antibiotic, yellow represents the different bacterial resistance actions. The picture acquired from Gonzalez-Bello.[32]

2.4 β-Lactamases, carbapenemases and their classification

The biological effect of β-lactams depends on their availability to their target and the ability to inhibit these targets. As mentioned before, bacteria have several resistance mechanisms. The most common mechanism of resistance towards β-lactam antibiotics in gram-negative bacteria is to produce specific hydrolytic enzymes that inactivate β-lactam antibiotics by hydrolyzing the drug core of the β-lactam ring, these hydrolyzing enzymes are known as β-lactamases.[38,39] They were first reported even before the clinical release of penicillin in *Escherichia coli* (*E. coli*) in 1940. So far 4944 β-lactamases have been reported in gram-positive, gram-negative bacteria and mycobacteria.[8,40-42] β-lactamases are of great diversity, they are classified based on their amino acid sequence and biochemical properties into four classes A, B, C, D; known as the Ambler classes.[5,43,44] Nevertheless, the 4 Ambler classes (Figure 4) can be structurally grouped into two super families: SBLs, which consist of class A, C and D, all the three classes

having a serine residue in their active site in a sequence of Ser-X-X-Lys motif, and MBLs, which consist of class B, they contain Zn atom(s) in the active site, which is very important for the catalytic activity of MBLs.[45] Both groups are β-lactam hydrolytic enzymes that use different hydrolysis mechanisms to inactivate the antibiotic. Among the most important BLs are those who are active against the last resort antibiotics - carbapenems (e.g. meropenem). These BLs are called carbapenemases and they belong to both class A and D SBLs (e.g. KPC, OXA-48, AmpC) and MBLs (e.g. VIM, NDM, GIM) as shown in Figure 4.
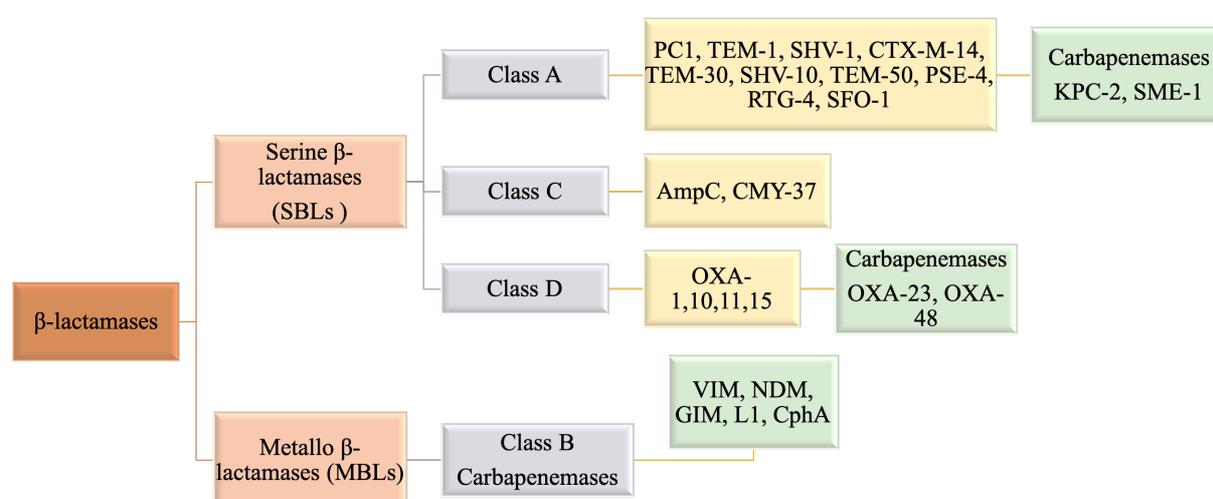
Figure 4. Ambler classification of lactamases and examples of BLs. Both metallo and serine carbapenemases are shown in green.

2.4.1 Serine β-lactamases

Generally, most β-lactamases are serine-β-lactamases; they constitute Ambler classes A, C, D, which share common active site features including the serine residue (Ser70). Only KPC-2 and SME-1 of class A and OXA-23 and OXA-48 of class D are described as carbapenemases with catalytic efficiencies for carbapenem hydrolysis. Among the most common serine carbapenemases are OXA-48 and KPC-2.[46] OXA-48 is the most efficient SBL in class D as it rapidly transfers high-level antibiotic-resistance genes to human pathogens such as *E. coli* and *Acinetobacter baumannii* (*A. baumannii*).[47] OXA-48 has a broad activity spectrum not only against carbapenems but also against penicillins and some cephalosporins (e.g. cefepime, ceftazidime or cefotaxime). OXA-48 was first reported in *Klebsiella pneumoniae* isolate in 2008, but it has been recently identified in range of *Enterobacteriacea*.[46-49] Serine carbapenemases including OXA-48 exhibit resistance through a mechanism of action that relies

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on the active serine residue (Ser 70 according to DBL numbering). The carboxylated Lys73 residue is believed to activate the catalytic Ser70 residue.[49]

The Ser 70 residue acts as a nucleophile and attacks the carbonyl group in the β-lactam ring forming a covalent acyl-enzyme intermediate (Figure 5, Inter I), which then forms an acyl-enzyme complex by breaking the C-N bond. Lys208 stabilizes the hydroxyl group that attacks the carbonyl group of the acyl-enzyme complex to form the second tetrahedral intermediate (Figure 5, Inter II) leaving the antibiotic inactive.[50]
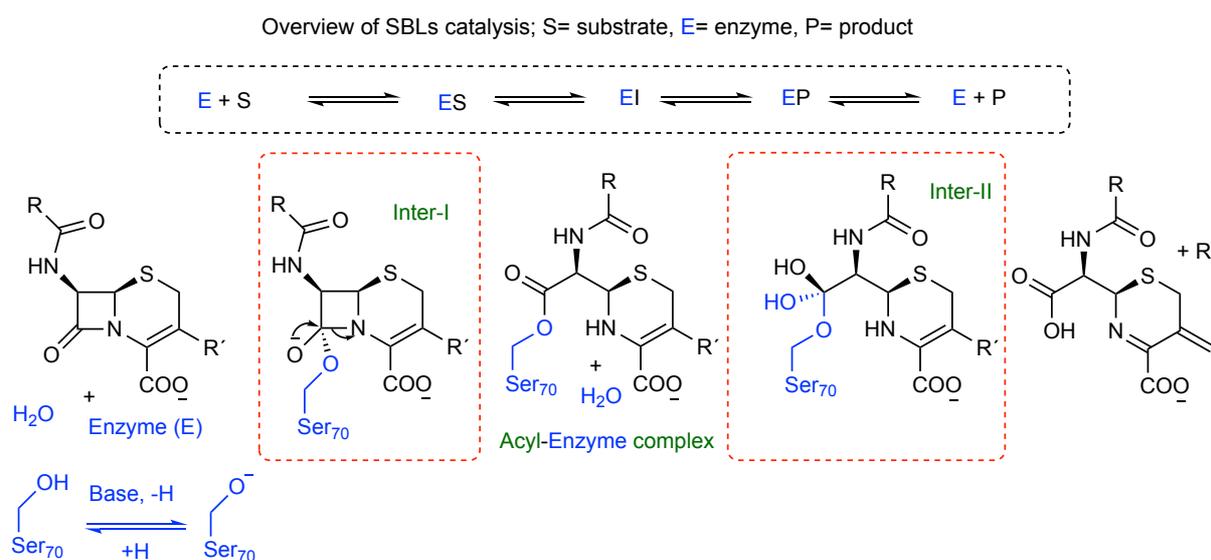
Figure 5. Mechanism of action of SBLs against an example of cephalosporin antibiotics. The picture modified from Brem et al.[50]

2.4.2 Metallo β-lactamases

MBLs belong to the metallo-hydrolase superfamily.[51] All MBLs are described as carbapenemases (metallo carbapenemases) as they exhibit enzyme activities against carbapenems. Metallo carbapenemases constitute Ambler class B, which shares common active site features including either one Zn^{2+} ion or two Zn^{2+} ions coordinated by different ligands and a hydroxyl ion, all of which are essential for the hydrolysis of the β-lactam ring.[52,44] MBLs are divided into three subclasses (B1, B2, B3) based on the structure and if they contain one or two zinc ions. All three classes contain a common four-layer "αβ/βα" motif, with the active site centered in the groove. The active site is in between the "ββ"- sandwich with Zn^{2+} ion(s), and two α-helices on either side.[53,54,171]

The mechanism of meropenem hydrolysis by NDM-1 was previously described and supported by X-ray structure in a published study on NDM-1.[55,56] The hydrolysis mechanism

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includes the activation of the hydroxyl groups of the hydroxyl group bridging the Zn^{2+} ions to attack the carbonyl group of the β-lactam ring cleaving the C-N bond.[57,58]After ring cleavage, the second Zn^{2+} ion coordinates to the negative charge on the nitrogen atom and stabilizes it. A proton transfer from the bridging hydroxyl group to Asp120, followed by insertion of a water molecule into the active site forms complex **2´**. Water molecules serve as a proton source throughout the catalytic cycle. The nitrogen will then abstract a proton from the water molecule in the binding site (Figure 6, complex **3** and **4´**), which would eventually lead to the detachment of the inactive meropenem and restoration of the active site **1** (Figure 6).[56]
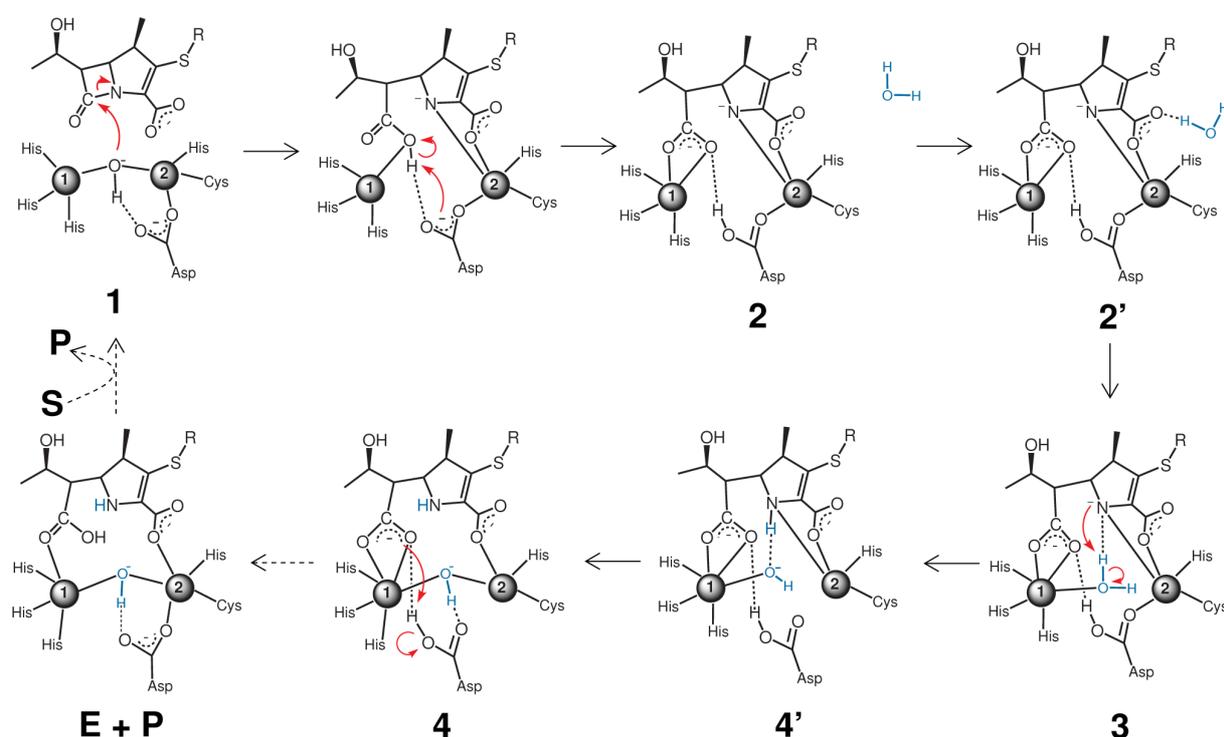
Figure 6. NDM-1 hydrolysis mechanism of meropenem. 1 and 2 grey spheres represent Zn+ ions. Figure acquired with permission from Triphati et al.[56]

2.5 Carbapenemase inhibitors

One of the most successful therapy approaches against BLs is combination therapy. The inhibitors combined with the β-lactam antibiotic inactivate the β-lactamase, thus preventing the hydrolysis of the antibiotic, making it possible for the antibiotic to reach its target. This method of using β-lactam/ β-lactamase inhibitors has proven to be an effective approach to restore the efficacy of the β-lactam antibiotic against pathogens producing BLs (e.g. ceftolozan/tazobactam, ceftazidime/avibactam, relebactam/imipenem, nacubactam/meropenem, vaborbactam/meropenem, ETX2514/sulbactam, VNRX-5133/cefepime, ANT431/meropenem).[1] Inhibitors such as clavulanic acid, sulbactam,

vaborbactam and tazobactam have reached clinical use but they are only active against SBLs and inactive against MBLs. Despite the efforts of finding new synthetic or natural compounds that show in vitro inhibition against MBLs, none of them have reached clinical use.[59,1]

The focus of this work was to develop inhibitors targeting various BL inhibitors including MBL and SBL inhibitors that especially show activity against carbapenemases VIM-2 (paper II, III), OXA-48(paper I).

2.5.1 Metallo-β-lactamase inhibitors

There are several compounds that have showed potency against MBLs (Figure 7).[160,61,1] However, there is still no MBL inhibitor that has reached clinical use until now.

However, recently, a boronic acid-based inhibitor called taniborbactam (Figure 7) has been reported as a "pan-spectrum β-lactamase inhibitor"[62] against gram-negative bacteria.[63,64] It showed a wider scope of activity than the clinically approved vaborbactam (Figure 8). Taniborbactam is considered a highly potent inhibitor of all four Ambler classes of β-lactamase enzymes. It exhibits inhibition activity against both MBLs (e.g. VIM-2) and SBLs (e.g. OXA-48, KPC-2) in a wide range of gram-negative bacteria. Structurally, taniborbactam is closely related to vaporbactam as they both possess a cyclic boronate, while taniborbactam is a bicyclic boronate with N-(2-aminoethyl) cyclohexylamine as the side chain (Figure 8). In vitro, cefepime/taniborbactam and meropenem/taniborbactam combinations are active against all six of the NDM-1-producing clinical isolates from *E. coli* and *K. pneumoniae*. Cefepime/taniborbactam also passed phase I of the clinical trials.[63]

ANT431 is in preclinical trials as MBL inhibitor in combination with meropenem.[1] As mentioned before, MBLs express resistance by a different hydrolysis mechanism than SBLs. MBLs rely on the Zn^{2+} in their active site to activate the hydroxyl group to initiate the hydrolysis mechanism. Therefore, enzyme activity is affected by the availability of the Zn^{2+} ions to deactivate the antibiotic. As a result, blocking the Zn^{2+} ions by using metal chelators would disturb the hydrolysis mechanism and prevent the antibiotic degradation. EDTA is an example of a metal chelator inhibitor (Figure 7) that inactivates the active site of MBLs by coordinating to the Zn^{2+} ions and hinders its hydrolysis ability of the β-lactam.[65] EDTA has not reached clinical use due to its toxicity. Recently, Samuelsen *et al*. reported a metal chelator ZN148 that has a great potential as a MBL inhibitor. *In vitro* analysis demonstrated that ZN148 was able to

restore the effect of meropenem against NDM-1.[66] Metal chelator inhibitors show activity against MBLs including VIM-1, VIM-2, NDM-1 IMP-1,IMP-8, IMP-7, NDM-4.[10,67,66]

Thiol-based mercaptocarboxylates (Figure 7) exhibit high potency and broad-spectrum inhibitory activity against MBLs (e.g. IMP-1, VIM-4, VIM-2, NDM-1, CphA, etc). For instance, 3-(3-mercaptopropionyl-sulfanyl)-propionic acid derivatives were reported as covalent and irreversible inhibitors of IMP-1 that restore the activity of mereopenem.[68] Captopril is a thiol derivative that has been studied as broad-spectrum inhibitor against MBLs, it has shown better potency against NDM-1, VIM-2 and IMP-1 rather than other MBL inhibitors.[69] It is also used as a standard to compare the inhibition potency of new inhibitors.[70,71] In addition, bisthiazolidine possessing inhibitors especially those containing a free thiol, a carboxylate group or a tetrahedral nitrogen were found to be effective against most MBLs. ME1071 is a maleic acid derivative; it showed in vitro activity against carbapenemases with less toxicity to animals compared to other MBL inhibitors. ME1071 potentiates carbapenems e.g. biapenem against NDM-1, VIM-2 and IMP-1.[72] Natural products and fungus extracts have also shown activity against MBLs. Aspergillomarasmine A is a fungal natural product that shows inhibition potency against VIM-2 and NDM-1.[73,74] Biphenyl tetrazoles were described as potent inhibitors of CcrA and IMP-1. Triazoles such as triazoleylthioacetamide and arylsulfonyl-NH-1,2,3-triazole were described to have inhibition potentiality against VIM-2. There are several other inhibitors (e.g. thioesters, trifluoromethyl alcohols and ketones, pyridine carboxylates, benzohydroxamic acid etc.) that showed inhibition activity against MBLs. Phthalic acid/derivatives have shown to express inhibition activity against the MBL IMP-1.[75] *The group of Prof. Leiros reported phthalic acid derivatives to have potential inhibition activity in vitro against VIM-2 (chapter 5).*[76]

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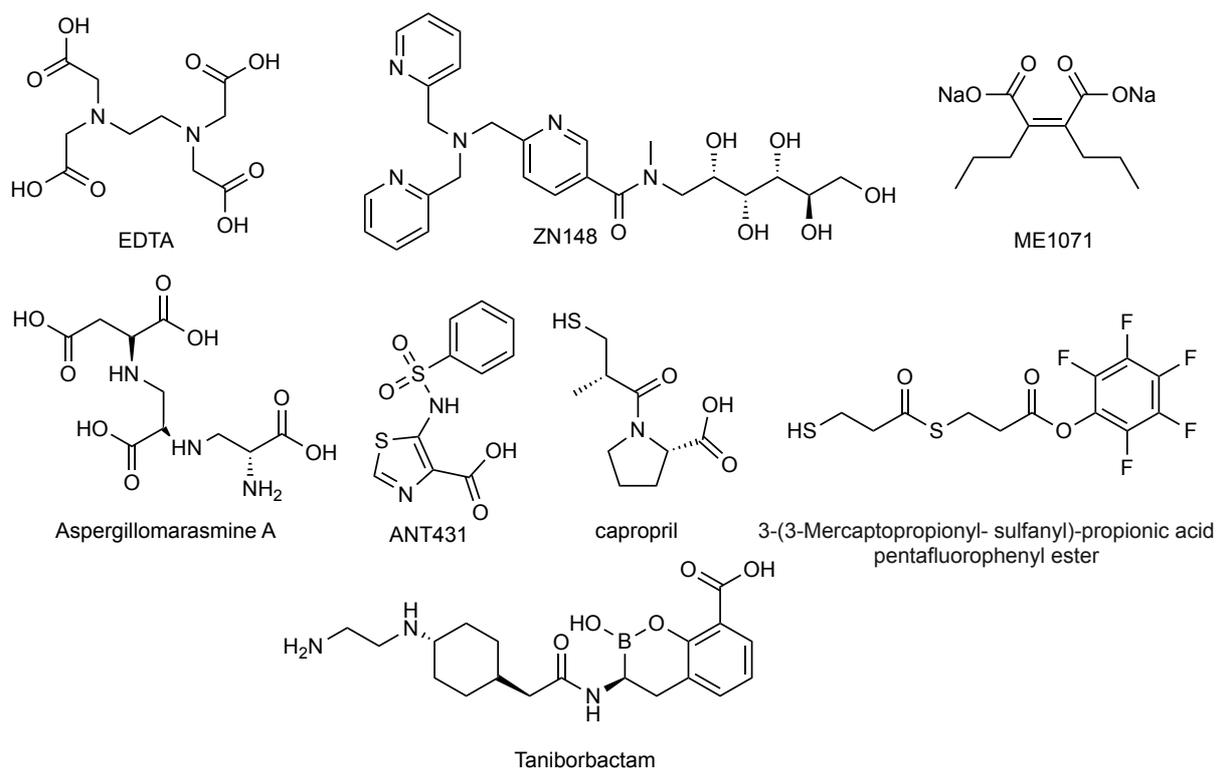
Figure 7. Examples of inhibitors against MBLs.

2.5.2 Inhibitors of serine-β-lactamases with carbapenemase activity

SBLs rely on the active serine residue (Ser70) to initiate the hydrolysis mechanism of the β-lactams. In principle, blocking the active serine residue would inactivate the enzyme and prevent it from hydrolyzing the drug. Inhibitors accompanied with the β-lactam antibiotic such as clavulanic acid and derivatives, tazobactam, sulbactam, avibactam, vaborbactam, relebactam, are shown to be efficient in suppressing the resistance mechanism in many examples for some SBLs. However, of the aforementioned inhibitors only avibactam, vaborbactam, relebactam have inhibition activity against carbapenemases.[1,77-78]

The combination between ceftazidime/avibactam was approved by the Food and Drug Administration (FDA) in February 2015 for the combination therapy.[77] Ceftazidime/avibactam combination is active against serine carbapenemases OXA-48 and KPC. However, resistance towards ceftazidime/avibactam has already been identified in clinical multi-resistant OXA-48.[79]

Avibactam is a reversible β-lactamase inhibitor that binds covalently to the active serine residue and inactivates the enzyme, it poses a broader spectrum of inhibitory activity compared

to tazobactam, sulbactam, and clavulanic acid. Avibactam exhibits activity against most BLs of class A and C such as TEM-1, KPC-2 and extended spectrum β-lactamases (ESBLs) such as CTX-M-15.[32,80] In addition, avibactam inhibits some of class D enzymes such as OXA-48.[80] Moreover, combinations of avibactam with aztreonam (monobactam) or ceftaroline (cephalosporine) were found to show inhibition activity against OXA-48 and OXA-24.[27] The avibactam/aztreonam combination has reached phase III of the clinical trials, while avibactam/ceftaroline has reached phase II of clinical trials.[78]

Relebactam (MK-7655) is structurally similar to avibactam (Figure 8), it also shares the same spectrum of activity as in the case of avibactam. Imipenem/cilastatin+ relebactam combination shows great activity against KPC-2 and restores the efficiency of imipenem. Moreover, the combination was approved in July 2019 by the FDA and it is used for the treatment of complicated urinary tract infections and intra-abdominal infections.[31,67,79,81]

Vaborbactam (RPX7009) is a novel boronic acid-based inhibitor that shows activity against SBLs.[82] The meropenem/vaborbactam combination was approved by the FDA in August 2017 for the inhibition of pathogens producing serine carbapenemases KPC-2, KPC-3, KPC-4.[83]

Taniborbactam (see also chapter 2.5.1) is a promising inhibitor of all four Ambler classes of β-lactamase enzyme including the carbapenemases OXA-48 and KPC-2 in a wide range of gram-negative bacteria.

Recently, Taylor *et al*. described the high potentiality of CDD-97 and its derivatives (Figure 8) against OXA-48.[84]
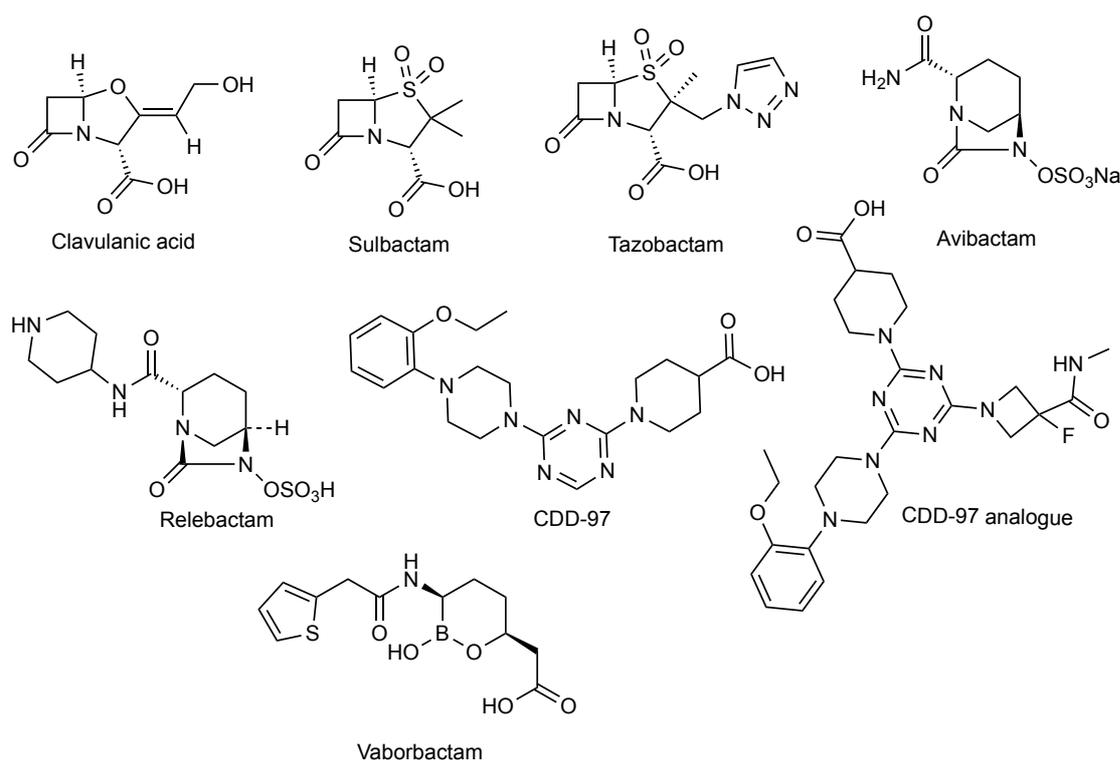
Figure 8. Examples of SBL inhibitors.

2.5.3 Summary of MBL and SBL inhibitors in different development stages

As mentioned before using combinations of β-lactam/ β-lactamase inhibitors has proven to be an effective approach to restore the efficacy of the β-lactam antibiotic against pathogens producing BLs.[1] Inhibitors such as clavulanic acid, sulbactam, avibactam, vaborbactam and tazobactam have reached clinical use but they are only active against SBLs and inactive against MBLs. However, the avibactam/aztreonam combination has reached phase III of clinical trials against MBLs.[59,1] Combinations such as VNRX-5133/Cefepime (phase I) and ANT431/Meropenem (preclinical stage) are also active against MBLs (Table 2).[1]

Table 2. Summary of BL inhibitors.[1]

Inhibitor	β-lactam	Stage	ESBL	AmpC	KPC	OXA-48	MBL
Clavulanic acid	Amoxicillin	approved	yes	-	-	-	-
	Ticarcillin	approved	yes	-	-	-	-
Sulbactam	Ampicillin	approved	yes	-	-	-	-
Tazobactam	Piperacillin	approved	yes	-	-	-	-
	Cefepime	approved					
	Ceftolozane	approved					
Enmetazobactam	Cefipeme	Phase II	yes	-	-	-	-
Avibactam	Ceftazidime	approved	yes	yes	yes	yes	
	Aztreonam	Phase III	yes	yes	yes	yes	yes
Relebactam	Imipenem	Phase III	yes	yes	yes		
Nacubactam	Meropenem	Phase I	yes	yes	yes		
Zidebactam	Cefepime	Phase I	yes	yes	yes		
ETX2514	Sulbactam	Phase II	yes	yes	yes	yes	
Vaborbactam	Meropenem	approved	yes	yes	yes	yes	
VNRX-5133	Cefepime	Phase I	yes	yes	yes	yes	yes
ANT431	Meropenem	preclinical	-	-	-	-	yes

– no useful inhibitory activity shown; DBO, diazabicyclooctanone analogue; ESBL, extended-spectrum β-lactamase; MBL, metallo-β-lactamase, carbapenemases (green).

2.6 Fragment based drug discovery (FBDD)

In drug discovery campaigns, the identification of lead compounds can be achieved through one of the two major approaches: high-throughput screening (HTS) or fragment-based drug discovery (FBDD).[85]

HTS is based on screening a large collection of drug-like compounds that follow the Lipinski's rule of five,[86,87] (i.e. the compounds should have ≤ 5 hydrogen bond donors (N-H and O-H bonds), ≤ 10 hydrogen bond acceptors (N, O atoms), molecular weight of ≤ 500 Da and an octanol-water partition coefficient (log P) ≤ 5) against a predefined drug target with the goal to find potent hits with activity in the low millimolar to nanomolar range. HTS has been successfully used in identifying novel inhibitors against MBLs.[88–90] One disadvantage of the HTS approach is that it can result in misleading information concerning inhibition and binding. In the case of large-sized compounds as the space in the binding site is restricted, they are prevented from binding efficiently to several different residues. In this way the inhibition might be acceptable not because of the good binding but rather by occupying the active site.

In contrast, FBDD[91] is based on the screening of a library of smaller compounds - fragments- that follow the rule of three (i.e. they have molecular weight < 300 Da, ≤ 3 hydrogen bond donors/acceptors, and CLogP below 3) in order to find efficient binders with a high possible binding efficiency.[92] Using smaller compounds increases the chance to detect binding possibilities as the smaller size makes the compound more flexible to the binding pocket when compared to larger compounds (Figure 9). A well-established value to evaluate the binding efficiency of fragments is their ligand efficiency (LE), which is a measure of the binding energy per heavy atom in the fragment. The higher the LE-values the better as it is recommended that good hits should have LE in the range of 0.3-0.4 kcal/(mol atom).[93] The LE can be obtained from half maximal inhibitory concentrations (IC_{50}) (or the dissociation constant (K_d)) according to the following formula(s):

$$\Delta G = -RT \ln(K_d)$$

$$LE = \Delta G / N, \text{ where } N = \text{ \# of non-hydrogen atoms } [93]$$

$$LE = 1.4 \, (-\log(IC_{50}))/N \quad [94]$$
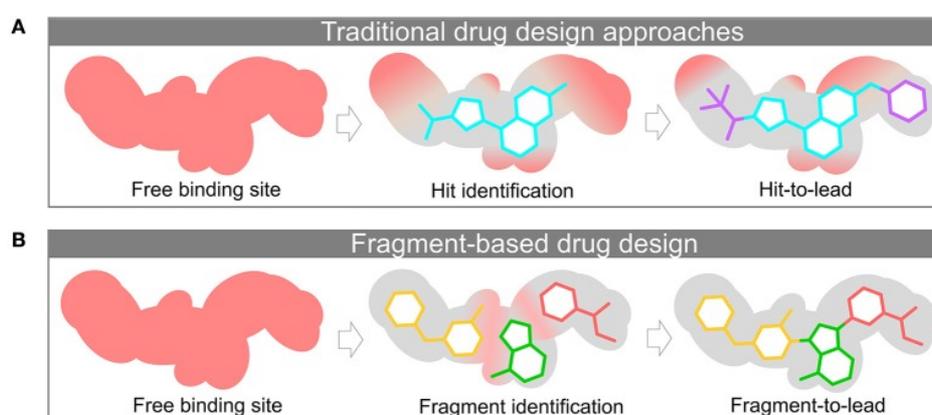
Figure 9. HTS hit (A) versus FBDD hit (B). Adapted from frontiers in chemistry, in silico strategies to support fragment to Lead optimization in Drug Discovery, Neto et al. Copyright (2020), open access.[95]

A challenge in FBDD is that the fragments bind only weakly to the enzymes (IC_{50} in the micro- or millimolar range), thus each atom of the fragment has to contribute to the overall binding of the fragment to be detected. Another challenge with fragments is the unspecific binding of fragments and pan assay interreference compounds (PAINS), which can be solved by using orthogonal assays, such as the combination of surface plasmon resonance (SPR) and a biochemical assays to identify false positive results.[76,96]

Fragments most likely do not have the required potency to be considered as a lead compound and would need further improvement. To guide the fragment evolution, structural

information of the fragment in complex with the targeted enzyme are needed to give insight into possible interactions in the binding site. This process is called structure-based drug design (SBDD) and it relies on the available information about the 3D structure of the drug target.[85,92,97] The 3D structure of the drug target can be mainly obtained through experimental approaches such as X-ray crystallography or nuclear magnetic resonance spectroscopy (NMR).[98,99] With the structural information in hand, it would be possible to predict the necessary characteristics for binding and use this information to evolve the fragments to drug candidates of high potentiality to bind to the drug target with higher affinity.[85] Fragments evolution can be achieved by several approaches:[97]

Fragment-growing: It employs modification of the fragments by adding more groups in order to increase the size of the fragments without losing binding efficiency (Figure 10. A). This approach was the aim of papers II and III.

Fragment-linking: With the help of the structural information of the inhibitor/enzyme complex, if several fragments that bind in adjacent binding sites can be identified, those fragments can be chemically connected to form a new optimized ligand with better binding and higher potency (Figure 10. B).

Fragment-merging: This approach is very useful if there are two identified binding site and their ligands are competing for the chemical space or if there are two different fragments that partially occupy the same site. In either of the cases, overlaying structures of the two fragments helps bring the dissimilar parts together and design a new potent fragment towards drug like compounds (Figure 10. C). We applied this approach in paper I to optimize fragments against OXA-48.
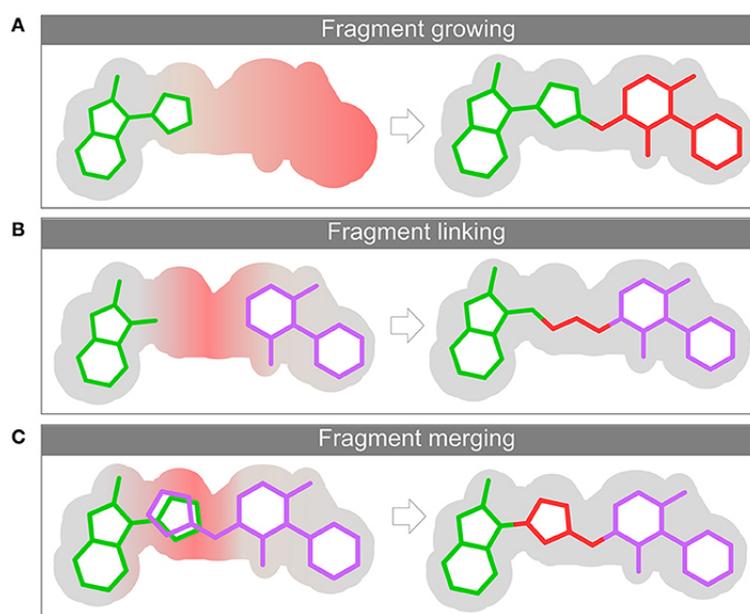
Figure 10. Different approaches towards fragment optimization. Adapted from frontiers in chemistry, in silico strategies to support fragment to Lead optimization in Drug Discovery, Neto et al. Copyright (2020), open access.[95]

The advantage of the FBDD approach is that it allows for lead optimization to detect the chemical space with compounds of high development potentiality within the rule of 5, required for identifying lead compounds. Moreover, it allows for more hydrophilic hits that can enhance the affinity via the accessible hydrogen bonding. The fragments identified by FBDD can be optimized further to acquire drug-like properties such as solubility properties, high potency, LE and the size of the compound.[100]

FBDD was first employed successfully against kinase targets.[101,102] However, it is now being applied against a diversity of targets. Zelboraf (a drug for the treatment of late-stage melanoma) was the first FDA approved drug developed by FBDD.[103,104] In addition, FBDD is proven to be a successful approach to develop drugs against both SBLs and MBLs. Chen *et al.* identified micromolar-range noncovalent inhibitors including thiol derivatives and dicarboxylates against class A β-lactamases using FBDD approach.[105] Moreover, Nicholas *et al*. have modified polycarboxylic acids-based fragments that are considered to be a starting point to target SBLs (class A and D) using FBDD (Table 3. entry 1).[106]

The group of Prof. Leiros has utilized surface plasmon resonance to identify potent inhibitory fragments against both serine- and metallo-carbapenemases (chapter 4.1 and 5.1). Christopeit *et al*. reported inhibitory fragments targeting the MBLs NDM-1 and VIM-2,[14,107,76] among them a novel inhibitor scaffolds against VIM-2 based on phthalic acid derivatives

(chapter 5).[13] Lund *et al* reported 3,5-disubstituted benzoic acid/ derivatives scaffolds against SBLs (OXA-48) using FBDD.[15]

Table 3. Examples inhibitors developed from fragments targeting BLs provided by Nicholas et al.[106] and by Leiros.[13–15,76,107]

1	K_i= 11 μM — fragment against MBLs (IMP-1) K_i = 20 μM — fragment against SBLs (OXA-10) K_i = 89 nM — fragment against SBLs (CTX-M-9)
2	IC$_{50}$= 14 μM — fragment against MBLs (VIM-2) (IC$_{50}$= 0.38, 0.31, 1.8 μM) fragment against MBLs VIM-2, GIM-2, NDM-1 respectively IC$_{50}$= 18 μM — fragment against SBLs (OXA-48)
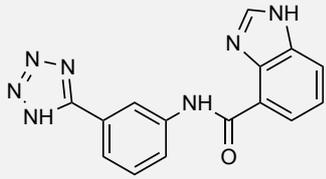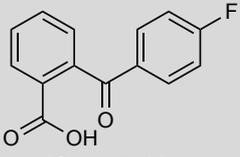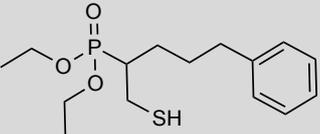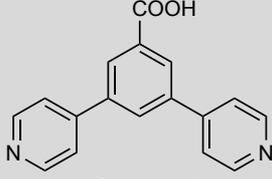
3. Relevant reactions

During the course of our research project on the synthesis of fragment libraries towards a new line of carbapenemase inhibitors (OXA-48 and VIM-2), reliable synthetic methods for preparing the designed fragment libraries were required.

Reactions relevant to the work presented in this thesis are:

* Suzuki-Miyaura coupling (SMC): used for the preparation of 3,5-disubstituted benzoic acids and acid derivatives as inhibitor scaffolds against the SBL OXA-48 (chapter 4).

* Carbonylative Suzuki-Miyaura coupling: used for the preparation of 2-aroylbenzoic acids and acid derivatives as inhibitor scaffolds against the MBL VIM-2 (chapter 5 & 6).

* Reaction for the preparation of 2-aroylbenzoic acids derivative (chapter 5 & 6).

* Aminocarbonylation & Alkoxycarbonylation: used for the preparation of primary and secondary amides and carboxylic esters as inhibitor scaffolds against MBL VIM-2 (chapter 5 & 6).

* The aforementioned reactions have been used as reaction models to test a new series of sustainable solvents aiming to find optimized conditions for the preparation of inhibitor scaffolds against MBL VIM-2 (chapter 6).

3.1 Palladium catalyzed C-C couplings - Suzuki-Miyaura reaction (SMC)

Palladium catalyzed couplings are a powerful tool for advanced chemical synthesis of C-C bonds for both academic and industrial applications. Negishi, Heck and Suzuki-Miyaura couplings are examples of the most commonly used palladium catalyzed reactions.[108] However, Suzuki-Miyaura coupling is extensively studied. The used boronic acids are generally nontoxic and thermally and moisture stable, which is an advantage over other cross-coupling reactions that include toxic additives and metals. Negishi couplings require the use of air and moisture sensitive organozinc compounds as the nucleophile, which makes the reaction relatively intolerant to functional groups in comparison to the Suzuki-Miyaura coupling.[108,109] The main disadvantage of Stille couplings is that they require the use of toxic organotin compound (Scheme 1).[108,110]
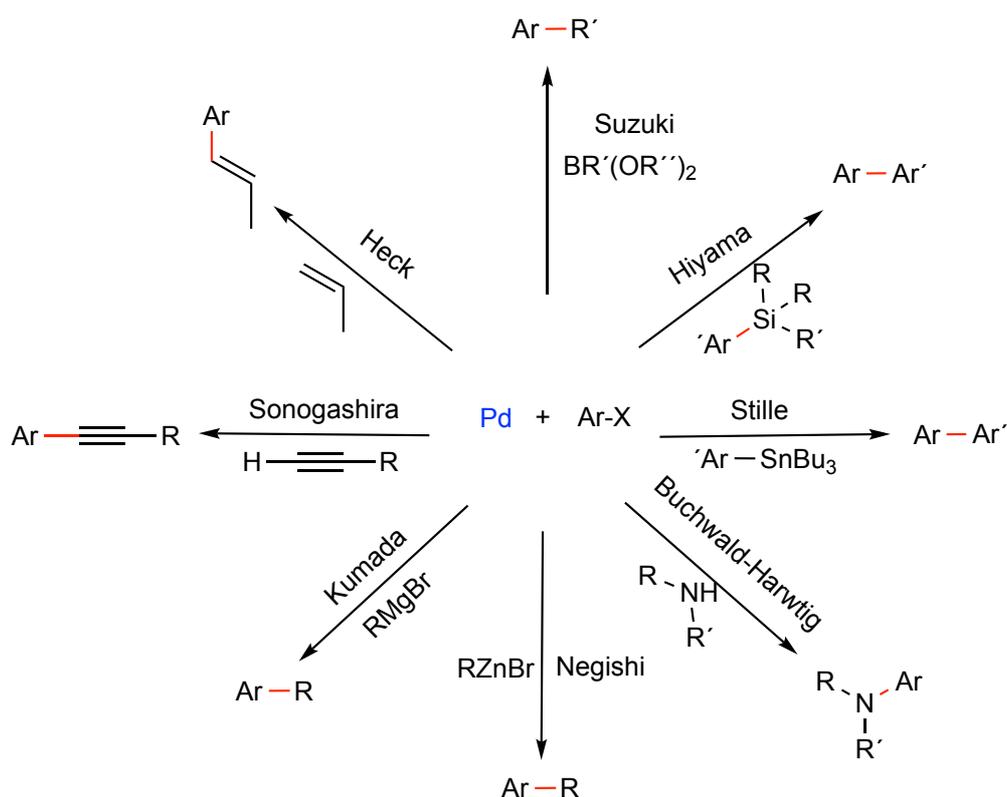
Scheme 1. Common palladium catalyzed cross-coupling reactions.

General mechanism of palladium catalyzed C-C cross-couplings

Palladium activation of Ar-X is commonly used for selective and specific formation of new C-C bonds in Suzuki-Miyaura coupling by coupling with the corresponding nucleophile. The reaction mechanism is similar to most of the cross-coupling reactions. The main difference is the choice of the transition metal. Considering the Suzuki-Miyaura coupling as an example of general palladium cross-coupling, the reaction mechanism proceeds via a three steps catalytic cycle (Scheme 2). The first step is oxidative addition of the organohalide to the active Pd^0 species forms complex A (X-LnPd^{II}-Ar). Electron-rich ligands are favored, as it gives an electron-rich metal center that facilitates the oxidative addition. The reactivity of organohalides/ pseudo-halides in C-C couplings varies with respect to the bond dissociation energy of the R-X (I > OTf > Br >Cl > OTs > OAc). The second step in the catalytic cycle is transmetalation with the nucleophile in presence of a base to from complex **B**. Different nucleophiles can be introduced in this step based on the type of couplings e.g; boronic acids and derivatives, organozinc or -tin reagents, etc. After the two organic groups are coordinated to the Pd^{II} complex, they undergo trans-cis isomerization to form the correct geometry needed for the

reductive elimination. This could be assisted by bulky ligands to furnish the coupled product **C** and to restore again the active Pd^0.
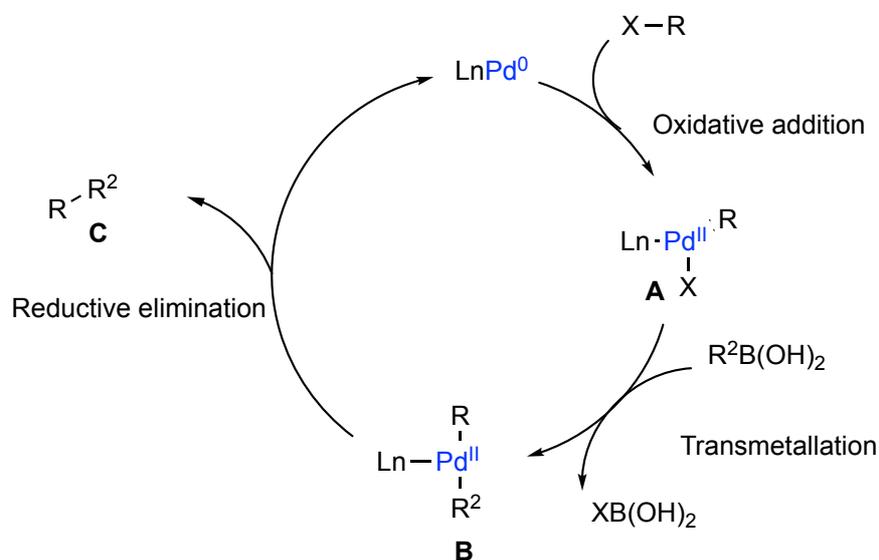
Scheme 2. General reaction mechanism for the Suzuki cross-coupling reaction.

The impact of the reaction components on the reaction rate

The nature of the coupling partners has a significant influence on the reactivity. It is known that palladium cross-coupling reactions can be selective in favor of less sterically hindered and electronically more deficient position of the electrophile (Ar-X).[111–113] Aryl iodides are more active in oxidative addition to Pd^0 center than their corresponding bromides and chlorides. Oxidative addition of iodobenzene with $Pd(PPh_3)_4$ could occur at room temperature while heating is required for bromobenzene to undergo oxidative addition. This is the reason for using additives such as NaI in reactions including aryl bromides to facilitate oxidative addition step by forming *in situ* aryl iodides. Electron-rich and bulky ligands such as $P(t\text{-}Bu)_3$, Buchwald phosphine-based ligands, carbene ligands are used for couplings of less reactive aryl bromides and chlorides.[120,121,116] For instance, coupling of 2,6-di-substituted aryl halides and aryl boronic acid was obtained in 91% yield using $Pd_2(dba)_3$ and a Buchwald ligand X-Phos[122] (Scheme 3).
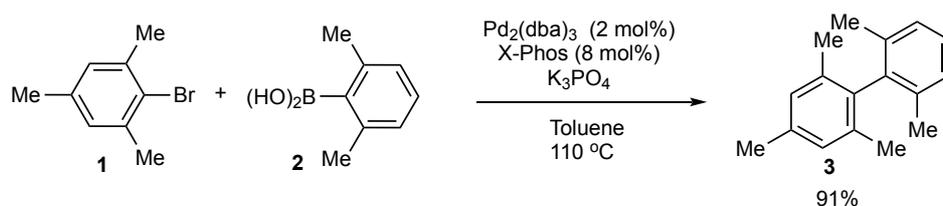
Scheme 3. Suzuki couplings of hindered electron-poor aryl bromides.

The difference in reactivity for example in di-haloaryls can be advantageous as it can lead to chemo- or regioselectivity in cross-coupling reactions. There is also reactivity difference between transmetalating agents. For example, electron deficient boronic acids or protected boronic acids are less reactive than electron rich unprotected boronic acids.

Chemo- and regio-selectivity in Suzuki-Miyaura coupling

Over the last decades many catalysts and ligands have been designed and tested in several palladium catalyzed cross-couplings. The achievements in this area are related to the design and development of ligands that not only promote the catalytic transformation but also provide both regio-, chemo- and enantioselective control over the reaction.[114]

Regioselectivity of substrates where two of the same halo group are present for coupling can be achieved by catalyst control.[117,118] Houpis and coworkers reported the regioselective coupling reaction of 2,4-dibromobenzoic acid with 4-tolylboronic acid, where the reaction gave excellent regioselective coupling at the ortho position in 80% yield when using $Pd_2(dba)_3$. On the other hand, using the bulky bidentate DPEPhos as a ligand together with $Pd(OAc)_2$ reversed the selectivity and the 4-tolyl-2-bromobenzoic acid was formed in 68% yield (Scheme 4).[119]
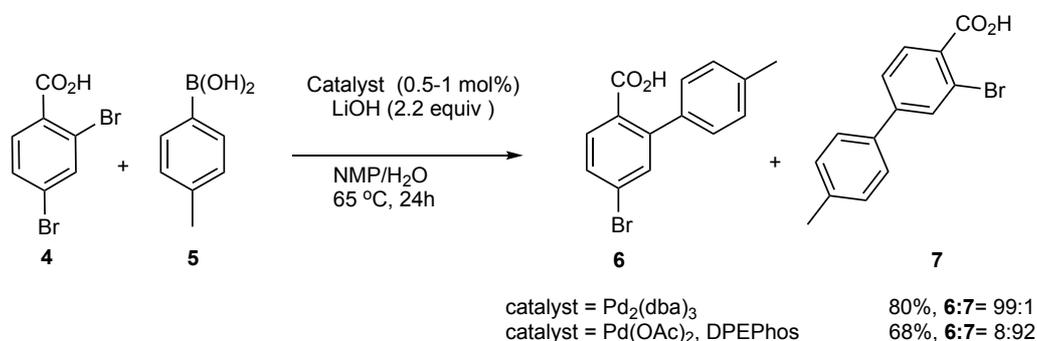
Scheme 4. Regioselective Suzuki-Miyaura coupling reaction of 2,4-dibromobenzoic acid with 4-toly-boronic acid.

An example showing the chemoselectivity is the reaction of 4-chlorophenyl triflate with 2-methylphenyl boronic acid using two different Pd catalysts, while using the same ligand. $Pd(OAc)_2$ and PCy_3 gave selective coupling at the triflate position and the product was obtained in 87% yield, while using $Pd_2(dba)_3$ and PCy_3 gave the selective coupling on the chloride position instead and the product was obtained in 95% yield (Scheme 5).[116]
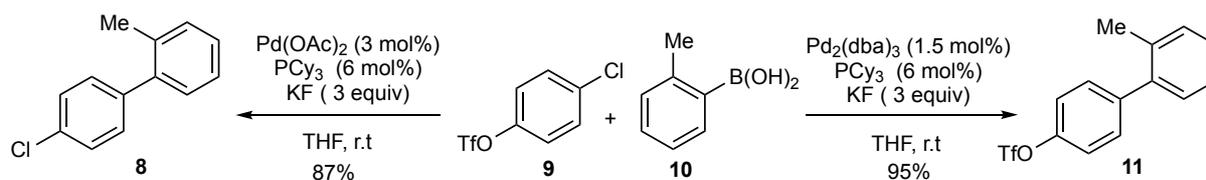
Scheme 5. Chemoselective cross-coupling of 4-chlorophenyl triflate with 2-methylphenyl boronic acid.

Selective Suzuki-Miyaura coupling on di-haloaryls are also considered challenging due to the high chances of obtaining mixtures of different coupling products in symmetrical or unsymmetrical fashion that might be hard to separate. The key in this process is tuning the reaction condition to allow the coupling of only one of the two halogens and result in monosubstituted product without affecting the other possible coupling position. For instance, using less equivalency of the boronic acid, low temperature, less catalyst loading or by changing the nature of the solvent.

Langer *et al.* reported chemo and site selective Suzuki-Miyaura coupling on 4-bromo-2,3,5-trichloro-6-iodopyridine.[112] Selective coupling on the active C-I on the 6-position occurred using only 1.5 equivalents of the boronic acid, K_3PO_4 (1.5 equiv.) and $Pd(PPh_3)_4$ in a solvent mixture of toluene, ethanol and water (6:1:1) (Scheme 6). Although a slight drop in yield in case of electron-poor arylborinc acid, the reaction still showed high degree of chemoselectivity at position 6. It was also shown that switching the catalyst system to a more reactive catalyst $Pd(OAc)_2$ and PCy_3 gave 4,6-biarylated compounds as the main product where the chemoselectivity on iodide was lost and the reaction occurred on both C-I and C-Br. Furthermore, increasing the amount of the base and boronic acid in addition to using more active catalyst (Pd/PCy_3) allows the chemoselective diarylation of pyridine on both C-I and C-Br. Although the less active C-Cl stayed unreacted under these conditions, traces of triarylated pyridine was observed. This indicated that increasing the amount of the boronic acid and the base could lead to highly arylated pyridine. Tuning the reaction conditions could allow for high degree of selectivity, which makes it a very useful tool for the synthesis of unsymmetrically arylated pyridines.
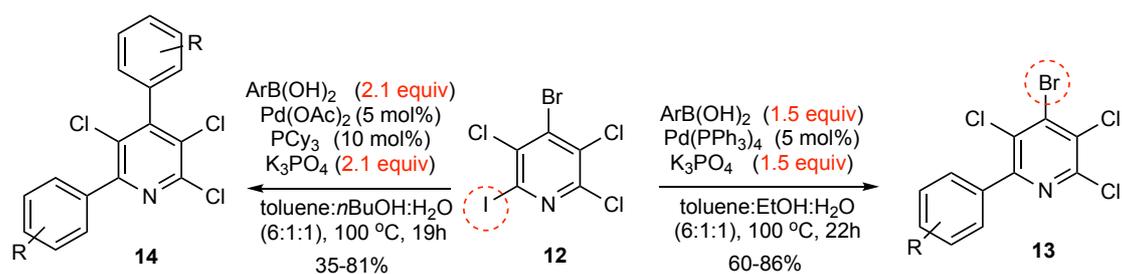
Scheme 6. Chemoselective SMC on 4-Bromo-2,3,5-trichloro-6-iodopyridine.

In some cases, the choice of the solvent can strongly influence the chemoselectivity of the reaction. This is illustrated by the selectivity of Suzuki-Miyaura coupling on chloroaryl triflate with o-tolylboronic acid (Scheme 7). The reaction using $Pd_2(dba)_3$ and $P(tert\text{-Bu})_3$, as catalytic system showed reactivity towards the chloride (95%) when using non-polar solvents such as toluene. In case of polar solvents such as MeCN and DMF the reactivity was opposite and the coupling occurred on the triflate (C-OTf) instead (74%).[123,116] This observation is explained by the hypothesis that polar solvents stabilizes the charged palladium species. A follow up study by Sharon *et al*. demonstrated that the SMC selectivity on the triflates using Pd/P(*t*-Bu)₃ does not generally follow the claimed trend using polar solvents.[124] Selectivity on C-OTf is only limited to few coordinating solvents such as NMP, DMF, MeCN, DMSO. On the other hand, reactivity on the C-Cl was observed with other polar solvents (H_2O, MeOH, *i*PrOH, etc.) as with non-polar (toluene, dioxane, etc.) solvents. This observation is related to solvent role where it does not only dissolve the reaction component into a homogenous mixture but also influences the reaction kinetics by stabilizing charged intermediates in the catalytic cycle.
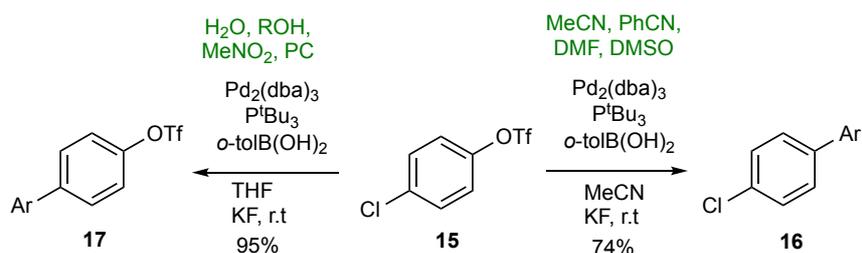
Scheme 7. Solvent effect on the chemoselectivity of arylchloride triflate.

3.2 Palladium catalyzed carbonylative transformation of aryl halides

Palladium carbonylative couplings covers many closely related reactions that incorporate CO into a substrate by adding it into an aryl-, benzyl- or vinylpalladium complex in the presence of various nucleophiles.[125] It is a very important tool for a wide range of synthetic transformations that allows direct formation of biaryl and hetero-aryl ketones, benzylic aldehydes, benzoic acid

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and acid derivatives, amides, etc (Scheme 8).[126] Based on the type of the nucleophile, the transition metal catalyzed carbonylation can be carbonylative Suzuki-Miyaura cross-coupling, aminocarbonylation and alkoxycarbonylation (Scheme 8. **A, B**, **C** respectively). The reaction can occur intermolecularly and/or intramolecularly, which allows a wide application of the reaction. Intramolecular carbonylation enables the synthesis of heterocyles for instance, alkoxy- or aminocarbonylation of hydroxy or amino-substituted aryl/vinyl halides enables the synthesis of lactones, lactams, oxazoles, thiazoles, imidazoles, and other heterocycles.[127,128,125]
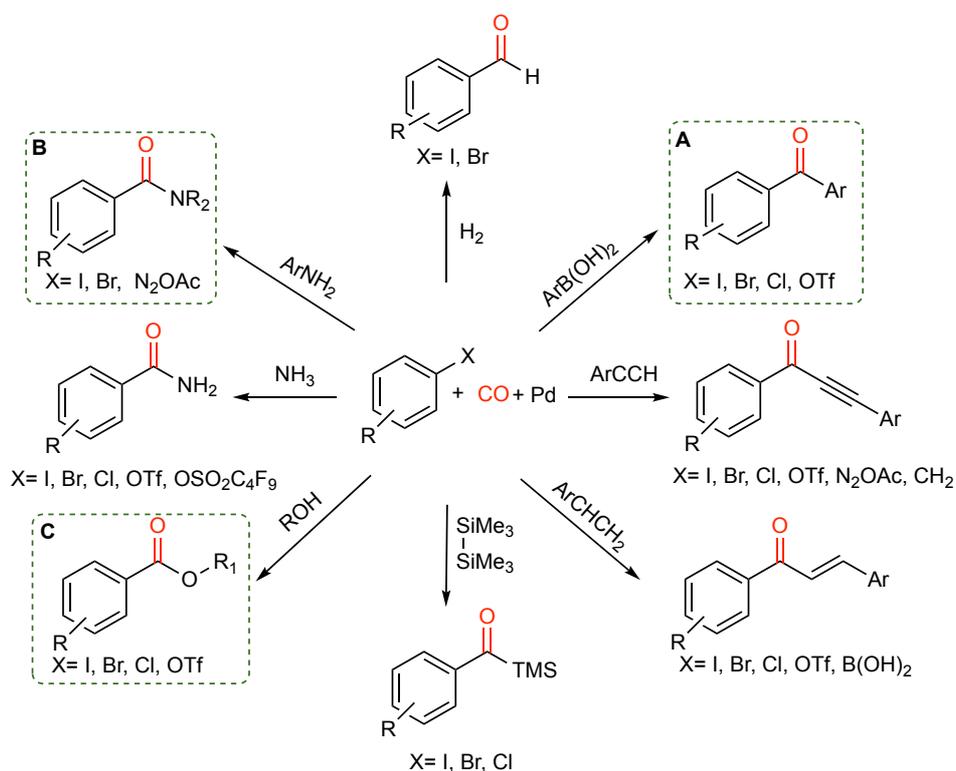
Scheme 8. Examples of palladium catalyzed carbonylation reactions.[126]

Palladium catalyzed carbonylation reaction (Scheme 9. cycle **B**) is mechanistically similar to the non-carbonylative one (Scheme 9. cycle **A**) as it consists of the same basic steps; oxidative addition, transmetalation, and reductive amination. It consists of an extra step, which is the coordination and the insertion of the CO after the oxidative addition forming the acylpalladium intermediate (Scheme 9, complex **2**). In general, the aromatic halides (ArX) react with an appropriate nucleophile in the presence of catalytic amounts of a palladium complex in carbon monoxide atmosphere, where the leaving group X (e.g. I, Br, Cl, OTf, etc.) is replaced by the nucleophile with incorporation of the CO molecule(s) (Scheme 9, cycle **B**).[129] The reaction often take place at 60–140 °C under 5–60 bar of CO, and may also require a stoichiometric amount of base to regenerate the catalyst.[125]

Several factors make it challenging to find suitable catalytic systems and reaction conditions for carbonylative couplings. For instance, in carbonylative Suzuki-Miyaura coupling, it is very challenging to find a catalytic system and reaction condition to favor the carbonylative reaction over the competing non carbonylative reaction. The oxidative addition can favor electron-rich metal center in carbonylative coupling reactions.[130,126] However, the CO insertion favors an electron-deficient metal center.[126] On the other hand, reductive elimination can be assisted with bulky ligands, while CO insertion requires less bulky ligands. In addition, elevated temperatures could be advantageous in favor of oxidative addition, while it could lead to decarbonylation of the acylpalladium after CO insertion.[128,130-132] Therefore, the success of the optimal catalyst/ligands depends most likely on the individual substrates, CO pressure and reaction conditions.
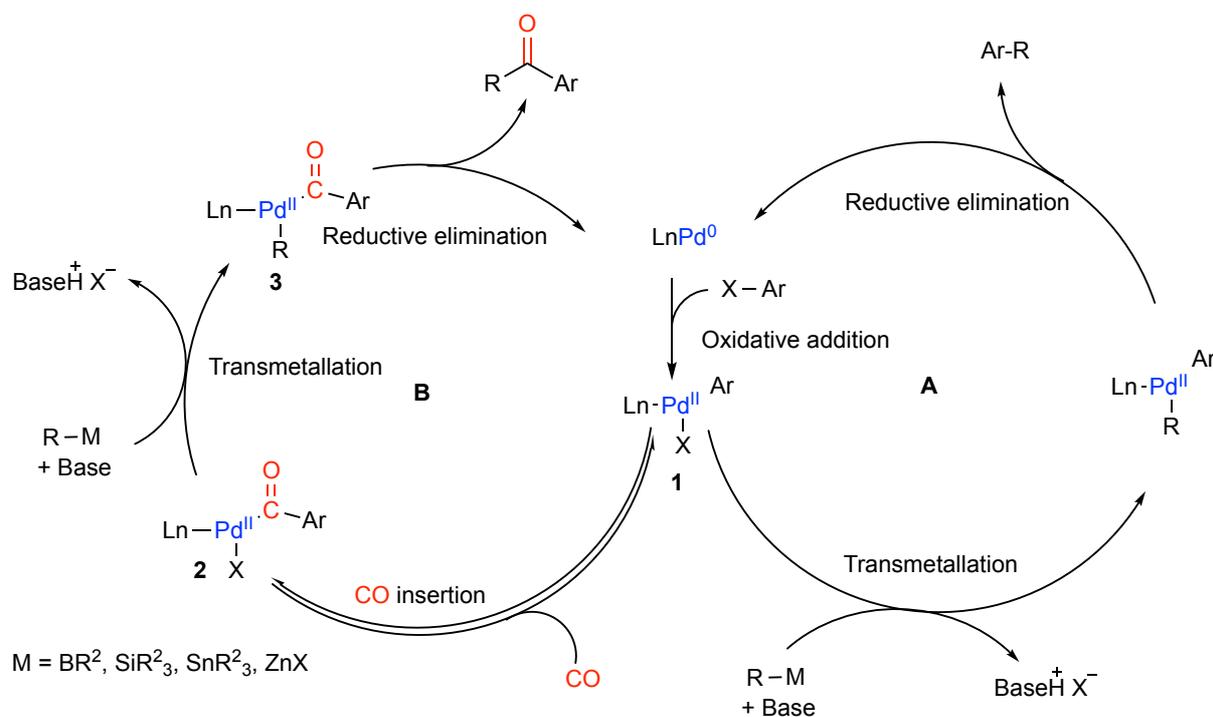
Scheme 9. General mechanism of non-carbonylative cross-coupling (A) versus carbonylative cross-coupling (B).

The product of the carbonylation reaction is dependent on the rate of the CO insertion, which should be faster than other processes like transmetalation in order to obtain the carbonylated product (Ar-CO-Nu) rather than the non-carbonylated by product (Ar-Nu).[133] This could be achieved by altering the other reagents by carefully choosing their functionalities or concentration by slow addition.[133] On the other hand, using CO in high pressure might increase the CO insertion rate and thus favor the carbonylative product rather than other by-products such as the non-carbonylative product.[133] However, if CO gas is used in excess hoping to

overcome these problems the result might be opposite to the intended one as the palladium atoms could cluster and agglomerate forming the nonactive palladium black.[134] The Pd[0] reactivity towards oxidative addition could be negatively influenced by the strong binding ability of the CO. This is because CO is a good π-acceptor and would receive electrons from the metal center to form a π-back bond.[130]

All these factors could interrupt the catalytic transformation in one way or another. However, a possibility to overcome this problem is to use electron-rich ligands. Generally, ligands with strong σ donor ability might prevent the direct coordination between Pd[0] and the CO.[130] Wide range of powerful ligands have been developed to accelerate many of the carbonylative reactions.[135,136,137] The achievement in this area did not only include the most studied phosphine ligands (monodentate and bidentate) but also included NHC and other nitrogen and thiourea ligands (Figure 11).[130,136,138]
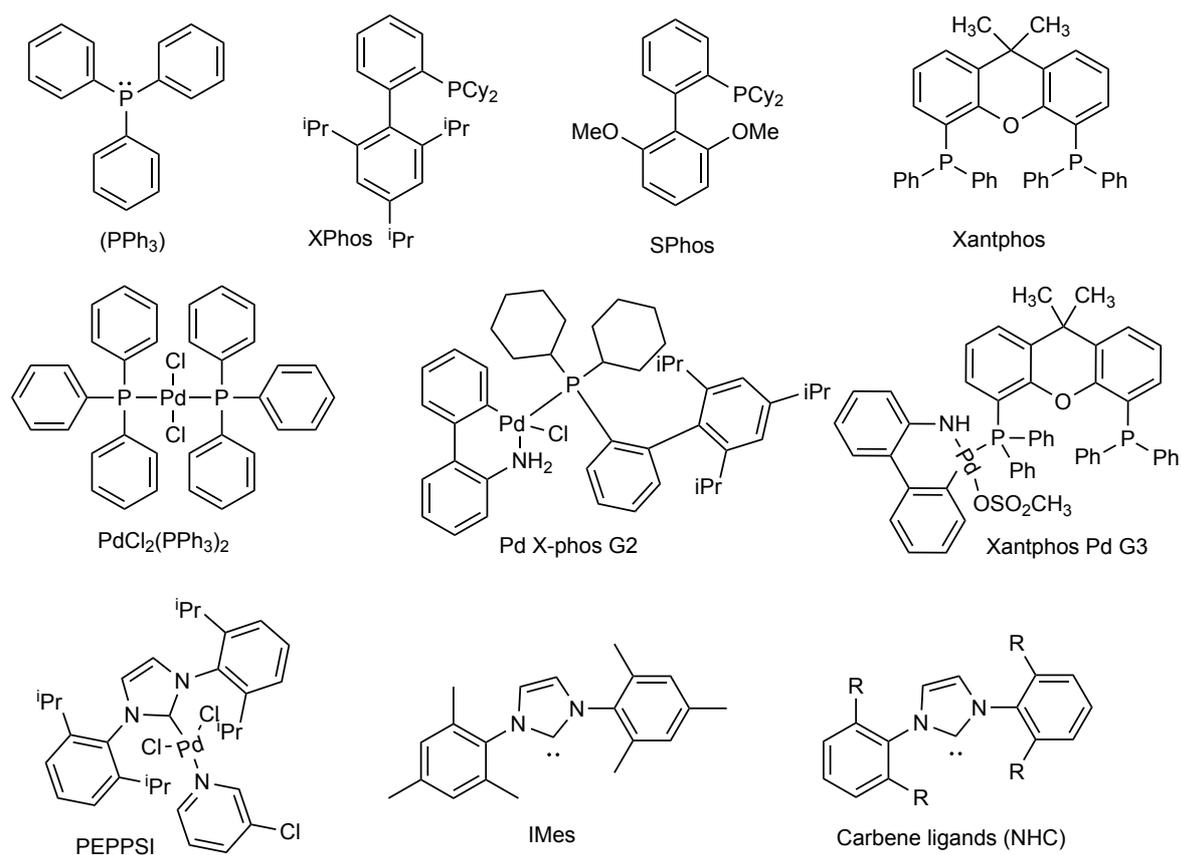
Figure 11. Selected examples of Pd complexes and commonly used ligands.

Use of CO gas and potential CO sources

The installation of the carbonyl group can be achieved by using CO gas. Despite the hazard related to the handling of the toxic, corrosive, and high flammable CO gas, it is widely used as an available and important C1 building block.[129] Synthetic transformations using gaseous reagents as CO are commonly performed in autoclaves under high pressure or under atmospheric pressure using a balloon. Safety equipment is necessary to reduce safety concerns when handling CO. However, it is commonly used in research and industrial process due to its availability and low cost.

Alternatively, safer sources of CO including transition metal carbonyl complexes (e.g. $Cr(CO)_6$, $W(CO)_6$, $Co_2(CO)_8$, $Mo(CO)_6$)[139], carbamoylsilane[140], oxalyl chloride[141], formats[142], aldehydes in addition to in situ decarbonylation protocols have been developed.[143,144] The use of these carbonyl complexes introduces potential byproducts from the CO surrogate, which interrupt or get mixed with the desired product and complicate workup and isolation.[145] Moreover, they could potentially inhibit the possibility of developing novel carbonylative transformations.

Skrydstrup and coworkers have developed a two-chamber system setup for in situ generation of CO from stable solid CO precursors, 9- methylfluorene-9-carbonyl chloride (COgen), which releases CO once activated by Pd catalyst or methyldiphenylsilacarboxylic acid (SilaCOgen), which is activated by adding fluoride (Figure 12).[146] The carbonylation reaction takes place in one chamber, while the other chamber is used for the CO release. CO releases upon treating the stable acid chloride (COgen) with tri-*tert*-butylphosphine ligated Pd catalyst and amine base in an aprotic solvent. The CO gas release is proven to be almost quantitative as illustrated throughout the wide synthetic applications using COgen as the carbonylating agent.[146]
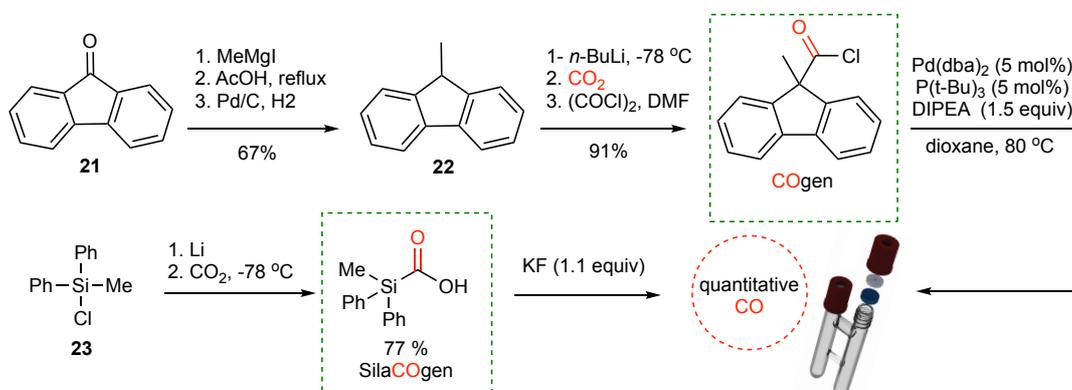
Figure 12. Synthesis and decarbonylation of COgen, SilaCOgen and COware.[146]

Despite COgen being an expensive source of CO and requiring the use of two chamber systems, it gives access to stoichiometric amounts of CO for many low pressure carbonylation reactions in a safer fashion than other CO sources. In addition, being a stable solid makes it convenient to handle in the lab. Releasing the CO in another chamber than the carbonylation reaction chamber prevents problems such as formation of undesired by-product, separation problems etc. Moreover, this method allows introducing isotopically labelled CO by using labelled COgen.[146–148]

3.2.1 Carbonylative Suzuki-Miyaura coupling

The carbonylative version of the SMC reaction has been investigated using different Pd-based complexes/catalysts and reaction conditions. However, most of the literature on this particular cross-coupling requires high CO pressure protocols except few reports applying carbonylation at atmospheric pressure.[129,149,132]

BY$_n$ = B(OH)$_2$, B(OH)$_3$Na, DABO boronate,…
X = I, Br, Cl, OTf, OTs,..
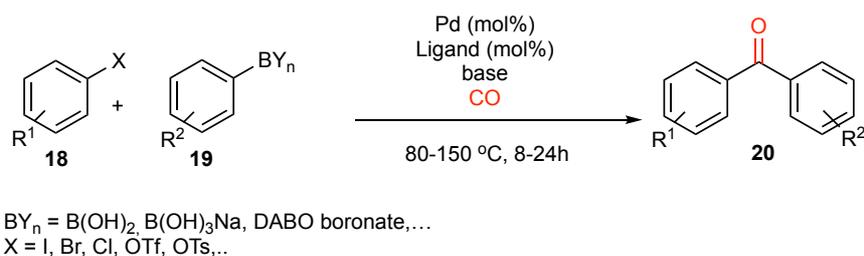
Scheme 10. General presentation of Suzuki-Miyaura coupling.

The common problem with this reaction lies in the formation of biaryl products, which results from the competing direct SMC coupling without carbon monoxide insertion. Nevertheless, the reaction conditions including nature of the palladium catalyst precursor, ligand, base, additive as well as the nature of the substrates (aryl halide and boronic acid), influence the ratio of ketone to direct coupling product.

Suzuki and coworkers described the palladium carbonylative SMC where they synthesized a variety of diaryl ketones from aryl iodides and boronic acids in high yields using PdCl$_2$(PPh$_3$)$_2$ and K$_2$CO$_3$ as a base in anisole (Scheme 11).[129] The choice of both base and solvent played an important role to obtain the desired ketone with minimum formation of biaryls as by-product. A range of bases; K$_2$CO$_3$, Cs$_2$CO$_3$, Tl$_2$CO$_3$, K$_3$PO$_4$ were tested in anisole to test reaction selectivity towards carbonylative coupling reaction versus non carbonylative one. Tl$_2$CO$_3$ gave the lowest selectivity towards the carbonylated product and resulted in 38% biaryl ketone and

24% biaryl by-product. On the other hand, K_2CO_3 in anisole was very efficient to yield the desired biaryl ketone in 84% yield, while it gave only 11% of the biaryl by-product.
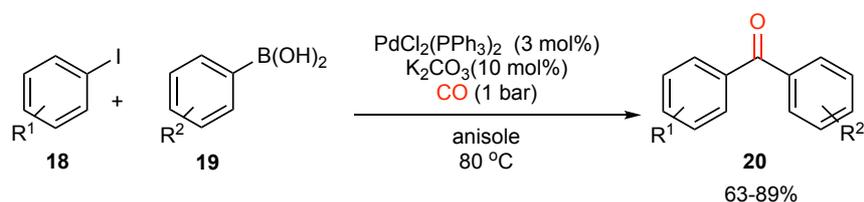
Scheme 11. Carbonylative Suzuki-Miyaura coupling of aryl iodides and boronic acids.

Skrydstrup coworkers tested several carbonylative Suzuki-Miyaura coupling of 1-(4-iodophenyl)ethan-1-on with phenylboronic acid using low CO pressure and a range of Pd sources resulted in different ratios between biaryl ketone and biaryl (Table 4, **23**, **24**, respectively).[149] The phosphine based $Pd(dba)_2$ and $PdCl_2$ were shown to be favoring the carbonylative coupling over the direct coupling (Table 4, entry 2, 4 respectively). It is noteworthy that increasing the catalyst loading to more than 1% increased the chance of obtaining the undesired biaryl product. The best selectivity towards the desired biaryl ketone was obtained using ligand free system based on $PdCl_2$ and K_2CO_3 in anisole under CO (1 atm). A range of substituted biaryl ketones was obtained in moderate to high yield (50-93%).

Table 4. Selected examples of different palladium sources used in carbonylative SMC.

Entry	Pd cat (mol %)	Ratio 23:24
1	Pd(OAc)$_2$ 1 mol%	69:31
2	Pd(dba)$_2$ 1 mol%	71:29
3	Pd(TFA)$_2$ 1mol%	58:42
4	PdCl$_2$ 1mol%	95:5

Bhanage and coworkers reported $Pd(tmhd)_2$ as a catalyst for carbonylative Suzuki-Miyaura coupling of aryl iodides with arylboronic acids in anisole under 8 bars of CO. Although the reaction gave access to a range of biaryl and heteroaryl ketones in moderate to high yields it

still lacks wider scope with respect to ortho substituted aryls and electron-withdrawing groups in addition to the required high pressure.[150]

The use of carbene ligands and thiourea based ligands has drawn a keen interest in carbonylative Suzuki-Miyaura coupling especially with sterically hindered substrates.[151] Keffe *et al*. reported the use of NHC palladium complex PEPPSI-iPr in the synthesis of sterically hindered biaryl ketones in moderate to high yields (Scheme 12).[132]
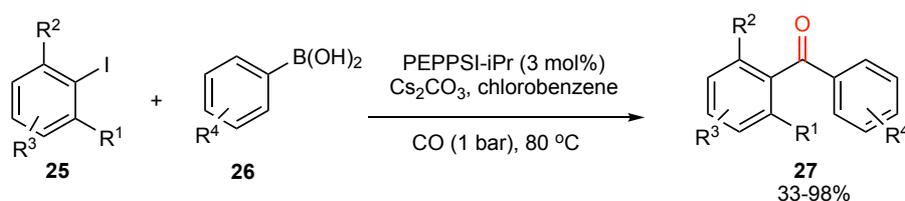
Scheme 12. Suzuki-Miyaura coupling of ortho-disubstituted aryl iodide with NHC catalyst.

Despite the achievements in this area, coupling of aryl bromides are still challenging especially in case of *ortho* substituted aryl bromides, which is noticeable in many of the published reports. Only few methods were successful for carbonylative coupling of aryl bromides and chlorides.[152,153] The carbonylative Suzuki-Miyaura coupling of aryl bromides and chlorides typically requires harsh conditions such as high temperature, high CO pressure and longer reaction time in comparison to their corresponding aryl iodides. Additives such as NaI, KI would enhance the reaction rate as it might involve in situ generation of aryl iodides and thus faster oxidative addition.[129]

Coupling of aryl bromides with aryl trihydroxyborates or DABO boronate using Pd(acac)$_2$ and the phosphine ligand catacxium A.HI as a ligand in toluene under CO (1 atm) gave access to a range of substituted biaryl ketones in moderate to high yields (Scheme 13).[153] Unfortunately, these conditions also showed several limiting factors, as they gave poor yields with electron-withdrawing groups and they did not support ortho substituted aryls as they have low conversion. In addition, an additional step is required for the preparation of the boronic acid derivatives.[153]
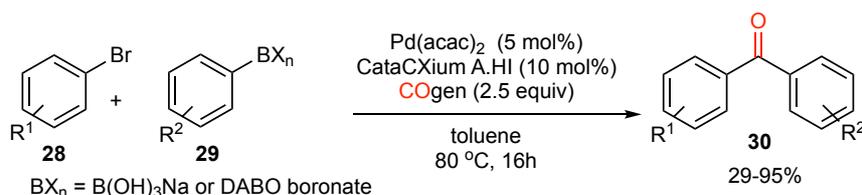
Scheme 13. Suzuki-Miyaura coupling of aryl bromides with organoboran using CataCXium A.HI.

Another catalytic system was reported by Beller and coworkers using CataCXium A as a ligand together with Pd(II)acetate to access a wide range of biaryl and heteroaryl ketones. Although the reaction showed good tolerance of both electron-rich and electron-deficient aryl halides and boronic acids, it required high CO pressure in case of aryl bromides with electron-withdrawing groups (2.5-5 bar).[152]

3.2.2 Aminocarbonylation

Amides are considered to be one of the most important functional groups in chemistry, they are essential in many biological process and chemicals required for sustaining life. Amides are normally found in many natural products, linking amino acids in proteins such as enzymes, they are also found in many medicinal and pharmaceutical products. Different synthetic approaches towards amides require stoichiometric amounts of amide-coupling reagents, which make it an expensive and wasteful procedures. On the other hand, palladium-catalyzed aminocarbonylation of aryl or heteroaryl halides give a direct access to the corresponding carboxamides.[137,139,157–159]

X= I, Br, Cl, OTf
R, R´= H, C
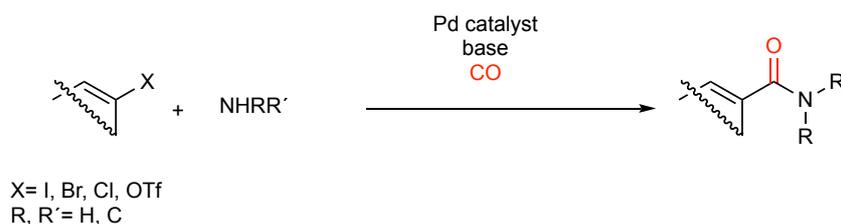
Scheme 14. General aminocarbonylation reaction.

The use of primary or secondary amines as the nucleophile under catalytic conditions will provide the desired amide following a similar catalytic cycle as the carbonylative cross-couplings with differences in the last steps. One possibility for the amine (nucleophile) to approach the catalytic cycle is that it could coordinate to the palladium followed be reductive elimination to obtain the amide. Another possibility, which is believed to be the dominant route, is nucleophilic attack on the acylpalladium carbonyl.[160]

Since common catalytic systems for aminocarbonylation showed good tolerance to a wide range of functional groups, it is considered to be a versatile method in organic synthesis to access amides with a variety of N-substituents. It has been applied for the synthesis of molecules of medicinal interest such as lotrafiban, itopride, bromopride and butoxycaine.[161–164] For example, the key step in the synthesis of lotrafiban is the aminocarbonylation step of the

aryl iodide and the amine using PdCl$_2$(PPh$_3$)$_2$ in anisole for 2.5 h under 1 atm of CO pressure to furnish the desired amide (Scheme 15).[161]
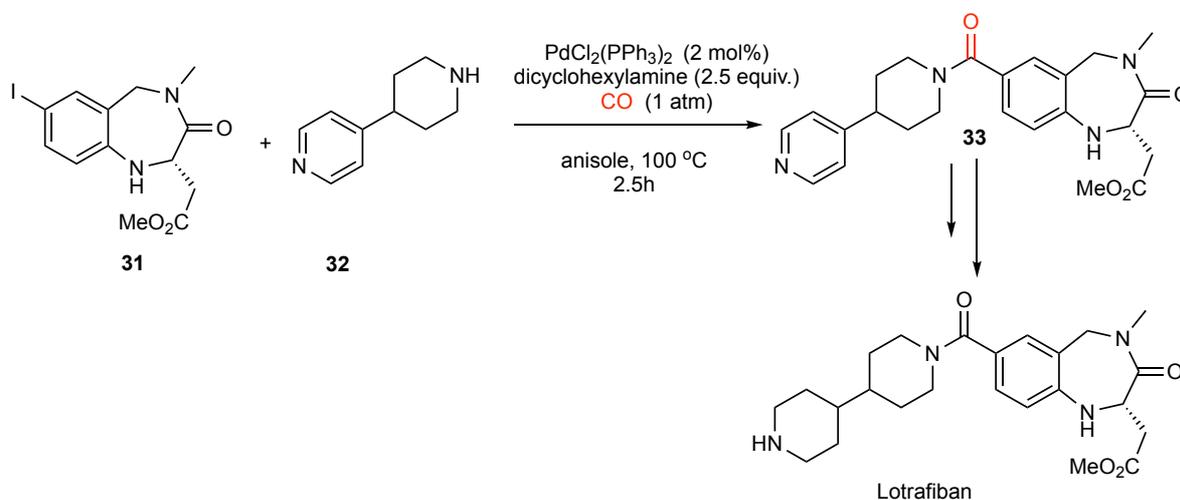
Scheme 15. Aminocarbonyation towards synthesis of lotrafiban.

Moreover, aminocarbonylation can be used for the synthesis of ferrocene based chiral ligands that are used in asymmetric catalysis.[165] For instance, the synthesis of asymmetrically disubstituted ferrocenbiscarboxamide (Scheme 16) was obtained via aminocarbonylation between symmetrical ferrocenyl di-iodide with morpholine and diethylamine under high CO pressure (40 atm) yielding the desired asymmetric ligand in 85%.[166]
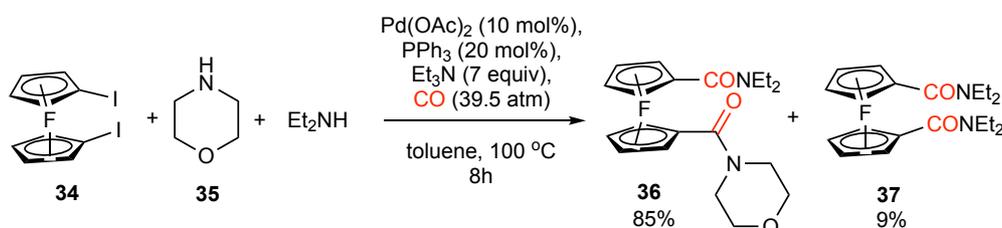
Scheme 16. Aminocarbonylation for the synthesis of asymmetrically disubstituted ferrocenebiscarboxamide.

Weinreb amides are also accessible via aminocarbonylation under mild conditions. Buchwald and coworkers reported the synthesis of Weinreb amides from a wide range of electron-rich and electron-deficient aryl and alkenyl halides using Pd(OAc) and Xantphos under 1 atm CO pressure to furnish the desired amide in moderate to excellent yields (Scheme 17).[167]
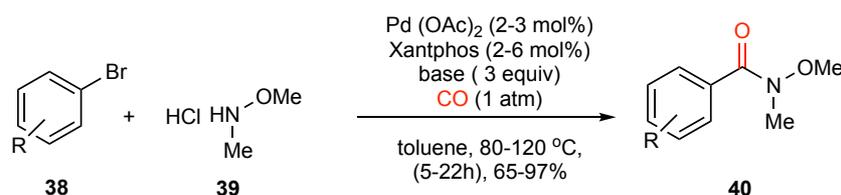
Scheme 17. Synthesis of weinreb amides via aminocarbonylation.

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3.2.3 Alkoxycarbonylation

Alkoxycarbonylation is an important method for the synthesis of esters. Different alkyl and aryl halides were converted into their corresponding carboxylic esters in presence of transition metal complexes and the corresponding alcohol under CO pressure (Scheme 18). Installing the carboxylic acid/ester into aryl/alkyl halides is a very attractive tool for late stage functionalization and C-C bond formation.

Y= H, Na, K, ...
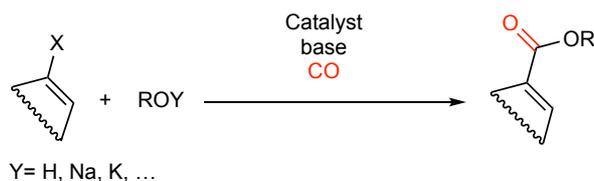
Scheme 18. General transformation of aryl or vinyl halide into their corresponding esters via alkoxycarbonylation.

Alkoxycarbonyltion follows a similar mechanism as aminocarbonylation where the nucleophile is the alcohol or metal alkoxides instead of the amine to form esters. Alkoxycarbonylation e.g. methoxycarbonylation are widely described including both inter- and intramolecular reactions.[168,169,134,170] Intramolecular alkoxycarbonylation of pendant alcohol leads to the formation of five, six, and seven membered ring lactones.[175]

Buchwald and coworkers reported methoxycarbonylation of a range of aryl bromides under low CO pressure (1 atm) using 2 mol% Pd(OAc)$_2$, 4 mol% Xantphos and 10 equiv MeOH at 70 °C for 24 h. The reaction gave access to a range of methyl esters with various function groups such as aryl nitriles, fluorides, ethyl ether, *tert*-butyl carbamate, in high yields (80-91%). However, scope limitations were described due to low reaction temperature.[176]

A variety of methods for the transition metal catalyzed alkoxycarbonyltion of aryl halides, tosylates and triflates has been described.[177,172] Lou *et al.* reported the synthesis of N-hydroxysuccinimido esters from aryl iodide or triflates using Pd(OAc)$_2$ and Xantphos in DMSO under 1 atm CO (Scheme 19).[177] In addition, Angelina *et al.* reported also the synthesis of N-hydroxysuccinimido esters together with active esters from pentafluorophenol, hexafluoroisopropyl alcohol, p-nitrophenol and N-hydroxyphthalimide from aryl bromide in excellent yields (59-99%) using 3 mol% (Pd(cinnamyl)Cl)$_2$, HBF$_4$P(*tert*-Bu)$_3$ (6 mol%) and Cy$_2$NMe (1.5 equiv) in toluene at 95 °C for 16 h.[172]
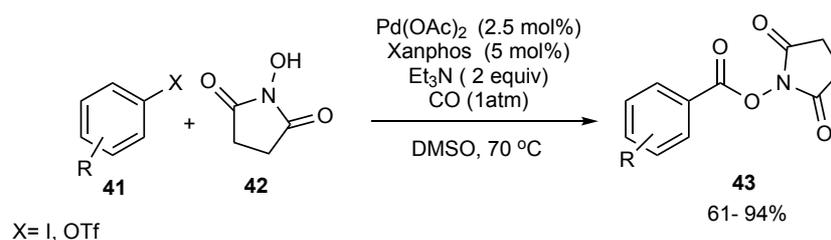
Scheme 19. Synthesis of N-hydroxysuccinimido esters via alkoxycarbonylation.

Palladium catalyzed alkoxycarbonylation has been performed with the inactivate alkyl halides such as inactivated secondary alkyl bromides and alkyl chlorides, which are challenging substrates that require harsh conditions, high CO pressure in comparison to more active alkyl iodide. Alexanian and coworkers, reported esterification of less active alkyl bromides to the corresponding *tert*-butyl ester version using Pd(PPh$_3$)Cl$_2$ and IMes as a ligand under CO pressure of only 2 atm at 50 °C in DMSO, which are milder conditions for this type of reactions (Scheme 20). The reaction was tolerant to a variety of function groups such as silyl protecting group, esters, five and six membered carbocycles and heterocycles and gave good results with alkyl possessing both electron-deficient and electron-withdrawing group with yield range of 50-87 %. Using carbene ligand (IMes) in this case shown to facilitate the reaction in combination with Pd(PPh$_3$)Cl$_2$. Being able to perform this reaction on the stable alkyl bromide makes it useful as late stage C-C bond formation.[170]
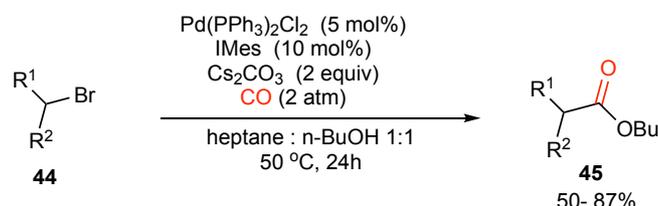
Scheme 20. tert-Butyl ester from deactivated alkylbromides.

Alkoxycarbonylation can be also done using metal alkoxide (e.g. EtONa, *tert*-BuONa, etc) instead of the direct use of the corresponding alcohol. This approach ensures presence of the nucleophile in the reaction medium and prevent volatile alcohols (e.g. MeOH, EtOH, etc) from escaping the reaction mixture.[171,178] Skrydstrup and coworkers reported alkoxycarbonylation of aryl bromides into their *tert*-butyl ester using Pd(dba)$_2$ and DiPrPF under 1 atm of CO pressure in THF (Scheme 21). The reaction showed great results with more bulky tertiary alcohols such as the sodium adamantoloxide and sodium 9-methyl-9-fluorenoxide, which indicates bulky nucleophiles are more favorable for efficient reductive elimination. While on the other hand

less bulky alcohols such as sodium methoxide were not successfully used as nucleophiles in this reaction.[171]
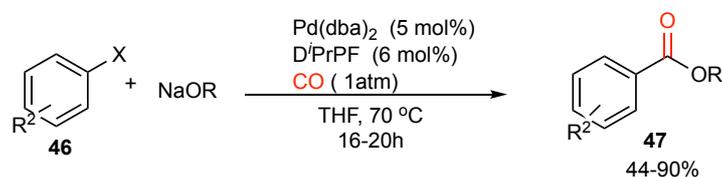
Scheme 21. Alkoxycarbonylation of aryl bromide using bulky sodium alkoxides.

3.3 Reactions for the preparation of 2-aroylbenzoic acid derivatives

2-Aroylbenzoic acids and derivatives have gained noticeable interest as synthetic intermediates for accessing bioactive compounds. and they were the aim of the work presented in paper II. Only few reported methods towards formation of 2-aroylbenzoic acids are found in literature, comprising Friedel-Craft acylation,[154] Pd-catalyzed ortho-C–H activation of aryl amides followed by coupling with aryl aldehydes,[155] Pd-catalyzed ortho-C–H activation of benzoic acids followed by decarboxylative coupling with α-oxocarboxylic acids.[156] The available methods generally show limitation regarding regiocontrol and/or substrate scope especially with regard to electron-deficient aryl groups.

Ge and coworkers reported the synthesis of a range of substituted 2-aroylbenzoic acids in moderate yields through chemoselective decarboxylative cross-coupling of benzoic acids via C-H bond functionalization with α-oxocarboxylic acid as the coupling partner. The reaction required the use of harsh conditions including use of an excess of the oxidant (Ag_2CO_3), high catalyst loading (10 mol%), the elevated temperatures (120-150 °C) and extended reaction time up to 48h (Scheme 22). Moreover, the substrate scope suffered from some limitations especially with electron withdrawing groups that were not well tolerated under these conditions.[156]
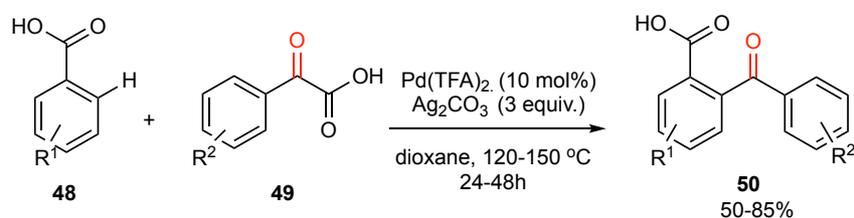
Scheme 22. Chemoselective decarboxylation cross-coupling of benzoic acids via C-H bond functionalization.

Another method to access 2-aroylbenzoic acids via C-H activation directed by aryl amides that would undergo ortho acylation followed by ring closing to form amide containing four-member ring and then ring opening to give the ortho imino carboxylic acid (Scheme 23). The reaction

then would be submitted to reflux in concentrated aqueous HCl in order to obtain the 2-aroylbenzoic acids. The reaction had a limited substrate scope, where functional groups like esters, nitriles, imines, etc. were not tolerant, due to the harsh acidic conditions required to eventually obtain the ketone form of the imino-aryl.[155]
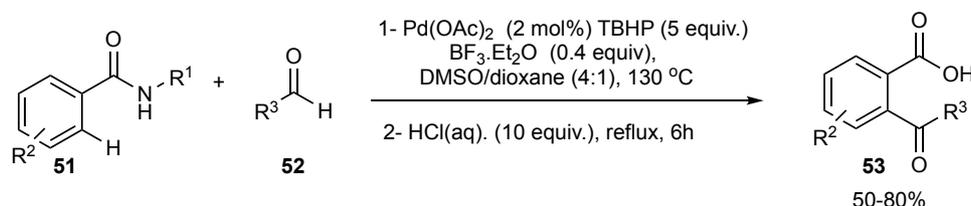
Scheme 23. C-H activation of aryl amides to form 2-aroylbenzoic acids.

3.4 Solvent effect and sustainability

The growing awareness of the impact of chemical process, e.g. solvent use on the environment and their contribution to the climate change, has resulted in an increasing interest in both research and industry in finding sustainable alternatives.[181] Sustainable alternatives are needed for media to perform reactions as well as for work-up and purification, catalysts and energy sources. Sustainability has been previously described as "*resources including energy should be used at a rate at which they can be replaced naturally and the generation of waste cannot be faster than the rate of their remediation.*" [181] This description coincides with the definition by the world commission on environment and development stating that sustainability is "development that meets the needs of the present without compromising the ability of future generations to meet their own needs".[181] A noticeable success has been achieved in the synthesis of new products since 1990s when the twelve principles of "green chemistry" were formulated.[182,183] These principles are considered to be the guidelines that chemists in both academia and industry try to follow while carrying out chemical reaction in a sustainable fashion. Despite the difficulties following all the twelve principle for preparative purposes, chemists and industries have already made noticeable moves towards sustainability by considering the key principle of green chemistry.

The solvent may perform a mechanical role in the mechanism, but sometimes it plays also an essential role of bringing the immiscible reactants together rapidly so that the reaction could occur. In addition to dissolving reactants, the solvent can participate in several ways to the reaction itself. The choice of the solvent could influence reactivity, introduce selectivity,

and produce different products.[179-184] It might interact with the reactants individually or get involved in the transition state.[180,181]

Many of the organic solvents that are commonly used in organic synthesis and post reaction processes are with poisonous and carcinogenic nature such as halogenated hydrocarbons (DCM, $CHCl_3$, CCl_4, etc.). This type of solvents has created serious harm to the environment and human health in general. However, two of the twelve principles of green chemistry are based on usage of safer solvent and reaction conditions and to prevent waste. One principle is "Safer Solvents and Auxiliaries" where the use of auxiliary substances such as solvent and separation agents are not favorable and should be decreased. The other principle is "use of renewable feedstock" where raw materials or feedstock are attractive renewable alternatives and should be used whenever possible.[182] As a consequence, the direction of using less amount of solvents and finding renewable and less toxic solvent alternatives has recently gained a lot of attention in the area of green chemistry.[183]

One approach is to run reaction in neat conditions without the use of solvent. Unfortunately, solvent free reactions are not necessarily solvent free as claimed. Even if the reaction itself took place in a solvent free medium, it would still need an appreciable amount of solvents for reaction adsorption, elution of products and pre or post handlings of the reaction mixture. In addition, many extractions, purifications, and cleaning processes also depend on solvents, with large excesses necessary to achieve sufficient product purity.[181] A brief survey of academic researchers were conducted in 2010 by Jessop, where a question brought up "…what class of solvent will be responsible for the greatest reduction in environmental damage?".[184] The answers to the raised question were in favor of CO_2 derived solvents, water and careful selection of organic solvents. This turn our focus now towards CO_2 and biomass derived solvents.

3.4.1 Biomass and CO_2 derived solvents and their application in Pd catalyzed C-C couplings

Plant biomass (crops) such as corn, sugar cane, citrus, grasses and agricultural residues are all considered to be the main feedstock for generating renewable fuels and solvents. Recently, biomass derived solvents as well as chemicals derived from the reduction of CO_2 have been increasingly tested as green medium replacing the common nonrenewable solvents utilized in organic synthesis. The most studied solvents available from biomass are polar protic solvents;

ethanol, glycerol and its derivatives, choline chloride based deep eutectic solvents, as polar aprotic solvents; 2-methyltetrahydrofuran (2-MeTHF), cyrene (Cyr) and γ-valerolactone (GVL), as well as non-polar aprotic solvent; limonene (Lim) and *p*-cymene (Cym). In case of CO_2-derived chemicals, particular attention has been paid to the use of carbonates and ethers like methylal (Figure 13). These solvents are shown to be suitable renewable solvent alternatives for different chemical transformations in classical condensation reactions and transition-metal catalyzed cross-couplings.[181,183,185,186]
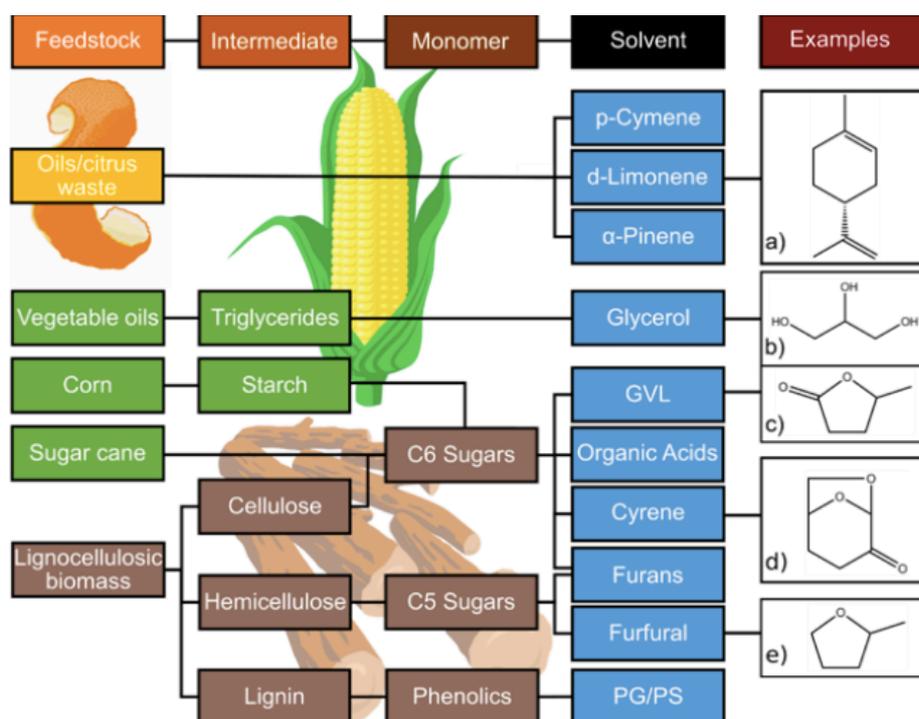
Figure 13. A number of sustainable solvents derived from plant biomass, sugars and oils. lignocellulosic biomass. *Adapted with permission from Clarke et al (2018).*[181]

2-MeTHF and GVL are both commercially available solvent obtained from furfural or levulinic acid, which are produced from lignocellulosic biomass.[181,135] Great attention has been paid to the use of these solvents as an alternative bio-based medium for several reactions including cross-couplings. Solvents, such as THF, toluene and highly regulated chlorinated solvents including dichloromethane and 1,2-dichloroethane can all theoretically be replaced by 2-MeTHF, due to its stability to acid and base in addition to its low miscibility with H_2O. It can also be used as a replacement of DCM in biphasic reactions and in work up process. 2-MeTHF was used as a sustainable media for a variety of organometallic reactions such as Grignard reactions, hydride reduction of carbonyl groups with $LiAlH_4$, lithiation, cross-coupling

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reactions.[181,187,188] Few examples of SMC coupling in 2-MeTHF have been reported. Nickel-catalyzed SMC coupling between arylboronic acids and aryl halides or phenol derivatives in 2-MeTHF was successfully reported by Garg and coworkers.[189] The reaction shown applicability with a notable substrate scope of 30 coupled products in 33-100% yield using 1-10 mol% of bis(tricyclohexylphosphine) Nickel(II)dichloride $NiCl_2(PCy_3)_2$. The reaction is also reproducible on 5-gram scale, coupling of 5-bromopyrimidine with 3-furanylboronic acid using just 0.5 mol% of the nickel catalyst yielded the product in 97% yield (Scheme 24). Nickel catalyzed amination of aromatic chlorides and O-sulfamates in 2-MeTHF was also reported by the same group using $NiCl_2(DME)_2$ as a pre-catalyst, the reaction showed general applicability in terms of substrate scope as well.[189]
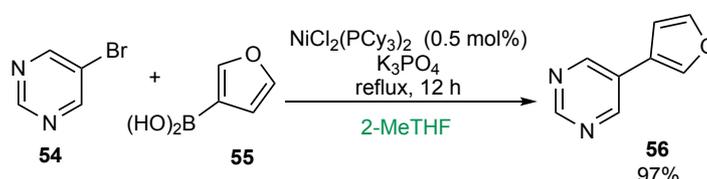
Scheme 24. Nickel catalyzed amination o f5-bromopyrimidine and 3-furanylboronic acid.

Recently, our group reported the activity of MeTHF and GVL among other solvents on Cu-catalyzed carboxylation and decarboxylation reactions. Although 2-MeTHF was not universal for all the tested carboxylation reactions, but it was the best alternative in most cases. Cu-catalyzed carboxylation of organoboronates with both electron-rich and electron-poor arylboronic acid pinacol esters showed best results over 16 examples where the yield was 68-98%. In addition, 2-MeTHF has shown to be a good reaction medium for Cu-catalyzed and Cu-free hydrocarboxylation of olefins (Scheme 25).[190]
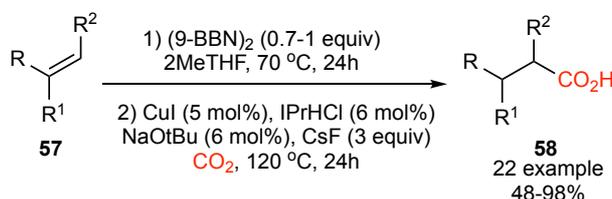
Scheme 25. Cu-Catalyzed and Cu-free hydrocarboxylation of olefins.

Similarly, GVL has lately drawn great attention to it as a green solvent. It has been frequently used as a food additive and a flavoring agent. It has similar polarity as dipolar aprotic solvents such as DMF and NMP. Therefore, it has been intensively studied on cross-coupling reactions since they often rely on the use of dipolar aprotic media.[188] A couple of examples illustrated the applicability of GVL as suitable bio-based medium for reactions involving C-H activation,

arylation and Hiayama couplings.[187] Mizoroki-Heck reaction between iodoarenes and styrenes or acrylates using 0.1 mol% Pd/C in GVL gave the coupled product after 2.5h (Scheme 26). The reaction showed general applicability through a substrate scope, over 20 examples in 80-90% yields.[191]

R[1]= H, OMe, COMe, NO$_2$
R[2]= CO$_2$Me, CO$_2$Et, CO$_2$n-Bu, CO$_2$H, ph, 4-Cl-C$_6$H$_4$

Scheme 26. Mizoroki-Heck reaction catalysed by Pd/C in GVL.

Glycerol is one of the common green solvents that has shown great applicability in many types of reactions such as; catalytic hydrogenation of various unsaturated organic compounds and cross-coupling reactions. In addition, condensation reactions are also compatible in glycerol due to its hydrogen bonding ability, which might stabilize transition states and intermediates. For example, catalyst free (e.g. Lewis acid) condensation of phenylenediamine and acetophenone was performed in glycerol with high yield (Scheme 27. condition A).[192] Condensation of phenylenediamine with benzaldehyde under solvent free conditions or reflux in ethanol was not successful. However, replacing the solvent with glycerol yielded 91% of the benzodiazepine, which support the advantage of using glycerol (Scheme 27. condition B).[192]
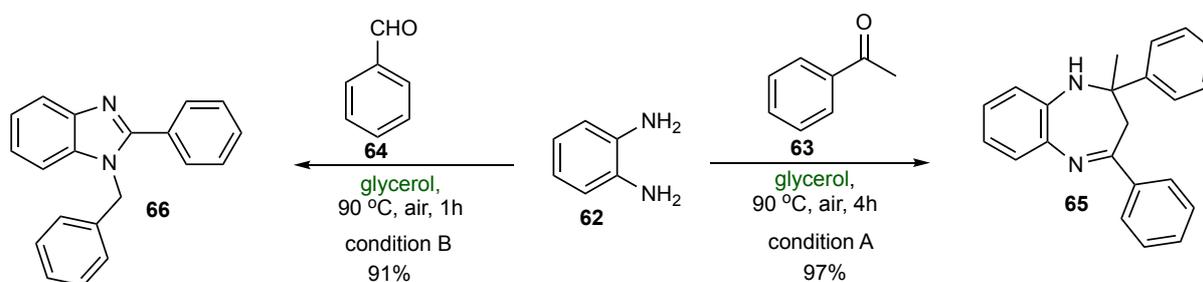
Scheme 27. Condensation of o-diaminobenzene in glycerol.

Organic carbonates are considered to be a promising renewable dipolar reaction media, due to their biodegradability and low toxicity.[193–196] Cyclic carbonates such as propylene carbonate (PC), ethylene carbonate (EC) are derived from CO$_2$ and bioethene, which make *t*hem of a high potential as bio-based solvents.[197] A previous study showed the successful application of PC and EC as the reaction solvent in the Mizoroki-Heck reaction between aryl iodides/bromides and acrylate (Scheme 28). The results in terms of conversion were comparable or even better to the same reaction performed in NMP as solvent or even better (80-100%). It is worth

mentioning that bromobenzene showed no reactivity in NMP, while it gave up to 40% conversion in case of EC of the desired product.[140]
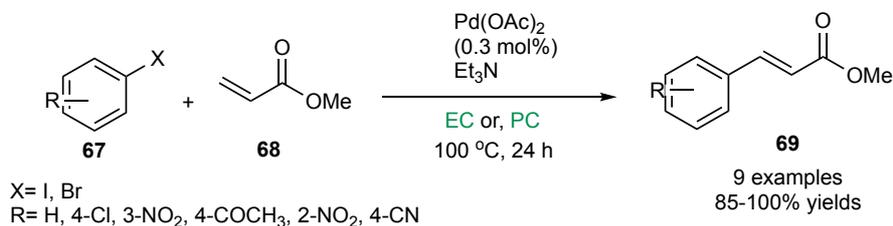
Scheme 28. Mizoroki-Heck cross-coupling reaction in ethylene carbonate or propylene carbonate.

Palladium catalyzed direct arylation of (hetero) aromatic derivatives has been carried out successfully in dialkyl carbonate such as dimethoxycarbonate (DMC), diethoxycarbonate (DEC). Direct arylation of benzoxazole with 4-bromoacetophenone using only 1 mol% of PdCl(C₃H₅)(dppb) as the catalyst was reported to provide the coupling product in 85% isolated yield (Scheme 29). The reaction performed in diethyl carbonate gave the best alternative compared to common organic solvents such as DMF, DMAc, NMP or dioxane as it gave only traces of unidentified side-products.[197]

solvent	yield (%)
DEC	85%
PC	78%
DMF*	78%
DMAc	31%
NMP	51%
Dioxane	73%

*5 % catalyst
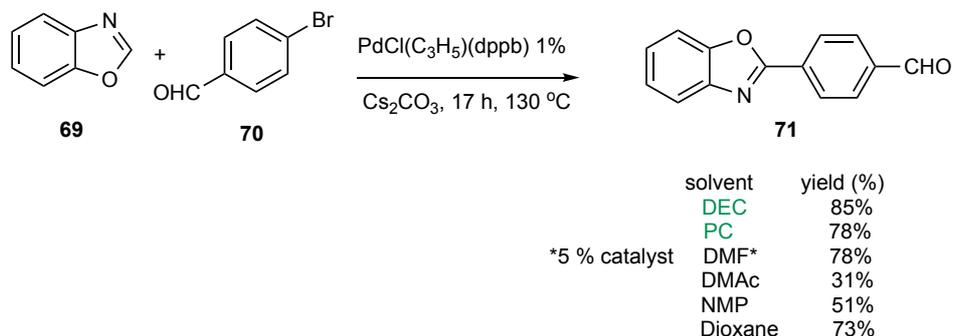
Scheme 29. Coupling of benzoxazole with 4-bromoacetophenone.

General discussion of results from the thesis

The numbering system applied in the discussion part is designed to be as follows:
Numbering of compounds introduced in papers is with the name Px-y, where x is the number
of the paper (I, II, III) and y is the compound number used in the paper. Other compounds that
are not included in the papers are numbered chronologically.

4. Design, synthesis and evaluation of *meta*-substituted benzoic acid derivatives as OXA-48 inhibitors (Paper I)

4.1 Background for the work in paper I

The work presented in paper I is a continuation of previous research conducted by the group of Prof. Leiros in collaboration with our group with focus on screening and development of fragments of the carbapenemase OXA-48.[15] Previously, a library of 490 fragments was screened to identify fragments that showed direct binding to the OXA-48 enzyme using SPR as the primary assay. The identified fragments from the SPR were examined further in a secondary biochemical screen via enzymatic assays in order to measure the binding efficiency of the fragments. Enzyme : inhibitor crystal structures were obtained for 3 fragments.[15]

The fragments shared the same core structure of a monosubstituted benzoic acid, and thus, shared some similar interactions such as hydrophobic interactions with Ser70, Ser118, Gly210, Tyr211. The carboxylate group showed an ionic interaction with Arg250 residue in the binding site. The negatively charged carboxylate had a charge induced hydrogen bond with the side-chain oxygen of Thr209. In addition, the π-system of the benzoic acid might allow for π-π stacking depending on the fragment conformation.

The crystal structure identified two different binding conformations of fragment **PI-1**. The first conformation (Figure 14, 1A) shows the fragment facing out of the active site and has hydrophobic interactions with Trp105, Thr209, Gly210, Tyr211, and Leu247 – the fragment is occupying the out-pocket (called R^2 side in Paper I). In the other conformation (Figure 14, 1B) the fragment is embedded in the active site and has hydrophobic interactions with Val120,

Leu158, and Tyr211 – the fragment is occupying the inn-pocket (called R^1 side in Paper I). The carboxylate group in both conformations forms ionic bonding with Arg250.
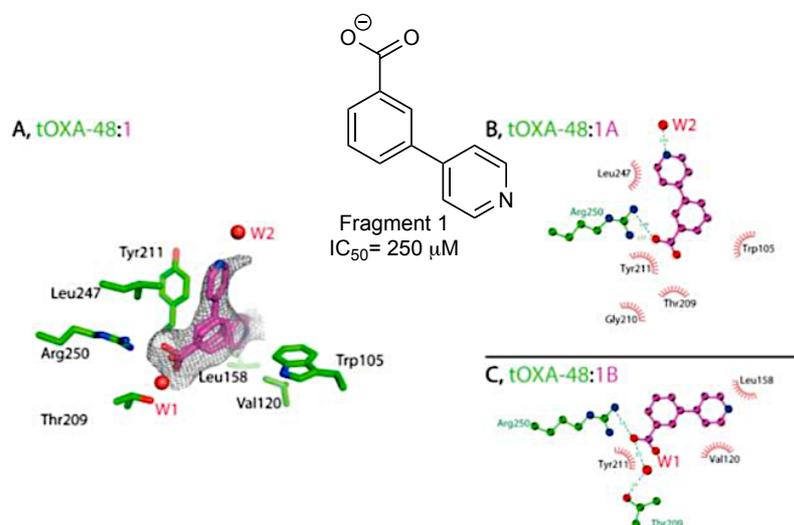
Figure 14. Crystal structures of OXA-48 (green) in complex with fragments (magenta). Two conformations are shown for compound 1 in A−C. Adapted with permission from Lund et al. (2016).[15]

As fragment **PI-1** tends to bind in two different conformations, it was suggested that structurally merging both conformations would lead to a better fragment with higher binding affinity occupying both the inn- and out-pocket. The merging resulted in a more potent inhibitor-fragment **PI-2** - with better K_d of 50 µM and lower IC_{50} of 18 µM (Figure 15).
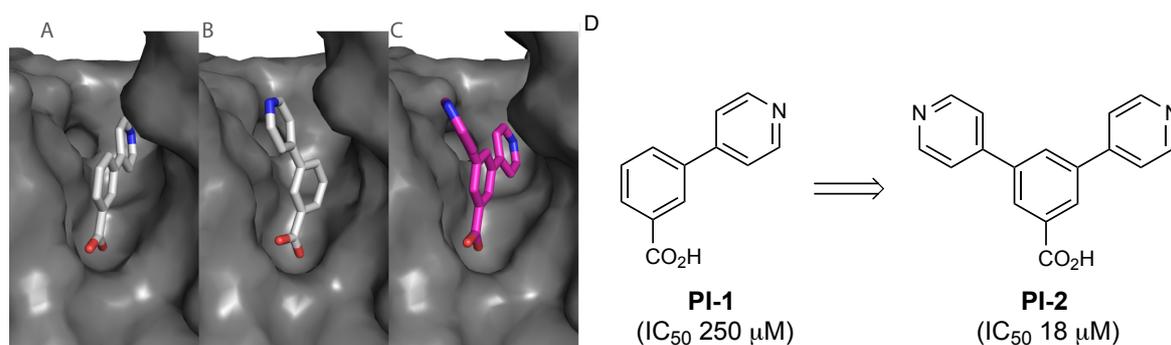
Figure 15. (A and B) Different conformations of fragment PI-1 (light grey) in complex with OXA-48 (dark grey surface), (C) the merged compound PI-2 (pink) in complex with OXA-48 (dark grey surface) and (D) a schematic view of the merging approach described in previous work.[15]

4.2 Research hypothesis of paper II

Based on the findings described in the previous section, the fragment hit **PI-1** was envisioned as the starting point for a library of mono-substituted analogues of fragment **PI-1** (Figure 16). The goal was to find good fragments with affinity for either the inn- or the out-pocket (R^1 or R^2 side) or both. The small size of the fragments makes them more flexible and efficient in exploring the binding site, which would allow us to identify better fragments for each pocket with a promising overlap. The best fragments that bind to each pocket would then be optimized further using a merging approach, which would lead to the synthesis of di-substituted fragments based on the suggestions from the overlay structures of the best identified fragments (Figure 16, **PI-2**).

Merged structures based on
Fragment **PI-2**

Fragment **PI-1**

Fragment **PI-1** analogues
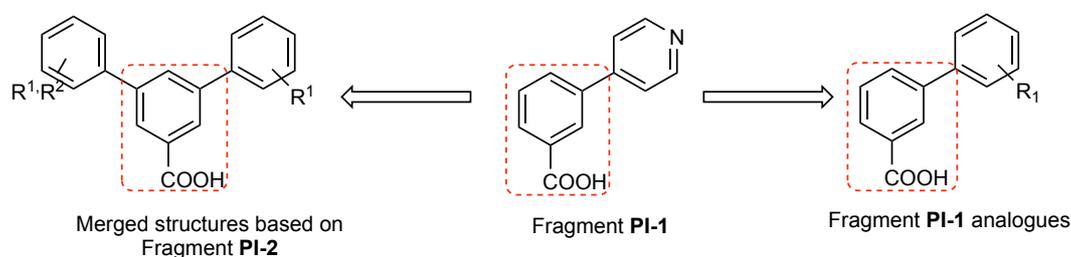
Figure 16. Fragment development approach.

4.3 Evaluation of 3-substituted benzoic acid derivatives

In paper I, co-authors were able to synthesize a fragment library of 49 candidates of 3-aryl benzoic acids and derivatives. The fragments were synthesized via SMC starting from 3-carboxyphenylboronic acid pinacol ester or 3-bromobenzoic acid, resulting in a wide range of 3-substitutedaryl benzoic acids. The coupling partners included heterocycles and substituted aryls with polar groups such as amides, phenols, sulphonic acid derivatives, esters and tetrazoles. The benzoic acid moiety was left unaltered due to the main interaction of the carboxylate group with the Arg250. Evaluation using a biochemical assay indicates that most of the tested fragments show a similar inhibition level with IC_{50} values ranging from 200 to 1000 μM and LE values ranging from 0.2 to 0.42 ($-\log_{10}IC_{50}$/heavy atom). All fragments share common interactions such as the ionic bond between the carboxylate group and the Arg250. Five fragments (Table 5, **PI-4a**, **PI-21a**, **PI-26a**, **PI-26b**, **PI-35**) show stronger inhibition with LE values of 0.38, 0.33, 0.3, 0.3, 0.42 μM, respectively.

Table 5. Selected best 6 fragments from the 49-fragment library.
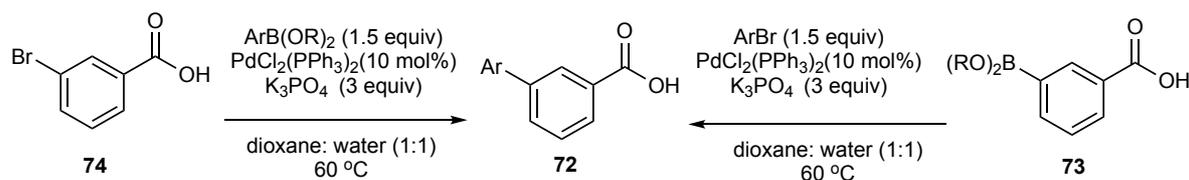
Entry	ID (Paper I)	Ar	IC$_{50}$ (μM)	K$_D$ (μM)	LE	Pocket
1	PI-**4a**		50	175	0.38	R^2
3	PI-**21a**		35	100	0.33	R^1
4	PI-**26a**		60	70	0.3	R^2
5	PI-**26b**		36	70	0.3	R^1
6	PI-**35**		35	159	0.42	both

Out of the 49 synthesized fragments, 33 fragments were co-crystallized with the enzyme OXA-48 and analyzed by X-ray crystallography in order to evaluate the binding poses of the fragments. All fragments formed an ionic bond between the carboxylate group and the Arg250. Most of the fragments were found to occupy the out-pocket (R^2) where they engaged in edge-to-face π-π stacking with Tyr211. Fragment **PI-4a** was shown to be the strongest among the R^2 binders with IC$_{50}$ of 50 μM and LE of 0.38 (Table 5, entry 1). Only fragments **PI-21a** and **PI-26b** were found to bind in the inn-pocket (R^1 side) with IC$_{50}$ of 35 and 36 μM, respectively, and LE of 0.33 and 0.30, respectively. Both fragments could form a hydrogen bond with the guanidine group of Arg214, which made them loose the π-π stacking with Tyr211 and direct them to be oriented towards R^1 binding site instead of the common R^2. Fragment **PI-35** occupied both binding sites so it was not classified as R^1 or R^2 binder. However, fragment **PI-35** was the best fragment among the tested fragments as it showed the best ligand efficiency with IC$_{50}$ of 35μM and LE of 0.42 (-log$_{10}$IC$_{50}$/heavy atom) (Table 5, entry 6).

In order to optimize the fragments into more potent fragments, a merging approach was initiated by overlaying two crystal structures of the most promising mono-substituted benzoic acids (Table 5). A structural overlay of fragments **PI-21a** and **PI-26b,** which were the only R^1 binders with different R^2 binders (PI-1, PI-28, PI-35) suggests some promising combination (Figure 17) leading to structures **PI-39**, **PI-40** and **PI-41**. Therefore, we initiated the synthesis of a small library including symmetrical and unsymmetrical 3,5-disubstituted benzoic acids including the suggested combination from the merging approach using SMC.
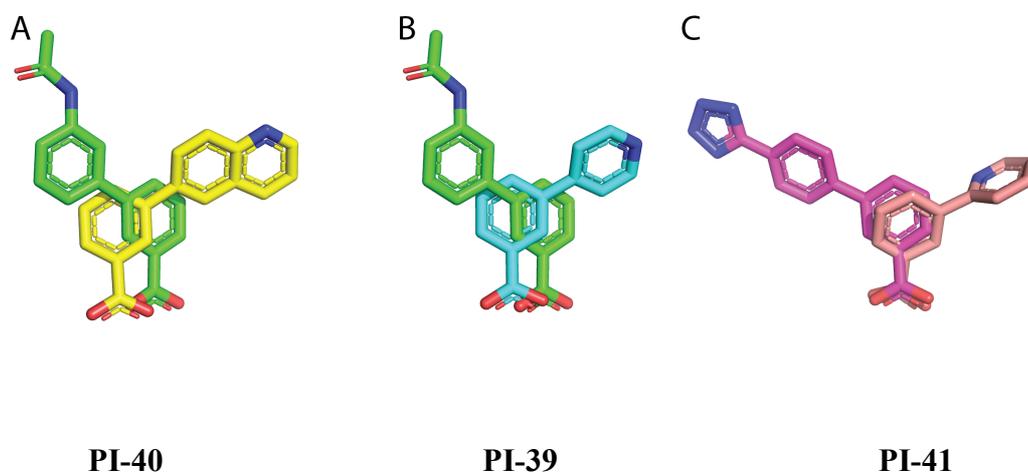
PI-40	**PI-39**	**PI-41**

*Figure 17. Overlay structure of the binding poses observed for PI-21a/28 (A), PI-21a/1 (B) and PI-26b/35 (C) leading to 3,5-disubstituted benzoic acids **PI-40**, **PI-39** and **PI-41**.*

4.4 Synthesis and evaluation of symmetrically and unsymmetrically 3,5-disubstituted benzoic acid derivatives

I was responsible for developing a method for the synthesis of unsymmetrically 3,5-disubstituted benzoic acid derivatives. I also contributed to the synthesis of the symmetrically 3,5-disubstituted benzoic acid derivatives.

Choosing 3,5-dibromobenzoic acid as a starting point allowed us to access symmetric 3,5-disubstituted benzoic acid. As 3,5-dibromobenzoic acid **75** contains two coupling positions (*m*-BrAr) of the same activity, so the reaction was not regioselective. Using an excess of the boronic acid and the base would allow the symmetrical substitution. The synthesis of three fragments (Scheme 30, Fragments **PI-36**, **PI-38**, **PI-37**) was achieved under the same reaction conditions as for mono-substituted fragments using Pd$_2$(dba)$_3$ (5mol%)/XPhos(5 mol%) or XPhos-Pd G2 (5 mol%) as catalysts, K$_3$PO$_4$ (5 equiv) and 2 equiv. of the corresponding boronic acid at 60 °C.

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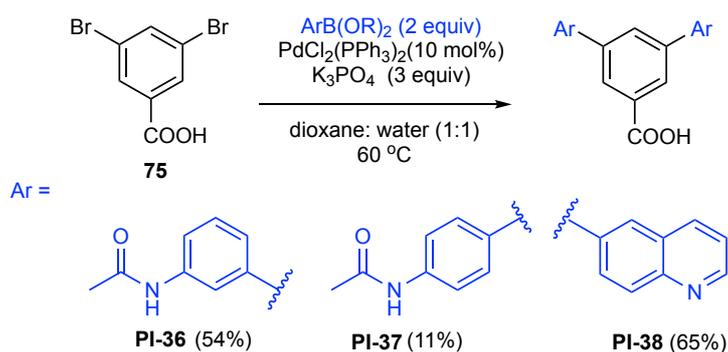
Scheme 30. Synthesis of symmetric 3,5-disubstituted benzoic acid derivatives.

For the synthesis of unsymmetrical 3,5-disubstituted benzoic acids, chemoselectivity was required in order to introduce different boronic acids to the 3- and the 5- position of the dihalobenzoic acid. The first approach was based on using 3,5-dibromobenzoic acid and sequentially adding the two different boronic acids and/or reducing the amount of the boronic acid under the previously established conditions (Scheme 31. **A**). This approach was not successful as it only yielded 15% of the desired product. For example, fragment **PI-39** was obtained from the 3,5-dibromobenzoic acid in a very low yield (11%). In addition, a mixture of mono-substituted 5-bromobenzoic acid, symmetrical and unsymmetrical 3,5-disubstituted benzoic acids was always obtained. Moreover, purification of the reaction mixture was found to be difficult and required several HPLC purifications.
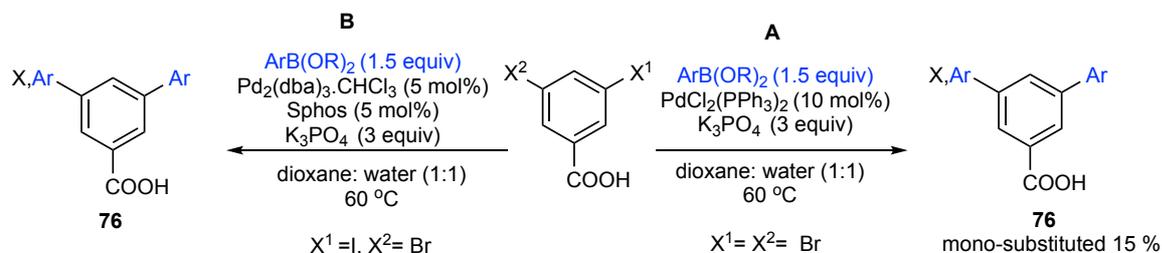
Scheme 31. Initial attempts of the preparation of unsymmetrical 3,5-disubstituted benzoic acids.

To introduce a higher degree of selectivity, we changed the starting material to 3-bromo-5-iodobenzoic acid (Scheme 31. **B**). As mentioned before (Chapter 3.1), Ar-I is more active than Ar-Br in SMC reactions, which could allow a faster reaction on C-I than C-Br and limit the formation of symmetrical compounds. We initiated a chemoselective reaction of 3-iodo-5-bromobenzoic acid with 6-quinolineboronic acid pinacol ester to form a mono-substituted product using $Pd_2(dba)_3$. $CHCl_3$ (5 mol%) and SPhos (5 mol%) in dioxane/water (1:1) at 60 °C. However, a second coupling on the bromide was always observed.

We then started reaction optimization to find conditions that would suppress the second coupling in favor of obtaining only the mono-substituted product after the first coupling. The model reaction was carried out between 3-bromo-5-iodobenzoic acid with 6-quinolineboronic acid pinacol ester. The reaction optimization included different catalysts (e.g. RuPhos-Pd G3, Sphos/Pd$_2$(dba)$_3$, Xphos/Pd$_2$(dba)$_3$, SPhos-Pd G3, XPhos-Pd G2, Pd$_2$(dppf)Cl$_2$), solvents (toluene/water, anhydrous THF, dioxane/water, *tert*-butanol), reaction temperature (40–80 °C) and time (10–48 h) (Table 6). The crude reaction mixtures were analyzed and the ratios between the mono- and disubstituted products as well as unreacted starting material were determined by mass spectrometry (MS).

Table 6. Reaction optimization for the coupling of 3-bromo-5iodobenzoic acid.
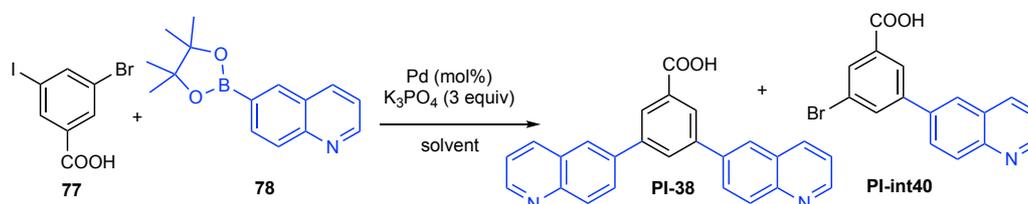
Entry	Catalyst (Mol%)	T (°C) /T (H)	Solvent	Ratio (PI-int40:38:80)	Isol. yield Int40 (%)
1	RuPhos-Pd G3 (10)	60/24	Dioxane/water (1:1)	8: 10: 10	nd
2	RuPhos-Pd G3 (5)	60/24	Dioxane/water (1:1)	10: 6: 0.3	nd
3	XantPhos-Pd G3 (5)	60/48	Dioxane/water (1:1)	10: 1: 0	nd
4	XantPhos-Pd G3 (5)	40/24	Dioxane/water (1:1)	10: 1: 3	70[a]
5	Pd$_2$(dppf)Cl$_2$	60/24	Dioxane/water (1:1)	10: 1: 3	80[a]
6	Xphos-Pd G2 (1)	60/24	Dioxane/water (1:1)	10: 7: 1	nd
7	SPhos-Pd G3 (5)	60/24	Dioxane/water (1:1)	10: 2: 0	40
8	Pd$_2$(dba)$_3$.CHCl$_3$/SPhos 1:1 (10)	60/24	Dioxane/water (1:1)	10: 1: 0.4	55
9	Pd$_2$(dba)$_3$.CHCl$_3$/SPhos 1:1 (10)	40/24	n-BuOH	10: 4: 4	nd
10	Pd$_2$(dba)$_3$.CHCl$_3$/SPhos 1:1 (10)	80/24	Dioxane/water (1:1)	10: 1: 0.3	55
11	Pd$_2$(dba)$_3$.CHCl$_3$/SPhos 1:1 (10)	40/20	Dioxane/water (1:1)	10: 1: 3	65
12	Pd$_2$(dba)$_3$.CHCl$_3$/SPhos 1:1 (10)	60/10	Dioxane/water (1:1)	5: 4: 10	nd
14	Pd$_2$(dba)$_3$.CHCl$_3$/SPhos 1:1 (10)	60/48	Dioxane/water (1:1)	10: 4: 1	nd
15	Pd$_2$(dba)$_3$.CHCl$_3$/SPhos 1:1 (10)	60/24	Dioxane/water (1:1)	10: 0.7: 0	40

Among the tested catalysts, XantPhos-Pd G3, $Pd_2(dppf)Cl_2$ and SPhos/$Pd_2(dba)_3$ showed the best selectivity for the aryl iodide when the reaction was performed with K_3PO_4 as the base in dioxane/water at 60 °C for 24 h (Table 6, entries 3, 8, 15). The mono-substituted intermediate **PI-int40** was obtained as the main product using SPhos/$Pd_2(dba)_3$, only small amounts of the disubstituted by-product (8–10%) were observed. Careful purification to remove any traces of the disubstituted compound provided **PI-int40** in a moderate yield (45%). The mono-substituted product was then subjected to a second coupling with (3-acetamidophenyl)boronic acid using XPhos-Pd G2 (5 mol%) as a catalyst to provide the unsymmetrical 3,5-disubstituted benzoic acid (Table 7, **PI-40**) in a high yield (90%).

The inhibitory activity of the disubstituted compounds against OXA-48 was evaluated and compounds **PI-36**, **PI-37** and **PI-40** (IC_{50} (µM)/LE: 2.9/ 0.27, 48/0.21 and 2.9/0.27) showed better inhibition activity in comparison to their corresponding mono-substituted fragments **PI-21a**, **PI-21b** and **PI-28** (IC_{50} (µM)/LE: 35/0.33, 450/0.26, 240/0.3). The best two fragments were the symmetrical 3,5-disubstituted benzoic acid PI-**36** and the unsymmetrical 3,5-disubstituted benzoic acid **PI-40** with IC_{50} values of 2.9 µM and LE of 0.27 (Table 7). Crystal structures of fragments **PI-36** and **PI-40** were obtained. They emphasized that the interactions exhibited by the individual fragments were also preserved in the merged structure.

Table 7. Inhibitory activity of 3,5-disubstituted benzoic acid analogues against OXA-48 (IC_{50}, K_d, LE).
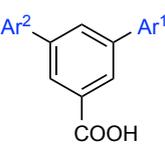
ID (Paper I)	Ar^1	Ar^2	IC_{50} (µM)	K_d (µM)	LE
PI-36			**2.9**	**20**	**0.27**
PI-37			48	70	0.21
PI-38			110	70	0.19
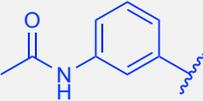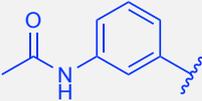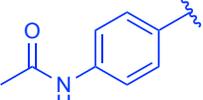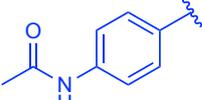
54
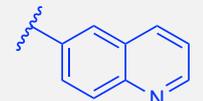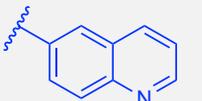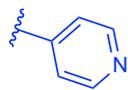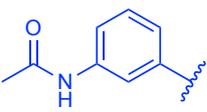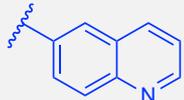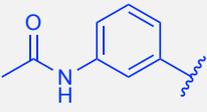
PI-39			100	70	0.22
PI-40			**2.9**	**49**	**0.27**

4.5 Additional results not included in Paper I

Attempts to synthesis the third fragment suggested from the merging approach compound **PI-41** (Figure 17). The strategy was based on using 3-(pyridin-2-yl)benzoic acid (Scheme 32, **PI-35**) and 4'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-3-carboxylic acid (Scheme 32, **PI-26b**). In order to synthesize 3-bromo-5-(pyridin-2-yl)benzoic acid (**PI-41**), two synthetic strategies were considered. The first strategy was SMC of 3-bromo-5-iodobenzoic acid and pyridin-2-ylboronic acid followed by a second SMC with (4-cyanophenyl)boronic acid. The resulting coupled product would then be submitted to a tetrazole formation step (Scheme 33, S1). The other strategy was to conduct the second coupling and install the tetrazole group first then submit the product to SMC with 2-pyridinylboronic acid (Scheme 33, S2).
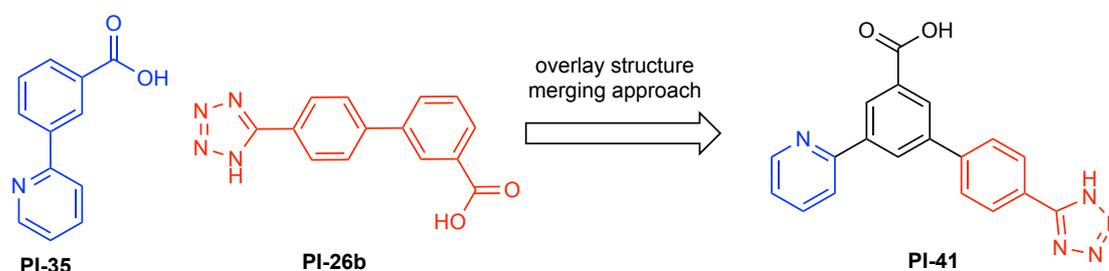
Scheme 32. Promising fragment based on overlay structures from paper I.

In both synthetic strategies coupling with 2-pyridinylboronic acid or ester was not accessible. This might be due to the low reactivity of pyridine boronic acid. It is known that pyridine boronic acids tend to have a slow transmetalation rate due to the electron-deficiency of the pyridine ring. Thus, they require higher temperatures and longer reaction times.[198]

The SMC with (4-cyanophenyl)boronic acid resulted in a mixture of mono- and di-substituted benzoic acids in 60% and 25% yield, respectively. The compounds were submitted for the tetrazole formation and the symmetrical 3,5-di-(4-1*H*-tetrazolyl)phenyl benzoic acid was tested against OXA-48. These compounds were tested in a cell-based assay showing that

the compounds killed the bacteria at 250 and 500 µM concentrations. Therefore, the compounds were not further evaluated as inhibitors.
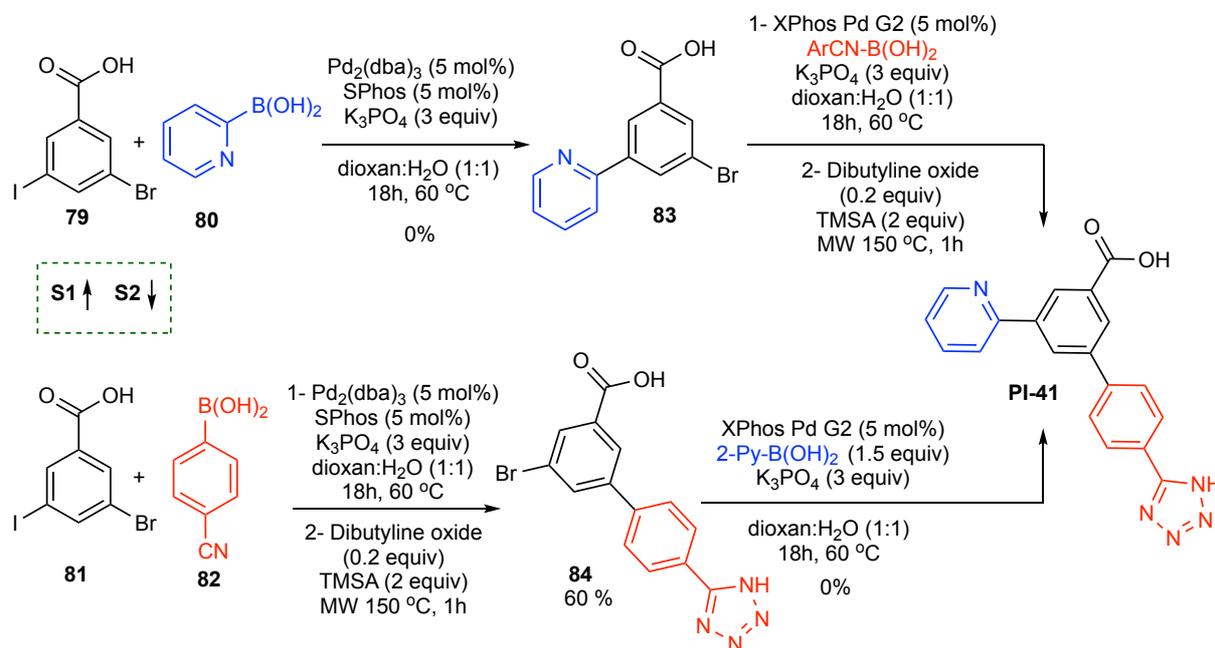
*Scheme 33. Two synthetic strategies to synthesize fragment **PI-41**.*

4.6 Conclusion from paper I

In summary, the Suzuki-Miyaura cross-coupling was a successful approach to access a fragment library of 49 candidates of 3-substituted boronic acids. The crystal structures of 33 fragments of the fragment library gave a closer insight into the possible interactions in the binding site R^2 and the preferred binding site R^1. The most efficient binders were selected to design a small fragment library based on the merging approach. Five fragments of both symmetrical and unsymmetrical 3,5-disubstituted benzoic acids were synthesized and tested for their inhibition activity. Selective Suzuki-Miyaura cross-coupling was applied to obtain the mono-substituted intermediate **PI-int40** in a moderate yield of 45%. The best inhibitors with the lowest IC_{50} values (2.9 µM) are **PI-36** and **PI-40**.

5. Development of carbonylative C-C couplings for the synthesis of VIM-2 inhibiting fragments (Paper II)

5.1 Paper II background

The group of our collaborator Prof. Leiros has previously identified novel fragments inhibiting the metallo-β-lactamase VIM-2.[13] The study involved an orthogonal screening approach based on a surface plasmon resonance (SPR) assay combined with an enzyme inhibition assay of a library of 490 fragments. The identified fragments were submitted for characterization by determining the K_d, LE, and IC_{50} values. The IC_{50} ranged from 14 to 1500 μM and the LE ranged from 0.48-0.23 kcal/mol per heavy atom.

Fragment **1** (IC_{50}/LE= 14/0.38) shows two important interactions with the residues in the binding site (Figure 18). The carboxyl group displayed two types of interactions, it interacts with Zn2 in the binding site and also forms hydrogen bonds with two water molecules (W1 and W2). The other carbonyl group participated in two interactions, weak chelation with Zn1 and hydrogen bond with Asn233. In addition, the phenyl ring on both sides shows parallel π−π stacking with His263 and a T-shaped π−π stacking with Tyr67. The side chain of Arg228 showed high mobility with different conformations partly forming a hydrogen bond with the carboxyl group in the fragment.
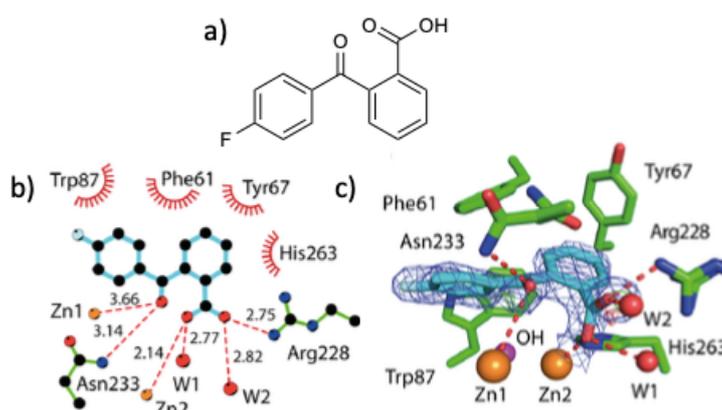
*Figure 18. X-ray structure of fragment **1** bound to the active site of VIM-2. Hydrogen bonds are shown as red dashed lines, and hydrophobic interactions are indicated by a red arc. Adapted from Tony et al. (2015).[13]*

Additional hydrophobic interaction of the fluorine substituted phenyl group with Phe61 and Trp87 stabilize the fragment binding. Furthermore, the carbonyl group favors the coplanar orientation of the two phenyl groups that enables the hydrophobic interactions with His263, Tyr67, Phe61, and Trp87. Based on the structural information in hand we used fragment **1** as the starting point for paper II.

5.2 Initial work and research focus of paper II

According to the previously reported observation and the information from the crystal structures, we used fragment **1** as a starting point for a fragment library. The 2-benzoylbenzoic acid system (Figure 19, B), where both the carbonyl group and the carboxylic acid are adjacent to each other is necessary for the binding. Phenyl rings could be changed to other heterocycles or substituted phenyl rings in order to keep the possibility of the π−π stacking.
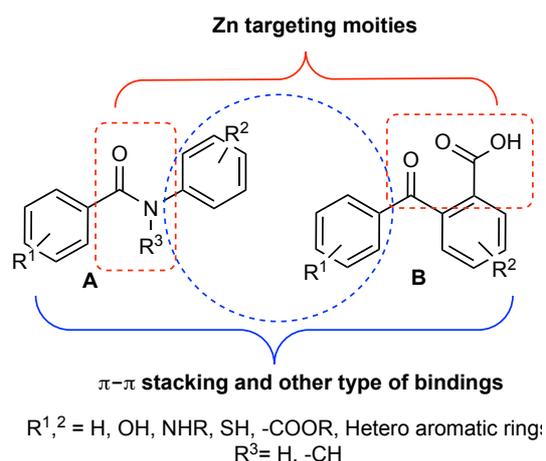
*Figure 19. Structure model based on fragment **1** (A) & (B). Red; moieties targeting Zn ions. Blue; substituted aromatic rings for π−π stacking and different ionic and hydrophilic interactions.*

In order to synthesize a library of these fragments, several synthetic routes were evaluated to develop a general strategy that would provide a wide range of functionalized 2-aroylbenzoic acids without increasing the number of reaction steps. Our initial attempts to synthesize 2-aroylbenzoic acids and derivatives were based on the most common methods such as the reaction of phthalic anhydride with organometallic reagents[199] (Scheme 34, B) or Friedel-Craft acylation with aromatic nucleophiles (Scheme 34, C).[154] Although we could obtain a small library of fragments (Chapter 5.5, Table 8, Fragment 1-7) using these methods, we found that they have limitations and are not suitable for obtaining a larger library of the desired

compounds. Many functional groups were not tolerated in these reactions due to the harsh conditions and the use of excess Lewis acids.

Simpler systems such as biaryl ketones have been synthesized by transition metal-catalyzed carbonylative cross-couplings of organometallic reagents and aryl electrophiles[174], or by the non-decarbonylative coupling of acyl electrophiles.[200–202]Although there are a number of reports describing the synthesis of biaryl ketones in general, only a few methods have proven to be applicable for the formation of 2-aroyl benzoic acid derivatives (Scheme 34. D-F).
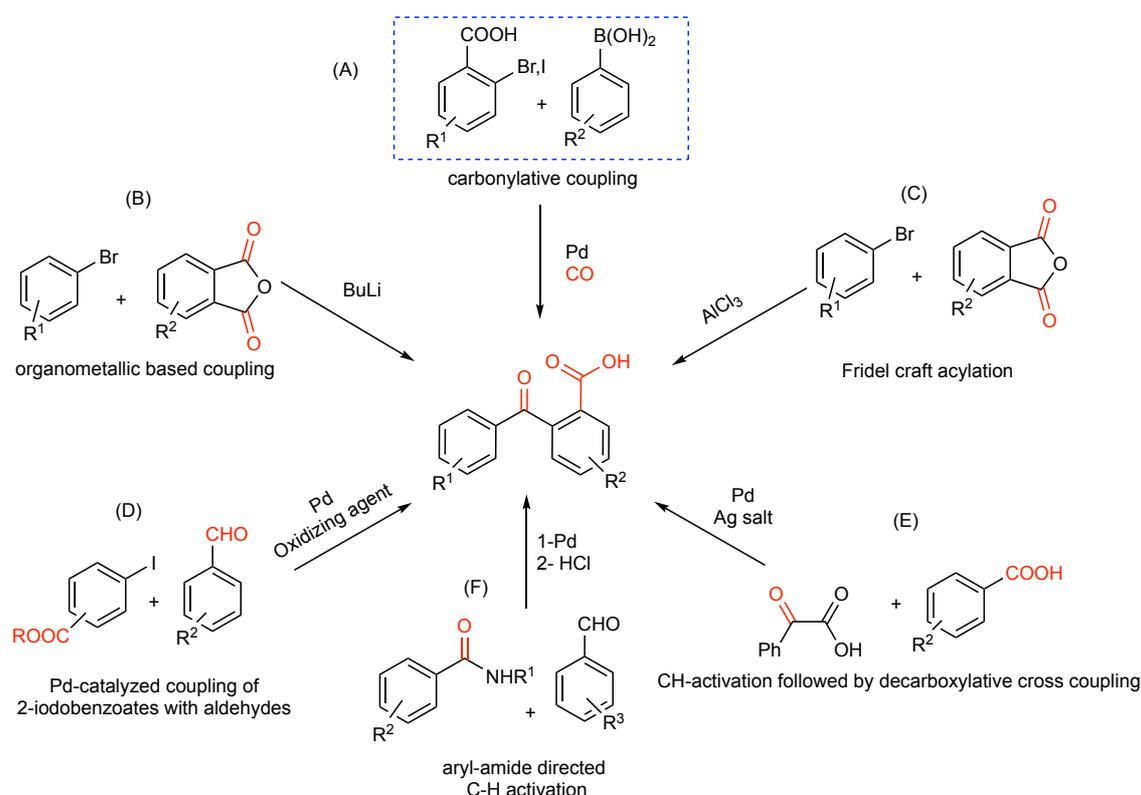
Scheme 34. Possible approaches towards 2-aroyl benzoic acid derivatives.

For instance, Pd-catalyzed *ortho*-C–H activation of benzoic acids followed by decarboxylative coupling with α-oxocarboxylic acids (Scheme 34, E) showed several limitations regarding reaction conditions and substrate scope.[156] This reaction was performed under harsh conditions in DME for 24-48h at 150 °C. In addition, the reaction might provide poor regioselectivity of the desired ortho position to the carboxylic group as there are several competing reaction sites. Although the reaction provided the 2-aroyl benzoic acid derivatives, it was not compatible with a wide range of functional groups, especially electron-withdrawing functional groups such as nitro groups, nitrile groups, amides, and aldehydes. The scope did not include highly substituted substrates and the yield range was from low to moderate (40-80%). In addition, it excluded

heterocyclic substrates as the coupling partner on both the benzoic acid side and/or the α-oxocarboxylic acids.[156]

Pd-catalyzed *ortho*-C–H activation of aryl amides followed by coupling with aryl aldehydes (Scheme 34, F) is another possibility to access 2-aroyl benzoic acid derivatives.[155] The reaction includes directed C–H activation, ortho-acylation of the aryl amide, then ring closure of the five-membered hydroxyl isoindolone. The five-member ring is then opened to give the biaryl imino carboxylic acid. The imine is then subjected to concentrated HCl in order to hydrolyze it to the keto form and eventually obtain the biaryl imino/keto carboxylic acids.[155] Regarding the substrate scope, the reaction shares the same limitations with the Pd-CH activation and decarboxylative coupling.

Another possible approach is the Pd-catalyzed coupling of 2-iodobenzoates with aldehydes (Scheme 34, D). The advantages of this method are that it does not require any directing group assistance or in situ enamine formation and it prevents the use of CO.[203] However, it showed poor tolerance of substituted benzaldehydes with electron-withdrawing groups such as nitro or nitrile groups. In addition, the yield ranged from low to moderate throughout the whole substrate scope, while it was unsuccessful with amides and heterocyclic aldehydes.[203]

5.3 Discussion of the results of Paper II

Based on the analysis above, we decided to develop an alternative route to functionalized 2-aroylbenzoic acids using palladium-catalysed carbonylative C-C couplings using CO as the carbonylating agent as key step. In particular we hoped to develop an approach that gave access to functionalized 2-aroyl benzoic acid derivatives where R^2 = OH, NHR or other functionalisable handles.

Based on a literature research, carbonylative C-C couplings the reaction showed widespread application in the synthesis of biaryl ketones. The vast majority of the studies reported carbonylative Suzuki-Miyaura couplings using aryl iodides with boronic acids, while few of them addressed the use of less reactive aryl bromides.[129,153,152,204] Only a few reports discussed the challenging ortho-substituted systems, especially the electron-deficient substituted substrates on both coupling partners, the aryl bromide and the boronic acid.[204,129] Despite the hazard related to the toxic CO gas, we could use it in a safe fashion to avoid the direct handling of the toxic gas by generating it *in situ* using COgen as the CO source.[146–148]

We addressed two possible routes towards 2-aroylbenzoate esters as illustrated in Scheme 35. The aim was to identify a route with a high degree of functional group compatibility that could be used to establish a VIM-2 fragment library of analogues of fragment **1**.
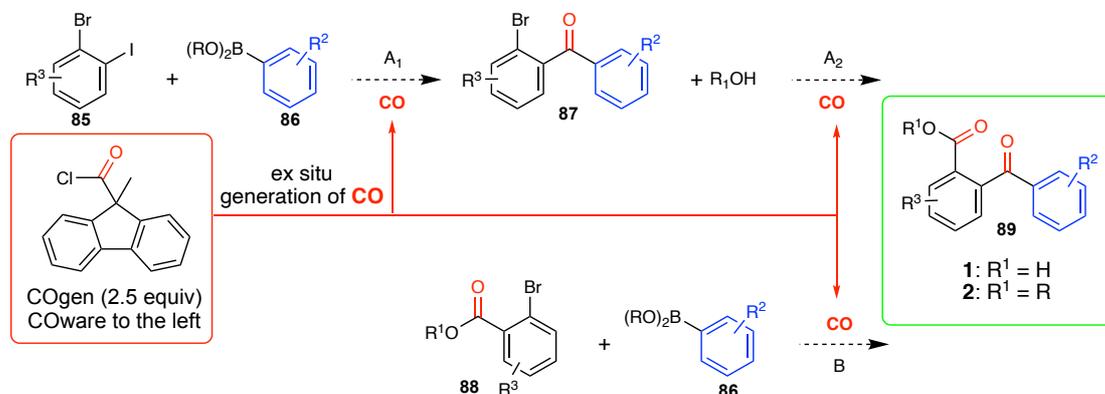
Scheme 35. Two possible routes towards 2-aroylbenzoate esters.

Route A

The first route (Scheme 35, route **A**) comprises a carbonylative Suzuki-Miyaura coupling of 2-bromoiodobenzene with phenyl/hetero-boronic acids via carbonylative Suzuki-Miyaura, followed by Pd catalyzed hydroxy- or alkoxycarbonylations of the 2-bromo functionalized biaryl ketones to obtain the 2-aroylbenzoic acids derivatives. The initial attempts of step 1 in route **A** indicated the high impact of the competing non-carbonylative SMC reaction on the results. The product of the competing direct coupling (bi-aryl) was always observed in a considerable amount together with the desired carbonylated product (bi-arylketone). The maximum obtained yield under the optimized conditions was 60 % of the carbonylated product. The competing SMC reaction is a common challenge concerning carbonylative SMC. It is known that in some cases the increase of the CO pressure, temperature and the catalyst loading could enhance the reaction in favor of the desired carbonylative SMC.[128,130-132,133] However, in our hands increasing the temperature and catalyst loading decreased the yield and favored the direct coupling. High CO pressure would require special equipment and is associated with a risk of faster formation of the inactive palladium black when compared to reactions closer to atmospheric CO pressure.[134]

Thus, we focused on finding conditions that enhanced the carbonylative SMC. First, we thought that making the CO available for the reaction before the transmetalation reagent may provide higher CO pressure before the reaction starts. Thus, the pre-generation of CO was

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attempted as it could help to enhance the rate of the CO insertion. However, having the boronic acid readily available for the reaction would not allow the CO insertion to occur faster than the transmetalation and the reductive elimination steps. As already known, the transmetalation and the reductive elimination steps are faster than the CO insertion.[133] Accordingly, slowing down the transmetalating agent from reaching the metal center might allow the CO insertion step to occur first. Introducing the boronic acid slowly into the reaction mixture after the complete release of the CO was an attractive approach to the test. Slow addition of the boronic acids was envisioned to enhance the reaction rate in favor of the desired carbonylative SMC. By adding the boronic acid slowly over 2-3h, the yield increased from 60% to 80%. This improvement encouraged us to proceed with the reaction scope, while applying the slow addition. The reaction was compatible with both electron-rich and electron-deficient aryl boronic acids giving moderate to high yields. In addition, electron-rich heterocycles and *ortho*-substituted boronic acids were also tolerated under the reaction conditions. However, some heterocyclic boronic acids (e.g. 2-furanyl boronic acid), hydroxy and N-acyl substituted aryl boronic acids were not tolerated and favored direct coupling instead of the carbonylative alternative.

To emphasize the effect of the slow addition, selected substrates were tested applying slow addition and normal addition. The yield of the carbonylative coupling products were higher, which concludes slow addition can impact the reaction result in favor of the carbonylative coupling. 13 examples of substituted 2-bromobiaryl ketones were synthesized in low to high yields (Scheme 36).
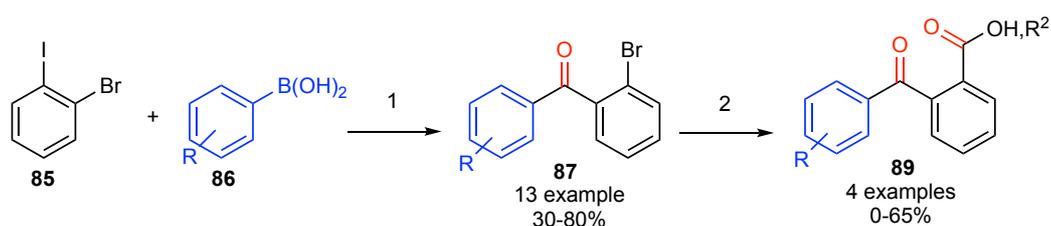
Scheme 36. Route **A**, 1) PdCl$_2$ (1 mol%), C$_2$CO$_3$ (3 equiv), COgen (2 equiv) in anisole. 2) PdCl$_2$ (1 mol%), Xantphos (2 mol%), C$_2$CO$_3$ (3 equiv), COgen (2 equiv) in anisole: n-BuOH (2:1).

The second step of route A (Scheme 36, 2) was hydroxy- or alkoxy-carbonylation of the obtained 2-bromo functionalized biaryl ketones. Our initial attempts to directly obtain carboxylic acids by hydroxycarbonylation using SilaCOgen were unsuccessful. This might be due to steric hindrance at the *ortho* position of the ketone. However, we intended to try alkoxycarbonylation on 2-bromo-4-methoxybenzophenones as a test substrate. We tested different reaction conditions including a range of Pd catalysts and ligands, nucleophiles, bases,

and solvents. Few reaction conditions gave access to the desired alkyl 2-(4-methoxybenzoyl)benzoate. The best result was obtained with PdCl$_2$ (1 mol%) and Xantphos (2 mol%), *n*-BuOH, and K$_2$CO$_3$ in anisole (Scheme 36, 2). The desired butyl 2-(4-methoxybenzoyl)benzoate was obtained with a 65% yield. Applying these conditions to a number of 2-bromobenzophenone derivatives from step 1, we found that the reaction is substrate-dependent. Thus, we concluded that this approach is limited and not suitable for synthesizing a larger library of 2-aroyl benzoic acid derivatives.

One-pot approach to synthesize 2-aroylbenzoic ester

The two steps of route **A** seemed to be feasible in one pot. The reagents required for the alkoxycarbonylation step such as the ligand and the nucleophile can be added later after 18 hours from the first step. In this case no excess of catalyst or COgen is required (Scheme 37). Unfortunately, our initial attempts of a one-pot synthesis of 2-aroylbenzoic ester were not successful. Introducing extra fresh catalyst to the second step did not prove to be beneficial. We obtained several products after the second step including the biaryl ketone **88**, the biphenyl coupled product **93** as a byproduct from the first step, the desired biphenyl keto ester **90** and the biaryl ketone without the bromide **94** (Scheme 37). Palladium black formation was always observed in the first step, which could be a reason that hindered the second step and decreased the activity of the freshly added PdCl$_2$. Despite the addressed limitations of the one-pot approach, we could still observe some of the biaryl keto esters, which indicated that the reaction could be further developed to obtain the desired activity. We were therefore interested to study the reaction from another direction to learn about the sequence influence on the reaction reactivity, so the second route was evaluated.
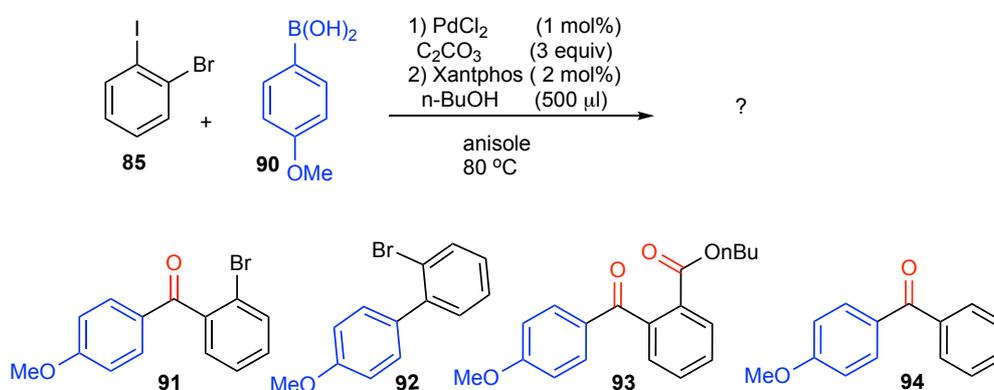
Scheme 37.One-pot synthesis of 2-aroyl benzoic ester.

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Route B

In route B, we started from commercially available 2-bromo substituted benzoate esters as starting material for the carbonylative SMC. 2-Bromobenzoate was submitted to a range of experimental conditions including different palladium and Ni sources and ligands such as (Pd(acac)$_2$ or Pd(OAc)$_2$/CataCXium A or A·HI, Pd(OAc)$_2$ or PdCl$_2$/Xantphos, Ni(COD)/dcype) and others to find the best conditions for the reaction (Paper II, Table ESI-6). Our observations mainly concluded the dominance of the undesired non-carbonylative coupling pathway. Only the Pd(IPr)-based catalytic systems showed promising results as it could accomplish the carbonylative SMC. In the carbonylative coupling of methyl 2-bromobenzoate with 4-methoxyboronic acid, PEPPSI-IPr (3 mol%) as catalyst precursor, Cs$_2$CO$_3$ as a base in chlorobenzene or anisole as solvent proved to be the best system, providing the desired product in 63% yield (paper II,S 4, 2aa). In order to enhance the yield, we tested the slow addition of the boronic acid to the reaction mixture over 2-3h. This approach showed great influence on the SMC in route **A**, so it was expected to give relatively similar results in route **B**. The yield was further increased to 80% by slow addition of the boronic acid. The reaction showed very good compatibility with different functional groups on both coupling partners including electron-withdrawing, electron-donating, and heterocyclic boronic acids (Scheme 38). Boronic acids with electron-donating groups such as -OMe, -SMe, and heterocyclic boronic acids such as thiophene and benzothiophene gave moderate to high yields. Boronic acids with electron-withdrawing groups such as -CN, -F, -COOMe gave low to moderate yields. Sterically hindered *ortho*-substituted boronic acids were also compatible under the reaction conditions and gave acceptable yields. Aryl bromides with both electron-withdrawing and electron-donating groups were tolerated and gave moderate yields (Paper II, Scheme 4, 5).
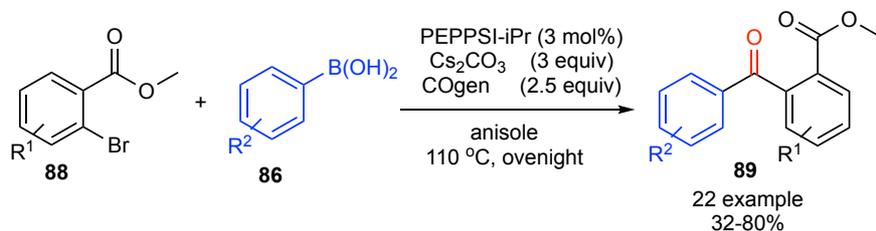
Scheme 38. Route B, Suzuki–Miyaura coupling of methyl 2-bromobenzoate.

Scope limitations and general findings

The paper aimed to establish a general method to synthesize a wide range of 2-aroylbenzoic acid derivatives to test against VIM-2. Initially, we designed the fragments to contain functional

groups on both aryl rings (Scheme 38, R^1 and R^2) with a potential binding ability to the VIM-2 binding site. Functional groups such as -OH, -NH$_2$, -CONHR, NO$_2$ could act as hydrogen bond donors and/or acceptors in the binding site. In addition, the fragments were also envisioned to contain functional groups that allow for late-stage functionalization of both aryl rings. Unfortunately, substituents such as hydroxy, amines, and amides could not be introduced with the developed method. Moreover, the solubility of the reagents including boronic acids or acid derivatives in the reaction solvent can impact the success of the reaction. As we developed the slow addition method, we introduced the boronic acid/anisole solution to the reaction mixture over 2-3h. Boronic acids with a low solubility in anisole were challenging substrates and thus were incompatible under reaction conditions. However, the strategy has good potential for further optimization. Therefore, an extended study to find a better system to overcome the scope limitations and allow for a wider range of VIM-2 inhibitors is an attractive research point for the future.

5.4 Conclusion from paper II

In conclusion, two routes for accessing 2-aroylbenzoate esters have been evaluated. This evaluation suggests that the second route (B), which employed a carbonylative Suzuki-Miyaura coupling of 2-bromobenzoate esters, could be a better strategy than route (A). Although the suggested slow addition of the boronic acids is dependent on the solubility of them in the reaction solvent, it is considered to be a finding of general value as it allowed us to enhance the reaction reactivity to favor carbonylative over non-carbonylative processes in Suzuki-Miyaura couplings. A range of diversely substituted 2-aroylbenzoate esters that share the same structure core as our targeted structure model (Figure 18, Fragment **1**) was prepared and sent for biological testing at Nordstruct. The fragments were lacking some promising functional groups such as OH, NO$_2$, NH$_2$, etc. These types of substituents on both aryl rings could enhance the binding of the fragments with the active site via hydrogen bonding, ionic or covalent interactions. Due to the lacking of such functional groups, further optimization to find better reaction conditions including the solvent and the catalytic system is suggested in paper III.

5.5 Additional results not included in Paper II

The initial trials of preparing 2-aroylbenzoic acids by reacting phthalic anhydride with organometallic reagents or by Friedel-Craft acylation of aromatic nucleophiles resulted in a small library of fragments (Table 8, Fragments **F1a-F7**). The fragments were evaluated against

VIM-2 and IC_{50} values were obtained. None of these fragments showed improved inhibition activity when compared to fragment **1** (IC_{50}/LE= 14/0.38).

Fragments obtained via carbonylative Suzuki-Miyaura coupling were also tested against VIM-2 and IC_{50} values were obtained (Table 8, Fragments **F8-F20**). All the tested fragments showed inhibition in the μM range. Two fragments (Table 8, Fragments **F9** and **F13**) showed inhibition activity comparable to fragment **1** with LE of 9.96 and 10.77, respectively. Fragment **F20** showed the best ligand efficiency with LE of 0.43. The obtained results can be used as a starting point for further optimization towards better hits against VIM-2.

Table 8. Biological data of tested fragments against VIM-2.

Fragment no.	Structure	IC_{50} (μM)	LE
F1-a		12.5	0.38
F2		97.6	0.23
F3		10.7	0.33
F4		8	0.35
F5		>1 mM	
F6		Preciptated undetected	-
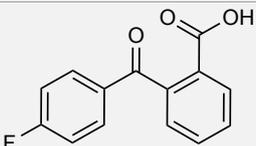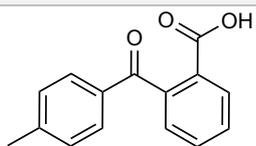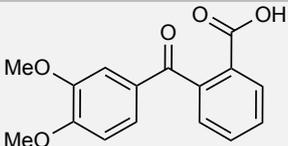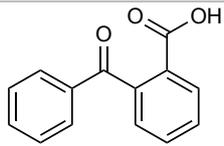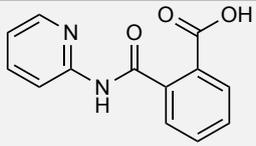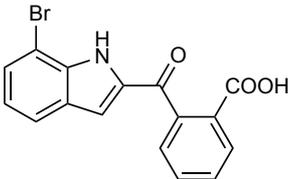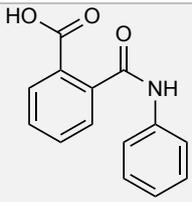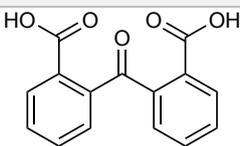
F7		1000	0.23
F8		160.4	0.27
F9		9.964	0.39
F10		111.7	0.22
F11		58.69	0.31
F12		32.59	0.31
F13		10.77	0.37
F14		117.4	0.24
F15		111.7	0.24
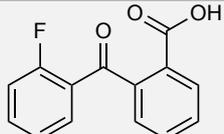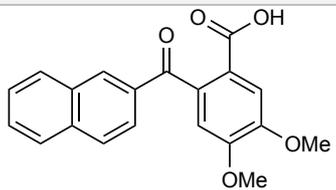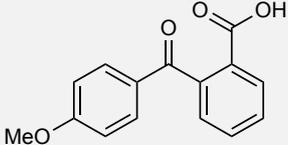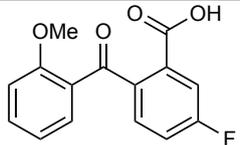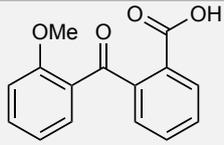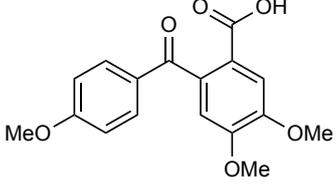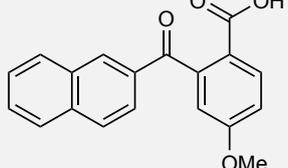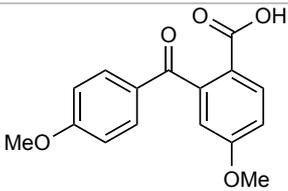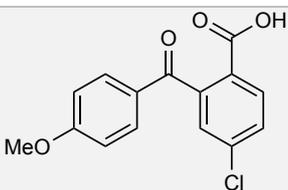
F16		176.9	0.25
F17		221.6	0.26
F18		298.9	0.25
F19		564	0.23
F20		2.852	0.43
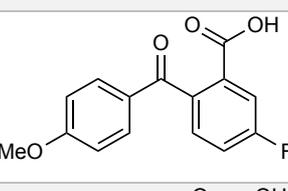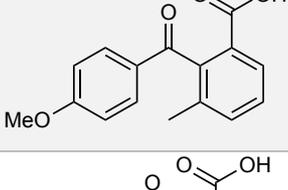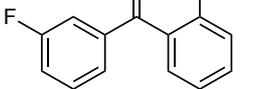
6. Development of carbonylative C-C, C-N, C-O couplings using renewable solvents

6.1 Paper III background

As the method developed in paper II still showed limitations with regard to substituents such as -OH, -NH$_2$, -NHR and -NO$_2$, we continued our efforts to improve the carbonylative SMC of aryl bromides with aryl boronic acids. In paper III, an alternative method for carbonylative SMC in green solvents is described.

Renewable solvents have been described to be suitable medium for several chemical transformations including classical condensation reactions and transition-metal (TM)-catalyzed cross-couplings.[211-213] including biphasic reactions such as metal catalyzed carboxylation reactions using CO$_2$.[190] However, carbonylative reactions have not been studied in renewable solvents. In addition, we extended the study to investigate the efficiency of green solvents in alkoxycarbonylation that showed carbonylative couplings of aryl bromides with amines and alcohols, both reactions that were investigated during the work leading to paper II. For the latter two, we focused on catalytic systems that have already proven to be suitable systems for Pd-catalyzed carbonylation reactions.[153,176,171]

6.2 Paper III results and discussion

Solvent properties

In general, liquids that are available form biomass and CO$_2$ derived chemicals have a great potential to replace non-renewable solvents that are frequently utilized in organic synthesis.[188,205,206,187,181] In this study, we examined both known renewable solvents and some recently introduced biomass-derived solvents[190] as shown in Figure 20.
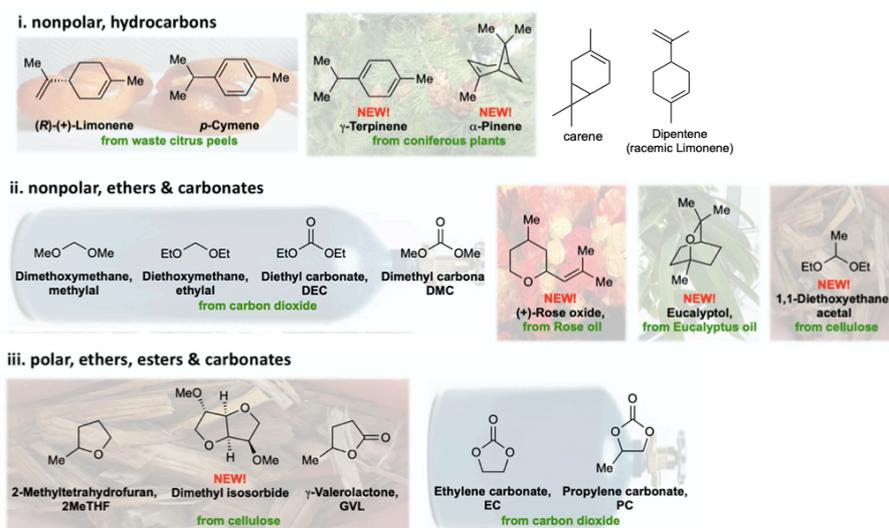
Figure 20. Structure of the renewable solvent used in paper III.

The polarity of the solvents was estimated based on their dielectric constant. Solvents with dielectric constant higher than 5 are considered to be polar, while solvents with dielectric constant below 5 were considered as non-polar (Table 9). Thus, the solvents could roughly be grouped into non-polar hydrocarbons (α-pinene, γ-terpinene, limonene, *p*-cymene), non-polar ethers (diethoxymethane (methylal), dimethoxymethane (ethylal), 1,1-diethoxyethane (acetal), rose oxide, eucalyptol) and carbonates (dimethylcarbonate (DMC), diethylcarbonate (DEC)), and polar ethers (dimethyl isosorbide, 2-methyltetrahydrofuran (2MeTHF)) comparable to e.g. THF and highly polar esters and carbonates (γ-valerolactone (GVL), propylenecarbonate (PC), ethylenecarbonate (EC)) comparable to e.g. DMF.

Table 9. Solvent properties and overview of the solvent performance in the three tested carbonylative reactions.

Solvent	MW (g/mol)	Bp (°C)	Dielectric constant[1]	Compound class	C-C yield (%)	C-N yield (%)	C-O yield (%)
non-polar							
α-Pinene	136.24	156	2.18	hydrocarbon	50	97	93
γ-Terpinene	136.24	174	2.27[207]	hydrocarbon	50	94	93
(+)-Limonene	136.24	178	2.37	hydrocarbon	80	99	56
p-Cymene	134.22	177	2.25[208]	hydrocarbon	75	97	
Toluene	92.14	111	2.38	hydrocarbon	90[153]	97[176]	
Diethoxymethane (ethylal)	104.15	87	2.53[209]	ether		62	64
Dimethoxymethane (methylal)	76.10	42	2.64	ether	50		45
Diethoxymethane (ethylal)	104.15	87	2.53[209]	ether		62	64
Diethylcarbonate (DEC)	118.13	126	2.82	carbonate		94	45
Dimethylcarbonate (DMC)	90.08	90	3.13[210]	carbonate	16	97	93
1,1-Diethoxyethane (acetal)	118.18	102	3.80	ether		62	55
(+)-Rose oxide	154.25	86/20 mmHg		ether	33	78	36
Eucalyptol	154.25	176	4.57	ether		89	82
polar aprotic							
Dimethyl isosorbide	174.20	94/0.1 mmHg	6.20[211]	ether		89	30
2-MeTHF	86.13	79	6.97[212]	ether	30	83	91
Tetrahydrofuran (THF)	72.11	65	7.52[213]	ether			88[171]
γ-Valerolactone (GVL)	100.12	207	36.47	ester		74	64
Propylenecarbonate (PC)	102.09	242	66.14	carbonate		80	60
Ethylenecarbonate (EC)	88.06	261	92.8	carbonate			30

[1] Values obtained from CRC Handbook of Chemistry and Physics (85th ed.) unless mentioned otherwise.

Solvents are organized by increasing dielectric constant.

Carbonylative SMC (C-C)

The reaction of 3-bromoanisole with *m*-tolylboronic acid was used as a model reaction for the screen. The reaction conditions were based on a catalytic system, which is originally developed in the group of Skrydstrup.[153] The catalytic system relied on using Pd(acac)$_2$ and di(1-adamantyl)-*n*-butylphosphine hydroiodide (cataCXium AHI) as a ligand. The original method relied on using boronic acid derivatives such as diethanolamine-complexed heterocyclic boronic acids (DABO boronates) or aryl trihydroxyborates in toluene/H$_2$O (10:1) or pure toluene as a solvent.[153] When repeating the original reaction using aryl trihydroxyborates, we could obtain comparable result and the desired product was achieved in 83% yield (see paper III ESI, Table S1, entry 3). However, we found that the extra step of preparing the aryl trihydroxyborates was not needed. We were able to simplify the method by generating the aryl trihydroxyborates *in situ* by adding 1M NaOH (aq) instead of preparing the organoborates separately.

We tested a range of renewable solvents using the model reaction of 3-bromoanisole with *m*-tolylboronic acid under the developed method. Non-polar ethers, like rose oxide and methylal, carbonate like DMC and polar ethers, like 2-MeTHF, gave the carbonylated product in low to moderate yield (16-50%) and favored direct coupling over the carbonylated product. On the other hand, non-polar hydrocarbons such as limonene, *p*-cymene, γ-terpinene, α-pinene gave better yields (80%, 75%, 50%, 50%, respectively) in correlation with the use of toluene in the original conditions. Limonene favored the carbonylative coupling reaction over the direct coupling and provided the desired biaryl ketone in 80%. Although limonene has a terminal no side product related to the Heck-type arylation of the solvent was observed under reaction conditions neither with rose oxide, γ-terpinene, α-pinene.

We tested the scope of the reaction to check the generality of the carbonylative SMC in limonene. We examined a wide range of boronic acids and aryl bromides, which have shown a good scope. As we are generating the trihydroxyborates *in situ*, this allowed us to use a wide range of boronic acids and avoid the limitations associated with isolation of unstable trihydroxyborate salts. The reaction showed excellent compatibility with electron-rich, electron-deficient and heterocyclic boronic acids and gave high to excellent yields (71-95%). Moreover, electron-rich, electron-deficient and heterocyclic aryl bromides were successfully transformed to the desired products in high to excellent yield (75-91%). It is also noteworthy

that the reaction still shows limitation regarding sterically hindered, electron-withdrawing group aryl bromide such as methyl 2-bromobenzoate, which gave the product in moderate yield (40%). The scope of the reaction allowed for 16 examples of substituted biaryl ketones in moderate to excellent yields (Scheme 39). We can conclude that the obtained yields were in correlation with original reports using non-renewable solvents such as toluene. This emphasizes that limonene is a renewable alternative for carbonylative SMC and can replace the commonly used non-renewable solvents such as toluene, dioxane, chlorobenzene, DMF.[131,134,137,156,181,155]

R[1]= -OMe, -Me, -CHO, CN, ..
R[2] = -OMe, -COOMe, -Me, -NMe$_2$….
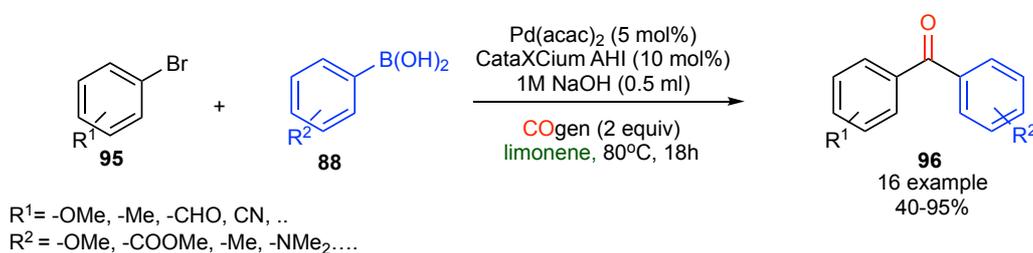
Scheme 39. Carbonylative SMC of aryl boronic acids with boronic acid in limonene.

Aminocarbonylation (C-N)

For aminocarbonylation we used the catalytic system developed by Buchwald and coworkers, where they used Pd(OAc)$_2$, Xantphos and triethylamine as base in toluene. The Pd-catalyzed aminocarbonylation of 4-bromobenzonitrile and N-methylaniline was used as model reaction for the solvent screening.[176] The aminocarbonylation reaction in sustainable solvents gave yields comparable to the result under original conditions in toluene, and even better in some cases.[176] Non-polar hydrocarbons such as limonene, *p*-cymene, γ-terpinene, α-pinene gave excellent yields (99, 97, 94, 97%, respectively), which was not surprising given that these solvents can be expected to have similar properties as toluene.[176] However, the performance of non-polar carbonates (DMC, DEC) was also excellent and the products were obtained in 97% and 94% yield, respectively. The performance of polar carbonates (PC, GVL) and polar/non-polar ethers (2-MeTHF, rose oxide, acetal, etc.) was less good than the other solvents but the product was also here obtained in moderate to high yields (62-89%). Under the reaction conditions, no sign of side reaction such as hydroamination or Mizoroki-Heck coupling for solvents possessing double bonds was observed. As we obtained excellent results in many of the tested solvents, we performed several experiments in the best 3 solvent candidates (limonene, DMC, α-pinene) to check their scope tolerance. We found that limonene, DMC gave comparable results and showed excellent performance in the tested reactions in contrast to α-

pinene, which showed high substrate dependence (Paper III, Scheme 2). Among other renewable solvents DMC is described to be less toxic, cheaper and more viable replacement for toluene.[216–219] Thus, we tested the reaction scope to check the generality of the reaction in DMC. The renewable solvent DMC showed excellent performance throughout the tested scope and showed tolerance for many functional groups on both coupling partners. In general, aryl bromides with electron-withdrawing groups provided the product in high to quantitative yields (81-99%). However, electron-rich aryl bromides were obtained from low to moderate yields (16-64%). Different amines were also tested and both electron-rich or electron-deficient primary and secondary amines were well tolerated and the desired products were obtained in high to excellent yields (85-94%). In addition, we could synthesize commercial drugs such as Trimetozine,[220,221] which is used as a sedative and analogue of Itopride,[222–224] which is used for treatment of gastrointestinal symptoms in excellent yields (Paper III, Scheme 2). The scope of the reaction allowed for 20 examples of primary and secondary substituted amides (Scheme 40) and the results were in correlation with reports of aminocarbonylation in non-renewable solvents. We therefore conclude that renewable solvents such as limonene and DMC can efficiently replace toluene, THF or dioxane that are usually used in Pd-catalyzed aminocarbonylation reactions.[139,158,159,163,166,176]

Scheme 40. Aminocarbonylation in dimethyl carbonate.

Alkoxycarbonylation (C-O)

Similarly, in case of alkoxycarbonylation, we preliminary tested the renewable solvents on a model reaction of 2-bromonaphthalene with sodium *tert*-butoxide and CO using the catalytic system based on Pd(dba)$_2$ as catalyst precursor and 1,1′-bis(diisopropylphosphino)ferrocene (dippf) as ligand in THF that was first developed in the Skrydstrup group.[171] As expected, 2-MeTHF gave excellent results (91%). Non-polar ethers like methylal, ethylal, acetal, rose oxide and eucalyptol and carbonates like DEC showed moderate efficiency and the product was obtained in 45, 64, 55, 36, 82 and 45% yield. Polar solvents such as PC, EC, GVL and dimethyl isosorbide were less efficient and the product was obtained in only low to moderate yields (30-

64%). In case of non-polar carbonate DMC, the alkoxycarbonylation worked well, but we obtained methyl ester in 93% isolated yield instead of *tert*-butyl ester. DMC played a dual role in the reaction where it worked as the reaction medium and as a reagent, which allowed for a transesterification step on the *tert*-butyl ester. However, the non-polar hydrocarbons γ-terpinene and α-pinene gave also excellent yields of 93%.

As several solvents showed good performance in *tert*-butoxycarbonylation, we tested the best 3 candidates (2-MeTHF, γ-terpinene, α-pinene) with several substrate to check their scope tolerance. The experiments showed that the performance of the solvent depends on the substrate. However, α-pinene showed good general tolerance with the tested substrates. Then we tested the reaction scope to evaluate the generality of *tert*-butoxycarbonylation in α-pinene. Electron-rich aryl bromides could be transformed to the corresponding *tert*-butyl ester in moderate to excellent yields (80-93%), while electron-deficient aryl bromides were less reactive and the products were obtained in low to moderate yields (25-51%). The scope resulted in 10 examples and the yields are comparable original reported results in THF.[171] Therefore, we suggest that renewable solvents such as 2-MeTHF, α-pinene and γ-terpinene can replace non-renewable solvents (DMSO, THF, TEA, etc.) that are usually used for alkoxycarbonylation reactions.[170-173]

Further studies on the renewable solvent DMC

As mentioned before (Chapter 3.3.1) Pd-catalyzed alkoxycarbonylation of aryl bromides are mainly based on using bulky alcohols, phenols or corresponding alkoxides.[168,169,134,170,171,172,173] Alcohols containing α-hydrogens were found to be challenging due to the side reactions they can undergo, such as β-hydride elimination. Moreover, low boiling point alcohols e.g; methanol could be challenging. Thus, we were encouraged to investigate the scope of the observed methoxycarbonylation in (Paper III, Scheme 4). Electron-rich aryl bromides gave excellent yields, while electron-deficient aryl bromides were less reactive and gave only moderate yields. Traces of *tert*-butoxycarbonylation product were always observed with the main methoxycarbonylation product throughout the whole scope.

We intended to perform a set of control experiments to gain closer overview of the possible products of the reaction and to confirm that obtaining the methyl ester occurs after the initial installation of the *tert*-butyl ester resulted from the *tert*-butoxycarbonylation mechanism (Paper III, Scheme 5). The *tert*-butyl-2-naphthoate was transformed to methyl-2-naphthoate

when treated with NaO*t*Bu in DMC. According to the experimental results, the transesterification happens both with and without the Pd-catalyst (Scheme 41). However, when testing methoxycarbonylation of 2-bromonaphtalene using MeONa as a nucleophile in DMC, the corresponding methyl ester resulted in 67% yield (Scheme 42, c). While the same reaction in α-pinene resulted in no product and the starting material was recovered (Scheme 42, d).
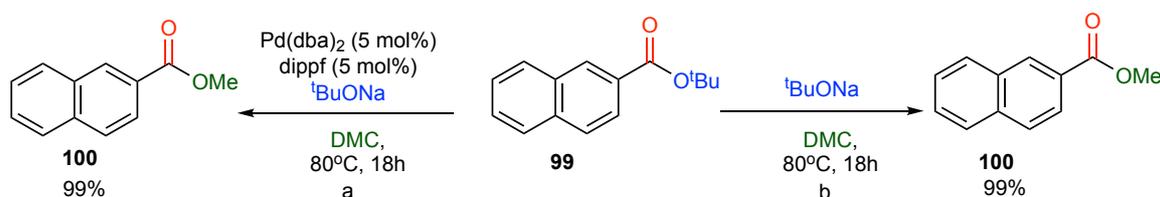
Scheme 41. Control experiment on tert-butyl 2-naphthoate.

These results indicate that the observed methoxycarbonylation can be a result of two simultaneous pathways. In one pathway, the *tert*-butyl ester is installed on the aryl bromide via Pd-catalyzed alkoxycarbonlyation followed by a transesterification with sodium methoxide generated *in situ* from the reaction of the excess sodium *tert*-butoxide with DMC. In the other pathway, *in-situ* generated sodium methoxide in involved in a Pd-catalyzed methoxycarbonylation.
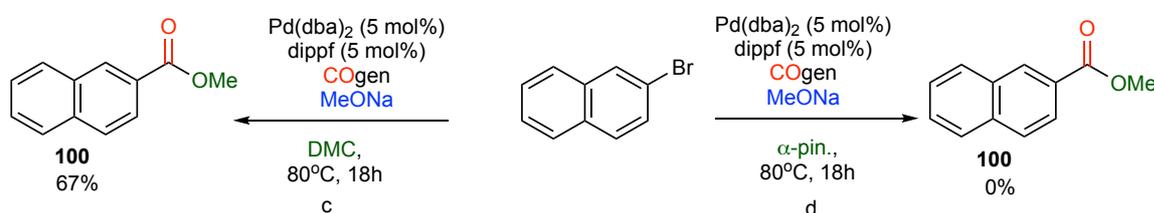
Scheme 42. MeONa initiated alkoxycarbonylation in DMC.

6.3 Additional results not included in Paper III

Column chromatography (C.C) and extraction are important means of purification. Common organic solvents used in these processes are heptane, DCM, MeOH, EtOAc, and many more. The amount of solvent needed for each synthesis until obtaining the pure product could reach couple of liters. Therefore, it is of high importance to find sustainable alternatives for the common solvents used in the purification process. The success of the renewable solvents as sustainable reaction medium in the reactions studied in paper III encouraged us to test them as a purification and isolation medium. Therefore, we attempted to replace the common non-polar hydrocarbon solvent heptane or pentane, commonly used in C.C and TLC systems, with greener alternatives.

Therefore, we tested some non-polar hydrocarbons such as *p*-cymene (bp = 177 °C), careen (bp = 171 °C) and dipentene (bp = 170-180 °C) as the mobile phase in C.C to each model reaction of the three transformation - carbonylative SMC, aminocarbonylation and alkoxycarbonylation. In case of *p*-cymene as eluent, we faced difficulties with visualizing the compounds spots on the TLC plate and thus difficult separation. As *p*-cymene is a UV active solvent with high boiling point (177 °C), evaporating the TLC plate and detecting the spots was not successful. In case of carene and dipentene, we saw good separation on TLC. The product was separated with similar solvent system as for heptane-EtOAc mixtures. However, after evaporation of the pure fractions, we always noticed some remaining solvent together with the pure product. The solvent residues could not be removed using rotavap, high vacuum pump or overnight freeze drying. Thus, with the time available, we were not able to provide a green CC system. However, among the introduced sustainable solvents and other new candidates there might be some solvent that could replace common organic solvent in purification processes. Finding green CC systems is an important goal that should gain research interest. The field of green chemistry is a wide field and the development of greener methods including finding new sustainable solvents and testing them for application is interesting and useful environmental wise.

6.4 Conclusion from Paper III

The goal of this study was to determine green solvents for Pd-catalyzed carbonylative C-C, C-N, and C-O bond forming reactions. A sub-goal was to find conditions that could be used in the synthesis of VIM-2 inhibitory fragments. We have found several renewable solvents, which can successfully substitute traditional non-renewable solvents for three types of palladium catalyzed cross-coupling transformations. Our investigation regarding carbonylative coupling reactions has proven that limonene and its derivatives (γ-Terp, α-Pin, Cym) can replace non-polar petroleum solvents such as toluene, dioxane in both carbonylative SMC, aminocarbonylations and alkoxycarbonylations.

Another stream of sustainable solvents including new candidates such as acetaldehyde diethyl acetal - readily available from ethanol; eucalyptol - from Eucalyptus oil; rose oxide - from rose oil has been introduced. However, they showed weaker performance in comparison to the other solvent candidates. We also reported the behavior of CO_2 derived solvents (DMC, DEC, PC) as the media for Pd-catalyzed cross-coupling reactions. The overall performance of these

solvents was found to be good. Especially DMC was an excellent media for aminocarbonylation and alkoxycarbonylation. In addition, DMC can be used in methoxycarbonylation reaction instead of using the low boiling point methanol to avoid associating problems such as evaporation or side reactions as β-hydride elimination. It also could serve as transesterification agent to obtain methyl ester in late stage optimization.

With regard to the synthesis of VIM-2 inhibitory fragments, more experiments are needed to evaluate if the procedures described in paper III will give excess to a broader substitution pattern compared with the method described in paper II.

7. Conclusion

The aim of the thesis was to develop methods for the synthesis of carbapenemase inhibitors targeting OXA-48 and VIM-2 using a fragment based approach based on previous work in our group[13–15,107] and to apply the methods to the synthesis of inhibitory fragments or inhibitors.

In chapter 4, a synthesis of a range of symmetrical and unsymmetrical 3,5-disubstituted benzoic acids using selective Suzuki-Miyaura coupling was developed. The synthesis of 3,5-disubstituted benzoic acids was according to the merging approach of the promising mono-substituted benzoic acids targeting OXA-48 reported in paper I. The synthesized di-substituted benzoic acid fragments were evaluated and their inhibition activity was found to be better than the mono-substituted benzoic acids. Crystal structures of the tested fragments were obtained and provided us with further knowledge about the active site of OXA-48 to be used for further development.

In chapter 5, I developed a method for the synthesis of 2-aroylbenzoic acids and derivatives via carbonylative SMC using CO gas in a safe fashion. Challenges found upon synthesizing 2-aroylbenzoic acids were also discussed together with suggested solutions. In addition, I discovered the importance of slow addition of the boronic acid to suppress the competing SMC and to favor the carbonylative SMC. The developed method resulted in a range of 2-aroylbenzoic acids that were tested and evaluated against the carbapenamase VIM-2. The tested fragments gave IC_{50} values in the μM range. However, we were not able to expand the fragment library to include specific groups such as OH, NH_2, NHR, etc. Accordingly, an expanded study to find a better system to include more challenging substrate was carried out.

In chapter 6, I tried to extend our study to find better reaction conditions to cover the scope limitations in paper II. In addition, I aimed to synthesize a larger fragment library to test against VIM-2. During the study, we found that sustainable solvents are efficient in Pd-catalyzed coupling reactions and a wide range of sustainable solvents was tested to evaluate their impact on Pd-catalyzed couplings. The effect of sustainable solvents in the challenging carbonylative SMC, alkoxycarbonylation and aminocarbonylation was investigated. The tested sustainable solvents showed very good results in all the aforementioned reactions. Due to time limitations the improved conditions were not evaluated in the synthesis of inhibitory fragments.

The work presented in the thesis could be a starting point towards the synthesis of inhibitors against VIM-2, OXA-48, and maybe other carbapenemases. The developed synthetic methods could also be applied in many other research projects where selective SMC and Pd-catalyzed carbonylation reactions are employed. The sustainability approach that we addressed in this work is a valuable approach to consider, while running organic chemical reactions. The promising results obtained with Pd-catalyzed carbonylations using sustainable solvents are very encouraging to be taken further and to be tested in many other chemical transformations. Therefore, our research recommends including sustainability considerations as a priority in the future studies. The addressed research points in paper I, II, III are of high interest for further development in order to answer the new research questions raised within this work.

8. Future direction

The ultimate goal of my thesis was to use fragment optimization approaches to improve previously identified fragments into drug like compounds with better binding affinity against carbapenemases VIM-2 & OXA-48. This goal is part of a larger goal to discover new inhibitors that can reach clinical trials and can be used in combination therapy with carbapenem in order to save the last resort antibiotic class carbapenems.

I focused on developing synthetic strategies to prepare 3,5-symmetrical and unsymmetrical disubstituted benzoic acids as extended fragments targeting OXA-48. These types of compounds were designed to reach the two identified binding sites. The future goal of this project is to further investigate the synthesis of the third fragment suggested by the merging approach **PI-41**.

In silico optimization study performed by Sundus Akhter suggested that growing the fragment in the 2-ortho position might favor binding in the inner binding pocket instead of pointing out to the solvent. Therefore, we intended to extend the fragments in the 2-ortho position instead of 3-meta position. I supervised a master student, Harald Magnussen, that was responsible of preparing a library of 2,5-disubstituted benzoic acids from methyl 2-amino-5-bromobenzoate. The synthesized fragment (Scheme 43, Fragment **32H**) was submitted for biological testing. The fragment showed comparable IC_{50} (3.275 μM) to fragment **PI-40.** However, the LE of fragment **32** (0.24 kcal/(mol atom) was slightly lower than fragment **PI-40** (0.27 kcal/(mol atom). In the future a crystal structure of fragment/OXA-48 complex is a logical step in order to identify the binding modes of 2,5-disubstituted fragments assembled in fragment **32**.
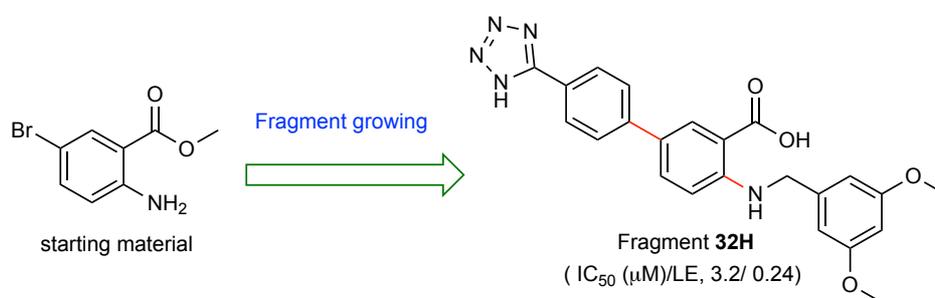
Scheme 43. Fragment growing towards a drug like compound. Fragment 32H was synthesized by Harald Magnussen.

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In paper II, I developed a method to synthesize a range of sterically hindered 2-aroylbenzoic acid derivatives from simple boronic acids via carbonylative SMC. Applying slow addition of boronic acid to the reaction is a promising approach to suppress the undesired direct SMC coupling. This work was continued in Paper III and the choice of the renewable solvents showed great impact on the tested Pd-catalyzed carbonylation reactions. Limonene showed good performance in carbonylative SMC and it favored the carbonylation product over the direct coupling product without applying the slow addition. In future work, it would be interesting to combine the findings of paper II and III - slow addition of boronic acid and the use of renewable solvent. The future goal regarding this project is to test carbonylative coupling to synthesize the challenging substrates, which contain functional groups such as phenols, amides, amines, and strong electron-withdrawing groups such as nitro, nitrile, which can allow for late stage functionalization.

9. Appendix

This chapter includes additional experimental procedures and spectral data for compounds not included in paper II and presented in Table 8, entry 1-7.

9.1 Experimental

9.1.1 General methods

All purchased chemicals were used as received without further purification. Solvents were dried according to standard procedures. Automated reverse-phase flash chromatography was performed using pre-packed C18-modified silica columns. The chemical shifts are reported in ppm relative to the solvent residual peak. NMR spectra were obtained on a 400 MHz Bruker Avance III HD equipped with a 5 mm SmartProbe BB/1H (BB = 19F, 31P-15N). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J, Hz) and integration. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak (CDCl$_3$: δ_H 7.26 and δ_C 77.16; Methanol-d$_4$: δ_H 3.31 and δ_C 49.00; Deuteriumoxide: δ_H 4.79; DMSO-d$_6$: δ_H 2.51 and δ_C 39.52). The raw data was analysed with MestReNova (Version 10.0.2-15465). Positive ion electrospray ionization mass spectrometry was conducted on a Thermo electron LTQ Orbitrap XL spectrometer. The data was analysed with Thermo Scientific Xcalibur software.

9.1.2 Experimental details

1- 2-(4-fluorobenzoyl)benzoic acid
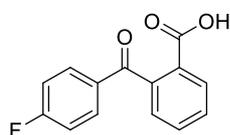
Anhydrous AlCl$_3$ (91 mg, 0.68 mmol) was suspended in fluorobenzene (20 ml) before phthalic anhydride (50 mg, 0.34 mmol) was added in portions to the reaction mixture at 0 °C while stirring. Upon complete addition of the phthalic anhydride, the reaction mixture was submitted to reflux for 3h. The reaction was quenched by adding ice-cold HCl (50%, 100 mL). The reaction mixture was concentrated on a rotavapor. The precipitate was dissolved in sodium carbonate solution and then filtered. The resulted filtrate was acidified with aqueous HCl and

the solid product was filtered and submitted for further purification by reverse phase flash chromatography using 30% acetonitrile: H_2O. The pure product was obtained (50 mg, 60%) as a white powder. ^{1}H NMR (400 MHz, CDCl$_3$) δ 10.22 (bs, 1H), 8.09 (d, J = 7.6 Hz, 1H), 7.80 – 7.71 (m, 2H), 7.69-7.65 (m, 1H), 7.59-7.55 (m, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.08 (t, J = 8.6 Hz, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 195.6, 170.9, 165.9 (d, J = 255.3 Hz), 142.4, 133.6 (d, J = 2.9 Hz), 133.5, 132.1 (d, J = 9.4 Hz), 131.1, 129.8, 127.8, 127.7, 115.9, 115.7, 77.5, 77.4, 77.2, 76.8. HRMS (ESI): Calcd. for $C_{14}H_9FNaO_3$ [M+H]$^+$ 267.0428; found $C_{14}H_9FNaO_3$ 267.0428.

2- 2-(4-methylbenzoyl)benzoic acid[226,227]
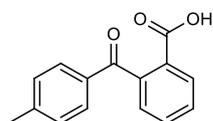
Anhydrous AlCl$_3$ (91 mg, 0.68 mmol) was suspended in toluene (20 ml) before phthalic anhydride (50 mg, 0.34 mmol) was added in portions to the reaction mixture at 0 °C while stirring. Upon complete addition of the phthalic anhydride, the reaction mixture was submitted to reflux for 3h-6h. The reaction was quenched by adding ice-cold HCl (50%, 100 mL). The reaction mixture was concentrated on a rotavapor. The precipitate was dissolved in sodium carbonate solution and then filtered. The resulted filtrate was acidified with aqueous HCl and the solid product was filtered and submitted for further purification by reverse phase flash chromatography. The pure product was obtained (71 mg, 87%) as a white powder. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.06 (d, J = 7.6 Hz, 1H), 7.66-7.62 (m, 3H), 7.54 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 7.8 Hz, 2H), 5.86 (bs, 1H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.4, 144.2, 142.9, 134.6, 133.1, 130.9, 129.7, 129.5, 129.3, 128.2, 127.7, 21.8. HRMS (ESI): Calcd. for $C_{15}H_{12}NaO_3$ [M+H]$^+$ 263.0679; found $C_{15}H_{12}NaO_3$ 263.0680.

3- 2-(3,4-dimethoxybenzoyl)benzoic acid[228]
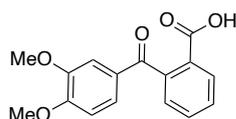
1,2-dimethoxybenzene (47 mg, 34 mmol) and phthalic anhydride (50 mg, 0.34 mmol) were added to a suspension of AlCl$_3$ (91 mg, 0.68 mmol) in DCM (20 ml) at 0 °C. The reaction was left stirring for 5h at rt. Upon reaction completion the reaction mixture was poured onto ice.

The organic layer was collected and dried over MgSO₄. The organic phase was concentrated on a rotavapor and the residue was triturated with diethyl ether. The product was submitted to reverse phase flash chromatography resulting in pure product (44 mg, 45%) as a yellowish solid. ^{1}H NMR (400 MHz, DMSO-d₆) δ 13.03 (s, 1H), 7.93 (d, J = 7.4 Hz, 1H), 7.72 – 7.54 (m, 2H), 7.35 (d, J = 12.3 Hz, 2H), 6.95 (s, 2H), 3.76 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d₆) δ 204.40, 176.45, 162.56, 158.23, 150.96, 141.65, 139.53, 139.38, 139.17, 139.02, 136.98, 134.22, 120.21, 119.60, 65.26, 64.95. HRMS (ESI): Calcd. for $C_{16}H_{14}NaO_5$ [M+H]⁺ 309.0739; found $C_{16}H_{15}NaO_5$ 309.0737.

4- 2-benzoylbenzoic acid[226,227]
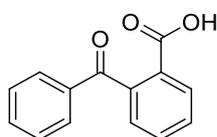
Anhydrous AlCl₃ (91 mg, 0.68 mmol) was suspended in benzene (20 ml) before phthalic anhydride (50 mg, 0.34 mmol) was added in portions to the reaction mixture at 0 °C while stirring. Upon complete addition of the phthalic anhydride, the reaction mixture was submitted to reflux for 5h. The reaction was quenched by adding ice-cold HCl (50%, 100 mL). The reaction mixture was concentrated on a rotavapor. The precipitated product was dissolved in sodium carbonate solution and then filtered. The resulted filtrate was acidified with aqueous HCl and the solid product was filtered. The pure product was collected without further purification (69 mg, 90%) as white powder. ^{1}H NMR (400 MHz, CDCl₃) δ 8.08 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.6 Hz, 2H), 7.69-7.65 (m, 1H), 7.59-7.52 (m, 2H), 7.45-7.35 (m, 3H), 5.07 (bs, 1H). ^{13}C NMR (101 MHz, CDCl₃) δ 197.5, 170.5, 143.0, 137.4, 133.6, 133.6, 131.3, 123.0, 129.9, 128.9, 128.4, 128.2, 77.8, 77.7, 77.5, 77.2. HRMS (ESI): Calcd. for $C_{14}H_{10}NaO_3$ [M+H]⁺ 249.0522; found $C_{14}H_{10}NaO_3$ 249.0527.

5- 2-(pyridin-2-ylcarbamoyl)benzoic acid[229]
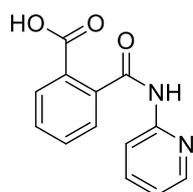
Phthalic anhydride (500 mg, 3.4 mmol) was added to the pyridine-2-amine (390 mg, 4.1 mmol) in DCM (20 mL) and the reaction mixture was left stirring for 18h at room temperature. The product was recrystallized in DCM, the pure product was obtained by vacuum filtration in (710 mg, 85%) yield.^{1}H NMR (400 MHz, MeOD) δ 8.24-8.20 (m, 1H), 7.93-7.91 (m, 1H), 7.81-7.78 (m, 1H), 7.69-7.65 (m, 1H), 7.62-7.50 (m, 2H), 7.12-7.09 (m, 1H), 6.78 (d, J = 8.7 Hz, 1H), 6.70 (t, J = 6.5 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 158.6, 154.2, 147.8, 146.6, 144.7, 137.0, 136.2, 135.9, 133.9, 126.2, 121.2, 118.8, 118.0, 54.9, 54.6, 54.4, 54.2, 54.0, 53.7, 53.5. HRMS (ESI): Calcd. For $C_{13}H_{11}O_3N_2$ [M+H]$^+$ 243.0770; found $C_{13}H_{11}O_3N_2$ 243.0771.

6- 2-(7-bromo-1*H*-indole-3-carbonyl)benzoic acid
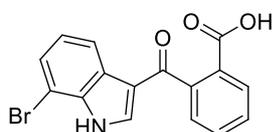
Anhydrous AlCl$_3$ (91 mg, 0.68 mmol) was suspended in DCM (20 ml) before phthalic anhydride (50 mg, 0.34 mmol) and 7-bromoindole (67 mg, 34 mmol) were added in portions to the reaction mixture at 0 °C while stirring. Upon complete addition of the phthalic anhydride, the reaction mixture was submitted to reflux for 6h. The reaction was quenched by adding ice-cold HCl (50%, 100 mL). The reaction mixture was concentrated on a rotavapor. The precipitated product was dissolved in sodium carbonate solution and then filtered. The resulted filtrate was acidified with aqueous HCl and extracted with EtOAc. The organic phase was collected, dried over Na$_2$SO$_4$ and concentrated on a rotavapor. The product was submitted for to reverse phase flash chromatography using 30-50% acetonitrile: H$_2$O. The pure product was obtained (78 mg, 67%) as a gummy solid. ^{1}H NMR (400 MHz, MeOD) δ 8.18 (d, J = 7.9 Hz, 1H), 8.05 (d, J = 7.7 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.49 (d, J = 7.4 Hz, 1H), 7.44 (d, J = 7.7 Hz, 2H), 7.15 (t, J = 7.8 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 194.6, 169.5, 144.1, 137.1, 136.9, 133.1, 131.4, 130.6, 128.9, 127.2, 124.5, 122.2, 119.8, 105.9. HRMS (ESI): Calcd. for $C_{16}H_{10}BrNNaO_3$ [M+H]$^+$ 365.9742; found $C_{16}H_{10}BrNNaO_3$ 365.9744.

7- 2-(phenylcarbamoyl)benzoic acid[229]
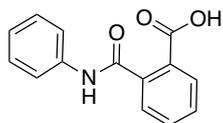
Phthalic anhydride (500 mg, 3.4 mmol) was added to the aniline (380 mg, 4.1 mmol) in DCM (20 mL) and the reaction mixture was left stirring for 6h at room temperature. The product was obtained by vacuum filtration. The precipitate was recrystallized in DCM-heptane mixture. The pure product was obtained (76 mg, 92%) a white solid. ^{1}H NMR (400 MHz, MeOD) δ 8.02 (d, J = 7.5 Hz, 1H), 7.65-7.63 (m, 3H), 7.57-7.55 (m, 2H), 7.33 (t, J = 7.7 Hz, 2H), 7.12 (m, 2H), 6.77-6.70 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 171.1, 169.3, 140.3, 140.1, 133.2, 131.4, 130.6, 130.1, 129.7, 128.8, 125.4, 121.7, 119.9, 117.1, 49.6, 5.4, 49.2, 49.0, 48.8, 48.6, 48.6. HRMS (ESI): Calcd. for $C_{14}H_{11}NNaO_3$ [M+H]$^{+}$ 264.0628; found $C_{14}H_{11}NNaO_3$ 264.0637.

9.1.3 Spectral data

1-
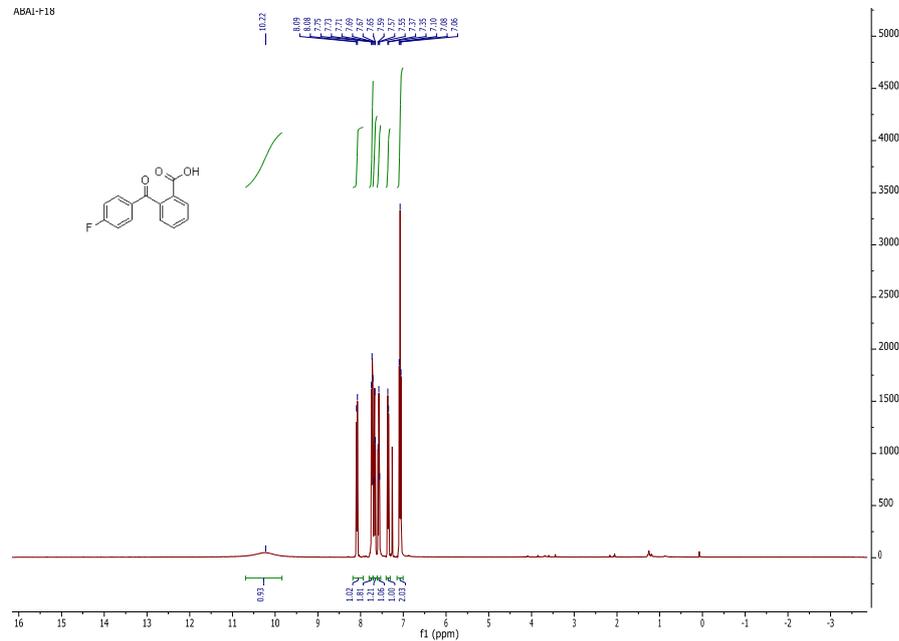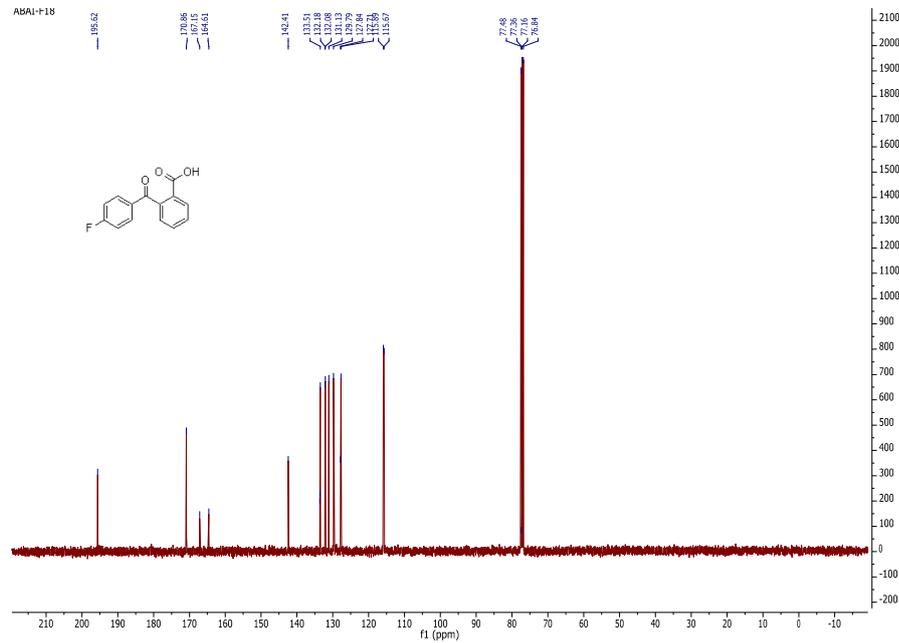
227.0505

267.0431
C $_{14}$ H $_9$ O $_3$ F Na = 267.0428
0.3037 mmu

279.0628

350.0174

455.0538

m/z

2-

f1 (ppm)

89

170.37

144.17
142.93
134.64
133.14
130.90
129.71
129.50
129.31
127.69

21.84

f1 (ppm)
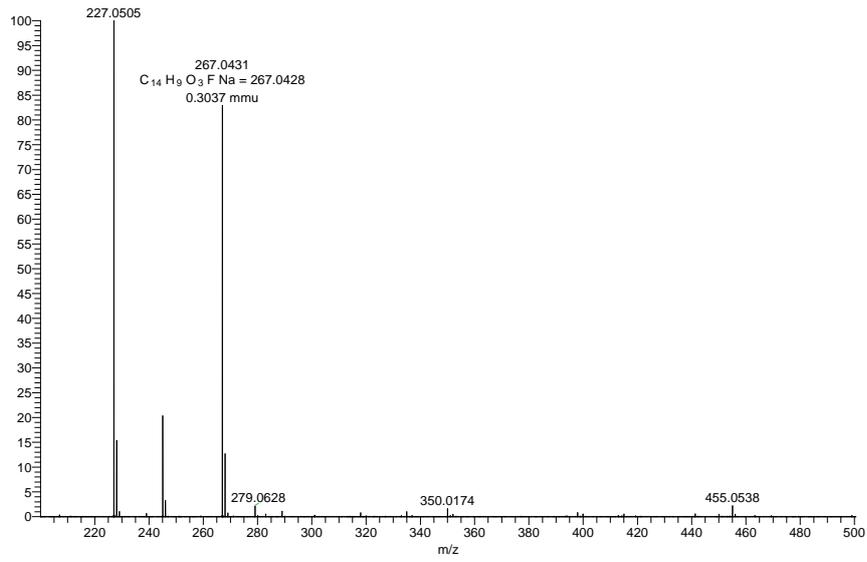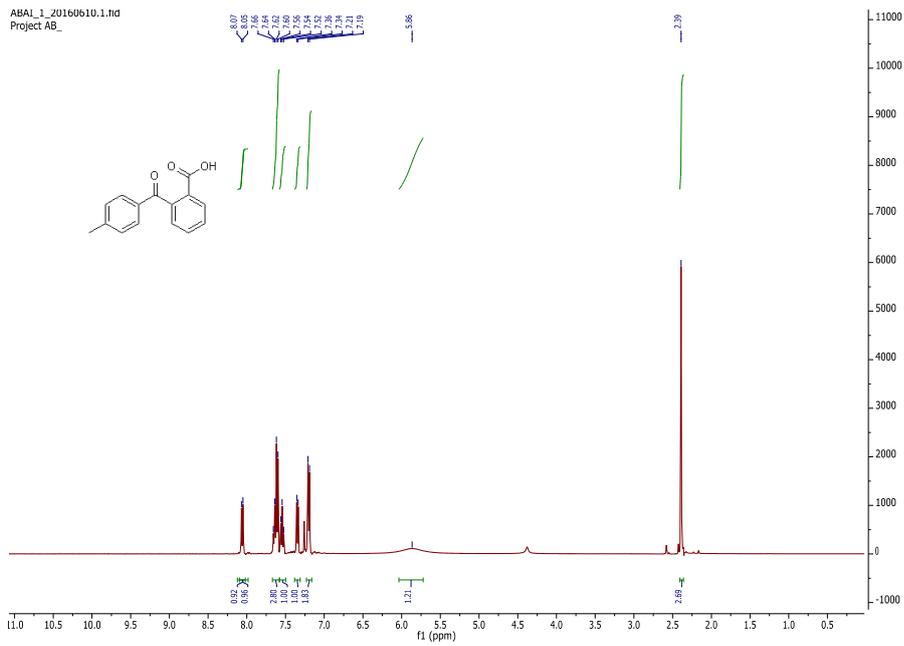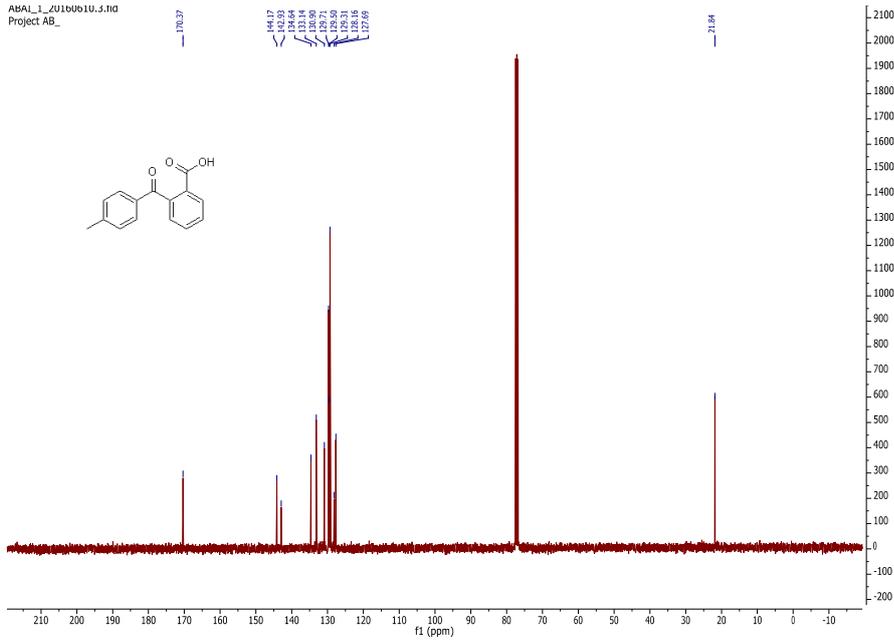
ABAI_1 #1-5   RT: 0.01-0.13   AV: 5   NL: 8.63E6
T: FTMS + p ESI Full ms [100.00-500.00]

263.0680
$C_{15}H_{12}O_3Na = 263.0679$
0.0929 mmu

223.0752
$C_{15}H_{11}O_2 = 223.0754$
-0.1911 mmu

149.0118

279.0416

327.0314

361.0580

m/z

3-

90

91

309.0737
C$_{16}$ H$_{14}$ O$_5$ Na = 309.0733
0.3870 mmu

228.0994
C$_{11}$ H$_{16}$ O$_5$ = 228.0992
0.1838 mmu

331.0552

353.2662

381.2975

393.1250

413.2661

475.2815

m/z

4-

8.09
8.07
7.73
7.71
7.69
7.67
7.65
7.59
7.57
7.54
7.52
7.43
7.41
7.39
7.37

5.07

1.02
1.84
0.99
1.98
2.86

1.20

f1 (ppm)

92

197.4520

170.45

143.01
137.42
133.63
133.61
131.33
129.99
129.90
128.91
128.35
128.18

77.80
77.68
77.48
77.16

1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

249.0527
$C_{14} H_{10} O_3 Na$ = 249.0522
0.5301 mmu

475.1156

100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0

172.9787   209.0599   265.0265   313.0163   353.0368   413.2667   497.0971
                           287.1395 321.0105   368.1473

200   250   300   350   400   450   500
m/z

5-

93

243.0771
$C_{13}H_{11}O_3N_2 = 243.0764$
0.6884 mmu

289.1187
$C_{15}H_{17}O_4N_2 = 289.1183$
0.4260 mmu

296.1861
$C_{16}H_{26}O_4N = 296.1856$
0.4272 mmu

321.1240

344.1974

217.0473

164.9846

369.2754
377.2125

413.2665

441.2977

463.2991

485.3375

m/z

6-

abai-7br_20160813.1.fid
Project JH_

f1 (ppm)

194.65

169.45

144.13
137.14
136.92
133.14
131.35
130.58
128.89
127.17
124.54
122.18
119.79

105.91

49.21
49.00
48.79

f1 (ppm)

abai_9_7bro #1-5 RT: 0.01-0.12 AV: 5 NL: 3.84E6
T: FTMS + p ESI Full ms [150.00-500.00]

365.9744
C 16 H 10 O 3 N Br Na = 365.9736
0.7881 mmu

403.0656
C 19 H 20 O 3 N 2 Br = 403.0652
0.4036 mmu

445.1124

239.2252

164.9845

266.2442   285.1726

461.9634

492.4045

m/z

7-

264.0628
$C_{14} H_{11} O_3 N Na = 264.0631$
-0.3063 mmu

224.0701

483.1541

m/z
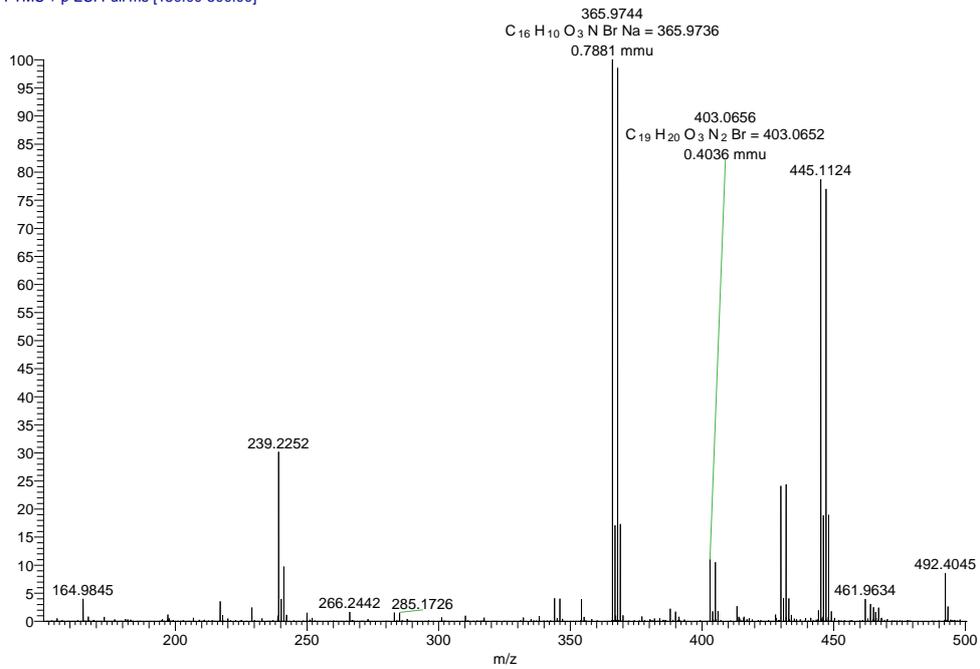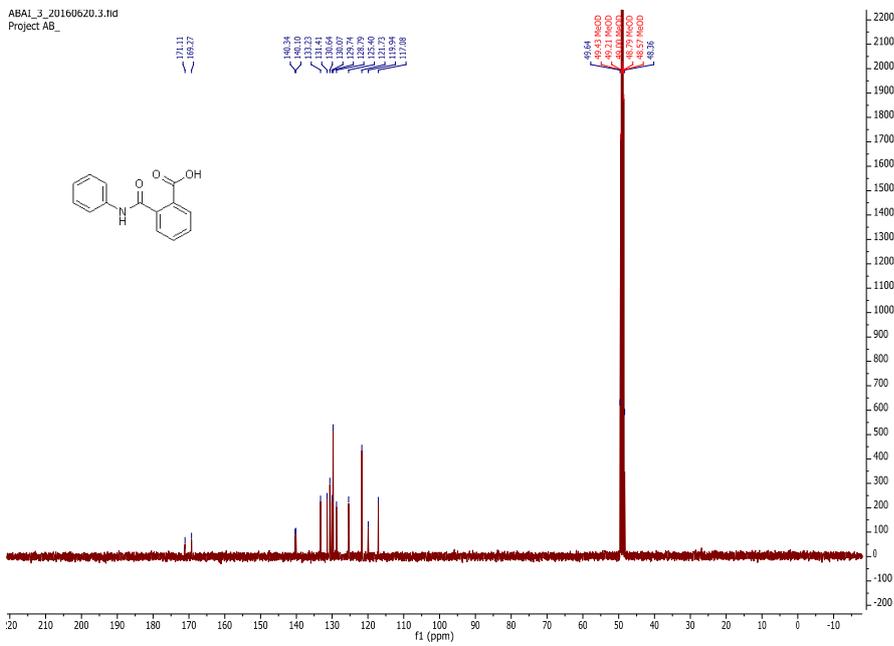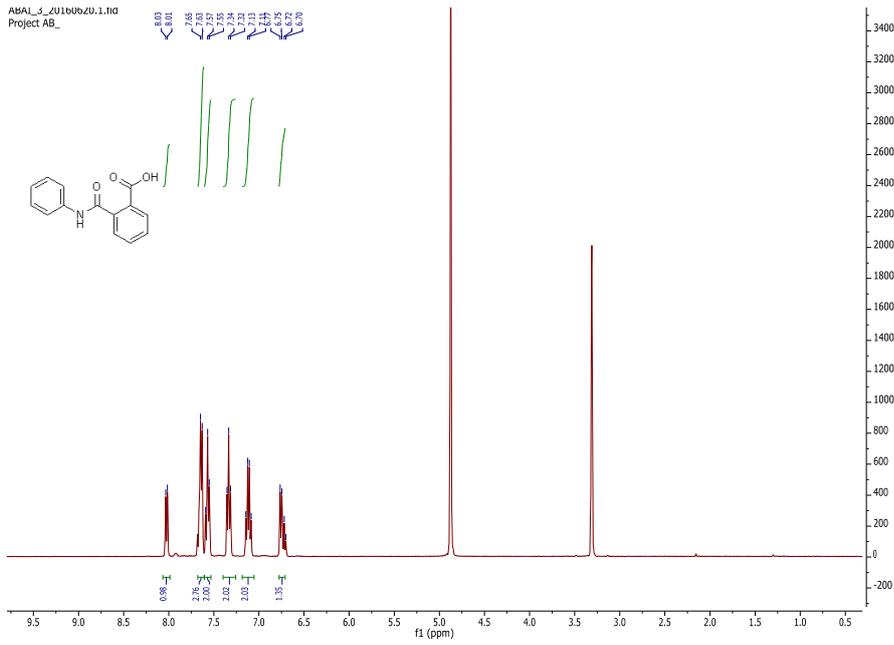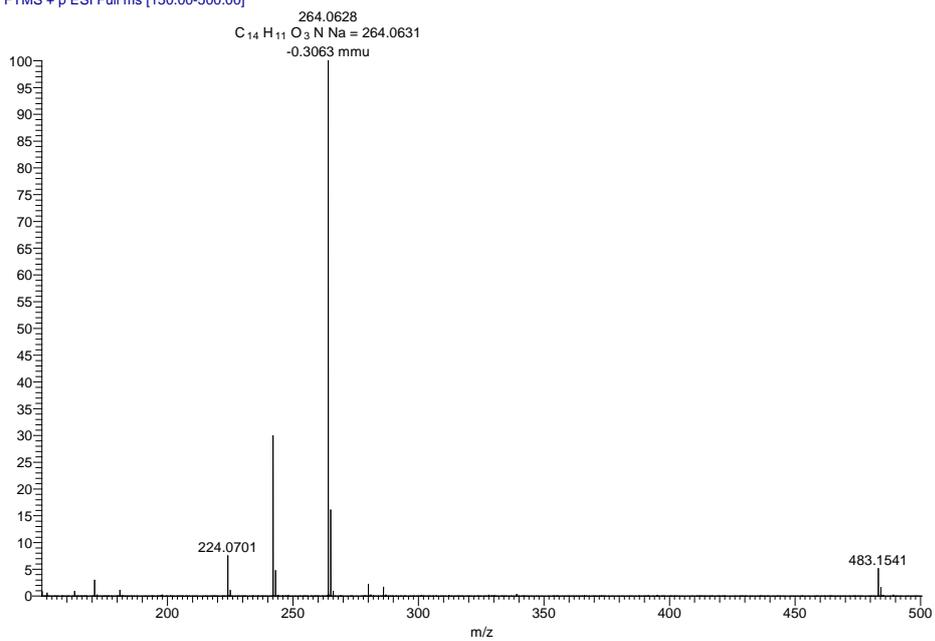
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Paper I

A focused fragment library targeting the antibiotic resistance enzyme - Oxacillinase-48: Synthesis, structural evaluation and inhibitor design

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Only the synthesis supporting information of this paper is included. Biological and structural information can be found on the webpages of the publisher.

Research paper

A focused fragment library targeting the antibiotic resistance enzyme - Oxacillinase-48: Synthesis, structural evaluation and inhibitor design

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A R T I C L E   I N F O

A B S T R A C T

β-Lactam antibiotics are of utmost importance when treating bacterial infections in the medical community. However, currently their utility is threatened by the emergence and spread of β-lactam resistance. The most prevalent resistance mechanism to β-lactam antibiotics is expression of β-lactamase enzymes. One way to overcome resistance caused by β-lactamases, is the development of β-lactamase inhibitors and today several β-lactamase inhibitors e.g. avibactam, are approved in the clinic. Our focus is the oxacillinase-48 (OXA-48), an enzyme reported to spread rapidly across the world and commonly identified in *Escherichia coli* and *Klebsiella pneumoniae.* To guide inhibitor design, we used diversely substituted 3-aryl and 3-heteroaryl benzoic acids to probe the active site of OXA-48 for useful enzyme-inhibitor interactions. In the presented study, a focused fragment library containing 49 3-substituted benzoic acid derivatives were synthesised and biochemically characterized. Based on crystallographic data from 33 fragment-enzyme complexes, the fragments could be classified into R^1 or R^2 binders by their overall binding conformation in relation to the binding of the R^1 and R^2 side groups of imipenem. Moreover, binding interactions attractive for future inhibitor design were found and their usefulness explored by the rational design and evaluation of merged inhibitors from orthogonally binding fragments. The best inhibitors among the resulting 3,5-disubstituted benzoic acids showed inhibitory potential in the low micromolar range ($IC_{50} = 2.9 \, \mu M$). For these inhibitors, the complex X-ray structures revealed non-covalent binding to Arg250, Arg214 and Tyr211 in the active site and the interactions observed with the mono-substituted fragments were also identified in the merged structures.

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1. Introduction

Years of overuse of antibiotics have selected for antibiotic resistant strains [1], and today medical personnel are frequently forced to administer last-resort antibiotics. However, the number of cases where last-resort antibiotics fail in treatment are increasing [2] and deaths due to antibiotic resistant infections are expected to surpass cancer deaths by 2050 [3]. Bacterial resistance towards clinically important β-lactam antibiotics [4] like penicillins, cephalosporins and carbapenems originates most often from the occurrence of β-lactam-hydrolysing enzymes – the β-lactamases.

The β-lactamase enzymes are of ancient origin [5] and today over 2600 enzymes spanning four classes of β-lactamases are known [6–8]. β-Lactamases are grouped into two super families based on the enzyme mechanism for β-lactam hydrolysis: the serine dependent β-lactamases (SBLs; Amber class A, C, and D) and metallo-β-lactamases (MBLs; Amber class B) [7,9]. SBLs are characterized by a serine residue in the active site, while MBLs require a metal co-factor, usually one or two zinc ions, for enzyme activity. This work focuses on the class D SBLs – also called oxacillinases (OXAs) – and in particular on the oxacillinase-48 (OXA-48).

The class D SBLs are characterized by a hydrophobic environment in the active site, that facilitates the carboxylation of a lysine residue. The *N*-carboxylated lysine plays a critical role in the substrate hydrolysis [10]. Originally, the OXAs were believed to have a limited substrate profile only hydrolysing penicillins, but with the emergence of carbapenem-hydrolysing OXA variants, e.g. OXA-23, OXA-24 and OXA-48, their clinical relevance has increased [11]. OXA-48 was reported for the first time in 2001 and has since then spread rapidly across the world [11]. It is commonly identified in *Escherichia coli* and *Klebsiella pneumoniae*.

One strategy to circumvent resistance in β-lactamase producing pathogens is the use of β-lactamases inhibitors [4,12] in combination with the β-lactam antibiotic. Inhibitors of class A SBLs like clavulanic acid, sulbactam and tazobactam became clinically available from the 1980s [13], but only a few class D β-lactamases are inhibited by these β-lactamase inhibitors e.g. OXA-2 and OXA-18 [14]. In 2015, a new SBL inhibitor, avibactam, targeting class A, C and some class D SBLs, including OXA-48, was approved by the FDA for treatment of complicated urinary tract and intra-abdominal infections [15]. However, the inhibition level of different class D β-lactamases by avibactam varies [16,17]. With the first reports of resistance to avibactam published [18], one can speculate that it will only be a matter of time before class D β-lactamases show resistance to avibactam as well.

The development of new OXA inhibitors, either with a different enzyme-inhibition profile compared to existing inhibitors, or as alternative when resistance to existing inhibitors arises, is of importance. We have previously reported a fragment-based screening approach to identify weak inhibitors of OXA-48 [19]. The most interesting hit was 3-(pyridin-4-yl)benzoic acid **1** with an IC$_{50}$ of 250 μM and a ligand efficiency (LE) of 0.32. Crystallographic data from enzyme-fragment complexes indicated two overlapping binding conformations of the fragment. Merging of the two conformations of **1** into one molecule **2** (Fig. 1) gave a 10-fold increase in binding affinity improving the IC$_{50}$ from 250 μM to 18 μM [19].

In this study, we describe the use of small mono-substituted fragments - analogues of fragment **1** - as probes to explore the OXA-48 binding site. The aim was to identify fragment-enzyme interactions in the two alternate binding pockets of the active site of OXA-48, which could be of general interest for the design of OXA-48 inhibitors. We wanted to exploit the ability of small fragments to efficiently explore the binding pocket as they are less restricted by size and more flexible compared to more elaborated inhibitors. Moreover, the smaller fragments generally have the advantage of being more easily prepared making the discovery process more work-efficient. Furthermore, we wanted to translate the knowledge gained into the rational design of di-substituted inhibitors related to compound **2** circumventing the laborious preparation of a large library of elaborated inhibitors.

Towards this goal, we prepared a focused fragment library containing 3-aryl benzoic acids decorated with a wide range of polar groups and a number of 3-heteroaryl benzoic acid derivatives. In total 49 fragments were tested for inhibitory activity against OXA-48 and the binding conformations of 33 fragment-enzyme complexes were analyzed by X-ray crystallography. Based on the structural information, fragments could be classified according to their preferred binding pocket and useful fragment-enzyme interactions e.g. hydrogen bonds were identified. Moreover, several new orthogonally binding fragments were found leading to the design of symmetrically and unsymmetrically di-substituted inhibitors with improved IC$_{50}$ in the low micromolar range. The structural data from enzyme-inhibitor complexes was compared with enzyme-fragment complexes.

2. Results and discussion

2.1. Synthesis

2.1.1. Synthesis of 3-substituted benzoic acids

A fragment library containing 49 3-substituted benzoic acid analogues **3a**–**35** was prepared (Table 1). The fragments generally fulfilled the demands of libraries for fragment-based ligand design (MW < 300, clogP < 3, hydrogen bond acceptor/donors < 3) [20]. For the synthesis, a strategy based on the Suzuki-Miyaura (SM) cross-coupling reaction to join two sp^2–hybridized carbons was employed [21]. Two alternate coupling strategies were successful starting with either 3-bromobenzoic acid (Table 1, strategy A) or 3-carboxyphenylboronic acid pinacol ester (Table 1, strategy B) as starting materials allowing for the utilisation of a wide range of aryl boronic acids or aryl bromides to introduce diversity in the library.

Many of the required aryl boronic acids and bromides were commercial available, while the aryl bromides used as starting materials for fragments **17**–**20**, **24**, **29** and **30** were prepared according to standard acylation and sulphonylation protocols. The *NH*-tetrazol-5-yl-substituted arylbromides (starting material for fragments **26a** and **26b**) were prepared by a [3 + 2] intermolecular cycloaddition of 3- or 4-bromobenzonitrile with trimethyl silyl azide in the presence of dibutyltin oxide in anhydrous 1,4-dioxane. The reaction mixture was subjected to microwave irradiation in a tightly sealed vessel for 50 min at 150 °C to afford 3- or 4-bromobenzotetrazole in 86% and 82% yield, respectively.

In general, couplings under standard aqueous conditions using PdCl$_2$(PPh$_3$)$_2$ as catalyst (5–10 mol%), K$_3$PO$_4$ as base (5 equiv.) in dioxane/water gave good yields. The couplings leading to fragments **9**, **17**–**20** and **22**–**24** were not successful under these standard conditions. More efficient catalysts (XPhos-Pd G2 or PdCl$_2$(dppf)) and water-free conditions (anhydrous THF instead of dioxane/water) were successfully employed to solve reactivity and solubility problems and to prevent hydrolysis for base sensitive products (**9** and **24**). However, for some products (**19a, 19b** and **20**) the yields were still low (<20%). Generally, the reactions were easily purified by automated C18 flash chromatography to provide compounds of high purity (>95% as determined by UHPLC). For some compounds (**15**, **16**, **19**, **23**, **24**, **32** and **34**), additional silica flash chromatography was necessary to provide sufficiently pure products.

2.1.2. Synthesis of 3,5-disubstituted benzoic acid derivatives

To study inhibitor properties like activity and enzyme interactions of merged fragments, a small series of symmetrical and unsymmetrical 3,5-disubstituted benzoic acids was designed (*vide infra*) and prepared. The synthesis of symmetrical 3,5-disubstituted compounds **36** and **38** was achieved under the conditions established for the coupling of mono-substituted fragments using Pd$_2$(dba)$_3$/XPhos or XPhos-Pd G2 as catalysts (Scheme 1) [19]. The di-substituted coupling products **36** and **38** were obtained from 3,5-dibromobenzoic acid as starting material and an increased amount of the boronic acid derivative (2 equiv.) in 54% and 65% yield, respectively. Compound **37** was isolated in 11% yield as by-product in an attempt to selectively mono-substituted 3,5-dibromobenzoic acid (*vide infra*).

For the synthesis of unsymmetrical 3,5-disubstituted benzoic acids **39**, the sequential addition of two different aryl boronic acids under the previously established conditions gave only 15% isolated yield (Scheme 2). In addition, the procedure involved tedious HPLC purifications as the reaction mixture was difficult to purify due to occurrence of symmetrical by-products with similar properties. To improve the selectivity of the reaction, we changed the starting material from 3,5-dibromobenzoic acid to 3-iodo-5-bromobenzoic
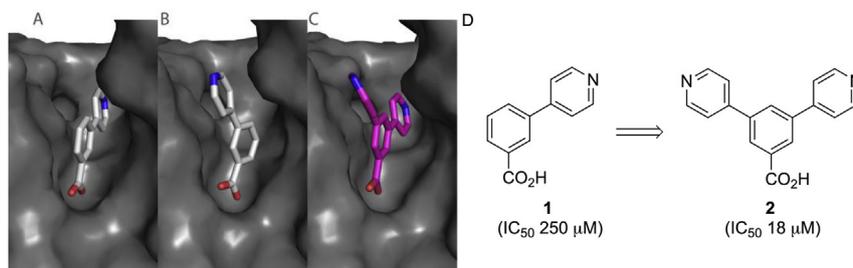
Fig. 1. The two alternate conformations of fragment **1** (light grey) in complex with OXA-48 (dark grey surface) (A and B), the merged compound **2** (pink) in complex with OXA-48 (dark grey surface) (C), and a schematic view of the merging approach described in previous work (D) [19]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

acid in order to take advantage of the faster coupling reaction of aryl iodides when compared with aryl bromides and thereby to prevent formation of symmetrical disubstituted by-products (Scheme 2). Investigation of the chemoselective coupling of 3-iodo-5-bromobenzoic acid with quinolin-6ylboronic acid pinacol ester to form mono-substituted **int-40** showed that a second, unwanted coupling was not easily prevented and a careful fine tuning of catalyst (RuPhos-Pd G3, XantPhos-Pd G3, Sphos/Pd$_2$ (dba)$_3$, Xphos/Pd$_2$ (dba)$_3$, SPhos-Pd G3, XPhos-Pd G2, Pd$_2$ (dppf)Cl$_2$), solvent (toluene/water, anhydrous THF, dioxane/water, *tert*-butanol), reaction temperature (40—80 °C) and time (10—48 h) was initiated (Table SI1, see Supporting information). The composition of the crude reaction mixtures with respect to mono- and disubstituted products as well as unreacted starting material was determined by mass spectrometry (MS). The most chemoselective catalysts were XantPhos-Pd G3, Pd$_2$ (dppf)Cl$_2$ and SPhos/Pd$_2$ (dba)$_3$ showing good selectivity for the aryl iodide when the reaction was performed with K$_3$PO$_4$ as base in dioxane/water at 60 °C for 24 h (Scheme 2). At this conditions with SPhos/Pd$_2$ (dba)$_3$ as catalyst, the mono-substituted intermediate **int-40** was obtained as main product together with small amounts of the disubstituted by-product (8—10%). Careful purification to remove any traces of the disubstituted compound provided **int-40** in moderate yield (45%). The mono-substituted **int-40** was further subjected to a second coupling with XPhos-Pd G2 (5 mol%) as catalyst to provide **40** in good yields (90%).

2.2. Evaluation of 3-substituted benzoic acids

2.2.1. Inhibitor activity of 3-substituted benzoic acids

The mono-substituted fragments **3**—**35** were initially investigated for their inhibitory activity against OXA-48 in an enzymatic assay and by SPR. Inhibition and binding data are given in Table 1 along with the associated ligand efficiencies (LE). The original hit fragment **1** had an IC$_{50}$ of 250 μM and an LE of 0.32. Most of the fragments in this study showed inhibition at a similar level with IC$_{50} > 200$ μM and LE ≤ 0.30. Fragments **4a** (IC$_{50}$ (μM)/LE: 50/0.38), **18** (IC$_{50}$ (μM)/LE: 60/0.24), **21a** (IC$_{50}$ (μM)/LE: 35/0.33), **26b** (IC$_{50}$ (μM)/LE: 36/0.30) and **35** (IC$_{50}$ (μM)/LE: 35/0.42) showed an order of magnitude stronger inhibition and were the most potent fragments. Even though there are some discrepancies between the inhibition and binding data, the same trends are maintained when comparing similar compounds, indicating that the compounds indeed bind specifically to one site of the enzyme.

2.2.2. Structural analysis of 3-substituted benzoic acids

To evaluate the binding poses of our fragments, enzyme-fragment complexes for x-ray crystallographic analysis were prepared. Rewardingly, 33 out of 49 fragments were successfully soaked with OXA-48 and yielded crystal structures with resolution

high enough to warrant placement of the inhibitor in the electron density (Table 1). In addition, a crystal structure of OXA-48 in complex with the substrate imipenem was obtained to better understand substrate binding and to compare substrate and fragment binding interactions.

The crystal structure of the acyl-enzyme complex of OXA-48 with imipenem (Fig. 2A) revealed a conformation close to previously observed conformations with OXA-13 (PDB-ID: 1h5x). In the complex the ring-opened imipenem was bound to OXA-48 covalently with continuous electron density from the hydroxyl group of Ser70. There was an ionic bond from the carboxylate group of imipenem to the guanidine group of Arg250. The carbonyl-group of the now ring-opened β-lactam ring was positioned in the oxyanion-hole forming hydrogen bonds to the main chain amides of Tyr211 and Ser70. The 6α-hydroxyethyl group (R^1) of imipenem was positioned towards the hydrophobic residues Trp105, Val120 and Leu158 and in the following discussion this region will be called the R^1 site. The amidine group (R^2) was situated in the cleft defined by Ile102, Tyr211, Leu247 and Thr213 and this region will be called the R^2 site. The R^1 and R^2 side chains of imipenem (Fig. 2A) had the same overall directions as the pyridinyl substituents in the two overlapping binding conformations observed with our initial hit 3-pyridin-4-ylbenzoic acid **1** [19].

In all our structures of OXA-48 in complex with fragments, an ionic bond between the carboxylate group of the fragments and the guanidine group of Arg250 was observed, which resembled the interaction of the carboxylate group of imipenem or the sulfamate group of avibactam with Arg250 [17,22]. In some cases, the carboxylate group was oriented in such a way that also Thr209 (fragments **9b**, **28**, **35**), Lys208 (fragment **34**) or both (fragment **26a**) participated in binding.

Another common feature found in almost all crystal structures, except for fragments **21a** and **26b**, was a π-π stacking interaction of the 3-aryl substituents attached to the benzoic acid scaffold with Tyr211. This is consistent with the binding of imipenem, where the R$_2$ side chain was oriented towards Tyr211 (Fig. 2C). The importance of Tyr211 as a non-polar patch that contributes in binding substrate side-chains has been recognised before [23]. We also observed this interaction with our unsubstituted pyridyl benzoic acids previously [19].

The weaker binding fragments (**3a, 3b, 4a**—**c, 5, 6a**—**c, 8a**—**c, 9b, 11b, 12a, 13, 14, 17, 24**) all bound in nearly the same conformation with the ionic bond of the benzoic acid and Arg250 and the π-π stacking interaction with Tyr211 as major interactions. In these structures, the 3-aryl substituent on the benzoic acid was directed towards the R$_2$ pocket (Fig. 2C). Only minor conformational differences were observed as described in the following. To help the reader in the following discussion, we will describe the fragments by the identity of the Ar groups (Table 1), as the structural differences of the fragments relate to this group *i.e.* 3-(2-methyl)

Table 1
Preparation strategy and inhibitor activities of a library of 3-substituted benzoic acids analogues against OXA-48 (IC$_{50}$, K$_d$ and LE).

Comp. ID	Ar =	Strateg. Yield	IC$_{50}$ (μM)	K$_D$ (μM)	LE[d]	Comp. ID	Ar =	Strateg. Yield	IC$_{50}$ (μM)	K$_D$ (μM)	LE[d]
3a*		B 78%	90	170	0.35	11b*		A 97%	180	350	0.29
3b*		B 67%	170	300	0.33	12a*		A 82%	120	150	0.29
4a*		A 94%	50	175	0.38	12b		A 90%	380	361	0.25
4b*		A 98%	110	110	0.35	13*		B 35%	330	330	0.29
4c*		A 39%	470	170	0.29	14*		A 95%	390	220	0.27
5*		A 84%	900	230	0.25	15a		B 36%	600	800	0.27
6a*		A 98%	250	123	0.30	15b		B 86%	1400	550	0.23
6b*		A 98%	360	226	0.28	16a		B 15%	110	300	0.31
6c*		A 86%	150	250	0.31	16b		B 67%	1000	970	0.23
7		A 91%	400	1000	0.28	17*		B[a, c] 41%	370	100	0.24
8a*		A 68%	130	170	0.34	18		B[a, c] 65%	60	210	0.24
8b*		A 98%	130	240	0.34	19a		B[a, c] 26%	110	110	0.26
8c*		A 78%	360	312	0.30	19b		B[a, c] 10%	450	240	0.22
9a		A[a, c] 57%	210	200	0.27	20		B[a, c] 11%	370	200	0.22
9b*		A 54%	260	144	0.26	21a*		A 98%	35	100	0.33
10		A 98%	380	280	0.27	21b*		A 98%	450	290	0.25
11a		A 98%	260	220	0.28	22		B[a, b] 87%	130	130	0.27
23a		B[a, c] 46%	230	170	0.24	29		B 36%	170	130	0.33
23b		B[a, c] 34%	520	190	0.22	30		B 45%	800	900	0.29

(*continued on next page*)

Table 1 (*continued*)

Comp. ID	Ar =	Strateg. Yield	IC$_{50}$ (μM)	K$_D$ (μM)	LE^d	Comp. ID	Ar =	Strateg. Yield	IC$_{50}$ (μM)	K$_D$ (μM)	LE^d
24*		A$^{a,\ b}$ 34%	250	140	0.25	31		B 67%	350	113	0.28
25		B 15%	1300	›1000	0.20	32		A 6%	500	590	0.31
26a*		B 98%	60	70	0.30	33		B 24%	800	900	0.31
26b		B 98%	36	70	0.30	34		B 20%	310	400	0.27
27*		B 67%	110	400	0.30	35*		A 98%	35	159	0.42
28*		B 87%	240	160	0.27						

*X-ray structure of fragment-enzyme complex available. ^{a} Reaction in anhydrous THF instead of dioxane:water as solvent; ^{b} XPhos-Pd G2 as catalyst instead of PdCl$_2$(PPh$_3$)$_2$; ^{c} PdCl$_2$(dppf) as catalyst instead of PdCl$_2$(PPh$_3$)$_2$. ^{d} LE = $(-1.4 * \log_{10} IC_{50})$/HeavyAtomCount, with units kcal/(mol per heavy atom).
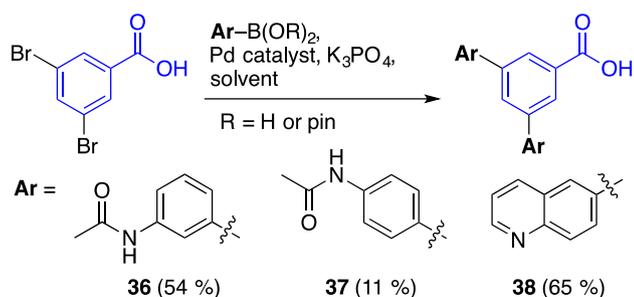

Scheme 1. Preparation of symmetrical 3,5-disubstituted benzoic acids. Reagents and conditions: **36**: 3-acetamidophenylboronic acid (1.5 equiv.), Pd$_2$ (dba)$_3$•CHCl$_3$ (5 mol%), XPhos (5 mol%), dioxane:water (1:1), 60 °C, 54%; **37**: 4-acetamidophenylboronic acid (0.75 equiv.), PdCl$_2$(PPh$_3$)$_2$ (10 mol%), dioxane:water (1:1), 95 °C, 11%; **38**: quinolin-6-ylboronic acid pinacol ester (2.0 equiv.), XPhos-Pd G2 (5 mol%), *tert*-butanol, 60 °C, 65%.

phenylbenzoic acid **3a** will be described as 2-methylphenyl substituted fragment.

The methylphenyl substituted fragments **3a** (IC$_{50}$ (μM)/LE: 90/0.35) and **3b** (IC$_{50}$ (μM)/LE: 170/0.33) had similar conformations, however, the 2-methyl group in **3a** was facing towards the hydrophobic C$^\beta$ of Ser244 explaining the more favourable binding.

Fragments **4a**–**c** (IC$_{50}$ (μM)/LE: 50/0.38, 110/0.35 and 470/0.29, respectively) also had very similar conformations, but again we saw that more favourable van der Waals interactions gave higher affinity for the 2-hydroxyphenyl substituted **4a**. The 4-hydroxy isomer **4c** had an unfavourable solvent exposure of the hydroxyl group. Adding a methylene bridge yielding 3-hydroxymethylphenyl **5** (IC$_{50}$ (μM)/LE: 900/0.25) did not lead to any favourable interactions. The methoxyphenyl fragments **6a**–**c** (IC$_{50}$ (μM)/LE: 250/0.30, 360/0.28 and 150/0.31) shared the canonical R^2 binding pose. The methoxy group of the *2*-substituted **6a** appeared more shielded from solvent exposure than in **6b** and **6c**, yet the methoxy group did not seem to make any contacts. The weak inhibition seen with methyl thioether **7** (IC$_{50}$ (μM)/LE: 400/0.28) corresponded to the results observed with the methoxy ethers **6**. The fluorophenyl substituted **8a**–**c** (IC$_{50}$ (μM)/LE: 130/0.34, 130/0.34 and 360/0.30) had nearly identical binding poses. The 4-substituted **8c** gave the highest IC$_{50}$ value, most likely due to the solvent exposed fluorine. The 2-substituted **8a** seemed more favourable based on the decreased solvent exposure of the fluorine atom, however, the difference to **8b** was negligible only observed by SPR.

The methoxyacetylphenyl esters **9a** and **9b** (IC$_{50}$ (μM)/LE: 210/0.27 and 260/0.26) showed no clear additional interactions in the complex structures with OXA-48, and the methyl group appeared to be unfavourably exposed to the solvent. The corresponding 4-

Scheme 2. Preparation of unsymmetrical 3,5-disubstituted benzoic acids. Reagents and conditions: **39**: i. X = Br, 3-acetamidophenylboronic acid (0.75 equiv.), PdCl$_2$(PPh$_3$)$_2$ (10 mol %), dioxane:water (1:1), 60 °C; ii. pyridin-4-ylboronic acid (1.2 equiv.), PdCl$_2$(PPh$_3$)$_2$ (10 mol%), dioxane:water (1:1), 60 °C; **int-40**: X = I, quinolin-6-ylboronic acid pinacol ester (2.0 equiv.), Pd$_2$ (dba)$_3$•CHCl$_3$ (5 mol%), SPhos (5 mol%), dioxane:water (1:1), 60 °C; **40**: 3-acetamidophenylboronic acid (1.5 equiv.), XPhos-Pd G2 (5 mol%), *tert*-BuOH, 60 °C.

Fig. 2. The crystal structure of imipenem in complex with OXA-48 (A) shows that the two side chains of imipenem extends in separate directions. The carbapenem substrates of OXA-48 have small R^1 side chains. We were however able to fit larger groups in the R^1 site like the N-acetamide substituted phenyl ring in compound **21a** (B). Yet, most of the tested 3-substituted benzoic acids bind towards the larger R^2 site, like the quinolin-7-yl substituted compound **28** (C).

acetylphenyl substituted **10** (IC$_{50}$ (μM)/LE: 380/0.27) and carbamoylphenyl substituted **11a** and **11b** (IC$_{50}$ (μM)/LE: 260/0.28 and 180/0.29) gave generally weak inhibition indicating that a carbonyl group attached to the aromatic ring was not contributing to binding. No complex structures are available for **10** and **11a**, but the complex structure of 4-carbamoylphenyl **11b** was similar in conformation to the esters **9a** and **9b**. Slightly tighter binding was observed with the *meta*-substituted sulfone **12a** (IC$_{50}$ (μM)/LE: 120/0.29), which also shares the same overall conformation.

The 4-aminophenyl substituent of **13** (IC$_{50}$ (μM)/LE: 330/0.30) did not appear to make any interaction with the enzyme, and the inhibition was weak. The complex structure of the corresponding *N,N*-dimethyl-4-aminophenyl substituted **14** (IC$_{50}$ (μM)/LE: 390/0.27) showed that the two methyl groups are solvent exposed, and this is reflected in the poor inhibition by this compound. Similar to the complex structure of **14**, the methyl 4-sulfonamidophenyl group of **17** (IC$_{50}$ (μM)/LE: 370/0.24) was seemingly pushed out of the active site and appears completely exposed to the solvent. The larger phenyl 4-sulfonamidophenyl substituted fragment **18** (IC$_{50}$ (μM)/LE: 60/0.24) showed lower IC$_{50}$ values probably driven by the increase in hydrophobicity, and no complex structure was obtained.

The corresponding *4*-acetamidophenyl **21b** (IC$_{50}$ (μM)/LE: 450/0.25) showed weak inhibition, likely due to the solvent exposure of the hydrophobic methyl group. The 3-acetamidophenyl containing fragment **21a** (Fig, 3), however, showed a 10-fold increased inhibition (IC$_{50}$ (μM)/LE: 35/0.33). The complex structure of OXA-48 with fragment **21a** revealed that the carbonyl of the acetyl formed a hydrogen bond to the guanidine group of Arg214, which directs the 3-acetamidophenyl substituent to the R^1 site (Fig. 2B) and lead to a T-shaped π-π-stacking interaction of the 3-acetamidophenyl substituent with Trp105. The π-π stacking of the 3-acetamidophenyl substituent to Tyr211 normally observed with these fragments was not observed; instead Tyr211 interacted with the benzoic acid by T-shaped π-π-stacking. The interaction of an acetamide with Arg214 has been described previously for the avibactam analogue FPI-1523 in complex with OXA-48 (PDB-ID: 5fas) [22].

Encouraged by the results for fragment **21a**, we designed a series of fragments incorporating a hydrocarbon linker between the phenyl ring and the amino, sulfonamido or acetamido groups of **13**, **18** and **21**. The amines **15** and **16**, the sulfonamides **19** and **20**, the amides **22**, **23a, 23b** and the acetate **24** are more flexible, thus, increasing the potential of hydrogen bonding. However, none of these fragments showed substantially improved binding (IC$_{50}$: 110–1000; LE: 0.19–0.30). Moreover, the crystal structures of the amides **22**, **23a**, **23b** and the acetate **24** (IC$_{50}$ (μM)/LE: 230/0.24, 520/0.22 and 250/0.25) did not show any specific interactions for the functional groups.

In fragments **26a** and **26b** *N*H-tetrazole substituted phenyl rings were investigated as Ar substituents. Introducing the weakly acidic tetrazol-5-ylphenyl substituent in either 3-position **26a** (IC$_{50}$ (μM)/LE: 60/0.30) or 4-position **26b** (IC$_{50}$ (μM)/LE: 36/0.30) yielded good binding for both fragments. However, the binding poses for the two compounds were very different. The 3-tetrazol-5-ylphenyl substituted **26a** bound in two alternate positions. The π-π-stacking with Tyr211 was maintained for both conformations, but the tetrazoles appeared completely solvent exposed with no interactions with the enzyme. The 4-tetrazol-5-ylphenyl substituted **26b** formed a hydrogen bond with the guanidine group of Arg214 (Fig. 4), interrupting the π-π-stacking with Tyr211. Fragment **26b** occupied the R^1 site rather than the more common R^2 site.

A number of heterocyclic aryl substituents were also evaluated (fragments **25**, **28**−**35**). With some exceptions of the pyridinyls **29** and **35** (IC$_{50}$ (μM)/LE: 170/0.33 and 35/0.42) most of these fragments showed only weak inhibition. The quinolin-7-yl substituted fragment **28** (IC$_{50}$ (μM)/LE: 240/0.30) did maintain the overall conformation of the previous R^2 binding fragments (Fig. 5), and so did the corresponding naphtalen-2-yl substituted fragment **27** (IC$_{50}$ (μM)/LE: 110/0.29). In the same manner the indol-5-yl substituted fragment **34** (IC$_{50}$ (μM)/LE: 310/0.27) did show acceptable binding, yet no specific interaction except for the π-stacking with Tyr211. In our previous paper, we investigated pyridin-4-yl and pyridin-3-yl substituted fragments [19], and both inhibited OXA-48 with the same potency (IC$_{50}$ (μM)/LE: 250/0.32). The pyridin-2-yl substituted fragments **35** (IC$_{50}$ (μM)/LE: 35/0.41) showed a 10-fold improvement in binding (Fig. 6A and B). In the crystal structure, two alternative conformations were observed (Fig. 6C). One conformation was the canonical with π-stacking of the pyridinyl ring with Tyr211 occupying the R^2 site (Fig. 6E), but in the other conformation the pyridinyl ring was orientated to the R^1 site. The second conformation showed a hydrogen bond from the protonated N atom in the pyridine ring to the backbone carbonyl of Tyr117,
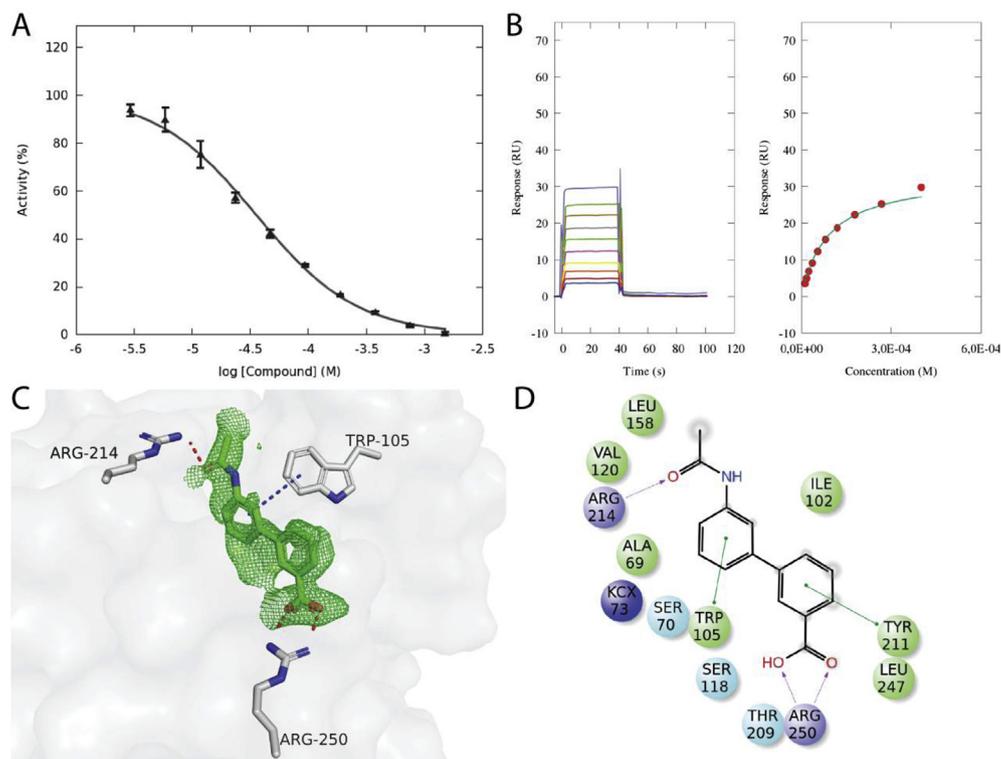
Fig. 3. Compound **21a** was one of the most potent 3-substituted benzoic acid derivatives we found. The IC_{50}-value (A) was determined to be 35 μM, while the K_d was found to be 100 μM (B). The crystal structure of the complex OXA-48:**21a** with an omit-type polder-map (2.5σ) (C) and its 2D-representation (D) shows that the carbonyl of the acetamido-group forms a hydrogen bond with the guanidine of Arg214. The interaction with Arg214 causes the B-ring to move away from Tyr211, introducing a new interaction with Trp105.

which represents a unique interaction for the fragments in the library (Fig. 6D). Only the protonated pyridinyl-nitrogen would be able to form hydrogen bonds to the Tyr117 mainchain, which may explain the slower on/off-rates observed for fragment **35** in the SPR-experiments (Fig. 6B).

In the discussion above most fragments were identified as R^2 binders with fragment **4a** (IC_{50} (μM)/LE: 50/0.38) being the strongest binder among them. For R^2 binders, the edge-to-face π-π-stacking with Tyr211 appears to be an important interaction in accordance with previous analyses [23]. Fragment **35** showed the best ligand efficiency (IC_{50} (μM)/LE: 35/0.42), but could not be classified as a R^1 or R^2 binder as both binding pockets showed useful interactions (Fig. 6C–E). Only two R^1 binders — fragments **21a** and **26b** - were identified, both showing hydrogen bonds with Arg214 as cause for the fragments orientation towards the R^1 site.

2.2.3. NMR studies

In order to evaluate the fragment-enzyme binding in solution, a ^{13}C NMR experiment for OXA-48 was developed based on previous studies [24,25]. OXA enzymes can be selectively carbamylated with bicarbonate at an active site lysine to provide the corresponding carbamic acid [24,26,27]. For OXA-48 the carbamylated residue is Lys73, which is situated in the R^1 site (Fig. 2B). By using ^{13}C-labeled sodium bicarbonate (NaH$^{13}CO_3$), a ^{13}C atom was introduced in the R^1 site of OXA-48, which can be used as a reporter probe for fragment binding in ^{13}C NMR studies.

Fragments binding in the R^1 site were expected to change the local environment of the ^{13}C labeled Lys73, which results in a change of the ^{13}C chemical shift of Lys−NH−$^{13}CO_2H$, while ligands binding in the R^2 site are further than ~9 Å away from the Lys73 carbamic acid, and are therefore not expected to directly affect the ^{13}C chemical shift.

NMR experiments were performed by equilibrating OXA-48 with ^{13}C-labeled sodium bicarbonate followed by the addition of inhibitor **2** and selected fragments **21a**, **28** and **35** with known binding modes from X-ray analysis. The results are shown in Fig. 7. The ^{13}C NMR spectrum of OXA-48 after equilibration with NaH$^{13}CO_3$ showed the carbamate resonance at 163.95 ppm as a broad signal (Fig. 7E), which is in good agreement with the reported chemical shift for carbamylated OXA-48 [28]. In addition, two unassigned signals were observed at 164.04 ppm similar to the results reported for carbamylation of OXA-58 [27]. Here the authors speculated that the unassigned signal may be related to a second carbamylation site [27].

On addition of R^1 binding fragment **21a** and inhibitor **2**, the ^{13}C chemical shifts of the carbamate signal were consistently deshielded in both experiments ($\delta = 164.25$, $\Delta\delta = 0.28$ ppm, Fig. 7E and F). These findings support that the compounds bind competitively in the active site. Moreover, the observed chemical shift perturbation indicates that the compounds occupy the R^1 site as found in the crystal structures. The R^2 binding fragment **28** showed a similar deshielding of the carbamate signal though at a smaller amplitude ($\delta = 164.13$, $\Delta\delta = 0.16$ ppm, Fig. 7D) supporting that the fragment binds in the active site, while fragment **35**, which was identified as R^1 or R^2 binder, only slightly affected the chemical shift ($\delta = 164.00$, $\Delta\delta = 0.04$ ppm, Fig. 7C). The observed chemical shift perturbations for fragments **28** and **35** may indicate that fragment **28** has an effect on carbamylated Lys73, while fragment **35** do not interact with the R^1 site, which is not consistent with the X-ray structures. However, a more detailed study of the NMR conformations would be needed to be conclusive about the binding poses in solution.

The small amplitudes of the observed chemical shift
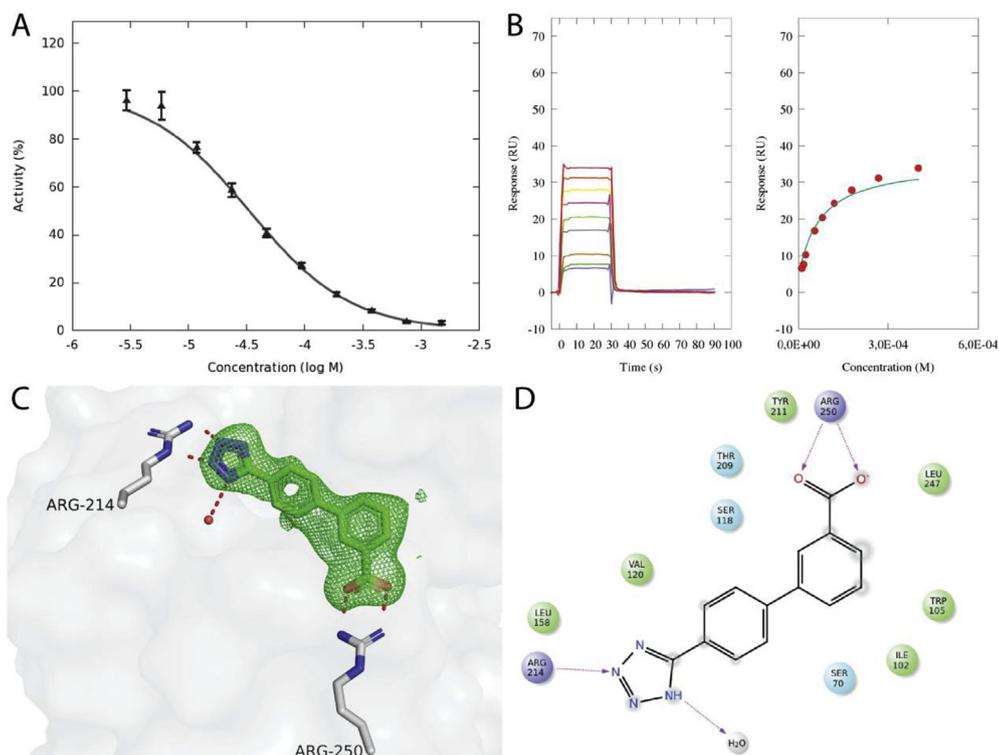
Fig. 4. The IC$_{50}$-value of compound **26b** (A) was determined to be 36 μM, while the K$_D$ was found to be 70 μM (B). The crystal structure of the complex OXA-48:**26b** with an omit-type polder-map (2.5σ) (C) and a 2D-representation of the protein:compound complex interactions. (D).
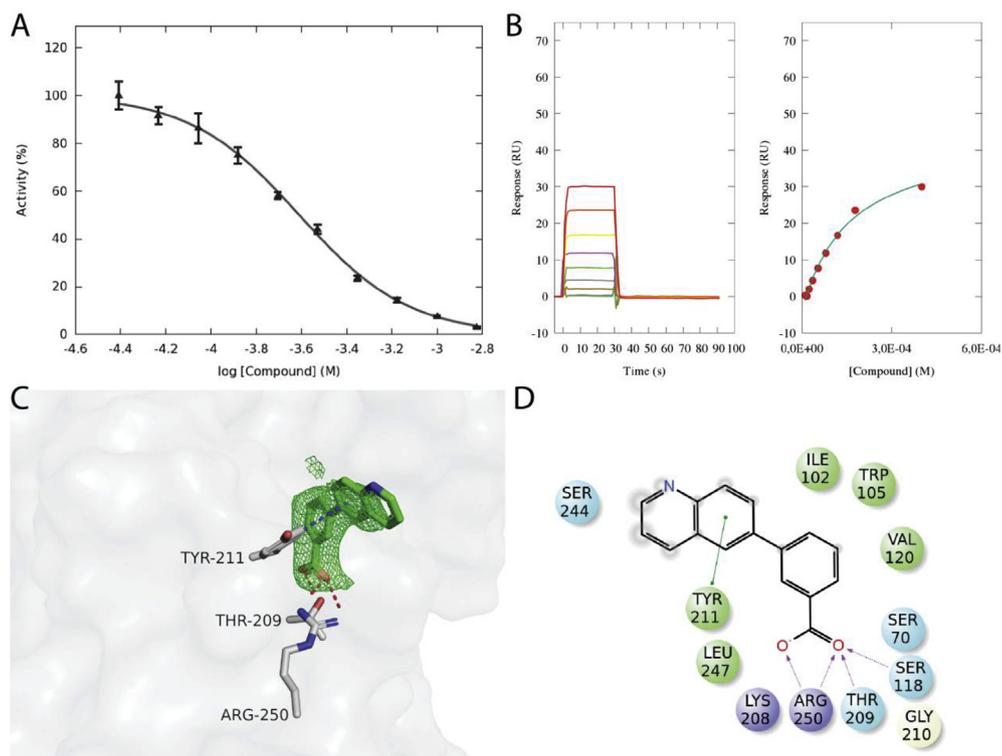
Fig. 5. The IC$_{50}$-value of compound **28** (A) was determined to be 240 μM, while the K$_D$ was found to be 160 μM (B). The crystal structure of the complex OXA-48:**28** with an omit-type polder-map (2.5σ) (C) and a 2D-representation of the protein:compound complex interactions. (D).
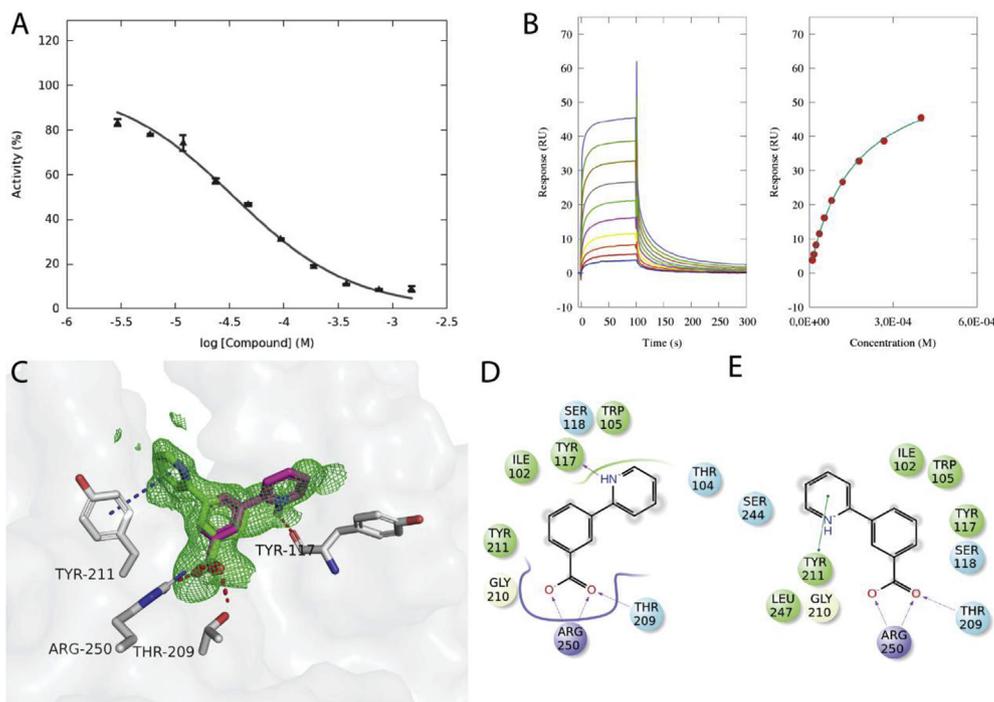
Fig. 6. Compound **35** bound in the two alternate conformations. The IC_{50}-value (A) was determined to be 35 μM, while the K_D was found to be 159 μM (B). The crystal structure of the complex OXA-48:**35** with an omit-type polder-map (2.5σ) (C) and a 2D-representation of the protein:compound complex interactions. (D for green colored conformation, E for magenta colored conformation). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

perturbations indicated that the effect is not caused by direct hydrogen bonding of the carbamic carbonyl, for which a $\Delta\delta$ of several ppm would be expected, even for a μM binder [29]. This was supported by the crystal structures of OXA-48 indicating that the Lys73 carbamic acid was preoccupied in hydrogen bonding to Trp157 and was not affected by ligand binding. The observed consistent, but rather subtle, deshielding of the Lys73 carbamic acid ($\delta = 164.25$, $\Delta\delta = 0.28$ ppm, Fig. 7E and F) for our R^1 binding fragments can possibly be explained by an anisotropic magnetic deshielding by the edge of the aromatic rings of these fragments, which were positioned roughly 5 Å away from the reporter carbon for R^1 binding fragments. Moreover, amplitude of the chemical shift perturbation observed with R^1 binding fragments **21a** and inhibitor **2** (Fig. 7E and F) were in line with the reported changes observed for OXA enzymes on coordination with inhibitors like β-hydroxyisopropylpenicillanates [24], cyclic boronates [25] and avibactam [28].

2.3. Inhibitor activity and structural analysis of 3,5-disubstituted benzoic acids

In an attempted to design more potent inhibitors from our fragments, the mono-substituted benzoic acids were evaluated for a merging approach (Fig. 8). By overlaying X-ray structures, promising combinations showing orthogonal binding poses were identified and some of the combined structures were prepared and evaluated with good results.

An overlay of fragment **21a** as well as **26b** with several R^2 binders identified the combinations of fragments **21a/28**, **21a/1** and **26b/35** as interesting partners (Fig. 9). The combination **21a/1** and **21a/28** were synthetically feasible and gave compounds **39** and **40** (Scheme 2), respectively. In addition, the symmetrical 3,5-disubstituted benzoic acids **36**–**38** representing the symmetrical combinations of fragments **21a**, **21b** and **28** were included in this
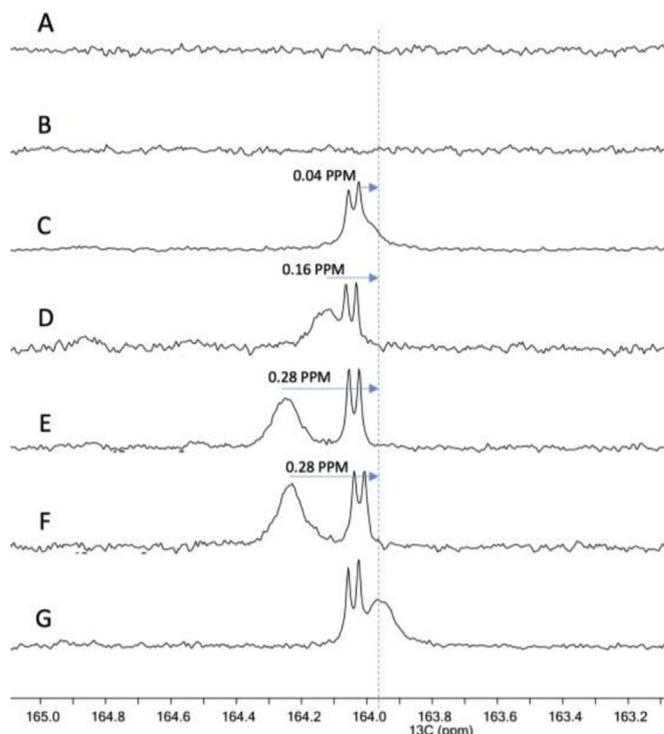
Fig. 7. ^{13}C NMR of the buffer alone including ^{13}C labeled bicarbonate (A); OXA-48 without ^{13}C labeled bicarbonate (B), OXA-48 with ^{13}C labeled bicarbonate and fragment **35** (C); OXA-48 with ^{13}C labeled bicarbonate and fragment **28** (D); OXA-48 with ^{13}C labeled bicarbonate and fragment **21a** (E); OXA-48 with ^{13}C labeled bicarbonate and 3,5-di (4-pyridinyl)benzoic acid **2** (F) and OXA-48 with ^{13}C labeled bicarbonate and no fragment (G). Two unassigned signals were observed at 164.1 ppm, and are believed to originate in a second carboxylated site of OXA-48.

study (Scheme 1).

The 3,5-disubstituted compounds **36–40** were evaluated for their inhibitory activity against OXA-48 as measured by their IC_{50}, K_d and LE and complex structures with OXA-48 and compounds **36**, **38** and **40** were obtained (Table 2). The merged compounds **37**, **38** and **39** (IC_{50} (μM)/LE: 110/0.19, 48/0.21, 100/0.22) failed to adequately maintain the binding interactions as the IC_{50} values were at a similar level as the corresponding mono-substituted fragments **28**, **1** and **21a** (IC_{50} (μM)/LE: 240/0.33, 250/0.32 and 35/0.33). When comparing the IC_{50} values of compounds **36, 37** and **40** (IC_{50} (μM)/LE: 2.9/0.27, 48/0.21 and 2.9/0.27) with the corresponding fragments **21a**, **21b** and **28** (IC_{50} (μM)/LE: 35/0.33, 450/0.26, 240/0.3), a 10-fold decrease of the IC_{50} value was observed. Nevertheless, the improved binding was associated with a decrease in LE showing that the fragment-enzyme interactions are less efficient with the merged compounds. The reduction in LE probably relates to the rigid structure of the merged compounds allowing for little conformational freedom. Overall, the strongest inhibitors in this study are compounds **36** and **40** with IC_{50} values of 2.9 μM and LE of 0.27.

The structural analysis of the OXA-48 complexes with **36**, **38** and **40** showed that the interaction of the carboxylic acid with Arg214 is maintained. For compound **36**, a near perfect overlay was obtained with the complex structure of fragment **21a** showing that all interactions seen with the fragments were preserved in the larger compound (Fig. 10). The second 3-*N*-acetamidophenyl group forms a not previously observed hydrogen bond with Ser244. In the SPR sensorgrams some concentration dependent aggregation was observed [30].

Interestingly, the conformation of compound **38** in complex with OXA-48 was changed compared with the mono-substituted fragment **28**. In the OXA-48:**38** complex, one quinolinyl group bound in the R^1 site similar to fragment **21a**. The other quinolinyl group positions itself in a conformation similar to the alternative conformation observed with fragment **35** (Fig. 6). No specific interactions were observed, but this conformation shielded the hydrophobic quinoline ring from solvent exposure by burying the compound deep in the hydrophobic cleft.

The complex structure of the unsymmetrical compound **40** (Fig. 11) that was composed of the quinoline ring of fragment **28** and the 3-*N*-acetamidophenyl substituent of fragment **13a** shared the key interactions of both mono-substituted fragments validating our approach, with an IC_{50} of 2.9 μM.

3. Conclusion

A targeted fragment library consisting of 49 diversely 3-substituted benzoic acid derivatives was prepared and biochemically analyzed for their inhibitory activity against OXA-48. Enzyme-fragment complexes for crystallographic studies were obtained for 33 fragments. By systematically changing the substituent-groups of the benzoic acid derivatives we were able to identify inhibitory fragments with $IC_{50} < 40$ μM (**21a**, **26b**, **35**). Based on the structural
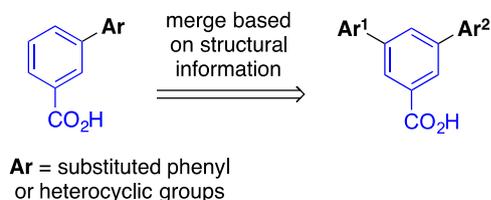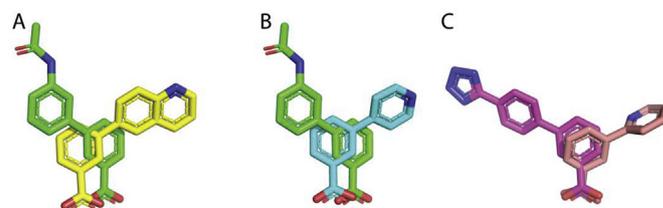
Fig. 9. Superimpositions of the binding poses observed for **21a/28** (A), **21a/1** (B, **1**: PDB-ID:5dva) and **26b/35** (C) showing some of the possible combinations for 3,5-disubstituted benzoic acids.

Table 2
Inhibitor activities of 3,5-disubstituted benzoic acids analogues against OXA-48 (IC_{50}, K_D and LE).

Ar¹	Ar²	ID	IC_{50} (μM)	K_D (μM)	LE[a]
(3-N-acetamidophenyl)	(3-N-acetamidophenyl)	**36***	2.9	20	0.27
(4-N-acetamidophenyl)	(4-N-acetamidophenyl)	**37**	48	70	0.21
(quinolinyl)	(quinolinyl)	**38***	110	70	0.19
(pyridinyl)	(3-N-acetamidophenyl)	**39**	100	70	0.22
(quinolinyl)	(3-N-acetamidophenyl)	**40***	2.9	49	0.27

*X-ray structure of fragment-enzyme complex available.
[a] LE = $(-1.4 * \log_{10}IC_{50})$/HeavyAtomCount, with units kcal/(mol heavy atom).

information, fragments could be classified according to their preferred binding pocket. Most fragments were orientated towards the R^2 site induced by a π-π-stacking with Tyr221. Unfortunately, no further interactions in the R^2 site could be identified from our library. The strongest binding fragments **21a** and **26b** were binding in the R^1 site due to a hydrogen bond to Arg214 and for fragment **35** a hydrogen bond to the carbonyl backbone of Tyr117 was observed. By overlaying the complex crystal structures of fragments **1, 21a, 26b, 28** and **35,** the design of five new 3,5-disubstituted inhibitors evolved. The strongest 3,5-disubstituted inhibitors **36** and **40** showed IC_{50} values as low as 2.9 μM, thus have improved inhibitory potential. The complex crystal structures of **36** and **40** revealed that the interactions of the individual fragments were mainly retained in the merged structures. In addition, for inhibitor **36** a previously not observed hydrogen bond from the 3-*N*-acetamidophenyl group in the R^2 site to Ser244 was found, which is interesting as we otherwise found few interactions in this region. Future work will focus on the evaluation of fragments with increased flexibility e.g. by introducing a CH_2 or heteroatom linker bridging the aromatic ring systems to further explore the active site.

Fig. 8. Strategy for substitution of the Ar^1 and Ar^2 groups in the focused fragment library of 3-substituted benzoic acids analogues.
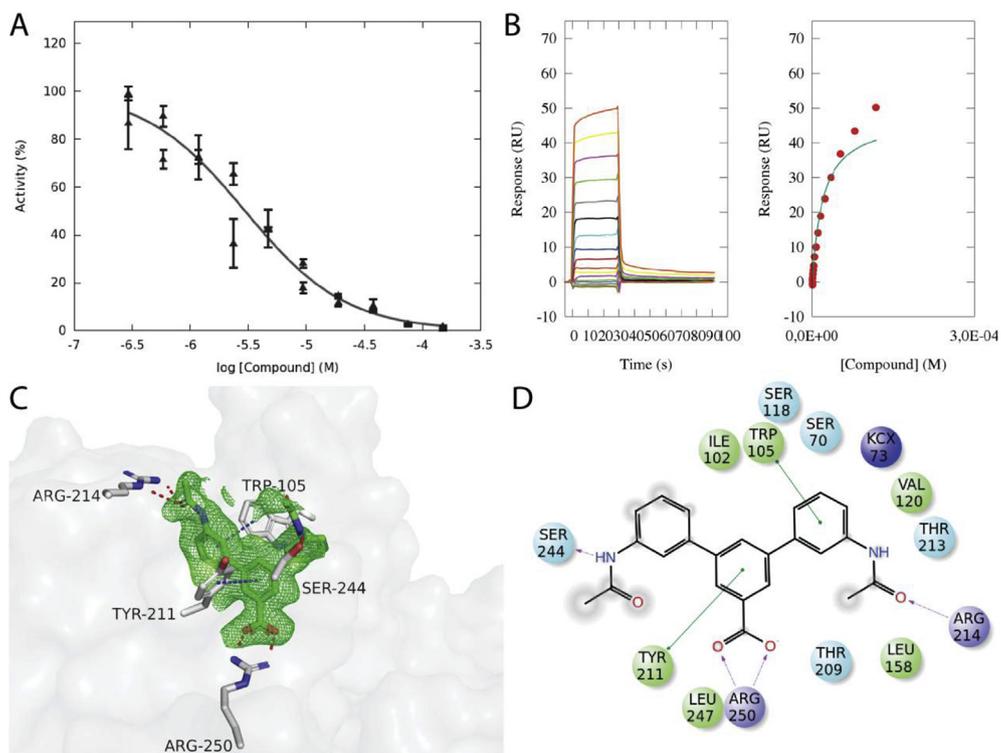
Fig. 10. Compound **36** maintained the interaction with Arg214 as we observed for the 3-substituted benzoic acid derivate. The IC_{50}-value (A) was determined to be 2.9 μM, while the K_D was found to be 30 μM (B). For the higher concentrations of compound **36** some unspecific binding was observed. The crystal structure of the complex OXA-48:**36** with an omit-type polder-map (2.5σ) (C) and its 2D-representation (D) shows one of the acetamide-groups interacted with the guanidine group of Arg214, while the other group was solvent exposed.
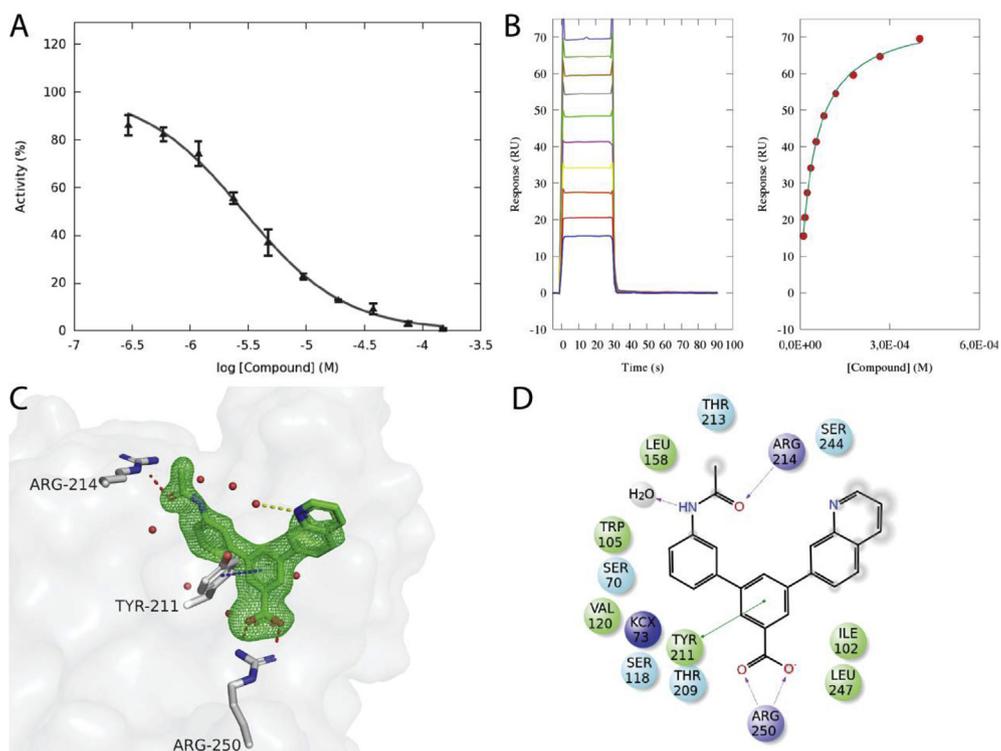
Fig. 11. Compound **40** maintained the interaction with Arg214 as we observed for the 3-substituted benzoic acid derivate. The IC_{50}-value (A) was determined to be 2.9 μM, while the K_D was found to be 49 μM (B). The crystal structure of the complex OXA-48:**40** with an omit-type polder-map (2.5σ) (C) and its 2D-representation (D) shows that the acetamide-group interacted with the guanidine group of Arg214, while the quinoline-ring was partially solvent exposed.

4. Experimental

4.1. Synthesis

4.1.1. Synthesis of 3-substituted benzoic acids (complete data for all procedures and compounds is found in the Supporting information)

4.1.1.1. General procedure A − aqueous conditions. The halo aryl (1.0 equiv) was dissolved in a mixture of water:dioxane (1:1). The boronic acid or ester (1.5 equiv) and potassium phosphate (5.0 equiv) were added. The solution was degassed by vacuum/Argon cycles (10 times) before addition of PdCl$_2$(PPh$_3$)$_2$ (10 mol%) and further degassed (5 times). The resulting mixture was stirred at 95 °C under argon atmosphere for 16−20 h. The reaction mixture was filtered through Celite and diluted with water (approx. 30 mL) before washing with chloroform (3 × 30 mL). If not stated otherwise, the aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a 10 g or 60 g C18 column with a gradient of acetonitrile in water (10−100%) to yield the desired product.

4.1.1.2. General procedure B − anhydrous conditions. The halo aryl (1.0 equiv) was dissolved in anhydrous THF. The aryl boronic acid or aryl boronic ester (1.5 equiv) and inorganic base (5.0 equiv) were added. The solution was degassed by vacuum/Argon cycles (10 times), before addition of a palladium catalyst (10 mol%) and further degassed (5 times). The resulting mixture was stirred at 75−90 °C under an inert atmosphere for 16−20 h. The reaction mixture was filtered through Celite and diluted with water (approx. 30 mL) before washing with ethyl acetate (3 × 30 mL). If not stated otherwise, the aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a 10 g or 60 g C18 column with a gradient of acetonitrile in water (10−80%) to yield the desired molecule.

4.1.2. Screening of catalysts (for results see Table SI1)

4.1.2.1. General procedure. 3-Bromo-5-iodobenzoic acid (0.03−0.06 mmol, 1.0 equiv.) was dissolved in the indicated solvent (0.5−1 mL/0.01 mmol substrate). The boronic acid or ester (1.5 equiv.) and base (5.0 equiv.) were added. The solution was degassed by vacuum/Ar cycles (10 times) before addition of the palladium catalyst and further degassed (5 times). The resulting mixture was stirred at the indicated temperature under an inert atmosphere for the indicated reaction time. The crude reaction mixture was analyzed by HRMS to determine the ratio of **int-39**: disubstituted **38**: starting material. The reaction mixture was filtered through Celite bed and diluted with water (approx. 30 mL) before washing with chloroform (3 × 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a 60 g C18 column with a gradient of acetonitrile in water (0−5% over 15 min) to yield the product.

4.1.3. Synthesis of symmetrical 3,5-disubstituted benzoic acid derivatives

4.1.3.1. 3,5-Di(3-acetamidophenyl)benzoic acid **36**. 3-Bromo-5-iodobenzoic acid (0.30 mmol, 100 mg, 1.0 equiv), 3-acetamidophenylboronic acid (0.45 mmol, 816 mg, 1.5 equiv), potassium phosphate (1.5 mmol, 324 mg, 5.0 equiv) were dissolved in a mixture of water/dioxane (1:1). The solution was degassed by vacuum/Ar cycles (10 times) before addition of Pd$_2$(dba)$_3$•CHCl$_3$ (15 mg, 5 mol%), and XPhos (7.2 mg, 5 mol%) and further degassed (5 times). The resulting mixture was stirred at 60 °C for 20−24 h. The reaction mixture was filtered through Celite bed and diluted with water (approx. 30 mL) before washing with chloroform (3 × 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a

60 g C18 column with a gradient of acetonitrile in water (0−5% over 15 min) to provide **36** (60 mg, 54%) as white powder. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.21 (s, 2H), 7.90 (t, J = 1.7 Hz, 1H), 7.81 (t, J = 1.7 Hz, 2H), 7.68 (d, J = 8 Hz, 2H), 7.43 (s, 1H), 7.49−7.46 (m, 2H), 7.43−7.39 (m, 2H), 2.16 (s, 6H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.0, 171.8, 142.9, 142.3, 140.5, 132.2, 130.4, 128.2, 128.1, 123.9, 120.3, 119.7, 24.0. HRMS (ESI): Calcd. for C$_{23}$H$_{19}$N$_2$O$_4$ [M-H]$^-$ 387.1350; found 387.1342. UPLC: purity = 97.5%

4.1.3.2. 3,5-di(4-acetamidophenyl)benzoic acid **37**. 3,5-Dibromobenzoic acid (1.01 mmol, 300 mg, 1.0 equiv), 3-acetamidophenylboronic acid (0.81 mmol, 178 mg, 0.75 equiv), potassium phosphate (3.76 mmol, 0.80 g, 3.5 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.11 mmol, 77 mg, 10 mol%) were stirred in a mixture of water/dioxane (1:1) for 24 h at 95 °C under argon atmosphere. The crude reaction mixture was filtered through Celite and diluted with water (approx. 30 mL) before washing with chloroform (3 × 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a 60 g C18 column with a gradient of acetonitrile in water (0−100% over 12 min). The fractions were analyzed by MS and fractions containing **37** were combined. The product was purified by reverse-phase automated flash chromatography before being subjected to purification by HPLC, to yield **37** (0.09 mmol, 34 mg, 11%) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.24 (s, 2H), 7.98 (d, J = 7.8 Hz, 2H), 7.85 (d, J = 7.9 Hz, 2H), 7.68−7.66 (m, 2H), 7.63−7.60 (m, 2H), 7.57−7.53 (m, 1H), 2.16 (s, 6H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.2, 171.7, 142.0, 140.2, 139.4, 137.9, 131.7, 128.4, 128.2, 127.6, 127.4, 123.3, 121.4, 116.2, 23.9. HRMS (ESI): Calcd. for C$_{23}$H$_{19}$N$_2$O$_4$ [M-H]$^-$ 387.1350; found 387.1340. UPLC: purity >99.5%

4.1.3.3. 3,5-Diquinolin-6-ylbenzoic acid **38**. 3,5-Dibromobenzoic acid (0.11 mmol, 33 mg, 1.0 equiv), 6-quinolinylboronic acid pinacol ester (0.23 mmol, 60 mg, 2.0 equiv), potassium phosphate (0.58 mmol, 125 mg, 5.0 equiv) were dissolved in tert-butanol. The solution was degassed by vacuum/Ar cycles (10 times) before addition of XPhos-Pd G2 (5 mol%, 5 mg) and further degassed (5 times). The resulting mixture was stirred at 60 °C for 20−24 h. The reaction mixture was filtered through Celite bed and diluted with water (approx. 30 mL) before washing with chloroform (3 × 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification by C18 RP flash chromatography with a gradient of acetonitrile in water (0−5% over 15 min) to yield **38** (0.08 mmol, 29 mg, 65%) as white powder. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.87−8.86 (m, 2H), 8.52 (s, 1H), 8.50 (s, 1H), 8.46 (m, 2H), 8.38 (m, 2H), 8.29−8.26 (m, 3H), 8.18 (s, 1H), 8.16 (s, 1H), 7.61−7.58 (dd, J = 8.3, 4.2 Hz, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 174.4, 151.1, 148.0, 141.5, 140.5, 138.6, 130.6, 130.1, 129.5, 128.7, 126.9, 122.8. HRMS (ESI): Calcd. for C$_{25}$H$_{15}$N$_2$O$_2$ [M-H]$^-$ 375.1139; found 375.1133. UPLC: purity = 99.1%

4.1.4. Synthesis of unsymmetrical 3,5-disubstituted benzoic acid derivatives

4.1.4.1. 3-(3′-Acetamidophenyl)-5-pyridin-4-ylbenzoic acid **39**: attempted synthesis from 3,5-dibromobenzoic acid. 3,5-Dibromobenzoic acid (1.01 mmol, 300 mg, 1.0 equiv), 3-acetamidophenylboronic acid (0.81 mmol, 178 mg, 0.75 equiv), potassium phosphate (3.76 mmol, 0.80 g, 3.5 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.11 mmol, 77 mg, 10 mol%) were stirred in a mixture of water/dioxane (1:1) for 24 h at 95 °C under argon atmosphere. The crude reaction mixture was filtered through Celite and diluted with water (approx. 30 mL) before washing with chloroform (3 × 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification by C18

RP flash chromatography with a gradient of acetonitrile in water (10−100% over 12 min). The fractions were analyzed by MS and fractions containing **int-39** were combined and reacted with pyridin-4-ylboronic acid (0.97 mmol, 119 mg, 1.2 equiv), potassium phosphate (4.05 mmol, 0.86 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.08 mmol, 56 mg, 10 mol%). The product was purified by reverse-phase automated flash chromatography before being subjected to purification by HPLC, to yield **39** (0.12 mmol, 39 mg, 15%) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.22 (s, 1H), 7.92 (d, $J = 7.6$ Hz, 1H), 7.76 (s, 2H), 7.68−7.60 (m, 3H), 7.46−7.33 (m, 4H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.3, 171.7, 143.0, 141.5, 140.4, 139.8, 130.3, 129.7, 129.3, 129.3, 128.9, 123.7, 120.1, 119.6, 23.9. UPLC: purity = 97.9%

4.1.4.2. 3-Bromo-5-(quinolin-6-yl) benzoic acid **int-40**. 3-Bromo-5-iodobenzoic acid (0.15 mmol, 50 mg, 1.0 equiv), 6-quinolinylboronic acid pinacol ester (0.22 mmol, 58 mg, 1.5 equiv) and potassium phosphate (0.76 mmol, 162 mg, 5.0 equiv) were dissolved in a mixture of water/dioxane (1:1). The solution was degassed by vacuum/Ar cycles (10 times) before addition of Pd$_2$(dba)$_3$·CHCl$_3$ (5 mol%, 7.5 mg), and SPhos (5 mol%, 3.1 mg) and further degassed (5 times). The resulting mixture was stirred at 60 °C for 20−24 h. The reaction mixture was filtered through a Celite bed and diluted with water (approx. 30 mL) before washing with chloroform (3 × 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a 60 g C18 column with a gradient of acetonitrile in water (0−5% over 20 min). Product **int-40** (0.07 mmol, 23 mg, 45%) was obtained as a white powder. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.92−8.91 (m,1H), 8.49−8.46 (m, 1H), 8.35 (s,1H), 8.28 (s, 2H), 8.10 (s, 2H), 8.02−8.01 (m, 1H), 7.97−7.96 (m,1H), 7.59−7.56 (dd, $J = 8.3$, 4.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.6, 150.8, 147.2, 143.6, 140.6, 136.8, 136.5, 131.7, 131.1, 129.6, 128.5, 128.2, 127.4, 126.5, 125.8, 121.9, 121.7; HRMS (ESI): Calcd. for C$_{16}$H$_9^{79}$BrNO$_2$ [M-H]$^-$ 325.9822; found 325.9822.

4.1.4.3. 3-(3′-Acetamidophenyl)-5-quinolin-6-ylbenzoic acid **40**. 3-Bromo-5-(quinolin-6-yl) benzoic acid **int-40** (0.039 mmol, 13 mg, 1.0 equiv), 3-acetamidophenylboronic acid (0.55 mmol, 10 mg, 1.5 equiv) and potassium phosphate (0.20 mmol, 0.42 g, 5.0 equiv) were dissolved in *tert*-butanol. The solution was degassed by vacuum/Ar cycles (10 times) before addition of Xphos-Pd G2 (5 mol%, 1.5 mg) and further degassed (5 times). The resulting mixture was stirred at 60 °C for 20−24 h. The reaction mixture was filtered through Celite bed and diluted with water (approx. 30 mL) before washing with chloroform (3 × 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a 60 g C18 column with a gradient of acetonitrile in water (0−5% over 20 min). Product **40** (0.023 mmol, 9 mg, 90%) was obtained as white powder. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.87−8.83 (m, 1H), 8.56−8.45 (m, 1H), 8.41−8.39 (m, 1H), 8.35−8.20 (m, 3H), 8.18−8.11 (m, 1H), 8.08 (t, $J = 1.8$ Hz, 1H), 7.87−7.86 (m, 1H), 7.72−7.68 (m, 1H), 7.62−7.56 (m, 1H), 7.56−7.49 (m, 1H), 7.46−7.42 (m, 1H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7, 171.8, 151.2, 148.2, 142.8, 142.5, 141.4, 140.8, 140.7, 140.5, 138.8, 130.8, 130.4, 130.3, 129.7, 128.6, 128.5, 128.5, 127.0, 123.9, 123.0, 120.3, 119.7, 23.9. HRMS (ESI): Calcd. for C$_{24}$H$_{18}$N$_2$O$_3$ [M-H]$^-$ 381.1245; found 381.1243.UPLC: purity = 96.4%

4.2. Protein production

For the biochemical assay OXA-48 was expressed with the native signal-peptide and purified from the periplasm as described earlier [31]. For surface plasmon resonance assays, nuclear magnetic resonance and crystallization a His-tagged construct was used

[19].

4.3. Biochemical assay

All experiments were performed using a Spectramax M2e at 25 °C in 100 mM sodium phosphate (pH 7.0) supplemented with 50 mM NaHCO$_3$ and 0.2 mg/mL bovine serum albumin (BSA). Velocities from the linear range were determined in the SoftMax Pro software (Molecular Devices). All experiments were done with a sample volume of 100 μL. IC$_{50}$ values were determined for all compounds in competition with 25 μM of the chromogenic substrate nitrocefin. The log$_{10}$ of the inhibitor concentrations to the response with bottom and top constant based on controls were fitted nonlinearly in GraphPad Prism 6 (GraphPad Software) to determine the IC$_{50}$ value.

4.4. Surface plasmon resonance

All SPR experiments were performed on a Biacore T200 at 25 °C. The data were analyzed using Biacore T200 Evaluation Software 2.0 (GE Healthcare). The sensorgrams were double reference subtracted using a reference surface and blank injections. The final running buffer included 50 mM HEPES pH 7.0, 50 mM K$_2$SO$_4$, 0.5% Tween-20, 50 mM NaHCO$_3$, and 2.5% DMSO. The enzyme, OXA-48, was diluted to 25 μg/mL in 10 mM MES pH 5.5. The enzyme was immobilized to a level of around 5000 RU on a CM5 chip using standard amine coupling.

Compounds were tested with 10 dilutions from 400 μM to 10.5 μM, with 30 s injection and 60 s dissociation time. Compounds exhibiting kinetic behavior had the dissociation time extended to 300 s. Seven startup cycles with buffer were performed. Solvent correction was performed every 48th cycle and a positive control was included every 24th cycle with 3.5-Di (4-pyridinyl)benzoic acid as the control [19]. Affinities were calculated from the steady-state affinity model with a constant R_{max} adjusted by the control and the molecular weight of the compound.

4.5. ^{13}C nuclear magnetic resonance

A solution of NaH^{13}CO3 in D$_2$O (50 mM) was prepared. The NaH^{13}CO$_3$/D$_2$O-mixture was added to 1 mM OXA-48 in 50 mM sodium phosphate and 50 mM sodium bicarbonate pH 6.5 in a 1: 9 ratio of bicarbonate to enzyme. Compounds were diluted from a 150 mM stock solution in 100% DMSO to a final concentration of 3.75 mM (2.5% DMSO). Sample volumes of 500 μL were used. We performed the experiment at 37 °C with a Bruker Avance III HD with an inverse detected TCI probe with cryogenic enhancement for ^{1}H, ^{13}C and ^{2}H, operating at 599.90 MHz for protons and 150.86 MHz for carbon. 10 000 scans at 30° pulse angle with 2 s relaxation delay were collected using 1D^{13}C NMR with power-gated decoupling of protons (zgpg30 using waltz16).

4.6. Crystallization and data processing

Crystals of OXA-48 was grown from hanging drops containing 0.1 M HEPES pH 7.5, 8−11% PEG 8000 and 4−8% 1-butanol as previously described [17]. Compounds were diluted to 3.75 mM in the cryo solution with 0.1 M HEPES pH 7.5, 10% PEG 8000, 5% 1-butanol, and 25% ethanediol, usually overnight. The exception was the crystal soaked in imipenem. Imipenem was added to saturation in the cryosolution, and the crystal was just given a quick soak.

Crystals were flash cooled in liquid nitrogen. X-ray diffraction data were collected at BL 14.1 and BL14.2 at BESSY (Berlin, Germany) [32], and at ID23-1, ID23-2 and ID30B at ESRF (Grenoble, France). In most cases the structures were solved by refining

against the protein-atoms of previous structures (P2$_1$2$_1$2$_1$ PDB ID: 5DVA and P2$_1$ PDB ID: 5DTK), but in cases where the unit cells were to different PHASER was used with chain A from PDB ID: 5dtk as the search model for molecular replacement. In most cases images were autoprocessed using the tools at the beamlines [33–37], but in some cases we found it useful to reprocess using DIALS or XDS together with AIMLESS [38–40].

The compounds were built into difference density maps after initial refinement in phenix.refine [41], with waters deleted from the active site. Restraints for the compounds were prepared using the GRADE Web Server [42]. Omit maps were calculated using the phenix.polder-tool which excludes bulk-solvent from the volume surrounding the ligand [43]. Figures were made using PyMOL [44]. Ligand-interaction diagrams were prepared using the Maestro-suite from Schrödinger Release 2016-3 (Schrödinger, LLC, New York).

Author contributions

Designed the experiments: AB, BAL, HKSL, SA, TC. Performed the organic synthesis: SA, AI, ML. Determined IC$_{50}$ values and K$_d$-values: BAL. Prepared and solved crystal structures: BAL. Analyzed 3D structures: AB, BAL, SA. NMR studies: BAL, JI. Analyzed data and wrote the paper: AB, BAL, HKSL, JI, SA, TC. All authors have given approval to the final version of the manuscript.

PDB accession codes

Coordinates and structure factors for all OXA-48 complexes are deposited in the Protein Data Bank. Accession numbers are listed with reference to the complexed compound. PDB IDs: imipenem: 5QB4; **3a**: 5QA4; **3b**: 5QA5; **4a**: 5QA6; **4b**: 5QA7; **4c**: 5QA8; **5**: 5QA9; **6a**: 5QAA; **6b**: 5QAB; **6c**: 5QAC; **8a**: 5QAD; **8b**: 5QAE; **8c**: 5QAF; **9a**: 5QAG; **9b**: 5QAH; **12a**: 5QAI; **13**: 5QAJ; **14**: 5QAK; **11b**: 5QAL; **17**: 5QAM; **19a**: 5QAN; **19b**: 5QAO; **21a**: 5QAP; **21b**: 5QAQ; **23a**: 5QAR; **23b**: 5QAS; **24**: 5QAT; **26a**: 5QAU; **26b**: 5QAV; **27**: 5QAW; **28**: 5QAX; **32**: 5QAY; **34**: 5QAZ; **35**: 5QB0; **36**: 5QB1; **38**: 5QB2; **40**: 5QB3.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejmech.2017.12.085.

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Supporting information for

A focused fragment library targeting the antibiotic resistance enzyme - oxacillinase-48: synthesis, structural evaluation and inhibitor design

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Table of content:

1 Synthesis

1.1 Material and methods

All reagents and solvents were purchased from commercial sources and used as supplied, unless otherwise stated. Solvent mixtures are given in (v|v). The water used for reactions, was purified on a Millipore RiOs™ device. The aqueous phase was concentrated under reduced pressure and Purification of compounds was carried out by automated RP flash chromatography with preloading to a C18 Samplet® cartridge (Biotage) before purification on a C18 RP column (Biotage) or by flash chromatography using silica gel from Merck (Silica gel 60, 0.040–0.063 mm). For thin layer chromatography TLC-PET sheets precoated with silica gel (60 F254) were used. Visualization was accomplished with either UV light or by immersion in potassium permanganate, phosphomolybdic acid (PMA) or ninhydrin followed by light heating with a heating gun. Purity analysis was carried out on Waters Acquity UHPLC® BEH C18 (1.7 µm, 2.1 × 100 mm) column on a Waters Acquity I-class UHPLC with a photodiode array setector. NMR spectra were recorded on a 400 MHz Bruker Avance III HD equipped with a 5 mm SmartProbe BB/1H (BB = ^{19}F, ^{31}P, ^{15}N). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dt = double triplet, m = multiplet), coupling constant (J, Hz) and integration. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak (CDCl$_3$: δ_H 7.26 and δ_C 77.16; methanol-d$_4$: δ_H 3.31 and δ_C 49.00, deuterium oxide: δ_H 4.79 and δ_C 49.00; DMSO-d_6 δ_H 2.51 and δ_C 39.52). The raw data was analysed with MestReNova (Version 10.0.2-15465). Electrospray ionization mass spectrometry was conducted on a Thermo electron LTQ Orbitrap XL spectrometer. The data was analyzed with Thermo Scientific Xcalibur software. Melting points were determined on a Büchi 535 device or a ThermoFischer Scientific IA9100 Digital Melting Point apparatus.

1.2 Synthesis of 3-substituted benzoic acids

General procedure A – Aqueous conditions:

The halo aryl (1.0 equiv) was dissolved in a mixture of water:dioxane (1:1). The boronic acid or ester (1.5 equiv) and potassium phosphate (5.0 equiv) were added. The solution was degassed by vacuum/argon cycles (10 times) before addition of PdCl$_2$(PPh$_3$)$_2$ (10 mol%) and further degassed (5 times). The resulting mixture was stirred at 95 °C under argon atmosphere for 16-20 hours. The reaction mixture was filtered through Celite and diluted with water (approx. 30 mL) before washing with chloroform (3 x 30 mL). If not stated otherwise, the aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a 10g or 60 g C18 column with a gradient of acetonitrile in water (10-100%) to yield the desired product.

General procedure B – Anhydrous conditions:

The halo aryl (1.0 equiv) was dissolved in anhydrous THF. The aryl boronic acid or aryl boronic ester (1.5 equiv) and inorganic base (5.0 equiv) were added. The solution was degassed by vacuum/Argon cycles (10 times), before addition of a palladium catalyst (10 mol%) and further degassed (5 times). The resulting mixture was stirred at 75–90 °C under an inert atmosphere for 16-20 hours. The reaction mixture was filtered through Celite and diluted with water (approx. 30 mL) before washing with ethyl acetate (3 x 30 mL). If not stated otherwise, the aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a 10 g or 60 g C18 column with a gradient of acetonitrile in water (10–80%) to yield the desired molecule.

2'-methylbiphenyl-3-carboxylic acid, 3a:

According to procedure A, 3-carboxyphenylboronic acid pinacol ester (1.32 mmol, 326 mg, 1.5 equiv), 2-bromotoluene (0.88 mmol, 150 mg, 1 equiv), potassium phosphate (4.39 mmol, 929 mg, 5 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.088 mmol, 62 mg, 10 mol%) gave **3a** (0.64 mmol, 136 mg, 78 %) as white solid. T$_m$ =

288-289°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.90-7.79 (m, 2H), 7.33-7.29 (m, 1H), 7.24 (dt, J = 7.6, 1.6 Hz, 1H), 7.18-7.07 (m, 4H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.4, 143.2, 142.9, 139.1, 136.4, 131.9, 131.3, 131.1, 130.7, 128.7, 128.5, 128.3, 126.8, 20.6. HRMS (ESI): Calcd. for $C_{14}H_{10}O_2$ [M-H]$^-$ 211.0765; found 211.0766. UHPLC: purity = 97.5 %

3'-methylbiphenyl-3-carboxylic acid, 3b:

According to procedure A, 3-carboxyphenylboronic acid pinacol ester (1.32 mmol, 326 mg, 1.5 equiv), 3-bromotoluene (0.88 mmol, 150 mg, 1.0 equiv), potassium phosphate (4.39 mmol, 929 mg, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.088 mmol, 62 mg, 10 mol%) gave 3b (0.59 mmol, 124 mg, 67 %) as white solid. T_m = 257-258°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.12 (s, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.40-7.28 (m, 3H), 7.21 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.4, 142.3, 142.1, 139.6, 139.5, 129.7, 129.7, 129.2, 129.1, 128.9, 128.9, 128.7, 125.1, 21.6. HRMS (ESI): Calcd. for $C_{14}H_{10}O_2$ [M-H]$^-$ 211.0765; found 211.0768. UHPLC: purity = 95.5 %

2'-hydroxybiphenyl-3-carboxylic acid, 4a:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 3-hydroxyphenylboronic acid (1.86 mmol, 256 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave 4a (1.17 mmol, 250 mg, 94 %) as white solid. T_m = 290-291°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.21 (dd, J = 7.6, 1.6 Hz, 1H), 7.14-6.99 (m, 2H), 6.82 (td, J = 7.2, 1.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.9, 155.6, 141.0, 138.2, 130.6, 130.4, 129.7, 128.7, 128.5, 127.7, 127.0, 119.2, 116.7. HRMS (ESI): Calcd. for $C_{13}H_9O_3$ [M-H]$^-$ 213.0557 found 213.0561. UHPLC: purity > 99.5%

3'-hydroxybiphenyl-3-carboxylic acid, 4b:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 3-hydroxyphenyl boronic acid (1.86 mmol, 256 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave, 4b (1.21 mmol, 260 mg, 98 %) as white solid. T_m = 279-280°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.82 (d, J = 7.5 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.23-7.17 (m, 2H), 7.01 (s, 1H), 6.73 (d, J = 7.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.5, 159.4, 142.2, 141.8, 139.7, 130.1, 128.4, 128.0, 127.6, 127.1, 116.8, 114.9, 114.1. HRMS (ESI): Calcd. for $C_{13}H_9O_3$ [M-H]$^-$ 213.0557; found 213.0565. UHPLC: purity = 96.0 %

4'-hydroxybiphenyl-3-carboxylic acid, 4c:

According to general procedure A, 3-bromobenzoic acid (0.75 mmol, 150 mg, 1.0 equiv), (4-hydroxyphenyl)boronic acid (1.12 mmol, 154 mg, 1.5 equiv), potassium phosphate (3.73 mmol, 792 mg, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.07 mmol, 52 mg, 10 mol%) were stirred at 95°C. The aqueous phase was washed with a mixture of hexane/ethyl acetate (1:1, v/v, 3 x 30 mL) instead of chloroform. After purification the title compound, 4c (0.29 mmol, 63 mg, 39%) was obtained as a dark brown solid. T_m = 257-259°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.13 (t, J = 1.8 Hz, 1H), 7.83 (dt, J = 7.7, 1.4 Hz, 1H), 7.62 (dt, J = 7.8, 1.4 Hz, 1H), 7.55-7.49 (m, 2H), 7.43 (t, J = 7.7 Hz, 1H), 6.95-6.88 (m, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.7, 157.5, 141.5, 138.8, 133.5, 129.4, 129.3, 129.0, 128.3, 128.0, 116.8. HRMS (ESI): Calcd. for $C_{13}H_9O_3$ [M-H]$^-$ 213.0557; found 213.0577. UHPLC: purity = 97.8 %

3'-(hydroxymethyl)biphenyl-3-carboxylic acid, 5:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 3-(Hydroxymethyl)phenylboronic acid (1.86 mmol, 282 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave 5, (1.04 mmol, 239 mg,

84 %) as white solid. T_m = 241-242°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 13.8 Hz, 2H), 7.58-7.52 (m, 2H), 7.42 (d, J = 8.0 Hz, 1H), 4.72 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.1, 143.7, 142.6, 141.1, 139.4, 129.1, 128.5, 128.1, 127.8, 126.9, 125.7, 125.3, 125.1, 63.4. HRMS (ESI): Calcd. for $C_{14}H_{11}O_3$ [M-H]$^-$ 227.0714; found 227.0716. UHPLC: purity = 95.1 %

2'-methoxybiphenyl-3-carboxylic acid, 6a:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 3-methoxyphenylboronic acid (1.86 mmol, 282 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **6a** (0.89 mmol, 205 mg, 73 %) as white solid. T_m = 88-89°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.38-7.22 (m, 4H), 7.10 (d, J = 8.2 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.2, 156.7, 141.9, 137.3, 131.1, 130.9, 130.4, 129.5, 128.9, 127.9, 126.9, 121.1, 112.1, 55.9. HRMS (ESI): Calcd. for $C_{14}H_{11}O_3$ [M-H]$^-$ 227.0714; found 227.0712. UHPLC: purity = 98.0 %

3'-methoxybiphenyl-3-carboxylic acid, 6b:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 3-methoxyphenylboronic acid (1.86 mmol, 282 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **6b** (1.04 mmol, 237 mg, 84 %) as white solid. T_m = 149-150°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.84 (d, J = 7.0 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.35 (dt, J = 18.7, 7.7 Hz, 2H), 7.21 (d, J = 7.6 Hz, 1H), 7.15 (s, 1H), 6.92 (dd, J = 8.2, 2.5 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.3, 159.7, 142.5, 138.7, 129.9, 128.3, 127.5, 127.3, 126.5, 118.9, 112.7, 111.9, 99.5, 55.1. HRMS (ESI): Calcd. for $C_{14}H_{11}O_3$ [M-H]$^-$ 227.0714; found 227.0711. UHPLC: purity > 99.5 %

4'-methoxybiphenyl-3-carboxylic acid, 6c:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 4-methoxyphenyl boronic acid (1.86 mmol, 282 mg, 1.5 equiv), potassium phosphate (7.44 mmol, 1.58 g, 6.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **6c** (1.07 mmol, 244 mg, 86 %) as white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.19 (s, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.75-7.51 (m, 3H), 7.40 (t, J = 7.7 Hz, 1H), 7.00 (d, J = 8.0 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.3, 160.6, 141.5, 139.4, 134.7, 129.2, 129.1, 128.9, 128.4, 128.3, 115.2, 55.6. HRMS (ESI): Calcd. for $C_{14}H_{11}O_3$ [M-H]$^-$ 227.0708; found 227.0724. UHPLC: purity = 98.8 %

4'-methylthiobiphenyl-3-carboxylic acid, 7:

According to general procedure B, 3-bromobenzoic acid (0.75 mmol, 150 mg, 1.0 equiv), 4-(methylthio)phenyl boronic acid (1.12 mmol, 188 mg, 1.5 equiv), Na$_2$CO$_3$ (3.73 mmol, 395 mg, 5.0 equiv), PdCl$_2$(dppf) (0.07 mmol, 55 mg, 10 mol%) in anhydrous THF (8 mL) was stirred at 75°C for 18h. After purification the title compound, **7** (0.68 mmol, 167 mg, 91%) was obtained as a brownish solid. T_m = 228°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.93-7.85 (m, 1H), 7.69-7.62 (m, 1H), 7.63-7.58 (m, 2H), 7.45 (t, J = 7.9 Hz, 1H), 7.37-7.30 (m, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.4, 141.0, 139.2, 138.9, 138.7, 129.5, 129.5, 129.0, 128.3, 127.8, 15.7. HRMS (ESI): Calcd. for $C_{14}H_{11}O_2S$ [M-H]$^-$ 243.0485; found 243.0483. UHPLC: purity = 98.4 %

2'-fluorobiphenyl-3-carboxylic acid, 8a:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 2-flourophenylboronic acid (1.86 mmol, 256 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **8a** (0.84 mmol, 181 mg, 68 %) as white

solid. T_m = 260-261°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.04 (s, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.37-7.20 (m, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.12-7.02 (m, 1H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.1, 161.1 (d, J = 246.5 Hz), 139.5, 136.6, 131.9 (d, J = 3.4 Hz), 131.8 (d, J = 3.5 Hz), 130.9 (d, J = 2.4 Hz), 130.3 (d, J = 8.4 Hz), 129.6, 128.8, 125.6 (d, J = 3.8 Hz), 116.9 (d, J = 22.9 Hz). HRMS (ESI): Calcd. for $C_{13}H_8FO_2$ [M-H]$^-$ 215.0514; found 215.0511. UHPLC: purity > 99.5%

3'-fluorobiphenyl-3-carboxylic acid, 8b:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 3-flourophenylboronic acid (1.86 mmol, 256 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **8b** (1.03 mmol, 222 mg, 83 %) as white solid. T_m = 239-241°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.13 (s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.49-7.20 (m, 4H), 6.97 (t, J = 8.6 Hz, 1H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.05, 164.71 (d, J = 244.0 Hz), 144.83, 140.56, 139.90, 131.53, 129.78, 129.68, 129.44, 128.89, 123.87, 123.84, 114.74 (dd, J = 25.9, 21.8 Hz). HRMS (ESI): Calcd. for $C_{13}H_8FO_2$ [M-H]$^-$ 215.0514; found 215.0511. UHPLC: purity = 98.7%

4'-fluorobiphenyl-3-carboxylic acid, 8c:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 4-flourophenylboronic acid (1.86 mmol, 256 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **8c** (0.97 mmol, 169 mg, 78 %) as white solid. T_m = 298-299°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.75-7.58 (m, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.42-7.19 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.9, 162.1 (d, J = 243.6 Hz), 142.8, 138.27, 137.8, 137.81, 128.9, 128.9, 128.6, 128.1, 127.7, 126.8, 116.1 (d, J = 21.2 Hz). HRMS (ESI): Calcd. for $C_{13}H_8FO_2$ [M-H]$^-$ 215.0514; found 215.0511. UHPLC: purity > 99.5%

2'-(methoxycarbonyl)biphenyl-3-carboxylic acid, 9a:

According to general procedure B, 3-bromobenzoic acid (0.75 mmol, 150 mg, 1.0 equiv), (2-(methoxycarbonyl)phenyl)boronic acid (1.12 mmol, 201 mg, 1.5 equiv), Na$_2$CO$_3$ (3.73 mmol, 395 mg, 5.0 equiv) and PdCl$_2$(dppf) (0.07 mmol, 55 mg, 10 mol%) in anhydrous THF (8 mL) was stirred at 90 °C for 20h. After purification the title compound, **9a** (0.43 mmol, 109 mg, 57%) was obtained as a brown solid. T_m = 206-208°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.97-7.92 (m, 2H), 7.77 (dd, J = 8.0, 1.5 Hz, 1H), 7.61-7.53 (m, 1H), 7.47-7.36 (m, 3H), 7.31 (dt, J = 7.7, 1.5 Hz, 1H), 3.60 (s, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.1, 171.0, 143.6, 142.1, 139.2, 132.5, 132.4, 131.8, 131.2, 130.6, 130.3, 129.2, 128.5, 128.3, 52.4. HRMS (ESI): Calcd. for $C_{15}H_{11}O_4$ [M-H]$^-$ 255.0663; found 255.0660. UHPLC: purity > 99.5%

3'-(methoxycarbonyl)biphenyl-3-carboxylic acid, 9b:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 3-Methoxycarbonylphenylboronic acid (1.86 mmol, 335 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **9b** (0.68 mmol, 174 mg, 54 %) as white solid. T_m = 163-164°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 8.18 (s, 1H), 7.97-7.94 (m, 2H), 7.88 (d, J = 7.6 Hz, 1H), 7.63 (t, J = 8.0 Hz, 2H), 7.38 (t, J = 7.6 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.6, 166.7, 142.9, 141.7, 138.1, 131.8, 130.7, 129.9, 129.1, 128.3, 128.2, 127.7, 127.4, 126.9, 52.7. HRMS (ESI): Calcd. for $C_{15}H_{11}O_4$ [M-H]$^-$ 255.0663; found 255.0660. UHPLC: purity = 97.8 %

4'-acetylbiphenyl-3-carboxylic acid, 10:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 4-acetylphenylboronic acid (1.86 mmol, 305 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5.0 equiv) and

PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **10** (0.68 mmol, 174 mg, 54 %) as white solid. T$_m$ = 287-289°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.06 (d, J = 8.2 Hz, 2H), 7.91 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 7.9 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 2.63 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.9, 168.7, 145.7, 142.9, 138.0, 135.8, 129.5, 129.4, 128.3, 127.9, 127.2, 127.2, 27.2. HRMS (ESI): Calcd. for C$_{15}$H$_{11}$O$_3$ [M-H]$^-$ 239.0714; found 239.0709. UHPLC: purity = 95.4 %

3'-carbamoylbiphenyl-3-carboxylic acid, 11a:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 3-aminocarbonylphenylboronic acid (1.86 mmol, 307 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **11a** (1.59 mmol, 383 mg, 85 %) as white solid. T$_m$ = 235-237°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.23 (s, 2H), 7.93-7.90 (m, 2H), 7.85 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.46-7.40 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.8, 168.4, 142.9, 141.3, 138.7, 135.4, 129.8, 129.3, 128.9, 128.1, 127.9, 126.9, 126.7, 126.1. HRMS (ESI): Calcd. for C$_{14}$H$_{10}$NO$_3$ [M-H]$^-$ 240.0666; found 240.0662. UHPLC: purity = 96.7 %

4'-carbamoylbiphenyl-3-carboxylic acid, 11b:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 4-aminocarbonylphenylboronic acid (1.86 mmol, 307 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **11b** (1.20 mmol, 290 mg, 97 %) as white solid. T$_m$ = 262-263°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.19 (s, 1H), 7.92-7.83 (m, 3H), 7.71-7.59 (m, 3H), 7.37 (t, J = 7.7 Hz, 1H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.0, 172.1, 145.8, 140.7, 139.9, 133.6, 130.7, 129.9, 129.8, 129.5, 129.3, 129.0, 128.0, 116.5. HRMS (ESI): Calcd. for C$_{14}$H$_{10}$NO$_3$ [M-H]$^-$ 240.0666; found 240.0671. UHPLC: purity = 97.5 %

3'-(methylsulfonyl)biphenyl-3-carboxylic acid, 12a:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 3-methanesufonylphenyl boronic acid (1.24 mmol, 248 mg, 1 equiv), potassium phosphate (3.72 mmol, 789 mg, 3 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **21a** (1.02 mmol, 283 mg, 82 %) as white solid. T$_m$ = 96-98°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.20 (s, 1H), 8.15 (s, 1H), 7.95-7.88 (m, 2H), 7.84 (d, J = 7.8 Hz, 1H), 7.67-7.61 (m, 2H), 7.40 (t, J = 7.7 Hz, 1H), 3.09 (s, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ 174.8, 143.9, 142.8, 140.2, 139.9, 133.3, 131.1, 130.2, 129.8, 129.7, 129.0, 126.9, 126.6, 44.4. HRMS (ESI): Calcd. for C$_{14}$H$_{11}$O$_4$S [M-H]$^-$ 275.0384; found 275.0389. UHPLC: purity = 95.4 %

4'-(methylsulfonyl)biphenyl-3-carboxylic acid, 12b:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 4-methanesufonylphenyl boronic acid (1.24 mmol, 248 mg, 1.0 equiv), potassium phosphate (3.72 mmol, 789 mg, 3.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **21b** (1.12 mmol, 309 mg, 90 %) as white solid. T$_m$ = 127-129°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.05-7.86 (m, 5H), 7.66 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 3.26 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.7, 146.2, 142.9, 139.7, 137.6, 129.8, 128.4, 128.10, 127.9, 127.4, 44.1. HRMS (ESI): Calcd. for C$_{14}$H$_{11}$O$_4$S [M-H]$^-$ 275.0384; found 275.0380. UHPLC: purity = 96.2 %

4'-aminobiphenyl-3-carboxylic acid, 13:

According to general procedure A, 4-bromoaniline (1.45 mmol, 250 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (2.18 mmol, 541 mg, 1.5 equiv) potassium phosphate (7.27 mmol, 1.54 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.15 mmol, 102 mg, 10 mol%), gave **13** (0.51 mmol, 109 mg, 35%) as a white solid. T$_m$ = 195°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.13 (t, J =

1.8 Hz, 1H), 7.85-7.77 (m, 1H), 7.65-7.57 (m, 2H), 7.41 (t, J = 7.7 Hz, 1H), 6.90-6.84 (m, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 169.0, 148.0, 141.9, 139.3, 128.2, 127.3, 127.0, 126.5, 126.1, 125.2, 114.2. HRMS (ESI): Calcd. for $C_{13}H_{10}O_2N$ [M-H]$^-$ 212.0717; found 212.0712. HPLC, purity = 98.3 %

4'-dimethylaminobiphenyl-3-carboxylic acid, 14:

According to general procedure A, 3-bromobenzoic acid (0.75 mmol, 150 mg, 1.0 equiv), 3-dimethylaminophenyl) boronic acid (1.12 mmol, 185 mg, 1.5 equiv), potassium phosphate (3.73 mmol, 792 mg, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.07 mmol, 52 mg, 10 mol%) gave 14 (0.71 mmol, 172 mg, 95%) as red solid. T_m = 192-194°C. ^{1}H NMR (400 MHz, deuterium oxide) δ 8.09 (t, J = 1.7 Hz, 1H), 7.89-7.80 (m, 1H), 7.68-7.60 (m, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.12 (t, J = 2.0 Hz, 1H), 7.11-7.04 (m, 1H), 6.96-6.88 (m, 1H), 2.80 (s, 6H). ^{13}C NMR (101 MHz, deuterium oxide) δ 175.3, 151.8, 141.2, 140.7, 136.8, 129.9, 129.6, 128.8, 127.9, 127.4, 118.1, 114.9, 113.8, 41.1. HRMS (ESI): Calcd. for $C_{15}H_{14}NO_2$ [M-H]$^-$ 240.1030; found 240.1029. HPLC purity = 95.1 %

3'-(aminomethyl)biphenyl]-3-carboxylic acid, 15a:

According to general procedure A, 3-bromobenzylamin hydrochloride (250 mg, 1.12 mmol, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzoic acid (1.69 mmol, 418 mg, 1.5 equiv), potassium phosphate (5.62 mmol, 1.19 g, 5.0 equiv), PdCl$_2$(PPh$_3$)$_2$ (0.11 mmol, 79 mg, 10 mol%), after purification by flash chromatography on silica gel using a mixture of an acidic stock solution (acetic acid/H$_2$O/MeOH/ethyl acetate, 3:2:3:3) and ethyl acetate (1:9), then acidic stock solution/ethyl acetate (1:2) as eluent, gave 15a (0.40 mmol, 91 mg, 36%) as a slightly yellow solid. T_m = 346°C (decomposes).^{1}H NMR (400 MHz, deuterium oxide) δ 8.06 (d, J = 1.8 Hz, 1H), 7.80-7.77 (m, 1H), 7.66-7.63 (m, 1H), 7.52-7.42 (m, 3H), 7.38 (t, J = 7.6 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 3.71 (s, 2H). ^{13}C NMR (101 MHz, deuterium oxide) δ 176.1, 144.2, 141.5, 141.4, 138.1, 130.4, 130.3, 129.8, 128.9, 128.3, 127.6, 126.7, 126.4, 45.8. HRMS (ESI): Calcd. for $C_{14}H_{12}NO_2$ [M-H]$^-$ 226.0874; found 226.0872. UHPLC: purity = 95.2 %

4'-(aminomethyl)biphenyl-3-carboxylic acid, 15b:

According to general procedure A, 4-bromobenzylamin hydrochloride (250 mg, 1.12 mmol, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzoic acid (1.69 mmol, 418 mg, 1.5 equiv), potassium phosphate (5.62 mmol, 1.19 g, 5.0 equiv), PdCl$_2$(PPh$_3$)$_2$ (0.11 mmol, 79 mg, 10 mol%), after purification by flash chromatography on silica gel using a mixture of an acidic stock solution (acetic acid/H$_2$O/ethyl acetate, 3:2:3:3) and ethyl acetate (1:9), then acidic stock solution/ethyl acetate (1:2) as eluent, gave 15b (0.96 mmol, 220 mg, 86%) as a slightly yellow solid. T_m = 213-215°C. ^{1}H NMR (400 MHz, deuterium oxide) δ 8.00 (s, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 7.7 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 3.67 (s, 2H). ^{13}C NMR (101 MHz, deuterium oxide) δ 175.3, 141.9, 140.1, 138.5, 136.9, 129.4, 128.9, 127.9, 127.8, 127.1, 127.0, 44.3. HRMS (ESI): Calcd. for $C_{14}H_{12}NO_2$ [M-H]$^-$ 226.0874; found 226.0872. UHPLC: purity = 83.2 %

3'-(2-aminoethyl)biphenyl-3-carboxylic acid, 16a:

According to general procedure A, 3-bromobenzylamin hydrochloride (250 mg, 1.25 mmol, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzoic acid (1.87 mmol, 465 mg, 1.5 equiv), potassium phosphate (1.33 mmol, 1.33 g, 5.0 equiv), PdCl$_2$(PPh$_3$)$_2$ (0.12 mmol, 88 mg, 10 mol%), after purification by flash chromatography on silica gel using a mixture of an acidic stock solution (acetic acid/H$_2$O/MeOH/ethyl acetate, 3:2:3:3) and ethyl acetate (1:9), then acidic stock solution/ethyl acetate (1:2) as eluent, gave 16a (0.19 mmol, 45 mg, 15%) as a slightly yellow solid. T_m = 232-235°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.23 (s, 1H), 7.93-7.91 (m, 1H), 7.65-7.63 (m, 1H), 7.52-7.48 (m, 2H), 7.43-7.31 (m, 2H), 7.20-7.18 (m, 1H), 2.97 (t, J = 7.1 Hz, 2H), 2.85 (t, J = 7.1 Hz, 2H). ^{13}C NMR (101 MHz,

methanol-d_4) δ 173.8, 141.1, 140.2, 139.4, 138.0, 128.5, 128.1, 127.7, 127.6, 127.4, 127.2, 127.0, 124.6, 42.3, 38.1. HRMS (ESI): Calcd. for $C_{14}H_{12}O_2N$ [M-H]$^-$ 240.1030; found 240.1028. UHPLC: purity = 95.5 %

#### 4'-(2-aminoethyl)biphenyl-3-carboxylic acid, 16b:

The compound was prepared according to general procedure A. 4-Bromophenethylamine (1.25 mmol, 250 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (1.87 mmol, 465 mg, 1.5 equiv), potassium phosphate (6.25 mmol, 1.33 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.12 mmol, 88 mg, 10 mol%), after purification by flash chromatography on silica gel with a mixture of an acidic stock solution (acetic acid/H$_2$O/MeOH/ethyl acetate, 3:2:3:3) and ethyl acetate (1:9), then acidic stock solution/ethyl acetate (1:2) as eluent, gave 16b (0.84 mmol, 201 mg, 67%) as a slightly brownish solid. T_m = 312°C (decomposes). ^{1}H NMR (400 MHz, deuterium oxide) δ 8.06 (s, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 7.9 Hz, 4H), 7.46 (t, J = 7.7 Hz, 2H), 7.27 (d, J = 7.9 Hz, 5H), 2.79 (t, J = 7.0 Hz, 4H), 2.69 (t, J = 6.9 Hz, 4H).^{13}C NMR (101 MHz, methanol-d_4) δ 176.2, 141.2, 140.7, 139.0, 138.0, 130.5, 130.3, 129.9, 128.7, 128.0, 127.9, 43.1, 38.8. HRMS (ESI): Calcd. for $C_{15}H_{14}NO_2$ [M-H]$^-$ 240.1030; found 240.1029. UHPLC: purity = 95.8 %

4'-(methylsulfonamido)biphenyl-3-carboxylic acid, 17:
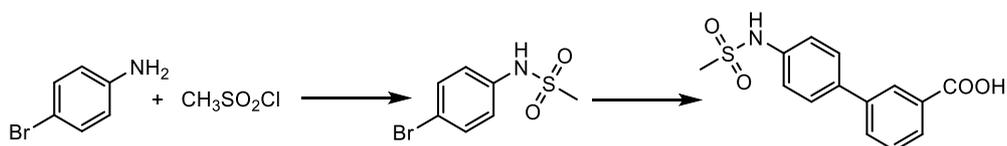
Synthesis of *N*-(4-bromobenzyl)methanesulfonamide: To a solution of methanesulfonyl chloride (1.60 mmol, 0.12 mL, 1.0 equiv) in ethanol (5 mL) 4-bromoaniline (3.20 mmol, 550 mg, 2.0 equiv) was added and the mixture was stirred at room temperature. The reaction was monitored by TLC until completion. After 2 h, the solvent was removed under reduced pressure and the remaining solid dissolved in a small amount of water. The remaining solid was dissolved in a small amount of water and applied to a C18 precolumn before purification on a 60 g C18 column with a gradient of acetonitrile in water (10-80%) to yield the sulfonamide (0.93 mmol, 232 mg, 93%) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4): δ 7.27 (2H, dd, J = 8.8 Hz, J = 2.0 Hz), 7.02 (2H, dd, J = 9.0 Hz, J= 2.1 Hz), 2.84 (3H, s). ^{13}C NMR (101 MHz, methanol-d_4): δ 146.5, 132.6, 123.8, 113.5, 39.0. HRMS (ESI): Calcd. for $C_7H_7O_2NBrS$ [M+H]$^+$ 247.9386; found 247.9389.

Synthesis of 4'-(methylsulfonamido)biphenyl-3-carboxylic acid, 17: The compound was prepared according to general procedure B. *N*-(4-bromobenzyl)methanesulfonamide, (0.72 mmol, 180 mg, 1.5 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (0.48 mmol, 119 mg, 1.0 equiv), Na$_2$CO$_3$ (2.40 mmol, 254 mg, 5.0 equiv) and PdCl$_2$(dppf) (0.05 mmol, 35 mg, 10 mol%) in anhydrous THF (6 mL) was stirred at 80 °C for 20h. After purification the title compound, 17 (0.20 mmol, 58 mg, 41%) was obtained as a yellowish solid. T_m = 280°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.20 (t, J = 1.8 Hz, 1H), 7.84 (dt, J = 7.7, 1.4 Hz, 1H), 7.66-7.58 (m, 1H), 7.55-7.49 (m, 2H), 7.38 (t, J = 7.7 Hz, 1H), 7.23-7.16 (m, 2H), 2.88 (s, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.7, 147.0, 142.0, 139.5, 134.1, 129.1, 129.0, 128.3, 128.2, 122.5, 39.0, 25.0. HRMS (ESI): Calcd. for $C_{14}H_{12}NO_4S$ [M-H]$^-$ 290.0493 found 290.0485. UHPLC: purity > 99.5%

4'-(phenylsulfonamido)biphenyl-3-carboxylic acid, 18:
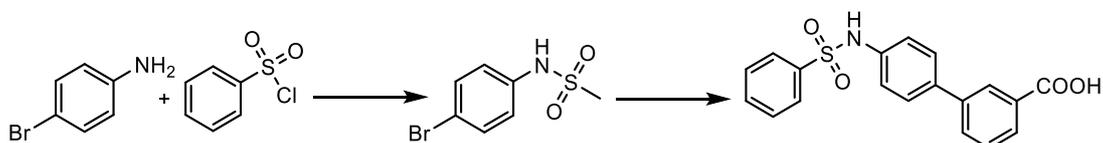
Synthesis of *N*-(4-bromophenyl)benzenesulfonamide: To a solution of benzenesulfonyl chloride (1.28 mmol, 0.16 mL, 1.0 equiv) in ethanol (5 mL) 4-bromoaniline (2.56 mmol, 441 mg, 2.0 equiv) was added and the mixture stirred at rt. The reaction was monitored by TLC until completion. After 2 h the solvent was removed and the remaining solid dissolved in ethyl acetate. The solution was submitted to a silica precolumn and purified on a silica column with a gradient of ethyl acetate in heptane (10-35%) and then a constant value of 35% ethyl acetate in heptane. The title compound (300 mg, 75%) was obtained as a yellowish solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.78-7.74 (m, 2H), 7.82-7.76 (m, 2H), 7.55 (m, 1H), 7.49-7.43 (m, 2H), 7.37-7.32 (m, 2H), 7.00-6.95 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 138.7, 135.6, 133.4, 132.5, 129.3, 127.3, 123.4, 118.9. HRMS (ESI): Calcd. for C$_{12}$H$_9$O$_2$BrNS [M+H]$^+$ 309.9543; found 309.9537.

Synthesis of 4'-(phenylsulfonamido)biphenyl-3-carboxylic acid, **18**: The compound was prepared according to general procedure B. *N*-(4-bromophenyl)benzenesulfonamide (0.48 mmol, 150 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (0.72 mmol, 180 mg, 1.5 equiv), potassium phosphate (1.92 mmol, 408 mg, 4.0 equiv) and XPhos-Pd G2 (4.8x10^{-3} mmol, 3.8 mg, 1 mol%) in anhydrous THF (4 mL) was stirred at 84 °C for 16 h. The aqueous phase was washed with hexane (3 x 30 mL). After purification **18** (0.31 mmol, 110 mg, 65%) was obtained as beige solid. T$_m$ = 303°C. ^{1}H NMR (400 MHz, methanol-*d*$_4$) δ 8.09 (s, 1H), 7.94-7.83 (m, 2H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.51 (d, *J* = 9.5 Hz, 1H), 7.41-7.24 (m, 6H), 6.98 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (101 MHz, methanol-*d*$_4$) δ 175.8, 148.9, 146.6, 142.2, 139.3, 132.8, 131.3, 129.3, 129.0, 128.9, 128.0, 127.9, 127.9, 127.8, 123.0. HRMS (ESI): Calcd. for C$_{19}$H$_{14}$NO$_4$S [M-H]$^-$ 352.0649; found, 352.0642. UHPLC: purity = 95.6 %

<p style="text-align:center">3'-(methylsulfonamidomethyl)biphenyl-3-carboxylic acid, 19a:</p>
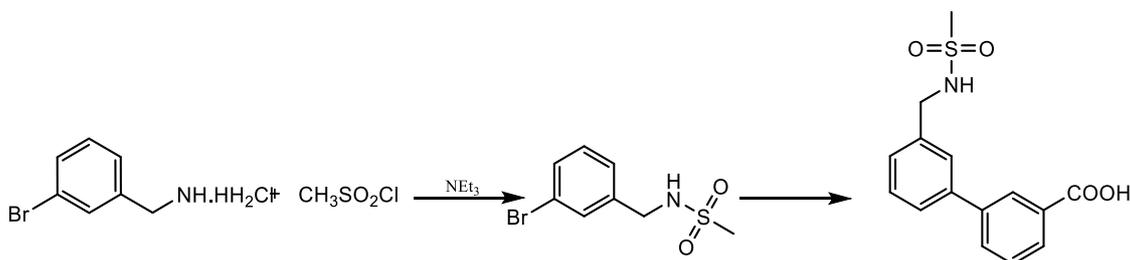
Synthesis of *N*-(3-bromobenzyl)methanesulfonamide: A solution of 3-bromobenzylamine hydrochloride (1.51 mmol, 337 mg, 1.0 equiv) and triethylamine (3.18 mmol, 0.44 mL, 2.1 equiv) in CH$_2$Cl$_2$ (5.5 mL) was cooled to 0 °C. Methanesulfonyl chloride (1.52 mmol, 0.12 mL, 1.01 equiv) was added dropwise and the reaction mixture was allowed to warm to room temperature with stirring. The reaction was monitored by TLC until completion. After 1h 45 minutes the reaction was stopped and the mixture was washed with water (3 x 10 mL). The organic layer was dried over MgSO$_4$, filtrated and the solvent removed under reduced pressure. The title compound (1.34 mmol, 349 mg, 88%) was obtained as a offwhite solid and used in the next step without further purification. ^{1}H NMR (400 MHz, methanol-*d*$_4$): δ 7.51 (t, J = 1.9 Hz, 1H), 7.45 (dt, J$_1$ = 7.6 Hz, J$_2$ = 1.6 Hz, 1H), 7.29 (m, 1H), 7.24 (t, J = 7.6 Hz, 1H), 4.81 (s, 1H), 4.30 (s, 2H), 2.90 (s, 3H). ^{13}C NMR (101 MHz, methanol-*d*$_4$): δ 139.2, 131.3, 131.0, 130.6, 126.6, 123.0, 46.6, 41.3. HRMS (ESI): Calcd. for C$_8$H$_{10}$O$_2$NBrNaS [M+Na]$^+$ 285.9508; found 285.9503.

Synthesis of 3'-(methylsulfonamidomethyl)biphenyl-3-carboxylic acid, **19a**: The compound was synthesized according to general procedure B. *N*-(3-bromobenzyl) methanesulfonamide, (0.57 mmol, 150 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzoic acid (0.85 mmol, 211 mg, 1.5 equiv), Na$_2$CO$_3$ (2.84 mmol, 301 mg, 5.0 equiv) and PdCl$_2$(dppf) (0.06 mmol, 42 mg, 10 mol%) in anhydrous THF (8 mL), was stirred at 84 °C for 20 h. Additional purification was carried out by flash

chromatography on silica gel with hexane/ethyl acetate/acetic acid (1:1:1%). To the resulting solid was added heptane (10 mL x 3) and removed under reduced pressure to remove residual acetic acid. The title compound, **19a** (0.15 mmol, 45 mg, 26%) was obtained as a slightly yellow solid. T_m = 175-177°C. ^{1}H NMR (400 MHz, methanol-d_4) δ) δ 8.28 (s, 1H), 8.01 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.68 (s, 1H), 7.60-7.54 (m, 4H), 7.47 (t, J = 7.6 Hz, 2H), 7.41 (d, J = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 169.9, 142.4, 141.9, 140.2, 132.9, 132.4, 130.4, 130.1, 129.7, 129.1, 128.4, 127.6, 127.3, 47.7, 40.6. HRMS (ESI): Calcd. for $C_{15}H_{14}NO_4S$ [M-H]$^-$ 304.0649; found 304.0647. UHPLC: purity = 95.0 %

4'-(methylsulfonamidomethyl)biphenyl-3-carboxylic acid, **19b**:
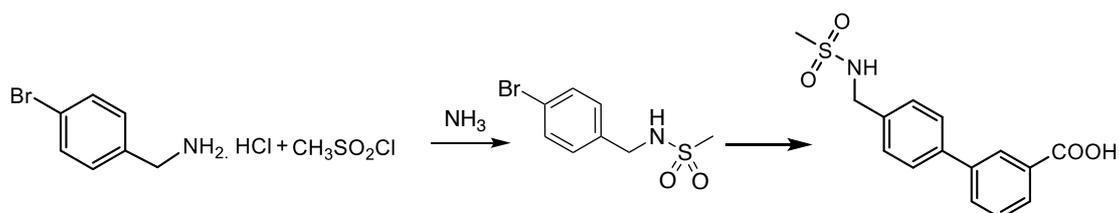
Synthesis of *N*-(4-bromobenzyl)methanesulfonamide: The compound was prepared according to the procedure described for *N*-(3-bromobenzyl)methanesulfonamide. The title compound (1.45 mmol, 380 mg, 95%) was obtained as a beige solid. ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.49 (m, 2H), 7.23 (m, 2H), 4.80 (s, 1H), 4.27 (d, J = 4.5 Hz, 2H), 2.88 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 135.9, 132.2 (2C), 129.7 (2C), 122.2, 46.7, 41.4. HRMS (ESI): Calcd. for $C_8H_{10}O_2NBrClS$ [M+Cl]$^+$ 285.9508; found, 299.2368.

Synthesis of 4'-(methylsulfonamidomethyl)biphenyl-3-carboxylic acid, **19b**. The compound was prepared according to general procedure B. *N*-(4-bromobenzyl)methanesulfonamide (0.57 mmol, 150 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (0.85 mmol, 211 mg, 1.5 equiv), Na$_2$CO$_3$ (2.84 mmol, 301 mg, 5.0 equiv) and PdCl$_2$(dppf) (0.06 mmol, 42 mg, 10 mol%) in anhydrous THF (8 mL) was stirred at 84 °C for 20 h. Additional purification was carried out by flash chromatography on silica gel with hexane/ethyl acetate/acetic acid (10:10:0.1) as eluent. To the resulting solid was added heptane (10 mL) and removed under reduced pressure (3 times) to remove residual acetic acid. The title compound, **19b** (0.06 mmol, 17 mg, 10%) was obtained as a white solid. T_m = 216-220°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.16 (s, 1H), 7.90 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.49-7.36 (m, 3H), 4.21 (s, 2H), 2.78 (s, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ 170.1, 142.2, 140.8, 139.0, 133.1, 132.2, 130.1, 129.6, 129.6, 129.0, 128.2, 47.4, 40.6. HRMS (ESI): Calcd. for $C_{15}H_{14}O_4NS$[M-H]$^-$ 304.0649; found 304.0646. UHPLC: purity = 96.4 %

3'-(2-methylsulfonamidoethyl)biphenyl-3-carboxylic acid, **20**:
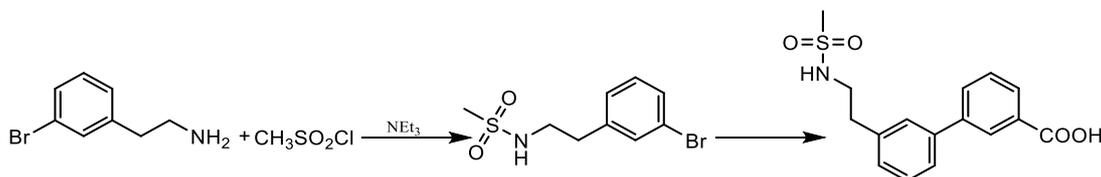
Synthesis of *N*-(3-bromophenethyl)methanesulfonamide: To a solution of methanesulfonyl chloride (1.60 mmol, 0.12 mL, 1.0 equiv) in ethanol (3 mL), 2-(3-bromophenyl)ethan-1-amine (3.20 mmol, 639 mg, 2.0 equiv) was added and the mixture was stirred at room temperature. The reaction was monitored by TLC. After completion the solvent was removed under reduced pressure and the remaining solid dissolved in a small amount of water. The solution was applied to a C18 precolumn before purification on a 60 g C18 column with a gradient of acetonitrile in water (10–80%). The title compound (1.07 mmol, 295 mg, 66%) was obtained as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.41-7.36 (m, 2H), 7.19 (t, J = 7.6 Hz 1H), 7.15 (m, 1H), 3.38 (t, J = 6.9 Hz, 2H), 2.86 (s, 3H), 2.85 (t, J = 7.6 Hz,

2H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 140.3, 132.0, 130.5, 130.2, 127.7, 123.0, 44.2, 40.6, 36.3. HRMS (ESI): Calcd. for C$_9$H$_{13}$O$_2$NBrS [M+H]$^+$ 277.9850; found 277.9674.

Synthesis of 3'-(2-methylsulfonamidoethyl)biphenyl-3-carboxylic acid, **20**: The compound was prepared according to general procedure B. *N*-(3-bromophenethyl)methanesulfonamide (0.72 mmol, 200 mg, 1.5 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (0.48 mmol, 119 mg, 1.0 equiv), Na$_2$CO$_3$ (2.40 mmol, 254 mg, 5.0 equiv) and PdCl$_2$(dppf) (0.05 mmol, 35 mg, 10 mol%) in anhydrous THF (8 mL) was stirred at 85 °C for 20h. The aqueous mixture was washed with hexane (3 x 30 mL) instead of ethyl acetate. After purification the title compound, **20** (0.11 mmol, 35 mg, 11%) was obtained as a white solid). T$_m$ = 130°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.24 (t, *J* = 1.8 Hz, 1H), 7.93 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.67 (s, 1H), 7.57 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.41 (m, 2H), 7.24 (d, *J* = 7.7 Hz, 1H), 3.40-3.34 (m, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.82 (s, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.3, 142.6, 141.8, 140.8, 139.7, 130.1, 129.7, 129.3, 129.2, 129.0, 128.9, 128.7, 126.2, 45.7, 39.9, 37.8. HRMS (ESI): Calcd. C$_{16}$H$_{16}$O$_4$NS [M-H]$^-$ 318.0806; found 318.0797. UHPLC: purity = 99.0 %

3'-acetamidobiphenyl-3-carboxylic acid, **21a**:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1 equiv), 3-acetamidophenylboronic acid (1.86 mmol, 333 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **21a** (1.21 mmol, 310 mg, 98 %) as white solid. T$_m$ = 294°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.15 (t, *J* = 1.7 Hz, 1H), 7.91 (t, *J* = 1.9 Hz, 1H), 7.84 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.52-4.49 (m, 1H), 7.40-7.27 (m, 3H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.0168.9, 142.6, 141.7, 140.4, 139.2, 129.6, 128.7, 128.1, 127.7, 126.8, 121.6, 118.1, 117.7, 24.5. HRMS (ESI): Calcd. for C$_{15}$H$_{12}$NO$_3$ [M-H]$^-$ 254.0823; found 254.0828. UHPLC: purity = 97.4 %

4'-acetamidobiphenyl-3-carboxylic acid, **21b**:

According to procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 4-acetamidophenylboronic acid (1.86 mmol, 307 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.32 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.124 mmol, 87 mg, 10 mol%) gave **21b** (1.20 mmol, 290 mg, 97 %) as white solid. T$_m$ = 295-296°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.13 (s, 1H), 7.80 (d, *J* = 7.4 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.9, 168.9, 142.7, 139.1, 138.9, 135.8, 128.1, 128.0, 127.3, 127.1, 126.4, 119.8, 24.50. HRMS (ESI): Calcd. for C$_{15}$H$_{12}$NO$_3$ [M-H]$^-$ 254.0823; found 254.0818. UHPLC: purity = 99.1 %

3'-(acetamidomethyl)biphenyl-3-carboxylic acid, **22**:
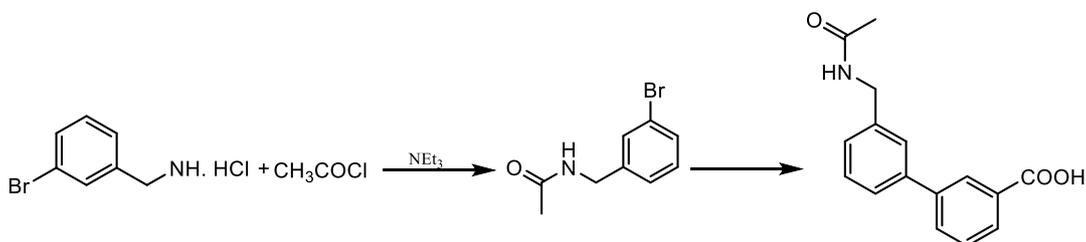
Synthesis of *N*-(3-bromobenzyl)acetamide: A solution of 3-bromobenzylamine hydrochloride (1.75 mmol, 389 mg, 1.0 equiv) and Et$_3$N (17.5 mmol, 2.44 mL, 10.0 equiv) in CH$_2$Cl$_2$ (3.5 mL) was cooled to 0 °C. Acetyl chloride (2.28 mmol, 0.16 mL, 1.3 equiv) was added and the mixture was stirred for 3 h at 30 °C. The solvent was removed under reduced pressure and the resulting solid dissolved in CH$_2$Cl$_2$ (40 mL). The organic phase was washed with 1N HCl (1 x) and water (3 x 30 mL). It was dried over Na$_2$SO$_4$,

filtered and the solvent removed under reduced pressure. The title compound (373 mg, 93%) was obtained as a yellowish solid and used without further purification for the next step. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.43-7.38 (m, 2H), 7.22-7.18 (m, 2H), 4.41 (m,2H), 2.03 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 170.1, 140.8, 130.8, 130.7, 130.4, 126.5, 122.8, 43.2, 23.4. HRMS (ESI): Calcd. for C$_9$H$_{11}$ONBr [M+H]$^+$ 228.0019; found, 228.0018; [M + Na]$^+$, calcd for C$_9$H$_{10}$ONBrNa, 249.9838; found, 249.9837.

Synthesis of 3'-(acetamidomethyl)biphenyl-3-carboxylic acid, **22**: According to general procedure B, *N*-(3-bromobenzyl)acetamide (0.66 mmol, 150 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (0.99 mmol, 245 mg, 1.5 equiv), potassium phosphate (2.63 mmol, 558 mg, 4.0 equiv) and XPhos-Pd G2 (6.6x10^{-3} mmol, 5.2 mg, 1 mol%) in anhydrous THF (4 mL) was stirred at 85 °C for 16.5 h. The aqueous mixture was washed with hexane (3 x 30 mL). After purification the title compound, **22** (0.57 mmol, 155 mg, 87%) was obtained as a white solid. T$_m$ = 129°C. ^{1}H NMR (400 MHz, methanol-*d$_4$*) δ 8.23 (s, 1H), 7.93 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 6.2 Hz, 1H), 7.62-7.51 (m, 2H), 7.38-7.45 (m, 2H), 7.27 (d, *J* = 7.5 Hz, 1H), 4.43 (s, 2H), 2.01 (s, 3H). ^{13}C NMR (101 MHz, methanol-*d$_4$*) δ 175.3, 173.1, 142.7, 141.7, 140.5, 139.8, 130.1, 129.7, 129.3, 129.3, 128.9, 127.6, 127.3, 126.9, 44.3, 25.0. HRMS (ESI): Calcd. for C$_{16}$H$_{14}$NO$_3$ [M-H]$^-$ 268.0979; found 268.0977. UHPLC: purity = 82.6 %

<div align="center">3'-(2-acetamidoethyl)biphenyl-3-carboxylic acid, 23a:</div>
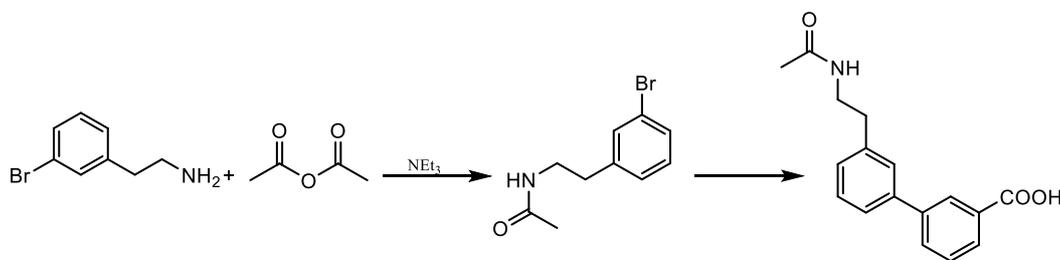
Synthesis of *N*-(3-bromophenethyl)acetamide: To a solution of 2-(3-bromophenyl)ethan-1-amine (1.65 mmol, 0.24 mL, 1.0 equiv) in CH$_2$Cl$_2$ (3.5 mL), Et$_3$N (1.82 mmol, 0.25 mL, 1.1 equiv) and acetic anhydride (1.98 mmol, 0.19 mL, 1.2 equiv) were added. The reaction mixture was stirred at rt and monitored by TLC. After 1.5 h the solvent was removed under reduced pressure and the resulting yellow oil diluted with CH$_2$Cl$_2$. The organic phase was washed with water (3 x 20 mL), dried over Na$_2$SO$_4$, filtered and the solvent removed under reduced pressure. The title compound (400 mg, 100%) was obtained as a yellowish oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.38-7.32 (m, 2H), 7.17 (m, 1H), 7.11 (m, 1H), 5.64 (1H, s), 3.48 (m, 2H), 2.78 (t, *J* = 7.0 Hz, 2H), 1.94 (3H, s). ^{13}C NMR (101 MHz, CDCl$_3$): δ 170.3, 141.4, 131.9, 130.3, 129.8, 127.5, 122.8, 40.6, 35.4, 23.4. HRMS (ESI): Calcd. for C$_{10}$H$_{13}$ONBr [M+H]$^+$ 242.0175; found 242.0174.

Synthesis of 3'-(2-acetamidoethyl)biphenyl-3-carboxylic acid, **23a**: The compound was prepared according to general procedure B. *N*-(3-bromophenethyl)acetamide (0.62 mmol, 150 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (0.93 mmol, 231 mg, 1.5 equiv), Na$_2$CO$_3$ (3.10, 328 mg, 5.0 equiv) and PdCl$_2$(dppf) (0.06 mmol, 45 mg, 10 mol%) in anhydrous THF (8 mL) was stirred at 85 °C for 19 h. After RP chromatography, the compound was further purified by flash chromatography on silica gel using a mixture of an acidic stock solution (acetic acid/H$_2$O/MeOH/ethyl acetate, 3:2:3:3) and ethyl acetate (1:25) as eluent. To the resulting solid heptane (10 mL x 3) was added and removed under reduced pressure to remove residual acetic acid. Compound **23a** (0.29 mmol, 80 mg, 46%) was obtained as a slightly yellow solid. T$_m$ = 54-56°C. ^{1}H NMR (400 MHz, methanol-*d$_4$*) δ 8.25 (s, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 8.7 Hz, 1H), 7.57 – 7.45 (m, 3H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 3.44 (t, *J* = 7.3 Hz, 2H), 2.87 (t, *J* = 7.3 Hz, 2H), 1.92 (s, 3H). ^{13}C NMR (101 MHz, methanol-*d$_4$*) δ 174.7, 171.9, 144.0, 143.1, 142.7, 133.5, 131.5, 131.3, 130.8, 130.6, 130.5, 129.9,

127.5, 43.4, 37.9, 23.9. HRMS (ESI): Calcd. for $C_{17}H_{16}NO_3$ [M-H]$^-$ 282.1136; found 282.1129. UHPLC: purity = 97.9 %

<div align="center">4'-(2-acetamidoethyl)biphenyl-3-carboxylic acid, 23b:</div>
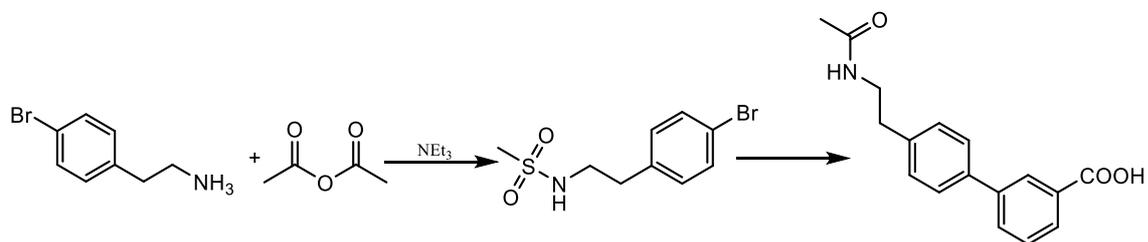
Synthesis of N-(3'-bromobiphenyl-3-yl)methylacetamide: The compound was prepared according to the procedure described for starting material of **23a**. The title compound (399 mg, 100%) was obtained as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.42 (m, 2H), 7.06 (m, 2H), 5.54 (s, 1H), 3.47 (m, 2H), 2.77 (t, J = 7.0 Hz, 2H), 1.93 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 170.2, 138.0, 131.8, 130.6, 120.5, 40.6, 35.2, 23.4. HRMS (ESI): Calcd. for $C_{10}H_{13}ONBr$ [M+H]$^+$ 242.0175; found 242.0177.

Synthesis of 4'-(2-acetamidoethyl)biphenyl-3-carboxylic acid, **23b**. The compound was prepared according to general procedure B. N-(3'-bromobiphenyl-3-yl)methylacetamide (0.62 mmol, 150 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (0.93 mmol, 231 mg, 1.5 equiv), Na$_2$CO$_3$ (3.10 mmol, 328 mg, 5.0 equiv) and PdCl$_2$(dppf) (0.06 mmol, 45 mg, 10 mol%) in anhydrous THF (8 mL) was stirred at 85 °C for 18.5 h. After RP chromatography, the compound was further purified by flash chromatography on silica gel using a mixture of an acidic stock solution (acetic acid/H$_2$O/MeOH/ethyl acetate, 3:2:3:3) and ethyl acetate (1:59) and then acidic stock solution/ethyl acetate (1:9) as eluent. To the resulting solid heptane (10 mL x 3) was added and removed under reduced pressure to remove residual acetic acid. Compound **23b** (0.21 mmol, 60 mg, 34%) was obtained as a white solid. T$_m$ = 204-205°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.24 (s, 1H), 7.98 (d, J = 7.7 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.62-7.47 (m, 3H), 7.32 (d, J = 8.2 Hz, 2H), 3.43 (t, J = 7.3 Hz, 2H), 2.84 (t, J = 7.3 Hz, 2H), 1.92 (s, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ 211.4, 174.7, 171.3, 143.9, 141.7, 140.9, 134.0, 133.7, 131.9, 131.4, 130.8, 130.3, 129.5, 129.4, 43.4, 37.5, 23.9. HRMS (ESI): Calcd. for $C_{17}H_{16}NO_3$ [M-H]$^-$ 282.1136; found 282.1129. UHPLC: purity = 99.2%

<div align="center">3'-acetoxymethylbiphenyl-3-carboxylic acid, 24:</div>
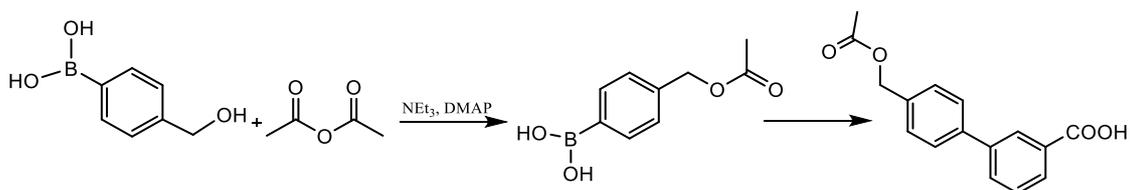
Synthesis of 3-(acetoxymethylphenyl)boronic acid: To a stirred mixture of (3-(hydroxymethylphenyl) boronic acid (1.03 mmol, 157 mg, 1.0 equiv), DMAP (0.11 mmol, 14 mg, 11 mol%) and Et$_3$N (3.09 mmol, 0.43 mL, 3.0 equiv) in CH$_2$Cl$_2$/anhydrous THF (7.2 mL, 5:1) and acetic anhydride (3.09 mmol, 0.29 mL, 3.0 equiv) was added. The solution was stirred at rt and monitored by TLC. After 5h the reaction mixture was washed with 1N HCl (3 x 20 mL) and NaHCO$_3$ solution (3 x 20 mL). The organic phase was dried over Na$_2$SO$_4$, filtered and the solvent removed under reduced pressure. The crude product was purified with flash chromatography on silica gel with 5% MeOH in CH$_2$Cl$_2$ as eluent. The title compound (0.86 mmol, 166 mg, 86%) was obtained as a white solid. ^{1}H NMR (400 MHz, methanol-d_4): δ 7.73-7.44 (m, 2H), 7.37-7.20 (m, 2H), 5.03 (2H, s), 2.00 (s, 3H). ^{13}C NMR (101 MHz, methanol-d_4): δ 172.7, 134.7,

<div align="center">13</div>

134.4, 131.1, 130.6, 128.7, 67.5, 20.8. HRMS (ESI): Calcd. for $C_9H_{10}O_4B$ [M-H]$^-$ 193.0678; found 193.0680.

Synthesis of 3'-acetoxymethyl-biphenyl-3-carboxylic acid **24**: According general procedure B, 3-(acetoxymethyl)phenyl)boronic acid, **7** (0.39 mmol, 75 mg, 1.5 equiv), potassium phosphate (1.03 mmol, 219 mg, 4.0 equiv), XPhos Pd G2 (2.58×10^{-3} mmol, 2.0 mg, 1 mol%), in anhydrous THF (6 mL) was stirred at 88 °C for 20 h. The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate/acetic acid (9:1:1%) as eluent gave **24** (0.13 mmol, 35 mg, 34%) as a brownish solid. T_m = 80°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.26 (s, 1H), 8.01 (d, J = 7.7 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.68-7.51 (m, 3H), 7.47 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 5.18 (s, 2H), 2.10 (s, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 172.7, 169.8, 142.4, 141.8, 138.5, 132.7, 132.5, 130.3, 130.1, 129.7, 129.1, 128.6, 127.9, 67.2, 20.8. HRMS (ESI): Calcd. for $C_{16}H_{13}O_4$ [M-H]$^-$ 269.0819; found 269.0817. UHPLC: purity = 95.7%

<p style="text-align:center; color:blue">3-(2-(1H-imidazol-1-yl)pyrimidin-5-yl)benzoic acid, 25:</p>

According to general procedure A, 5-bromo-2-(1H-imidazol-1-yl)pyrimidine (0.39 mmol, 100 mg, 1.0 equiv), 3-carboxyphenylboronic acid pinacol ester (0.39 mmol, 97 mg, 1.0 equiv), potassium phosphate (1.95 mmol, 413 mg, 5.0 equiv) and $PdCl_2(PPh_3)_2$ (0.04 mmol, 27 mg, 10 mol%) after purification gave **25** (0.28 mmol, 75 mg, 72%) was obtained as a white solid. T_m = 297°C. ^{1}H NMR (400 MHz, deuterium oxide) δ 8.78 (s, 2H), 8.37 (s, 1H), 7.95 (s, 1H), 7.82-7.72 (m, 1H), 7.68 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.46-7.35 (m, 1H), 7.11 (s, 1H), 7.04 (s, 1H). ^{13}C NMR (101 MHz, deuterium oxide) δ 174.2, 156.4, 152.3, 137.2, 136.2, 131.9, 131.3, 129.4, 129.3, 129.2, 128.6, 126.6, 121.7, 117.0. HRMS (ESI): Calcd. for $C_{14}H_9N_4O_2$ [M-H]$^-$ 265.0731; found 265.0731. UHPLC: purity = 95.2%

<p style="text-align:center; color:blue">3'-(1H-tetrazol-5-yl)-biphenyl-3-carboxylic acid, 26a:</p>
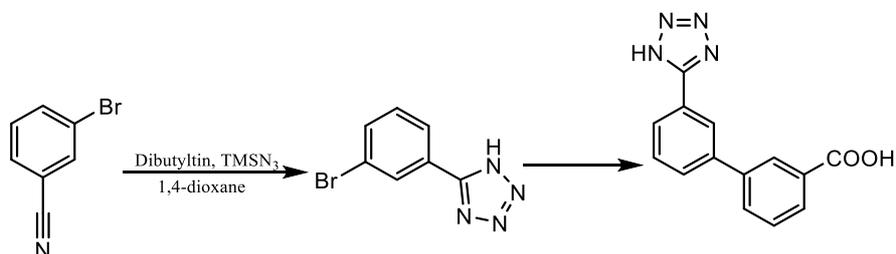
Synthesis of 5-(3-bromophenyl)-1H-tetrazole: Dibutyltin oxide (0.33 mmol, 82 mg, 0.2 equiv), and trimethylsilyl azide (3.33 mmol, 383 mg, 2 equiv) were added to a solution of 3-bromobenzonitrile (300 mg, 1.67 mmol, 1 equiv) in anhydrous 1,4-dioxane (2 mL/mmol). The reaction mixture was subjected to microwave irradiation in a tightly sealed microwave vessel for 50 min at 150 ^{0}C, then cooled to room temperature. The solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (10 mL and extracted with 2 M aq. NaOH (3 x 10 mL). The aqueous layer was acidified with 4 M aq. HCl to pH 1 and extracted with ethyl acetate (4 x 10 mL). The organic extract was washed with brine (10 mL), dried over MgSO4, and evaporated under reduced pressure to give the intermediate tetrazole(1.45 mmol, 326 mg, 86%) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.22-8.21 (m, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.50 (t, J = 7.9 Hz, 1H). ^{13}C NMR (101 MHz, methanol-d_4) δ 157.3, 135.3, 132.3, 131.0, 128.0, 126.9, 124.2.

According to general procedure A, 5-(3-bromophenyl)-1H-tetrazole (0.73 mmol, 163 mg, 1.2 equiv), 3-carboxyphenylboronic acid pinacol ester (0.60 mmol, 150 mg, 1.0 equiv), potassium phosphate (3.00 mmol, 636 mg, 5.0 equiv) and $PdCl_2(PPh_3)_2$ (0.06 mmol, 42 mg, 10 mol%) after purification gave **26a** (0.58 mmol, 159 mg, 99%) as a white solid. T_m = 295-297°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.41 (s, 1H), 8.35 (s, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 7.9

Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (101 MHz, methanol-*d₄*) δ 175.3, 162.9, 142.8, 141.6, 139.8, 131.9, 130.2, 129.8, 129.3, 128.9, 126.6, 126.3, 128.3. HRMS (ESI): Calcd. $C_{14}H_9N_4O_2$ [M-H]⁻ 265.0731; found 265.0728. UHPLC: purity = 96.7%

4'-(1H-Tetrazol-5-yl)biphenyl-3-carboxylic acid, 26b:
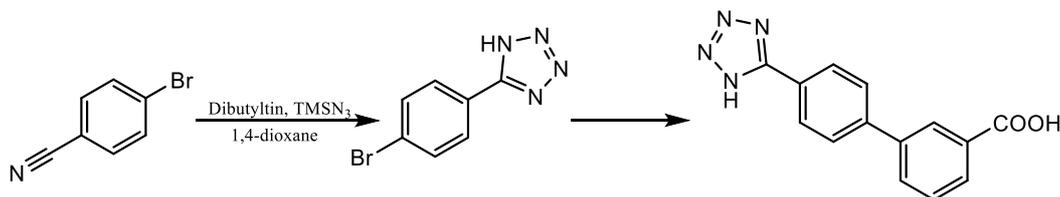
Synthesis of 5-(4-bromophenyl)-1H-tetrazole: Dibutyltin oxide (0.33 mmol, 82 mg, 0.2 equiv), and trimethylsilyl azide (3.33 mmol, 383 mg, 2 equiv) were added to a solution of 4-bromobenzonitrile (300 mg, 1.67 mmol, 1 equiv) in anhydrous 1,4-dioxane (2 mL/mmol). The reaction mixture was subjected to microwave irradiation in a tightly sealed vessel for 50 min at 150 0C, then cooled to room temperature. The solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (10 mL and extracted with 2 M aq. NaOH (3 x 10 mL). The aqueous layer was acidified with 4 M aq. HCl to pH 1 and extracted with ethyl acetate (4 x 10 mL). The organic extract was washed with brine (10 mL), dried over MgSO4, and evaporated under reduced pressure to give the intermediate tetrazole (1.36 mmol, 307 mg, 82%) as a white solid. ^{1}H NMR (400 MHz, DMSO-*d₆*) δ 8.07-7.92 (m, 2H), 7.91-7.76 (m, 2H). ^{13}C NMR (101 MHz, DMSO-*d₆*) δ 155.6, 132.9, 129.3, 125.0, 124.3.

According to general procedure A, 5-(4-bromophenyl)-1H-tetrazole (0.58 mmol, 130 mg, 1.2 equiv), 3-carboxyphenylboronic acid pinacol ester (0.48 mmol, 120 mg, 1.0 equiv), potassium phosphate (2.93 mmol, 614 mg, 5.0 equiv) and PdCl₂(PPh₃)₂ (0.05 mmol, 34 mg, 10 mol%) after purification gave the title compound, **26b** (0.44 mmol, 119 mg, 93%) as a white solid. T_m = 301°C. ^{1}H NMR (400 MHz, methanol-*d₄*) δ 8.32 (s, 1H), 8.15 (d, *J* = 8.3 Hz, 2H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.83-7.72 (m, 3H), 7.48 (t, *J* = 7.7 Hz, 1H). ^{13}C NMR (101 MHz, methanol-*d₄*) δ 175.2, 162.7, 142.6, 141.4, 139.8, 130.4, 129.7, 129.4, 128.8, 128.3, 128.2. HRMS (ESI): Calcd. for $C_{14}H_9N_4O_2$ [M-H]⁻ 265.0731; found 265.0722. UHPLC: purity = 98.3%

3-(Naphthalen-2-yl)benzoic acid, 27:

According to general procedure A, 2-bromonaphthalene (1.20 mmol, 250 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (1.81 mmol, 448 mg, 1.5 equiv), potassium phosphate (6.02 mmol, 1.28 g, 5.0 equiv) and PdCl₂(PPh₃)₂ (0.124 mmol, 85 mg, 10 mol%) after purification gave **27** (0.81 mmol, 200 mg, 67%) was obtained as a white solid. T_m = 263-266 °C. ^{1}H NMR (400 MHz, deuterium oxide) δ 8.04 (t, *J* = 1.8 Hz, 1H), 7.74 (m, 1H), 7.35 (s, 0H), 7.23-7.08 (m, 4H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.99-6.87 (m, 2H).^{13}C NMR (101 MHz, deuterium oxide) δ 175.0, 139.8, 136.9, 136.7, 132.9, 132.0, 129.3, 128.6, 128.2, 127.8, 127.8, 127.4, 127.2, 126.0, 125.7, 125.0, 124.7. HRMS (ESI): Calcd. for $C_{17}H_{11}O_2$ [M-H]⁻ 247.0765; found 247.0759. UHPLC: purity = 98.6%

3-(Quinolin-7-yl)benzoic acid, 28:

The compound was prepared according to general procedure A. 6-Bromoquinoline (1.20 mmol, 250 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzoic acid (1.80 mmol, 447 mg, 1.5 equiv), potassium phosphate (6.00 mmol, 1.28 g, 5.0 equiv) and PdCl₂(PPh₃)₂ (0.12 mmol, 84 mg, 10 mol%) gave **28** (1.04 mmol, 260 mg, 87%) as a white solid. T_m = 295-298 °C. ^{1}H NMR (400 MHz, methanol-*d₄*) δ ^{1}H NMR (400 MHz,) δ 8.86 (dd, *J* = 4.4, 1.7 Hz, 1H), 8.47 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.43 (t, *J* = 1.8 Hz, 1H), 8.25 (d, *J* = 1.9 Hz, 1H), 8.20-8.10 (m, 2H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.87 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.63-7.42 (m, 2H). ^{13}C NMR (101 MHz, ethanol-*d₄*) δ 175.0, 151.1, 148.1, 140.9, 140.6, 140.0,

138.7, 130.7, 130.2, 130.1, 129.8, 129.6, 129.6, 129.3, 126.7, 122.9. HRMS (ESI): Calcd. for $C_{16}H_{10}NO_2$ [M-H]$^-$ 248.0717; found 248.0714. UHPLC: purity = 96.2 %

3-(6-Aminopyridin-3-yl)benzoic acid, 29:

According to general procedure A, 5-bromopyridin-2-amine (0.87 mmol, 150 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (1.30 mmol, 323 mg, 1.5 equiv), potassium phosphate (4.34 mmol, 920 mg, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.09 mmol, 61 mg, 10 mol%) gave **29** (0.26 mmol, 56 mg, 36%) as an orange solid. T$_m$ = 277°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.21 (s, 1H), 8.14 (t, J = 1.8 Hz, 1H), 7.88 (dt, J = 7.7, 1.4 Hz, 1H), 7.80 (dd, J = 8.7, 2.5 Hz, 1H), 7.60-7.50 (m, 1H), 7.41 (t, J = 7.7 Hz, 1H), 6.82-6.55 (m, 1H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.3, 160.1, 145.9, 139.8, 138.9, 138.0, 129.4, 128.7, 128.6, 127.8, 127.4, 110.3. HRMS (ESI): Calcd. for $C_{12}H_9N_2O_2$ [M-H]$^-$ 213.0670; found 213.0669. UHPLC: purity = 96.3 %

3-(Pyrimidin-5-yl)benzoic acid, 30:

According to general procedure A, 5-bromopyrimidine (1.57 mmol, 250 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (2.36 mmol, 585 mg, 1.5 equiv), potassium phosphate (7.86 mmol, 1.67 g, 5.0 equiv), PdCl$_2$(PPh$_3$)$_2$ (0.16 mmol, 110 mg, 10 mol%), gave **30** (0.70 mmol, 140 mg, 45%) as a light brown solid. T$_m$ = T$_m$ = 289°C decomposes. ^{1}H NMR (400 MHz, deuterium oxide) δ 9.00 (s, 1H), 8.88 (s, 2H), 7.99 (t, J = 1.8 Hz, 1H), 7.86 (m, 1H), 7.67-7.61 (m, 1H), 7.50 (t, J = 7.7 Hz, 1H). ^{13}C NMR (101 MHz, deuterium oxide) δ 174.5, 155.7, 154.6, 137.3, 133.7, 132.8, 129.5, 129.3, 129.2, 127.0. HRMS (ESI): Calcd. for $C_{11}H_7N_2O_2$ [M-H]$^-$ 199.0513 found 199.0511. UHPLC: purity = 99.4 %

3-(2-Aminopyrimidin-4-yl)benzoic acid, 31:

According to general procedure A, 5-bromo-4-methylpyrimidin-2-amine (0.80 mmol, 150 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzoic acid (1.20 mmol, 298 mg, 1.5 equiv), potassium phosphate (4.01 mmol, 851 mg, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.08 mmol, 56 mg, 10 mol%) gave **31** (0.53 mmol, 122 mg, 67%) as a yellow solid. T$_m$ = 330°C (decomposes). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.12 (s, 1H), 8.03-7.92 (m, 1H), 7.89 (s, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.44-7.33 (m, 1H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.0, 167.4, 162.8, 158.7, 139.1, 136.9, 132.2, 131.0, 129.4, 129.3, 126.0, 22.6. HRMS (ESI): Calcd. for $C_{12}H_{10}N_3O_2$ [M-H]$^-$ 228.0778; found 228.0776. UHPLC: purity = 99.0 %

3-(1-Methyl-1H-pyrrol-2-yl)benzoic acid, 32:

The compound was prepared according to general procedure A. 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 1-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole (1.87 mmol, 386 mg, 1.5 equiv), potassium phosphate (6.22 mmol, 1.32 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.12 mmol, 81 mg, 10 mol%) after purification by flash chromatography on silica gel using 2% methanol in CH$_2$Cl$_2$ as eluent afforded **32** (0.03 mmol, 15 mg, 6%) as a white solid. T$_m$ = 162-165 °C. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.94 (s, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 6.2 Hz, 1H), 7.39 (t, J = 7.8 Hz, 2H), 6.65 (s, 1H), 6.18-5.82 (m, 5H), 3.56 (s, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ 169.8, 135.3, 134.5, 133.7, 132.2, 130.3, 129.6, 128.7, 125.5, 110.0, 108.8, 35.3. HRMS (ESI): Calcd. for $C_{12}H_{10}NO_2$ [M-H]$^-$ 200.0717; found 200.0715. UHPLC: purity = 95.5 %

3-(Thiazol-5-yl)benzoic acid, 33:

The compound was prepared according to general procedure A. 5-bromothiazole (1.52 mmol, 250 mg, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (2.29 mmol, 567 mg, 1.5 equiv), potassium phosphate (7.62 mmol, 1.62 g, 5.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.15 mmol, 107 mg, 10

mol%), gave **33** (0.37 mmol, 76 mg, 24%) as a brownish solid. T_m = 208°C (decomposes).^{1}H NMR (400 MHz, deuterium oxide) δ 8.21 (t, *J* = 1.8 Hz, 1H), 7.93-7.83 (m, 2H), 7.77 (d, *J* = 3.3 Hz, 1H), 7.52 (d, *J* = 3.3 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H). ^{13}C NMR (101 MHz, deuterium oxide) δ 174.5, 168.9, 142.8, 137.2, 132.4, 130.6, 129.2, 128.7, 126.8, 120.6. HRMS (ESI): Calcd. for $C_{10}H_6O_2NS$ [M-H][-] 204.0125; found 204.0120. UHPLC: purity = 96.0 %

3-(1H-Indol-5-yl)benzoic acid, **34**:

According to general procedure A, 5-bromo-1H-indole (1.28 mmol, 250 mg, 1 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (1.91 mmol, 475 mg, 1.5 equiv), potassium phosphate (6.38 mmol, 1.35 g, 5.0 equiv) and $PdCl_2(PPh_3)_2$ (0.13 mmol, 90 mg, 10 mol%) after purification by flash chromatography on silica gel using hexane/ethyl acetate/acetic acid (9:1:0.01) as eluent gave **34** (0.25 mmol, 60 mg, 20 %) as a yellowish solid. T_m = 190-192 °C ^{1}H NMR (400 MHz, methanol-d_4) δ 8.30 (s, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.82 (s, 1H), 7.57-7.35 (m, 3H), 7.27 (d, *J* = 3.1 Hz, 1H), 6.52 (d, *J* = 3.3 Hz, 1H). ^{13}C NMR (101 MHz, methanol-d_4) δ 170.2, 144.5, 137.5, 132.6, 132.6, 132.3, 130.1, 129.8, 129.2, 128.3, 126.5, 121.7, 119.7, 112.6, 102.9. HRMS (ESI): Calcd. for $C_{15}H_{10}O_2N$ [M-H][-] 236.0717; found 236.0716. UHPLC: purity = 95.8 %

3-(Pyridin-2-yl)benzoic acid, **35**:

According to general procedure A, 3-bromobenzoic acid (1.24 mmol, 250 mg, 1.0 equiv), 2-Pyridineboronic acid N-phenyldiethanolamine ester (1.86 mmol, 499 mg, 1.5 equiv), potassium phosphate (6.20 mmol, 1.31 g, 5.0 equiv) and $PdCl_2(PPh_3)_2$ (0.12 mmol, 87 mg, 10 mol%) gave **35** (1.13 mmol, 224 mg, 91%) as white solid. T_m = 101-103°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.64 (d, *J* = 5.0 Hz, 1H), 8.56 (s, 1H), 8.08 (t, *J* = 7.6 Hz, 2H), 8.03-7.89 (m, 2H), 7.57-7.50 (m, 1H), 7.47-7.30 (m, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 173.6, 158.7, 150.3, 140.2, 138.9, 138.2, 132.1, 131.1, 130.5, 129.5, 129.1, 128.9, 123.8, 122.6. HRMS (ESI): Calcd. for $C_{12}H_8O_2N$ [M-H][-] 198.0561; found 198.0552. UHPLC: purity = 98.6 %

1.3 Screening of catalysts

General procedure:

3-Bromo-5-iodobenzoic acid (0.03–0.06 mmol, 1.0 equiv.) was dissolved in the indicated solvent (0.5–1 mL/0.01 mmol substrate). The boronic acid or ester (1.5 equiv.) and base (5.0 equiv.) were added. The solution was degassed by vacuum/Ar cycles (10 times) before addition of the palladium catalyst and further degassed (5 times). The resulting mixture was stirred at the indicated temperature under an inert atmosphere for the indicated reaction time. The crude reaction mixture was analysed by HRMS to determine the ratio of **int-39** : disubstituted **38** : starting material. The reaction mixture was filtered through Celite bed and diluted with water (approx. 30 mL) before washing with chloroform (3 x 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a 60 g C18 column with a gradient of acetonitrile in water (0–5% over 15 min) to yield the product.

Entry	Catalyst [mol% in Pd]	Base	Temp [^{o}C] / Time [h]	Solvent	Ratio (**int-39**:**38**:sm)	Isol. yield [%]
1	RuPhos-Pd G3 (10)	K_3PO_4	60 / 24	dioxane/water (1:1)	8 : 10 : 10	nd
2	RuPhos-Pd G3 (5)	K_3PO_4	60 / 24	toluene/water (1:1)	10 : 6 : 0.3	nd
3	XantPhos-Pd G3 (5)	K_3PO_4	40 / 48	dioxane/water (1:1)	10 : 1 : 0	nd
4	XantPhos-Pd G3 (5)	K_3PO_4	40 / 24	toluene/water (1:1)	10 : 1 : 3	70
5	Pd(dppf)Cl$_2$ (5)	K_3PO_4	60 / 24	dioxane/water (1:1)	10 : 1 : 3	80
6	XPhos-Pd G2 (1)	K_3PO_4	60 / 24	dioxane/water (1:1)	10 : 7 : 1	nd
7	SPhos-Pd G3 (5)	K_3PO_4	60 / 24	dioxane/water (1:1)	10 : 2 : 0	40
8	Pd$_2$(dba)$_3$•CHCl$_3$/SPhos 1:1 (10)	K_3PO_4	60 / 24	dioxane/water (1:1)	10 : 1 : 0.4	55
9	Pd$_2$(dba)$_3$•CHCl$_3$/SPhos 1:1 (10)	K_3PO_4	80 / 24	dioxane/water (1:1)	10 : 1 : 0.3	55
8	Pd$_2$(dba)$_3$•CHCl$_3$/SPhos 1:1 (10)	K_3PO_4	40 / 24	*tert*-BuOH	10 : 4 : 4	nd
9	Pd$_2$(dba)$_3$•CHCl$_3$/SPhos 1:1 (10)	K_3PO_4	40 / 20	toluene/water (1:1)	10 : 1 : 3	65
10	Pd$_2$(dba)$_3$•CHCl$_3$/SPhos 1:1 (10)	K_3PO_4	60 / 10	dioxane:water (1:1)	5 : 4 : 10	nd
11	Pd$_2$(dba)$_3$•CHCl$_3$/SPhos 1:1 (10)	K_3PO_4	60 / 48	dioxane:water (1:1)	10 : 4 : 1	nd
12	Pd$_2$(dba)$_3$•CHCl$_3$/SPhos 1:2 (5)	K_3PO_4	60 / 24	dioxane/water (1:1)	10 : 0.7 : 0	40

1.4 Synthesis of symmetrical 3,5-disubstituted benzoic acid derivatives

3,5-Di(3-acetamidophenyl)benzoic acid 36:

3-Bromo-5-iodobenzoic acid (0.30 mmol, 100 mg, 1.0 equiv), 3-acetamidophenylboronic acid (0.45 mmol, 816 mg, 1.5 equiv), potassium phosphate (1.5 mmol, 324 mg, 5.0 equiv) were dissolved in a mixture of water/dioxane (1:1). The solution was degassed by vacuum/Ar cycles (10 times) before addition of Pd$_2$(dba)$_3$•CHCl$_3$ (15 mg, 5 mol%), and XPhos (7.2 mg, 5 mol%) and further degassed (5 times). The resulting mixture was stirred at 60 °C for 20–24 hours. The reaction mixture was filtered through Celite bed and diluted with water (approx. 30 mL) before washing with chloroform (3 x 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a 60 g C18 column with a gradient of acetonitrile in water (0–5% over 15 min) to provide **36** (60 mg, 54%) as white powder. T$_m$ = 211-212°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.21 (s, 1H), 7.90 (t, *J* = 1.7 Hz, 1H), 7.81 (t, *J* = 1.7 Hz , 2H), 7.68 (d, *J* = 8 Hz, 2H), 7.43 (s, 1H), 7.49-7.46 (m, 2H), 7.43-7.39 (m, 2H), 2.16 (s, 6H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.0, 171.8, 142.9, 142.3, 140.5, 132.2, 130.4, 128.2, 128.1, 123.9, 120.3, 119.7, 24.0. HRMS (ESI): Calcd. for C$_{23}$H$_{19}$N$_2$O$_4$ [M-H]$^-$ 387.1350; found 387.1342. UHPLC: purity = 97.5 %

3,5-di(4-acetamidophenyl)benzoic acid 37:

3,5-Dibromobenzoic acid (1.01 mmol, 300 mg, 1.0 equiv), 3-acetamidophenylboronic acid (0.81 mmol, 178 mg, 0.75 equiv), potassium phosphate (3.76 mmol, 0.80 g, 3.5 equiv) and PdCl$_2$(PPh$_3$)$_2$ (0.11 mmol, 77 mg, 10 mol%) were stirred in a mixture of water/dioxane (1:1) for 24 hours at 95 °C under argon atmosphere. The crude reaction mixture was filtered through Celite and diluted with water (approx. 30 mL) before washing with chloroform (3 x 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a 60 g C18 column with a gradient of acetonitrile in water (0–100 % over 12 minutes). The fractions were analysed by MS and fractions containing **37** were combined. The product was purified by reverse-phase automated flash chromatography before being subjected to purification by HPLC, to yield **37** (0.09 mmol, 34 mg, 11%) as a white solid. T$_m$ = 245-247°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.24 (s, 2H), 7.98 (d, *J* = 7.8 Hz, 2H),

7.85 (d, J = 7.9 Hz, 2H), 7.68-7.66 (m, 2H), 7.63-7.60 (m, 2H), 7.57-7.53 (m, 1H), 2.16 (s, 6H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.2, 171.7, 142.0, 140.2, 139.4, 137.9, 131.7, 128.4, 128.2, 127.6, 127.4, 123.3, 121.4, 116.2, 23.9. HRMS (ESI): Calcd. for $C_{23}H_{19}N_2O_4$ [M-H]$^-$ 387.1350; found 387.1340. UHPLC: purity = 100 %

3,5-diquinolin-6-ylbenzoic acid 38:

3,5-Dibromobenzoic acid (0.11 mmol, 33 mg, 1.0 equiv), 6-quinolinylboronic acid pinacol ester (0.23 mmol, 60 mg, 2.0 equiv), potassium phosphate (0.58 mmol, 125 mg, 5.0 equiv) were dissolved in tert-butanol. The solution was degassed by vacuum/Ar cycles (10 times) before addition of XPhos-Pd G2 (5 mol%, 5 mg) and further degassed (5 times). The resulting mixture was stirred at 60 °C for 20–24 hours. The reaction mixture was filtered through Celite bed and diluted with water (approx. 30 mL) before washing with chloroform (3 x 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification by C18 RP flash chromatography with a gradient of acetonitrile in water (0–5% over 15 min) to yield 38 (0.08 mmol, 29 mg, 65%) as white powder. T_m = 291-292°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.87-8.86 (m, 2H), 8.52-8.50 (m, 2H), 8.46 (m, 2H), 8.38 (m, 2H), 8.29-8.26 (m, 3H), 8.18 (s, 1H), 8.16 (s, 1H), 7.61-7.58 (dd, J = 8.3, 4.2 Hz, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 174.4, 151.1, 148.0, 141.5, 140.5, 138.6, 130.6, 130.1, 129.5, 128.7, 126.9, 122.8. HRMS (ESI): Calcd. for $C_{25}H_{15}N_2O_2$ [M-H]$^-$ 375.1139; found 375.1133. UHPLC: purity = 99.1 %

1.5   Synthesis of unsymmetrical 3,5-disubstituted benzoic acid derivatives

3-(3'-Acetamidophenyl)-5-pyridin-4-ylbenzoic acid 39: attempted synthesis from 3,5-dibromobenzoic acid

3,5-Dibromobenzoic acid (1.01 mmol, 300 mg, 1.0 equiv), 3-acetamidophenylboronic acid (0.81 mmol, 178 mg, 0.75 equiv), potassium phosphate (3.76 mmol, 0.80 g, 3.5 equiv) and $PdCl_2(PPh_3)_2$ (0.11 mmol, 77 mg, 10 mol%) were stirred in a mixture of water/dioxane (1:1) for 24 hours at 95 °C under argon atmosphere. The crude reaction mixture was filtered through Celite and diluted with water (approx. 30 mL) before washing with chloroform (3 x 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification by C18 RP flash chromatography with a gradient of acetonitrile in water (10–100 % over 12 minutes). The fractions were analysed by MS and fractions containing int-39 were combined and reacted with pyridin-4-ylboronic acid (0.97 mmol, 119 mg, 1.2 equiv), potassium phosphate (4.05 mmol, 0.86 g, 5.0 equiv) and $PdCl_2(PPh_3)_2$ (0.08 mmol, 56 mg, 10 mol%). The product was purified by reverse-phase automated flash chromatography before being subjected to purification by HPLC, to yield 39 (0.12 mmol, 39 mg, 15%) as a white solid. T_m = 244°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.22 (s, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.76 (s, 2H), 7.68-7.60 (m, 3H), 7.46-7.33 (m, 4H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, methanol-d_4) δ 175.3, 171.7, 143.0, 141.5, 140.4, 139.8, 130.3, 129.7, 129.3, 129.3, 128.9, 123.7, 120.1, 119.6, 23.9. UHPLC: purity = 97.9%

3-Bromo-5-(quinolin-6-yl) benzoic acid int-40:

3-Bromo-5-iodobenzoic acid (0.15 mmol, 50 mg, 1.0 equiv), 6-quinolinylboronic acid pinacol ester (0.22 mmol, 58 mg, 1.5 equiv) and potassium phosphate (0.76 mmol, 162 mg, 5.0 equiv) were dissolved in a mixture of water/dioxane (1:1). The solution was degassed by vacuum/Ar cycles (10 times) before addition of $Pd_2(dba)_3 \bullet CHCl_3$ (5 mol%, 7.5 mg), and SPhos (5 mol%, 3.1 mg) and further degassed (5 times). The resulting mixture was stirred at 60 °C for 20–24 hours. The reaction mixture was filtered through a Celite bed and diluted with water (approx. 30 mL) before washing with chloroform (3 x 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a 60 g C18 column with a gradient of acetonitrile in water (0–5% over 20 min). Product int-40 (0.07 mmol, 23 mg, 45%) was obtained as a white powder. T_m = 288°C. ^{1}H NMR (400

MHz, methanol-d_4) δ 8.92-8.91 (m, 1H), 8.49-8.46 (m, 1H), 8.35 (s, 1H), 8.28 (s, 2H), 8.10 (s, 2H), 8.02-8.01 (m, 1H), 7.97-7.96 (m,1H), 7.59-7.56 (dd, J = 8.3, 4.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.6, 150.8, 147.2, 143.6, 140.6, 136.8, 136.5, 131.7, 131.1, 129.6, 128.5, 128.2, 127.4, 126.5, 125.8, 121.9, 121.7; HRMS (ESI): Calcd. for $C_{16}H_9{}^{79}BrNO_2$ [M-H]$^-$ 325.9822; found 325.9822.

3-(3'-Acetamidophenyl)-5-quinolin-6-ylbenzoic acid 40:

3-Bromo-5-(quinolin-6-yl) benzoic acid **int-40** (0.039 mmol, 13 mg, 1.0 equiv), 3-acetamidophenylboronic acid (0.55 mmol, 10 mg, 1.5 equiv) and potassium phosphate (0.20 mmol, 0.42 g, 5.0 equiv) were dissolved in tert-butanol. The solution was degassed by vacuum/Ar cycles (10 times) before addition of Xphos-Pd G2 (5 mol%, 1.5 mg) and further degassed (5 times). The resulting mixture was stirred at 60 °C for 20–24 hours. The reaction mixture was filtered through Celite bed and diluted with water (approx. 30 mL) before washing with chloroform (3 x 30 mL). The aqueous phase was concentrated under reduced pressure and applied to a C18 precolumn before purification on a 60 g C18 column with a gradient of acetonitrile in water (0–5% over 20 min). Product **40** (0.023 mmol, 9 mg, 90%) was obtained as white powder. T_m = 261-264°C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.87-8.83 (m, 1H), 8.56-8.45 (m, 1H), 8.41-8.39 (m, 1H), 8.35-8.20 (m, 3H), 8.18-8.11 (m, 1H), 8.08 (t, J = 1.8 Hz, 1H), 7.87-7.86 (m, 1H), 7.72-7.68 (m, 1H), 7.62-7.56 (m, 1H), 7.56-7.49 (m, 1H), 7.46-7.42 (m, 1H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7, 171.8, 151.2, 148.2, 142.8, 142.5, 141.4, 140.8, 140.7, 140.5, 138.8, 130.8, 130.4, 130.3, 129.7, 128.6, 128.5, 128.5, 127.0, 123.9, 123.0, 120.3, 119.7, 23.9. HRMS (ESI): Calcd. for $C_{24}H_{18}N_2O_3$ [M-H]$^-$ 381.1245; found 381.1243. UHPLC: purity = 96.4 %.

2 NMR spectra of compounds 3–40:

2.1 2'-methylbiphenyl-3-carboxylic acid, **3a**:

2.1.1 ^{1}H NMR of **3a**
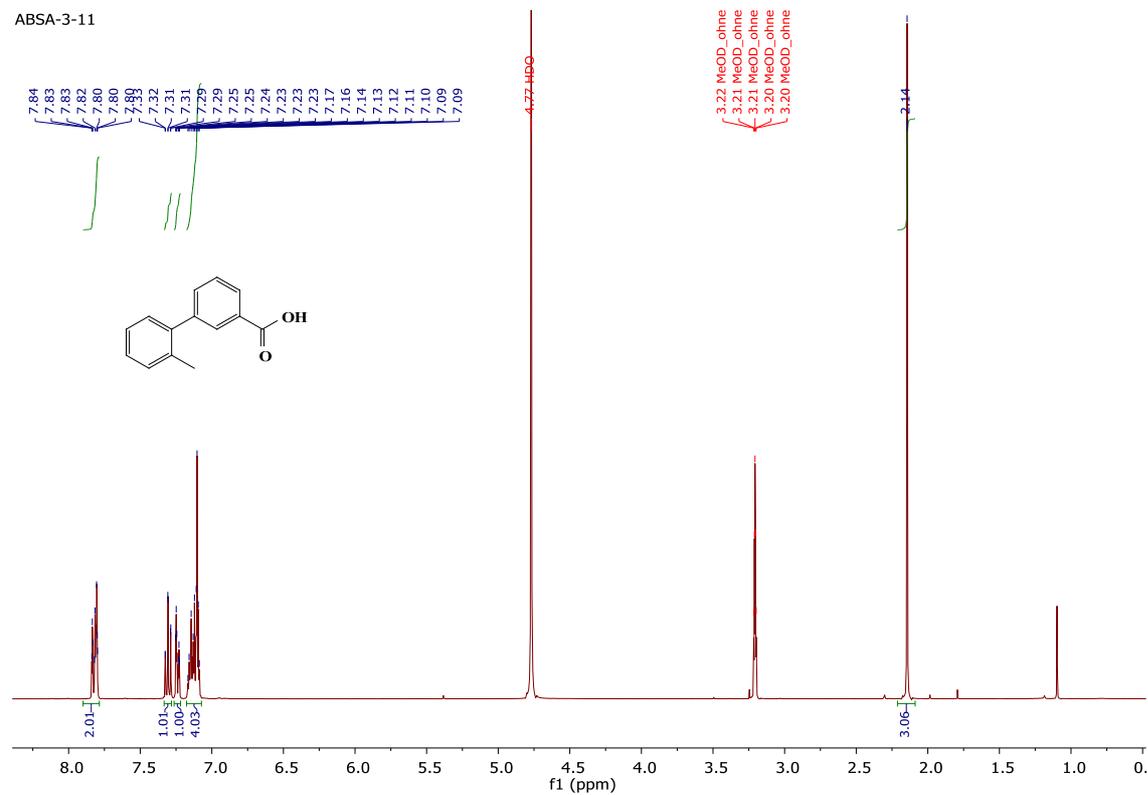
ABSA-3-11

2.1.2 ^{13}C NMR of **3a**
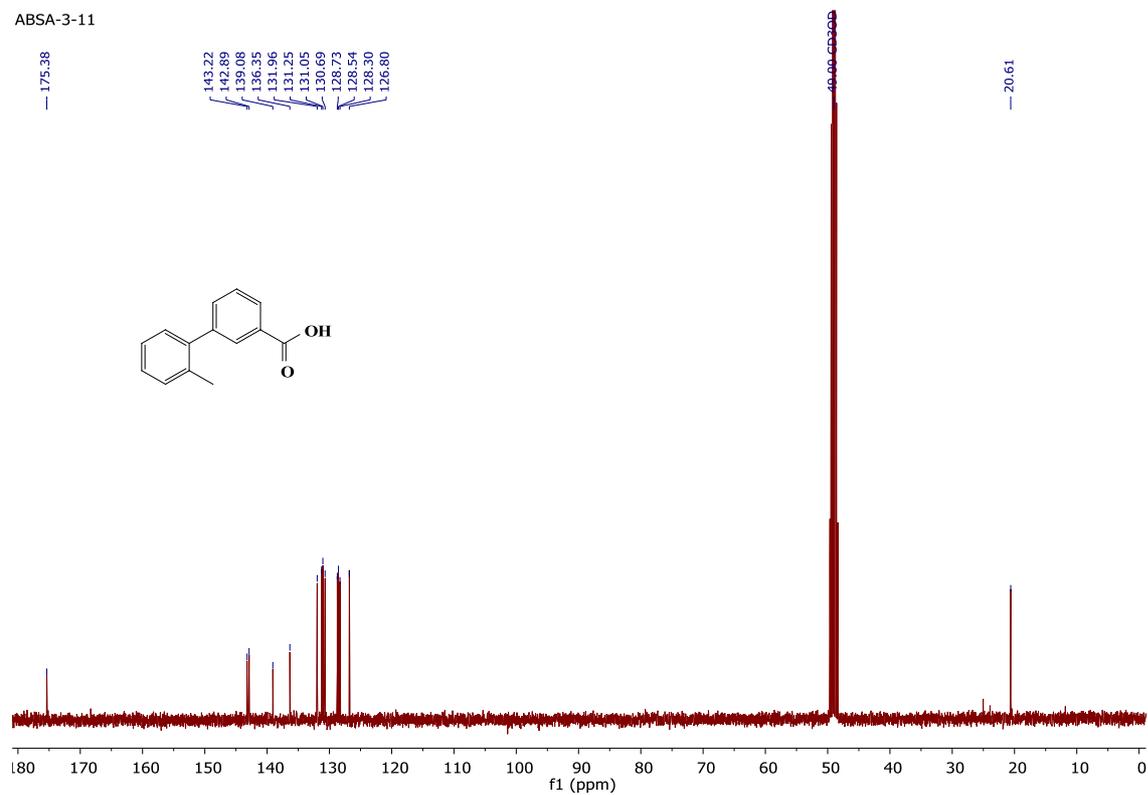
ABSA-3-11

2.2 3'-methylbiphenyl-3-carboxylic acid, **3b**:

2.2.1 ^{1}H NMR of **3b**

ABSA-3-10
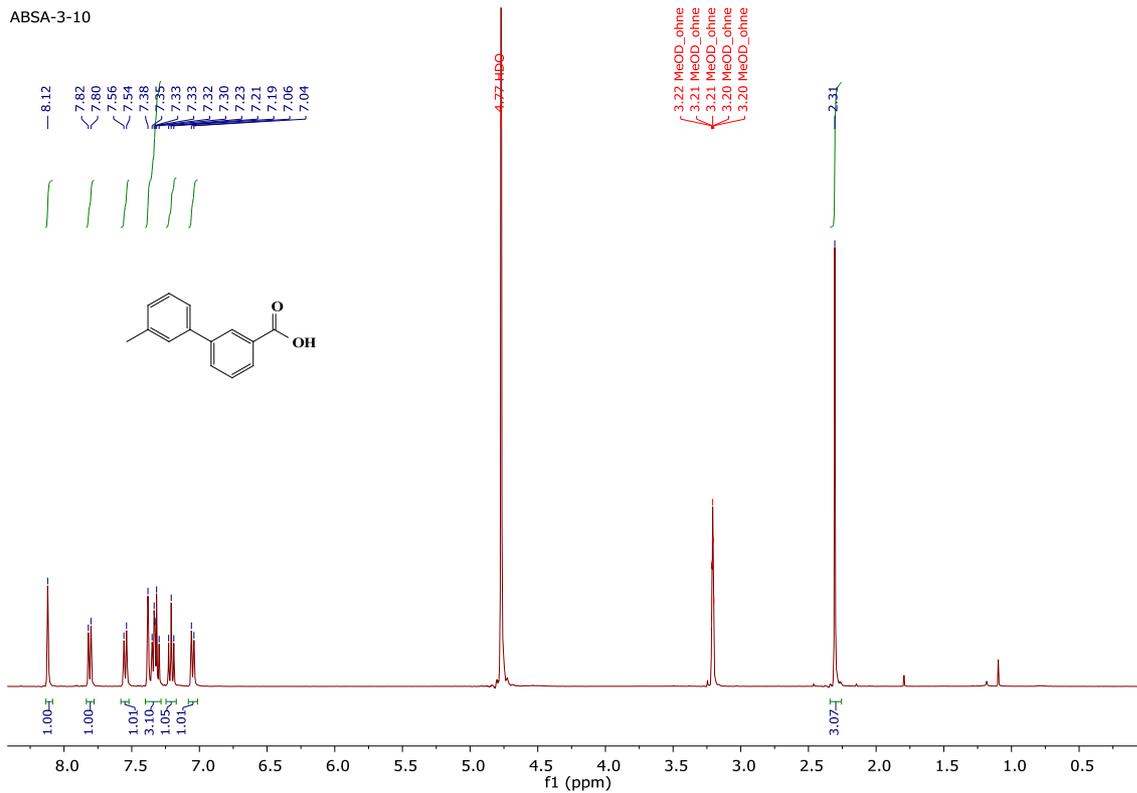
2.2.2 ^{13}C NMR of **3b**

ABSA-3-10
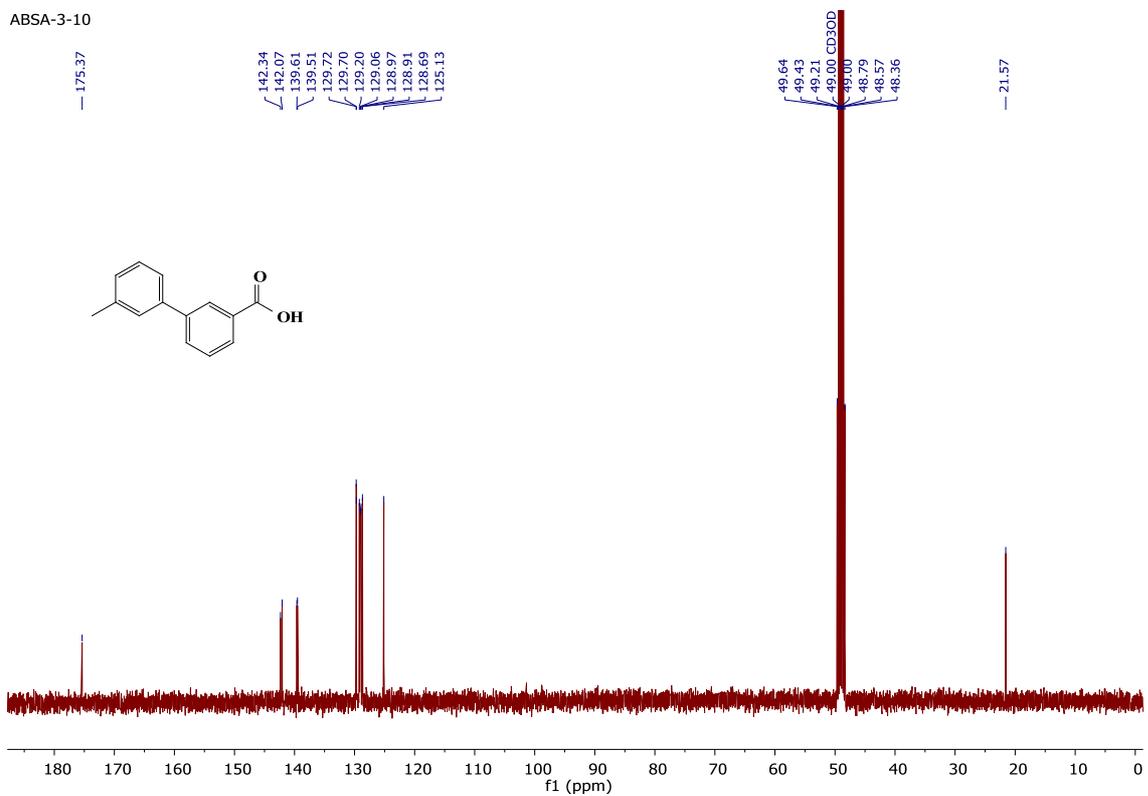
2.3   2'-hydroxybiphenyl-3-carboxylic acid **4a**:

2.3.1 ^{1}H NMR of 4a

ABSA-3-14
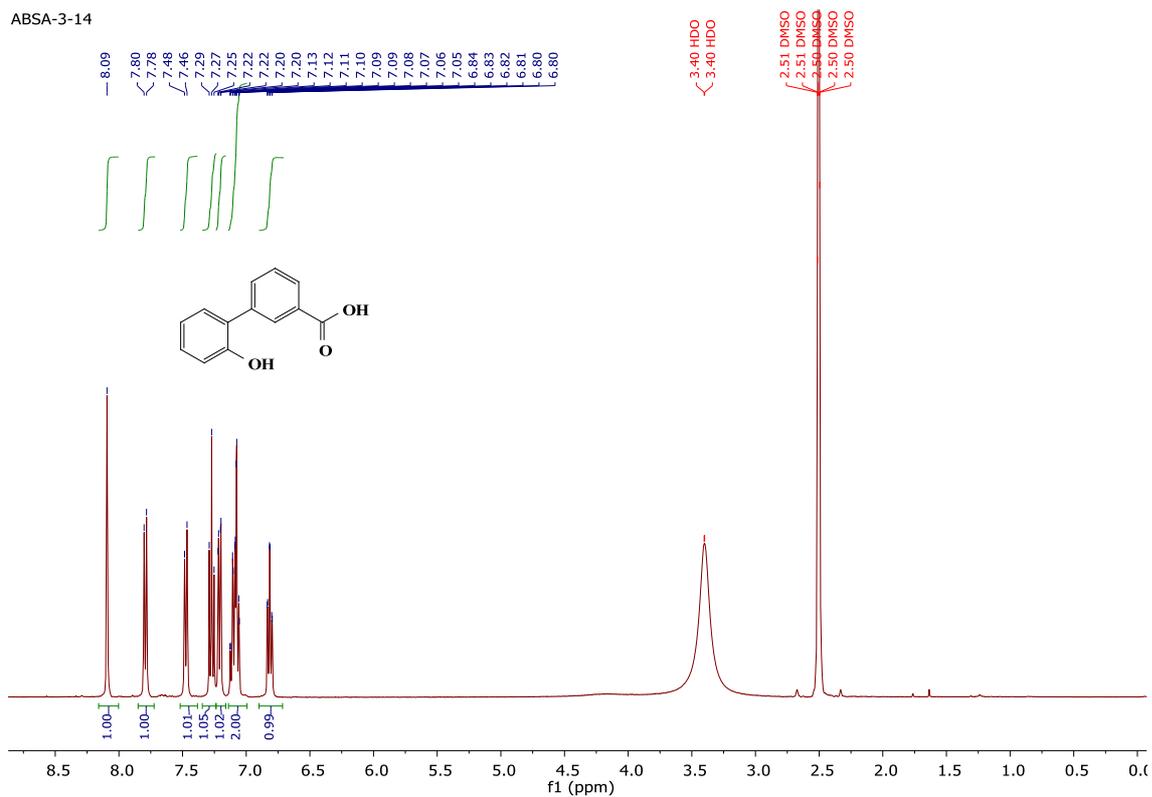
2.3.2 ^{13}C NMR of **4a**

ABSA-3-14
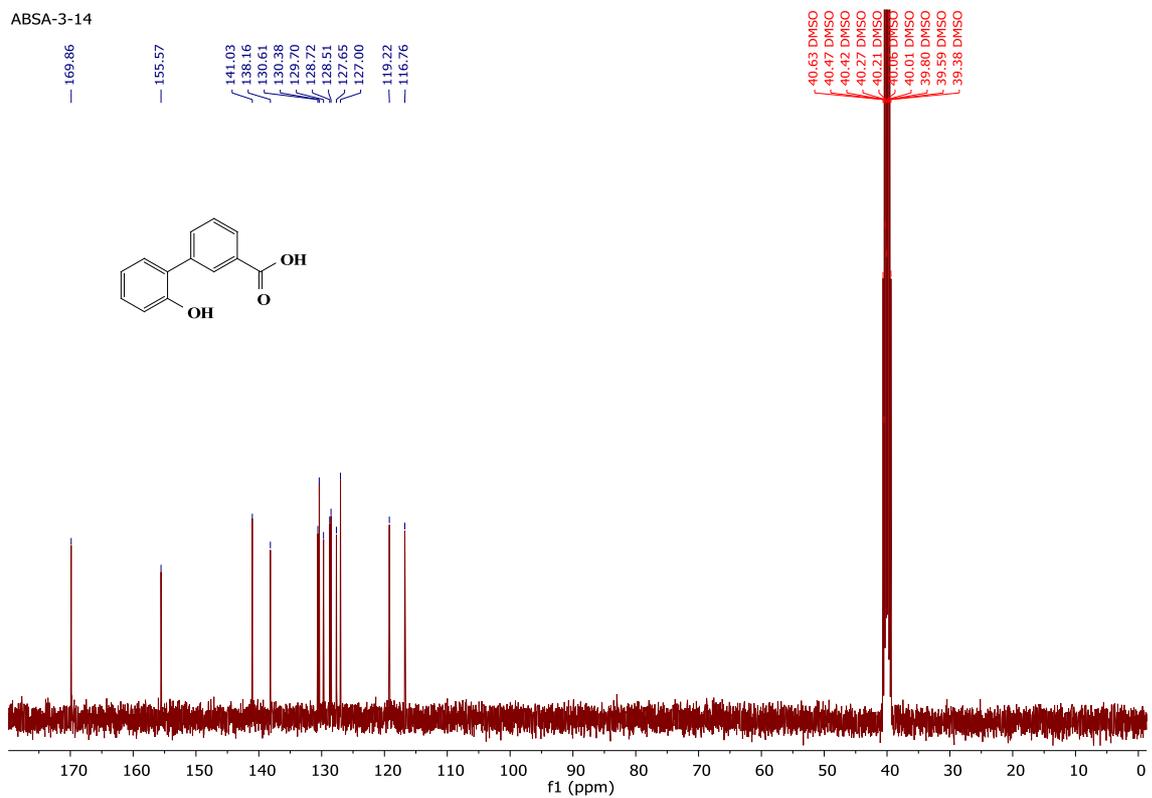
2.4   3'-hydroxybiphenyl-3-carboxylic acid, **4b**:

2.4.1   ¹H NMR of **4b**

2.4.2   ¹³C NMR of **4b**

ABSA-3-02
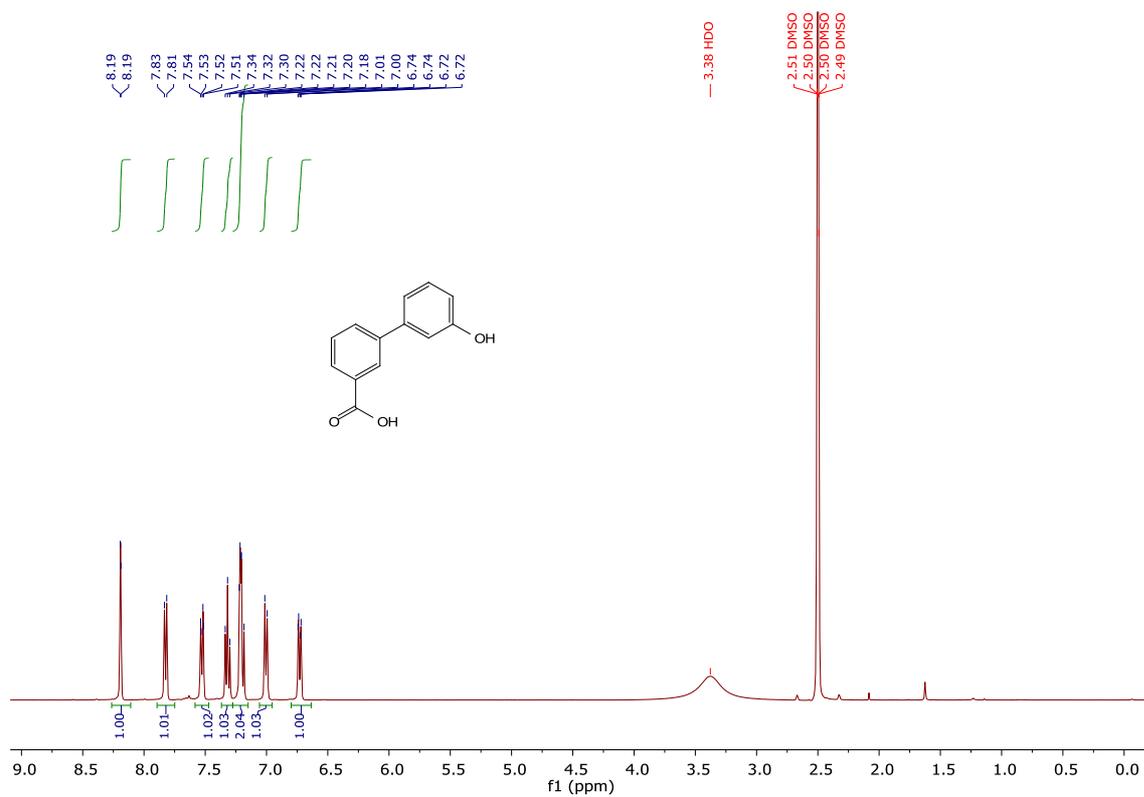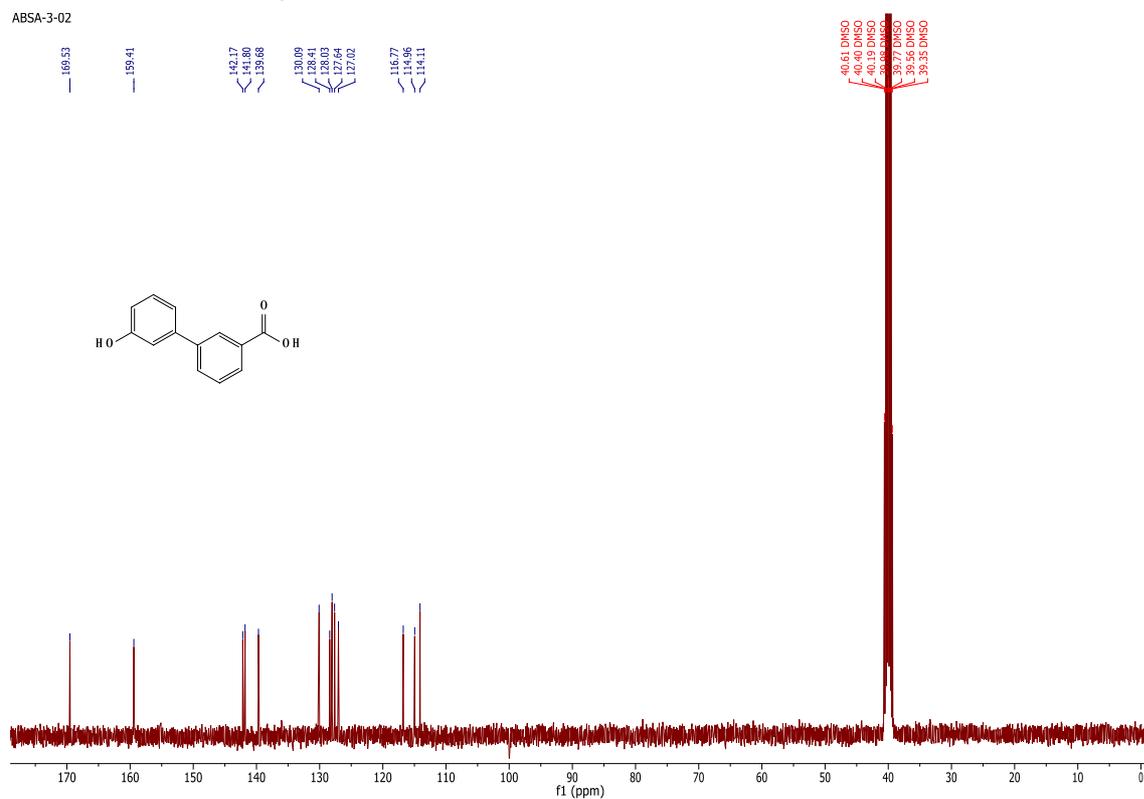
2.5 4'-hydroxybiphenyl-3-carboxylic acid, **4c**:

2.5.1 ^{1}H NMR of **4c**
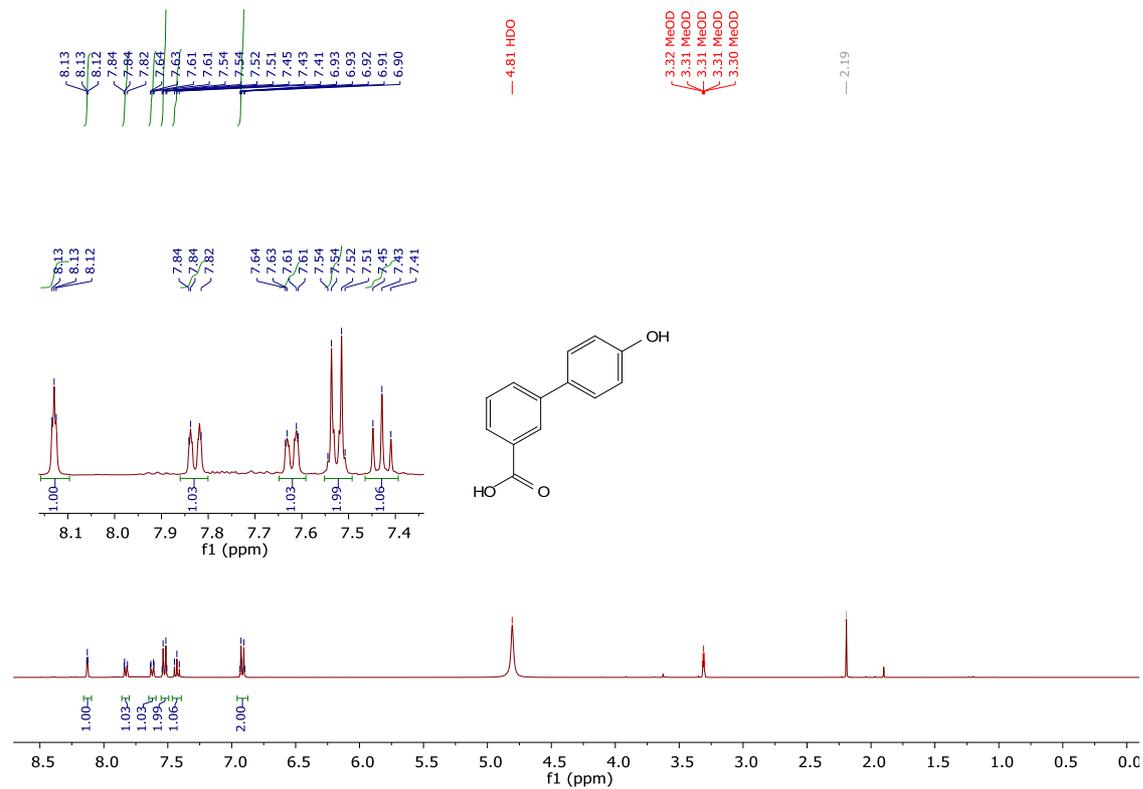
2.5.2 ^{13}C NMR of **4c**
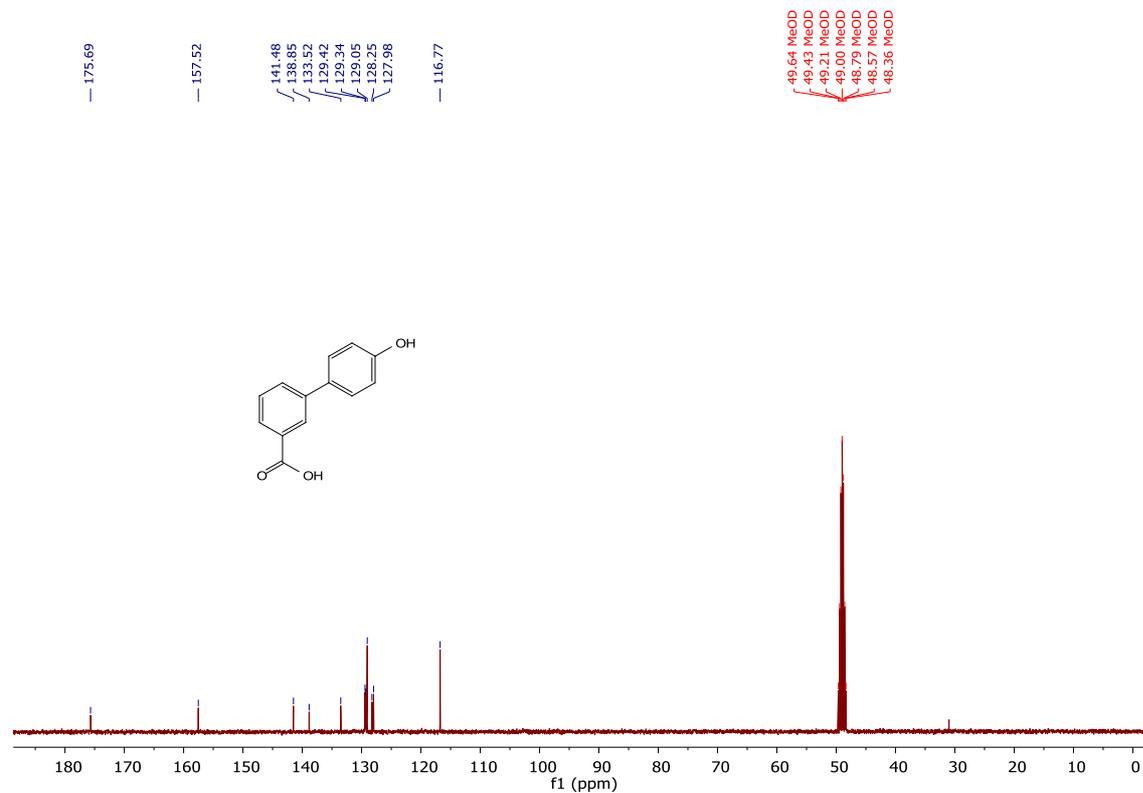
2.6 3'-(hydroxymethyl)biphenyl-3-carboxylic acid 5:

2.6.1 ^{1}H NMR of 5

2.6.2 ^{13}C NMR of 5
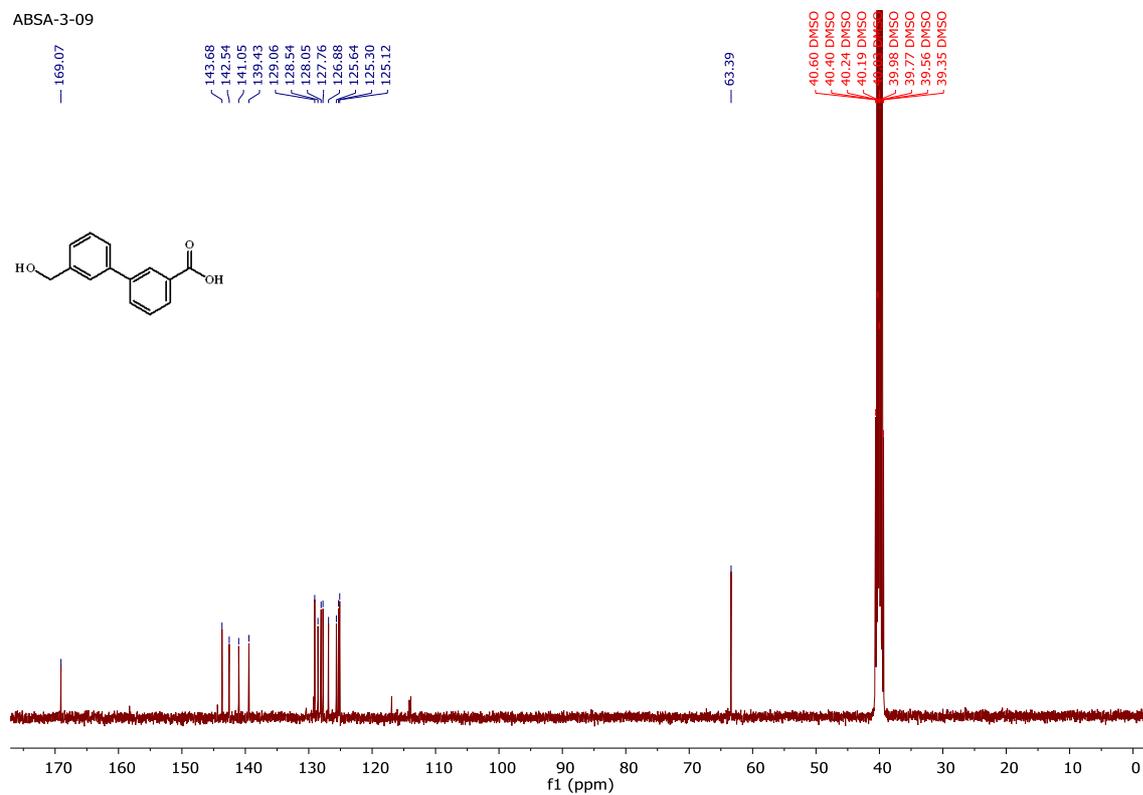
ABSA-3-09

2.7 2'-methoxybiphenyl-3-carboxylic acid, **6a**:

2.7.1 ^{1}H NMR of **6a**

ABSA-3-12

7.93
7.80
7.78
7.36
7.34
7.32
7.31
7.30
7.28
7.26
7.24
7.24
7.11
7.09
7.04
7.02
7.00

3.75

3.39 HDO

2.52 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
2.50 DMSO

1.00
1.00
4.04
1.02
1.02
3.00

f1 (ppm)

2.7.2 ^{13}C NMR of **6a**

ABSA-3-12

169.15

156.62

141.93
137.29
131.10
130.85
130.44
129.49
128.92
127.96
126.92
121.13

112.11

55.90

40.66 DMSO
40.61 DMSO
40.46 DMSO
40.40 DMSO
40.25 DMSO

40.04 DMSO
39.99 DMSO
39.78 DMSO
39.57 DMSO
39.36 DMSO

f1 (ppm)

27
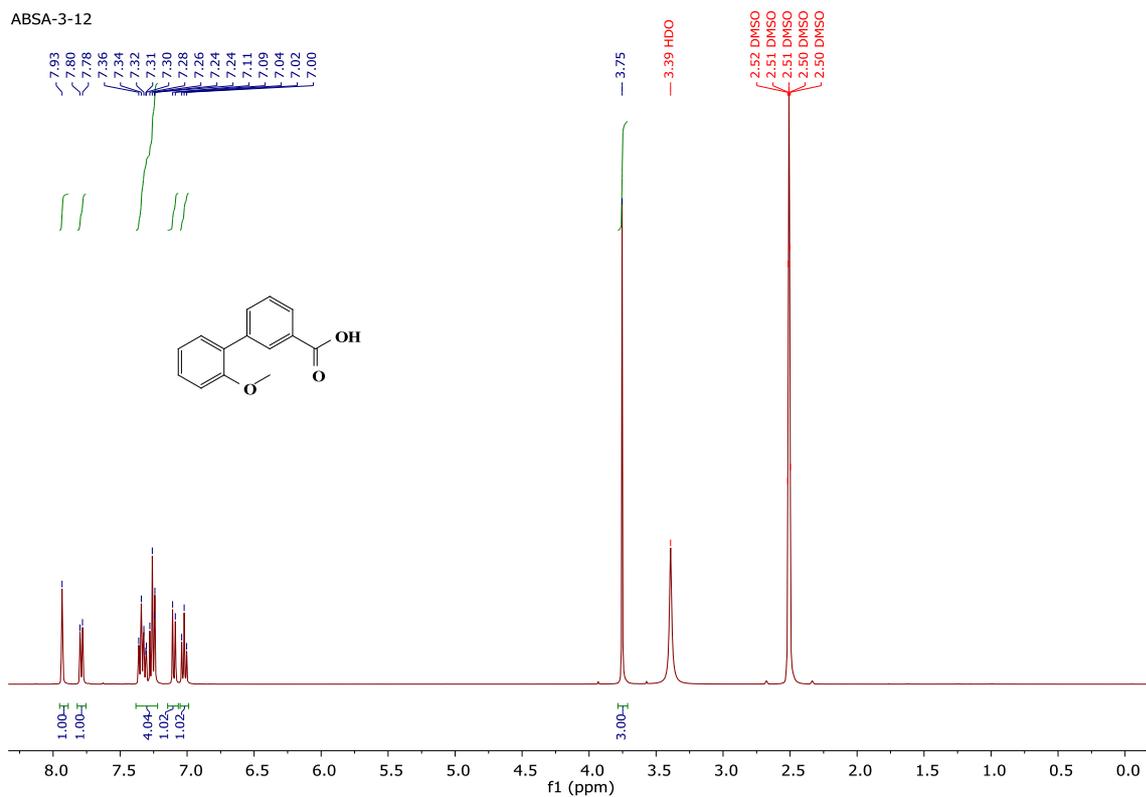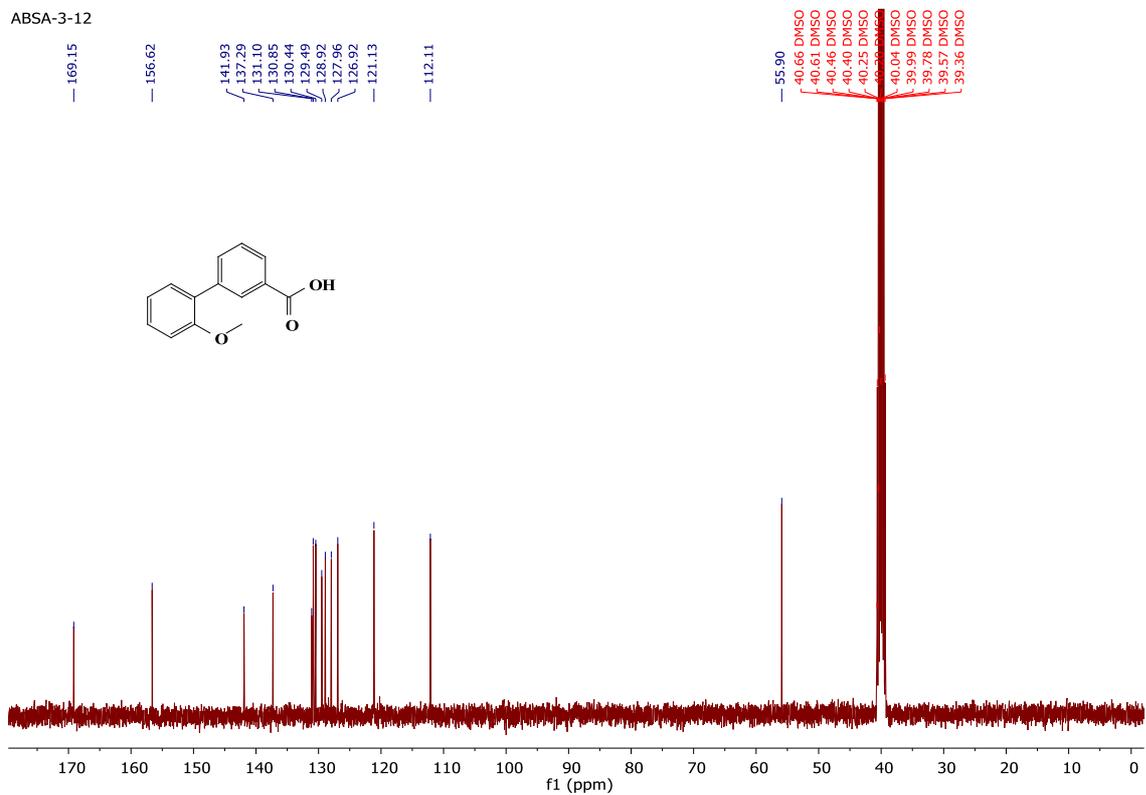
2.8   3'-methoxybiphenyl-3-carboxylic acid, **6b**:

2.8.1 ^{1}H NMR of **6b**

ABSA-3-13

8.12
7.85
7.83
7.56
7.54
7.40
7.38
7.36
7.35
7.33
7.31
7.22
7.20
7.15
6.93
6.93
6.91
6.91

3.83

3.38 HDO

2.68 DMSO
2.52 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
2.50 DMSO
2.33 DMSO

1.00
1.00
1.01
2.05
1.01
1.00
1.03

3.06

f1 (ppm)

2.8.2 ^{13}C NMR of **6b**:

168.33

159.68

142.47
138.71

129.89
128.27
127.51
127.30
126.48

118.95

112.74
111.90

99.52

55.08

40.20 DMSO
40.15 DMSO
39.99 DMSO
39.94 DMSO
39.78 DMSO
39.57 DMSO
39.52 DMSO
39.31 DMSO
39.10 DMSO
38.89 DMSO

f1 (ppm)
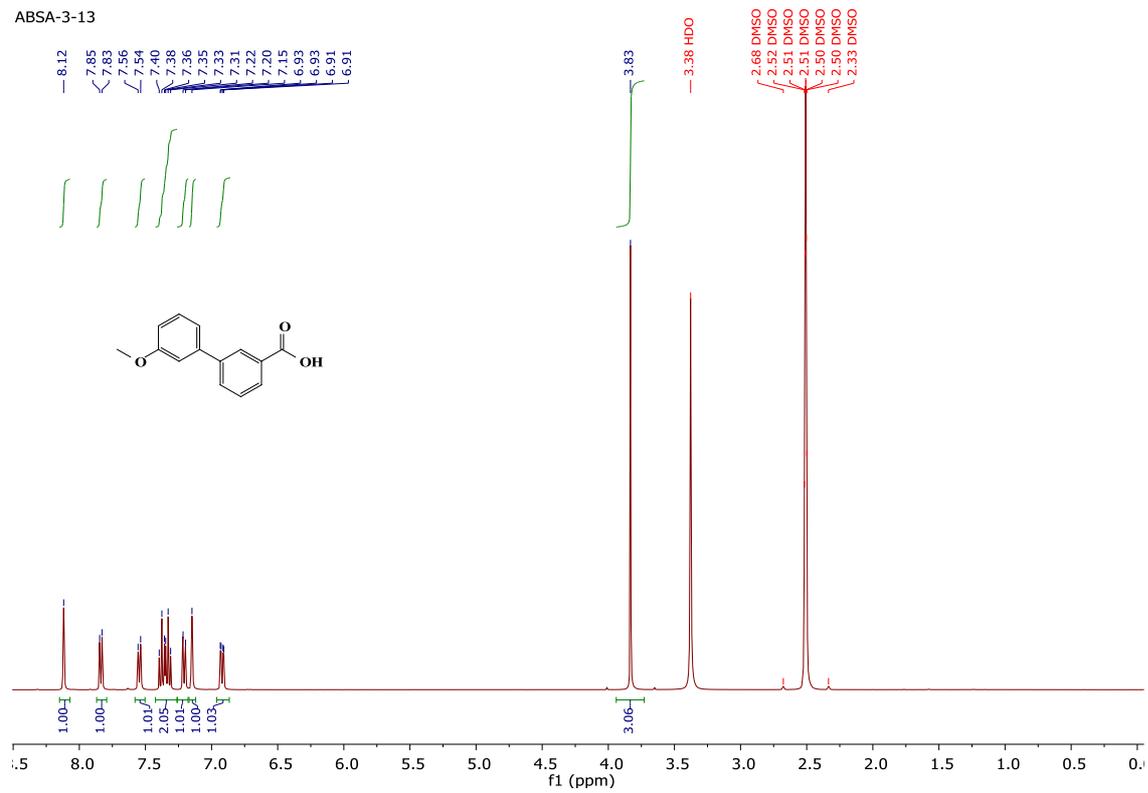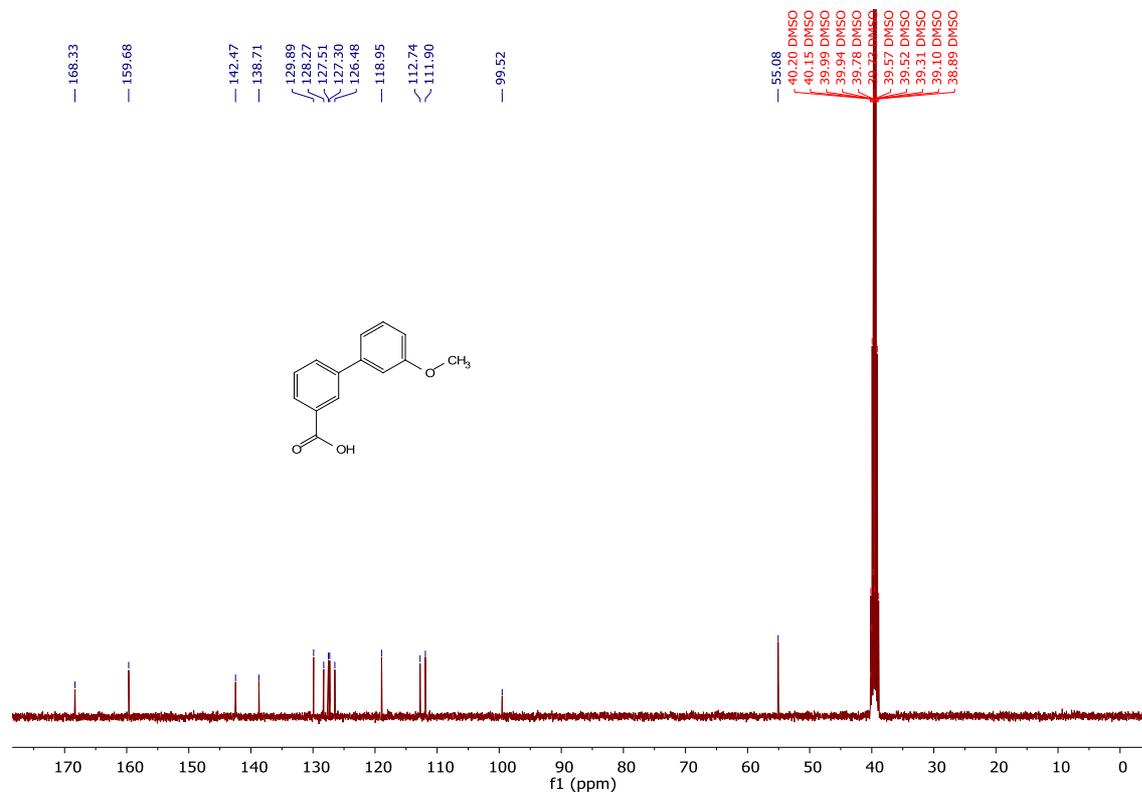
2.9 4'-methoxybiphenyl-3-carboxylic acid **6c**:

2.9.1 ^{1}H NMR of **6c**

ABSA-3-01
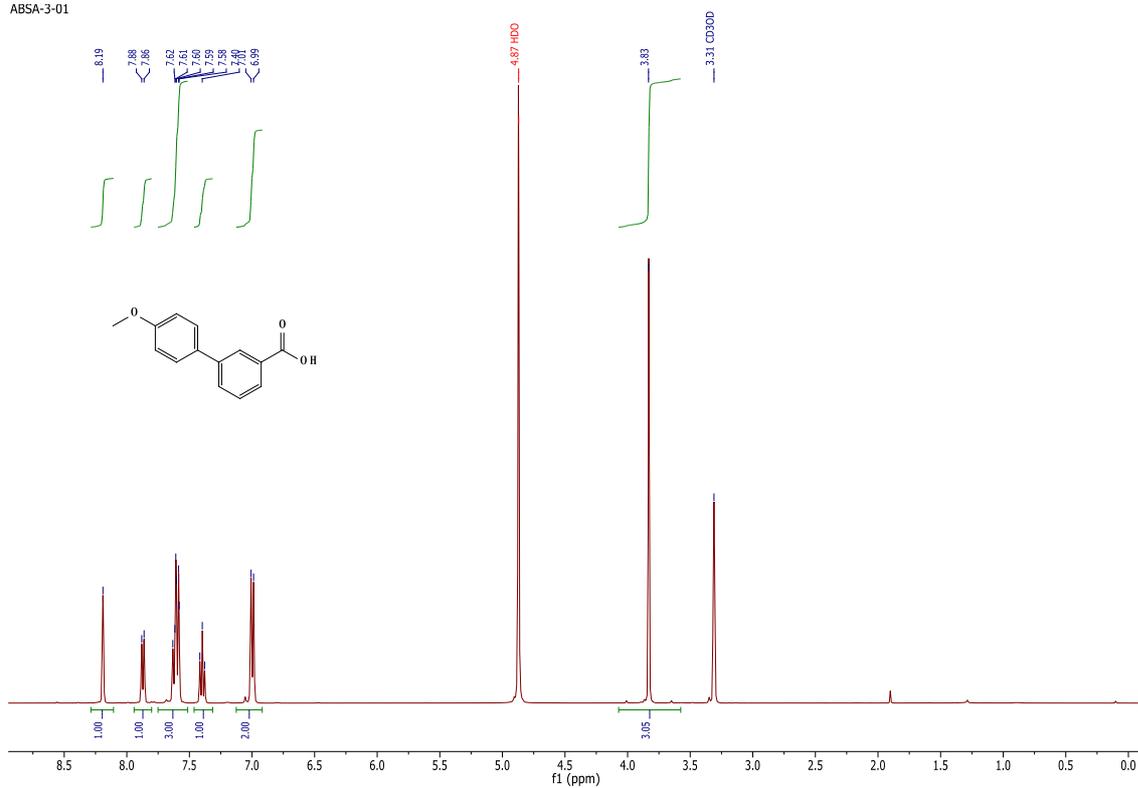
2.9.2 13C NMR of **6c**

ABSA-3-01
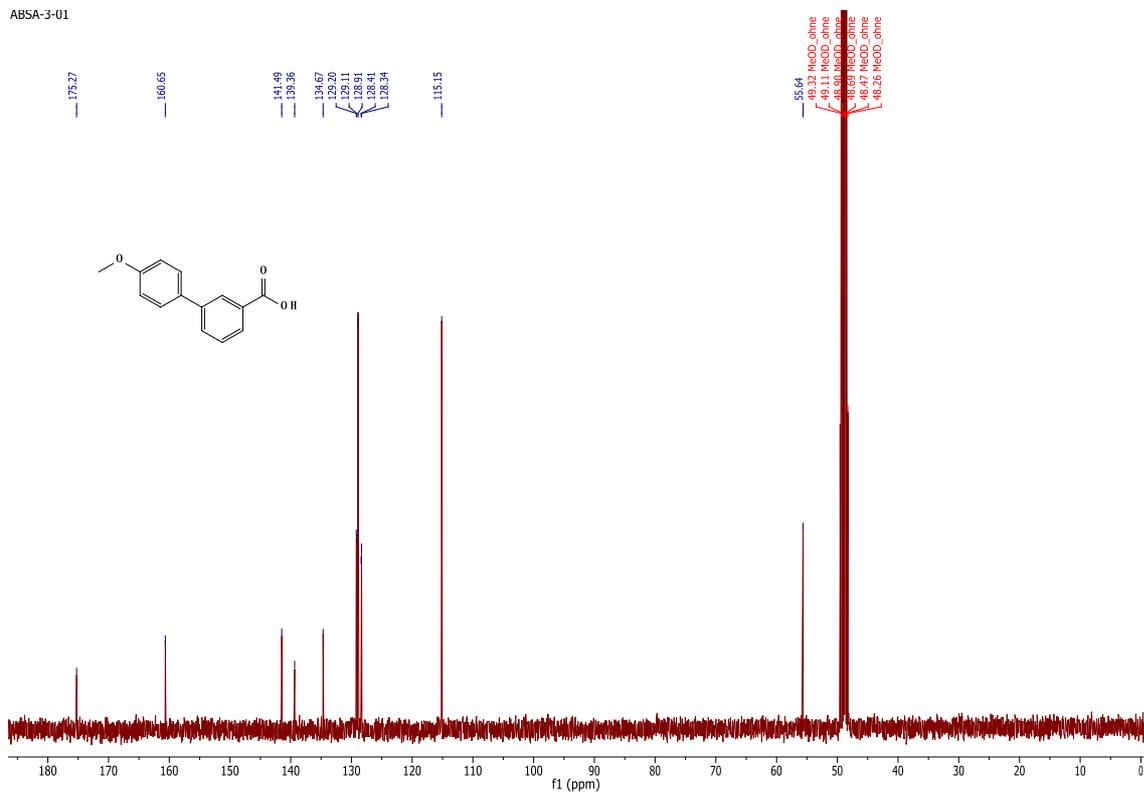
2.10 4'-methylthiobiphenyl]-3-carboxylic acid, 7:

2.10.1 ¹H NMR of 7
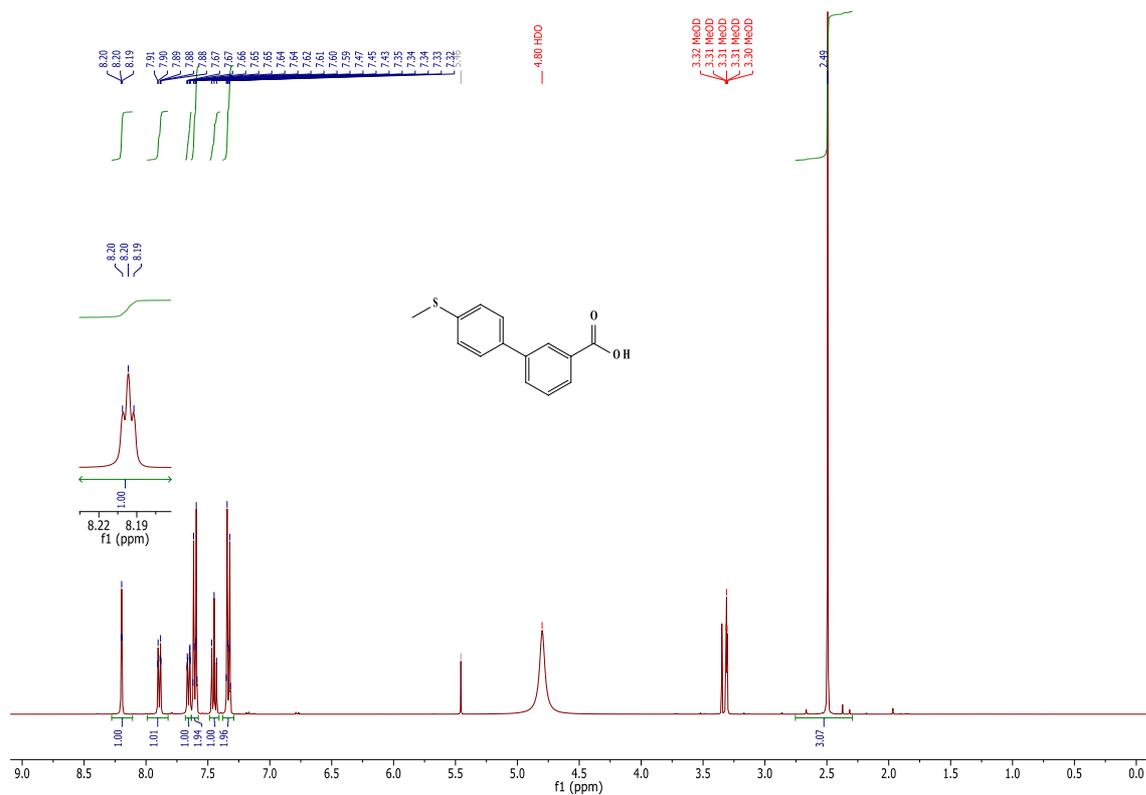
2.10.2 ¹³C NMR of 7
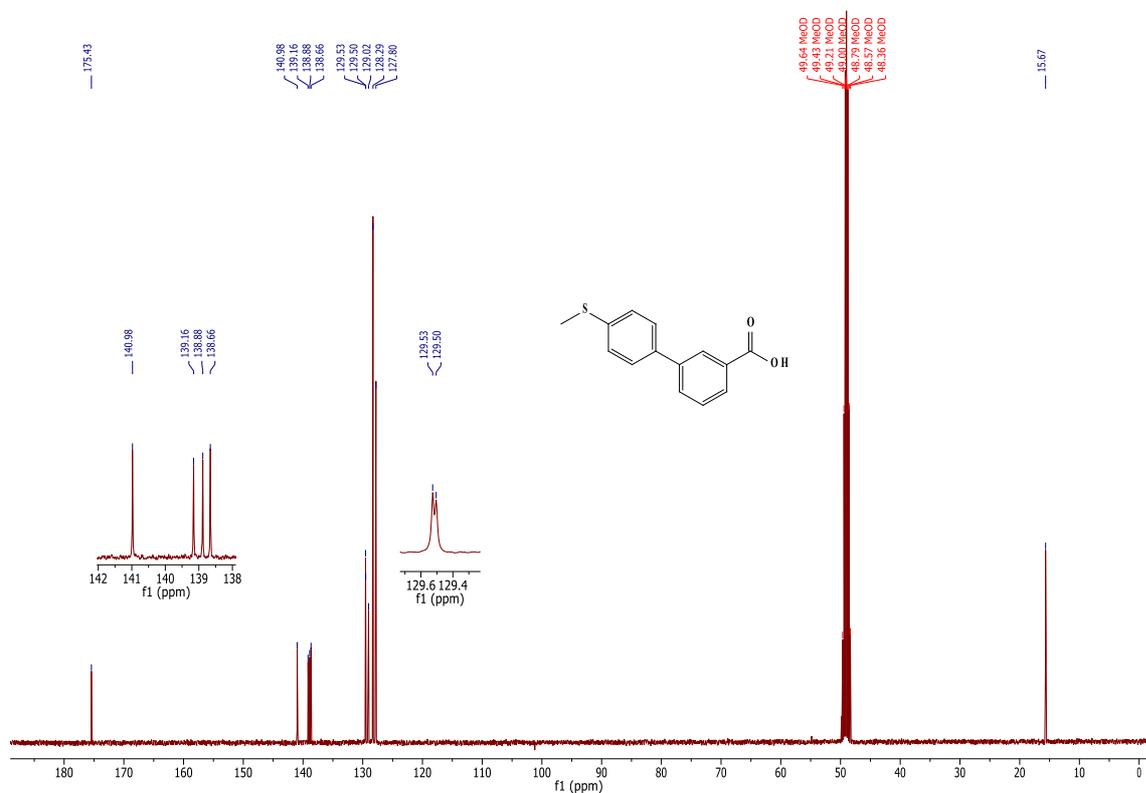
2.11 2'-fluorobiphenyl-3-carboxylic acid, **8a**:

2.11.1 ^{1}H NMR of **8a**

ABSA-3-17
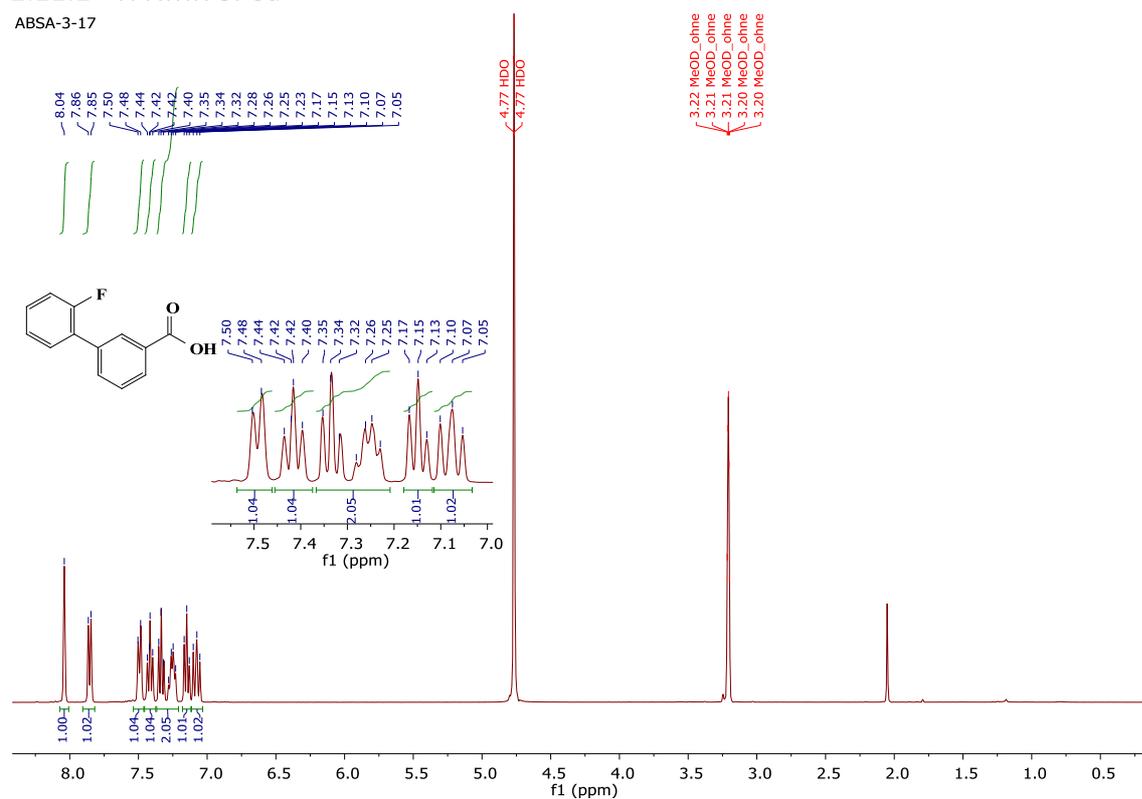
2.11.2 ^{13}C NMR of **8a**

ABSA-3-17
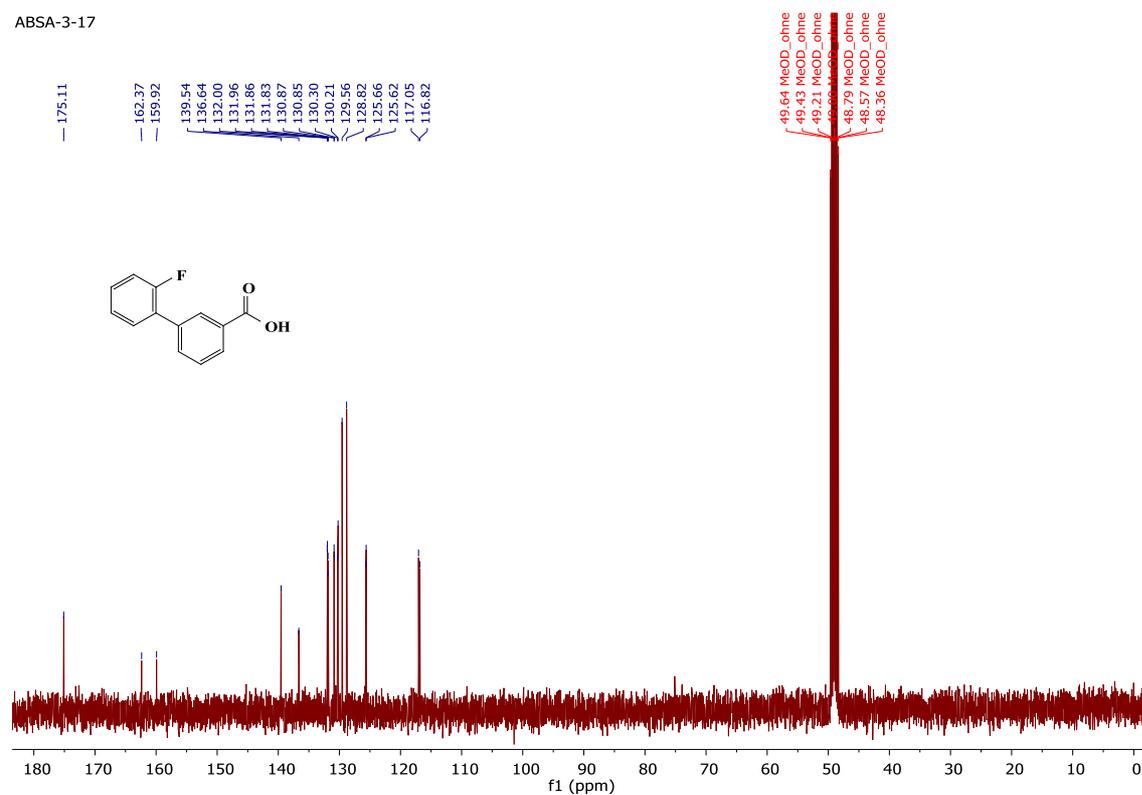
2.12 3'-fluorobiphenyl-3-carboxylic acid **8b**:

2.12.1 ^{1}H NMR of **8b**

ABSA-3-18
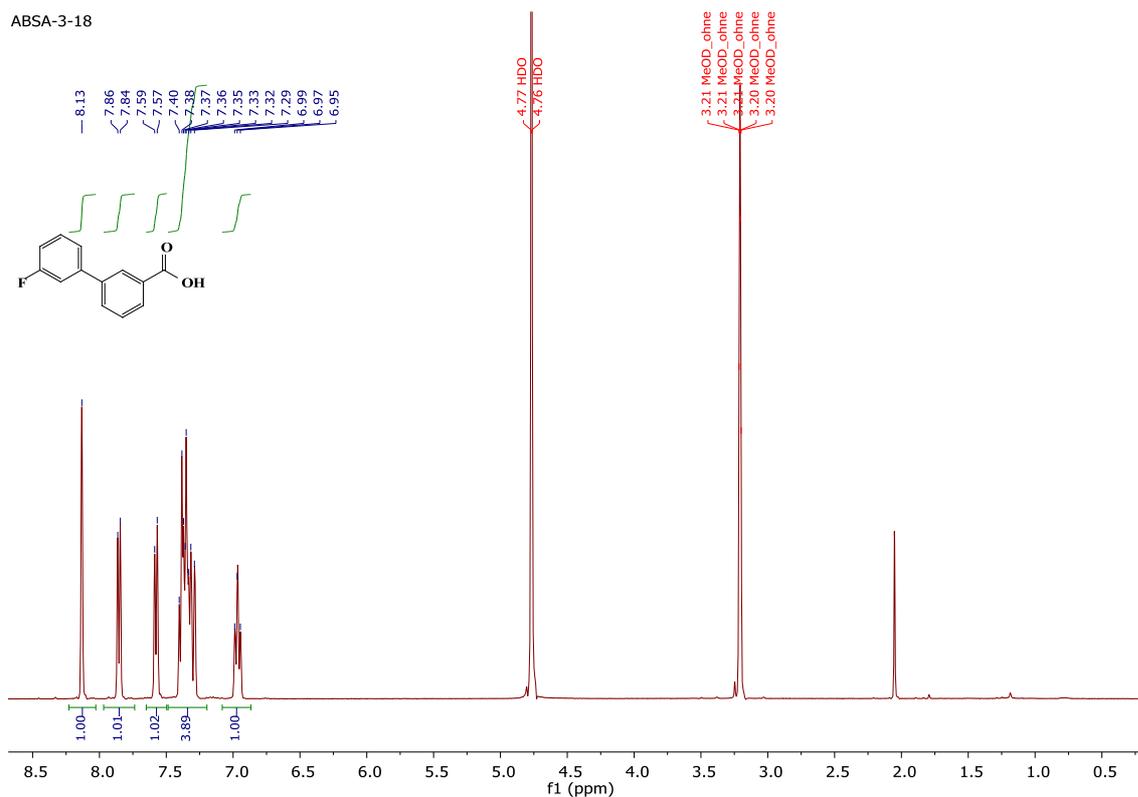
2.12.2 ^{13}C NMR of **8b**

ABSA-3-18
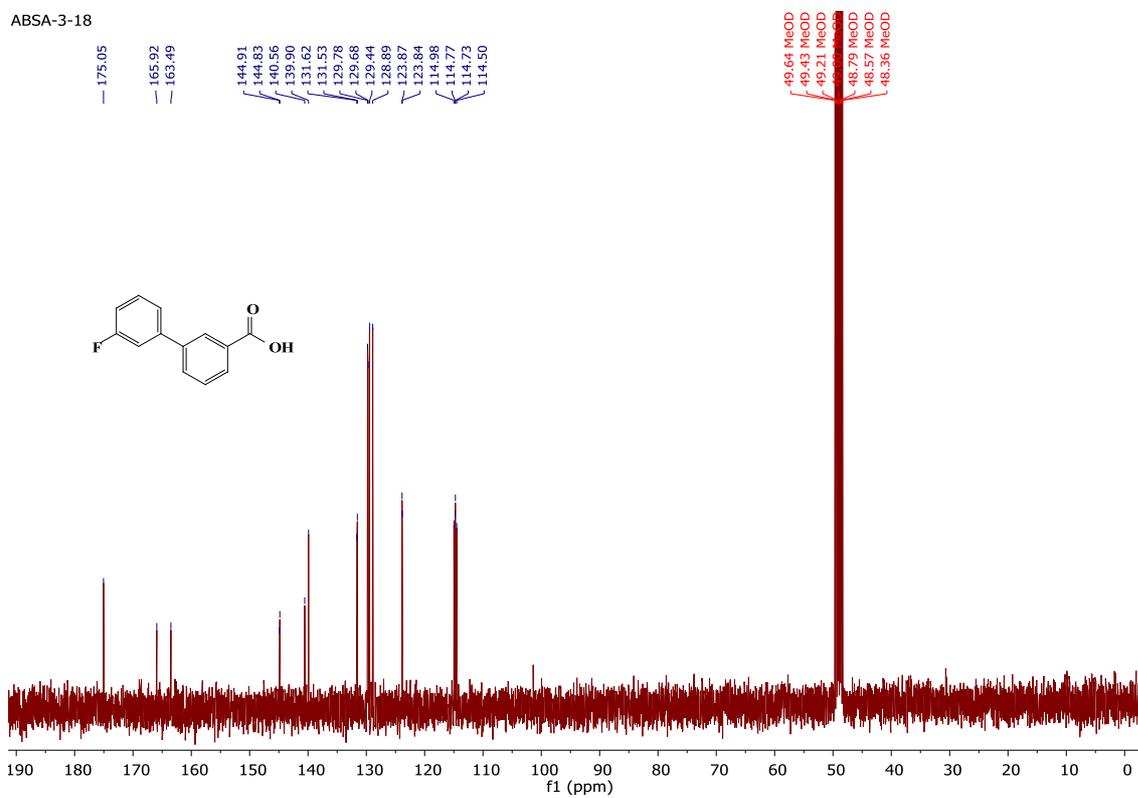
2.13 4'-fluorobiphenyl-3-carboxylic acid, **8c**:

2.13.1 ^{1}H NMR of **8c**

ABSA-3-19

2.13.2 ^{13}C NMR of **8c**

ABSA-3-19
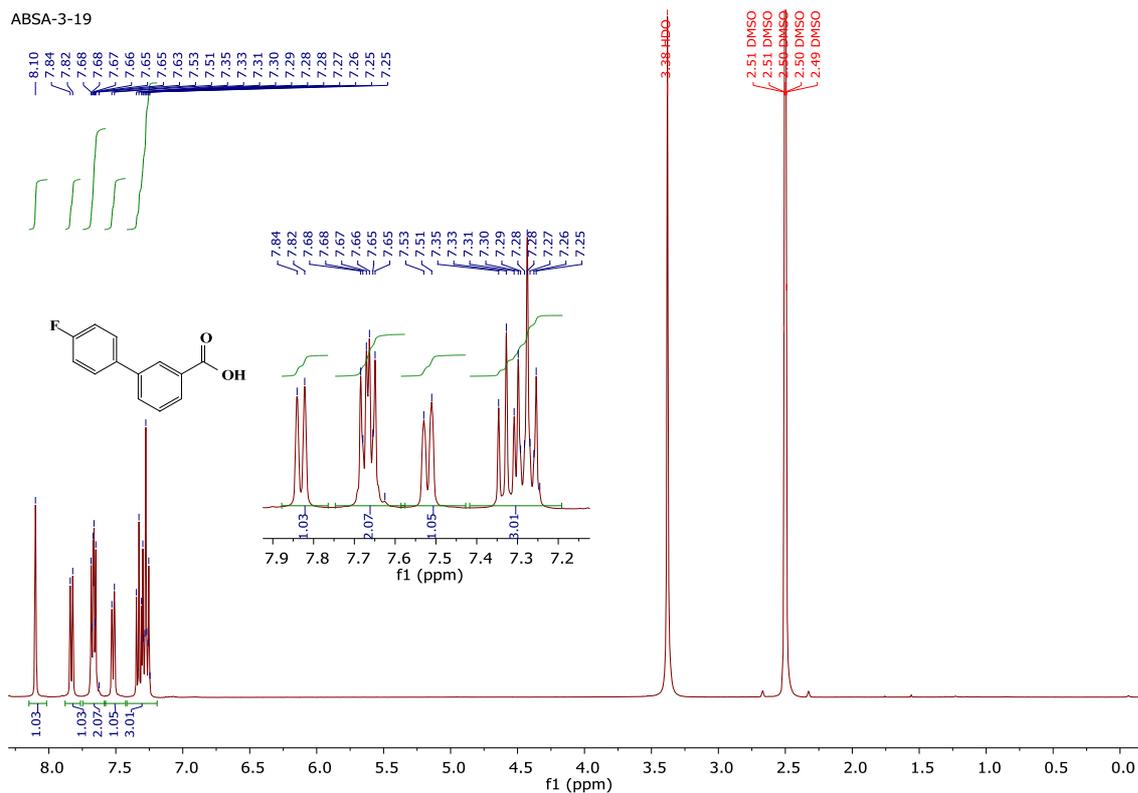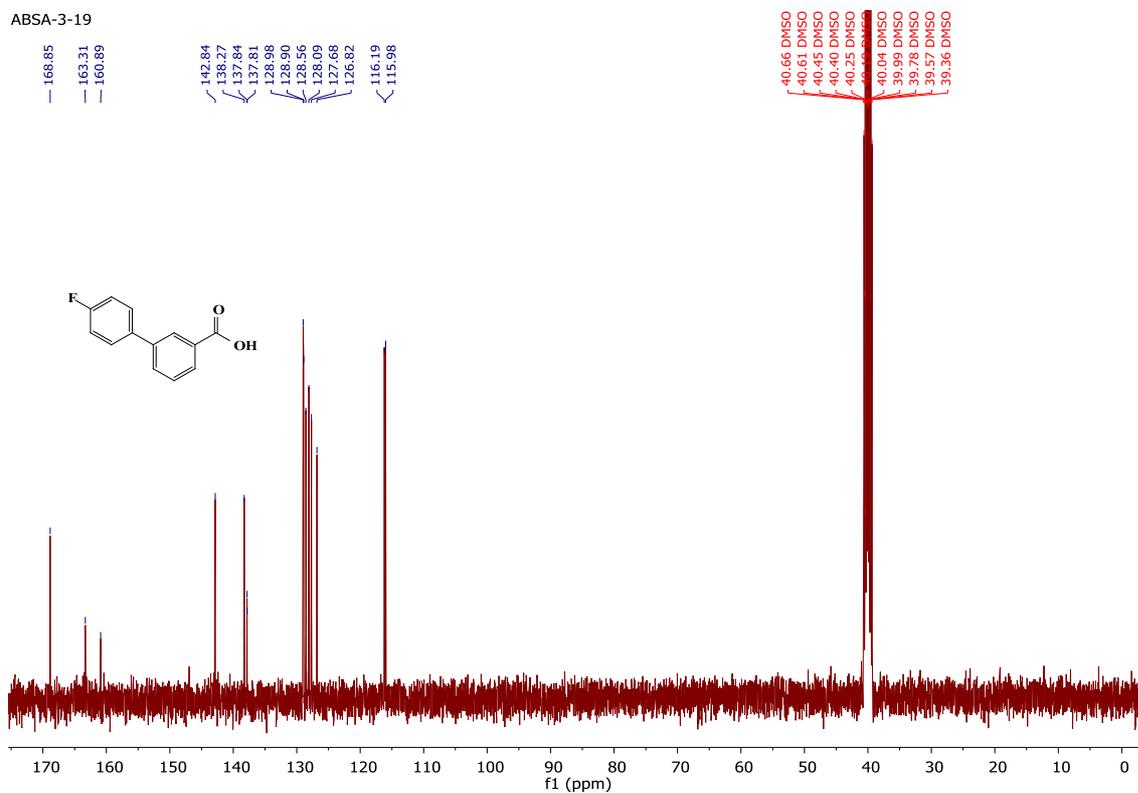
2.14 2'-(methoxycarbonyl)biphenyl-3-carboxylic acid, 9a:

2.14.1 ^{1}H NMR of 9a
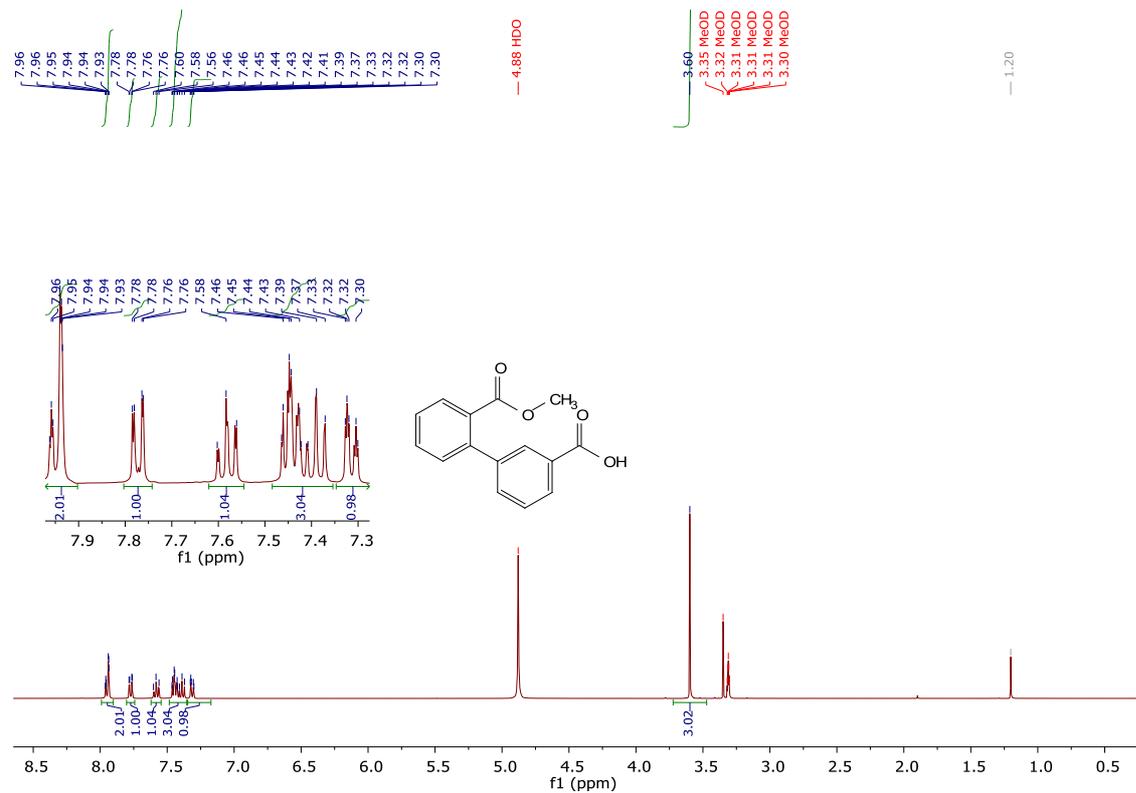
2.14.2 ^{13}C NMR of 9a
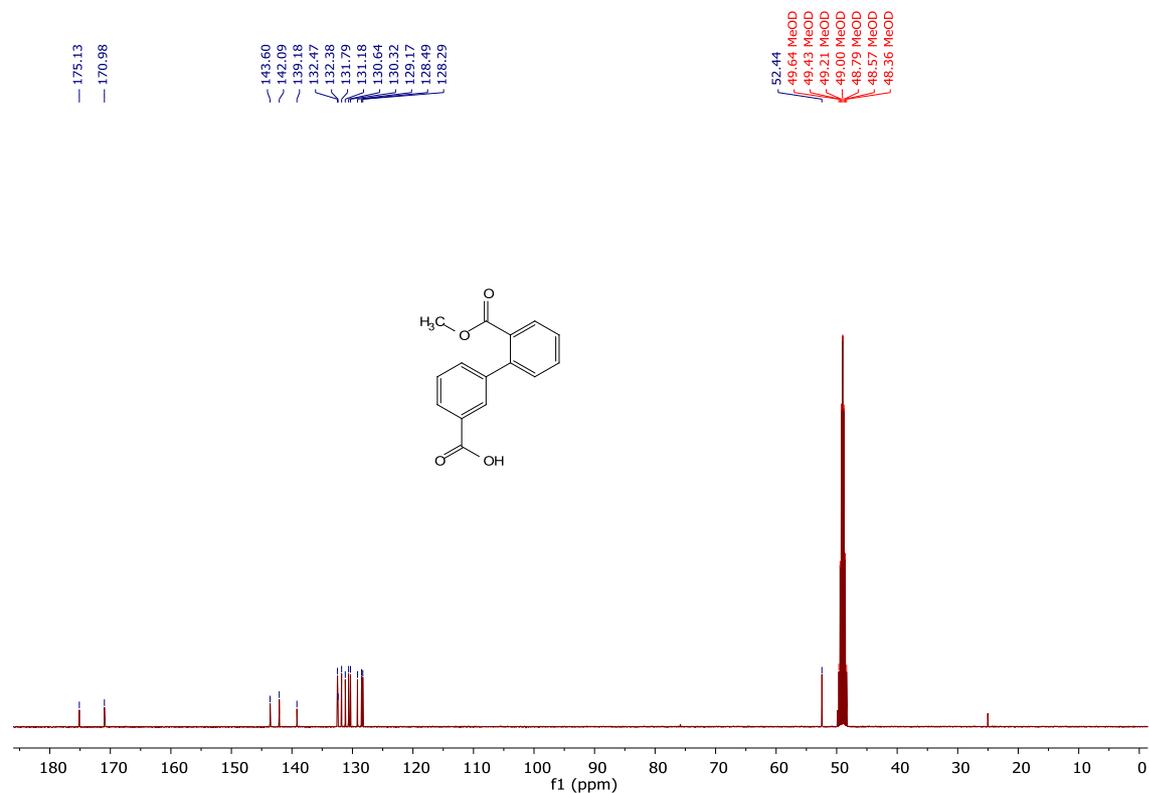
2.15 3'-(methoxycarbonyl)biphenyl-3-carboxylic acid, **9b**:

2.15.1 ^{1}H NMR of **9b**

ABSA-3-05-9
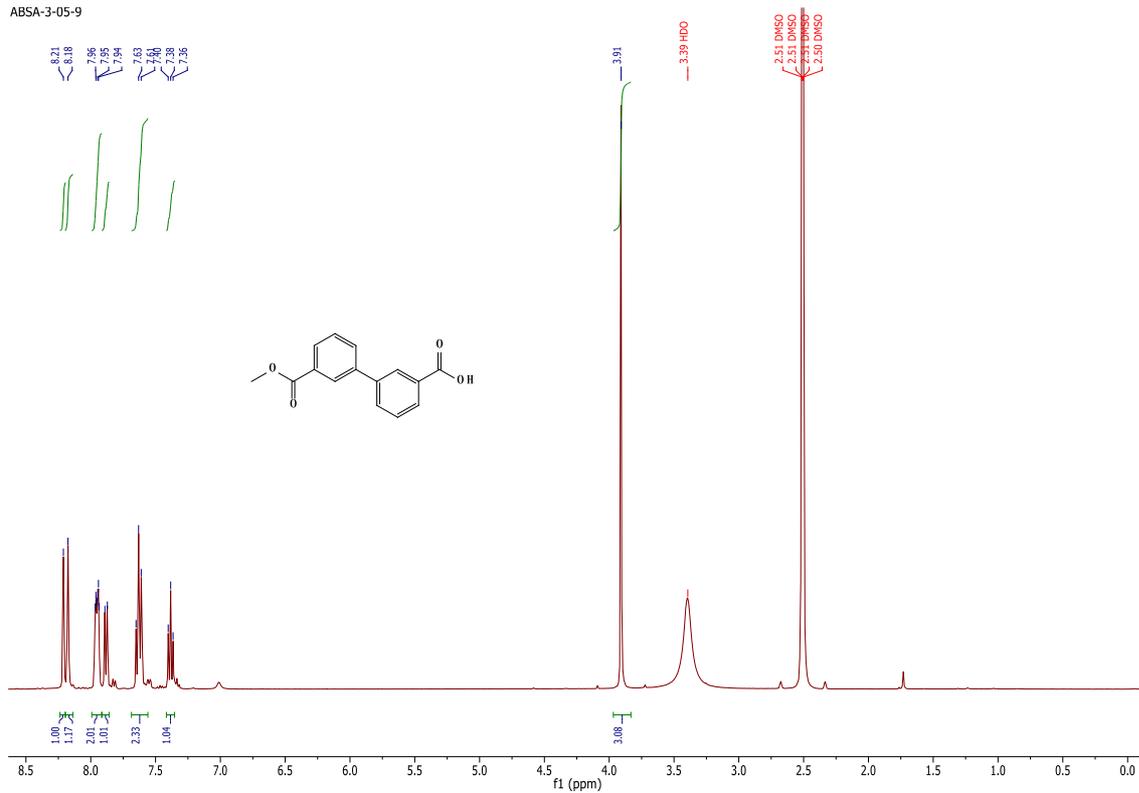
2.15.2 ^{13}C NMR of **9b**

ABSA-3-05-9
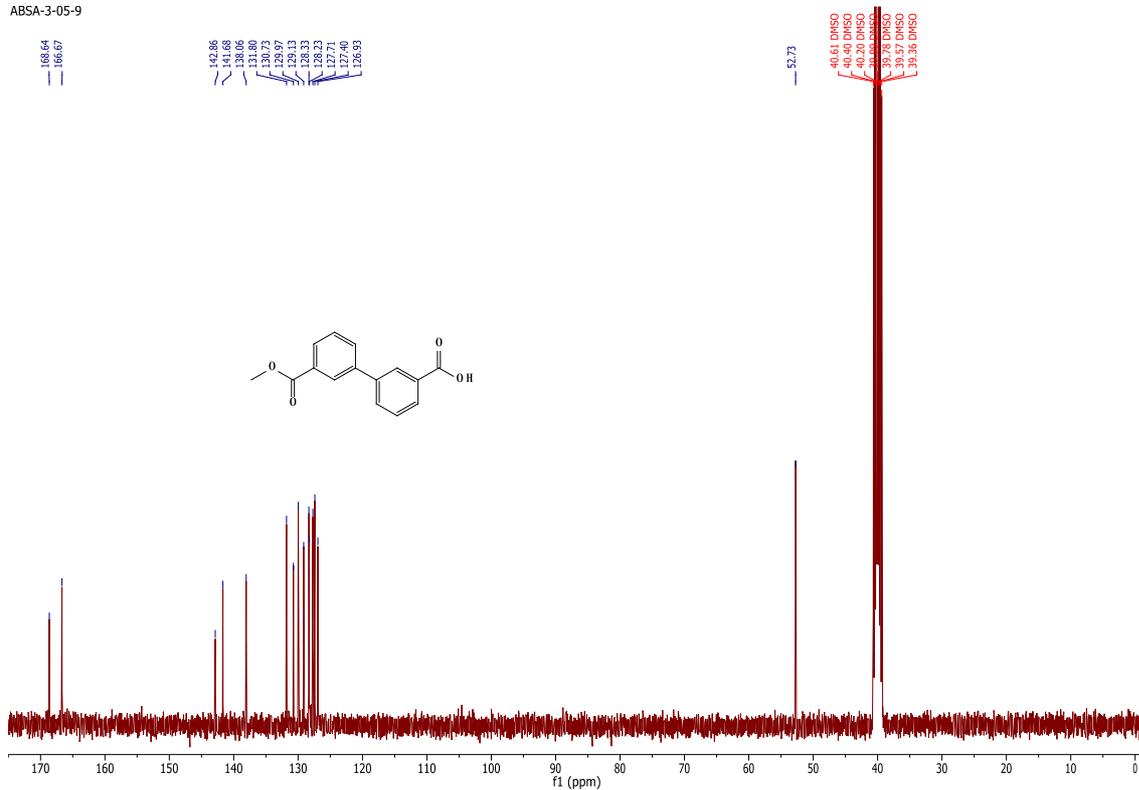
2.16 4'-acetylbiphenyl-3-carboxylic acid 10:

2.16.1 1H NMR of 10

ABSA-3-21
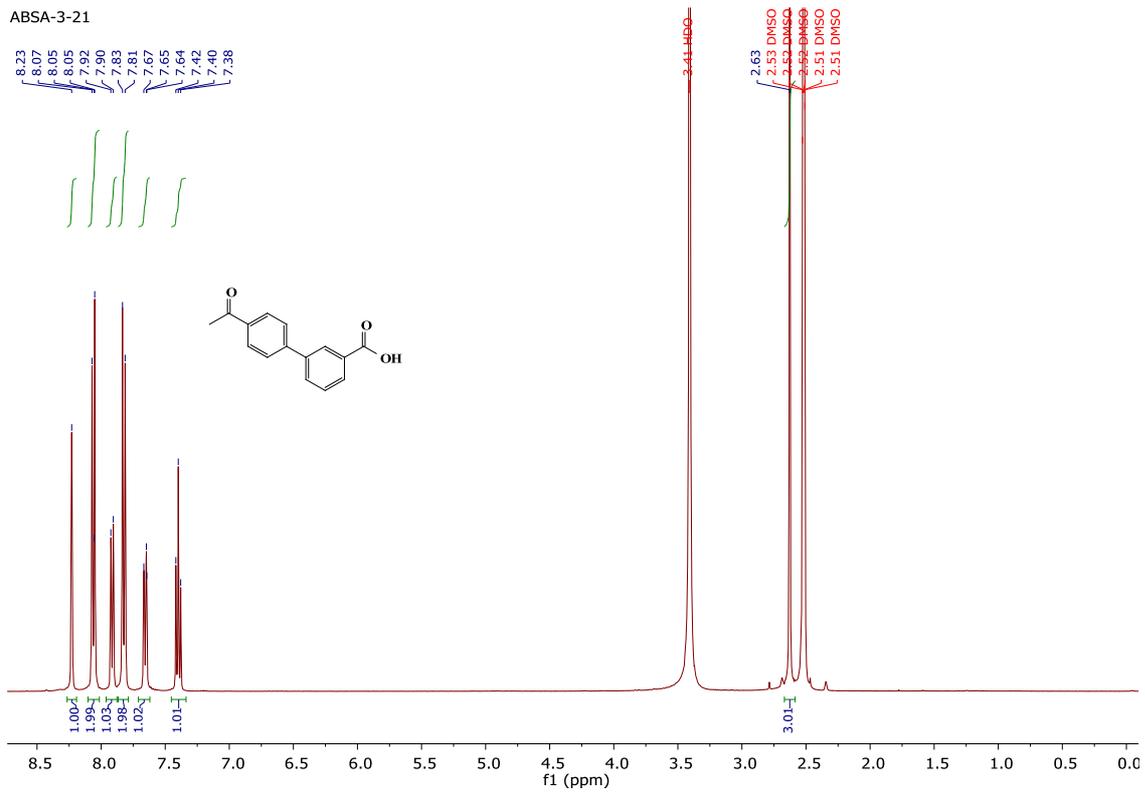
2.16.2 ^{13}C NMR of 10

ABSA-3-21
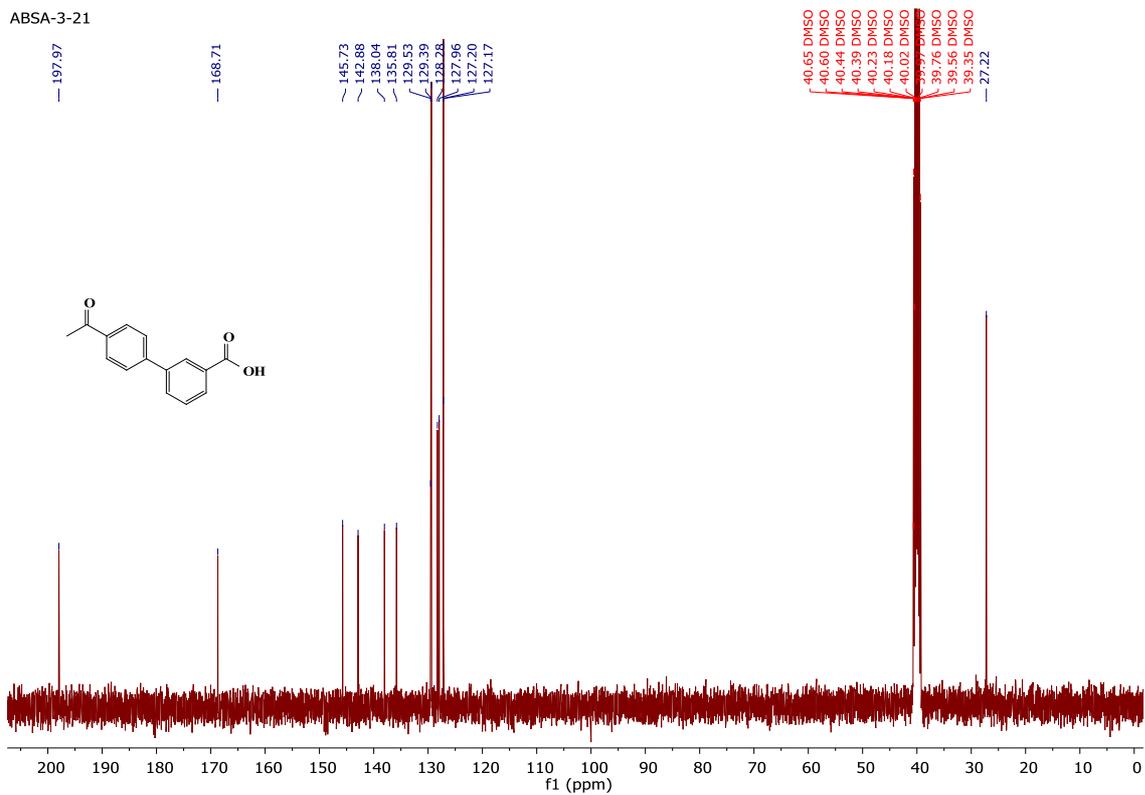
2.17 3'-carbamoylbiphenyl-3-carboxylic acid, **11a**:

2.17.1 ^{1}H NMR of **11a**

ABSA-3-23
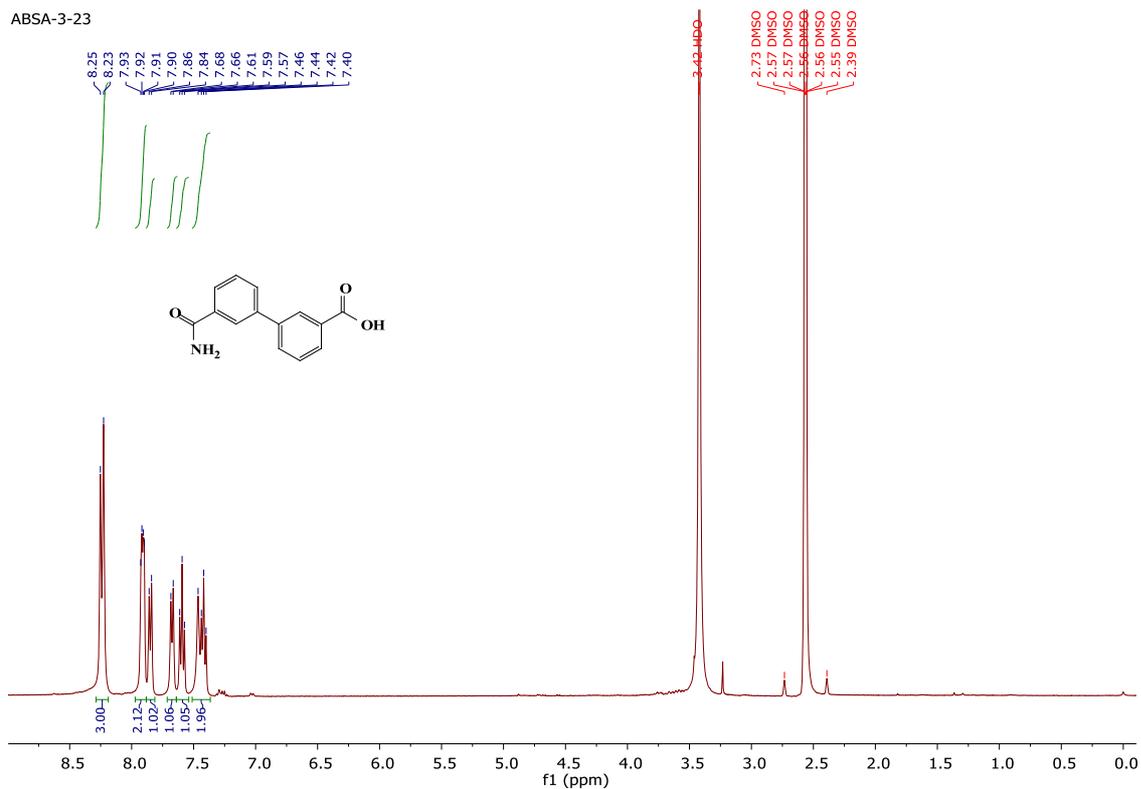
2.17.2 ^{13}C NMR of **11a**

ABSA-3-23

37
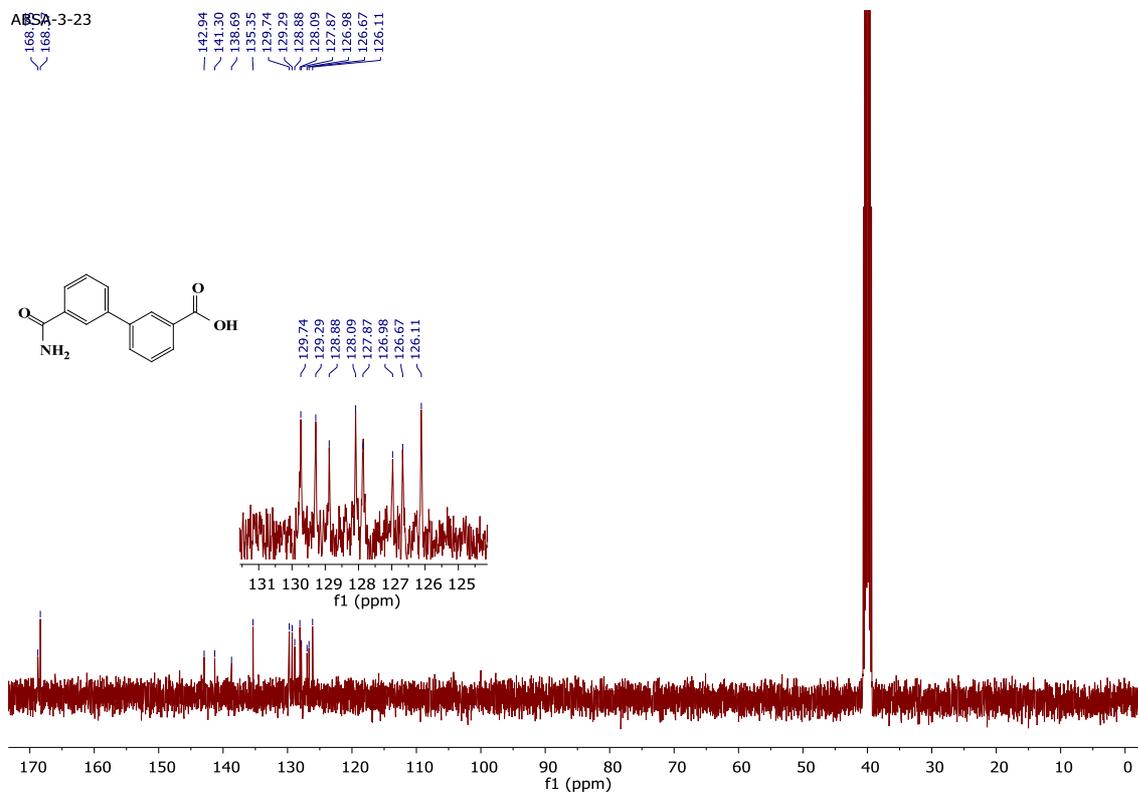
2.18 4'-carbamoylbiphenyl-3-carboxylic acid, **11b**:

2.18.1 ^{1}H NMR of **11b**
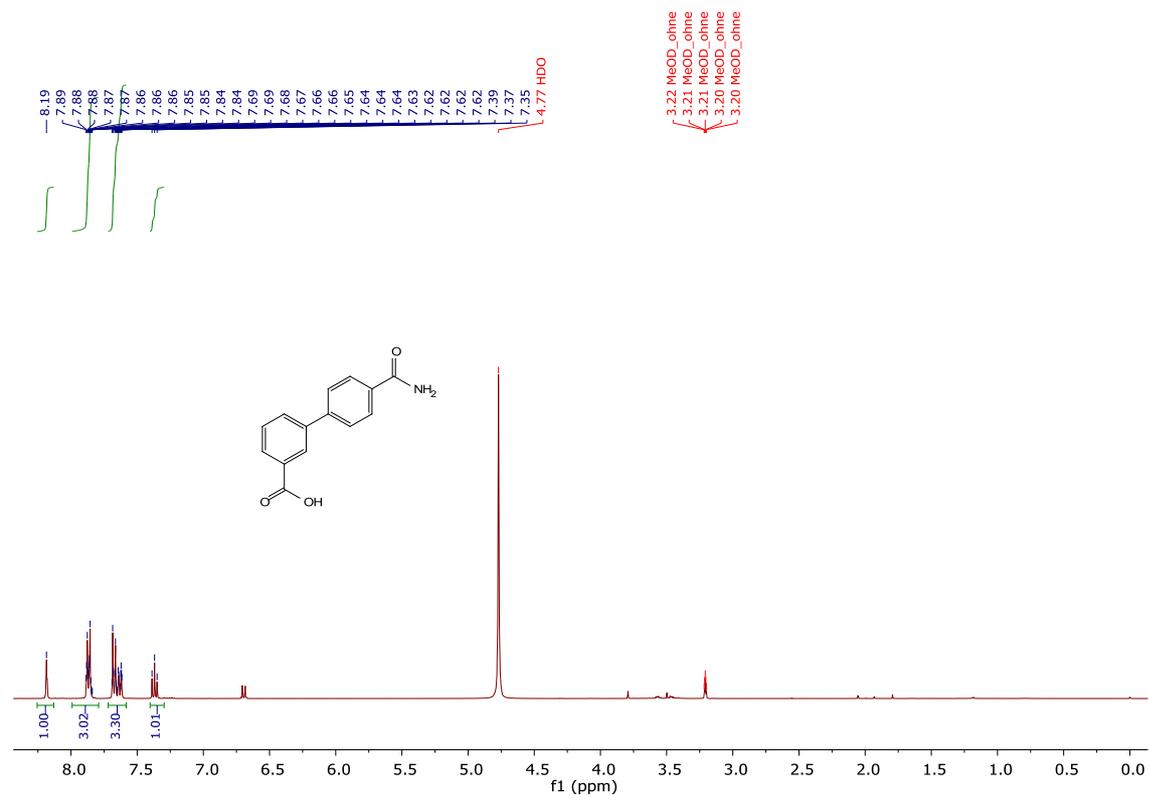
2.18.2 ^{13}C NMR of **11b**
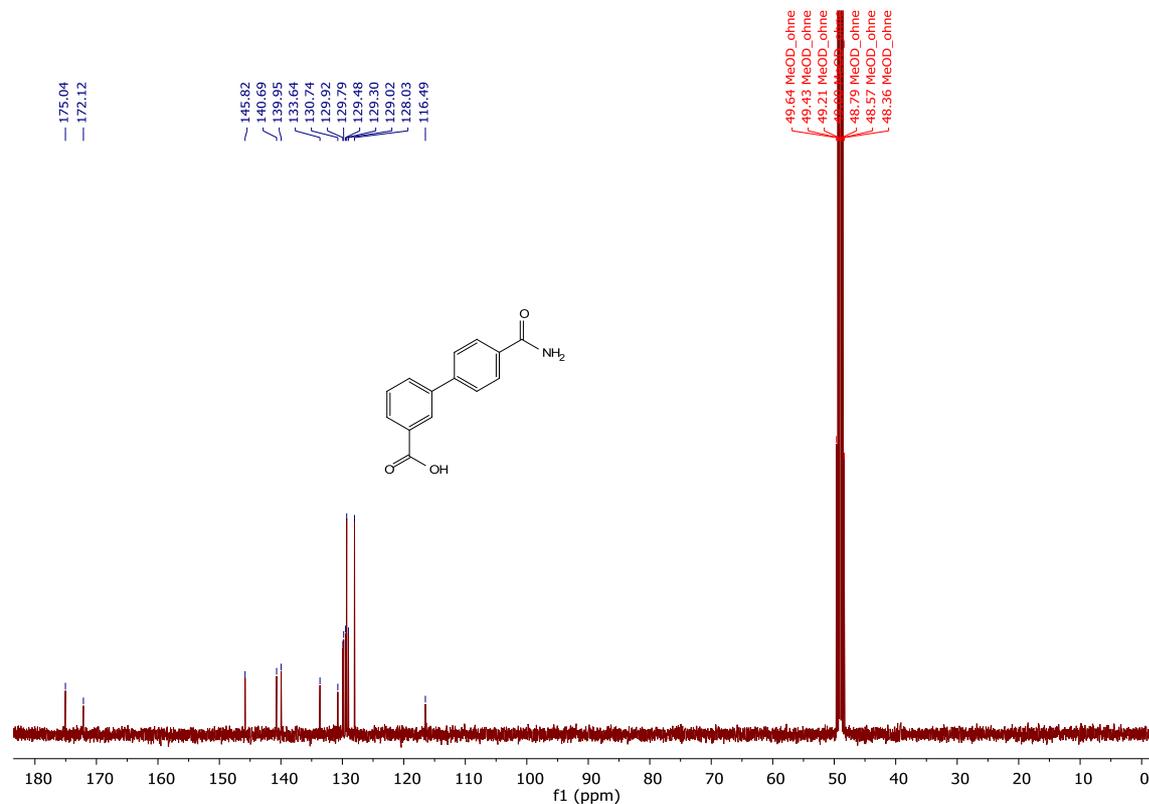
2.19 3'-(methylsulfonyl)biphenyl-3-carboxylic acid, **12a**:

2.19.1 ^{1}H NMR of **12a**

ABSA-3-04
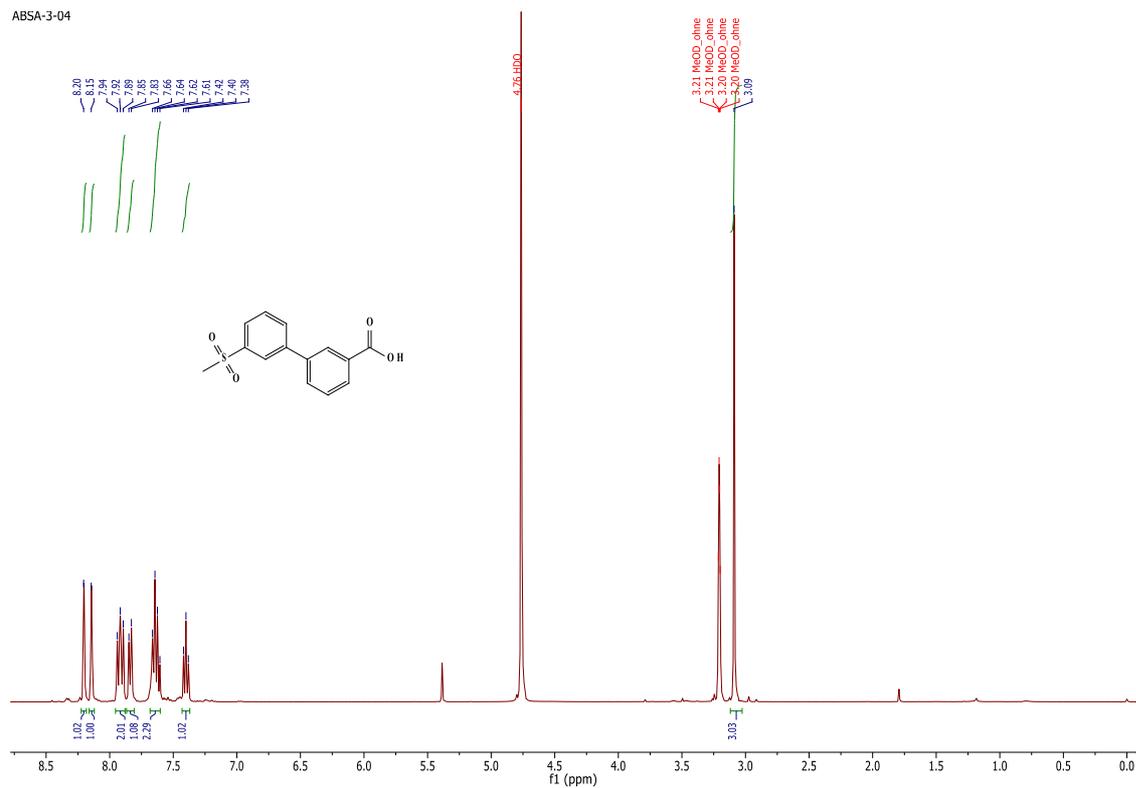
2.19.2 ^{13}C NMR of **12a**

ABSA-3-04
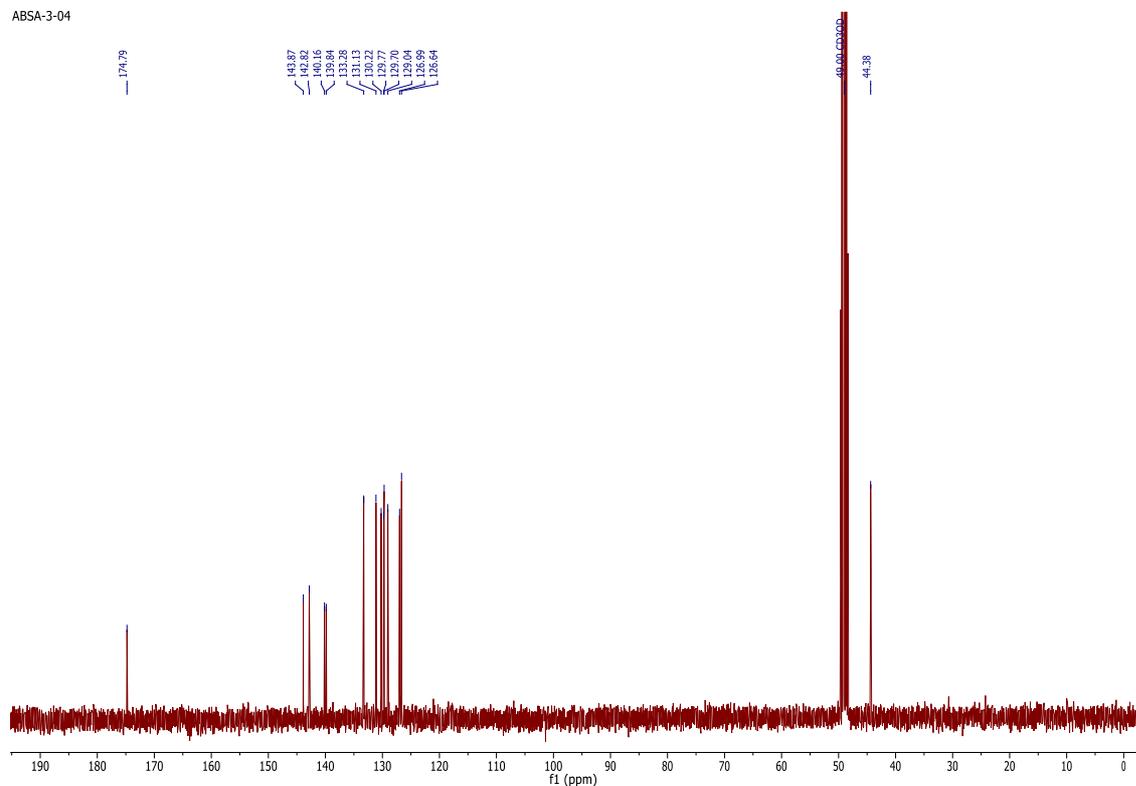
2.20 4'-(methylsulfonyl)biphenyl-3-carboxylic acid, 12b:

2.20.1 ^{1}H NMR of 12b

ABSA-3-16

8.23
8.01
8.00
7.99
7.94
7.94
7.92
7.92
7.67
7.65
7.43
7.41
7.39

3.41 HDO
3.26

2.51 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO

1.01
5.19
1.00
1.00
3.19

f1 (ppm)
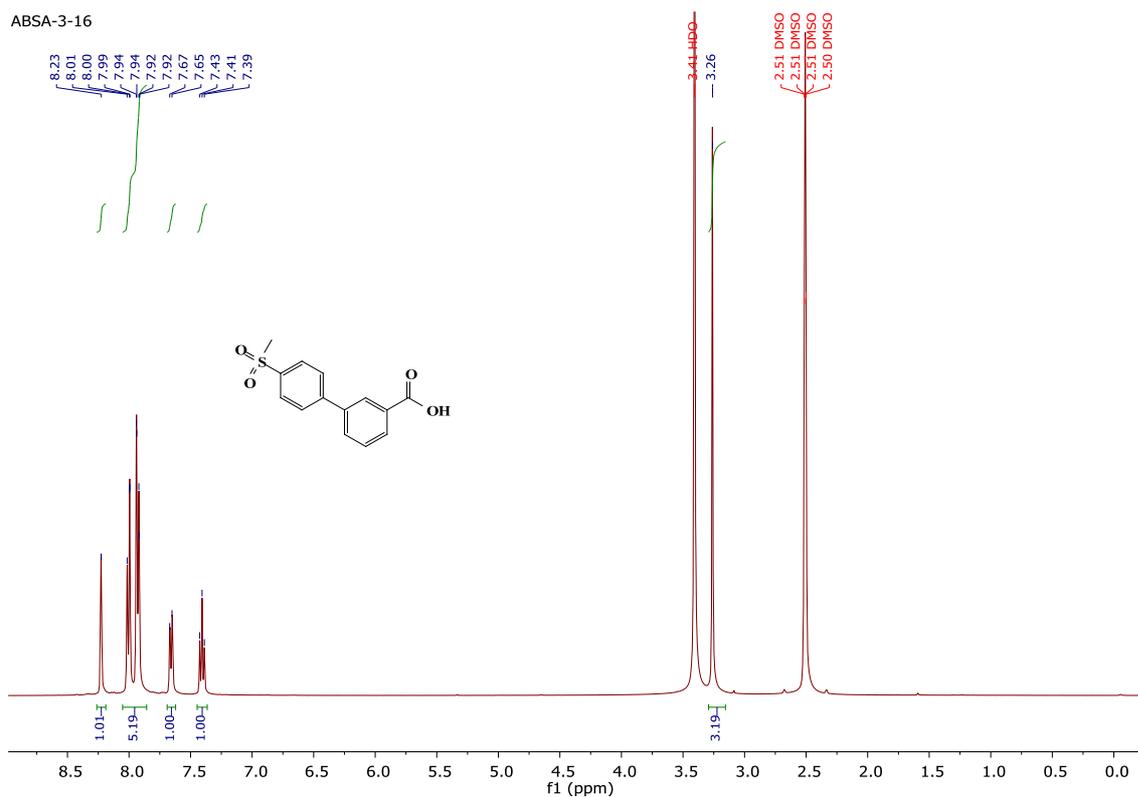
2.20.2 ^{13}C NMR of 12b

ABSA-3-16

168.66

146.24
142.97
139.66
137.54

129.80
128.39
128.10
127.86
127.39

44.10
40.60 DMSO
40.39 DMSO
40.23 DMSO
40.18 DMSO
39.77 DMSO
39.56 DMSO
39.35 DMSO

f1 (ppm)
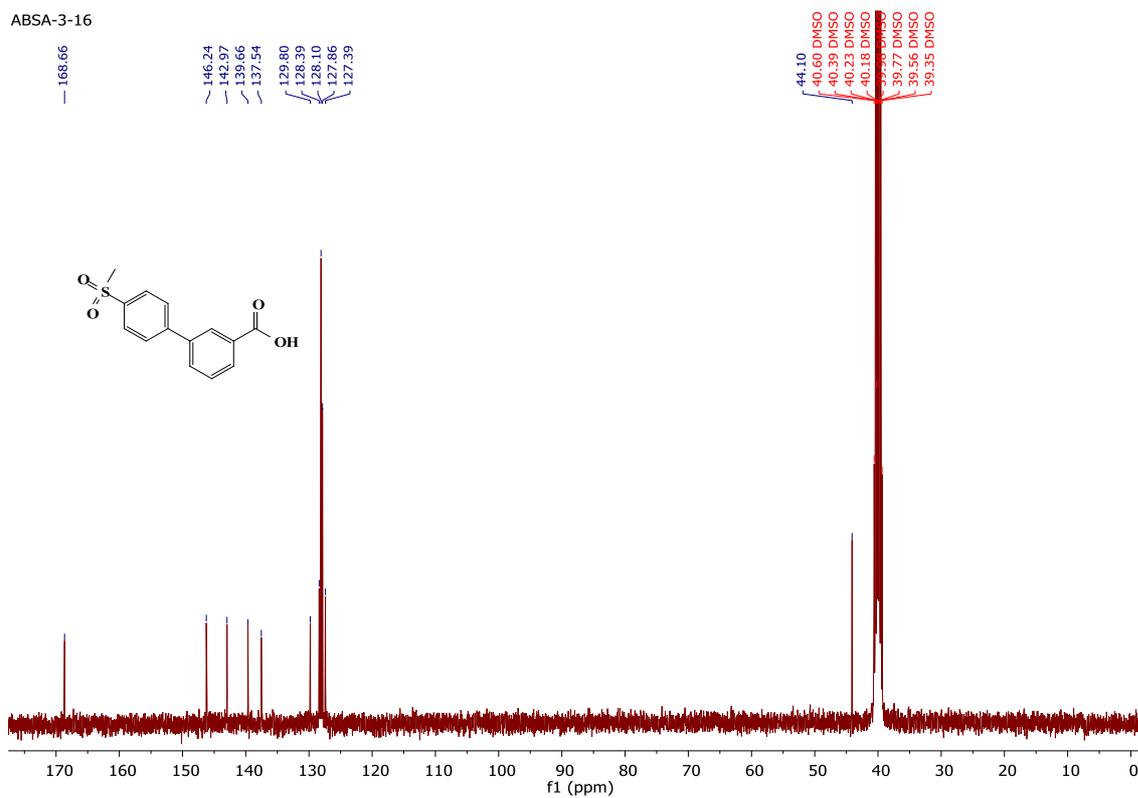
2.21 4'-aminobiphenyl-3-carboxylic acid, 13:

2.21.1 ¹H NMR of 13
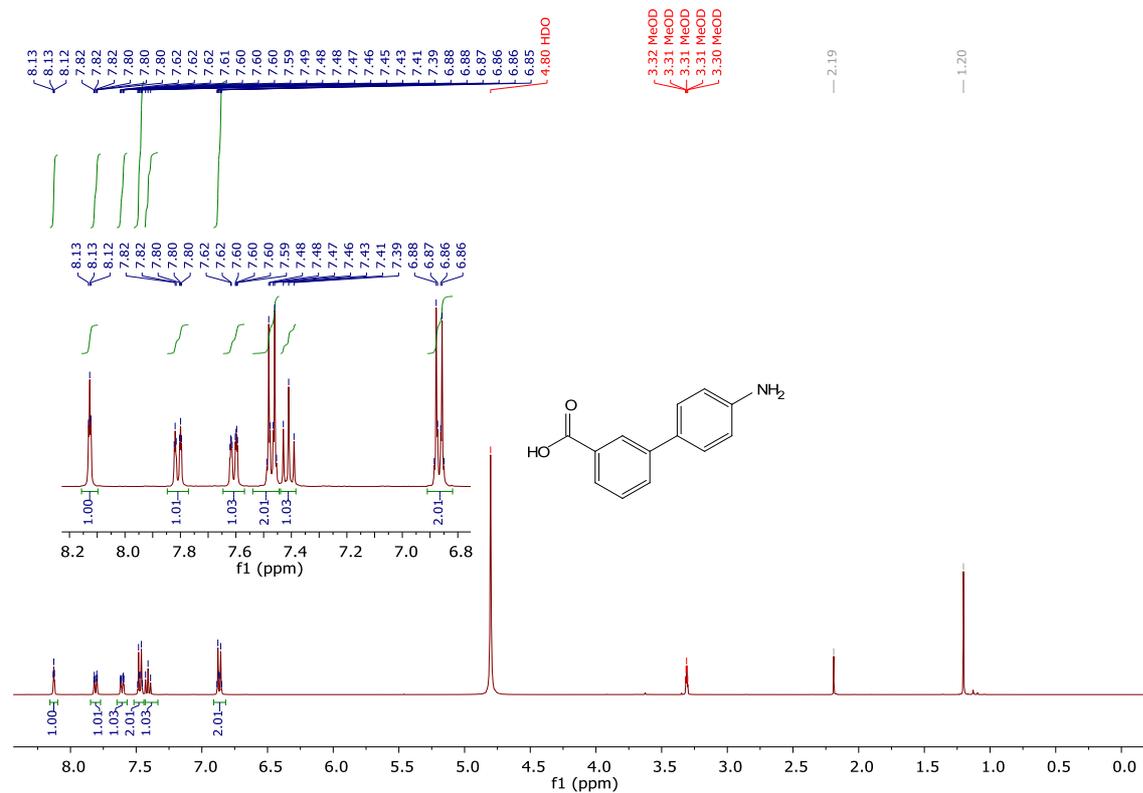
2.21.2 ¹³C NMR of 13

2.22 4'-dimethylaminobiphenyl-3-carboxylic acid, **14**:

2.22.1 ¹H NMR of **14**
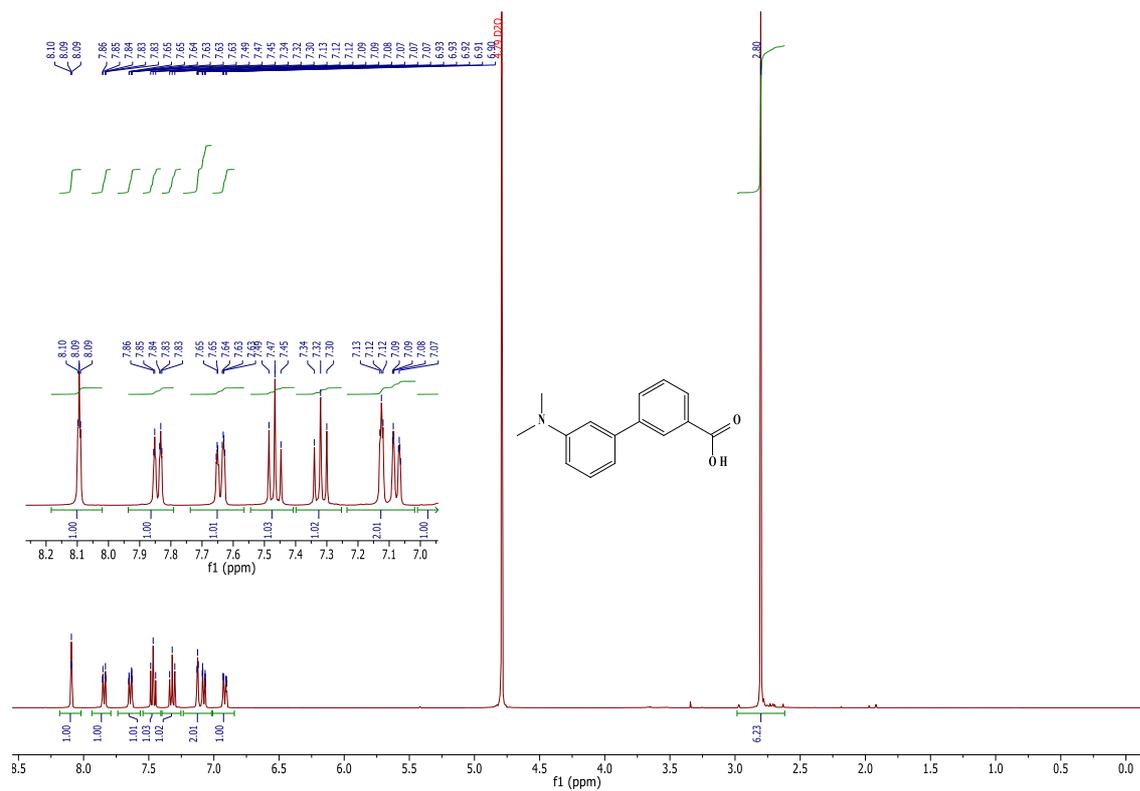
2.22.2 13C NMR of 14
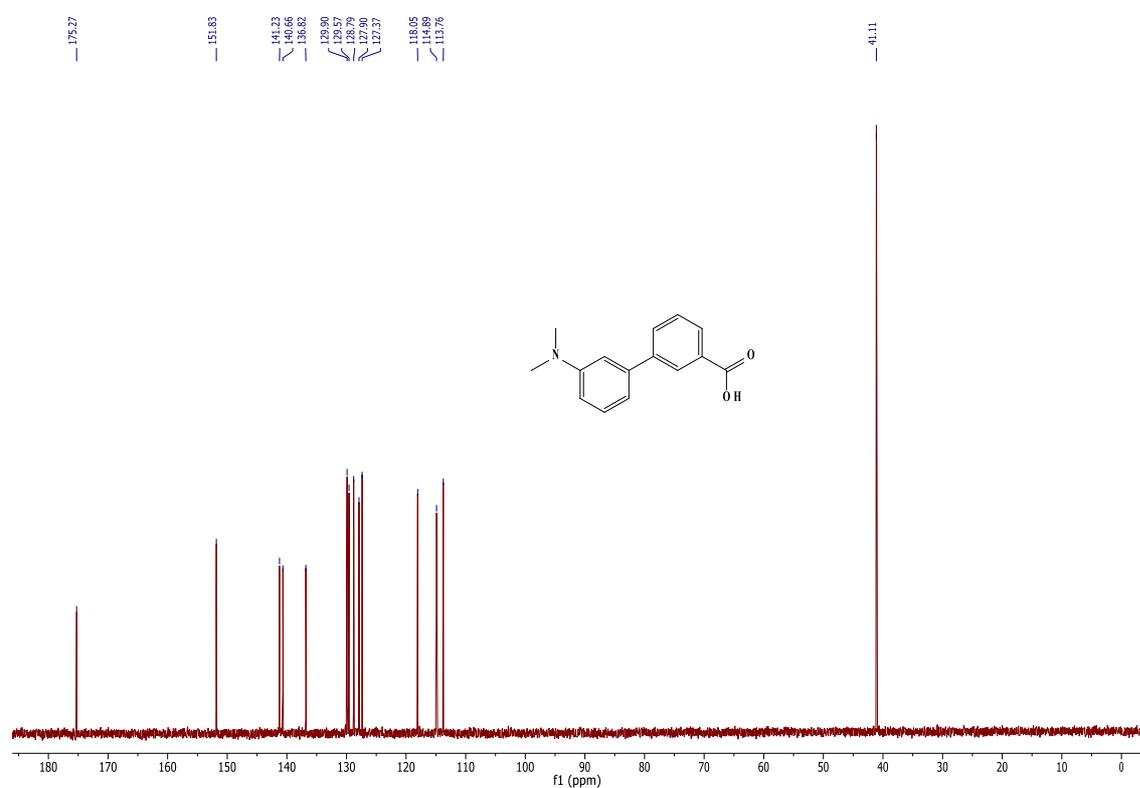
2.23 3'-aminomethylbiphenyl-3-carboxylic acid, 15a:

2.23.1 ^{1}H NMR of 15a
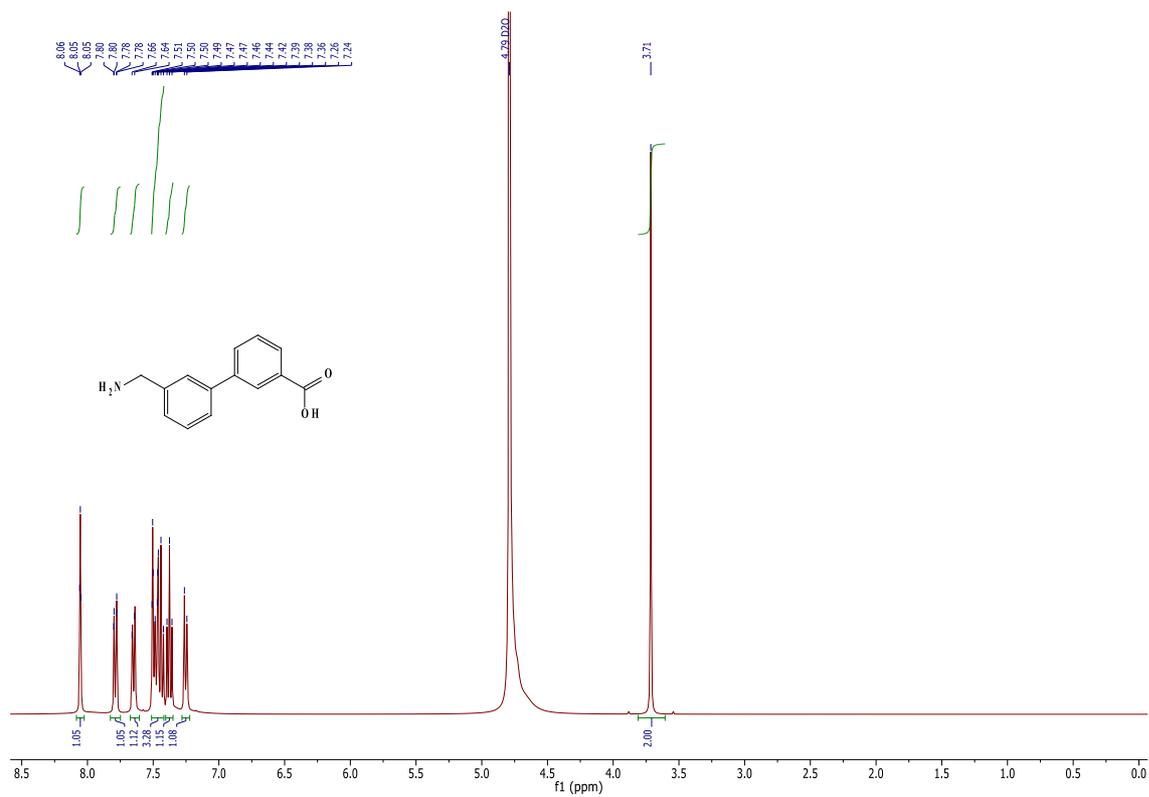
2.23.2 ^{13}C NMR of 15a
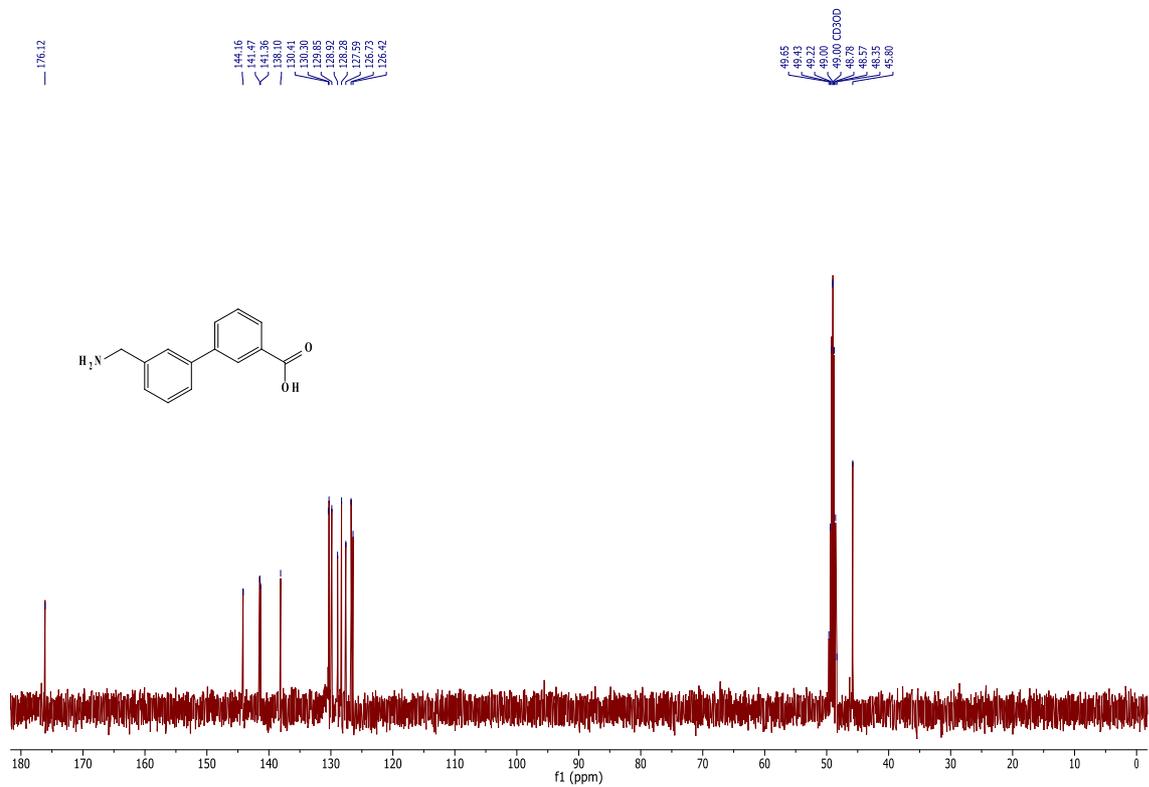
2.24 4'-(aminomethyl)biphenyl-3-carboxylic acid, **15b**:

2.24.1 ^{1}HNMR of 15b
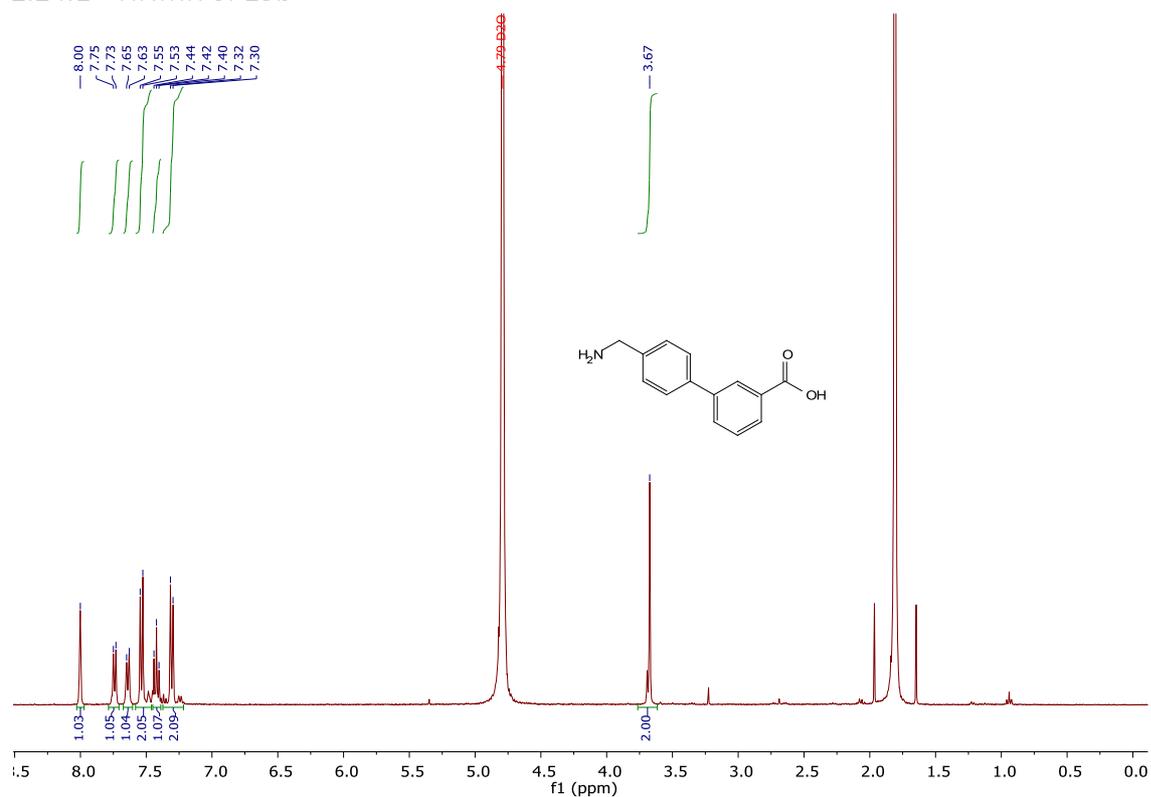
2.24.2 ^{13}CNMR of 15b
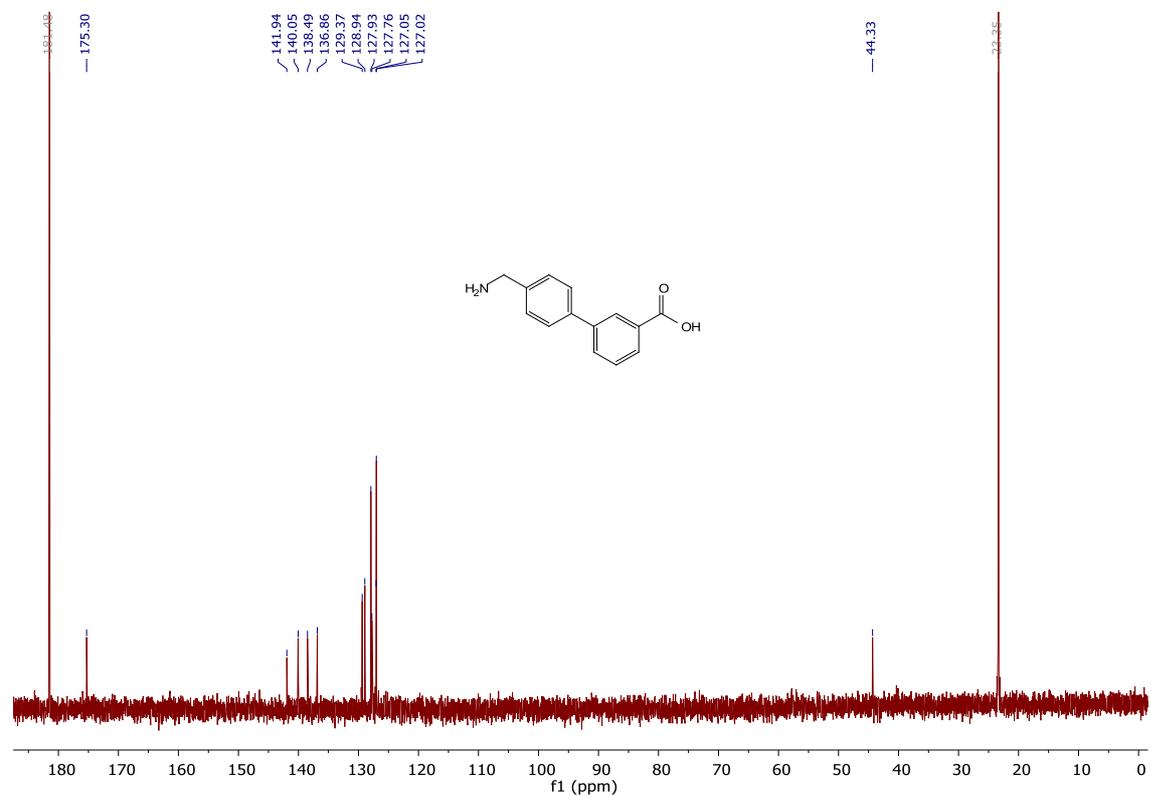
2.25 3'-(2-aminoethyl)biphenyl-3-carboxylic acid, **16a**:

2.25.1 1H NMR of **16a**
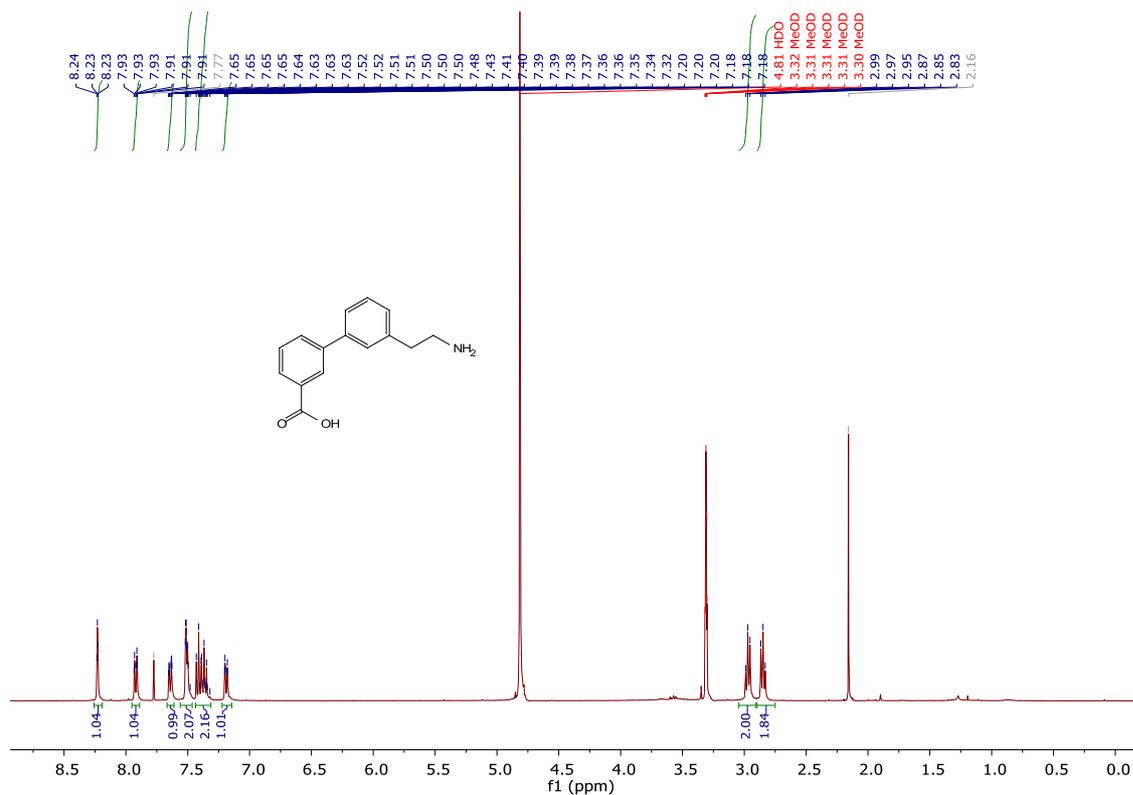
2.25.2 13C NMR of **16a**
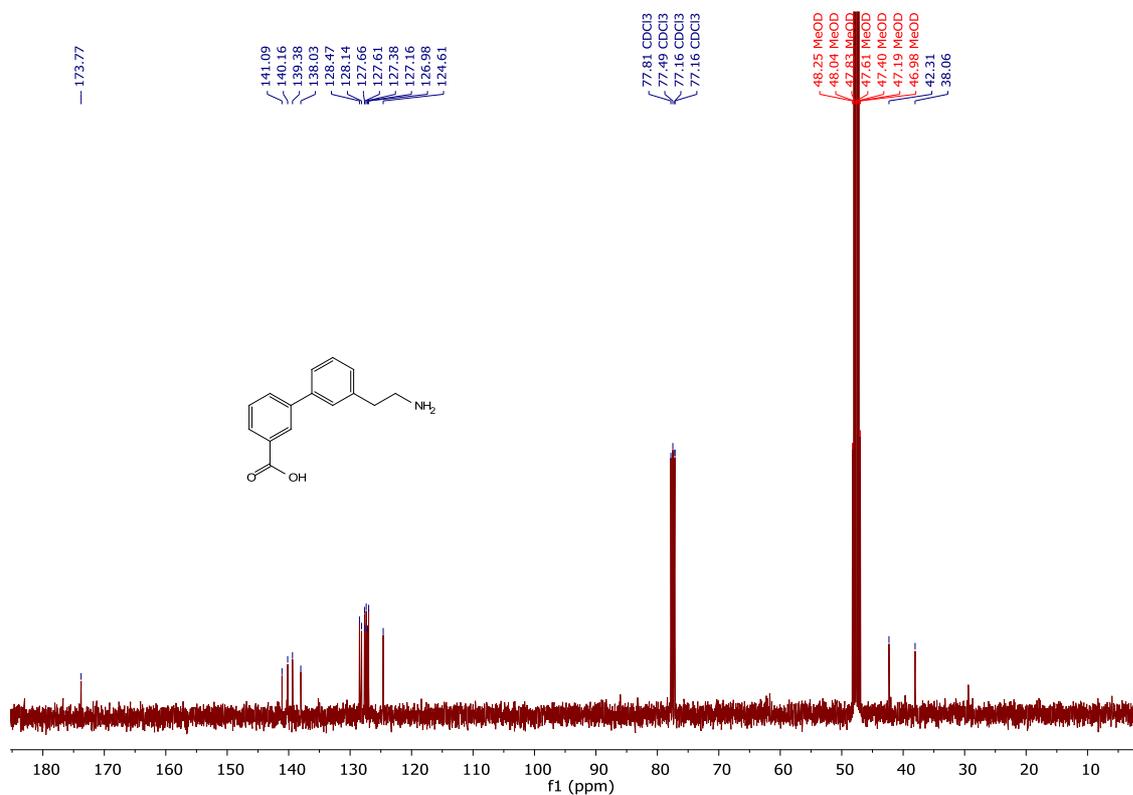
2.26 4'-(2-aminoethyl)biphenyl-3-carboxylic acid, **16b**:

2.26.1 1H NMR of **16b**
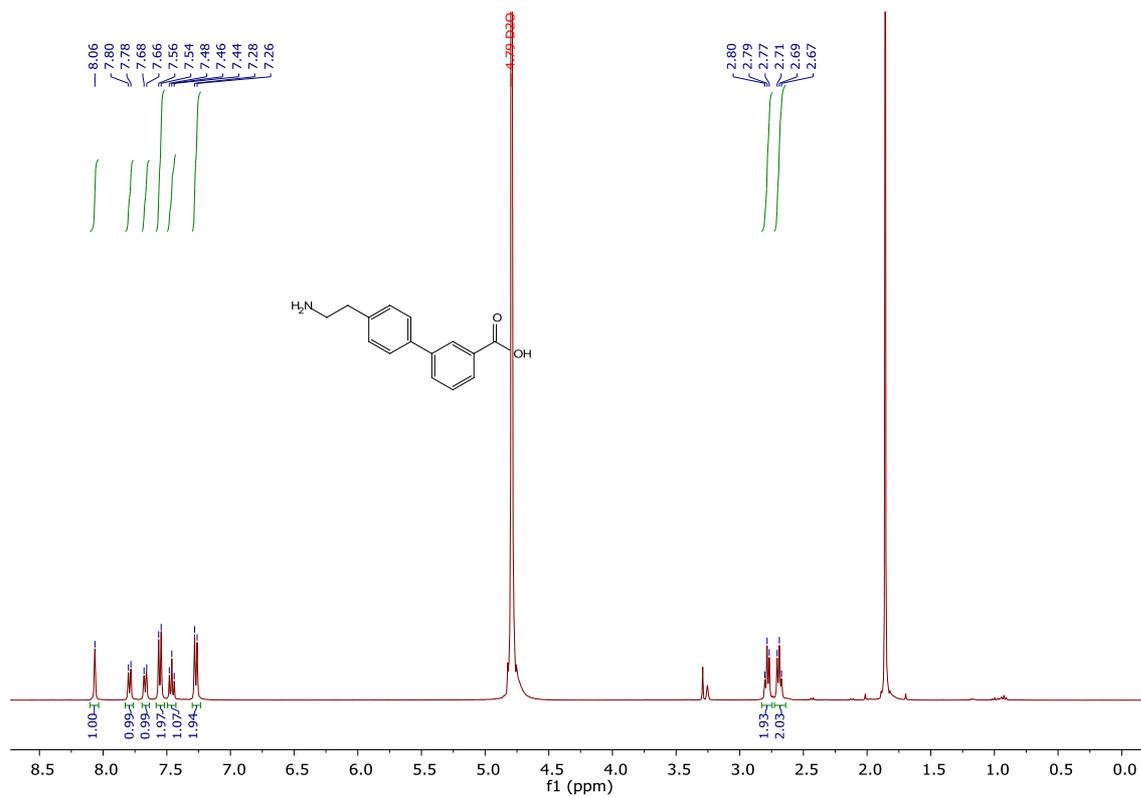
2.26.2 ^{13}C NMR of **16b**
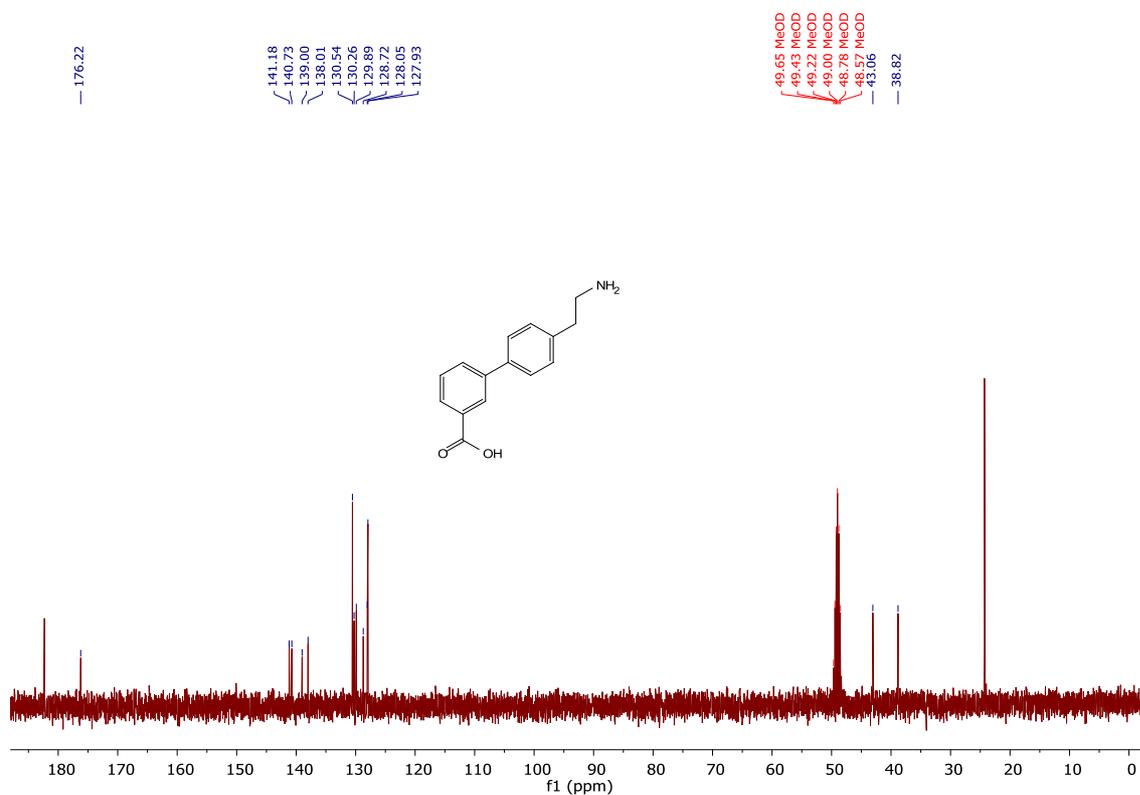
2.27 4'-(methylsulfonamido)biphenyl-3-carboxylic acid, 17:

2.27.1 ¹H NMR of 17
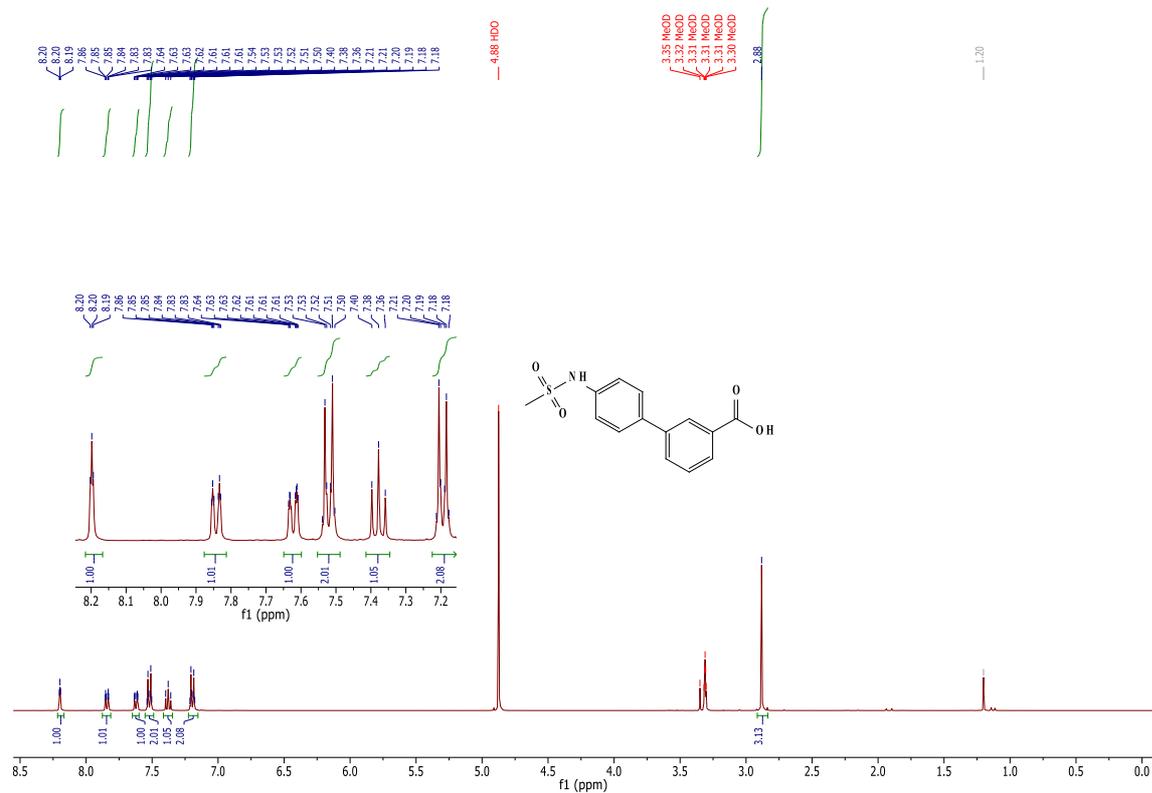
2.27.2 ¹³C NMR of 17
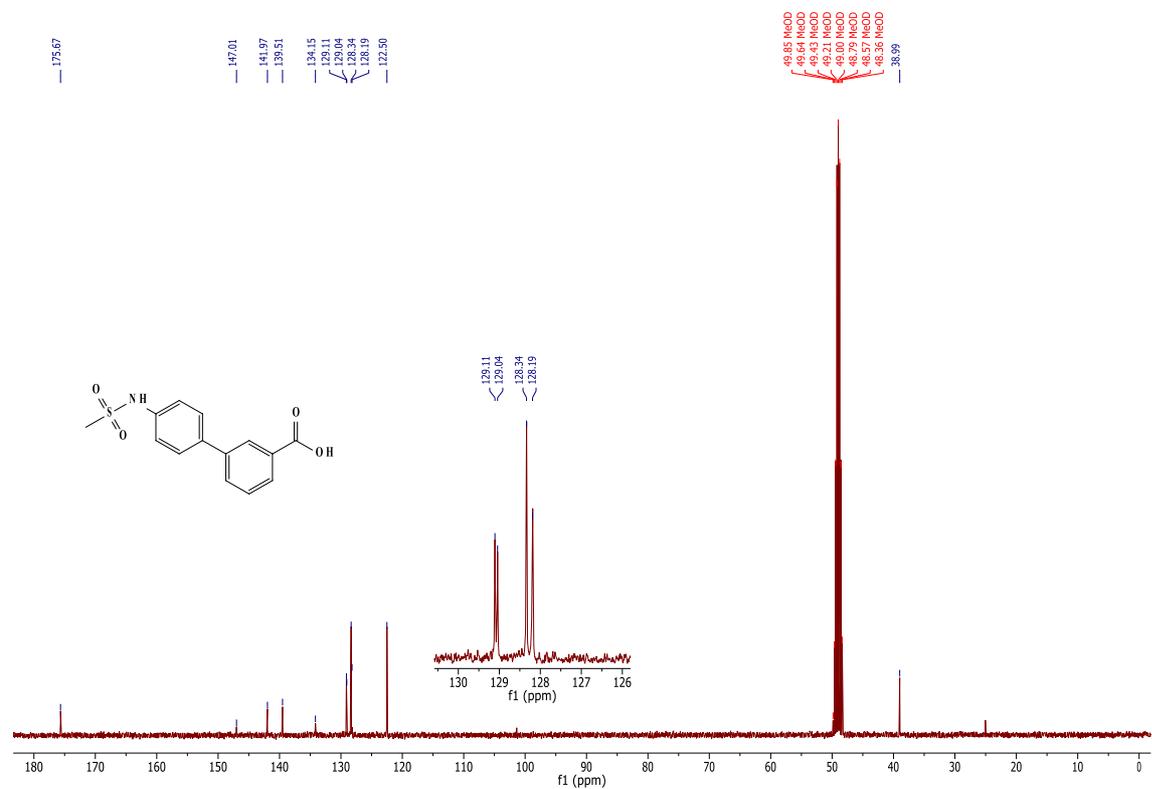
2.28 4'-(phenylsulfonamido)biphenyl-3-carboxylic acid, 18:

2.28.1 ¹H NMR of 18
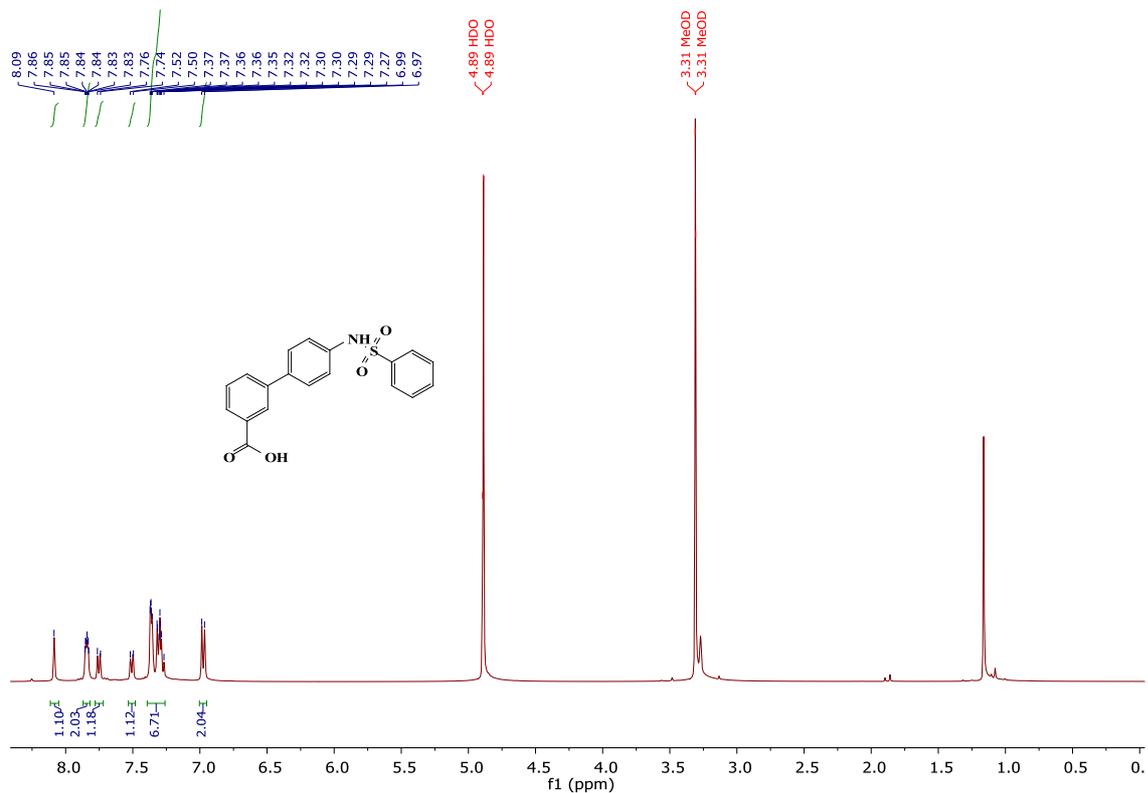
2.28.2 ¹³C NMR of 18
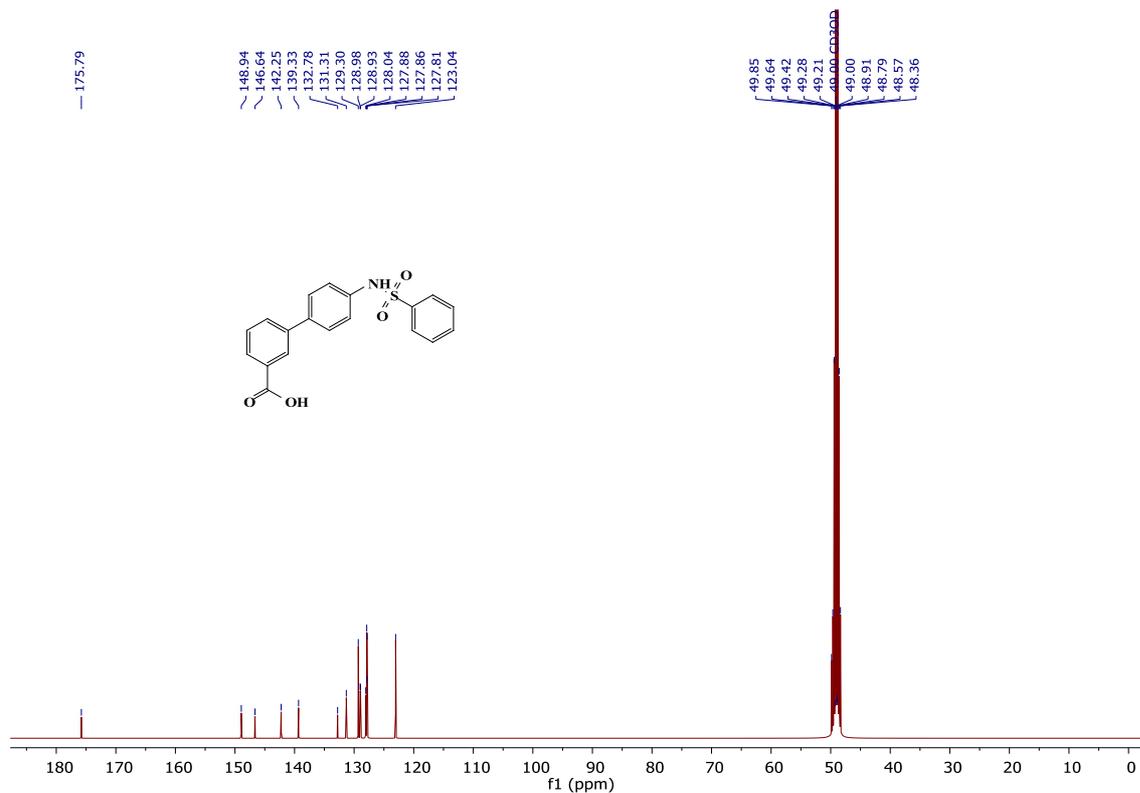
2.29 3'-(methylsulfonamidomethyl)biphenyl-3-carboxylic acid, **19a**:

2.29.1 ^{1}H NMR of **19a**

2.29.2 ^{13}C NMR of **19a**

^{13}C NMR (400, CD$_3$OD)
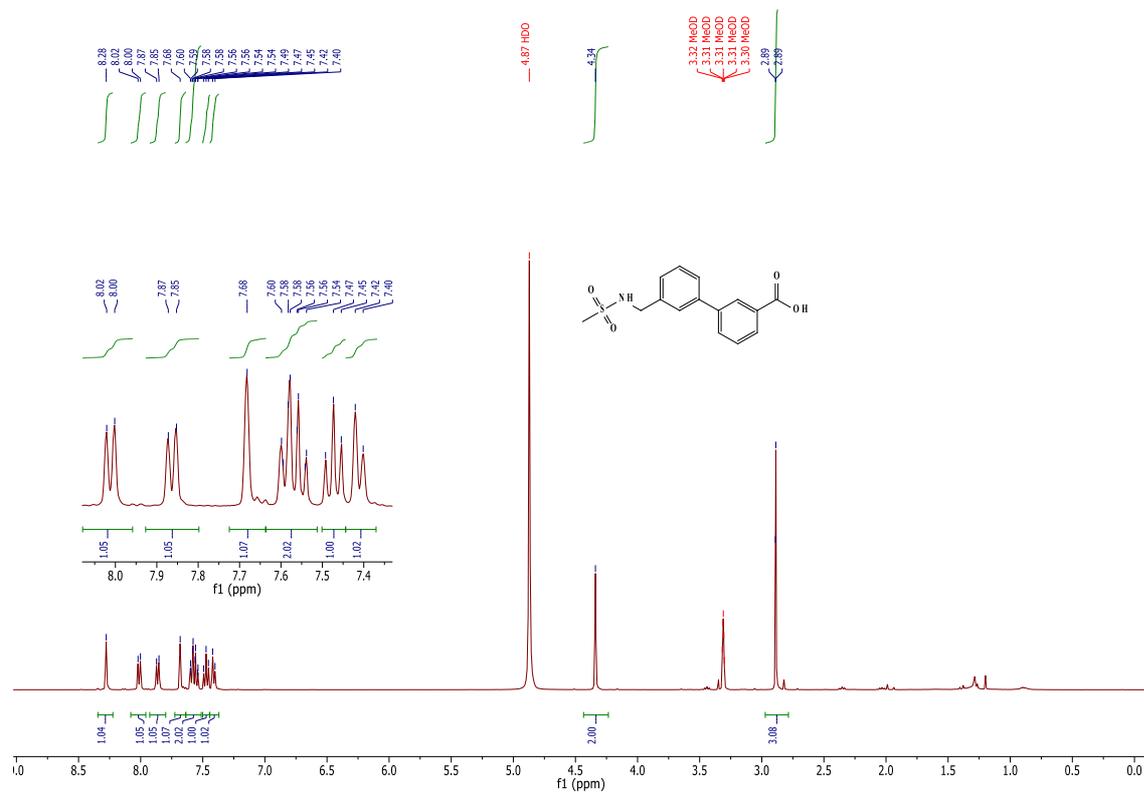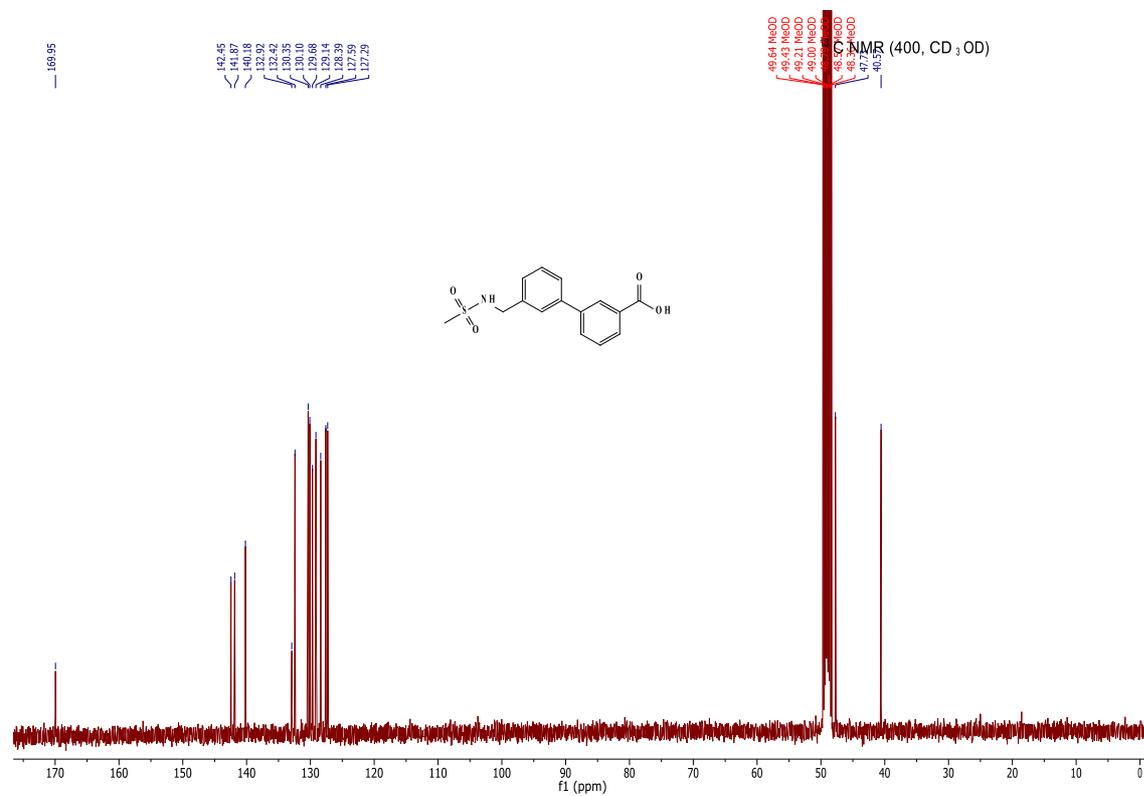
2.30 4'-(methylsulfonamidomethyl)biphenyl-3-carboxylic acid, 19b:

2.30.1 ^{1}H NMR of 19b
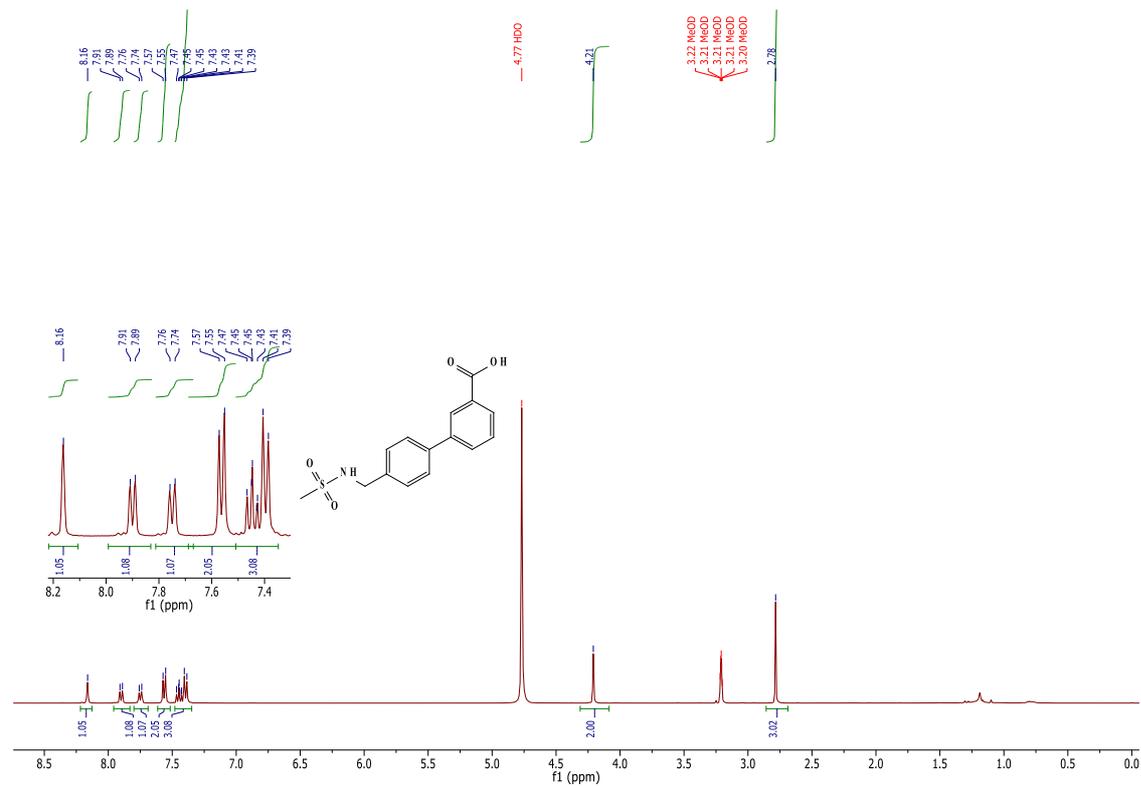
2.30.2 ^{13}C NMR of 19b
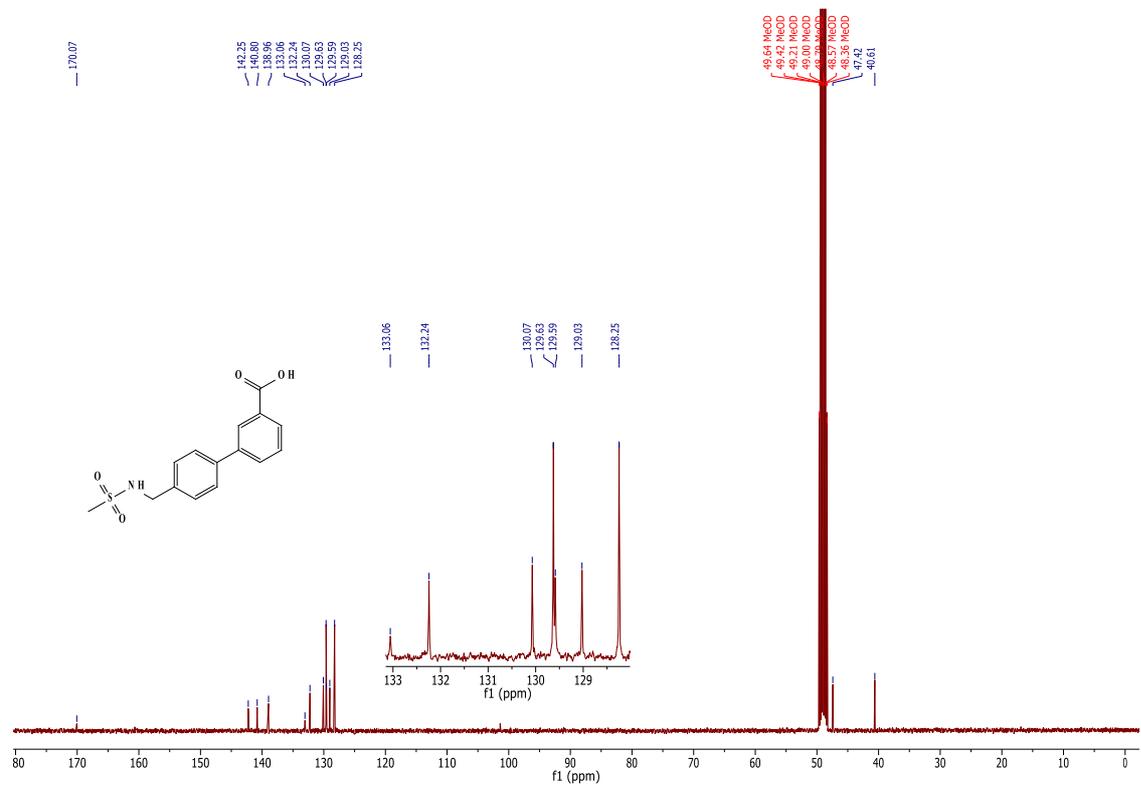
2.31 3'-(2-methylsulfonamidoethyl)biphenyl-3-carboxylic acid, **20**:

2.31.1 ^{1}H NMR of **20**
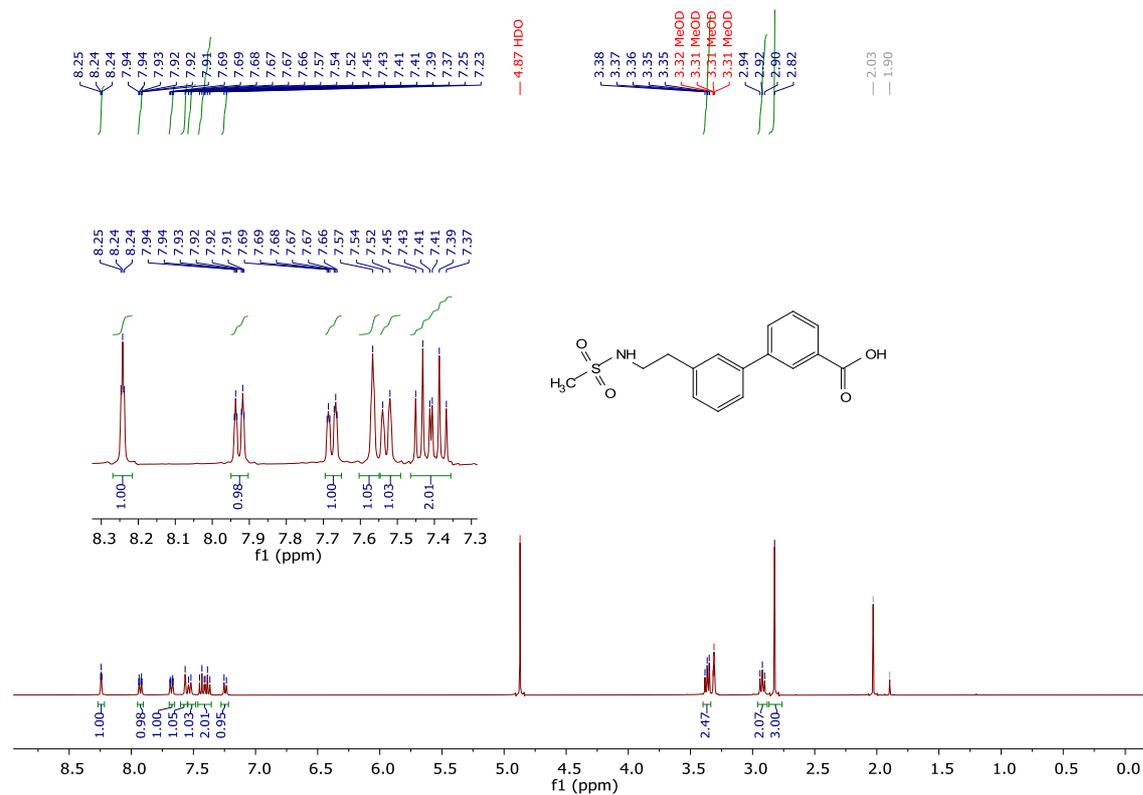
2.31.2 ^{13}C NMR of **20**
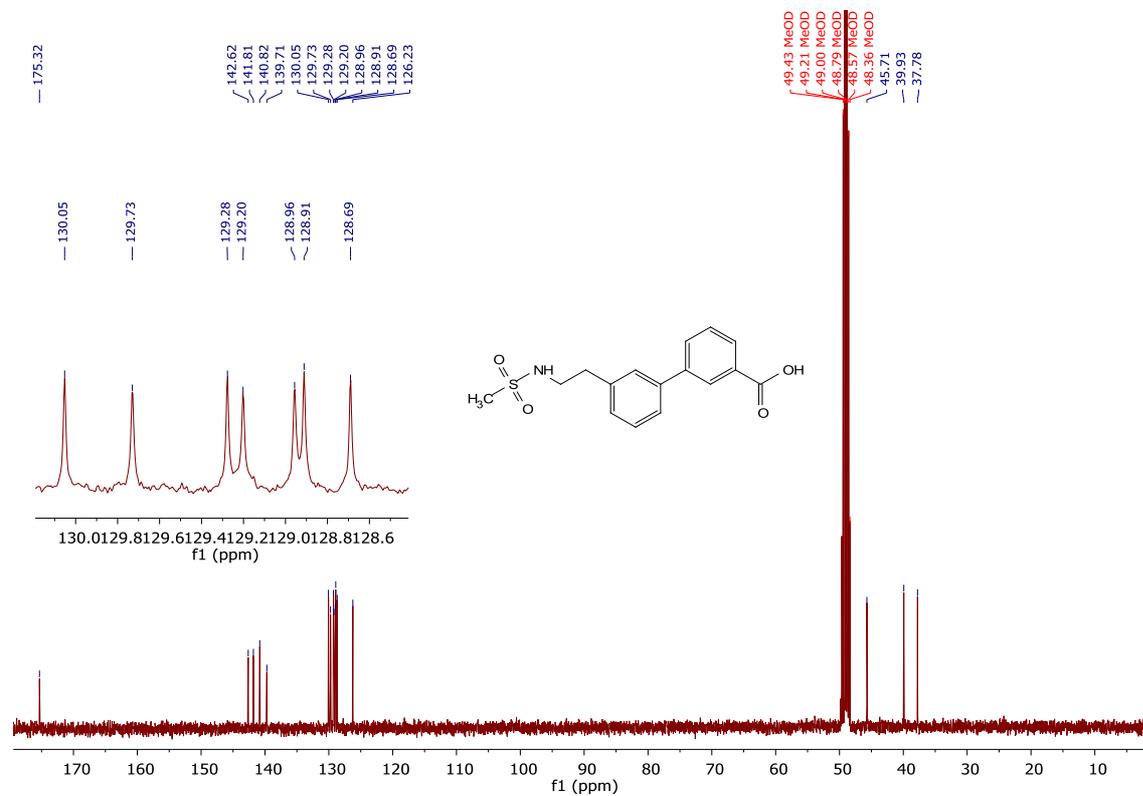
2.32 3'-acetamidobiphenyl-3-carboxylic acid, 21a:

2.32.1 ^{1}H NMR of 21a

ABSA-3-06

2.32.2 ^{13}C NMR of 21a

ABSA-3-06
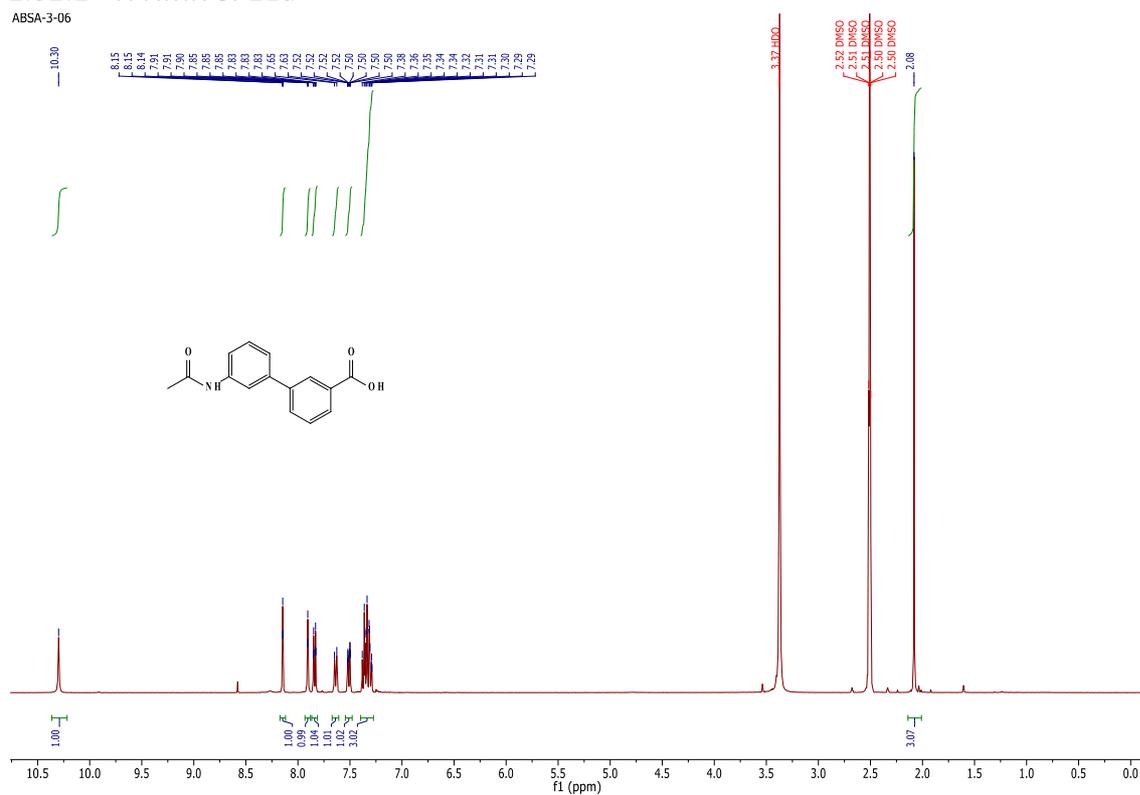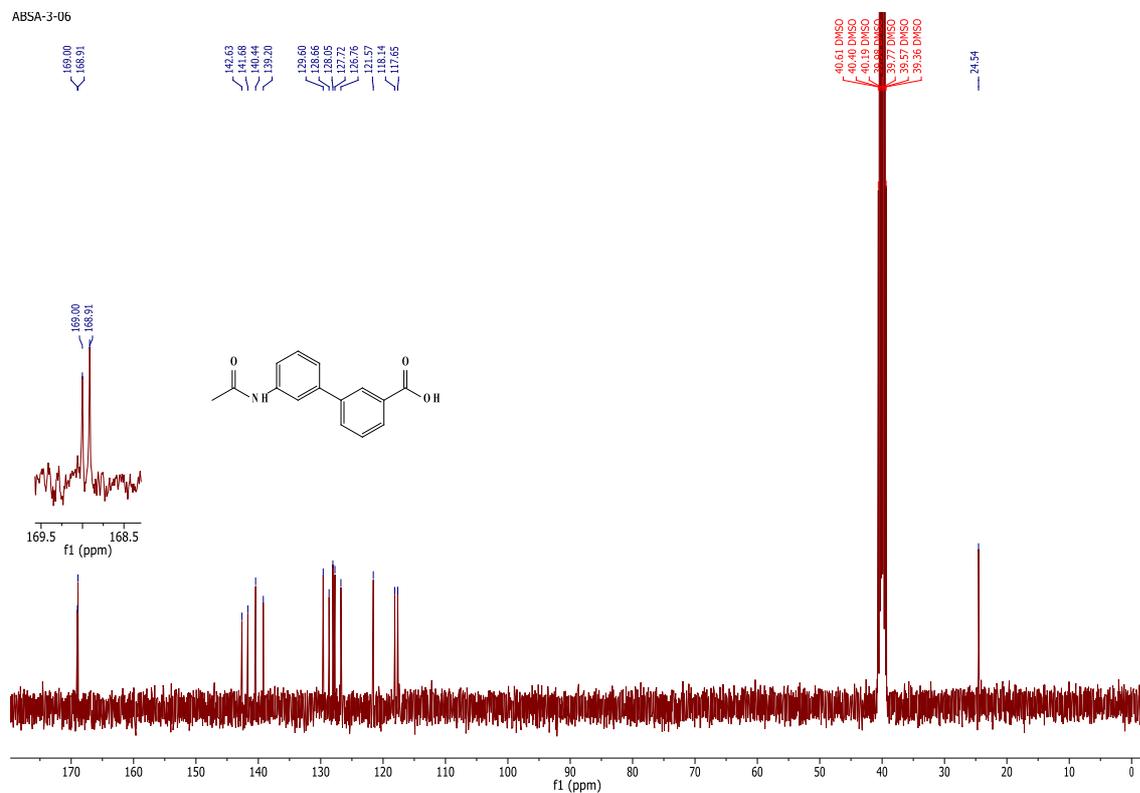
2.33 4'acetamidobiphenyl-3-carboxylic acid, **21b**:

2.33.1 ^{1}H NMR of **21b**

ABSA-3-22
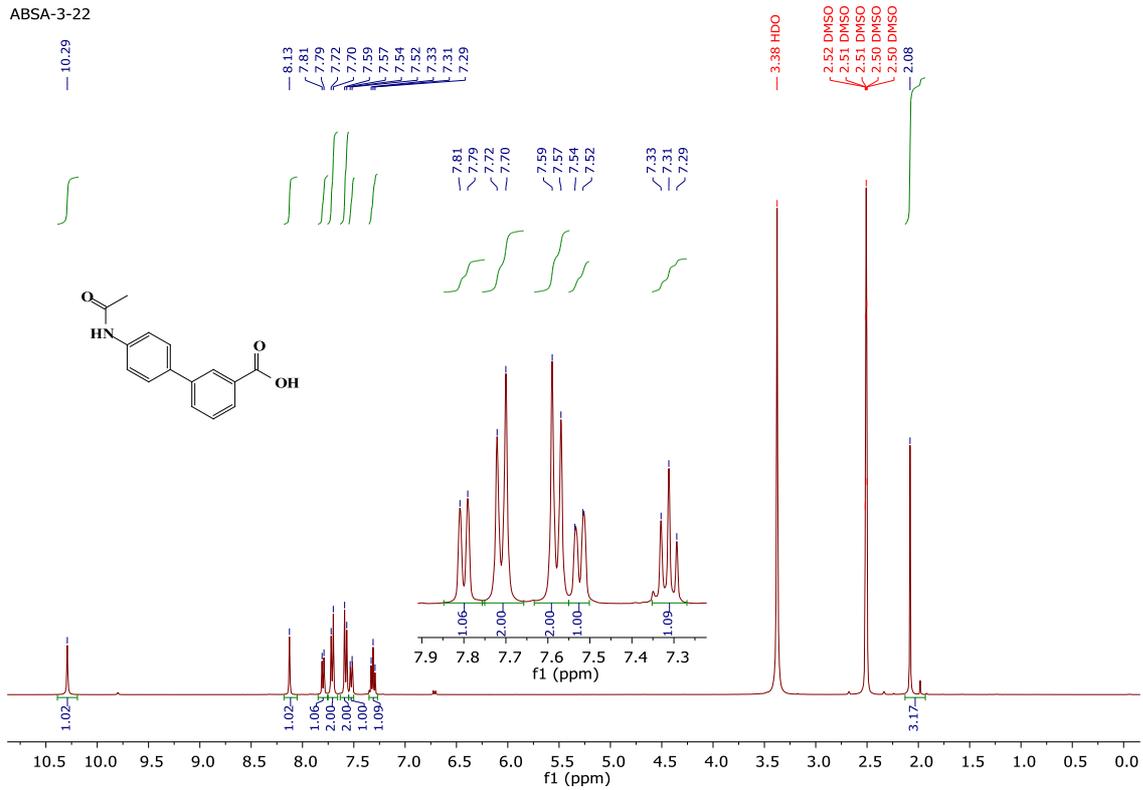
2.33.2 ^{13}C NMR of **21b**

ABSA-3-22
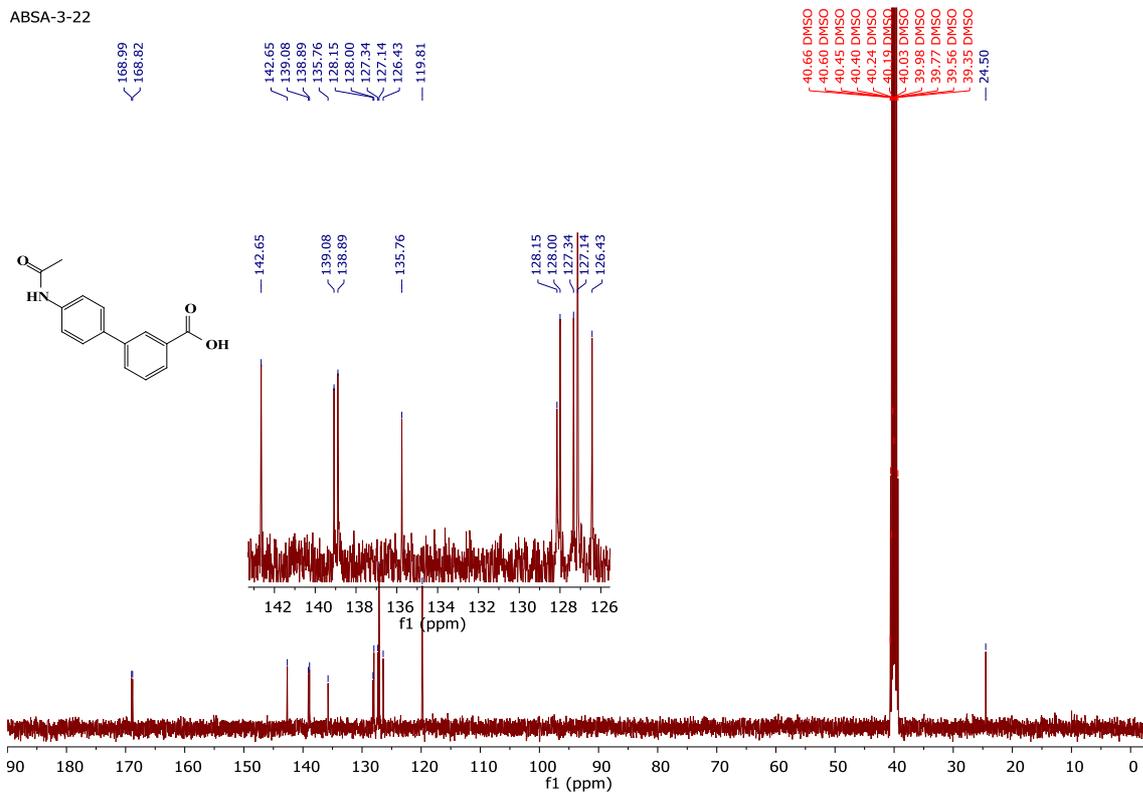
2.34 3'-(acetamidomethyl)biphenyl]-3-carboxylic acid, 22:

2.34.1 ^{1}H NMR of 22
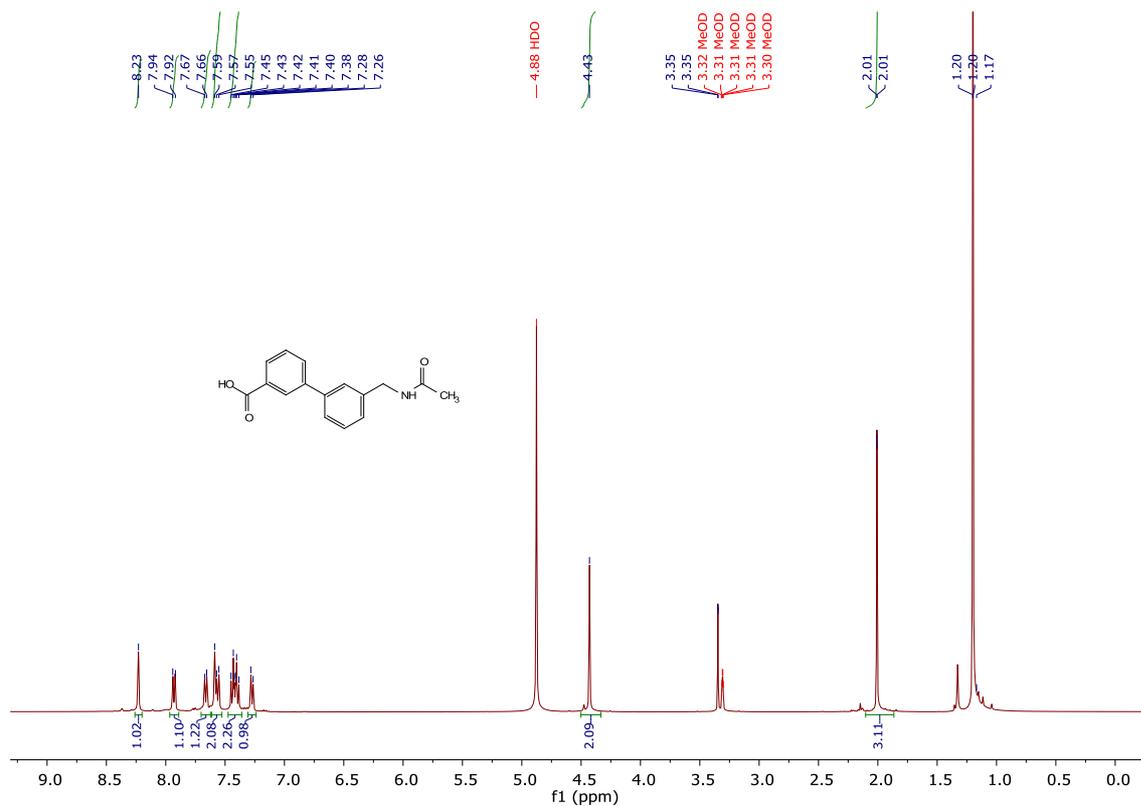
2.34.2 ^{13}C NMR of 22
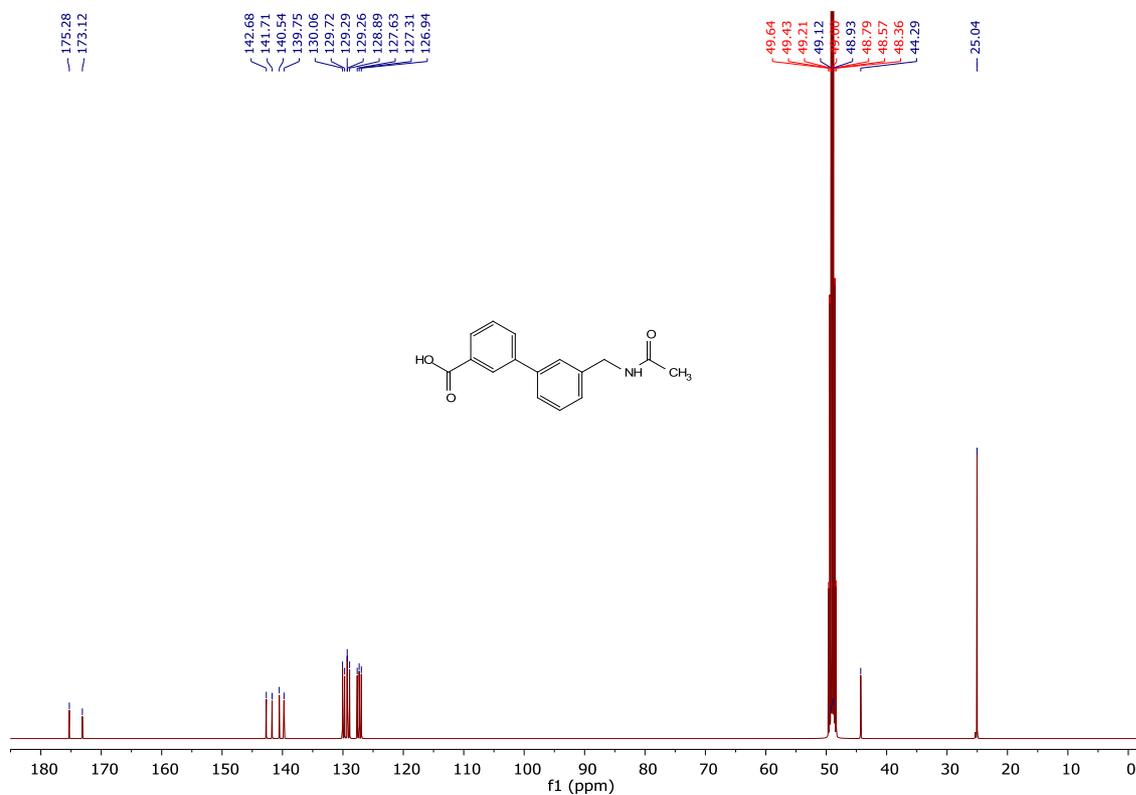
2.35 3'-(2-acetamidoethyl)biphenyl]-3-carboxylic acid, **23a**:

2.35.1 ^{1}H NMR of **23a**
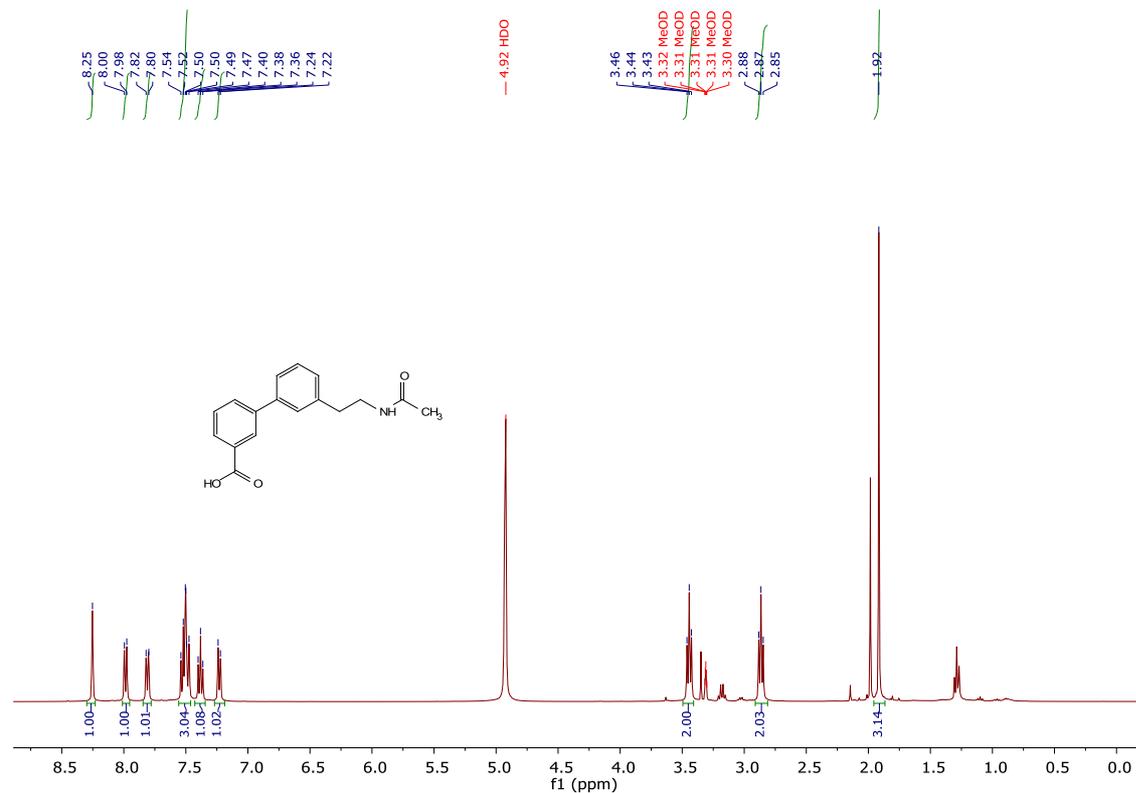
2.35.2 ^{13}C NMR of **23a**
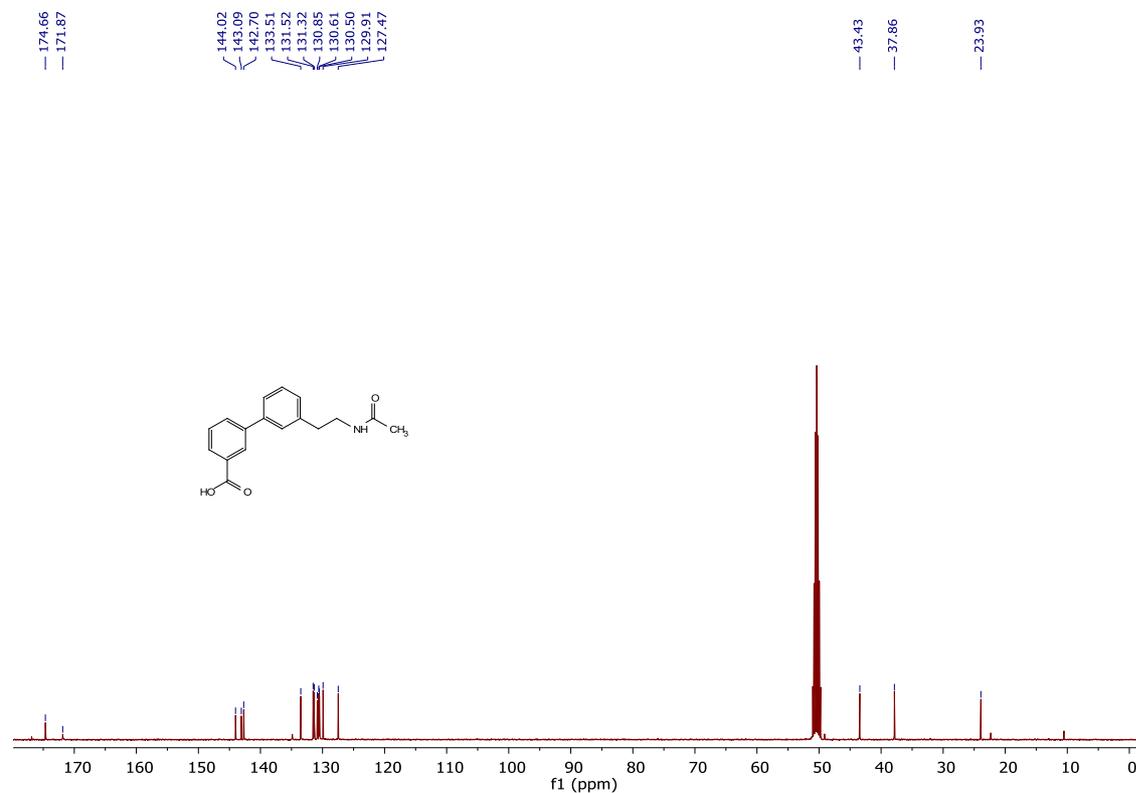
2.36 4'-(2-acetamidoethyl)biphenyl]-3-carboxylic acid, 23b:

2.36.1 ^{1}H NMR of 23b
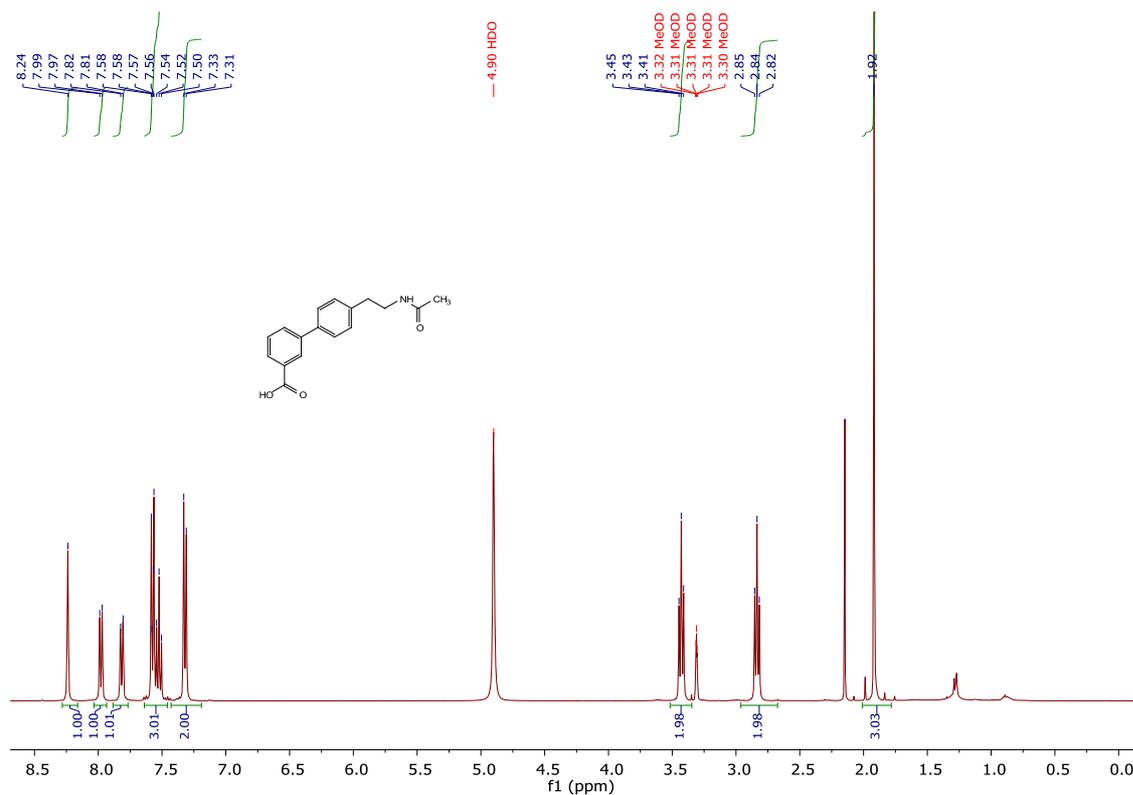
2.36.2 ^{13}C NMR of 23b
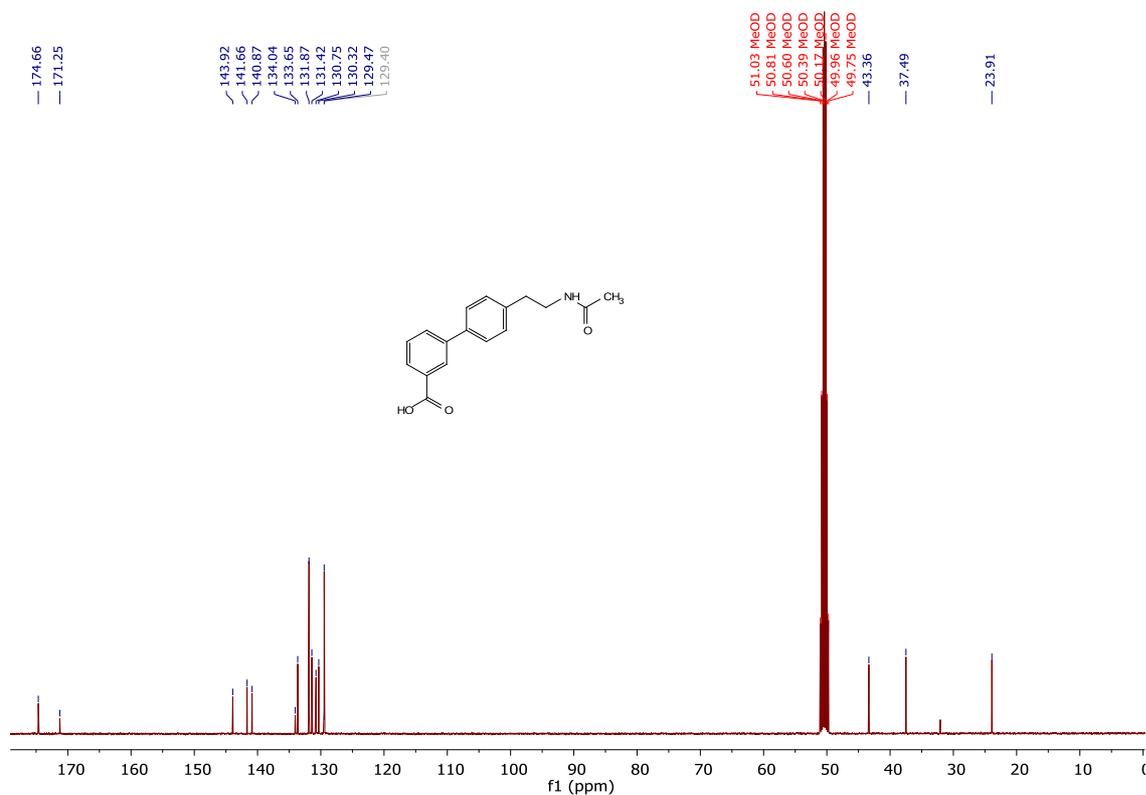
2.37 3'-acetoxymethylbiphenyl-3-carboxylic acid, **24**:

2.37.1 ^{1}H NMR of **24**
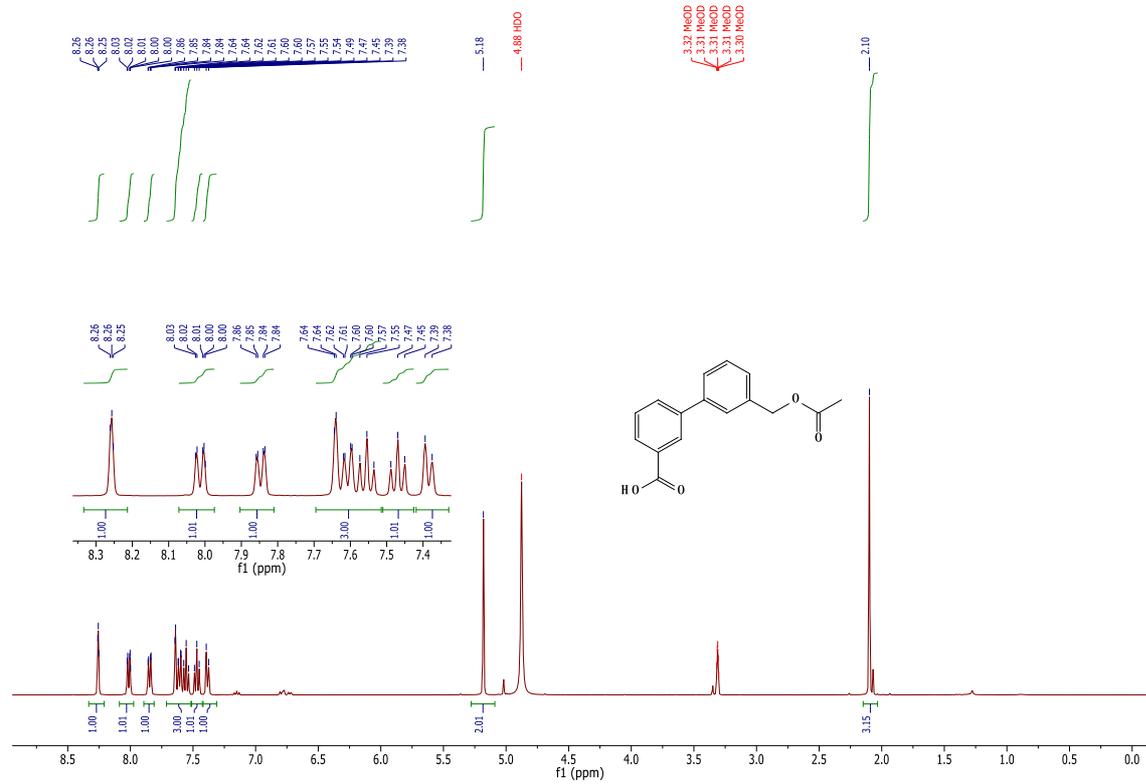
2.37.2 ^{13}C NMR of **24**
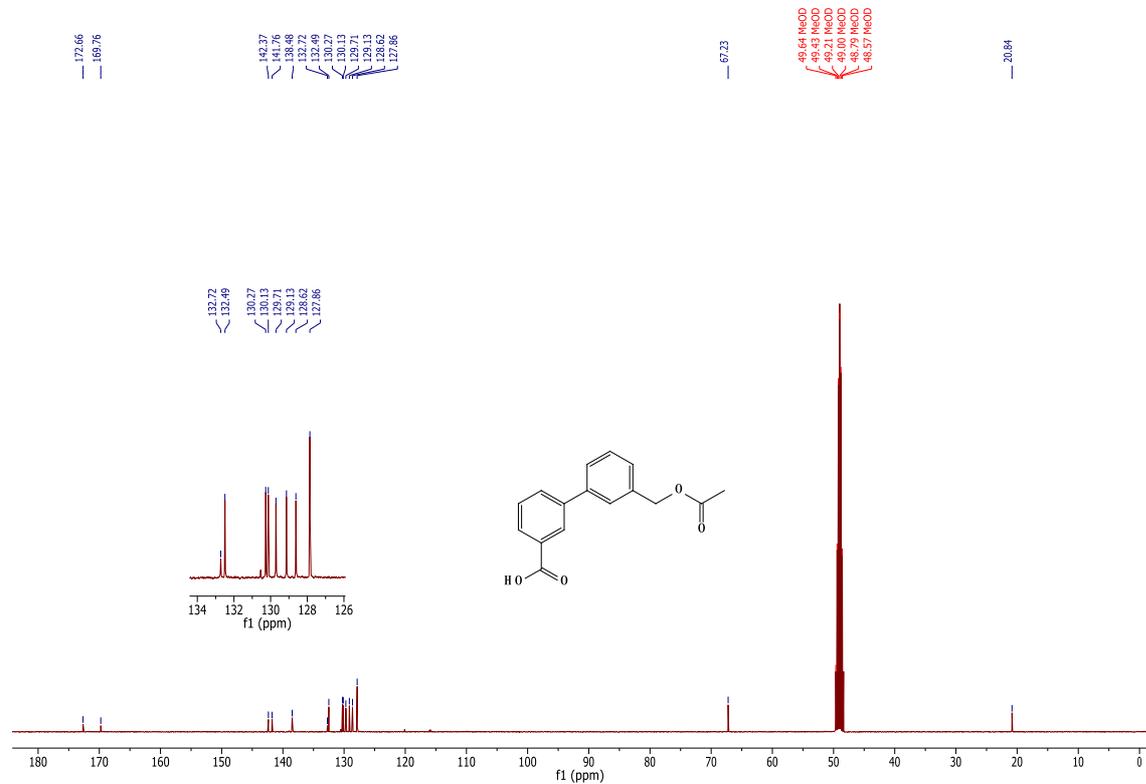
2.38 4'-(1H-imidazol-1-yl)biphenyl-3-carboxylic acid, 25:

2.38.1 ^{1}H NMR of 25

ABSA-3-51-7
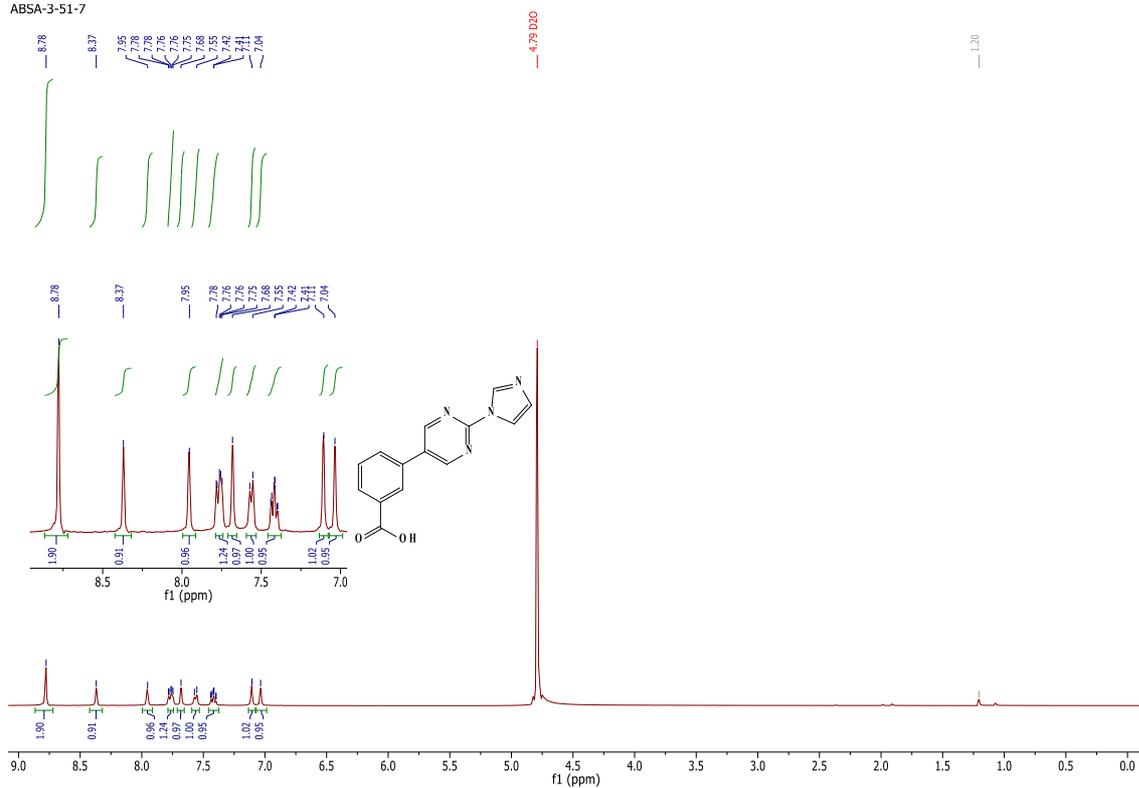
2.38.2 ^{13}C NMR of 25

ABSA-3-51-7
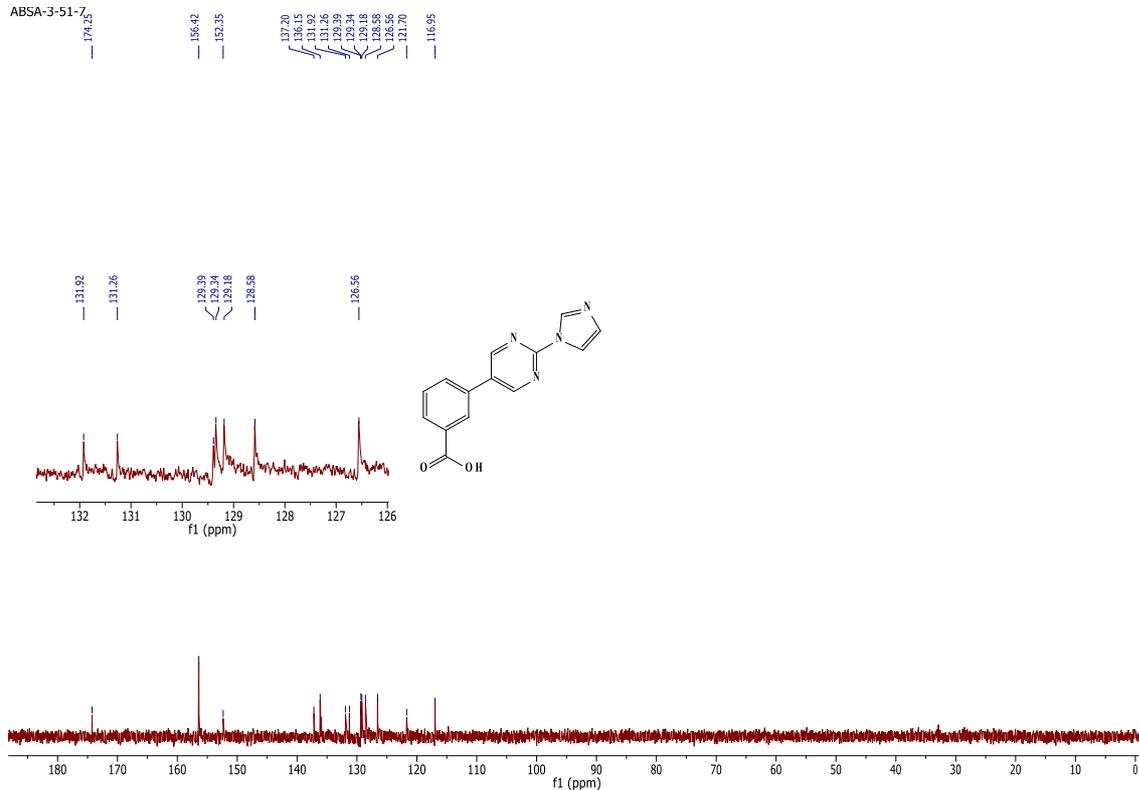
2.39 3'-(1H-tetrazol-5-yl)biphenyl-3-carboxylic acid, **26a**:

2.39.1 ^{1}H NMR of **26a**

ABSA-3-42
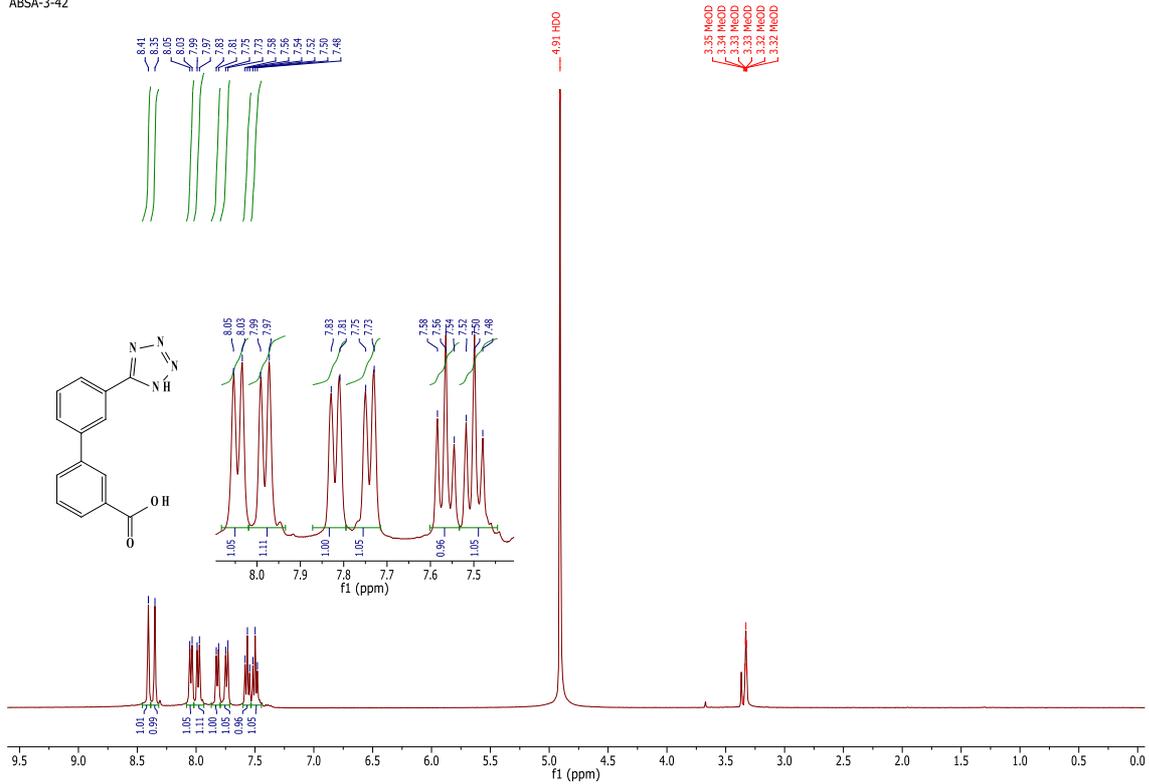
2.39.2 ^{13}C NMR of **26a**

ABSA-3-42
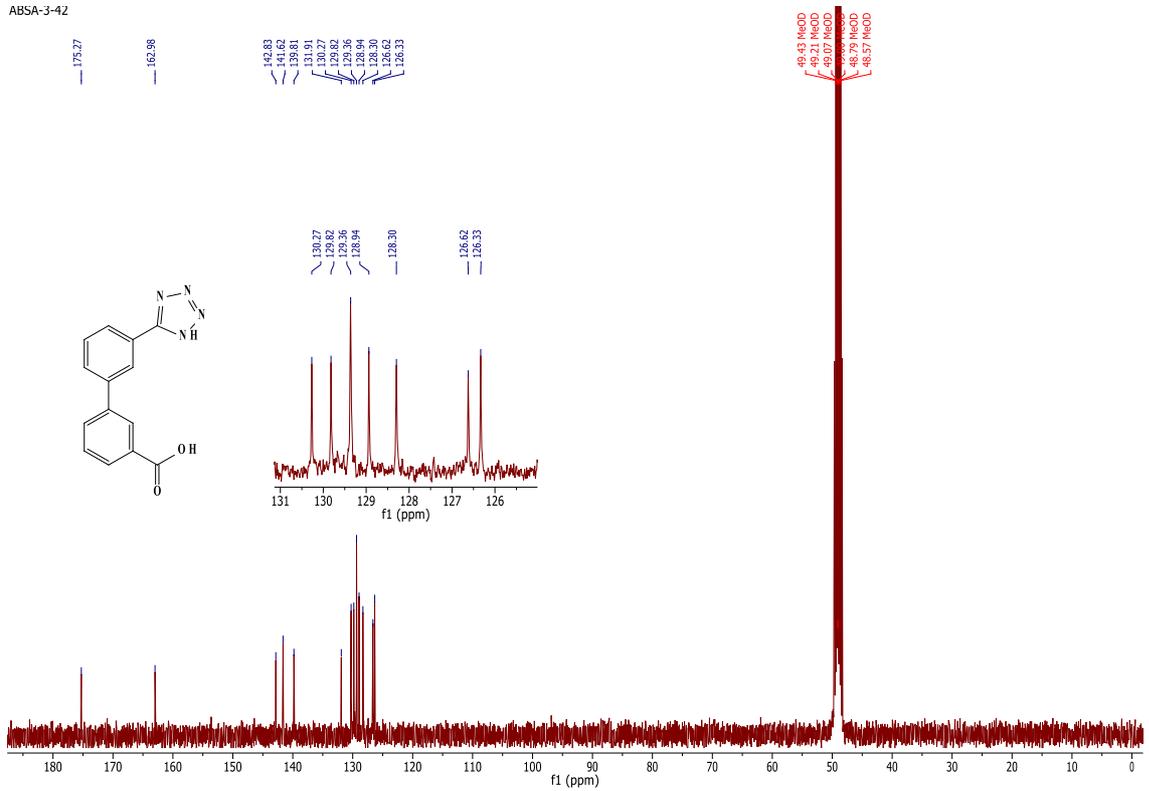
2.40 4'-(1H-tetrazol-5-yl)biphenyl-3-carboxylic acid, **26b**:

2.40.1 ^{1}H NMR of **26b**

ABSA-3-43

8.32, 8.16, 8.14, 7.98, 7.96, 7.94, 7.81, 7.79, 7.79, 7.78, 7.77, 7.76, 7.75, 7.50, 7.48, 7.46

4.89 HDO

3.34 MeOD, 3.33 MeOD, 3.33 MeOD, 3.32 MeOD, 3.32 MeOD

1.00, 2.07, 1.10, 3.16, 1.07

2.40.2 ^{13}C NMR of **26b**

ABSA-3-43, Sol: MEOH

175.24

162.69

142.56, 141.38, 139.77, 130.35, 129.66, 129.38, 128.79, 128.27, 128.18

49.64 MeOD, 49.43 MeOD, 49.21 MeOD, 48.79 MeOD, 48.57 MeOD, 48.36 MeOD

130.35, 129.66, 129.38, 128.79, 128.27, 128.18

60
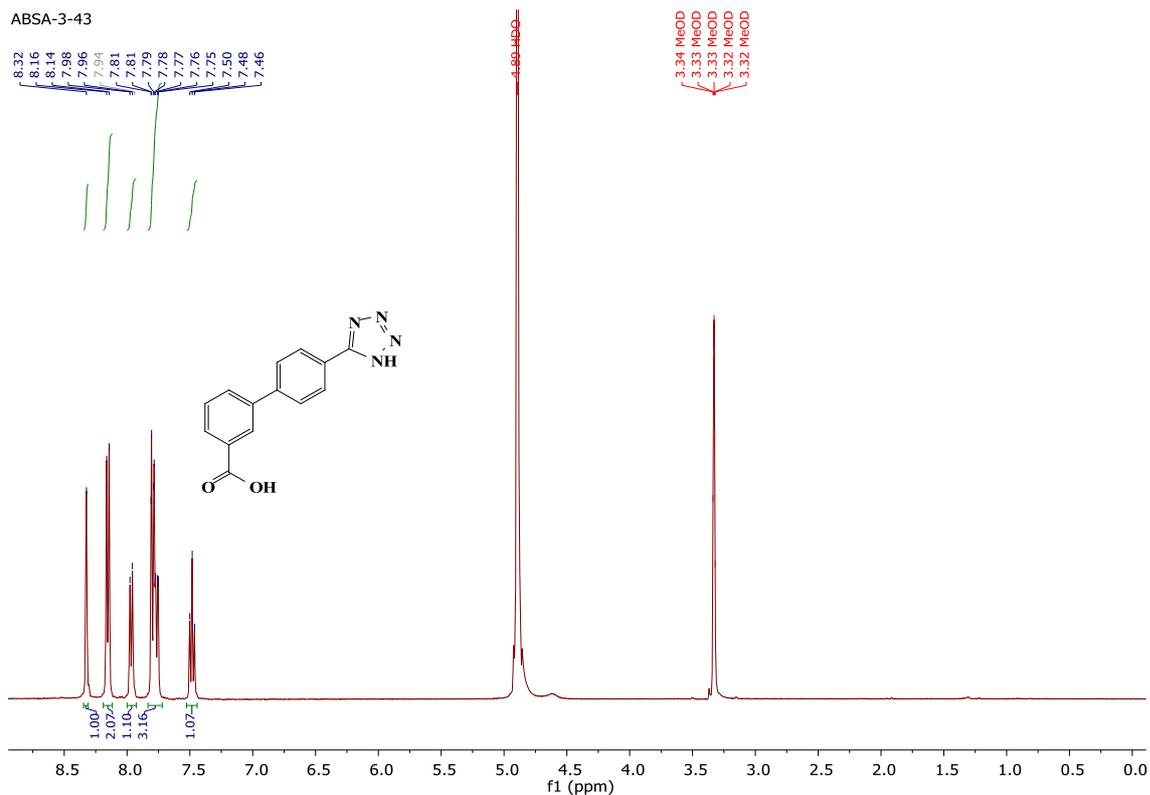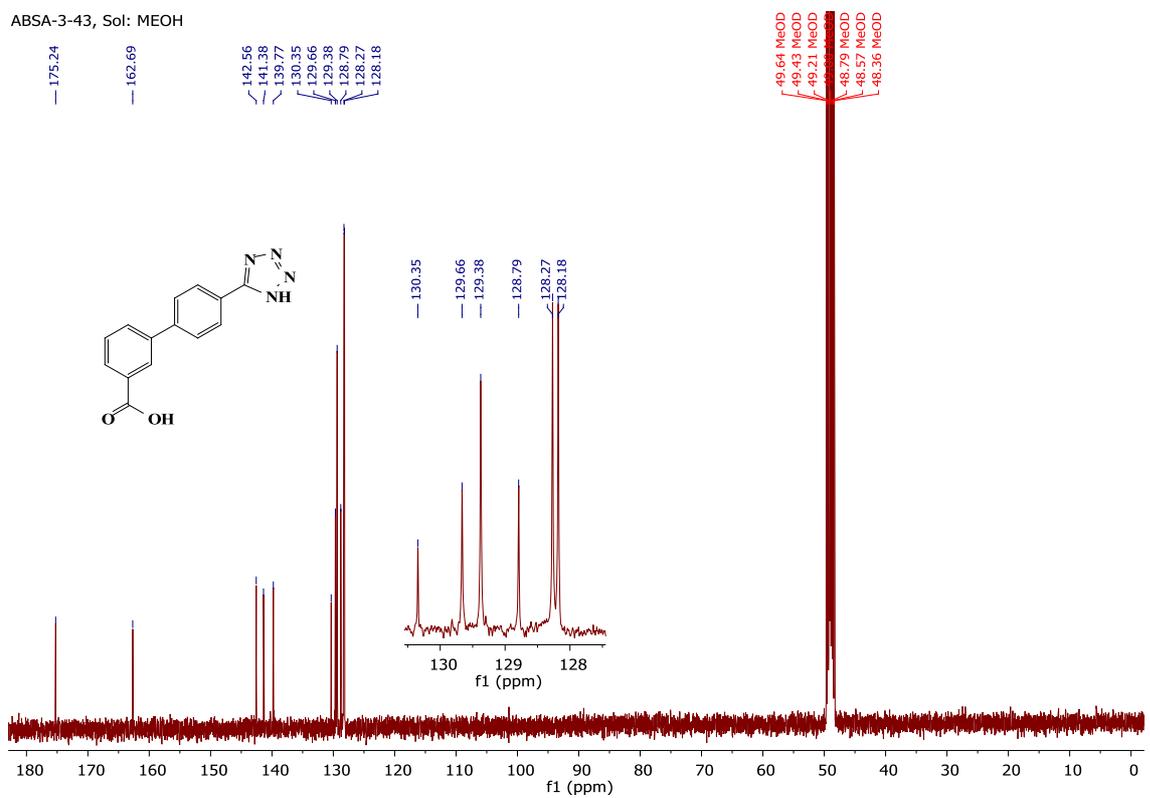
2.41 3-(naphthalen-2-yl)benzoic acid, 27:

2.41.1 ^{1}H NMR of 27
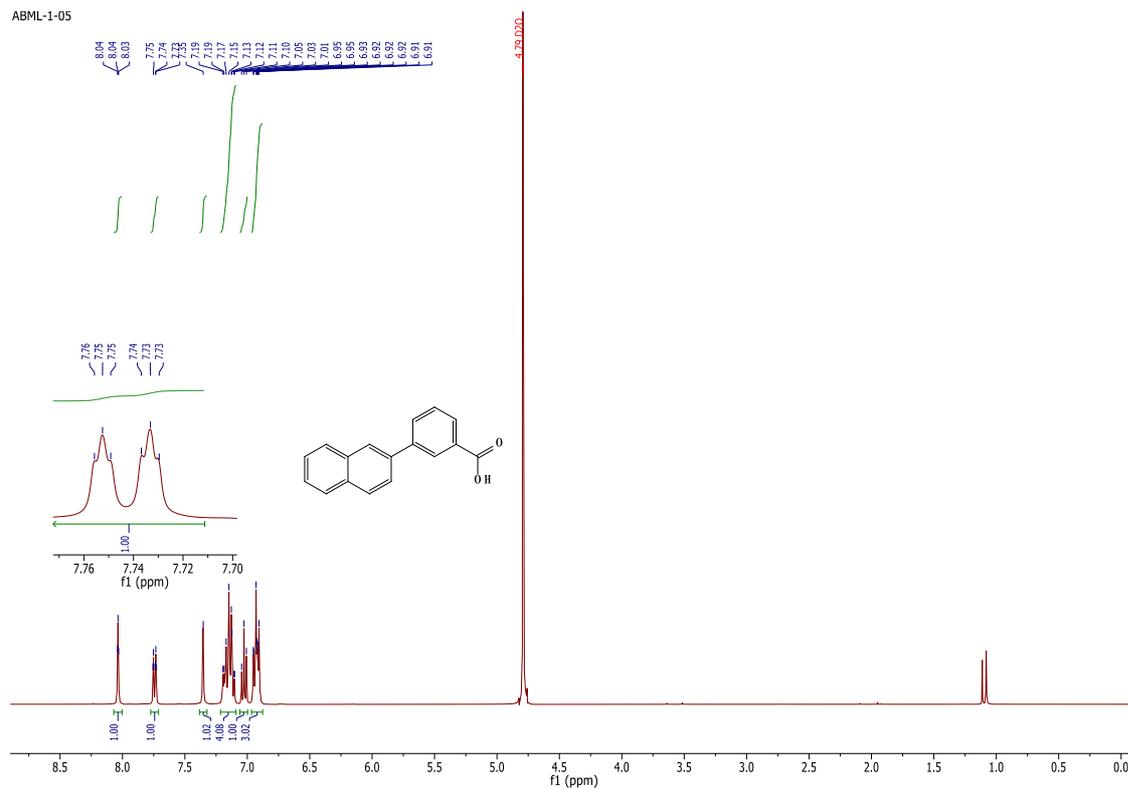
2.41.2 ^{13}C NMR of 27
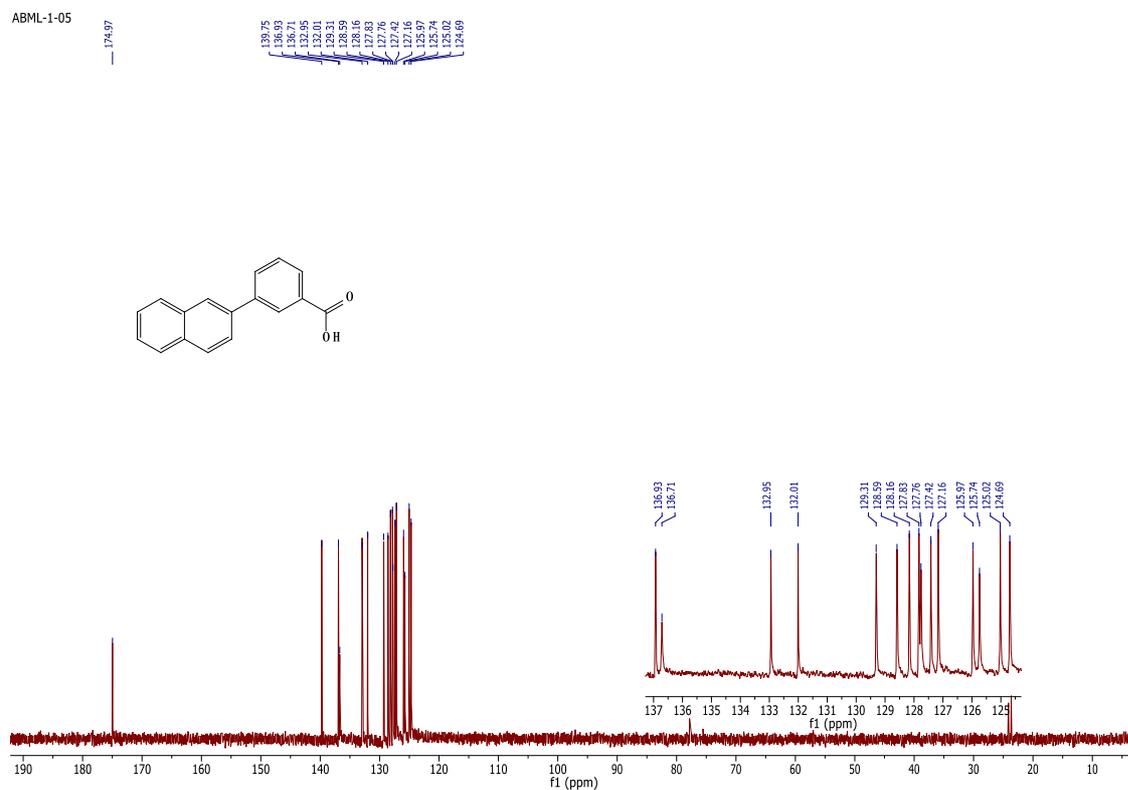
2.42 3-(quinolin-7-yl)benzoic acid, 28:

2.42.1 ^{1}H NMR of 28
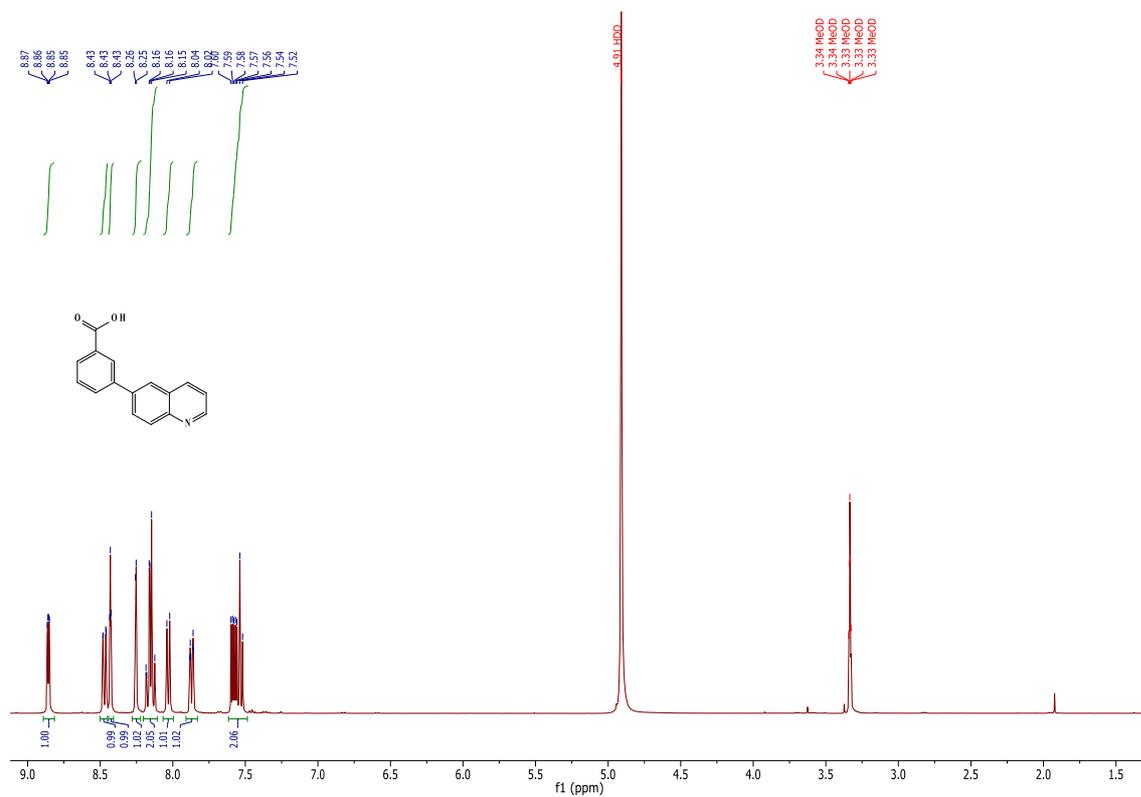
2.42.2 ^{13}C NMR of 28
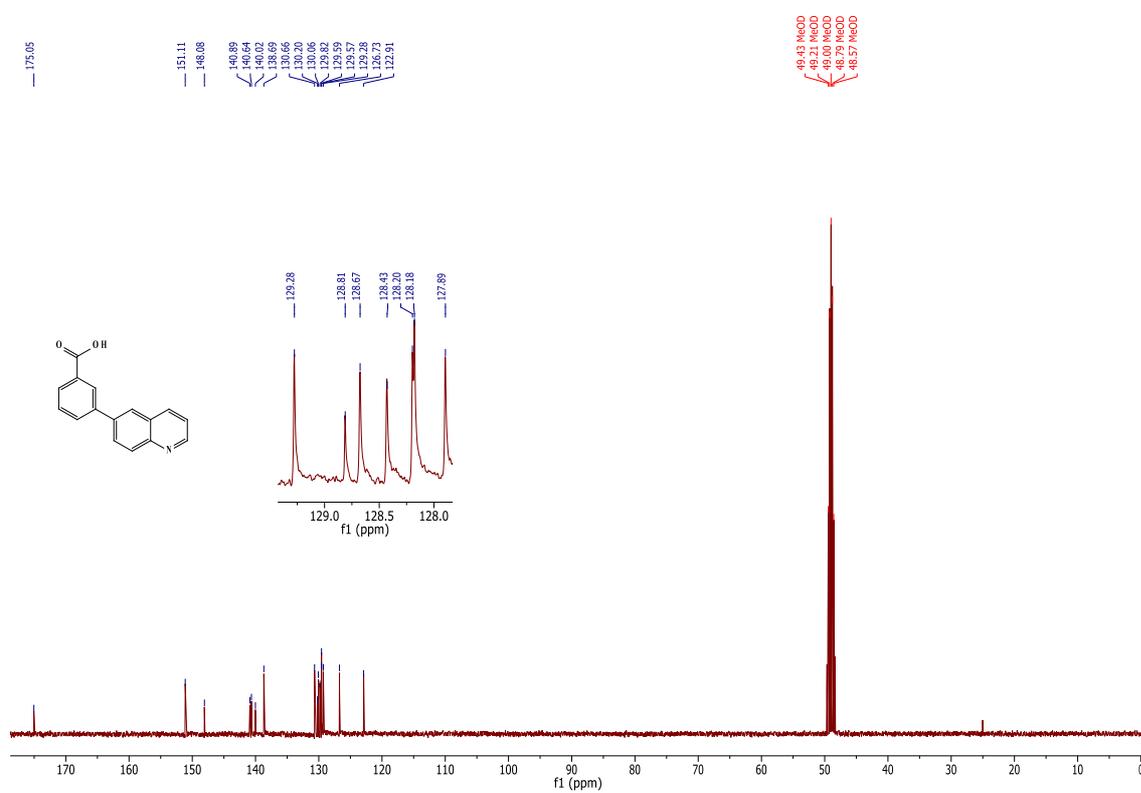
2.43 3-(6-aminopyridin-3-yl)benzoic acid, 29:

2.43.1 ^{1}H NMR of 29
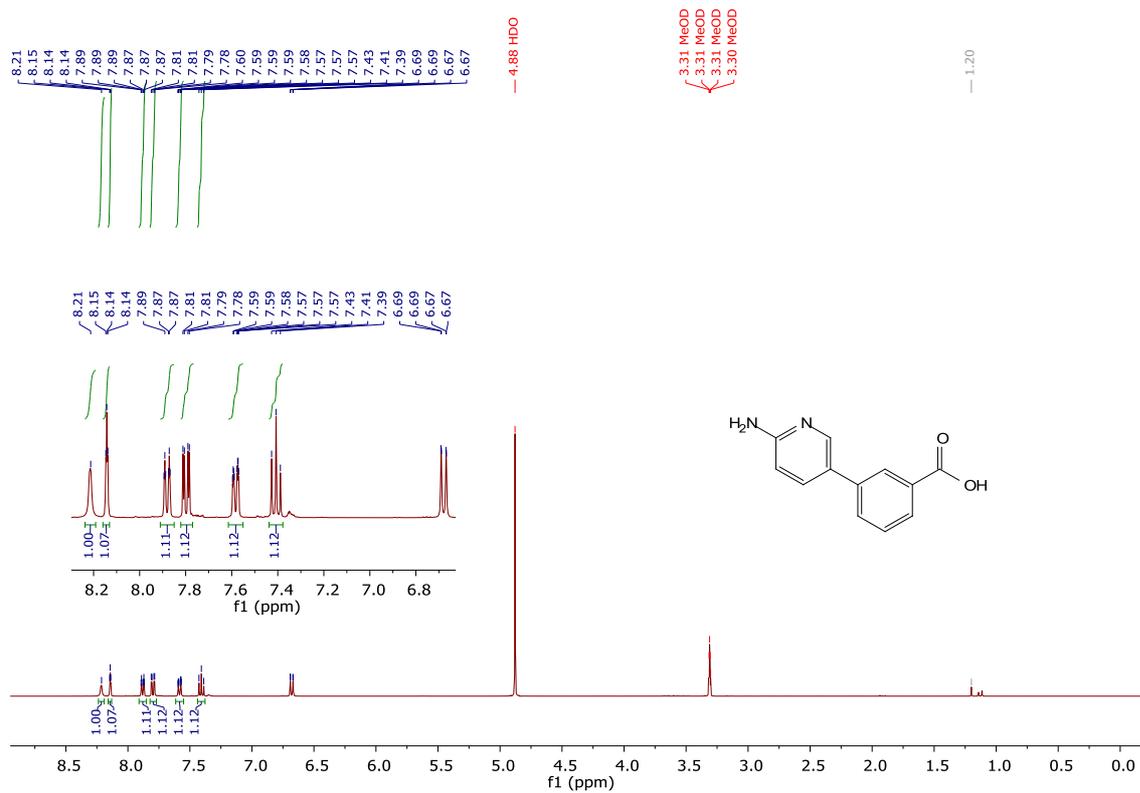
2.43.2 ^{13}C NMR of 29
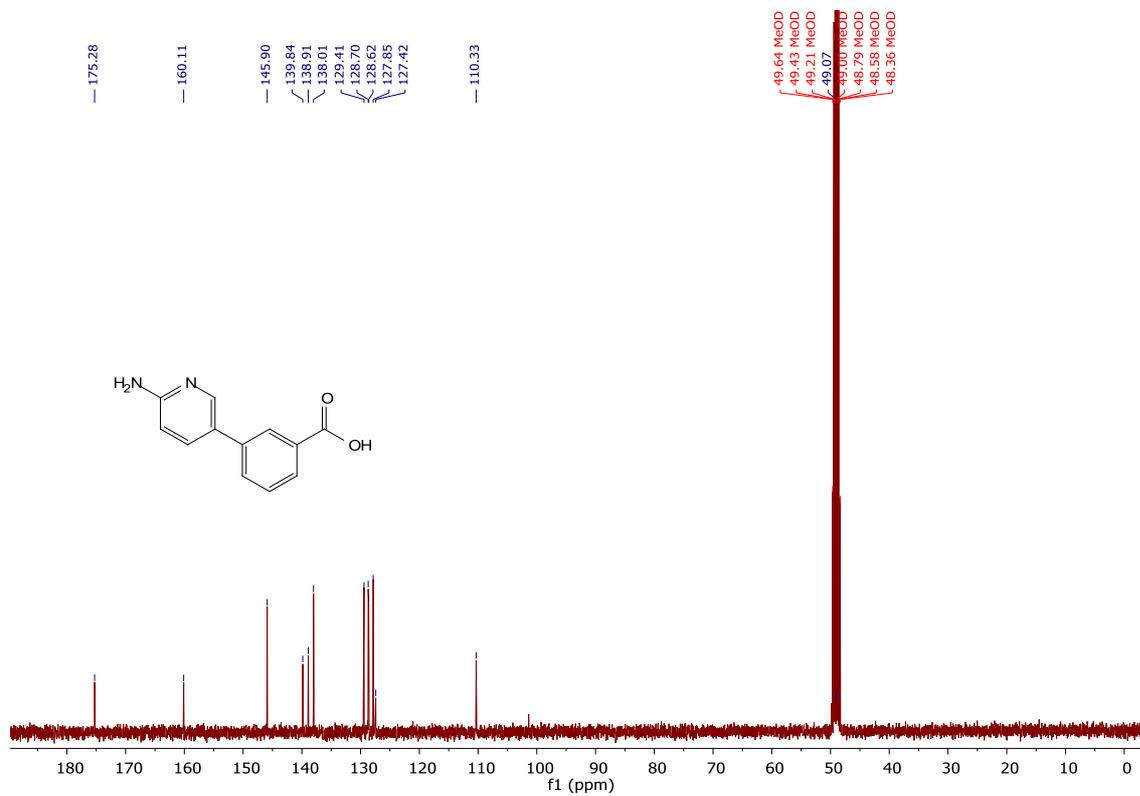
2.44 3-(pyrimidin-5-yl)benzoic acid, **30**:

2.44.1 ^{1}H NMR of **30**
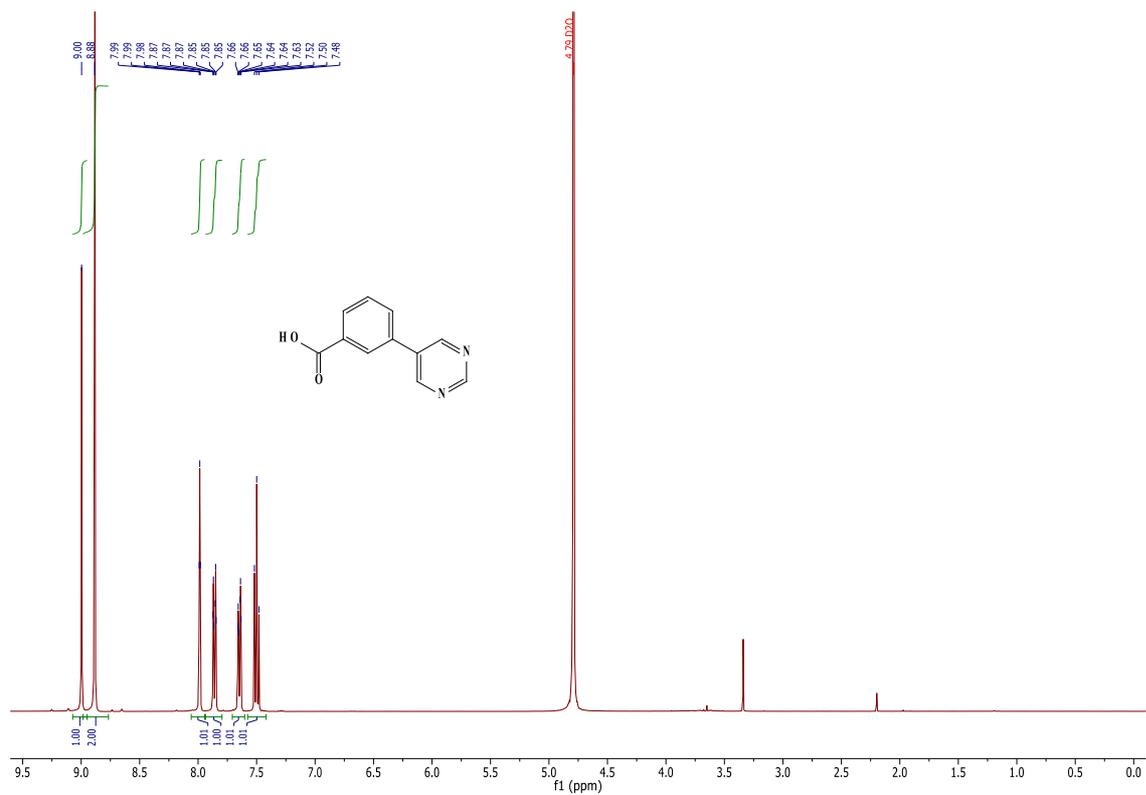
2.44.2 ^{13}C NMR of **30**
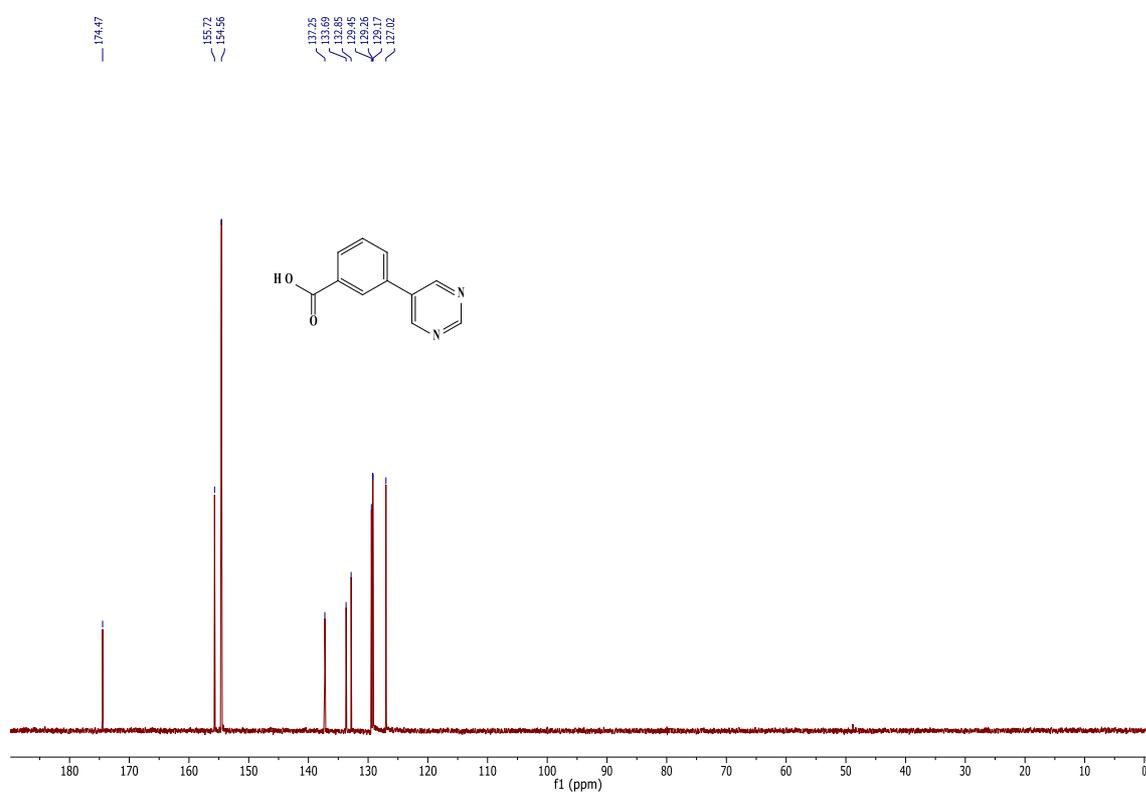
2.45 3-(2-aminopyrimidin-4-yl)benzoic acid, 31:

2.45.1 ^{1}H NMR of 31

2.45.2 ^{13}C NMR of 31

^{13}C NMR (101 MHz, CD$_3$OD)
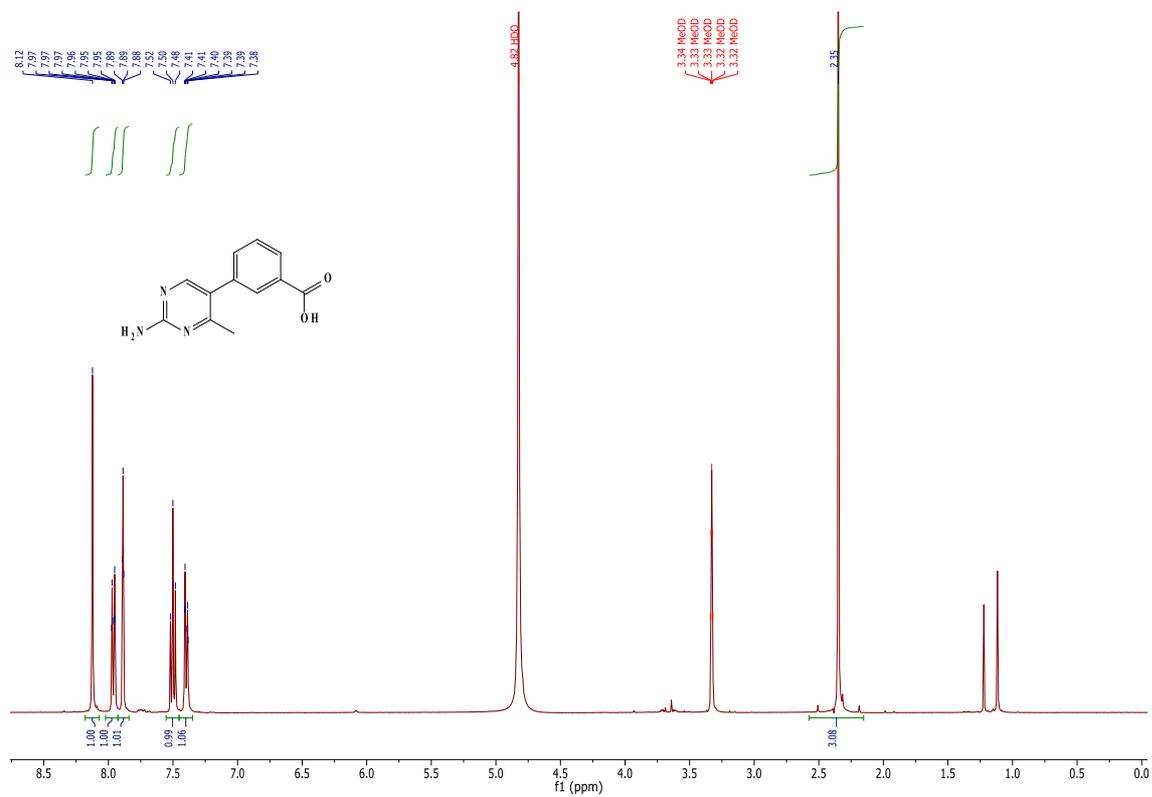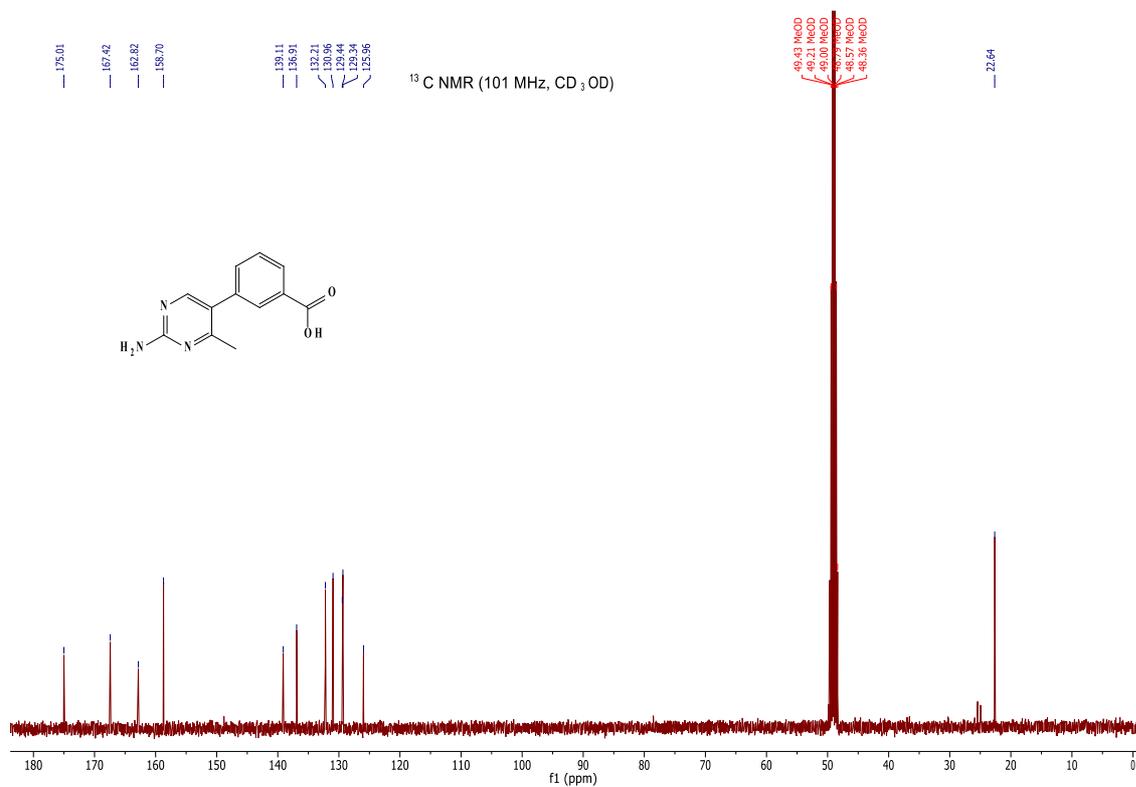
2.46 3-(1-methyl-1H-pyrrol-2-yl)benzoic acid, **32**:

2.46.1 ^{1}H NMR of **32**

ABML-1-06
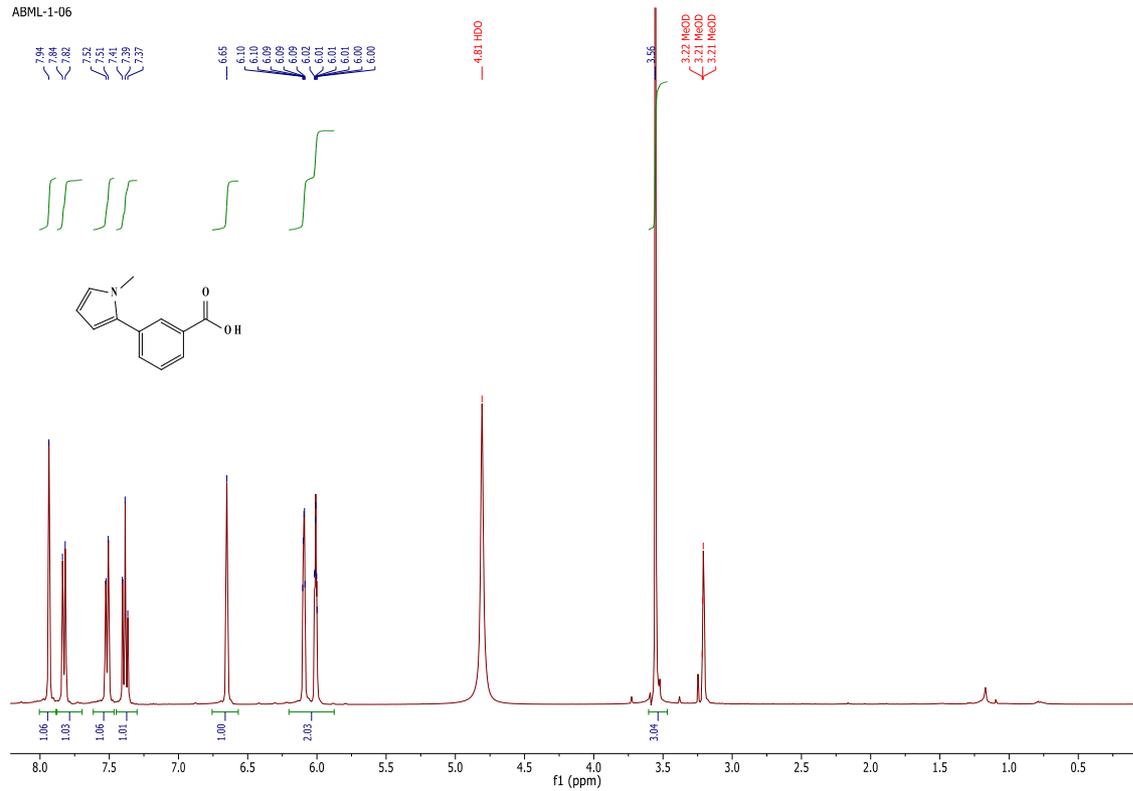
2.46.2 ^{13}C NMR of **32**
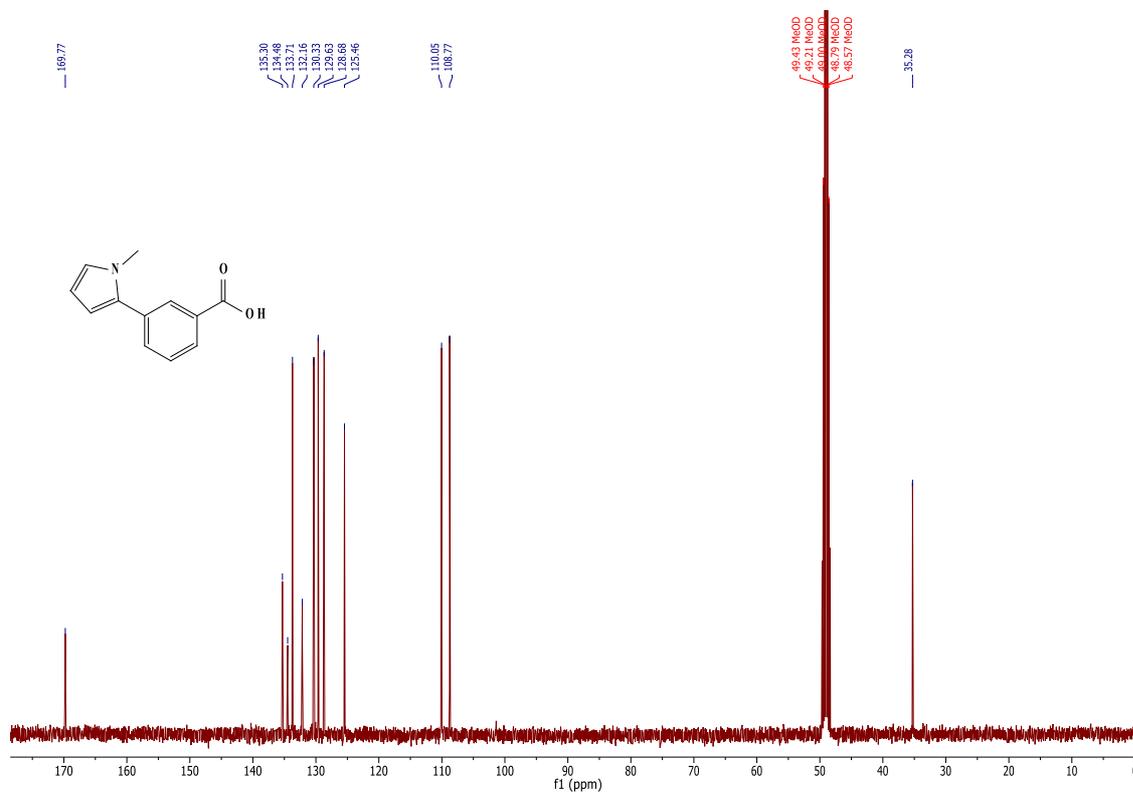
2.47 3-(thiazol-5-yl)benzoic acid, **33**:

2.47.1 ^{1}H NMR of **33**
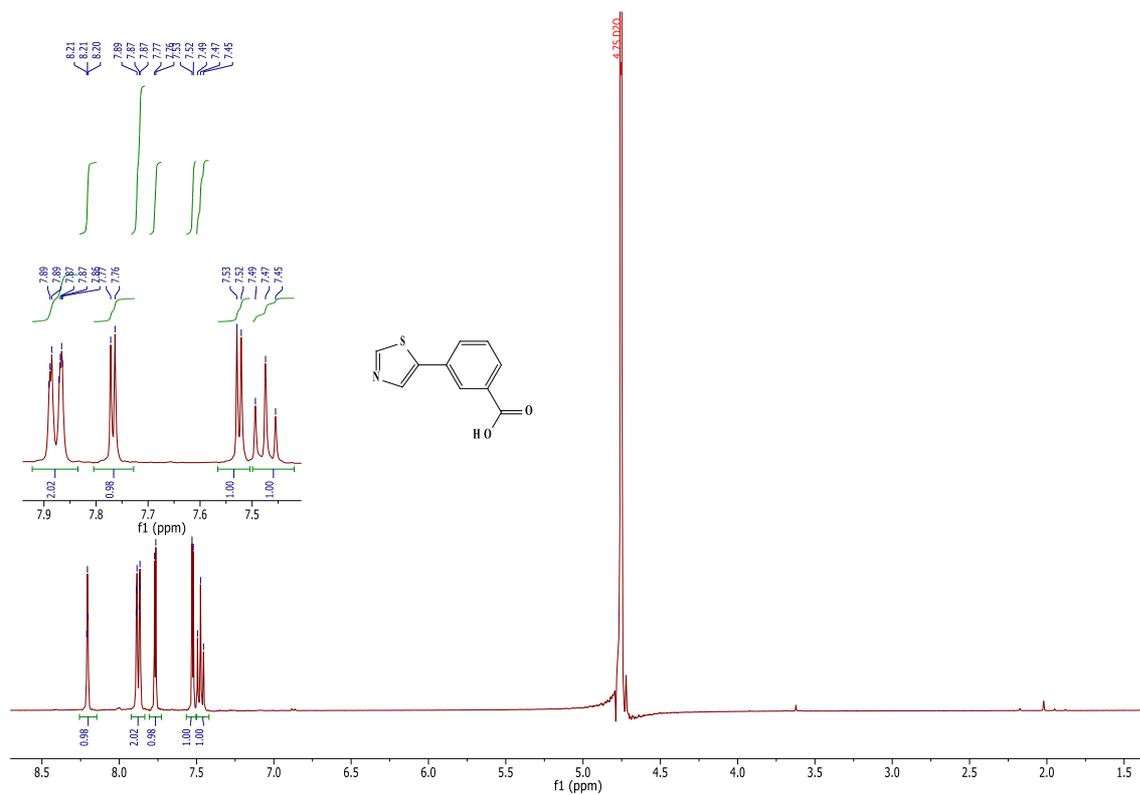
2.47.2 ^{13}C NMR of **33**
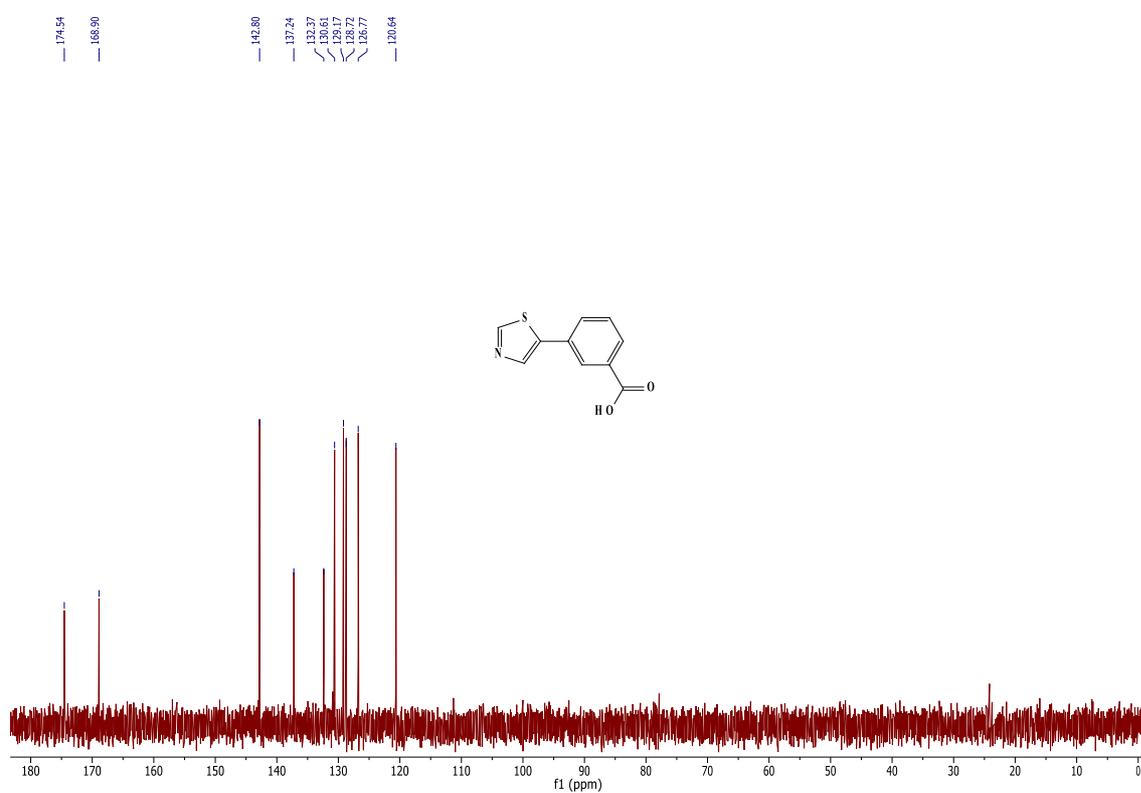
2.48 3-(1H-indol-5-yl)benzoic acid, **34**:

2.48.1 ^{1}H NMR of **34**

ABML-1-03

2.48.2 ^{13}C NMR of **34**

ABML-1-03

2.49 3-(pyridin-2-yl)benzoic acid, 35:
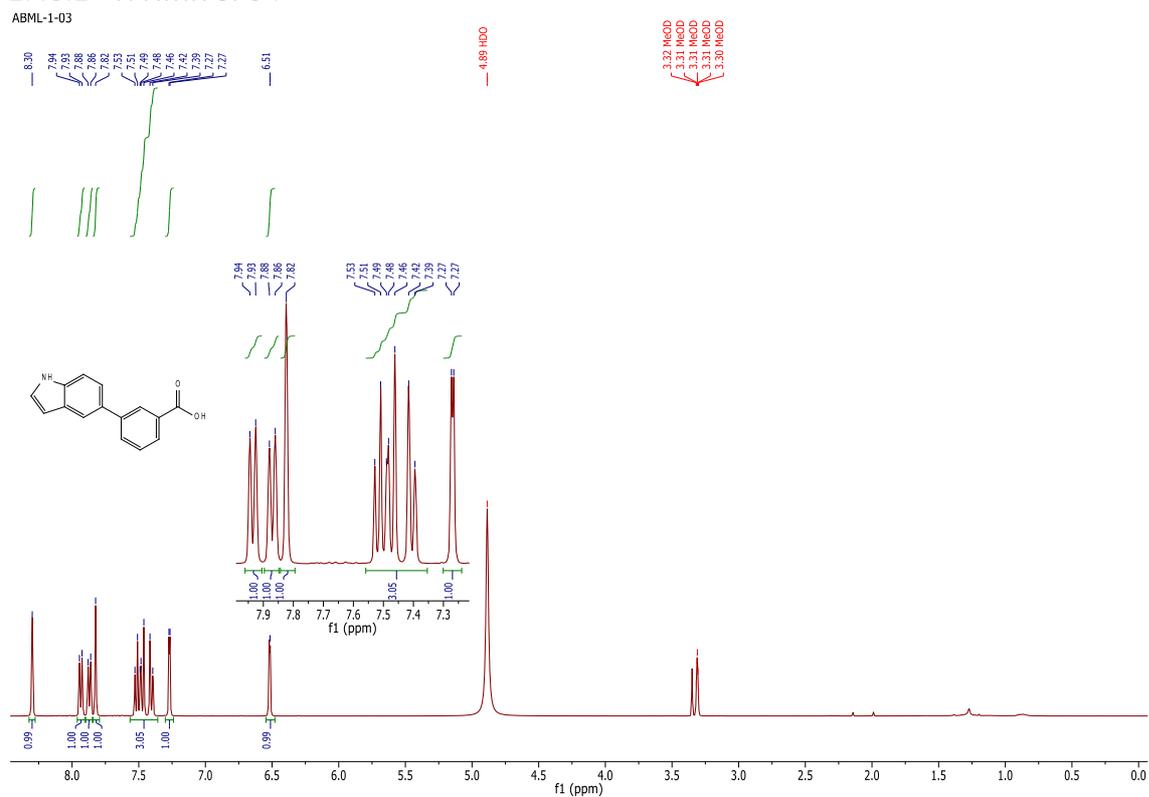
2.49.1 1H NMR of 35
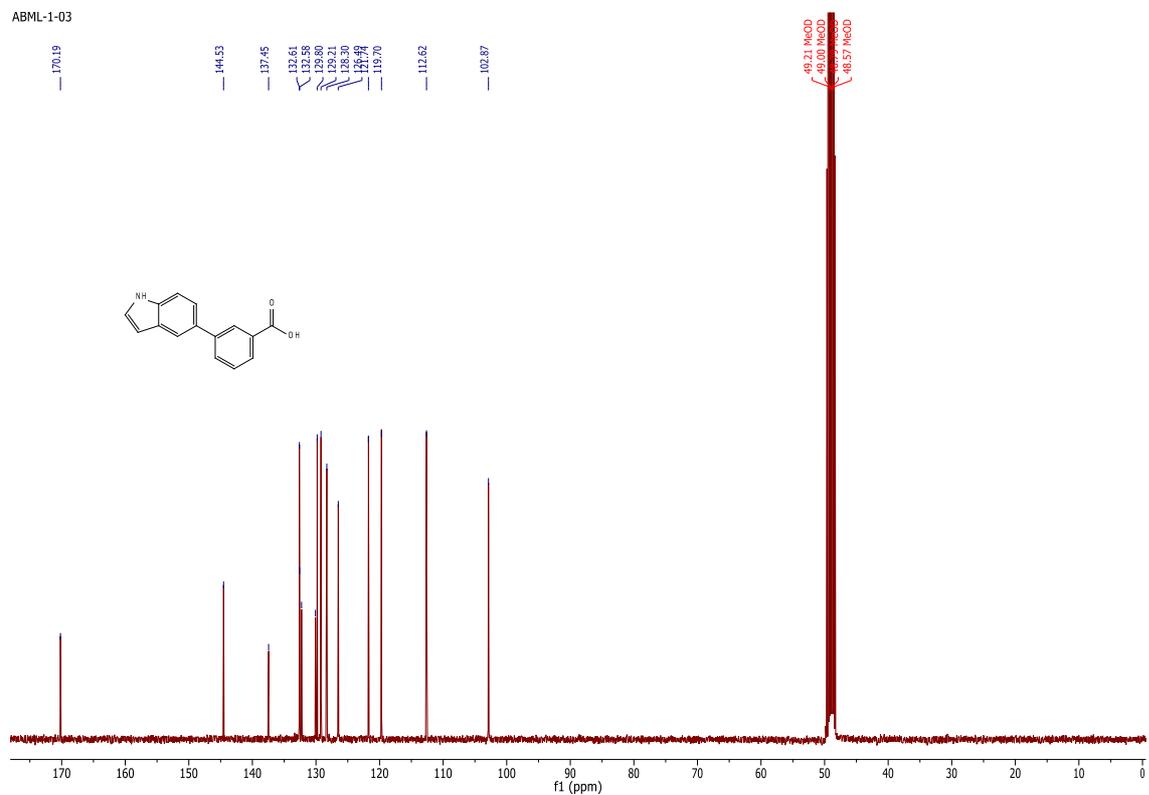
2.49.2 13C NMR of 35

2.50 symmetrical 3,5-disubstituted benzoic acid derivatives

2.51 3,5-Di(3-acetamidophenyl)benzoic acid 36:

2.51.1 1H NMR of 36

ABAI-33-2
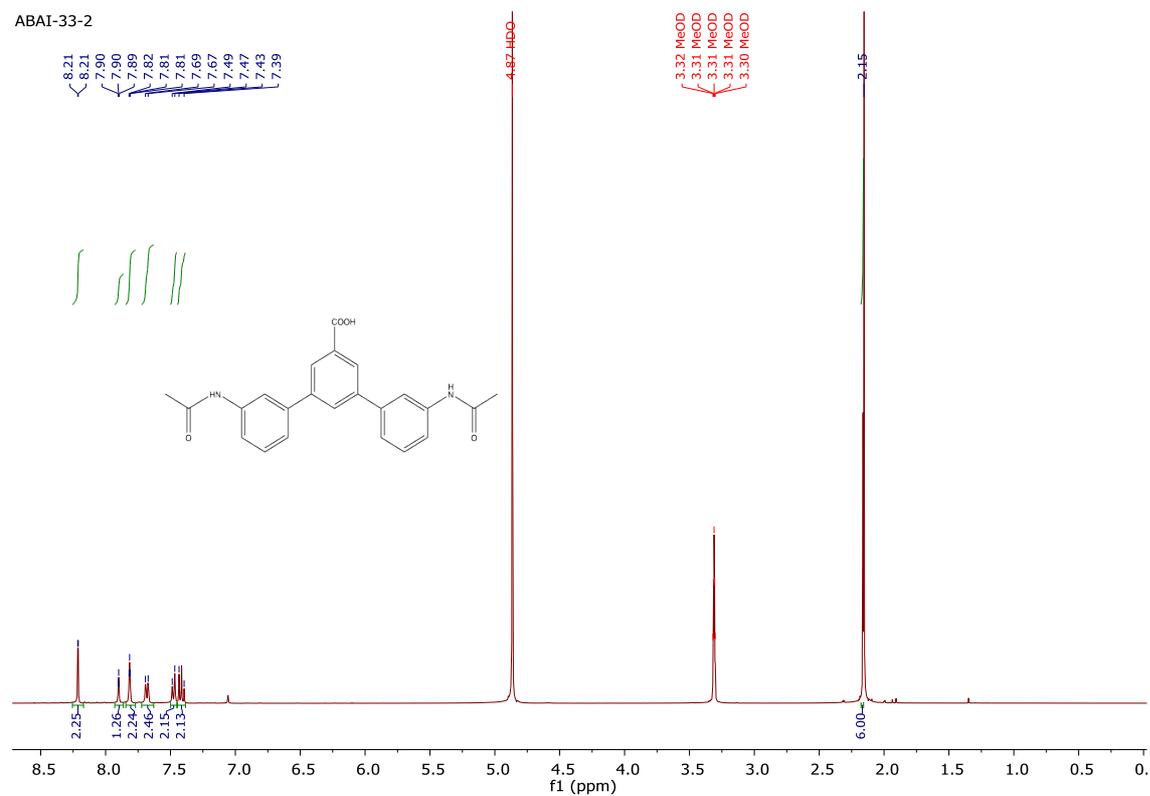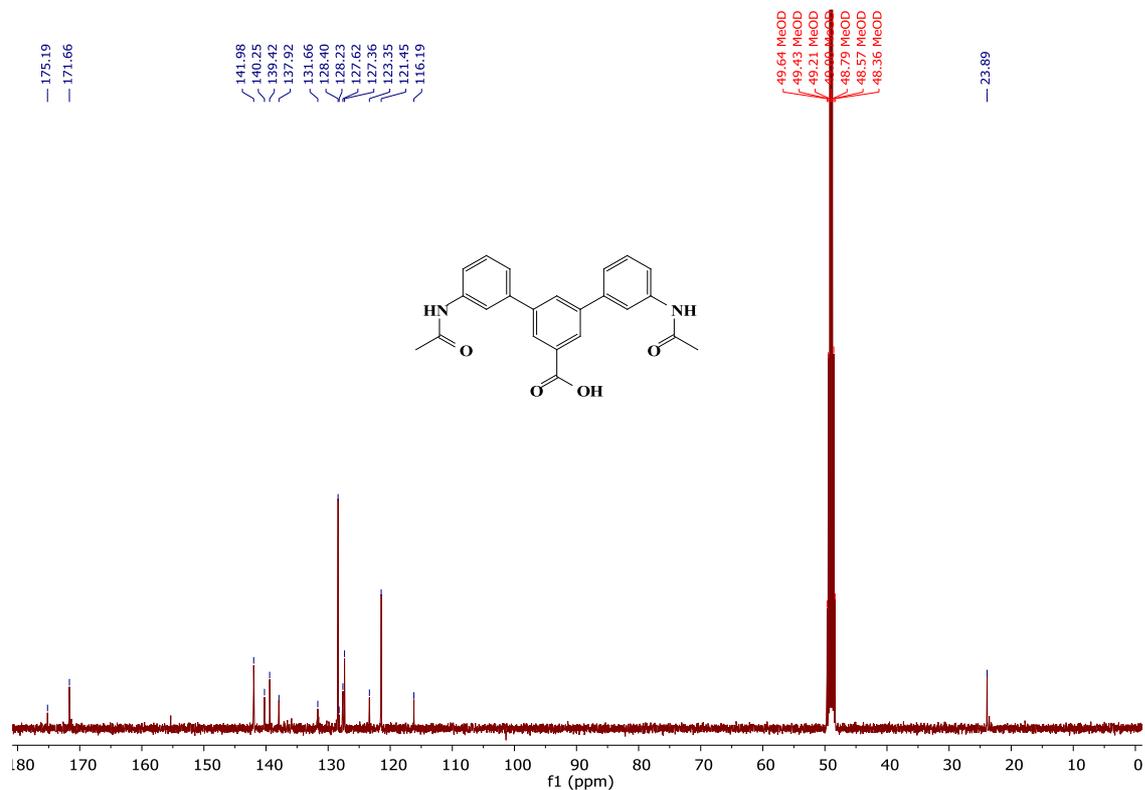
2.51.2 13C NMR of 36

2.52 3,5-di(4-acetamidophenyl)benzoic acid 37:

2.52.1 1H NMR of 37
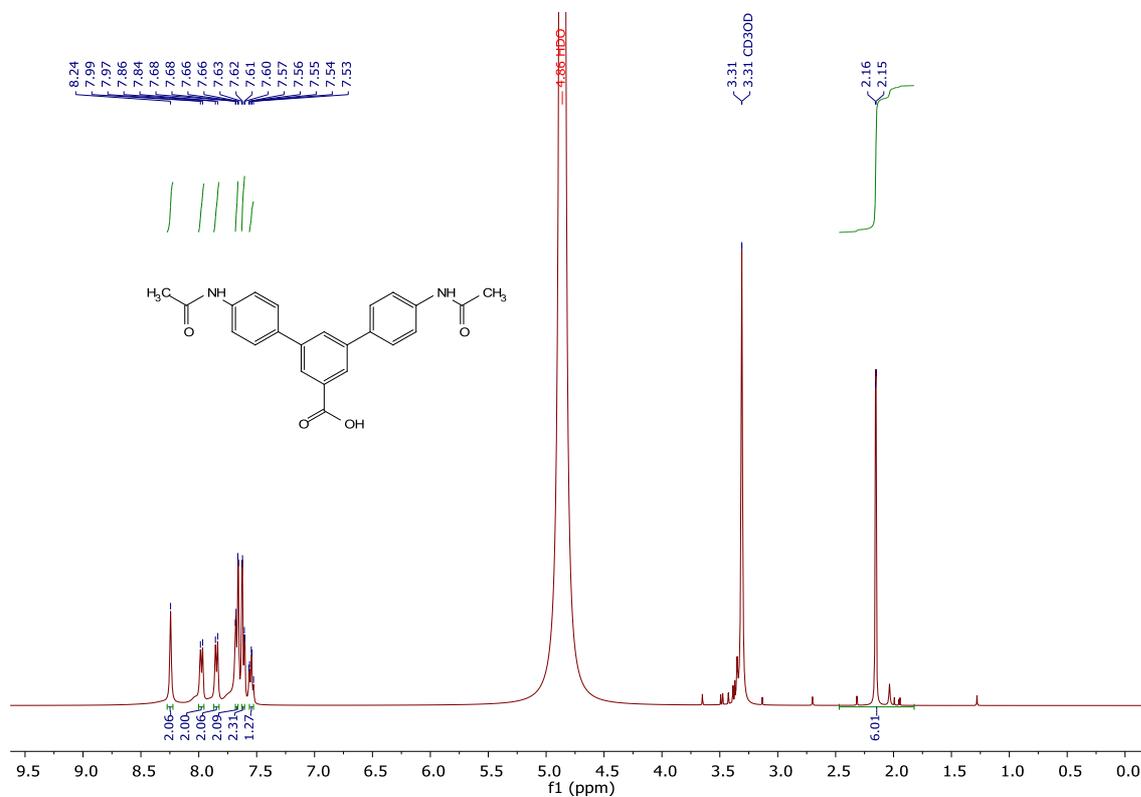
2.52.2 13C NMR of 37
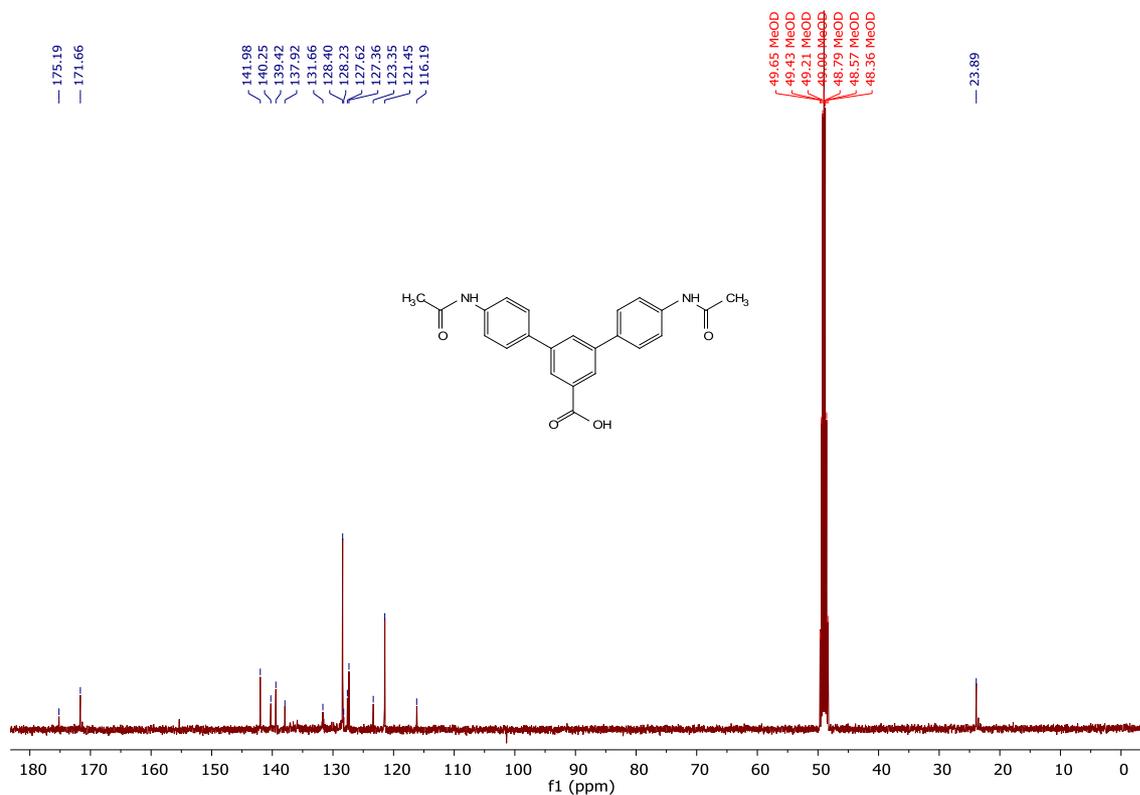
2.53 3,5-diquinolin-6-ylbenzoic acid **38**:

2.53.1 1H NMR of **38**

ABAI-52

2.53.2 13C NMR of **38**

ABAI-52
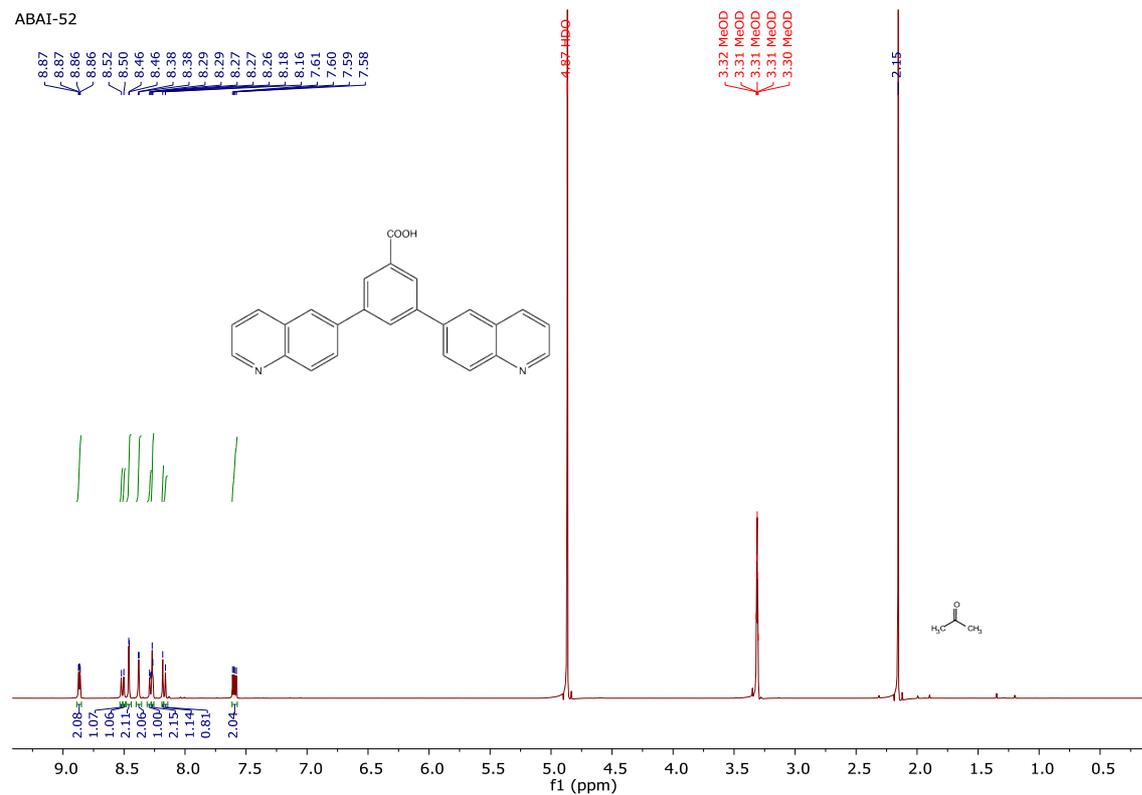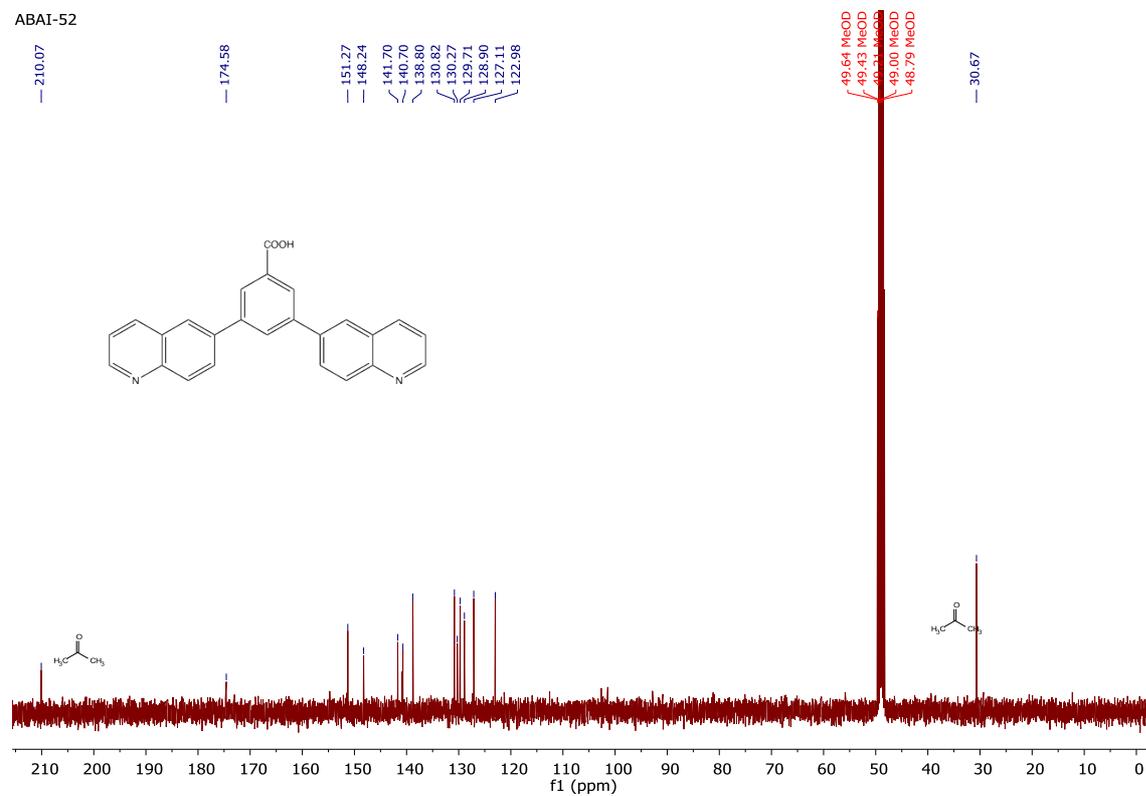
2.54 unsymmetrical 3,5-disubstituted benzoic acid derivatives

2.55 3-(3'-Acetamidophenyl)-5-pyridin-4-ylbenzoic acid 39:

2.55.1 1H NMR of 39
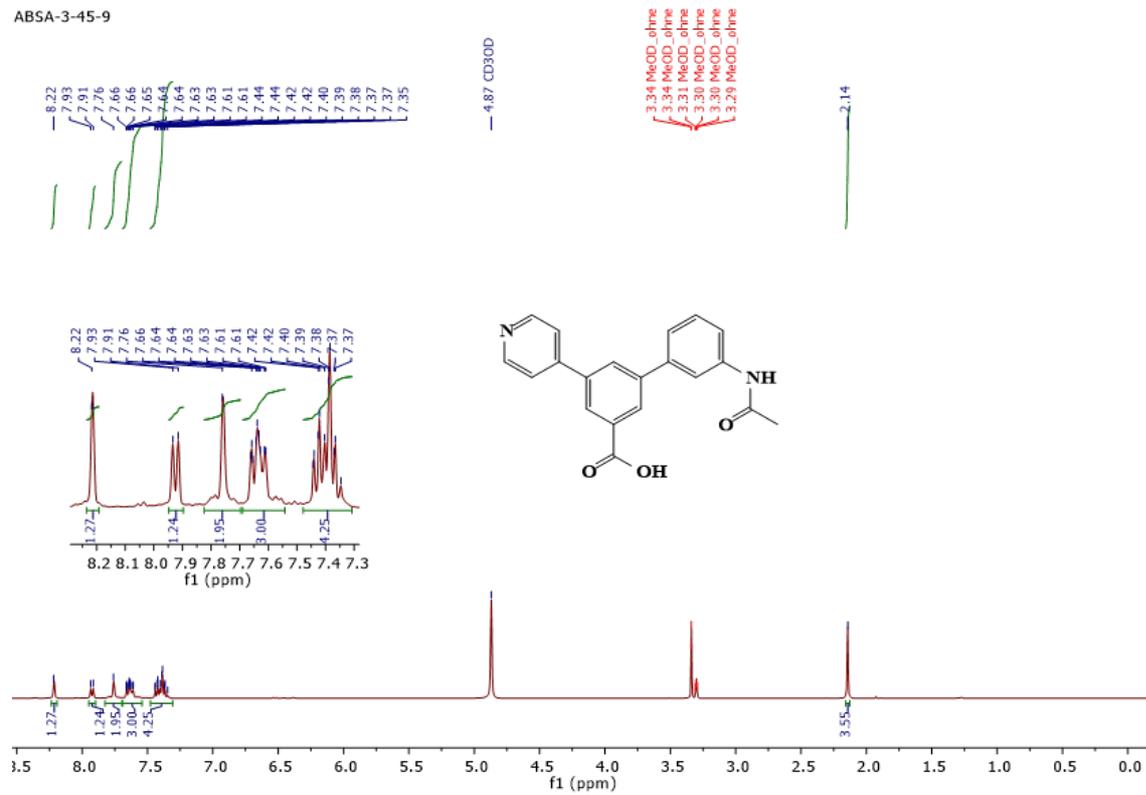
2.55.2 13C NMR of 39
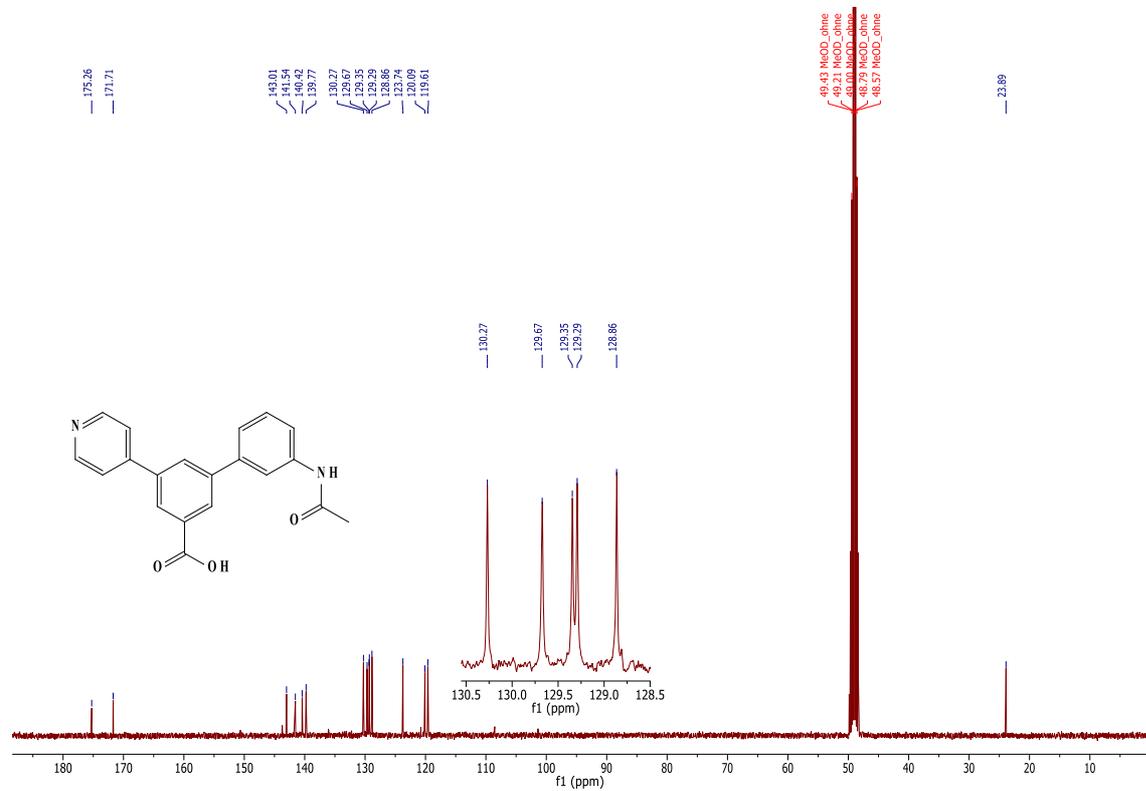
2.56 3-Bromo-5-(quinolin-6-yl) benzoic acid int-40:

2.56.1 1H NMR of **int-40**

abai-44
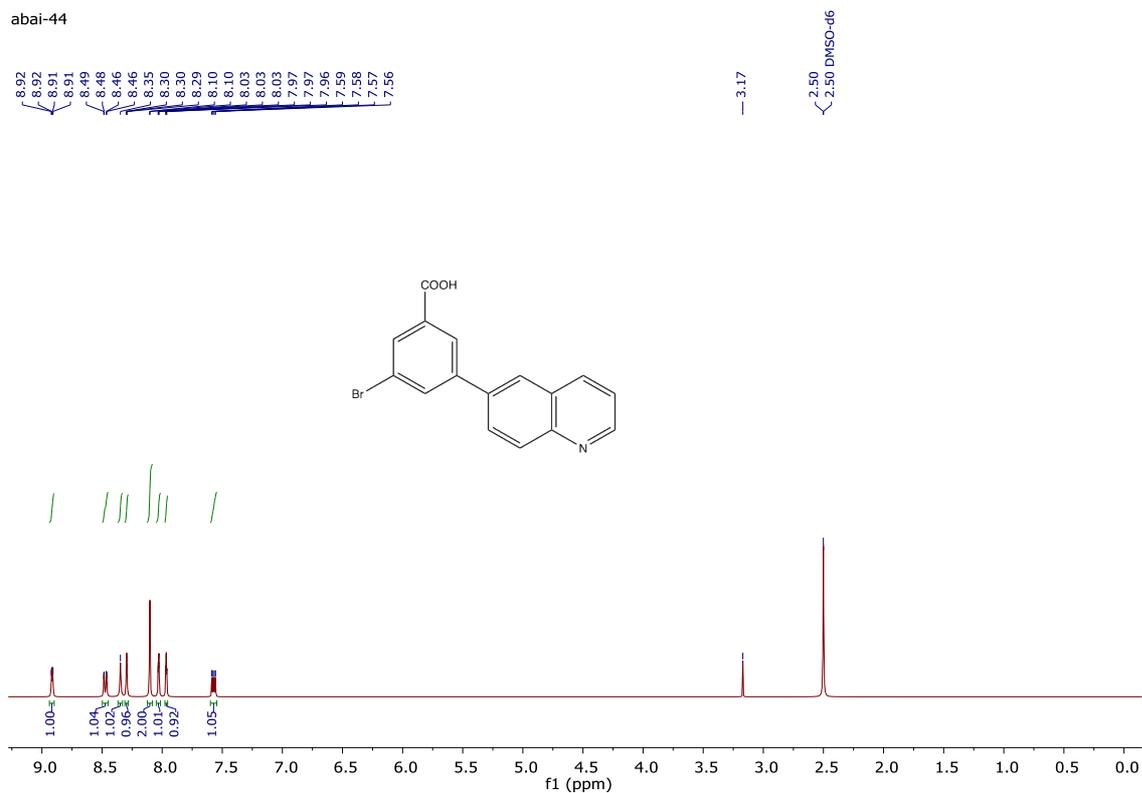
2.56.2 13C NMR of **int-40**

ABAI-44
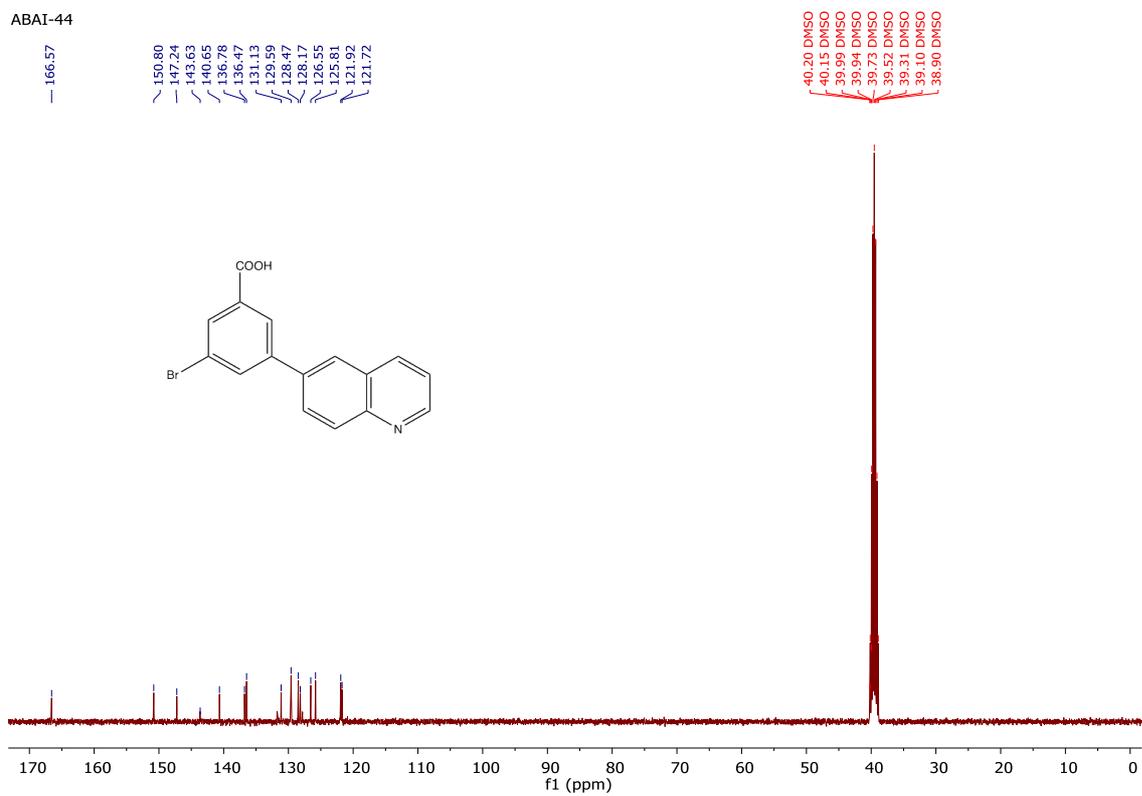
2.57 3-(3'-Acetamidophenyl)-5-quinolin-6-ylbenzoic acid **40**:

2.57.1 1H NMR of **40**

2.57.2 13C NMR of **40**
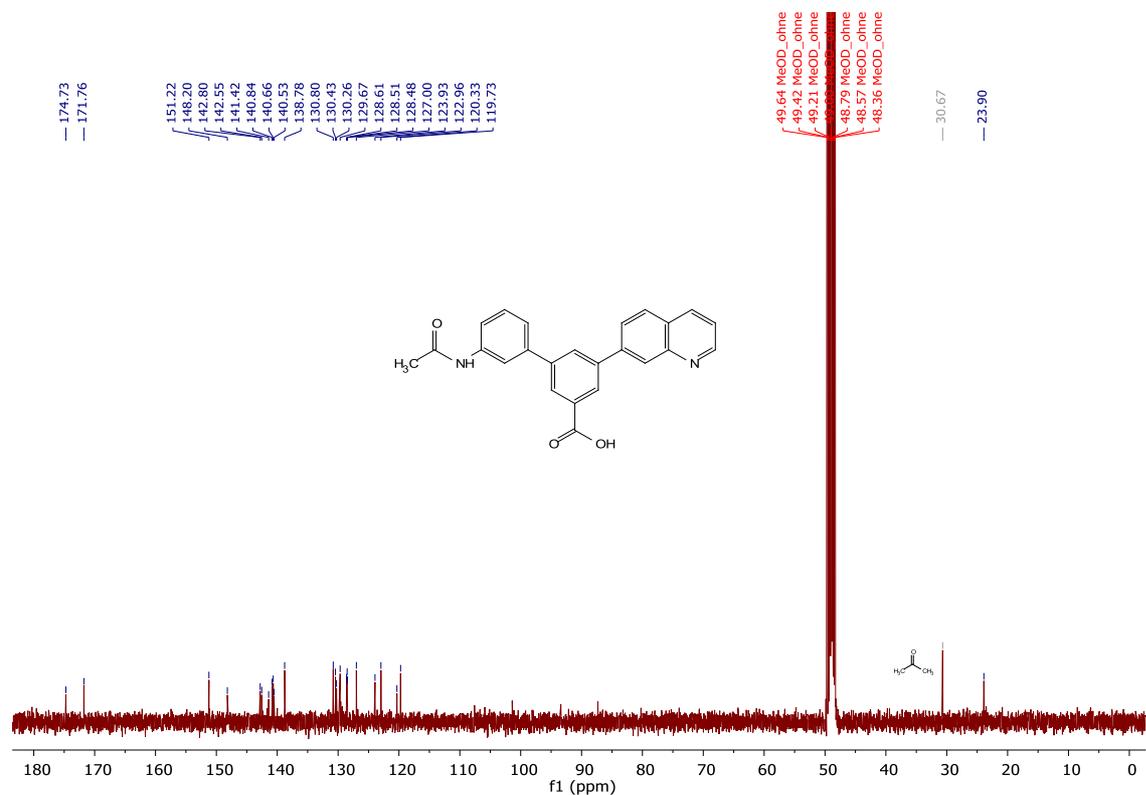
Paper II

Carbonylative Suzuki–Miyaura couplings of sterically hindered aryl halides: synthesis of 2-aroylbenzoate derivatives

Aya Ismael, Troels Skrydstrup, and Annette Bayer.

PAPER

Carbonylative Suzuki–Miyaura couplings of sterically hindered aryl halides: synthesis of 2-aroylbenzoate derivatives†

Aya Ismael, [a] Troels Skrydstrup [b] and Annette Bayer *[a]

We have developed a carbonylative approach to the synthesis of diversely substituted 2-aroylbenzoate esters featuring a new protocol for the carbonylative coupling of aryl bromides with boronic acids and a new strategy to favour carbonylative over non-carbonylative reactions. Two different synthetic pathways – (i) the alkoxycarbonylation of 2-bromo benzophenones and (ii) the carbonylative Suzuki–Miyaura coupling of 2-bromobenzoate esters – were evaluated. The latter approach provided a broader substrate tolerance, and thus was the preferred pathway. We observed that 2-substituted aryl bromides were challenging substrates for carbonylative chemistry favouring the non-carbonylative pathway. However, we found that carbonylative Suzuki–Miyaura couplings can be improved by slow addition of the boronic acid, suppressing the unwanted direct Suzuki coupling and, thus increasing the yield of the carbonylative reaction.

Introduction

Through our program on fragment-based design of metallo-β-lactamase inhibitors, we became interested in the development of efficient strategies for the synthesis of functionalized 2-aroylbenzoic acids **1** (Scheme 1).[1] Among other, 2-aroylbenzoic acids have gained keen interest as synthetic intermediates for accessing bioactive compounds,[2–7] as subunits of natural products and pharmaceuticals *e.g.* (−)-balanol[8] and pitfenone, and as fragment-sized inhibitors of the human aldo-keto reductase AKR1C3 [9] and the hepatitis C virus NS3 protease.[10] Most commonly, 2-aroylbenzoic acids are prepared from phthalic anhydride by treatment with organometallic reagents[2,7,11] or by a Friedel–Crafts acylation[3,5,12] with aromatic nucleophiles. However, these methods are incompatible with many functional groups, requiring excess Lewis acid and harsh reaction conditions, and often provide poor regioselective control. On the other hand, the biaryl ketone subscaffold of 2-aroylbenzoic acids has been synthesized by transition metal-catalyzed carbonylative cross-couplings of organometallic reagents and aryl electrophiles,[13–15] or the non-decar-bonylative coupling of acyl electrophiles, *e.g.* carboxylic acids,[16–18] esters[19–21] or amides.[19,22] Despite the advances in the synthesis of biaryl ketones, only few methods have been demonstrated to be applicable for the formation of 2-aroyl benzoic acid derivatives. Such methods comprise of the Pd-catalyzed *ortho*-C–H activation of benzoic acids followed by decarboxylative coupling with α-oxocarboxylic acids,[23] Pd-catalyzed *ortho*-C–H activation of aryl amides followed by coupling with aryl aldehydes,[24] and the Pd-catalyzed coupling of 2-iodo-benzoates with aldehydes.[25] However, the available protocols have limited regiocontrol and/or substrate scope especially with regard to electron-deficient aryl groups.

In this study, we investigated two alternative routes towards 2-aroylbenzoate esters **2** featuring carbonylative couplings using safe and easy to handle *ex situ* generated CO as a key step (Scheme 1). In the first approach (route A), we examined the Pd-catalyzed alkoxycarbonylation of 2-bromo functionalized biaryl ketones, which in turn could be prepared by carbonylative Suzuki–Miyaura couplings of 2-bromoiodobenzene. In the second approach (route B), we investigated the carbonylative Suzuki–Miyaura coupling of 2-bromo substituted benzoate esters. A new protocol for the carbonylative coupling of aryl bromides and simple boronic acids preventing the use of iodide salts as additives or high-pressure CO gas was developed. Moreover, we demonstrate that slow addition of the nucleophilic coupling reagent is an uninvestigated strategy to enhance formation of the carbonylative product over the non-carbonylative side-product. The latter discovery was essential for sterically-demanding *ortho*-substituted aryl bromides in order to provide useful yields of the carbonylative coupling products.

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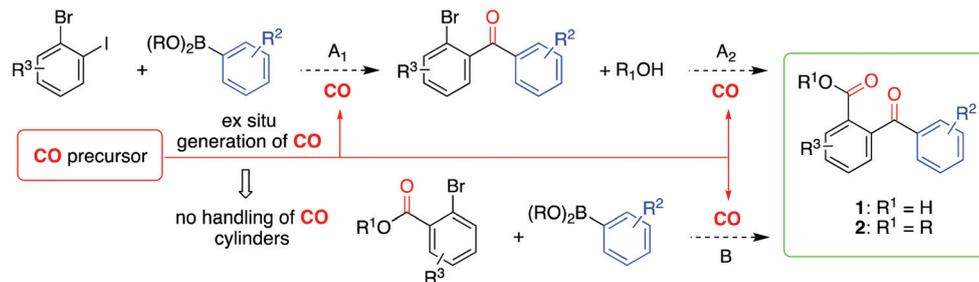
Scheme 1 Routes towards 2-aroylbenzoic acid derivatives explored in this work.

Results and discussion

Carbonylative Suzuki–Miyaura of 2-bromoiodobenzene (step A₁)

Initially, we focused on the Pd-catalyzed carbonylative Suzuki–Miyaura coupling of 2-bromoiodobenzene **3** with aryl boronic acids **4** in order to prepare substituted 2-bromobenzophenone derivatives **5** as starting materials for further alkoxycarbonylation reactions (Scheme 2). A range of catalysts derived from a variety of Pd sources including Pd(OAc)$_2$,[26] Pd(dba)$_2$,[27] Pd(PPh$_3$)$_2$Cl$_2$,[28] PdCl$_2$, PEPPSI-IPr[29] were evaluated for the carbonylative coupling of the aryl iodide in presence of a bromide using 2-bromoiodobenzene **3** and 4-methoxyphenyl boronic acid **4a** (Table ESI-1†). The yields varied from 10% to 65% of the furnished benzophenone (Table ESI-1,† entries 1–5), and

competitive formation of the direct coupling product (biphenyl) was a major limitation. The most promising catalytic system identified from the screening used PdCl$_2$ as catalyst precursor, K$_2$CO$_3$ as base, and anisole as solvent (Table ESI-1,† entry 5).
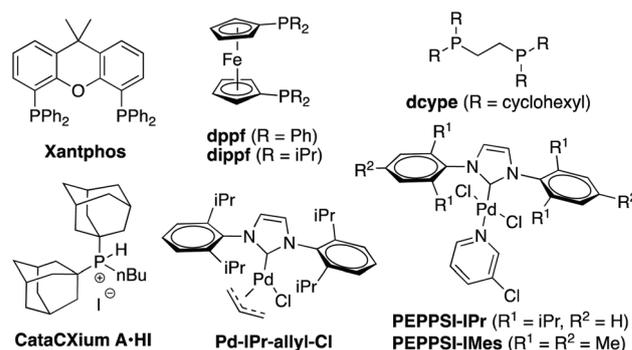
In addition, several methods for the *ex situ* generation of carbon monoxide from formic acid,[30] oxalyl chloride,[31] COgen,[32] and electrochemical reduction of CO$_2$ to CO[33] were screened to prevent the risk of handling toxic carbon monoxide from a cylinder (Table ESI-2†). The most promising and convenient CO source turned out to be 9-methylfluorene-9-carbonyl chloride (COgen) (Table ESI-2,† entry 3). Oxalyl chloride as CO source provided comparable results if the CO gas was generated outside the reaction chamber making the handling more inconvenient (Table ESI-2,† entry 5), while both formic acid and electrochemical reduction of CO$_2$ resulted in substantially reduced yields (Table ESI-2,† entries 1 and 7).

The catalytic system employing PdCl$_2$ as precatalyst was further optimized with regard to different reaction times, temperatures, and slow addition of the boronic acid. Yields up to 65% of the carbonylated product were obtained with PdCl$_2$ (3 mol%) at 80 °C for 20 h (Table ESI-1,† entry 5). Reduction of the catalyst loading to 1 mol% led to a slight decrease in yield to 60% (Table ESI-1,† entry 6) and 1 mol% of precatalyst was used in the following reactions. A lower reaction temperature led to incomplete conversion and lower yields (Table ESI-1,† entries 7 and 8). Addition of KI to favour carbonylative over direct coupling[28] did not improve the yield (Table ESI-1,† entry 11). However, when the aryl boronic acid was added slowly over 2 h, direct coupling was suppressed and the yield

Scheme 2 Carbonylative Suzuki–Miyaura coupling of 2-bromoiodobenzene with boronic acids. Reaction conditions: Chamber A: **3** (0.18 mmol), PdCl$_2$ (1 mol%) and K$_2$CO$_3$ (0.55 mmol) in anisole (3 ml). Chamber B: COgen (0.45 mmol), Pd(dba)$_2$ (5 mol%) and TTBP·HBF$_4$ (5 mol%) in anisole (3 ml). DIPEA (3 equiv.) was added to chamber B to start CO formation, before **4** (1.2 equiv.) in anisole (3 ml) was added slowly to chamber A (general procedure A, ESI†).[a] Yield obtained when **4** (1.2 equiv.) was added to chamber A before CO release (general procedure B, ESI†).

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improved up to 80% (Table ESI-1,† entry 13). Similarly, the yield of the carbonylated product was improved from 30% to 60% by slow addition of the aryl boronic acid for reactions with PEPPSI-IPr as the precatalyst (Table ESI-1,† entries 4 and 15).

Then, we explored the scope of the Pd-catalyzed reaction using PdCl$_2$ with respect to different aryl and heteroaromatic boronic acids 4 (Scheme 2). In all cases, slow addition of the aryl boronic acid increased the yield by 20–35 percentage points. Both electron-rich and electron-deficient aryl boronic acids (4a–c, e, f, j, l, m) gave moderate to high yields (60–80%) of the products. However, some electron-deficient boronic acids 4g, i and k provided lower yields in the range of 30–40%. ortho-Substituents on the boronic acid (4c, h and m) and some electron-rich heterocycles (4e and f) were well tolerated to the reaction conditions. However, hydroxy and N-acyl substituted aryl boronic acids and 2-furanyl boronic acid only provided products from the direct coupling instead of carbonylative coupling.

Hydroxy- or alkoxycarbonylation of 2-bromo-substituted biaryl ketones (step A$_2$)

With a set of 2-bromobenzophenone derivatives 5a–m in hand, we investigated the Pd-catalyzed hydroxy- and alkoxycarbonylation to transform the aryl bromide into the carboxylic acid or ester, respectively.[34] Previous reports on Pd-catalyzed hydroxycarbonylation[30,34–36] or alkoxycarbonylation[26,34,37,38] have had little focus on ortho-substituted aryl bromides. Unfortunately, all attempts to transform 2-bromo-4′-methoxy-benzophenone 5a directly to 2-(4-methoxybenzoyl)benzoic acid via a hydroxycarboxylation using MePh$_2$SiCO$_2$H[35] were unsuccessful (Table ESI-3†).

Next, we turned our attention to the alkoxycarbonylation of 2-bromobenzophenones 5 (Scheme 3).[37] Using 5a as the test substrate, a range of precatalysts and ligands (Pd(OAc)$_2$, PdCl$_2$ or Pd(dba)$_2$ with Xantphos, dippf or PPh$_3$, Pd(PPh$_3$)$_2$Cl$_2$/IMes,[39] dppf(PdCl$_2$), PEPPSI-IPr or PEPPSIIMes), nucleophiles (MeOH, iPrOH, n-BuOH, t-BuONa, EtONa), bases and solvents

were screened (Table ESI-4†). Only few systems were able to provide the corresponding alkyl 2-(4-methoxybenzoyl)benzoate 2. Comparison of the catalyst performance for 2-bromo-substituted 5a and the corresponding 4-bromo-substituted analog showed that the yields were highly influenced by the substitution pattern. For example, for catalyst systems based on dppf (PdCl$_2$) or Pd(OAc)$_2$/Xantphos, the yields dropped from >95% for the 4-bromo-substituted analog to an 11% yield for 2-bromo-substituted 5a under otherwise identical conditions (Table ESI-5†). The best results for the latter were obtained with PdCl$_2$ and Xantphos as catalytic system, n-butanol as the nucleophile, K$_2$CO$_3$ as the base and anisole as solvent furnishing the ester 2a in acceptable yield (65%) (Table ESI-4,† entry 12). We applied these conditions to our library of 2-bromobenzophenone derivatives 5a–m (Scheme 2). While the substrates 5a, b, k and m gave alkoxycarbonylation products 2a–d in acceptable yields (65%, 60%, 63% and 55%, respectively), compounds 5c–h and 5l gave low yields to no product. Over all, we conclude that while the carbonylative Suzuki–Miyaura coupling was tolerant to a variety of aryl boronic acids, the alkoxycarbonylation of 2-bromo-biaryl ketones displayed a high dependence on the substrate structure rendering the approach unsuitable for the synthesis of a larger library of compounds.

Carbonylative Suzuki–Miyaura coupling with 2-bromobenzoates (route B$_1$)

Due to the limited substrate scope of the alkoxycarbonylation of 2-bromobenzophenone derivatives, we decided to study the carbonylative Suzuki–Miyaura coupling of methyl 2-bromobenzoates 6 (Table 1). Few examples of carbonylative couplings with aryl bromides[28,40–43] have been reported and those rely on the use of iodide salts as additives (3 equiv.),[28] high pressure of CO gas (5 bar)[41–43] or the use of less accessible boronate esters[40] like DABO boronates[44] or aryl trihydroxyborates[45] instead of boronic acids. Only two examples of successful

Table 1 Boronate derivatives in carbonylative Suzuki–Miyaura couplings

Boronic acid derivatives	Catalyst system	Yield
7a	Pd(acac)$_2$/cataXCium A·HI	67%
8	Pd(acac)$_2$/cataXCium A·HI	65%
4a	Pd(acac)$_2$/CataXCium A·HI	30%
	PEPPSI-IPr	63%
	PEPPSI-IPr/slow addition of 4a	80%
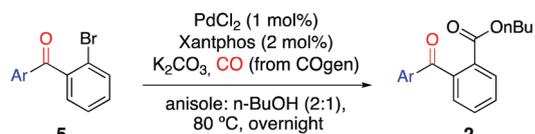
Scheme 3 Palladium-catalyzed alkoxycarbonylation of 2-bromo biaryl ketones. Reaction conditions: Chamber A: 5 (1.0 equiv., 0.18 mmol), PdCl$_2$ (2 mol%), Xantphos (3 mol%) K$_2$CO$_3$ (3 equiv., 0.55 mmol) in anisole : n-BuOH (2 : 1, 3 ml). Chamber B: COgen (107 mg, 2.5 equiv., 0.45 mmol), Pd(dba)$_2$ (12 mg, 5 mol%) and TTBP·HBF$_4$ (6.3 mg, 5 mol%) in anisole (3 ml). DIPEA (240 mg, 3 equiv.) was added to chamber B to start CO release.

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couplings with *ortho*-substituted substrates were reported.[41] While carbonylative couplings of sterically hindered, electron-rich aryl iodides have been achieved with PEPPSI-IPr as the precatalyst,[29] electron-poor aryl bromides like **6** have been shown to be challenging substrates favouring non-carbonylative direct couplings providing biaryl derivatives.[28,41] In this perspective, general methods for carbonylative Suzuki–Miyaura couplings of aryl bromides with boronic acids are still needed.

With methyl 2-bromobenzoate **6a** as the test substrate, the protocol reported by Skrydstrup and Molander[40] using Pd(acac)$_2$/CataCXium A·HI (5/10 mol%) afforded acceptable yields of **2aa** with 65–67% when the DABO boronate[44] **7a** or aryl trihydroxyborate[45] **8** were used as the nucleophilic coupling reagent (Table 1). However, the yield decreased to 30% with the boronic acid **4a**. Attempts to increase the yield by slow addition of the DABO boronate **6** or the trihydroxyborate **7** were not successful due to low solubility of these boronic acid derivatives in the reaction medium (toluene/water). The use of other solvent systems dramatically reduced the yields (Table ESI-6,† entries 4–8).

Therefore, we proceeded to identify reaction conditions for the coupling of 2-bromobenzoate **6a** with aryl boronic acids **4a** using COgen as the carbon monoxide source. A range of experimental conditions including different palladium sources and ligands (Pd(acac)$_2$ or Pd(OAc)$_2$/CataCXium A or A·HI,[40]

Pd(OAc)$_2$ or PdCl$_2$/Xantphos, Xantphos-G2, PEPPSI-IPr, [Pd (IPr)(allyl)Cl], Pd(PPh$_3$)$_2$Cl$_2$ [28,43] and Ni(COD)/dcype) and solvents were screened (Table ESI-6,† entries 9–20). In most of the systems, the undesired non-carbonylative coupling was the dominant reaction pathway (Table ESI-6,† entries 9–15). Only the Pd(IPr)-based catalytic systems were able to accomplish the carbonylative Suzuki–Miyaura coupling (Table ESI-6,† entries 16–19). The best system using PEPPSI-IPr (3 mol%) as catalyst precursor, Cs$_2$CO$_3$ as base in chlorobenzene or anisole as solvent provided the product **2aa** in 63% yield (Table 1 and Table ESI-6,† entry 16). The yield could be further increased to 80% by slow addition of the boronic acid (Table 1 and Table ESI-6,† entry 17).

A range of aryl boronic acids **4** were tested to examine the scope of the reaction as depicted in Scheme 4. Most of the electron rich boronic acids (**4a, c** and **d**) provided good yields (**2aa**: 80%; **2ac**: 75%; **2ad**: 76%), while electron-deficient boronic acids (**4g, i, j, k** and **l**) generally led to lower yields (**2ag**: 47%; **2ai**: 32%; **2aj**: 40%; **2ak**: 37%; **2al**: 58%). Yields obtained with slow addition of the aryl boronic acid were consistently higher (**2aa**: 80%; **2ac**: 75%; **2ai**: 32%; **2aj**: 40%; **2al**:

Scheme 4 Suzuki–Miyaura coupling of methyl 2-bromobenzoate **6a** with boronic acids **4**. Reaction conditions: Chamber A: **6a** (1.0 equiv., 0.47 mmol), PEPPSI-IPr (3 mol%) and Cs$_2$CO$_3$ (3 equiv., 1.4 mmol) in anisole (3 ml). Chamber B: COgen (282 mg, 2.5 equiv., 1.2 mmol), Pd (dba)$_2$ (30 mg, 5 mol%) and TTBP·HBF$_4$ (10 mg, 5 mol%) in anisole (3 ml). DIPEA (450 mg, 3 equiv.) was added to chamber B, before **4** (1.5 equiv.) was added slowly to chamber A (general procedure C, ESI†).[a] Yield obtained when **4** (1.5 equiv.) was added to chamber A before CO release (general procedure D, ESI†). [b] Yield obtained by reaction with DABO boronate **7** (1.5 equiv.) using Pd(acac)$_2$/2 CataCXium A·HI (5 mol%) as catalyst (general procedure E, ESI†).

Scheme 5 Substrate scope of carbonylative Suzuki–Miyaura coupling of methyl 2-bromobenzoate derivatives **6** with boronic acids **4**. Reaction conditions: Chamber A: **6** (1.0 equiv., 0.47 mmol), PEPPSI-IPr (3 mol%) and Cs$_2$CO$_3$ (3 equiv., 1.4 mmol) in anisole (3 ml). Chamber B: COgen (282 mg, 2.5 equiv., 1.2 mmol), Pd(dba)$_2$ (30 mg, 5 mol%) and TTBP·HBF$_4$ (10 mg, 5 mol%) in anisole (3 ml). DIPEA (450 mg, 3 equiv.) was added to chamber B, before **4** (1.5 equiv.) was added slowly to chamber A (general procedure C, ESI†).

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58%; **2am:** 65%), when compared with yields obtained by instantaneous addition (**2aa:** 63%; **2ac:** 26%; **2ai:** 16%; **2aj:** 24%; **2al:** 43%; **2am:** 42%). Slow addition of the boronic acid under reaction conditions seems to favour the CO insertion step by slowing down the faster transmetallation[28,41] due to limited access to the organometallic nucleophile.

Aryl boronic acids containing acidic protons and the heteroaromatic boronic acid **4n** only underwent direct coupling instead of carbonylative coupling using PEPPSI-IPr. Couplings with heteroaromatic organometallic reagents could be achieved using the corresponding DABO boronates providing **2an** and **2ao** with Pd(acac)₂/CataCXium A·HI as the catalytic system.

We further investigated the scope of the reaction with regard to a range of substituted methyl 2-bromobenzoates **6b–i** (Scheme 5). Aryl bromide **6** with both electron-withdrawing **6b–e** and donating substituents **6f–i** gave acceptable yields (50–72%). Surprisingly, also the coupling of *ortho* disubstituted **6g** provided good yields (**2ga:** 68%). The lowest yield (**2bh:** 40%) was obtained for the coupling of the electron-deficient **6b** with the electron-deficient boronic acid **4p**.

Conclusions

In summary, two routes for accessing 2-aroylbenzoate esters have been evaluated. In the first strategy, the key step was the alkoxycarbonylation of 2-bromo-diarylketones, which unfortunately appeared sensitive to the substitution pattern of the aryl bromide. The second strategy employed a carbonylative Suzuki–Miyaura coupling of 2-bromobenzoate esters, which was more robust with regard to the structure of aryl bromide and the aryl boronic acid. The latter approach was exploited to prepare a range of diversely substituted 2-aroylbenzoate esters.

Moreover, we found that slow addition of the boronic acid is a strategy to favour carbonylative over non-carbonylative processes in Suzuki–Miyaura couplings – a finding that should be of general value.

Conflicts of interest

The authors declare the following competing financial interest (s): T.S. is co-owner of SyTracks A/S, which commercializes the two-chamber system (COware) and COgen.

Acknowledgements

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Supporting information for

Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides: Synthesis of 2-aroylbenzoate derivatives.

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Table of content:

1   Experimental procedures

1.1   General

Unless otherwise noted, purchased chemicals were used as received without further purification. Solvents were dried according to standard procedures on molecular sieves 4A.[1] MePh$_2$SiCO$_2$H (silaCOgen) was prepared as reported previously.[2] DABO boronates **7a** and sodium trihydroxy(4-methoxyphenyl)borate **8a** were prepared according to the previously reported protocol.[3] Flash chromatography was carried out on silica gel 60 (230−400 mesh). NMR spectra were obtained on a 400 MHz NMR spectrometer. The chemical shifts are reported in ppm relative to the solvent residual peak. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dt = double triplet, m = multiplet), coupling constant (J, Hz) and integration. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak (CDCl$_3$: δH 7.26 and δC 77.16; Methanol-d$_4$: δH 3.31 and δC 49.00; deuterium oxide: δH 4.79; DMSO-d$_6$ δH 2.51 and δC 39.52). Positive ion electrospray ionization mass spectrometry was conducted on a Thermo Electron LTQ Orbitrap XL spectrometer. The reactions were performed in the previously reported two-chamber system[2] under an argon atmosphere, and a glovebox was employed for weighing out the reagents.

1.2   General procedures

General procedure A: Carbonylative Suzuki Miyaura coupling of 2-bromoiodobenzene 3 with slow addition.

Chamber A: 2-Bromoiodobenzene **3** (50 mg, 1.0 equiv, 0.18 mmol), PdCl$_2$ (0.3 mg, 1 mol%), K$_2$CO$_3$ (70 mg, 3 equiv, 0.55 mmol) were dissolved in anisole (1 ml). Chamber B: COgen (107 mg, 2.5 equiv, 0.45 mmol), Pd(dba)$_2$ (12 mg, 5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (6.3 mg, 5 mol%) and DIPEA (240 mg, 3 equiv) were dissolved in anisole (3 ml). Chamber B was stirred and heated to 80 °C to release CO until gas evolution stops. After release of the CO, both chambers were stirred and heated to 80 °C and a solution of aryl boronic acid **4** (1.2 equiv) in anisole (2 ml) was added slowly (1-2 h) to the reaction mixture in chamber A. The two-chamber system was then placed in an oil bath and stirred at 80 °C for 20 hours. The reaction mixture was filtered through celite and concentrated on a rotavapor. The crude was purified by column chromatography with pentane: EtOAc (8:2) as eluent.

General procedure B: Carbonylative Suzuki Miuara coupling of 2-bromoiodobenzene 3 with instantaneous addition.

Chamber A: 2-Bromoiodobenzene **3** (50 mg, 1.0 equiv, 0.18 mmol), PdCl$_2$ (0.3 mg, 1 mol%), K$_2$CO$_3$ (70 mg, 3 equiv, 0.55 mmol) and aryl boronic acid **4** (1.2 equiv) were dissolved in anisole (3 ml). Chamber B: COgen (107 mg, 2.5 equiv, 0.45 mmol), Pd(dba)$_2$ (12 mg, 5 mol%), TTBP•HBF$_4$ (6.3 mg, 5 mol%) were added together and dissolved in anisole (3 ml) before DIPEA (240 mg, 3 equiv) was added. Both chambers were stirred and heated at 80°C under tightly closed system for 20 hours. The reaction mixture was filtered through celite and concentrated on a rotavapor. The crude was purified by column chromatography with pentane: EtOAc (8:2) as eluent.

General procedure C: Carbonylative Suzuki-Miyaura coupling of methyl 2-bromobenzoate 6 with slow addition.

Chamber A: Methyl 2-bromobenzoate **6** (100 mg, 1.0 equiv, 0.47 mmol), PEPPSI-IPr (9.4 mg, 3 mol%), Cs$_2$CO$_3$ (450 mg, 3 equiv, 1.4 mmol) were dissolved in anisole (1 ml). Chamber B: COgen (282 mg, 2.5 equiv, 1.2 mmol), Pd(dba)$_2$ (30 mg, 5 mol%), TTBP•HBF$_4$ (10 mg, 5 mol%) and DIPEA (240 mg, 3 equiv) were dissolved in anisole (3 ml). The reaction mixture in Chamber B was stirred and heated to 80

°C to release CO until gas evolution stops. After release of the CO, both chambers were stirred and heated to 110 °C and a solution of aryl boronic acid **4** (1.5 equiv) in anisole (2 ml) was added slowly (1-2 h) to the reaction mixture in chamber A. The two-chamber system was then placed in an oil bath and stirred at 110 °C for 20 hours. The reaction mixture was filtered through celite and concentrated on a rotavapor. The crude was purified by column chromatography with pentane: EtOAc (7:3) as eluent.

General procedure D: Carbonylative Suzuki-Miyaura coupling of methyl 2-bromobenzoate 6.

Chamber A: Methyl 2-bromobenzoate **6** (1.0 equiv, 0.47 mmol), aryl boronic acid **4** (1.5 equiv), PEPPSI-IPr (3 mol%), Cs_2CO_3 (3 equiv, 1.4 mmol) were dissolved in anisole (3 ml). Chamber B: COgen (282 mg, 2.5 equiv, 1.2 mmol), Pd(dba)$_2$ (30 mg, 5 mol%), TTBP•HBF$_4$ (10 mg, 5 mol%) were dissolved in anisole (3 ml) before DIPEA (450 mg, 3 equiv) was added. The two-chamber system was then placed in an oil bath and stirred at 110 °C for 20 hours. The reaction mixture was filtered through celite and concentrated on a rotavapor. The crude was purified by column chromatography with pentane:EtOAc (7:3) as eluent.

General procedure E: Carbonylative Suzuki Miuara coupling of methyl 2-bromobenzoate with DABO boronates or sodium borate salt.

Chamber A: Methyl 2-bromobenzoate **6** (50 mg, 1.0 equiv, 0.23 mmol), Pd(acac)$_2$ (3.5 mg, 5 mol%), CataCXium A•HI (11 mg, 10 mol%), and the DABO boronate **7** or sodium borate salt **8** (1.5 equiv) were dissolved in toluene: H$_2$O (1:1; 3 ml). Chamber B: COgen (140 mg, 2.5 equiv, 0.58 mmol), Pd(dba)$_2$ (26 mg, 5 mol%), TTBP•HBF$_4$ (13 mg, 5 mol%) were dissolved in anisole (3 ml) before DIPEA (241 mg, 3 equiv) was added. The two-chamber system was then placed in an oil bath and stirred at 110 °C for 20 hours. The reaction mixture was filtered through celite and concentrated on a rotavapor. The crude was purified by column chromatography with pentane:EtOAc (7:3) as eluent.

General procedure F: Alkoxy carbonylation of 2-bromobenzophenone derivatives 5 with *n*-BuOH.

Chamber A: 2-bromobenzophenone **5** (1 equiv), PdCl$_2$ (2 mol%), Xantphos (4 mol%), K$_2$CO$_3$ (3 equiv) were dissolved in anisole: n-BuOH (1:1; 3 ml). Chamber B: COgen (2.5 equiv), Pd(dba)$_2$ (5 mol%), TTBP•HBF$_4$ (5 mg, 5 mol%) were dissolved in anisole (3 ml) before DIPEA (3 equiv) was added. The two-chamber system was then placed in an oil bath and stirred under heating for 20 hours. The reaction mixture was filtered through celite and concentrated on a rotavapor. The crude was purified by column chromatography with pentane: EtOAc (7:3).

1.3   Preparation and characterization of 2-bromobenzophenone derivatives 5.

2-Bromophenyl 4-methoxyphenyl methanone (5a). 2-Bromoiodobenzene **3** (50 mg) was reacted with 4-methoxyphenyl boronic acid **4a** (35 mg, 0.21 mmol, 1.2 equiv). Reactions were performed both by the general procedure A or B to provide **5a** (procedure A: 41 mg, 80%; procedure B: 31 mg, 60%) as a colourless solid. Mp 91-93 °C. NMR: δH (400 MHz; CDCl$_3$) 7.79 (2H, d, *J* 8.8), 7.64 (1H, d, *J* 7.9), 7.40 (1H, d, *J* 7.9), 7.33 (2H, t, *J* 7.5), 6.94 (2H, d, *J* 8.8), 3.88 (3H, s). δC (101 MHz, CDCl$_3$) 194.9, 164.6, 141.6, 133.5, 133.1, 131.3, 129.6, 129.2, 127.6, 119.9, 114.4, 56.0. HRMS (ESI): Calcd. for C$_{14}$H$_{11}$O$_2$^{79}BrNa [M+H]$^+$ 312.9840; found 312.9827. The spectroscopic data is corresponding to the previously reported in literature.[4]

2-Bromophenyl 3-methoxyphenyl methanone (5b). 2-Bromoiodobenzene **3** (50 mg) was reacted with 3-methoxyphenyl boronic acid **4b** (35 mg, 0.21 mmol, 1.2 equiv). Reactions were performed both by the general procedure A or B to provide **5b** (procedure A: 35 mg, 65%; procedure B: 18 mg, 35%) as a white solid. Mp 85-87 °C. NMR: δH (400 MHz, CDCl$_3$) 7.56 (1H, d, *J* 7.7), 7.36 (1H, s), 7.32 (1H, d, *J* 7.7), 7.26 (3H, t, *J* 7.6), 7.21-7.15 (1H, m), 7.08-7.05 (1H, m), 3.77 (3H, s). δC (101 MHz, CDCl$_3$) 195.8,

160.0, 140.8, 137.6, 133.3, 131.3, 129.7, 129.0, 127.3, 123.6, 120.6, 119.6, 113.8, 55.6. HRMS (ESI): Calcd. for $C_{14}H_{11}O_2{}^{79}BrNa$ [M+H]$^+$ 312.9840; found 312.9827. The spectroscopic data is corresponding to the previously reported in literature.[5]

2-Bromophenyl 2-methoxyphenyl methanone (5c). 2-Bromoiodobenzene **3** (50 mg) was reacted with (2-methoxyphenyl) boronic acid (35 mg, 0.21 mmol, 1.2 equiv) according to the general procedure A to provide **5c** (31 mg, 60%) as a white solid. Mp 66.3-68 °C. NMR: δH (400 MHz, CDCl₃) 7.56-7.52 (1H, m), 7.48-7.44 (1H, m), 7.39 (1H, t, *J* 7.6), 7.27-7.23 (2H, m), 7.19-7.12 (1H, m), 6.91 (1H, t, *J* 7.6), 6.82-6.80 (1H, m), 3.53 (s, 3H). δC (101 MHz, CDCl₃) 195.3, 159.5, 142.8, 134.5, 133.1, 131.9, 131.0, 129.4, 127.3, 127.1, 120.8, 119.6, 112.1, 55.9. HRMS (ESI): Calcd. for $C_{14}H_{11}O_2{}^{79}BrNa$ [M+H]$^+$ 312.9840; found 312.9827. The spectroscopic data is corresponding to the previously reported in literature.[5]

*2-Bromophenyl 4-(methylthio)*phenyl methanone (**5d**). 2-Bromoiodobenzene **3** (50 mg) was reacted with (4-(methylthio) phenyl) boronic acid (45 mg, 0.27mmol, 1.5 equiv) according to the general procedure A to provide **5d** (30 mg, 55%) as a white solid. NMR: δH (400 MHz, CDCl₃) 7.70 (2H, d, *J* 8.4), 7.63 (1H, d, *J* 7.6), 7.40 (1H, d, *J* 7.6), 7.37-7.27 (2H, m), 7.27-7.20 (2H, m), 2.51 (3H, s). δC (101 MHz, CDCl₃) 195.0, 147.3, 140.9, 140.5, 133.3, 132.5, 131.2, 130.7, 129.0, 128.2, 127.4, 125.0, 119.6, 14.8. HRMS (ESI): Calcd. for $C_{14}H_{11}{}^{81}BrOS$ [M+H]+ 308.9727; found 308.9756

tert-Butyl 2-(2-bromobenzoyl)-1H-pyrrole-1-carboxylate (5e). 2-Bromoiodobenzene **3** (50 mg) was reacted with (1-(tert-butoxycarbonyl)-1H-pyrrol-2-yl)boronic acid **4e** (45 mg, 0.21 mmol, 1.2 equiv) according to the general procedure A to provide **5e** (43 mg, 70%) as a yellow oil. NMR: δH (400 MHz, CDCl₃) 7.63 (1H, d, *J* 7.7), 7.48-7.46 (2H, m), 7.38 (2H, t, *J* 7.5), 7.33 (2H, t, *J* 7.5), 6.53-6.52 (1H, m), 6.18 (1H, t, *J* 3.3), 1.56 (9H, s). δC (101 MHz, CDCl₃) 184.6, 149.2, 140.9, 134.0, 133.7, 132.1, 130.6, 129.6, 127.5, 125.3, 121.0, 110.9, 85.6, 77.8, 77.7, 77.5, 77.2, 28.0. HRMS (ESI): Calcd. for $C_{16}H_{16}{}^{81}BrNNaO_3$ [M+H]+ 374.0278; found 374.0177.

tert-Butyl 2-(2-bromobenzoyl)-1H-indole-1-carboxylate (5f). 2-Bromoiodobenzene **3** (50 mg) was reacted with (1-(tert-butoxycarbonyl)-1H-indol-2-yl)boronic acid **4f** (55 mg, 0.21 mmol, 1.5 equiv) according to the general procedure A to provide **5f** (53 mg, 76%) as a yellow oil. NMR: δH (400 MHz, CDCl₃) 8.14 (1H, d, *J* 9.2), 7.69-7.67 (1H, m), 7.58-7.56 (2H, m), 7.49-7.45 (1H, m), 7.44-7.36 (2H, m), 7.28 – 7.24 (1H, m), 6.84 (1H, s), 1.58 (9H, s). δC NMR (101 MHz, CDCl₃) 186.0, 149.5, 139.7, 139.2, 137.8, 134.0, 132.4, 131.0, 127.9, 127.4, 127.3, 123.5, 122.9, 121.1, 118.7, 115.0, 84.9, 27.9. HRMS (ESI): Calcd. for $C_{20}H_{18}{}^{79}BrNNaO_3$ [M+H]+ 422.0368; found 422.0353.

Methyl 3-(2-bromobenzoyl)benzoate (5g). 2-Bromoiodobenzene **3** (50 mg) was reacted with 3-(methoxycarbonyl)phenyl boronic acid **4g** (38 mg, 0.21 mmol, 1.2 equiv) according to the general procedure A to provide **5g** (22 mg, 40 %) as a colorless oil. NMR: δH (400 MHz, CDCl₃) 8.43 (1H, s), 8.27 (1H, d, *J* 7.8), 8.01 (1H, d, *J* 7.8), 7.67 (1H, d, *J* 7.8), 7.57(1H, t, *J* 7.8), 7.47-7.43 (1H, m), 7.41 – 7.36 (2H, m), 3.93 (3H, s). δC (101 MHz, CDCl₃) 195.2, 166.3, 140.2, 136.7, 134.5, 134.3, 133.5, 131.7, 131.3, 131.0, 129.3, 129.1, 127.6, 119.7, 52.7. HRMS (ESI): Calcd. for $C_{15}H_{11}O_3{}^{79}BrNa$ [M+H]+; 340.9789 found 340.9757.

Methyl 2-(2-bromobenzoyl)benzoate (5h). 2-Bromoiodobenzene **3** (50 mg) was reacted with 2-(methoxycarbonyl) phenyl boronic acid 4h (35 mg, 0.21 mmol, 1.2 equiv) according to the general procedure A to provide **5h** (33 mg, 58%) as a viscous colourless oil. NMR: δH (400 MHz, CDCl₃) 7.88-7.86 (1H, m), 7.70-7.68 (1H, m), 7.60-7.57 (2H, m), 7.50-7.48 (1H, m), 7.39-7.36 (1H, m), 7.33-7.31 (2H, m), 3.69 (3H, s). δC (101 MHz, CDCl₃) 195.49, 167.58, 140.09, 138.43, 134.68, 132.64, 131.78, 131.27, 131.15, 129.94, 129.57, 127.16, 121.55, 77.48, 77.16, 76.84, 52.72. HRMS (ESI): Calcd. for $C_{15}H_{11}O_3{}^{81}BrNa$ [M+H]+; 342.9769 found 342.9757. The spectroscopic data is corresponding to the previously reported in literature.[6]

4-(2-Bromobenzoyl)benzonitrile (5i). 2-Bromoiodobenzene **3** (50 mg) was reacted with (4-cyanophenyl) boronic acid **4i** (31 mg, 0.21 mmol, 1.2 equiv). Reactions were performed both by the general procedure A or B to provide **5i** (procedure A: 15 mg, 30%; procedure B: 0 mg, 0%) as a white solid. Mp 113-115

°C. NMR: δH (400 MHz, CDCl$_3$) 7.90 (2H, d, J 8.2), 7.77 (2H, d, J 8.2), 7.67 (1H, d, J 7.8), 87.49 – 7.39 (1H, m), 7.38-7.36 (1H, m). δC (101 MHz, CDCl$_3$) 194.6, 139.6, 139.4, 133.6, 132.6, 132.1, 130.5, 129.4, 127.7, 119.7, 118.0, 116.9. HRMS (ESI): Calcd. for C$_{14}$H$_8$ ^{79}BrNNaO [M+H]+ 307.9687; found 307.9672. The spectroscopic data is corresponding to the previously reported in literature.[7]

3-(2-Bromobenzoyl)benzonitrile (5j). 2-Bromoiodobenzene **3** (50 mg) was reacted with (3-cyanophenyl) boronic acid **4j** (31 mg, 0.21 mmol, 1.2 equiv). Reactions were performed following the general procedure A or B to provide **5j** (procedure A: 33 mg, 65%; procedure B: 15 mg, 30%) as a colorless oil. NMR: δH (400 MHz, CDCl$_3$) 8.06 (1H, d, J 8.2), 8.03 (1H, s), 7.87 (1H, d, J 7.7), 7.68 (1H, d, J 7.7), 7.62 (1H, t, J 7.8), 7.49-7.40 (2H, m), 7.37-7.35 (1H, m). δC (101 MHz, CDCl$_3$) 194.0, 139.4, 137.2, 136.6, 133.9, 133.8, 133.6, 132.1, 129.9, 129.3, 127.8, 119.6, 117.9, 113.4. HRMS (ESI): Calcd. for C$_{14}$H$_8$ ^{81}BrNNaO [M+H]+ 309.9666; found 309.9653.

2-Bromophenyl *4-fluorophenyl methanone (5k)*. 2-Bromoiodobenzene **3** (50 mg) was reacted with (4-fluorophenyl) boronic acid **4k** (30 mg, 0.13mmol, 1.2 equiv), according to the general procedure A to provide **5k** (15 mg, 30%) as a white solid. Mp 51-53 °C. NMR: δH (400 MHz, CDCl$_3$) 7.84 (2H, m), 7.65 (1H, d, J 7.8), 7.45-7.41 (1H, m), 7.40-7.30 (2H, m), 7.14 (2H, t, J 8.5). δC (101 MHz, CDCl$_3$) 194.5, 166.3 (d, J 256.5), 140.6, 133.4, 133.0 (d, J 10.1), 132.7 (d, J 2.9), 131.4, 129.0, 127.5, 119.6, 116.0 (d, J 22.2). HRMS (ESI): Calcd. for C$_{13}$H$_8$^{79} BrFNaO [M+H]$^+$ 300.9640; found 300.9630. The spectroscopic data is corresponding to the previously reported in literature.[8]

2-Bromophenyl 3-fluorophenyl methanone (5l). 2-Bromoiodobenzene **3** (50 mg) was reacted with 3-fluorophenyl boronic acid **4l** (30 mg, 0.13 mmol, 1.2 equiv), according to the general procedure A to provide **5l** (37 mg, 76%) as a white solid. NMR: δH (400 MHz, CDCl$_3$) 7.66 (1H, d, J 7.8), 7.54 (2H, t, J 9.7), 7.47-7.42 (2H, m), 7.40-7.34 (2H, m), 7.33-7.28 (1H, m). δC (101 MHz, CDCl$_3$) 194.7, 162.9 (d, J 249.5), 140.2, 138.4 (d, J 6.1), 133.5, 131.6, 130.5 (d, J 8.1), 129.1, 127.5, 126.3 (d, J 3.0), 120.9 (d, J 22.2), 119.6, 116.7 (d, J 22.2). HRMS (ESI): Calcd. for C$_{13}$H$_8$ ^{79}BrFNaO [M+H]$^+$ 300.9640; found 300.9630.

2-Bromophenyl 2-fluorophenyl methanone (5m). 2-Bromoiodobenzene **3** (50 mg) was reacted with 2-fluorophenyl boronic acid 4m (30 mg, 0.13 mmol, 1.2 equiv) according to the general procedure A to provide **5m** (39 mg, 80%) as a white solid. NMR: δH (400 MHz, CDCl$_3$) 7.61 (1H, t, J 7.5), 7.47 (1H, d, J 7.8), 7.44-7.38 (1H, m), 7.26-7.25 (2H, m), 7.23-7.17 (1H, m), 7.10 (1H, t, J 7.6), 6.97-6.92 (1H, m). δC (101 MHz, CDCl$_3$) 192.90, 161.8 (d, J 259.6), 141.7, 135.23 (d, J 8.1), 133.5, 131.8, 129.4, 127.5, 125.9 (d, J 10.1), 124.5 (d, J 3.0), 119.5, 116.8 (d, J 22.2). HRMS (ESI): Calcd. for C$_{13}$H$_8$ ^{81}BrFNaO [M+H]+ 302.9620; found 302.9608.

1.4 Preparation and characterization of 2-benzoylbenzoate esters 2 from 2-bromobenzophenones 5 by alkoxycarbonylation.

Butyl 2-(4-methoxybenzoyl)benzoate (2a). (2-Bromophenyl)(4-methoxyphenyl)methanone **5a** (40 mg, 0.14 mmol) was transformed to **2a** (28 mg, 65%) according to the general procedure F. NMR: δH (400 MHz, CDCl$_3$) 8.05 (1H, d, J 8.8), 7.73 (2H, d, J 8.9), 7.63-7.59 (1H, m), 7.56-7.52 (1H, m), 7.36 (1H, d, J 8.8), 6.90 (2H, d, J 8.9), 4.05 (2H, t, J 6.6), 3.85 (3H, s), 1.46-1.39 (2H, m), 1.27-1.18 (3H, m), 0.82 (3H, t, J 7.4). δC (101 MHz, CDCl$_3$) 195.82, 166.24, 163.69, 142.06, 132.32, 131.92, 130.41, 130.32, 129.41, 129.38, 127.67, 113.83, 77.48, 77.16, 76.84, 65.53, 55.62, 30.40, 19.21, 13.78. HRMS (ESI): Calcd. for C$_{19}$H$_{20}$NaO$_4$ [M+H]$^+$ 335.1259; found 335.1260.

Butyl 2-(3-methoxybenzoyl)benzoate (2b). (2-Bromophenyl)(3-methoxyphenyl)methanone **5b** (30 mg, 0.1 mmol) was transformed to **2b** (19 mg, 60%) according to the general procedure F. NMR: δH (400 MHz, CDCl$_3$) 8.06 (1H, d, J 7.6), 7.63 (1H, t, J 7.5), 7.56 (1H, t, J 7.5), 7.44-7.43 (1H, m), 7.39-7.37 (1H, m), 7.30 (1H, t, J 7.9), 7.21-7.18 (1H, m), 7.11-7.09 (1H, m), 4.05 (2H, t, J 6.6), 3.84 (3H, s), 1.48 – 1.41 (2H, m), 1.28-1.15 (2H, m), 0.83 (3H, t, J 7.4). δC (101 MHz, CDCl$_3$) 196.9, 166.1, 159.9, 141.8,

138.6, 132.4, 130.3, 129.7, 129.6, 129.6, 127.8, 122.9, 120.0, 113.1, 77.5, 77.2, 76.8, 65.6, 55.6, 30.4, 19.2, 13.8. HRMS (ESI): Calcd. for $C_{19}H_{20}NaO_4$ [M+H]$^+$ 335.1259; found 335.1260.

Butyl 2-(4-fluorobenzoyl)benzoate (2c). (2-Bromophenyl)(4-fluorophenyl)methanone **5k** (15mg, 0.054 mmol), was transformed to **2c** (10 mg, 63%) according to the general procedure F. δH (400 MHz, CDCl$_3$) 8.07 (1H, d, J 8.6), 7.81-7.77 (2H, m), 7.66-7.62 (1H, m), 7.59-7.55 (1H, m), 7.37 (1H, d, J 8.6), 7.10 (2H, t, J 8.6), 4.06 (2H, t, J 6.6), 1.49-1.41 (2H, m), 1.27-1.21 (3H, m), 0.84 (3H, t, J 7.4). δC (101 MHz, CDCl$_3$) 195.6, 166.0, 165.9 (d, J 255.5), 141.6, 133.8, 132.5, 132.2, 132.2 (d, J 10.1), 132.1, 130.4, 129.8, 129.4, 127.6, 115.9, 115.7, 77.5, 77.2, 76.8, 65.6, 30.4, 19.2, 13.9, 13.8. HRMS (ESI): Calcd. for $C_{18}H_{17}FNaO_3$ [M+H]$^+$ 323.1059; found 323.1059.

*Butyl 2-(2-fluorobenzoyl)*benzoate (**2d**). (2-Bromophenyl)(4-methoxyphenyl)methanone **5m** (40 mg, 0.47 mmol) was transformed to **2d** (22 mg, 50%) according to the general procedure F. NMR: δH (400 MHz, CDCl$_3$) 8.53 (1H, d, J 7.6), 8.38-8.33 (1H, m), 8.12-8.10 (1H, m), 8.07-8.05 (1H, m), 7.89-7.87 (2H, m), 7.77-7.75 (1H, m), 7.69-7.61 (1H, m), 7.60-7.55 (1H, m), 4.62 (2H, t, J 6.6), 2.03-1.99 (2H, m), 1.84-1.71 (3H, m), 1.36 (3H, t, J 7.4). δC (101 MHz, CDCl$_3$) 193.7, 166.3, 163.2, 161.9 (d, J 258.6), 160.7, 143.5, 134.99, 135.0 (d, J 9.1), 134.6, 132.3, 131.5, 130.1, 129.7, 127.0, 125.9, 124.3 (d, J 4.0), 124.3, 117.0, 116.9 (d, J 23.2), 116.8, 65.6, 30.5, 19.2, 13.8. HRMS (ESI): Calcd. for $C_{18}H_{17}FNaO_3$ [M+H]+ 323.1059; found 323.1059.

1.5 Preparation and characterization of 2-benzoylbenzoate esters 2 from 2-bromobenzoates 6 by Suzuki-Miyaura couplings.

Methyl 2-(4-methoxybenzoyl)benzoate (2aa). Methyl 2-bromobenzoate **6a** (100 mg for procedure C and D; 50 mg for procedure E) was reacted with 4-methoxyphenyl boronic acid **4a** (105 mg, 1.5 equiv, 0.66 mmol), DABO boronate 2-(4-methoxyphenyl)-1,3,6,2-dioxazaboroane **7a** (82 mg, 1.5 equiv, 0.37 mmol) or sodium trihydroxy(4-methoxyphenyl)borate **8a** (72 mg, 1.5 equiv, 0.37 mmol). Reactions were performed following general procedure C, D or E to provide **2aa** as a colorless oil. Procedure C with **4a**: 100 mg, 80%; procedure D with **4a**: 80 mg, 63%; procedure E with **7a**: 45 mg, 67%; procedure E with **8a**: 44 mg, 65%. NMR: δH (400 MHz, CDCl$_3$) 8.02 (1H, d, J 7.6), 7.71 (2H, d, J 8.8), 7.61 (1H, t, J 7.5), 7.53 (1H, t, J 7.5), 7.37 (1H, d, J 7.6), 6.89 (2H, d, J 8.8), 3.83 (3H, s), 3.63 (3H, s). δC (101 MHz, CDCl$_3$) 195.9, 166.5, 163.6, 142.1, 132.4, 132.3, 131.7, 130.3, 130.2, 129.4, 129.2, 127.8, 113.8, 55.6, 52.3. HRMS (ESI): Calcd. for $C_{16}H_{14}NaO_4$ [M+H]$^+$ 293.0790; found 293.0784. The spectroscopic data is corresponding to the previously reported in literature.[6]

Methyl 2-(3-methoxybenzoyl) benzoate (2ab). Methyl 2-bromobenzoate **6a** (100 mg) was reacted with 3-methoxyphenyl boronic acid **4b** (105 mg, 1.5 equiv, 0.66 mmol) according to the general procedure C to provide **2ab** (65 mg, 52%) as a colorless oil. NMR: δH (400 MHz, CDCl$_3$) 7.90 (1H, d, J 8.7), 7.61-7.46 (1H, m), 7.46-7.33 (1H, m), 7.28 (2H, s), 7.21-7.08 (1H, m), 7.05 (1H, d, J 7.7), 6.96 (1H, dd, J 8.7, 3.2), 3.70 (3H, s), 3.50 (3H, s). δC (101 MHz, CDCl$_3$) 196.9, 166.5, 159.9, 141.8, 138.6, 132.5, 132.0, 131.2, 130.1, 130.0, 129.7, 129.6, 129.3, 129,0, 127.8, 122.5, 119.8, 113.0, 55.5, 55.3, 52.7, 52.3. HRMS (ESI): Calcd. for $C_{16}H_{14}NaO_4$ [M+H]$^+$ 293.0790; found 293.0784.

Methyl 2-(2-methoxybenzoyl)benzoate (2ac). Methyl 2-bromobenzoate **6a** (100 mg) was reacted with 2-methoxyphenyl boronic acid **4c** (105 mg, 1.5 equiv, 0.66 mmol) according to the general procedure C to provide **2ac** (93 mg, 74%) as a white solid, Mp 100-103 °C. NMR: δH (400 MHz, CDCl$_3$) 7.87 (1H, d, J 8.7), 7.74-7.67 (1H, m), 7.53 (1H, t, J 7.5), 7.50-7.42 (2H, m), 7.36 (1H, d, J 8.7), 6.99 (1H, t, J 7.9), 6.90 (1H, d, J 8.3), 3.59 (3H, s), 3.57 (3H, s). δC (101 MHz, CDCl$_3$) 195.7, 167.3, 159.0, 143.8, 134.2, 131.7, 131.6, 129.5, 129.3, 127.5, 127.0, 120.5, 112.2, 77.4, 55.7, 52.1. HRMS (ESI): Calcd. for $C_{16}H_{14}NaO_4$ [M+H]$^+$ 293.0790; found 293.0784.

Methyl 2-(4-(methylthio)benzoyl) benzoate (2ad). Methyl 2-bromobenzoate **6a** (100 mg) was reacted with 4-(methylthio) phenyl boronic acid (110 mg, 1.5 equiv, 0.65 mmol) according to the general procedure C to provide (101 mg, 76%) as a white solid, Mp 84-87 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

8.02 (1H, d, J 8.6), 7.64 (2H, d, J 8.5), 7.61-7.59 (1H, m), 7.53-7.51 (1H, m), 7.36 (2H, d, J 8.6), 7.21(2H, d, J 8.5), 3.62 (3H, s), 2.47 (3H, s). δC NMR (101 MHz, CDCl$_3$) 196.1, 166.4, 146.1, 141.8, 133.5, 132.4, 130.1, 129.7, 129.5, 129.1, 127.7, 124.9, 52.3, 14.7. HRMS (ESI): Calcd. for C$_{16}$H$_{14}$ NaO$_3$S [M+H]$^+$ 309.0561; found 309.0559.

Methyl 2-(3-(methoxycarbonyl)benzoyl)benzoate (2ag). Methyl 2-bromobenzoate **6a** (100 mg) was reacted with 3-(methoxycarbonyl)phenyl boronic acid **4g** (125 mg, 1.5 equiv, 0.70 mmol) according to the general procedure C to provide **2ag** (65 mg, 47%) as a colorless oil. NMR: δH (400 MHz, CDCl$_3$) 8.37 (1H, s), 8.23-8.21 (1H, m), 8.07 (1H, d, J 8.6), 7.96-7.95 (1H, m), 7.70-7.63 (1H, m), 7.63-7.56 (1H, m), 7.53 (1H, t, J 7.8), 7.40 (1H, d, J 8.6), 3.90 (3H, s), 3.64 (3H, s). δC (101 MHz, CDCl$_3$) 196.4, 166.4, 141.4, 137.7, 134.0, 133.4, 132.8, 130.8, 130.5, 130.4, 130.0, 129.2, 128.9, 127.8, 52.5, 52.4. HRMS (ESI): Calcd. for C$_{17}$H$_{14}$ NaO$_5$ [M+H]$^+$ 321.0739; found 321.0730

Dimethyl 2,2'-carbonyldibenzoate (2ah). Methyl 2-bromobenzoate **6a** (100 mg) was reacted with 2-(methoxycarbonyl)phenyl boronic acid **4h** (125 mg, 1.5 equiv, 0.70 mmol). Reactions were performed both by the general procedure C and D to provide **2ah** as a white solid, Mp 205-207 °C. Procedure C: 103 mg, 75%; procedure D: 36 mg, 26%. NMR: δH (400 MHz, CDCl$_3$) 7.78 (2H, d, J 8.6), 7.58-7.56 (2H, m), 7.53-7.48 (2H, m), 7.40 (2H, d, J 8.6), 3.73 (6H, s). δC (101 MHz, CDCl$_3$) 195.7, 168.3, 138.5, 132.0, 131.4, 131.2, 129.7, 129.4, 128.9, 77.4, 52.6. HRMS (ESI): Calcd. for C$_{17}$H$_{14}$ NaO$_5$ [M+H]$^+$ 321.0739; found 321.0730.

Methyl 2-(4-cyanobenzoyl) benzoate (2ai). Methyl 2-bromobenzoate **6a** (100 mg) was reacted with 4-cyanophenyl boronic acid **4i** (102 mg, 1.5 equiv, 0.7 mmol). Reactions were performed following general procedure C or D to provide **2ai** as a colourless oil. Procedure C: 40 mg, 32%; procedure D: 20 mg, 16%. NMR: δH (400 MHz, CDCl$_3$) 8.08 (1H, d, J 8.6), 7.83 (2H, d, J 8.6), 7.73 (2H, d, J 8.6), 7.69-7.67 (1H, m), 7.64 − 7.60 (1H, m), 7.40 (1H, d, J 8.6), 3.67 (3H, s). δC (101 MHz, CDCl$_3$) 195.4, 165.8, 140.6, 140.2, 132.7, 132.2, 130.1, 130.0, 129.2, 128.8, 127.4, 117.8, 116.0, 52.3. HRMS (ESI): Calcd. for C$_{16}$H$_{11}$NNaO$_3$ [M+H]$^+$ 288.0637; found 288.0630.

Methyl 2-(3-cyanobenzoyl) benzoate (2aj). Methyl 2-bromobenzoate **6a** (100 mg) was reacted with (3-cyanophenyl) boronic acid **4j** (102 mg, 1.5 equiv, 0.7 mmol). Reactions were performed following general procedure C or D to provide **2aj** as a colourless oil. Procedure C: 48 mg, 40%; procedure D: 32 mg, 26%. NMR: δH (400 MHz, CDCl$_3$) 8.10 (1H, d, J 8.6), 8.03-7.01 (1H, m), 7.96 (1H, s), 7.83-7.81 (1H, m), 7.70 (1H, t, J 7.5), 7.66 − 7.59 (1H, m), 7.58-7.56 (1H, m), 7.38 (1H, d, J 8.6), 3.70 (3H, s). δC NMR (101 MHz, CDCl$_3$) 195.5, 166.4, 141.1, 138.6, 136.3, 133.4, 133.3, 133.2, 130.9, 130.6, 130.1, 129.3, 127.9, 118.4, 113.5, 52.9. Calcd. for C$_{16}$H$_{11}$NNaO$_3$ [M+H]$^+$ 288.0637; found 288.0630.

Methyl 2-(4-fluorobenzoyl) benzoate (2ak). Methyl 2-bromobenzoate **6a** (100 mg for procedure C; 50 mg for procedure E) was reacted with 4-fluorophenyl boronic acid **4k** (100 mg, 1.5 equiv, 0.7 mmol) or 2-(4-fluorophenyl)-1,3,6,2-dioxazaborocane **7k** (73 mg, 1.5 equiv, 0.35 mmol) according to the general procedure C or E to provide **2ak** as a colourless oil. Procedure C: 45 mg, 37%; procedure E: 15 mg, 25%. NMR: δH (400 MHz, CDCl$_3$) 8.05 (1H, d, J 8.7), 7.79-7.75 (2H, m), 7.66-7.62 (1H, m), 7.59-7.55 (1H, m), 7.38 (1H, d, J 8.7), 7.12-7.07 (2H, m), 3.65 (3H, s). δC (101 MHz, CDCl$_3$) 195.5, 166.4, 165.8 (d, J 256.5), 164.4, 141.5, 133.8 (d, J 3.0), 132.5, 132.0 (d, J 9.1), 130.3, 129.8, 129.2, 127.6, 115.8 (d, J 20.2), 52.3. HRMS (ESI): Calcd. for C$_{15}$H$_{11}$ FNaO$_3$ [M+H]$^+$ 281.0590; found 281.0584. The spectroscopic data is corresponding to the previously reported in literature.[6]

Methyl 2-(3-fluorobenzoyl) benzoate (2al). Methyl 2-bromobenzoate **6a** (100 mg) was reacted with (3-fluorophenyl) boronic acid **4l** (100 mg, 1.5 equiv, 0.7 mmol). Reactions were performed following general procedure C or D to provide **2al** as a colorless oil. Procedure C: 70 mg, 58%; procedure D: 51 mg, 43%. NMR: δH (400 MHz, CDCl$_3$) 8.06 (1H, d, J 8.7), 7.67-7.63 (1H, m), 7.60-7.56 (1H, m), 7.50-7.44 (2H, m), 7.41-7.35 (2H, m), 7.29-7.21 (1H, m), 3.66 (3H, s). δC (101 MHz, CDCl$_3$) 196.2, 166.6, 163.2 (d, J 249.5), 141.8, 139.7 (d, J 7.1), 133.0, 130.7, 130.6, 130.3, 129.5, 128.1, 125.5 (d, J 3.0), 120.6 (d, J 21.6), 116.1 (d, J 23.2), 52.7. HRMS (ESI): Calcd. for C$_{15}$H$_{11}$ FNaO$_3$ [M+H]$^+$ 281.0590; found 281.0584.

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

Methyl 2-(2-fluorobenzoyl) benzoate (2am). Methyl 2-bromobenzoate **6a** (100 mg for procedure C and D; 50 mg for procedure E) was reacted with 2-fluorophenyl boronic acid **4m** (100 mg, 1.5 equiv, 0.7 mmol) or 2-(2-fluorophenyl)-1,3,6,2-dioxazaborocane **7m** (73 mg, 1.5 equiv, 0.35 mmol). Reactions were performed following general procedure C, D or E to provide **2am** as a white solid, Mp 56-59 °C. Procedure C: 78 mg, 65%; procedure D: 50 mg, 42%; procedure E: 21 mg, 35%. NMR: δH (400 MHz, CDCl₃) 8.02 (1H, d, J 8.8), 7.85-7.81 (1H, m), 7.67-7.63 (1H, m), 7.61-7.52 (2H, m), 7.44-7.42 (1H, m), 7.31-7.24 (1H, m), 7.12-7.07 (1H, m), 3.72 (3H, s). δC (101 MHz, CDCl₃) 193.8, 166.8, 161.7 (d, J 258.6),134.8 (d, J 9.1), 132.5, 131.3, 130.00 (d, J 19.2), 128.9, 127.2, 125.9 (d, J 10.0), 124.3 (d, J 4.0), 116.87 (d, J 22.2), 52.4. HRMS (ESI): Calcd. for $C_{15}H_{11}FNaO_3$ [M+H]⁺ 281.0590; found 281.0584.

Methyl 2-(thiophene-2-carbonyl) benzoate (2an). Methyl 2-bromobenzoate **6a** (50 mg), was reacted with 2-(thiophen-2-yl)-1,3,6,2-dioxazaborocane **7n** (69 mg, 1.5 equiv, 0.35 mmol) according to the general procedure E to provide **2an** (29 mg, 50%) as a colourless oil. NMR: δH (400 MHz, CDCl₃) 8.02 (1H, d, J 7.6), 7.65-7.61 (2H, m), 7.58-7.54 (2H, m), 7.45 (1H, d, J 7.6), 7.35-7.33 (1H, m), 3.67 (3H, s). δC (101 MHz, CDCl₃) 190.7, 166.7, 142.8, 142.2, 133.9, 132.4, 130.3, 129.9, 129.3, 127.8, 127.4, 126.8, 52.4. The spectroscopic data is corresponding to the previously reported in literature.[9]

Methyl 2-(benzo[b]thiophene-2-carbonyl) benzoate (2ao). Methyl 2-bromobenzoate **6a** (50 mg), was reacted with 2-(benzo[*b*]thiophen-2-yl)-1,3,6,2-dioxazaborocane **7o** (86 mg, 1.5 equiv, 0.35 mmol) according to the general procedure E to provide **2ao** (55 mg, 75%) as a yellow solid. Mp 78-80 °C. NMR: δH (400 MHz, CDCl₃) 7.89 (1H, d, J 7.5), 7.68 (1H, d, J 8.0), 7.57 (1H, d, J 8.0), 7.48-7.45 (2H, m), 7.42 − 7.39 (1H, m), 7.33(1H, d, J 7.5), 7.25-7.22 (1H, m), 7.17-7.14 (1H, m), 3.48 (3H, s). δC (101 MHz, CDCl₃) 190.7, 166.3, 144.1, 142.8, 140.8, 138.9, 132.4, 131.6, 130.3, 130.1, 129.2, 127.7, 127.5, 126.1, 125.0, 123.0, 52.4. HRMS (ESI): Calcd. for $C_{17}H_{12}NaO_3$ S [M+H]⁺ 319.0405; found 319.0407.

Methyl 5-fluoro-2-(4-methoxybenzoyl)benzoate (2ba). Methyl 2-bromo-5-fluorobenzoate **6b** (50 mg, 0.21 mmol), was reacted with (4-methoxyphenyl) boronic acid **4a** (48 mg, 1.5 equiv, 0.32 mmol) according to the general procedure E to provide **2ba** (44 mg, 72%) as a colourless oil. NMR: δH (400 MHz, CDCl₃) 7.72-7.68 (3H, m), 7.44-7.37 (1H, m), 7.33-7.28 (1H, m), 6.92-6.90 (2H, m), 3.85 (3H, s), 3.64 (3H, s). δC (101 MHz, CDCl₃) 194.8, 165.5 (d, J 3.0), 163.8, 162.8 (d, J 251.5), 138.1 (d, J 3.0), 131.7, 130.2, 130.0 (d, J 8.1), 119.4 (d, J 22.2), 117.2 (d, J 23.2), 113.9, 77.4, 55.6, 52.6. HRMS (ESI): Calcd. for $C_{16}H_{13}FNaO_4$ [M+H]⁺ 311.0696; found 311.0695.

Methyl 4-fluoro-2-(4-methoxybenzoyl)benzoate (2ca). Methyl 2-bromo-4-fluorobenzoate **6c** (57 mg, 0.24 mmol), was reacted with (4-methoxyphenyl) boronic acid **4a** (48 mg, 1.5 equiv, 0.32 mmol) according to the general procedure E to provide **2ca** (35 mg, 50%) as a colourless oil. NMR: δH (400 MHz, CDCl₃) 8.08 (1H, dd, J 8.7, 5.4), 7.72 (2H, d, J 9.0), 7.24-7.19 (1H, m), 7.07 (1H, dd, J 8.3, 2.6), 6.92 (2H, d, J 9.0), 3.86 (3H, s), 3.64 (3H, s). δC (101 MHz, CDCl₃) 194.2, 165.5, 164.9 (d, J 257.5), 163.9, 145.1 (d, J 7.1), 133.1 (d, J 10.1), 131.8, 129.7, 125.2 (d, J 3.0), 116.5 (d, J 21.2), 115.2 (d, J 24.2), 114.0, 55.7, 52.4. HRMS (ESI): Calcd. for $C_{16}H_{13}FNaO_4$ [M+H]⁺ 311.0696; found 311.0695.

Methyl 5-chloro-2-(4-methoxybenzoyl)benzoate (2da). Methyl 2-bromo-5-chlorobenzoate **6d** (50 mg, 0.20 mmol), was reacted with (4-methoxyphenyl) boronic acid **4a** (45 mg, 1.5 equiv, 0.30 mmol) according to the general procedure E to provide **2da** (30 mg, 50%) as a colourless oil. NMR: δH (400 MHz, CDCl₃) 8.01 (1H, d, J 2.1), 7.71 (2H, d, J 9.0), 7.59 (1H, dd, J 8.1, 2.1), 7.33 (1H, d, J 8.1), 6.91 (2H, d, J 9.0), 3.86 (3H, s), 3.65 (3H, s). δC (101 MHz, CDCl₃) 194.8, 165.5, 163.9, 140.4, 135.7, 132.4, 131.8, 131.0, 130.3, 130.1, 129.3, 114.0, 55.6, 52.7. HRMS (ESI): Calcd. for $C_{16}H_{13}ClNaO_4$ [M+H]⁺ 327.0400; found 327.0401.

Methyl 4-chloro-2-(4-methoxybenzoyl)benzoate (2ea). Methyl 2-bromo-4-chlorobenzoate **6e** (50 mg, 0.20 mmol), was reacted with (4-methoxyphenyl) boronic acid **4a** (46 mg, 1.5 equiv, 0.30 mmol) according to the general procedure E to provide **2ea** (40 mg, 65%) as a colourless oil. NMR: δH (400 MHz, CDCl₃) 7.99 (1H, d, J 8.4), 7.72 (2H, d, J 9.0), 7.51 (1H, dd, J 8.4, 2.0), 7.36 (2H, d, J 2.0), 6.92 (2H, d, J 9.0), 3.86 (3H, s), 3.65 (3H, s). δC (101 MHz, CDCl₃) 194.2, 165.7, 163.9, 143.8, 139.1, 131.8,

131.8, 129.8, 129.6, 127.9, 127.4, 114.0, 55.7, 52.5. HRMS (ESI): Calcd. for $C_{16}H_{13}ClNaO_4$ [M+H]$^+$ 327.0400; found 327.0402.

Methyl 2-(4-methoxybenzoyl)-5-methylbenzoate (2fa). Methyl 2-bromo-5-methylbenzoate **6f** (57 mg, 0.19 mmol), was reacted with (4-methoxyphenyl) boronic acid **4a** (49 mg, 1.5 equiv, 0.32 mmol) according to the general procedure E to provide **2fa** (50 mg, 71%) as a colourless oil. NMR: δH (400 MHz, CDCl$_3$) 7.82 (1H, s), 7.72 (2H, d, *J* 9.0), 7.41 (1H, d, *J* 8.4), 7.28 (1H, d, *J* 7.7), 6.89 (2H, d, *J* 9.0), 3.84 (3H, s), 3.60 (3H, s), 2.45 (3H, s). δC (101 MHz, CDCl$_3$) 196.0, 166.9, 163.5, 139.8, 139.2, 132.9, 131.7, 130.6, 129.4, 128.0, 113.8, 77.4, 55.6, 52.2, 21.3. HRMS (ESI): Calcd. for $C_{17}H_{16}NaO_4$ [M+H]$^+$ 307.0900; found 307.0947.

Methyl 2-(4-methoxybenzoyl)-3-methylbenzoate (2ga). Methyl 2-bromo-3-methylbenzoate **6g** (59 mg, 0.26 mmol), was reacted with (4-methoxyphenyl) boronic acid **4a** (49 mg, 1.5 equiv, 0.32 mmol) according to the general procedure E to provide **2ga** (50 mg, 68%) as a colourless oil. NMR: δH (400 MHz, CDCl$_3$) 7.92 (1H, d, *J* 8.5), 7.73-7.71 (2H, m), 7.45-7.40 (2H, m), 6.90 (2H, d, *J* 9.1), 3.84 (3H, s), 3.67 (3H, s), 2.17 (3H, s). δC (101 MHz, CDCl$_3$) 197.0, 166.4, 163.7, 141.9, 135.6, 135.0, 131.1, 130.7, 128.6, 128.3, 127.9, 114.0, 77.4, 19.3. HRMS (ESI): Calcd. for $C_{17}H_{16}NaO_4$ [M+H]$^+$ 307.0946; found 307.0945.

Methyl 4-methoxy-2-(4-methoxybenzoyl) benzoate (2ha). Methyl 2-bromo-4-methoxybenzoate **6h** (50 mg, 0.20 mmol), was reacted with (4-methoxyphenyl) boronic acid **4a** (46 mg, 1.5 equiv, 0.30 mmol) according to the general procedure E to provide **2ha** (47 mg, 77%) as a colourless oil. NMR: δH (400 MHz, CDCl$_3$) 8.01 (1H, d, *J* 8.8), 7.73 (2H, d, *J* 9.0), 7.00 (1H, dd, *J* 8.8, 2.6), 6.89 (2H, d, *J* 9.0), 6.83 (1H, d, *J* 2.6), 3.85 (3H, s), 3.84 (3H, s), 3.61 (3H, s). δC (101 MHz, CDCl$_3$) 195.6, 166.0, 163.6, 162.9, 144.6, 132.4, 131.7, 130.2, 120.9, 114.8, 113.9, 112.7, 77.4, 55.8, 55.6, 52.0. HRMS (ESI): Calcd. for $C_{17}H_{16}NaO_5$ [M+H]$^+$ 323.0895; found 323.0894.

Methyl 2-(4-methoxybenzoyl)-5-methylbenzoate (2ia). Methyl 2-bromo-4,5-dimethoxybenzoate **6i** (50 mg, 0.18 mmol), was reacted with (4-methoxyphenyl) boronic acid **4a** (40 mg, 1.5 equiv, 0.26 mmol) according to the general procedure E to provide **2ia** (44 mg, 73%) as a white solid, Mp 151-153 °C. NMR: δH (400 MHz, CDCl$_3$) 7.70 (2H, d, *J* 9.0), 7.50 (1H, s), 6.89 (2H, d, *J* 9.0), 6.84 (1H, s), 3.97 (3H, s), 3.90 (3H, s), 3.84 (3H, s), 3.55 (3H, s). δC (101 MHz, CDCl$_3$) 195.6, 166.2, 163.5, 152.3, 149.3, 136.0, 131.5, 130.7, 121.5, 113.8, 112.2, 110.3, 56.3, 55.6, 52.1. HRMS (ESI): Calcd. for $C_{18}H_{18}NaO_6$ [M+H]$^+$ 353.1001; found 353.1001. The spectroscopic data is corresponding to the previously reported in literature.[10]

Methyl 5-fluoro-2-(2-methoxybenzoyl)benzoate (2bc). Methyl 2-bromo-5-fluorobenzoate **6b** (50 mg, 0.24 mmol), was reacted with (2-methoxyphenyl) boronic acid **4c** (49 mg, 1.5 equiv, 0.32 mmol) according to the general procedure E to provide **2bc** (40 mg, 66%) as a colourless oil. NMR: δH (400 MHz, CDCl$_3$) 7.72 (1H, dd, *J* 7.7, 1.8), 7.54 (1H, dd, *J* 8.9, 2.6), 7.51-7.44 (1H, m), 7.42-7.38 (1H, m), 7.25-7.20 (1H, m), 7.02 (1H, t, *J* 7.5), 6.92 (1H, d, *J* 8.4), 3.61 (3H, s), 3.60 (3H, s). δC (101 MHz, CDCl$_3$) 194.6, 166.5, 166.4 (d, *J* 2.0), 162.9 (d, *J* 252.5), 158.9, 139.7 (d, *J* 4.0), 134.4, 132.3 (d, *J* 7.1), 131.5, 130.2 (d, *J* 8.1), 127.0, 120.7, 118.6 (d, *J* 22.2), 116.4 (d, *J* 24.2) , 112.2, 55.7, 52.5. HRMS (ESI): Calcd. for $C_{16}H_{13}FNaO_4$ [M+H]$^+$ 311.0696; found 311.0693.

Methyl 5-fluoro-2-(2-(methoxycarbonyl)benzoyl)benzoate (2bh). Methyl 2-bromo-5-fluorobenzoate **6b** (50 mg, 0.24 mmol), was reacted with 2-(methoxycarbonyl)phenylboronic acid **4h** (58 mg, 1.5 equiv, 0.32 mmol) according to the general procedure E to provide **2bh** (30 mg, 40%) as a colorless oil. NMR: δH (400 MHz, CDCl$_3$) 7.85 (1H, d, *J* 8.8), 7.61-7.53 (2H, m), 7.44 (1H, dd, *J* 5.9, 2.6), 7.42-7.41 (1H, m), 7.40 (1H, s), 3.78 (3H, s), 3.74 (3H, s). δC (101 MHz, CDCl$_3$) 194.5, 167.9, 167.5 (d, *J* 2.0), 164.1 (d, *J* 255.5) , 138.9, 135.2 (d, *J* 8.1), 134.3 (d, *J* 4.0), 132.6 (d, *J* 9.1), 131.5, 131.4 (d, *J* 27.3), 129.5 (d, *J* 37.4), 117.9, 117.8 (d, *J* 22.2), 116.7 (d, *J* 24.2), 77.4, 53.0, 52.7. HRMS (ESI): Calcd. for $C_{17}H_{13}FNaO_5$ [M+H]$^+$ 339.0645; found 339.0640.

Methyl 2-(2-naphthoyl)-4-methoxybenzoate (2hp). Methyl 2-bromo-4-methoxybenzoate **6h** (50 mg, 0.20 mmol), was reacted with 2-napthylboronic acid **4p** (52 mg, 1.5 equiv, 0.30 mmol) according to the general procedure E to provide **2hp** (57 mg, 61%) as a colourless oil. NMR: δH (400 MHz, CDCl$_3$) 8.09-8.07 (2H, m), 8.02 (1H, dd, *J* 8.6, 1.7), 7.93-7.88 (1H, m), 7.86-7.83 (2H, m), 7.60-7.56 (1H, m), 7.53-7.48 (1H, m), 7.08 (1H, dd, *J* 8.8, 2.6), 6.93 (1H, d, *J* 2.6), 3.89 (3H, s), 3.57 (3H, s). δC (101 MHz, CDCl$_3$) 197.0, 166.0, 163.0, 144.4, 135.8, 134.7, 132.6, 132.5, 131.6, 129.8, 128.7, 127.9, 126.8, 124.4, 121.1, 115.1, 112.9, 77.4, 55.8, 52.1. HRMS (ESI): Calcd. for C$_{19}$H$_{14}$NaO$_4$ [M+H]$^+$ 329.0790; found 329.0790.

2 Additional experimental information

2.1 Two-chamber set-up:

The reactions were performed in the previously reported two-chamber system (Fig 1) under an argon atmosphere.
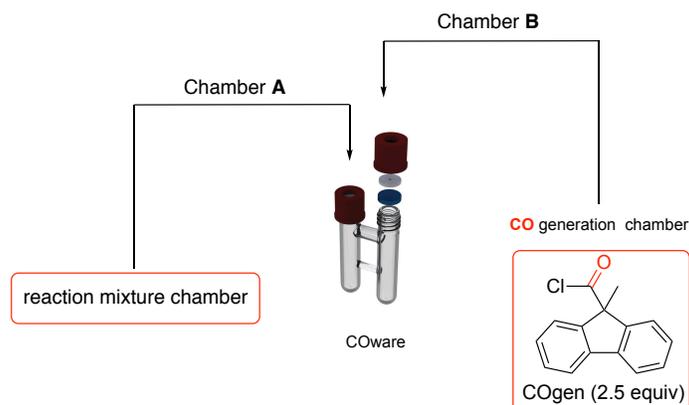
Fig 1. The two-chamber system used in the reactions, and the CO generator (COgen)

2.2 Screening of catalysts and conditions for the Suzuki- Miyaura coupling of 2-bromoiodobenzene 3 with 4-methoxyphenyl boronic acid 4a.
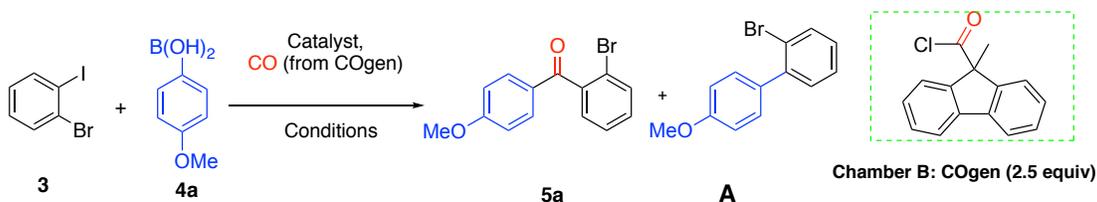
Procedure:

Chamber A: 2-Bromoiodobenzene **3** (50 mg, 1.0 equiv, 0.18 mmol), aryl boronic acid **4a** (1.2 equiv), catalyst and base were dissolved in a solvent (3 ml).

Chamber B: COgen (107 mg, 2.5 equiv, 0.45 mmol), Pd(dba)$_2$ (12 mg, 5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (6.3 mg, 5 mol%) were dissolved in anisole (3 ml).

DIPEA (240 mg, 3 equiv) was added to chamber B to release CO. The mixture was stirred at 80 °C in a tightly closed system for 20 hours. The reaction mixture was filtered through celite and concentrated on a rotavapor. The crude was purified by column chromatography with pentane: EtOAc (8:2) as eluent. The ratio (5a: A) has been evaluated based on the crude ^{13}C NMR spectra. The experimental data and the NMR spectra of the byproduct A is shown later.

Characterization of 2-bromo-4'-methoxy-1,1'-biphenyl A (from direct coupling).

The title compound was isolated as a side product from reactions towards **5a**. NMR: δH (400 MHz, CDCl$_3$) 7.66 (1H, d, *J* 7.8), 7.40-7.31 (4H, m), 7.22-7.13 (1H, m), 6.97
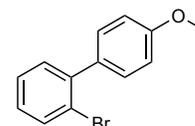
(2H, d, J 8.7), 3.87 (3H, s). δC (101 MHz, CDCl$_3$) 159.2, 142.3, 133.7, 133.2, 131.5, 130.7, 128.5, 127.9, 127.5, 123.0, 114.3, 113.5, 77.5, 77.2, 76.8, 55.5, 55.4.

Table ESI-1. Carbonylative Suzuki-Miyaura coupling of 2-bromoiodobenzene **3** with 4-methoxyphenyl boronic acid **4a**.

Entry	Catalyst (mol%)	base	Rxn. time (h)	T (ºC)	Solvent	Addition	Approx. ratio[c] 5a : A	Isol. yield (%)
1	Pd(PPh$_3$)$_2$Cl$_2$ (3)	K$_2$CO$_3$	20	80	Anisole	normal	0.7 : 1	50
2	Pd(OAc)$_2$ (2)	K$_2$CO$_3$	20	80	Anisole	normal	0.1 : 1	10
3	Pd(dba)$_2$ (3)	K$_2$CO$_3$	20	80	Anisole	normal	0.5 : 1	35
4	PEPPSI-IPr (3)	Cs$_2$CO$_3$	20	80	Chlorobenzene	normal	0.7 : 1	30
5	PdCl$_2$ (3)	K$_2$CO$_3$	20	80	Anisole	normal	0.7 : 1	65
6	PdCl$_2$ (1)	K$_2$CO$_3$	20	80	Anisole	normal	0.7 : 1	60
7	PdCl$_2$ (1)	K$_2$CO$_3$	20	50	Anisole	normal	0.2 : 1	30
8	PdCl$_2$ (1)	K$_2$CO$_3$	20	60	Anisole	normal	0.3 : 1	35
9	PdCl$_2$ (1)	K$_2$CO$_3$	40	80	Anisole	normal	1 : 1	65
10	PdCl$_2$[b] (1)	K$_2$CO$_3$[b]	20	80	Anisole	normal	1 : 0.9	55
11	PdCl$_2$ (1)	K$_2$CO$_3$/KI	20	80	Anisole	normal	0.6 : 1	55
12	PdCl$_2$ (1)	Cs$_2$CO$_3$	20	80	Anisole	normal	1 : 1	60
13	PdCl$_2$ (1)	K$_2$CO$_3$	20	80	Anisole	slow[a]	1 : 0.1	80
14	PdCl$_2$ (1)	K$_2$CO$_3$	20	100	Anisole	slow[a]	1 : 0.1	80
15	PEPPSI- IPr (3)	Cs$_2$CO$_3$	20	80	Chlorobenzene	slow[a]	1 : 1	60
16	PEPPSI- IPr (3)	Cs$_2$CO$_3$	20	120	Chlorobenzene	slow[a]	1 : 1	65

a Instead of dissolving **4a** in chamber A before CO release, a solution of aryl boronic acid **4a** (1.2 equiv) in anisole (2 ml) was added slowly (1-2 h) to the reaction mixture in chamber A after CO release. See General procedure A. b PdCl$_2$ and K$_2$CO$_3$ were used as a premix with ratio 1:300. c The ratio (5a : A) is approximately determined using ^{13}C NMR of the crude product mixture.

2.3 Screening of precursors for ex-situ generation of CO.

Procedures:

Chamber A: 2-Bromoiodobenzene **3** (50 mg, 1.0 equiv, 0.18 mmol), PdCl$_2$ (0.3 mg, 1 mol%), K$_2$CO$_3$ (70 mg, 3 equiv, 0.55 mmol) were dissolved in a solvent (3 ml). In case of normal addition, the aryl boronic acid **4a** (1.2 equiv) was added to the mixture before CO generation was started. In case of slow addition, the aryl boronic acid **4a** (1.2 equiv) was dissolved in anisole (2 ml) and added after CO generation over a period of 1-2 hours.

Chamber B for entry 1 and 2: Fe-tetraphenylporphyrin (6 mg), TBABF$_4$ (1.1g), DMF (30 ml), and tetrafluoroethylene (2 ml) were introduced to chamber B. Electrodes were mounted and the COware was sealed tightly with the screw caps fitted with teflon-coated silicon seals.

The reaction mixture in chamber A was bubbled through with CO$_2$ for 10-15 min until saturation. The ElectroWare[4] was set up using galvanostatic configuration. The electrodes were connected and the electrolysis began, while both reaction chambers were stirring. Chamber B kept stirring at room temperature, while the other chamber A was placed in a preheated hotplate at 80 °C for 18 h. The reaction mixture was filtered through celite and concentrated on a rotavapor. The crude was purified by column chromatography with pentane: EtOAc (8:2) as eluent.[11]

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

Chamber B for entry 3 and 4: COgen (107 mg, 2.5 equiv, 0.45 mmol), Pd(dba)$_2$ (12 mg, 5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (6.3 mg, 5 mol%) and DIPEA (240 mg, 3 equiv) were dissolved in anisole (3 ml).

The mixture was stirred at 80 °C in a tightly closed system for 20 hours. The reaction mixture was filtered through celite and concentrated on a rotavapor. The crude was purified by column chromatography with pentane: EtOAc (8:2) as eluent.

For entry 5 and 6: To a two necked round bottomed flask degassed and charged with aqueous solution of NaOH (2 M, 20 ml), a balloon was fitted via 5 ml syringe cylinder at one neck. The syringe cylinder was filled with CaCl$_2$ as a drying agent, that was kept in place by cotton wool pads at both sides. Through the other neck oxalyl chloride was added slowly with a syringe to the basic solution. The evolved gas was collected in the balloon. The CO balloon was transferred to the reaction mixture vial (chamber A). The mixture was stirred at 80 °C in a tightly closed system for 20 hours. The reaction mixture was filtered through celite and concentrated on a rotavapor. The crude was purified by column chromatography with pentane: EtOAc (8:2) as eluent.[12]

Chamber B for entry 7 and 8: Sulfuric acid (1.5 mmol) was introduced before the two-chamber system was tightened and heated at 80 °C. Then formic acid was added slowly to chamber B. The reaction mixture was allowed to stir at 80 °C for 18h.[13]

Table ESI-2. Screening of CO precursors.
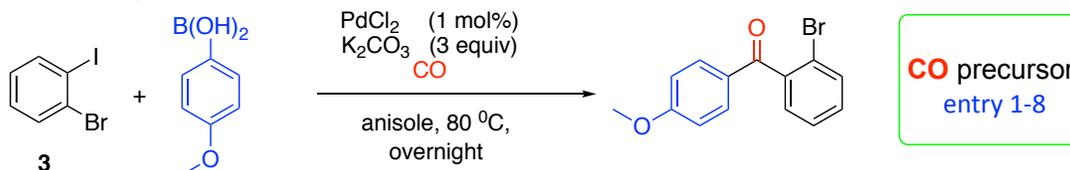
no	CO source	Addition of boronic acid	Isolated yield (%)
1	CO$_2$ reduction	Normal	29
2	CO$_2$ reduction	Slow addition	30
3	COgen	Normal	60
4	COgen	Slow addition	80
5	Oxalyl chloride+ NaOH (aq)	Normal (ballon)	60
6	Oxalyl chloride + NaOH (aq)	Slow addition (ballon)	60
7	Formic acid+ H$_2$SO$_4$ (1.2 mmol)	Normal (ballon)	10
8	Formic acid+ H$_2$SO$_4$ (1.2 mmol)	In situ	0

2.4 Attempts to hydroxycarbonylate 2-bromoiodobenzene 3 or 2-bromobenzophenone 5a
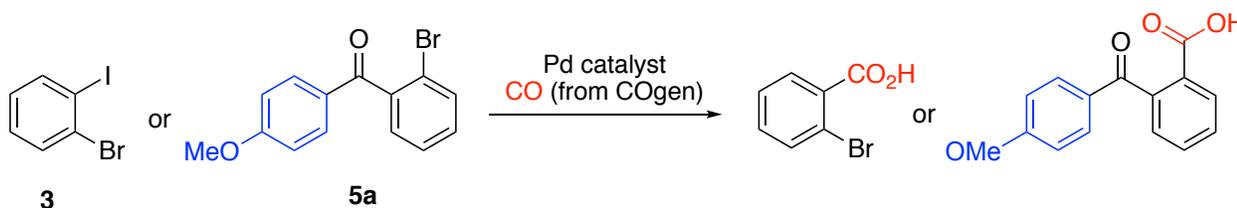
Procedures:

In a dry and clean 8 ml vial equipped with a stirring bar, the aryl halide (1 equiv.), MePh$_2$SiCOOH (64 mg, 1.5 equiv), base (2-3 equiv.), palladium precursor and ligand were dissolved in 3 ml dioxane. The vial was tightly sealed with a screw cap. The reaction was allowed to stir for overnight at 40 °C. The crude mixture was then poured into water (30 ml) and diluted with DCM before pH was adjusted to 10.

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

The aqueous phase was washed with DCM several times. The combined aqueous phase was acidified to pH 2-3 using HCl (4M) and then washed with DCM for several times. The combined organic phase was then dried over MgSO₄, filtered by suction and concentrated *in vacuo* to leave the product as colorless solid.

Table ESI-3. Screening of catalyst and conditions for hydroxycarbonylation of **3** or **5a**.

Entry	Subst.	Pd source (mol%)	Ligand (mol%)	Base	Carboxylate source	Solvent	eq. CO	T (°C)	Isol. yield %
4	3	Pd(dba)₂ (5)	-	TMSOLi	MePh₂SiCO₂H	dioxane	2.5	110	-
6	3	Pd(dba)₂ (5)	Xantphos (5)	TMSOK	MePh₂SiCO₂H	toluene	1.5	60	traces
7	3	Pd(dba)₂ (5)	Xantphos (5)	TMSOK	MePh₂SiCO₂H	dioxane	1.5	60	60
8	5a	Pd(dba)₂ (5)	Xantphos (5)	TMSOLi	MePh₂SiCO₂H	dioxane	1.5	80	-
9	5a	Pd(dba)₂ (5)	Xantphos (5)	TMSOLi	MePh₂SiCO₂H	dioxane	1.5	115	-
10	5a	Pd(dba)₂ (5)	PPh₃ (10)	TMSOLi	MePh₂SiCO₂H	dioxane	2.5	110	-

The following control experiments were performed to establish that the procedure gives the wanted carboxylation product for standard substrates.
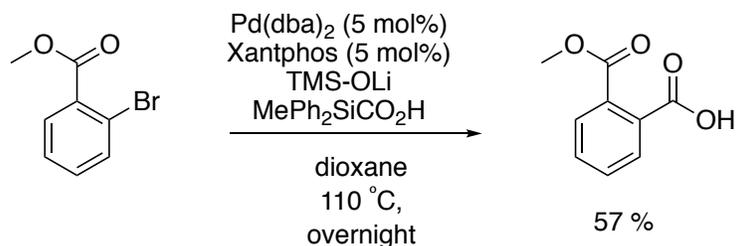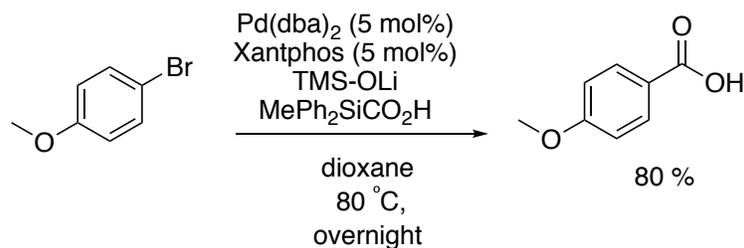
2.5 Screening for catalysts and conditions for the alkoxycarbonylation of 2-bromobenzophenone 5a
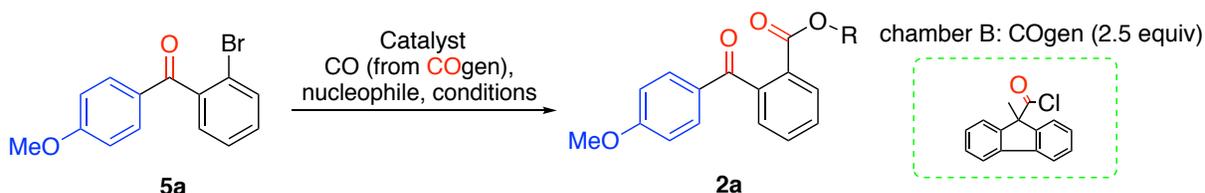
Procedure:

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

Chamber A: 2-Bromophenyl-4-methoxyphenylmethanone **5a** (1.0 equiv, 0.47 mmol), Pd precursor and base (3 equiv) were dissolved in solvent (2 ml). The nucleophile (2 equiv) was added to the reaction mixture.

Chamber B: COgen (2.5 equiv), Pd(dba)$_2$ (5 mol%), TTBP•HBF$_4$ (5 mol%) were dissolved in anisole (3 ml) before DIPEA (3 equiv) was added. The mixture was stirred with heating in a tightly closed system for 20-24 hours.

The reaction mixture in chamber A was filtered through celite and concentrated on a rotavapor. The crude was purified by column chromatography with pentane : EtOAc (7:3) as eluent.

Table ESI-4. Screening for conditions for alkoxycarbonylation on the 2-bromobenzophenone.

Entry	Pd source (mol%)	Ligand (mol%)	Nucl.	Base	Solvent	T (ºC)	Isol. yield (%)
1	dppf(PdCl$_2$) (10)		H$_2$O	TEA	H$_2$O: THF (1:4)	120	-*
2	dppf(PdCl$_2$) (10)	Dppf (20)	iPrOH	TEA	DMF	80	11
3	dppf(PdCl$_2$) (10)	Dppf (20)	nBuOH	TEA	DMF	80	-*
4	Pd(OAc)$_2$ (2)	Xantphos (4)	iPrOH	TEA	TEA	80	15
5	Pd(OAc)$_2$ (2)	Xantphos (4)	nBuOH	TEA	TEA	80	11
6	Pd(OAc)$_2$ (2)	Xantphos (4)	MeOH	TEA	Dioxane	110	5
7	dppf(PdCl$_2$) (10)	Dppf (20)	MeOH	TEA	DMF	80	-*
8	Pd(dba)$_2$ (5)	Dippf (5)	EtONa	-	THF	80	-*
9	PEPPSI-IPr (3)		nBuOH	Cs$_2$CO$_3$	Chlorobenzene	80	-*
10	PEPPSI (5)	IMes (10)	nBuOH	Cs$_2$CO$_3$	Chlorobenzene	110	-*
11	Pd(PPh$_3$)$_2$Cl$_2$ (5)	IMes (10)	nBuOH	Cs$_2$CO$_3$	Heptane	120	-*
12	PdCl$_2$ (2)	Xantphos (2)	nBuOH	K$_2$CO$_3$	Anisole	110	65

* Only starting material or the corresponding biphenyl were detected.

Table ESI-5. Control experiments for alkoxycarbonylation with 4-bromobenzophenone.
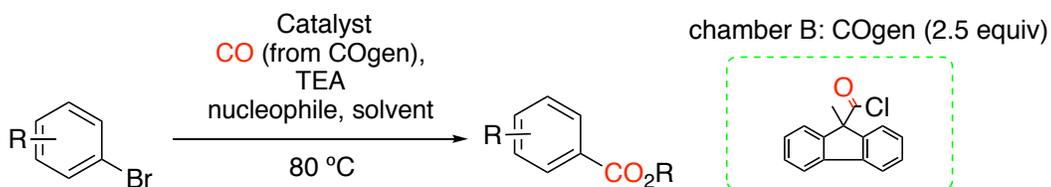
Entry	Substrate	Pd source (mol%)	Ligand (mol%)	Nucl.	Base	Solvent	Isol. yield (%)
1		Pd(OAc)$_2$ (2)	Xantphos (4)	nBuOH	TEA	TEA	99
2		dppfPdCl$_2$ (10)	Dppf (20)	iPrOH	TEA	DMF	97
3		Pd(OAc)$_2$ (2)	Xantphos (4)	nBuOH	TEA	TEA	11
4		dppfPdCl$_2$ (10)	Dppf (20)	iPrOH	TEA	DMF	11
5		Pd(dba)$_2$ (5)	Dippf (5)	tBuONa	-	THF	60

2.6 Screening for catalysts and conditions for the carbonylative Suzuki-Miyaura coupling of methyl 2-bromobenzoate 6a

Table ESI-6. Optimization of reaction conditions for the palladium catalyzed carbonylative Suzuki-Miyaura coupling of methyl-2-bromobenzoate **6a**.
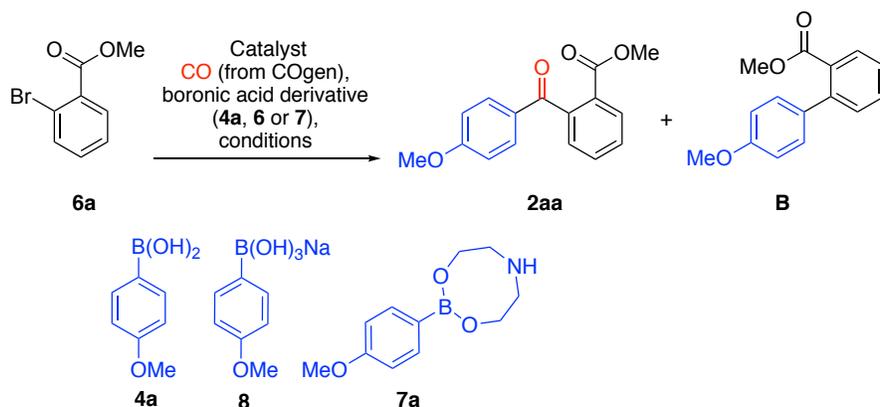
Entry	Pd-source (mol%)	Ligand (mol%)	Nuc.	base	solvent	T (ºC)	addition	Ratio[d] 2aa: B	Isol. yield (%)
1[a]	Pd(acac)$_2$ (5)	CataCXium A·HI (10)	8	-	Toluene: H$_2$O (10:1)	80	normal	1 : 0.45	65[a]
2[a]	Pd(acac)$_2$ (5)	CataCXium A·HI (10)	7a	-	Toluene: H$_2$O (10:1)	95	normal	1 : 0.3	67[a]
3	Pd(acac)$_2$ (5)	CataCXium A (10)	4a	K$_2$CO$_3$	Toluene: H$_2$O (10:1)	100	normal	-	30
4[a]	Pd(acac)$_2$ (5)	CataCXium A·HI (10)	7a	-	DMSO	90	normal	-	traces[a]
5[a]	Pd(acac)$_2$ (5)	CataCXium A·HI (10)	7a	-	DMF: H$_2$O (10:1)	90	normal	-	-[*,a]
6	Pd(acac)$_2$ (5)	CataCXium A·HI (10)	7a	-	Toluene: H$_2$O: MeOH (10:1:1)	90	slow	-	traces
7	Pd(acac)$_2$ (5)	CataCXium A·HI (10)	7a	-	Toluene: H$_2$O: TBAB (1:1:0.5)	95	slow	-	traces
8[a]	Pd(acac)$_2$ (5)	CataCXium A·HI (10)	7a	-	Dioxane: H$_2$O (10:1)	95	normal	-	-[*,a]
9[b]	PdCl$_2$ (1)		4a	K$_2$CO$_3$	Anisole	110	normal	-	-[*,b]
10[b]	Pd(OAc)$_2$ (5)	CataCXium A (10)	4a	K$_2$CO$_3$	Toluene: H$_2$O (10:1)	110	normal	-	-[*,b]
11[b]	Pd(PPh)$_3$Cl$_2$ (10)		4a	K$_2$CO$_3$	Anisole	110	normal	0.2 : 1	20[b]
12[b]	Pd(OAc)$_2$ (5)	Xantphos (5)	4a	Cs$_2$CO$_3$	Toluene	80	normal	0.3 : 1	20[b]
13[c]	Xantphos G2 (5)		4a	K$_2$CO$_3$	Anisole	100	slow	-	traces[c]
14[b]	Pd(OAc)$_2$ (5)	CataCXium A (10)	4a	K$_2$CO$_3$	Dioxane	100	normal	-	traces[b]
15[b]	PdCl$_2$ (2)	Xantphos (4)	4a	K$_2$CO$_3$	Toluene	100	normal	-	-[*,b]
16[b]	PEPPSI-IPr (3)		4a	Cs$_2$CO$_3$	Chlorobenzene	80	normal	1 : 0.5	60[b]
17[c]	PEPPSI-IPr (3)		4a	Cs$_2$CO$_3$	Chlorobenzene	110	slow	1 : 0.15	80[c]

18[c]	PEPPSI-IPr (3)		4a	Cs$_2$CO$_3$	Anisole	110	slow	1 : 0.15	80[c]
19[b]	PEPPSI-Allyl (3)		4a	Cs$_2$CO$_3$	Anisole	110	normal	1 : 0.6	50[b]
20[b]	Ni(COD)$_2$	dcype	4a	Cs$_2$CO$_3$	Toluene	110	normal	-	-*,[b]

a Following general procedure E. b Following general procedure D. c Following general procedure C. d The ratio (2aa : B) was determined using ^{13}C NMR of the crudes. *Only starting material or the corresponding biphenyl B were detected.

*Characterization of methyl 4'-methoxy-[1,1'-biphenyl]-2-carboxylate **B**.*
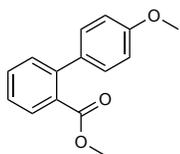
The title compound was isolated as a side product from reactions towards **2aa**. NMR: δH (400 MHz, CDCl$_3$) 7.70 (1H, d, *J* 8.2), 7.41 (1H, t, *J* 8.3), 7.29 (2H, d, *J* 7.3), 7.16 (2H, d, *J* 8.8), 6.85 (2H, d, *J* 8.8), 3.75 (3H, s), 3.58 (3H, s). δC (101 MHz, CDCl$_3$) 169.5, 159.1, 142.1, 133.7, 131.3, 131.0, 130.8, 129.8, 129.6, 126.9, 113.7, 77.5, 77.2, 76.8, 55.4, 52.1.

3   References

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4 Spectra

4.1 Spectra for diaryl ketones 5

2-Bromophenyl 4-methoxyphenyl methanone 5a.

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

312.9827
$C_{14} H_{11} O_2 Br Na$ = 312.9835
-0.7961 mmu

291.0007
$C_{14} H_{12} O_2 Br$ = 291.0015
-0.8187 mmu

341.1135

319.1316

393.2960

2-bromo-4'-methoxy-1,1'-biphenyl **A** *(from direct coupling)*

abai−s1−1f5

D (m)
7.34

A (d)
7.66

C (d)
6.97

E (m)
7.18

B (s)
3.87

— 18 —
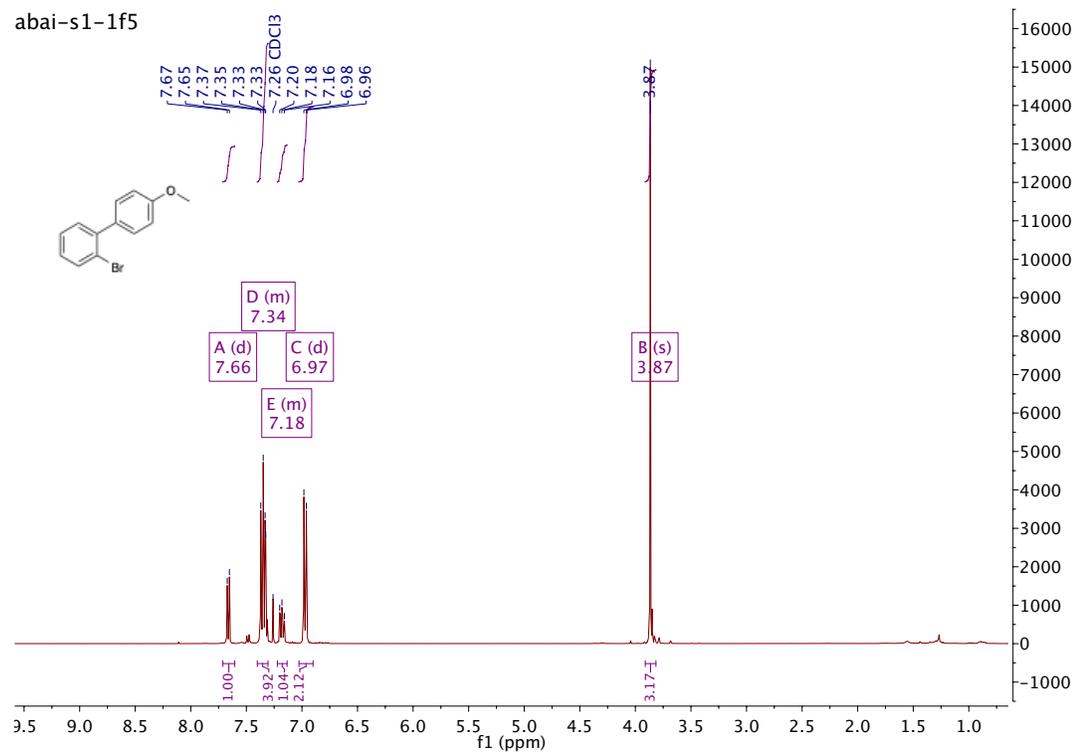
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

abai-s1-1f5
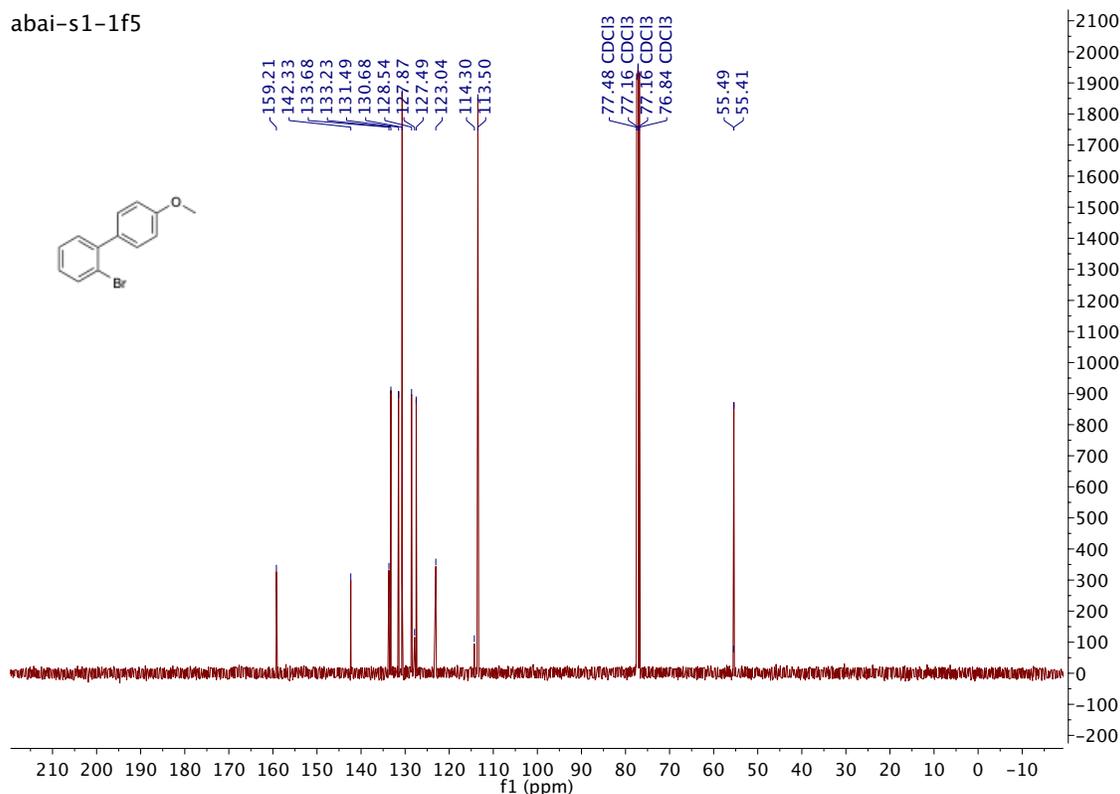
*2-Bromophenyl 3-methoxyphenyl methanone **5b***

abai-85-1f1p_20180220.1.fid
Project AB_
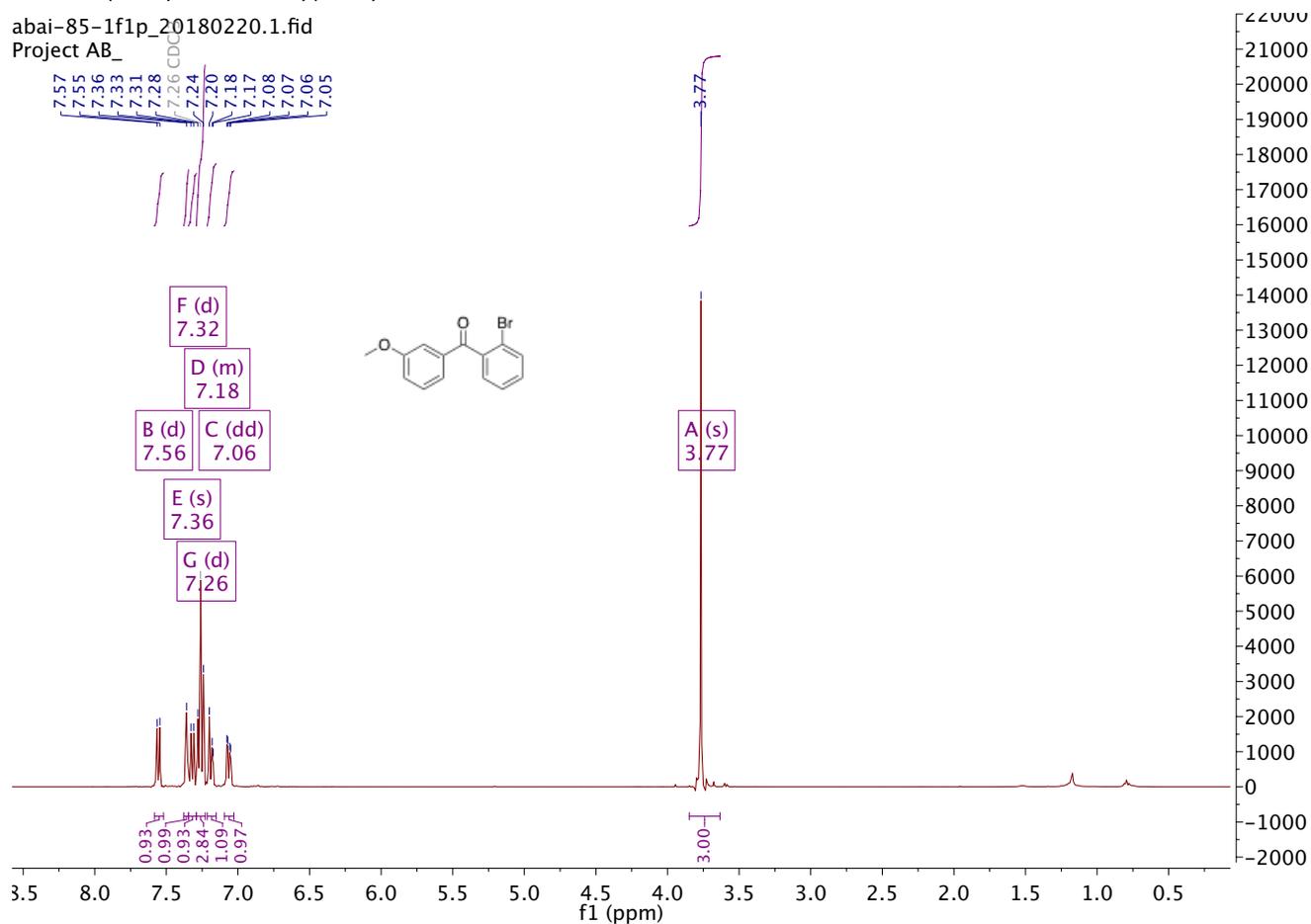
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

abai-85-1f1p_20180220.3.fid
Project AB_

195.78
159.98
140.82
137.56
133.29
131.25
129.71
129.03
127.26
123.63
120.58
119.63
113.76
77.16 CDCl3
55.61

f1 (ppm)
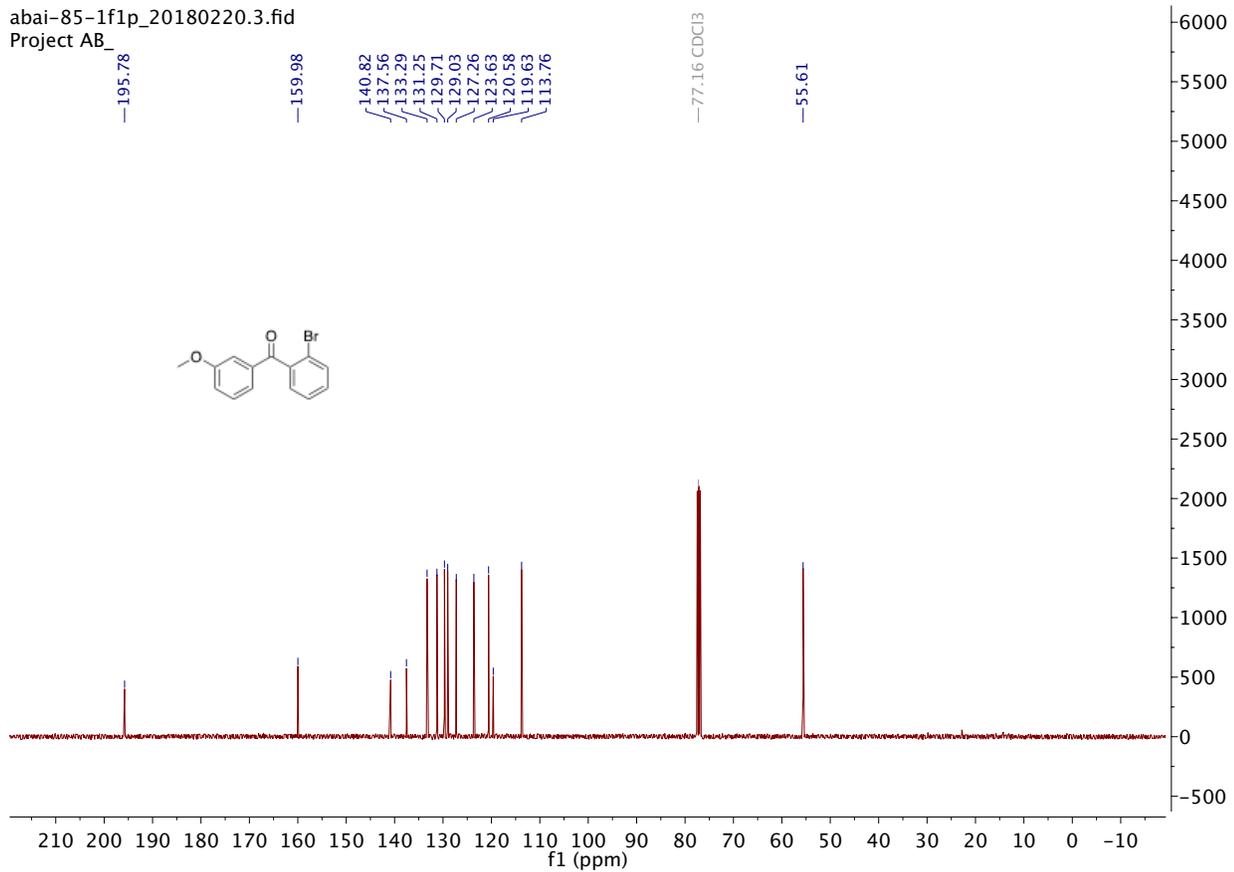
abai-85-1_180618144811 #1-4 RT: 0.00-0.09 AV: 4 NL: 2.58
T: FTMS + p ESI Full ms [200.00-400.00]
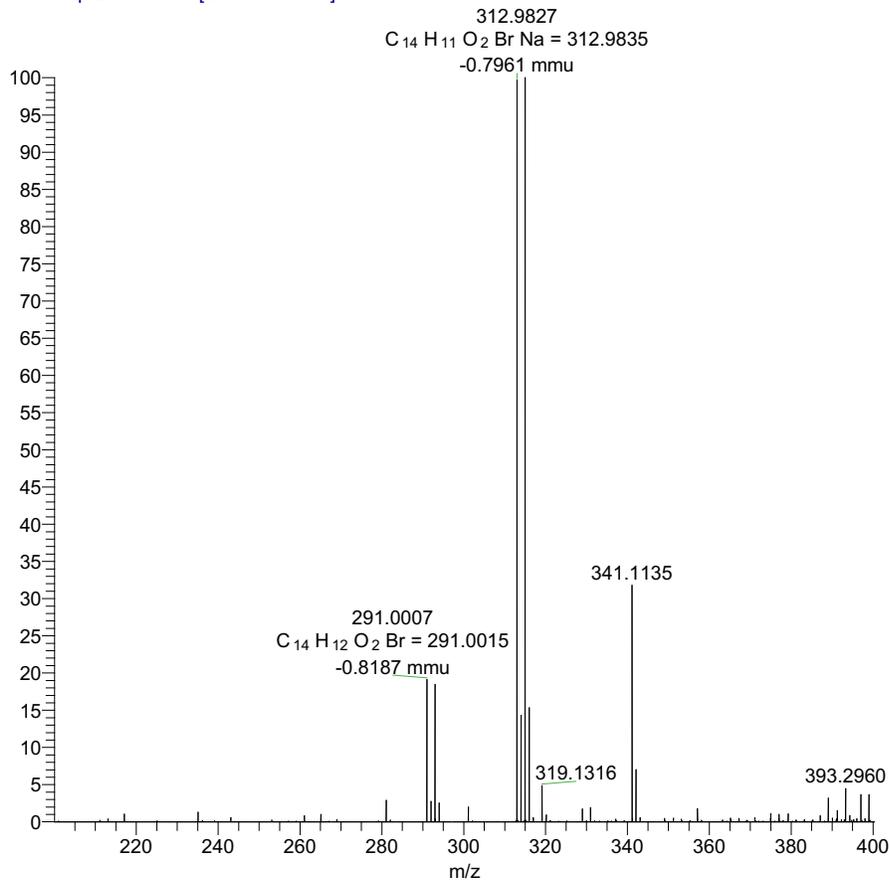
312.9827
$C_{14}H_{11}O_2BrNa$ = 312.9835
-0.7961 mmu

341.1135

291.0007
$C_{14}H_{12}O_2Br$ = 291.0015
-0.8187 mmu

319.1316

393.2960

m/z

– 20 –

2-Bromophenyl 2-methoxyphenyl methanone **5c**

abai–85–2p_20180220.1.fid
Project AB_

7.57
7.55
7.49
7.47
7.43
7.41
7.39
7.26 CDCl
7.26
7.26
7.24
7.19
7.17
7.16
6.94
6.93
6.91
6.84
6.82

3.55

G (m)
7.17

C (d)
7.48

F (t)
6.93

B (m)
7.56

E (d)
6.83

A (s)
3.55

D (t)
7.41

H (m)
7.25

0.95
0.96
1.03
1.69
1.14
1.08
1.07

3.00

f1 (ppm)

abai–85–2p_20180220.3.fid
Project AB_

195.34

159.46

142.80
134.51
133.13
131.85
131.04
129.39
127.32
127.15
120.76
119.57
112.11

77.16 CDCl3

55.91

f1 (ppm)

– 21 –

312.9827
$C_{14} H_{11} O_2 Br Na$ = 312.9835
-0.7361 mmu

291.0008
$C_{14} H_{12} O_2 Br$ = 291.0015
-0.7447 mmu

341.1134

235.1106

265.0826

319.1315

m/z

*2-Bromophenyl 4-(methylthio)phenyl methanone **5d***

ABAI–86–52NDP_20180224.1.fid
Project AB_

7.72
7.69
7.64
7.62
7.41
7.39
7.35
7.33
7.31
7.30
7.26 CDCl3
7.26
7.25
7.24

2.51

F (d)
7.40

C (d)
7.63

B (d)
7.70

D (m)
7.25

E (m)
7.32

A (s)
2.51

1.78
1.00
0.95
2.02
2.10

3.00

f1 (ppm)

— 22 —

ABAI-86-52NDP_20180224.3.fid
Project AB_
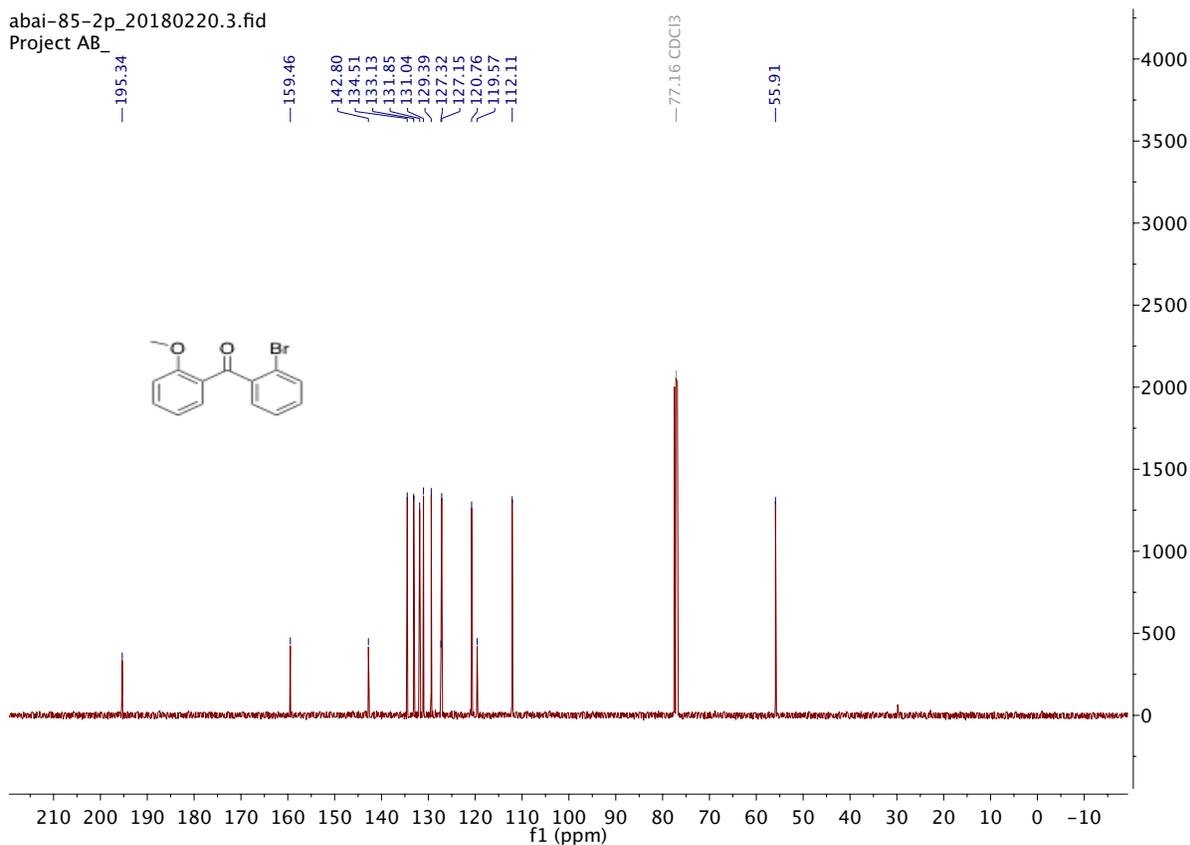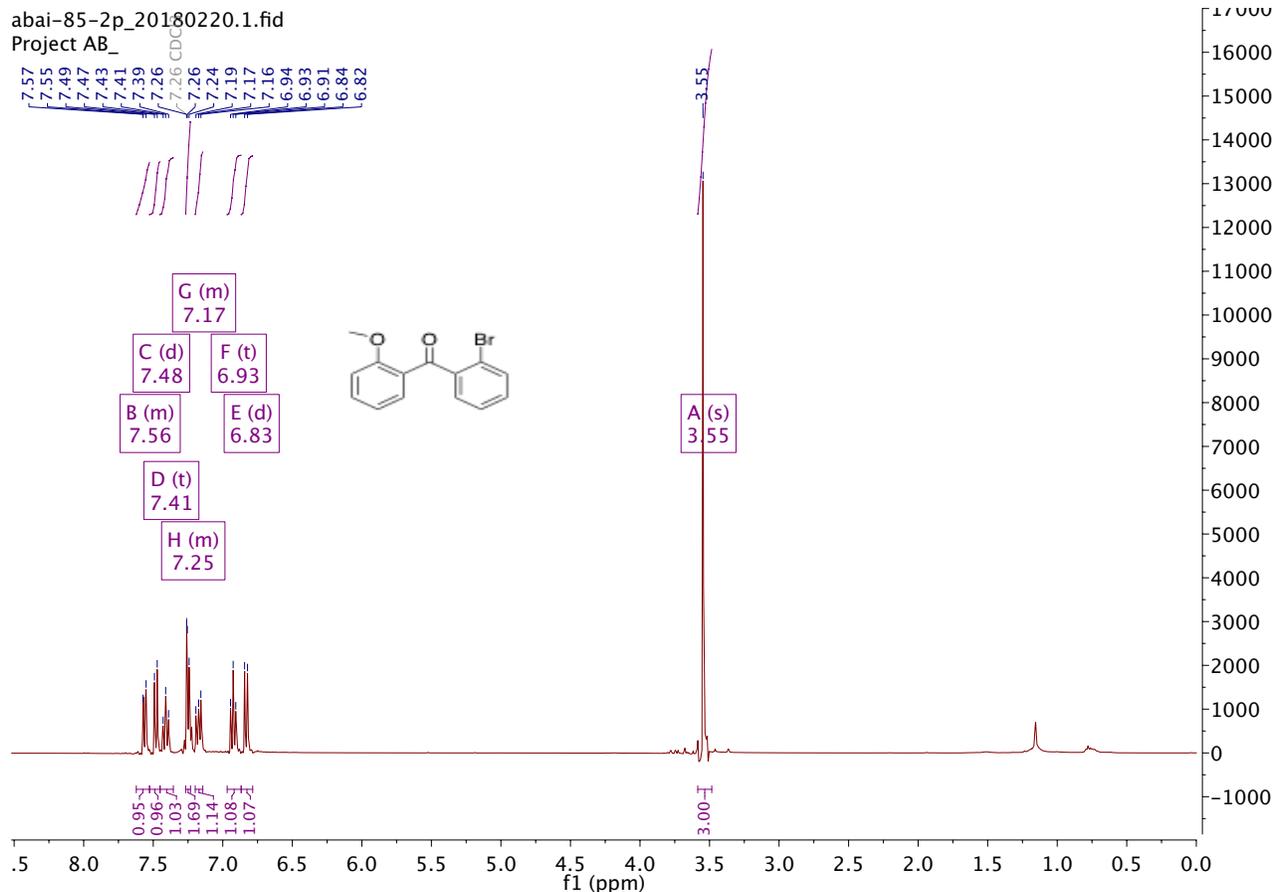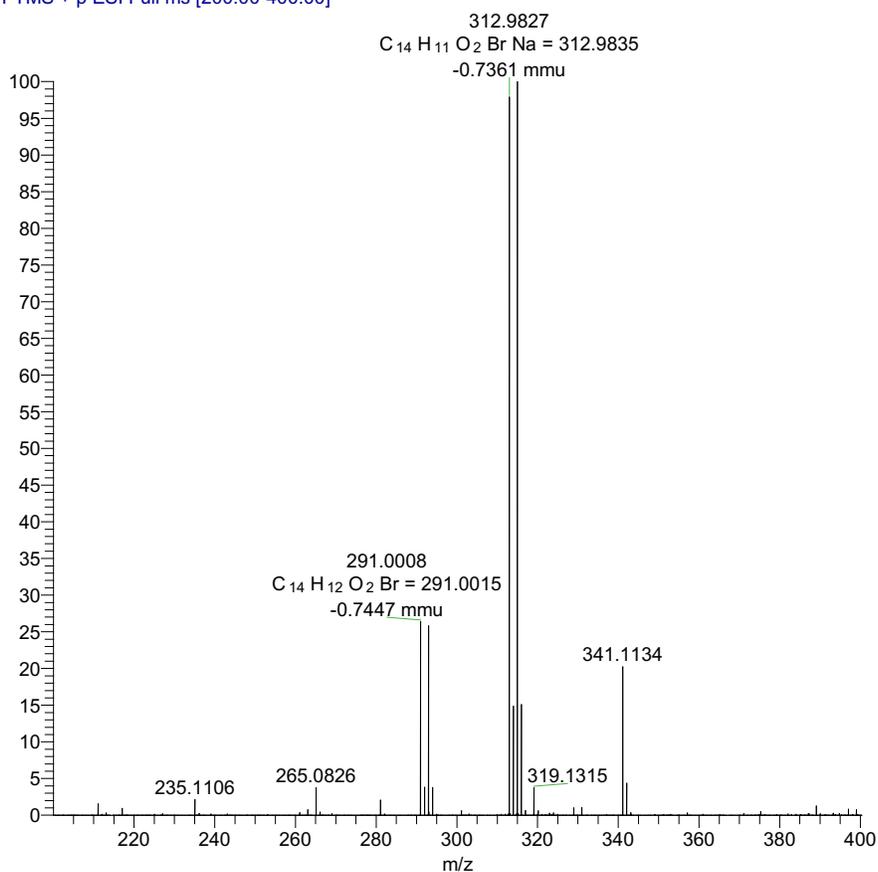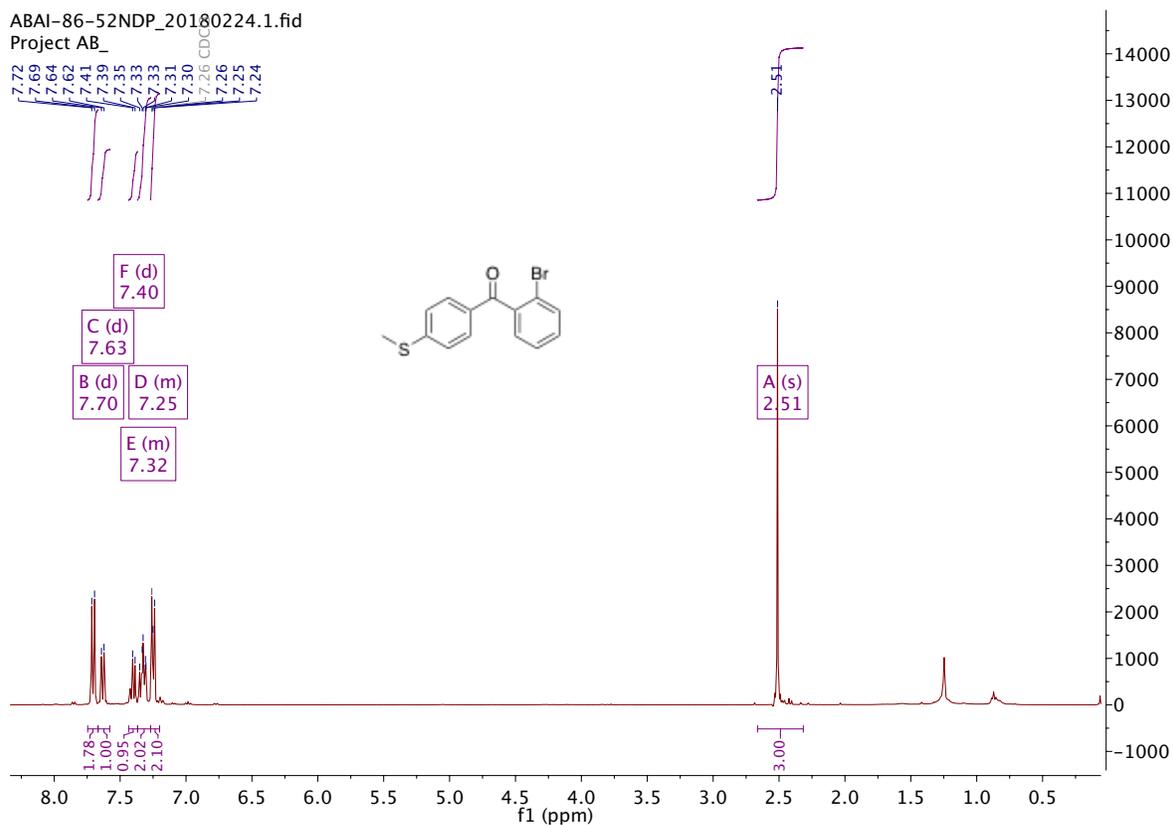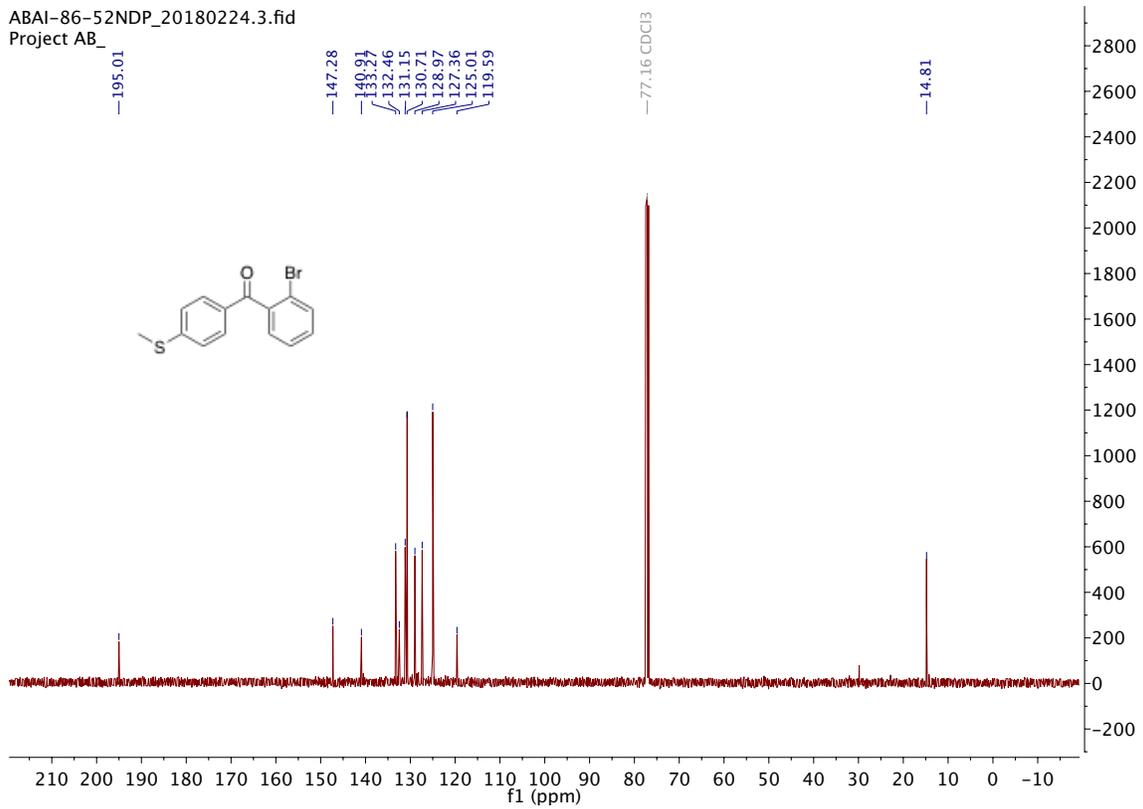
abai-86-5_180618152120 #1-5 RT: 0.01-0.12 AV: 5 NL: 2.15
T: FTMS + p ESI Full ms [200.00-400.00]

308.9756
$C_{14}H_{12}O\,^{81}Br\,S = 308.9766$
-0.9848 mmu

330.9573

351.0858   373.0678

227.0493
$C_{12}H_{12}O\,Na\,S = 227.0501$
-0.7818 mmu

275.0550
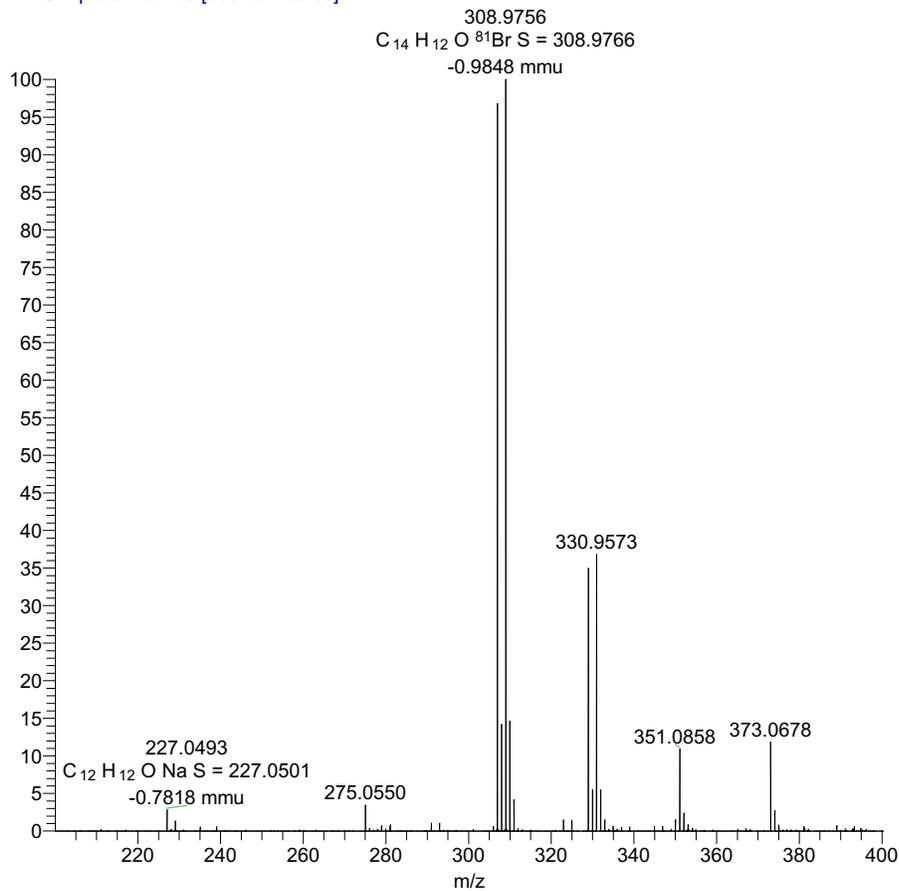
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

tert-Butyl 2-(2-bromobenzoyl)-1H-pyrrole-1-carboxylate **5e**

abai−91−2−f2_20180314.2.fid
Project AB_
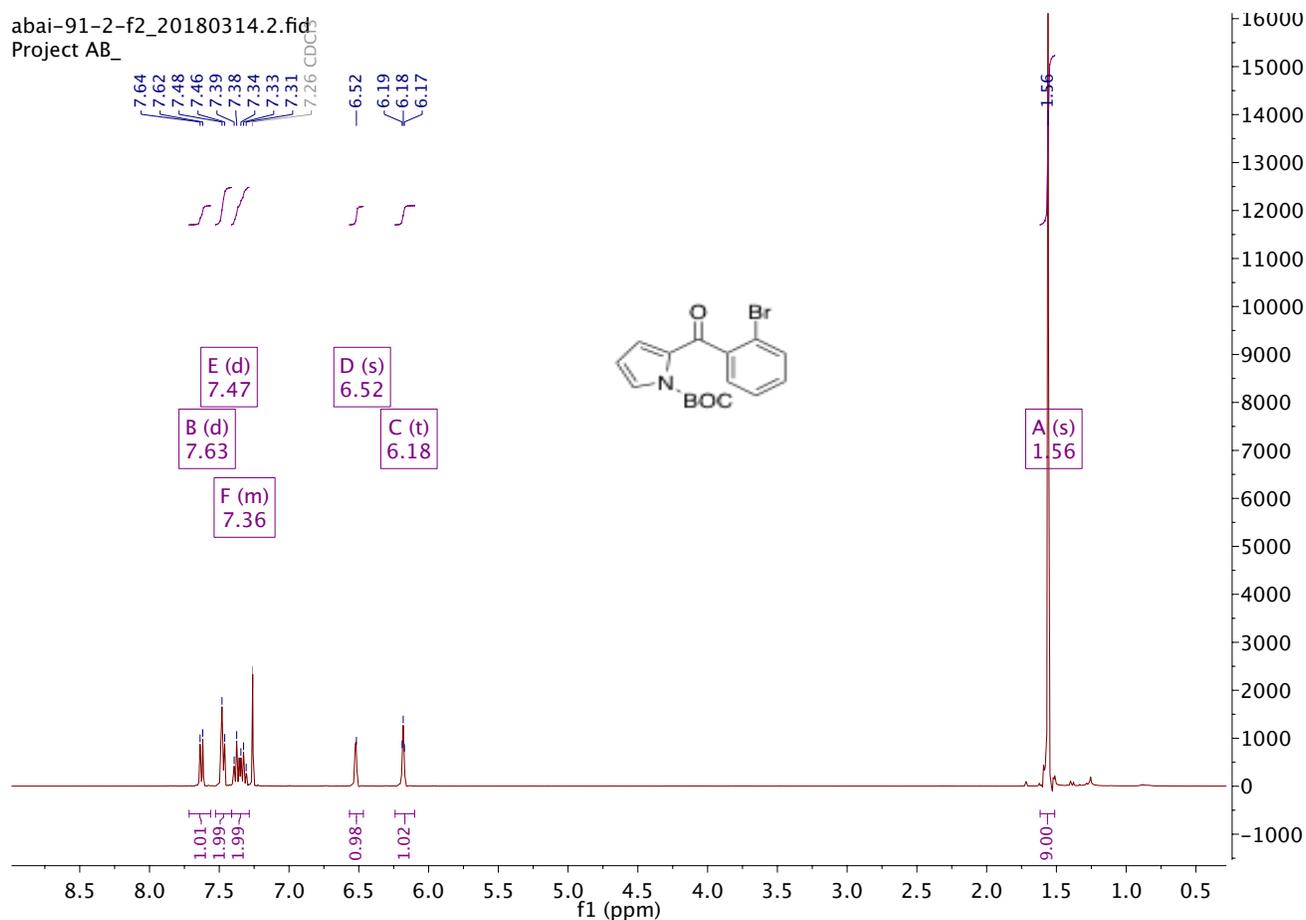
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

abai-91-2-f2_20180314.4.fid
Project AB_
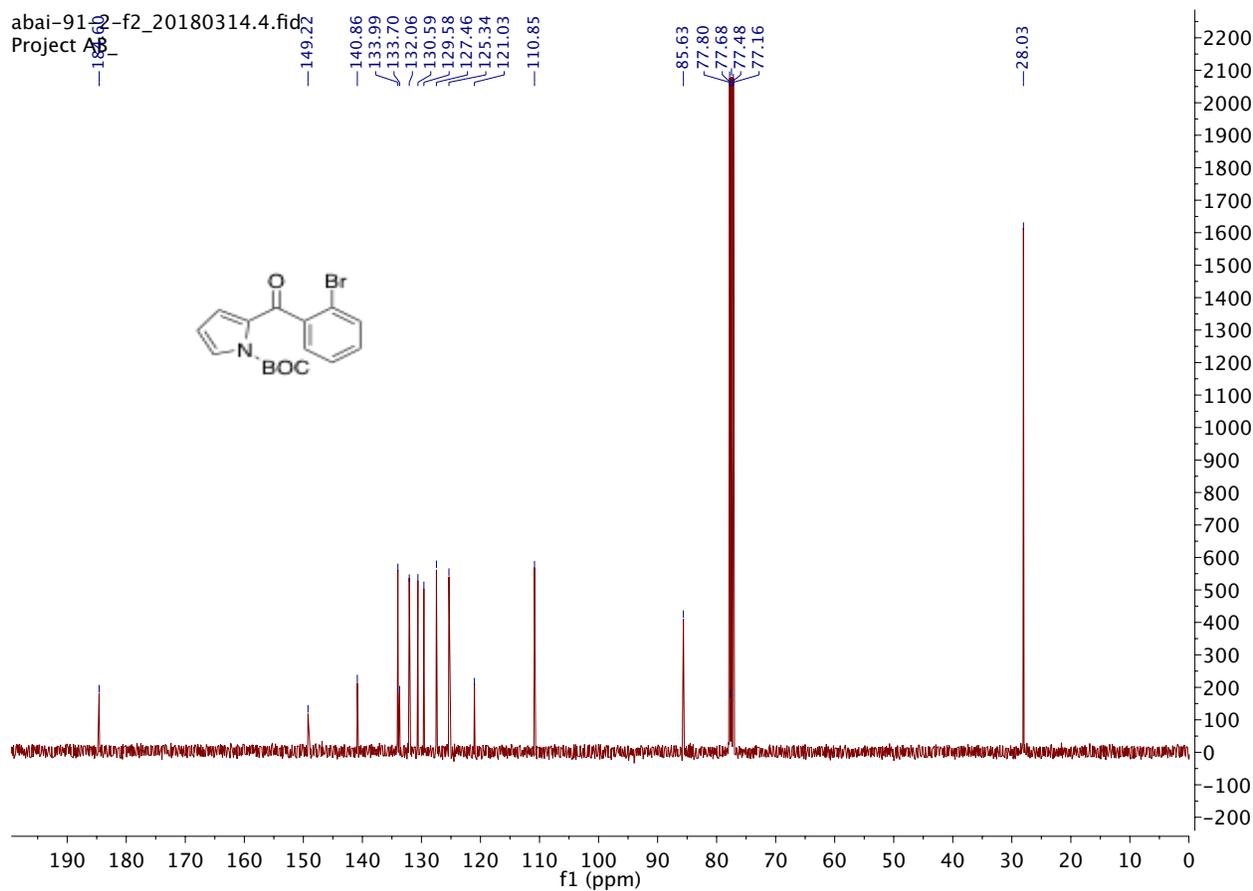
abai-91-2f2_180618163441 #1-5 RT: 0.02-0.13 AV: 5 NL: 1.8
T: FTMS + p ESI Full ms [200.00-500.00]

374.0177
$C_{16}H_{16}O_3N\ ^{81}Br\ Na = 374.0185$
-0.8596 mmu

383.1563

394.1610

429.0793

tert-butyl 2-(2-bromobenzoyl)-1H-indole-1-carboxylate **5f**

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

422.0353
$C_{20} H_{18} O_3 N Br Na$ = 422.0362
-0.9489 mmu
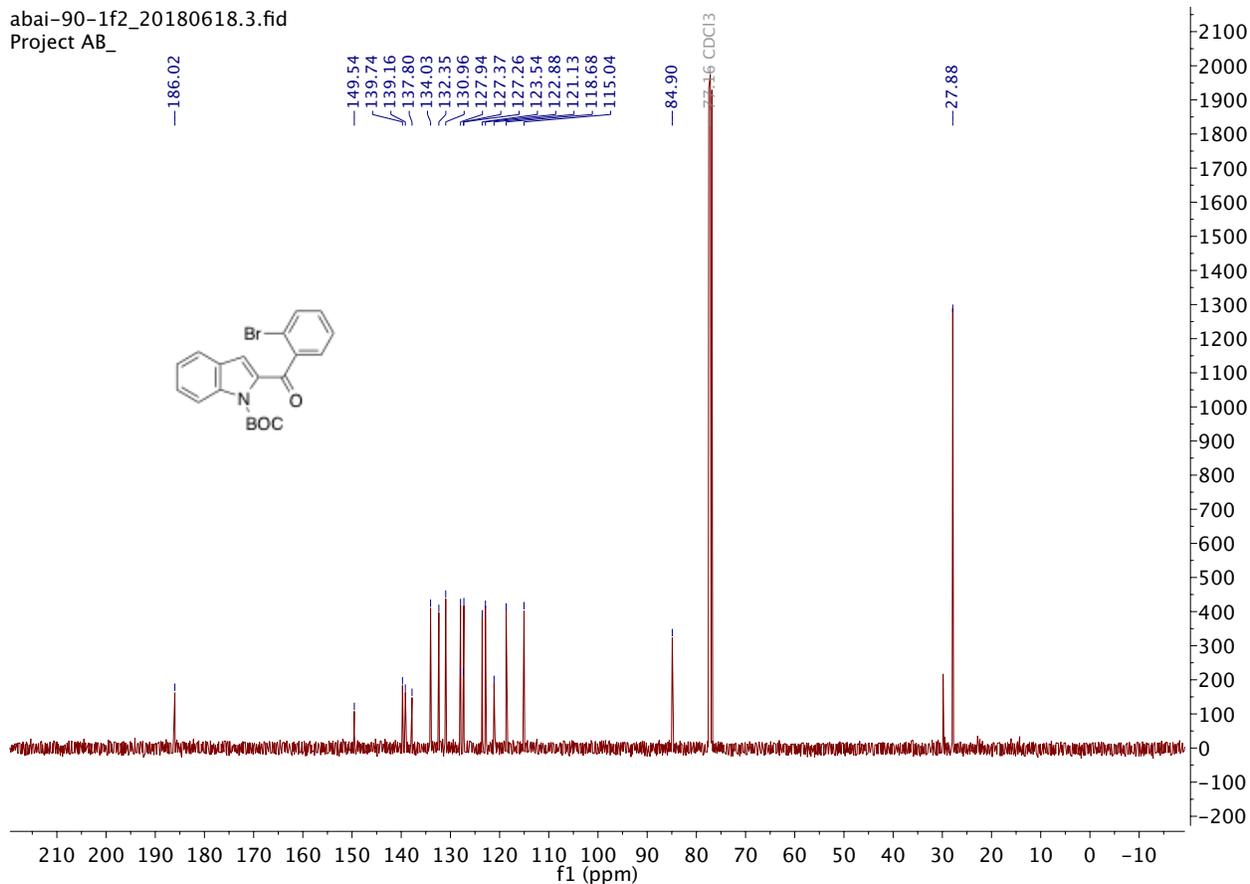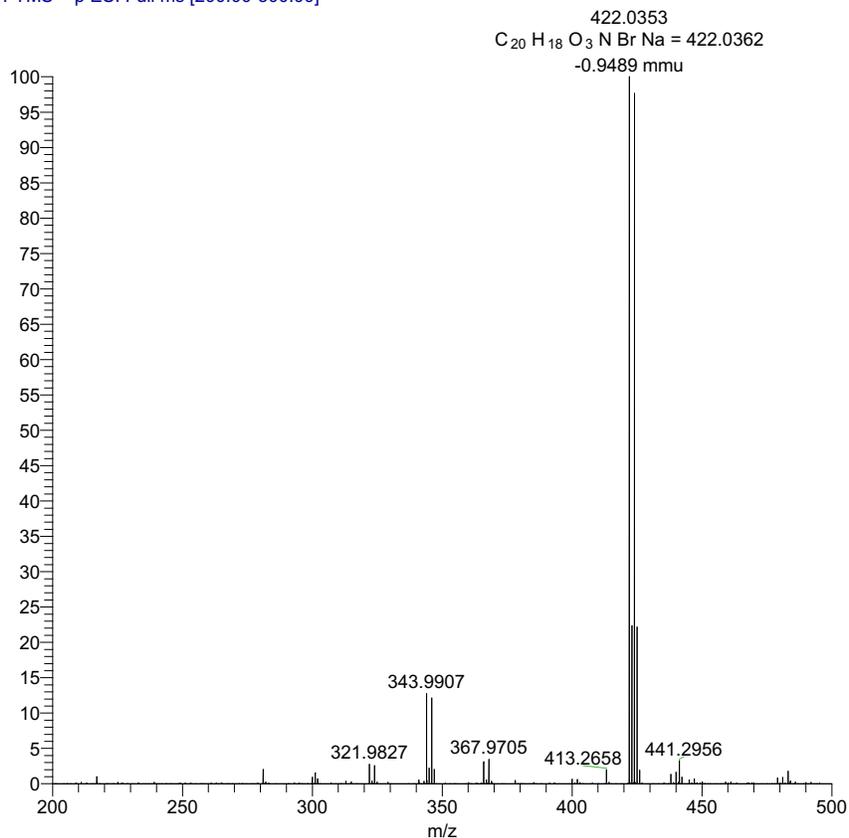
Methyl 3-(2-bromobenzoyl)benzoate **5g**

abai–89–1p_20180227.1.fid
Project AB_DEFACTO
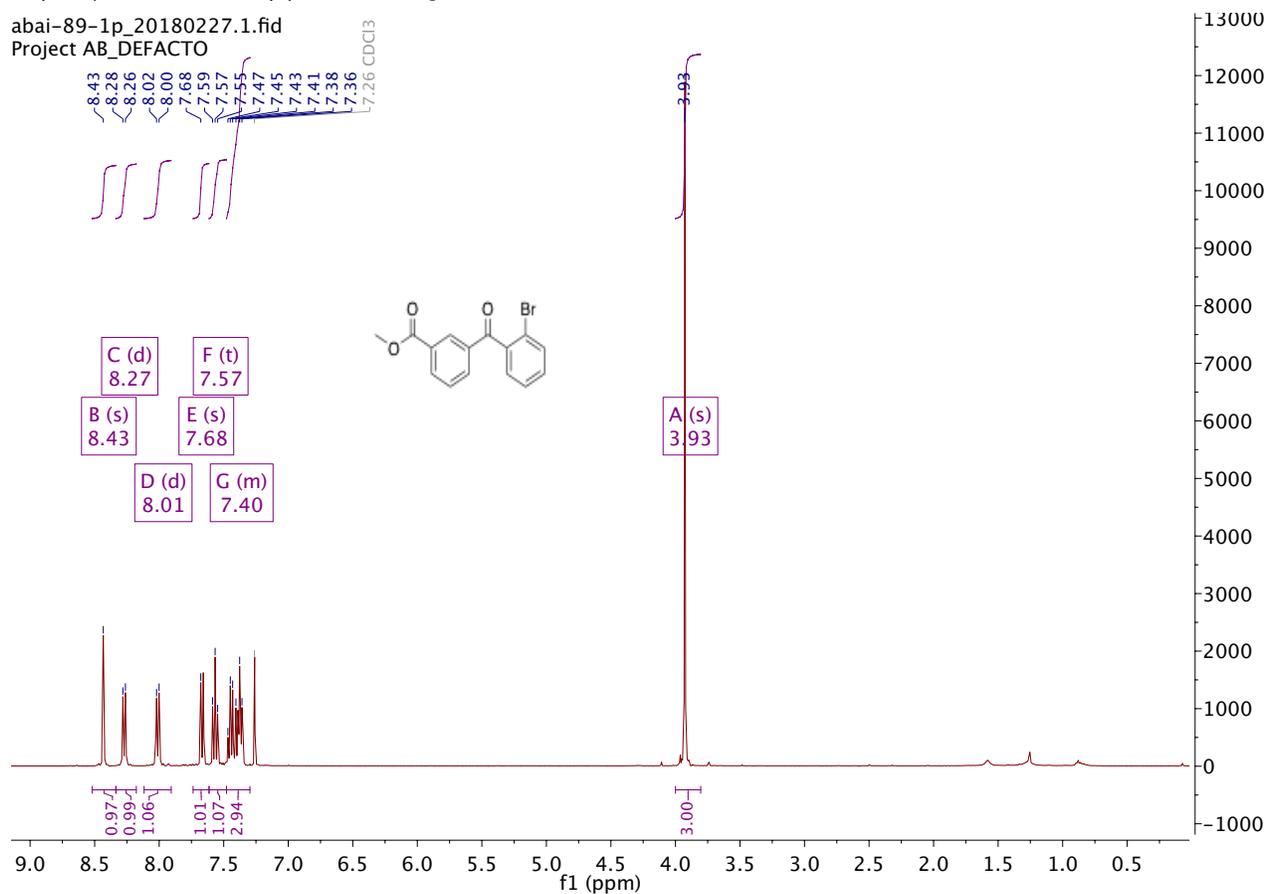
C (d)	F (t)
8.27	7.57

B (s)	E (s)
8.43	7.68

D (d)	G (m)
8.01	7.40

A (s)
3.93

abai–89–1p_20180227.3.fid
Project AB_DEFACTO
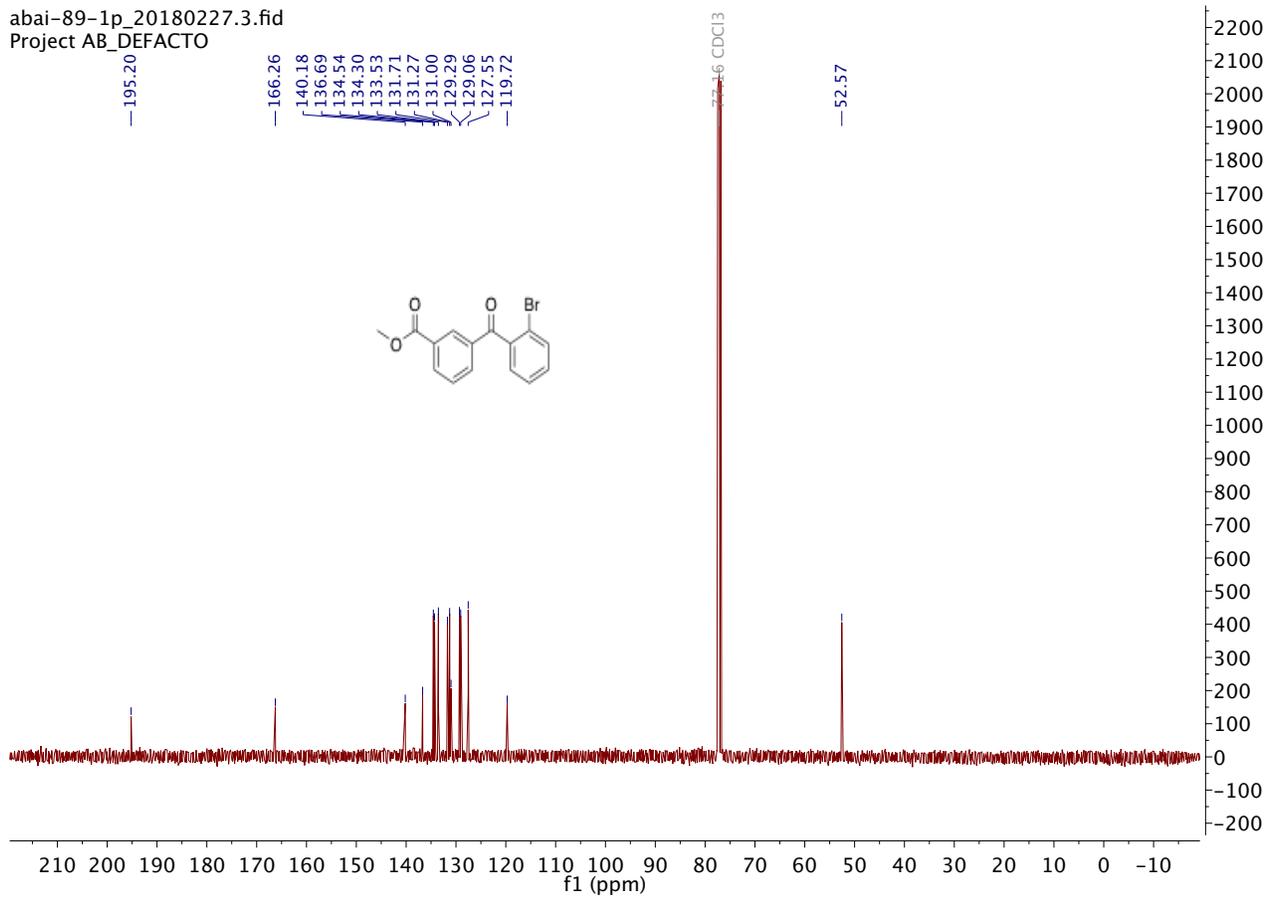
abai-89-1_180618154346 #1-5   RT: 0.02-0.13   AV: 5   NL: 1.39
T: FTMS + p ESI Full ms [200.00-400.00]
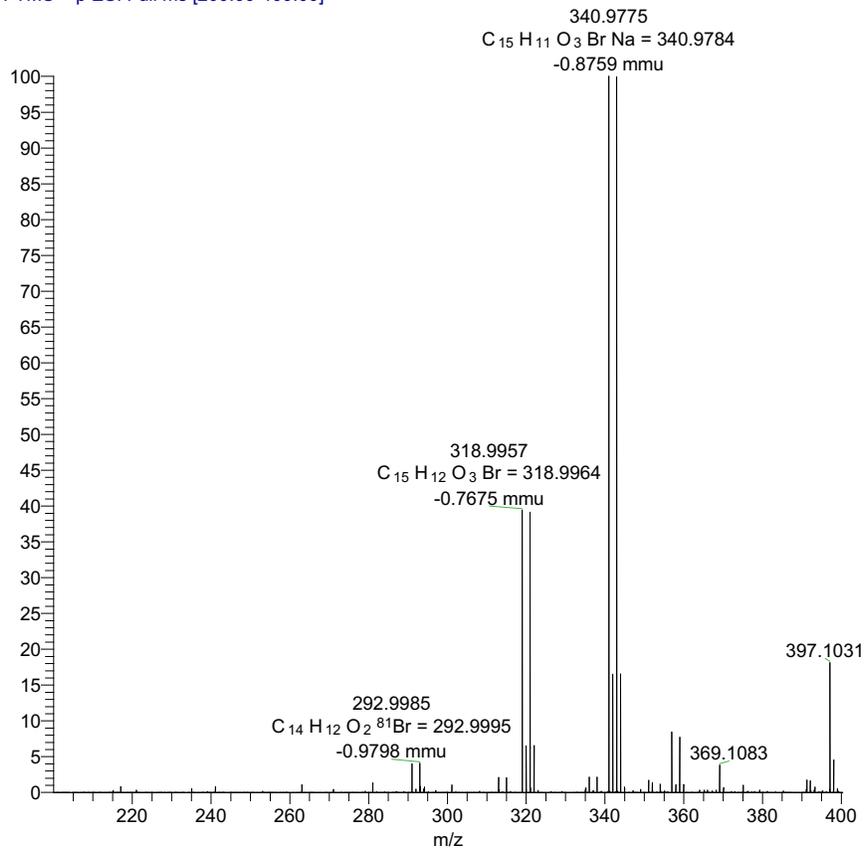
340.9775
$C_{15} H_{11} O_3 Br Na$ = 340.9784
-0.8759 mmu

318.9957
$C_{15} H_{12} O_3 Br$ = 318.9964
-0.7675 mmu

397.1031

292.9985
$C_{14} H_{12} O_2\ ^{81}Br$ = 292.9995
-0.9798 mmu

369.1083

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

Methyl 2-(2-bromobenzoyl)benzoate **5h**

ABAI−90−3P
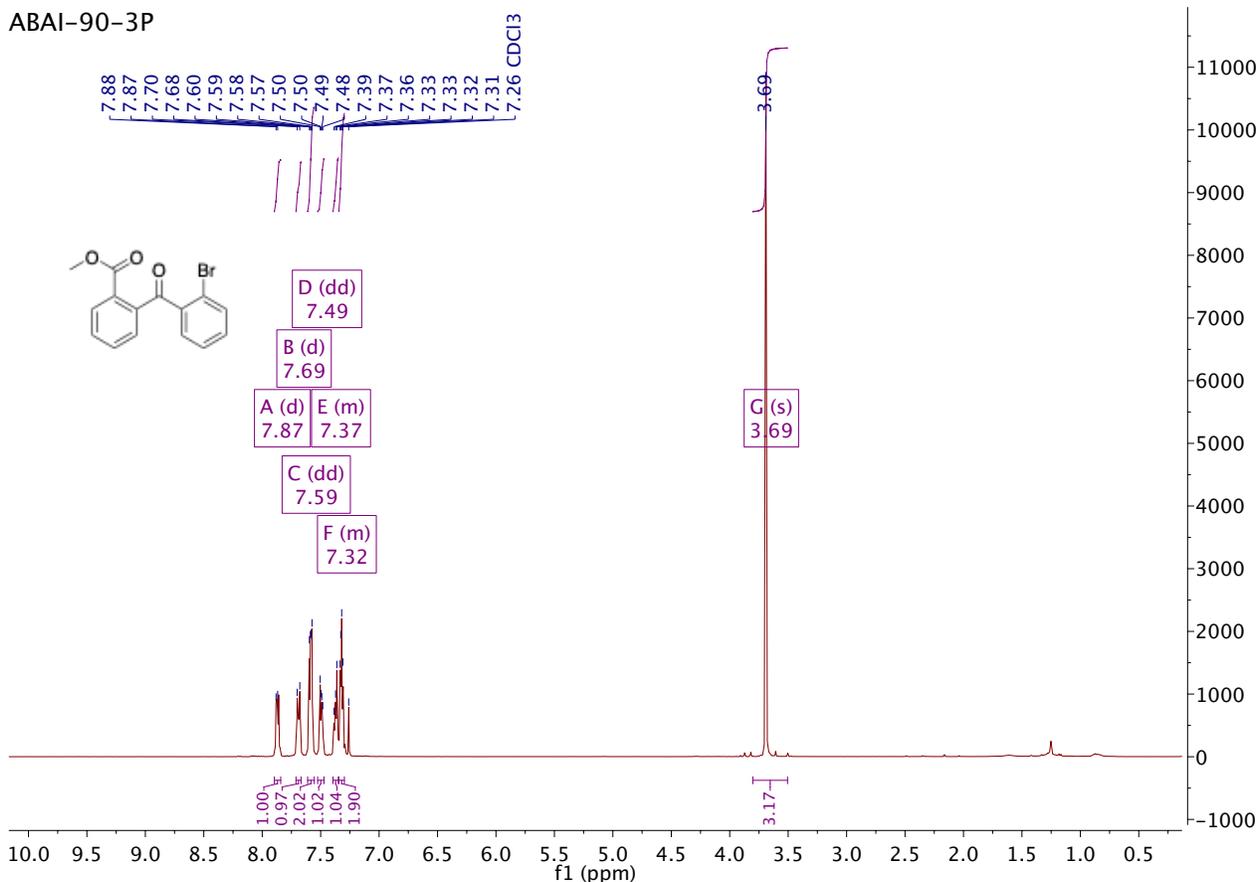
ABAI−90−3P
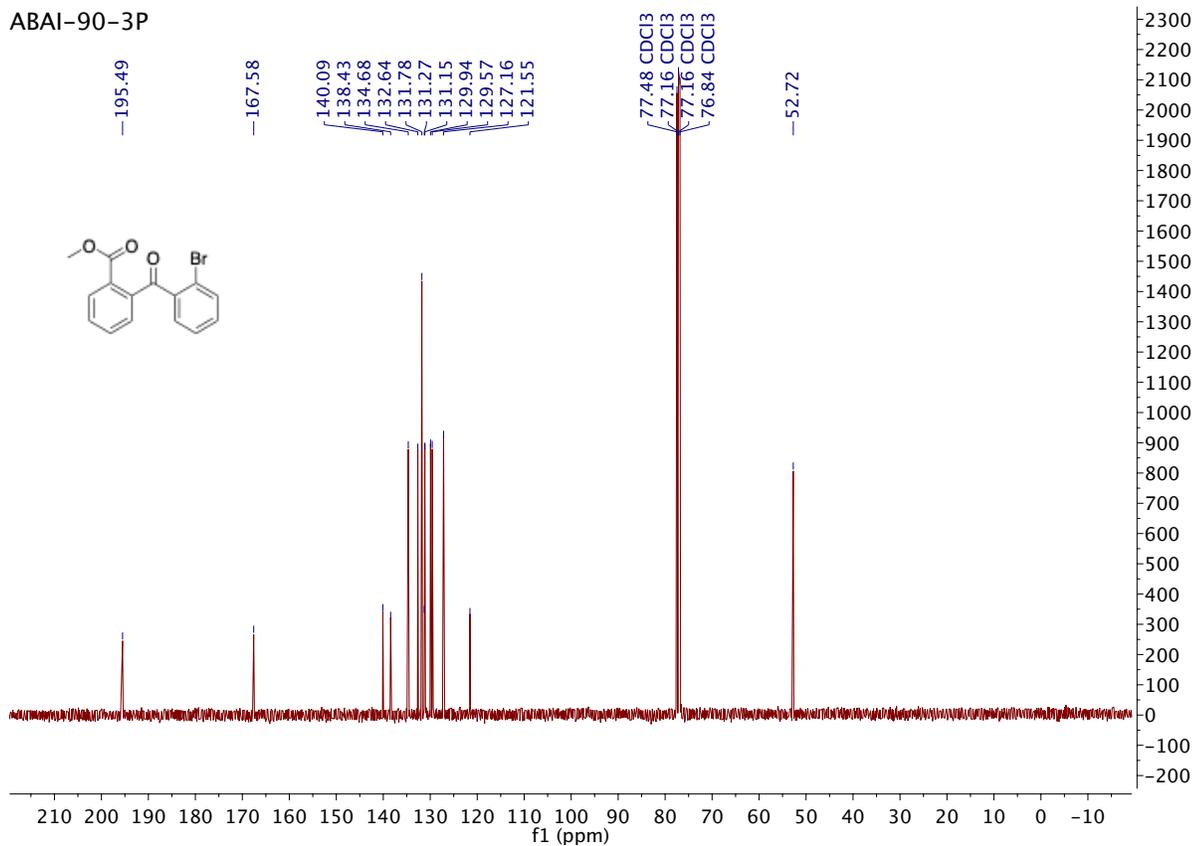
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

342.9757
$C_{15} H_{11} O_3\ ^{81}Br\ Na = 342.9763$
-0.6234 mmu

286.9696
$C_{14} H_8 O_2\ Br = 286.9702$
-0.6141 mmu

397.1034

369.1085

441.2961

m/z
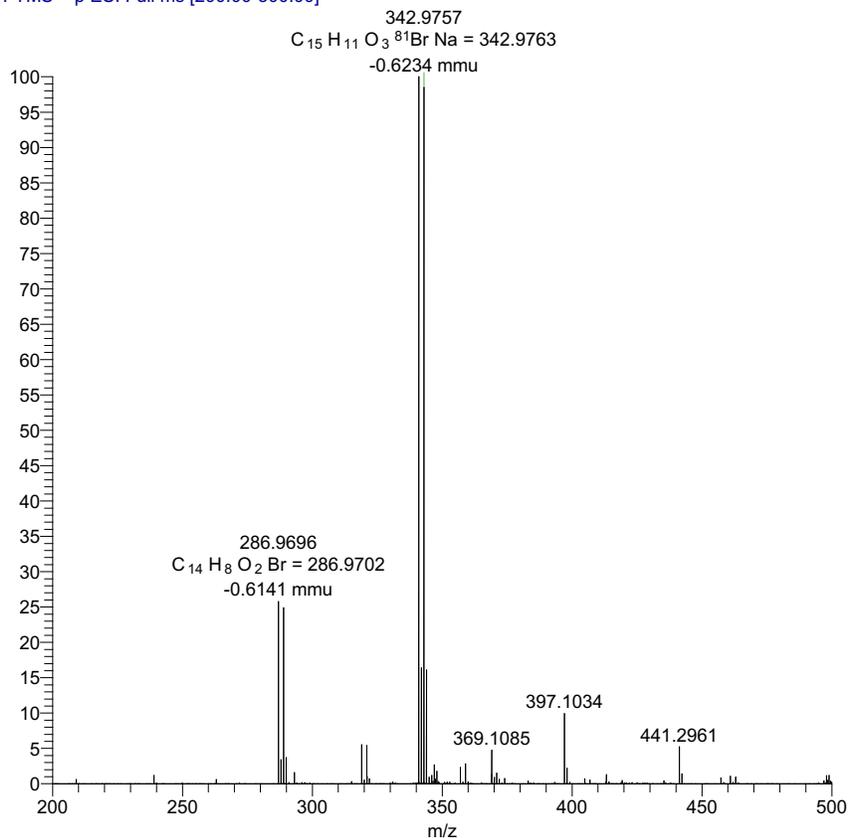
*4-(2-Bromobenzoyl)benzonitrile **5i***

ABAI–87–5P_20180223.1.fid
Project AB_
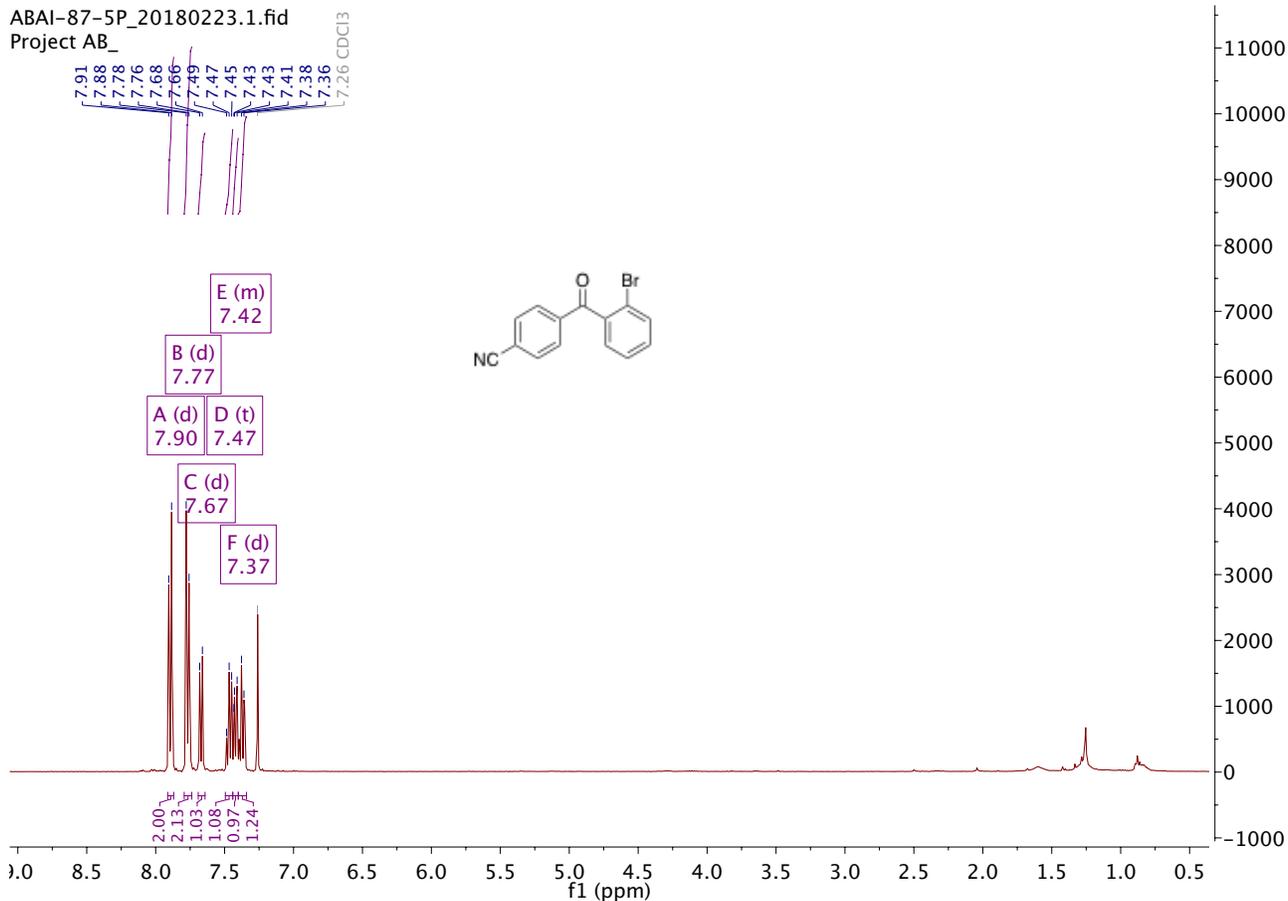
7.26 CDCl3

7.91
7.88
7.78
7.76
7.68
7.66
7.49
7.47
7.45
7.43
7.41
7.38
7.36

E (m)
7.42

B (d)
7.77

A (d)   D (t)
7.90   7.47

C (d)
7.67

F (d)
7.37

2.00
2.13
1.03
1.08
0.97
1.24

f1 (ppm)

–   30   –

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

ABAI-87-5P_20180223.3.fid
Project AB_

194.62

139.56
139.44
133.58
132.63
132.11
130.49
129.40
127.72
119.68
118.03
116.94

77.16 CDCl3
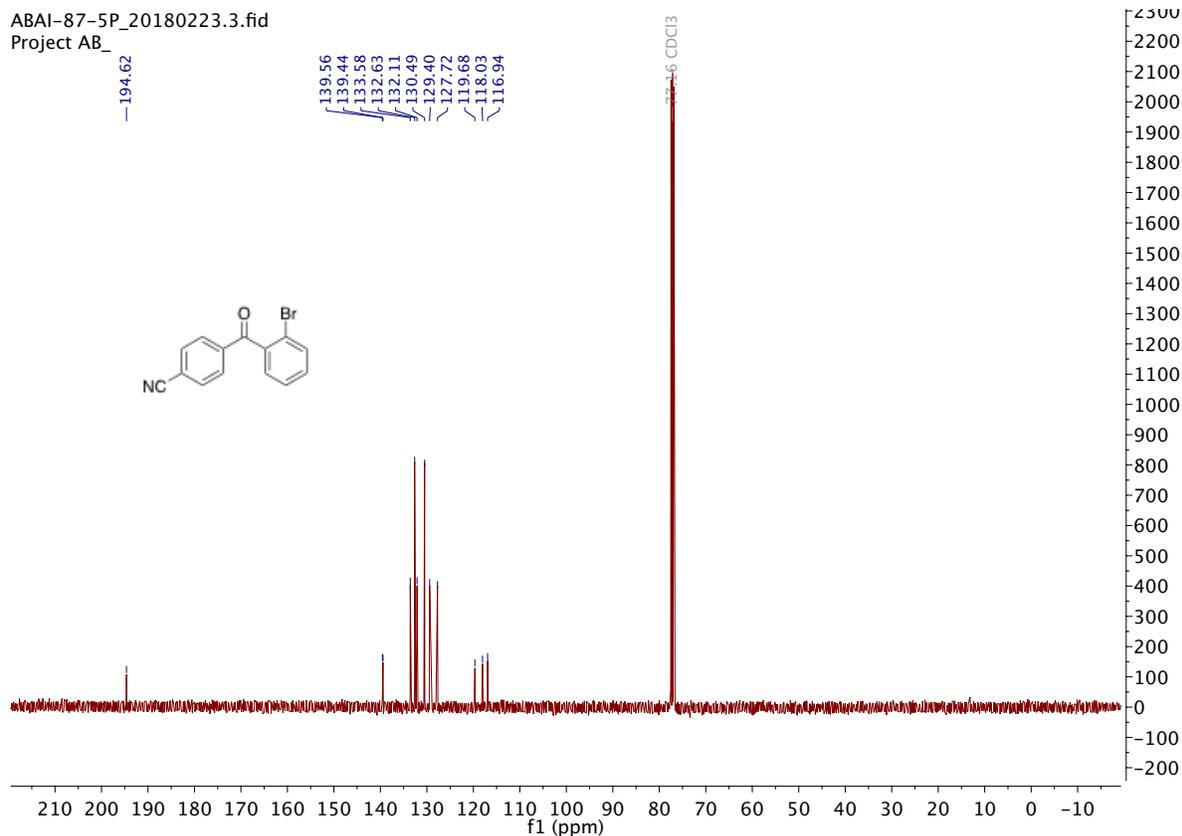
abai-87-5_180618154346 #1-5   RT: 0.02-0.13   AV: 5   NL: 1.76
T: FTMS + p ESI Full ms [200.00-400.00]
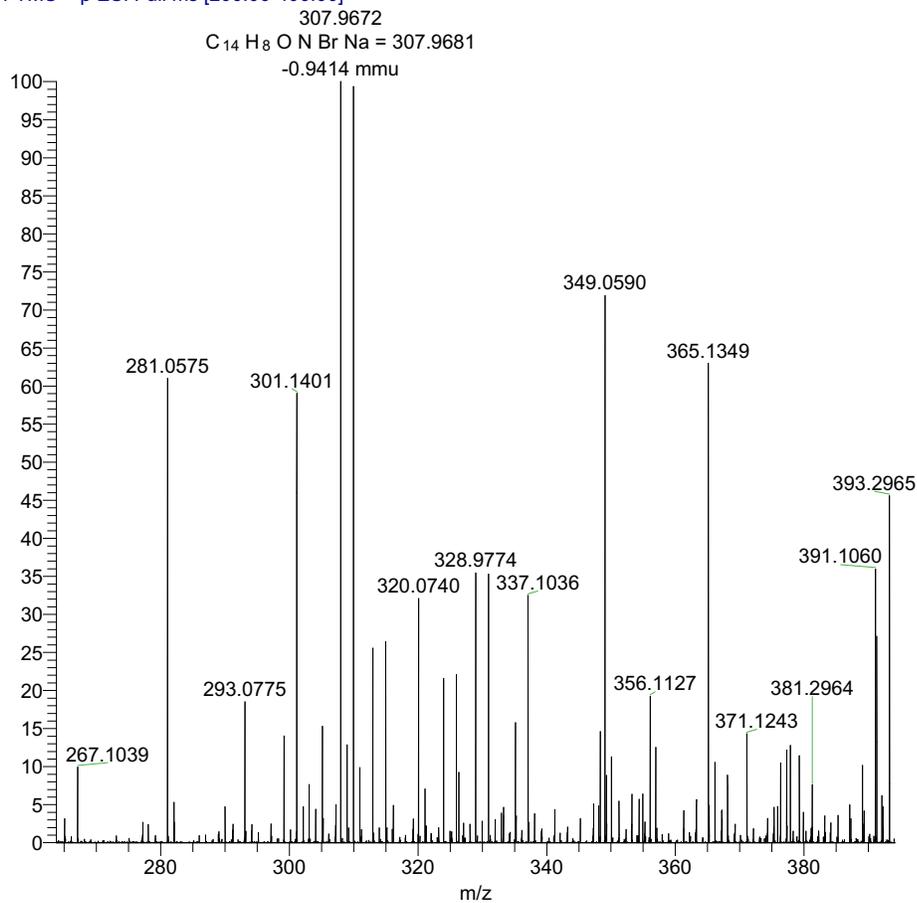
307.9672
$C_{14}H_8ONBrNa = 307.9681$
-0.9414 mmu

267.1039
281.0575
293.0775
301.1401
320.0740
328.9774
337.1036
349.0590
356.1127
365.1349
371.1243
381.2964
391.1060
393.2965

m/z

3-(2-Bromobenzoyl)benzonitrile **5j**

ABAI–87–2P_20180222.1.fid
Project AB_

ABAI–87–2P_20180222.3.fid
Project AB_

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

309.9653
C 14 H 8 O N 81Br Na = 309.9661
-0.8136 mmu
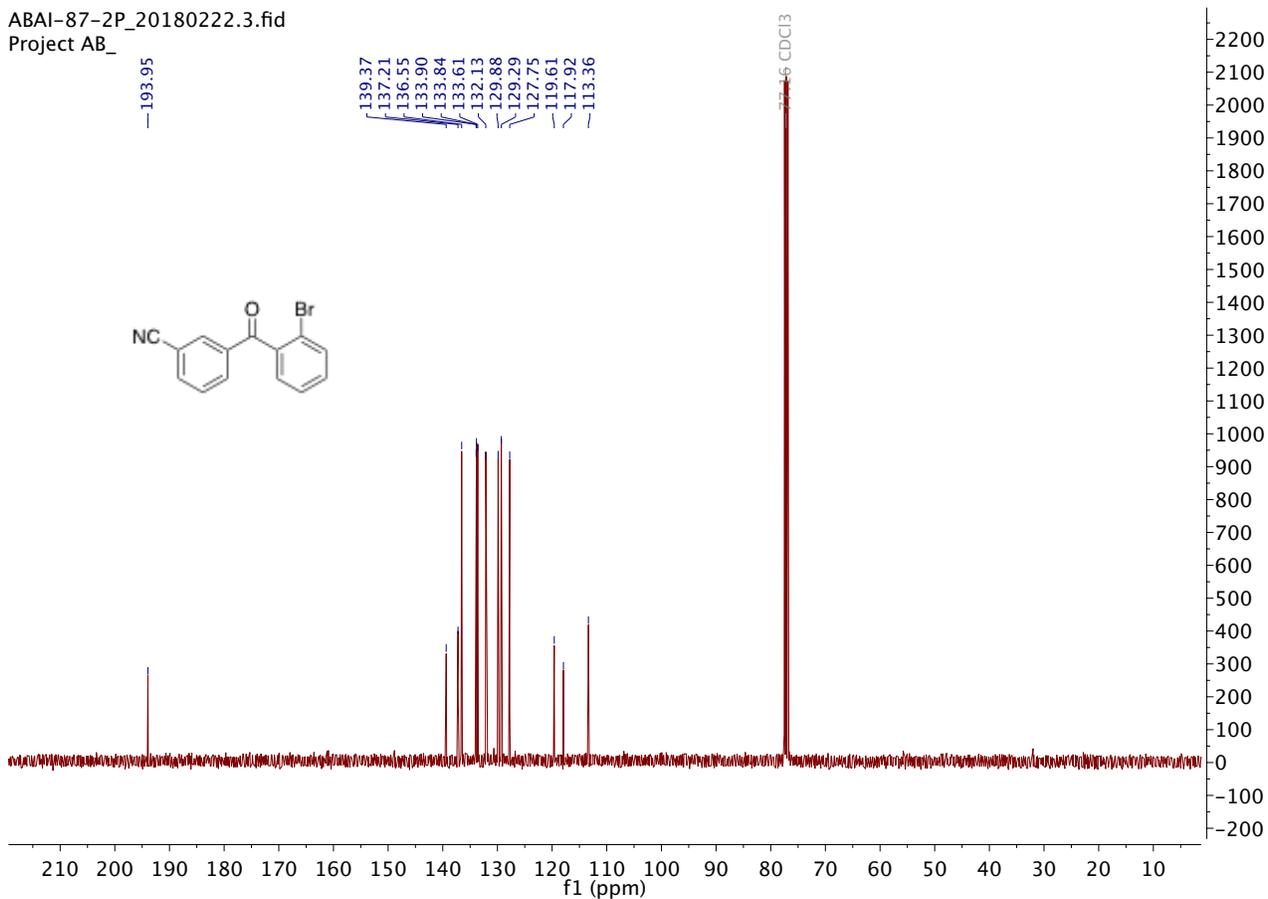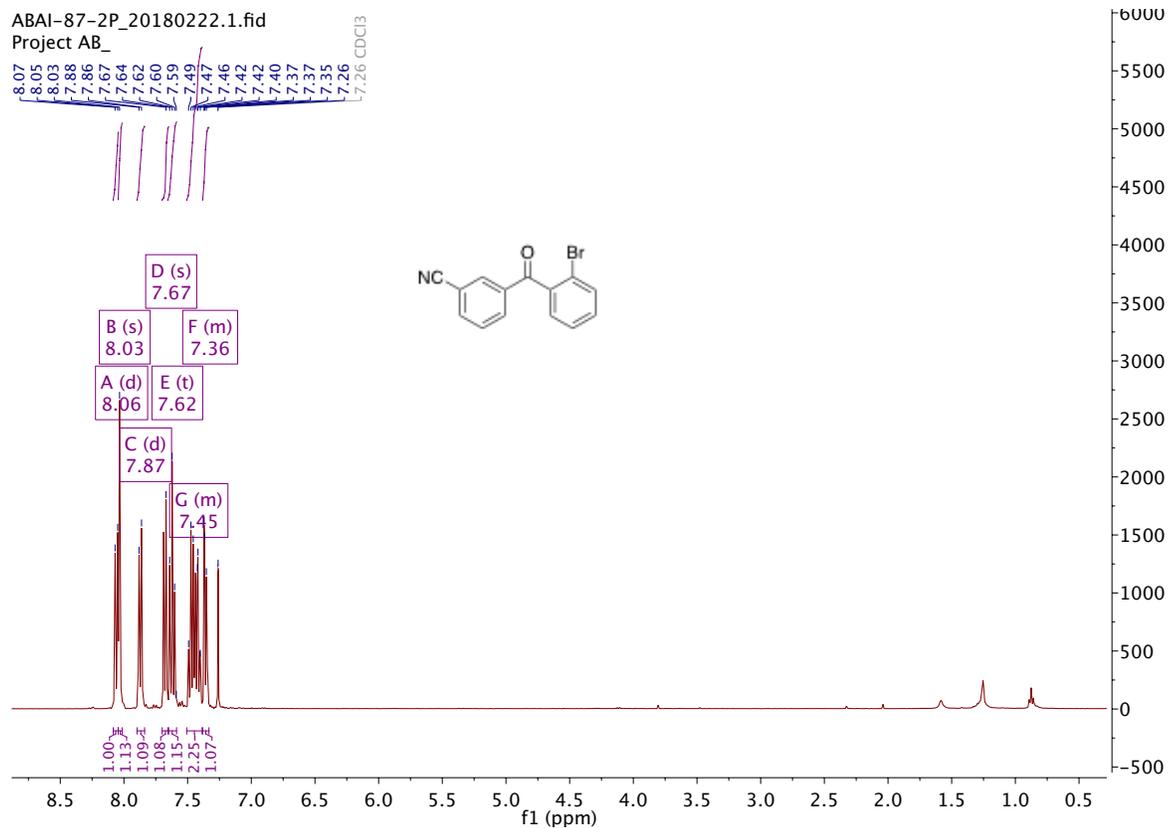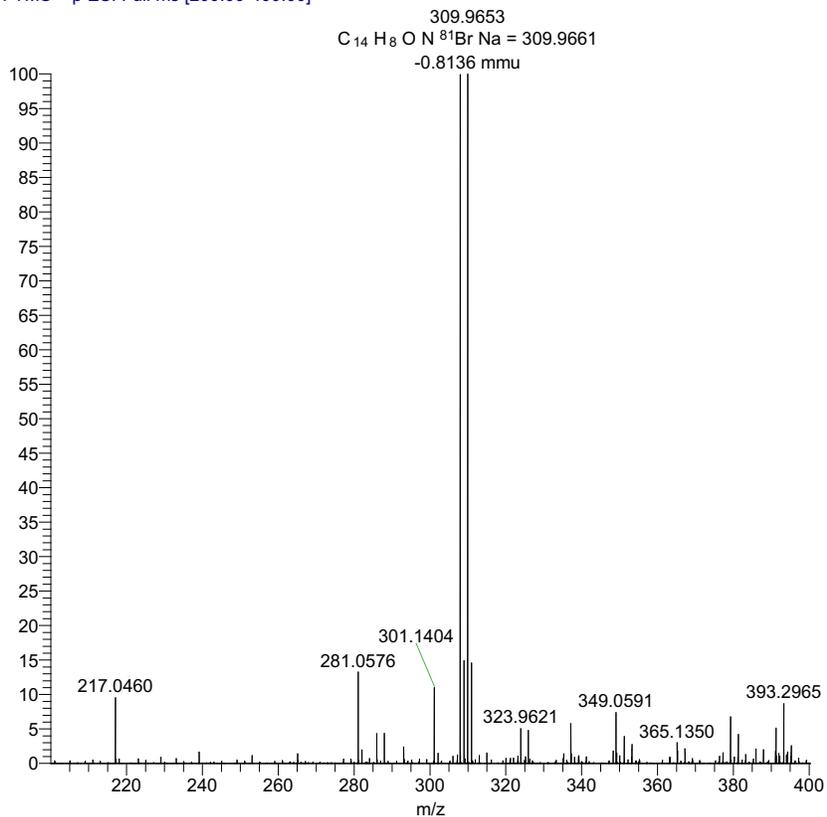
2-Bromophenyl 4-fluorophenyl methanone **5k**

ABAI–87–1F1_20180222.1.fid
Project AB_
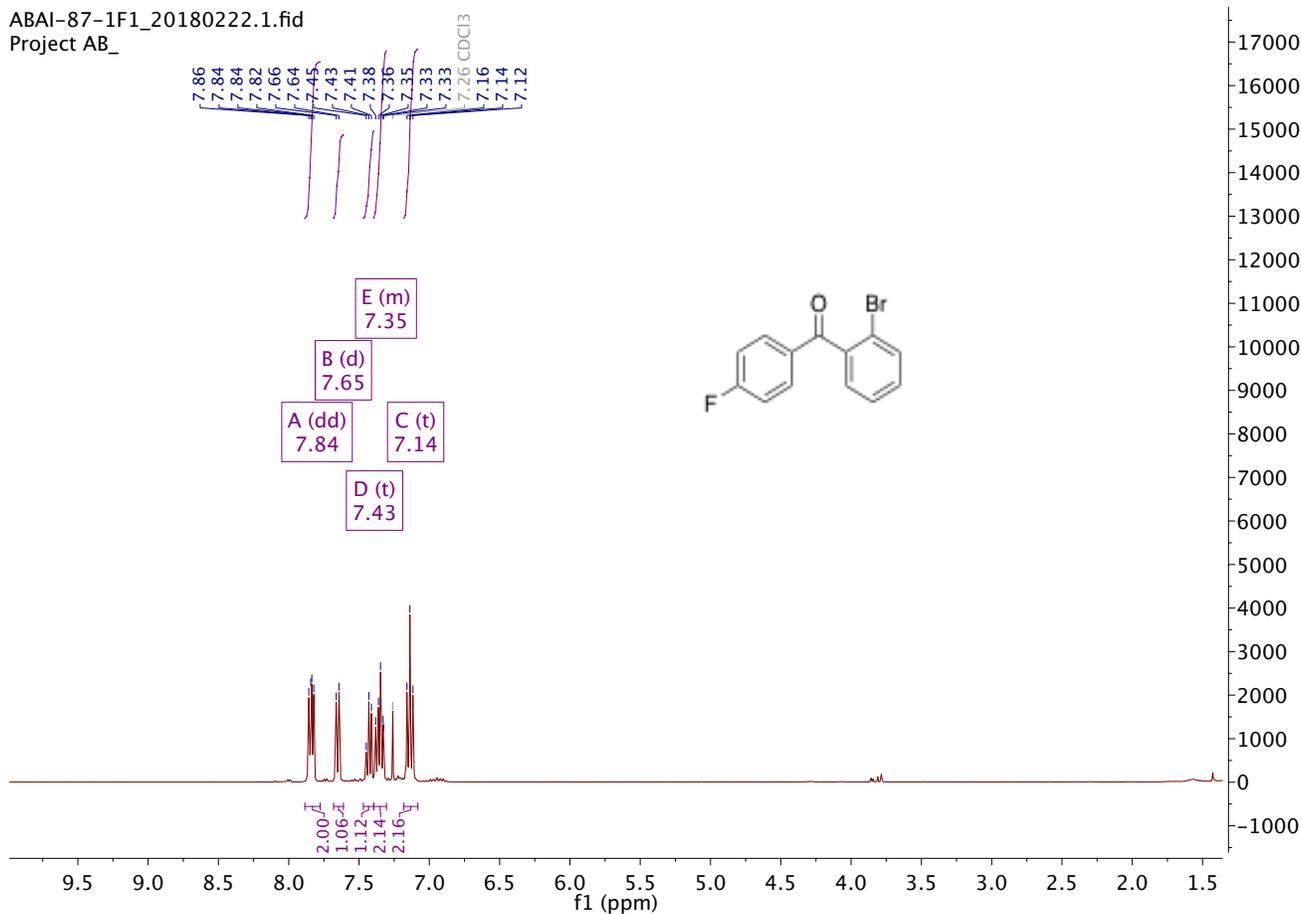
E (m)
7.35

B (d)
7.65

A (dd)
7.84

C (t)
7.14

D (t)
7.43

ABAI–87–1F1_20180222.3.fid
Project AB_
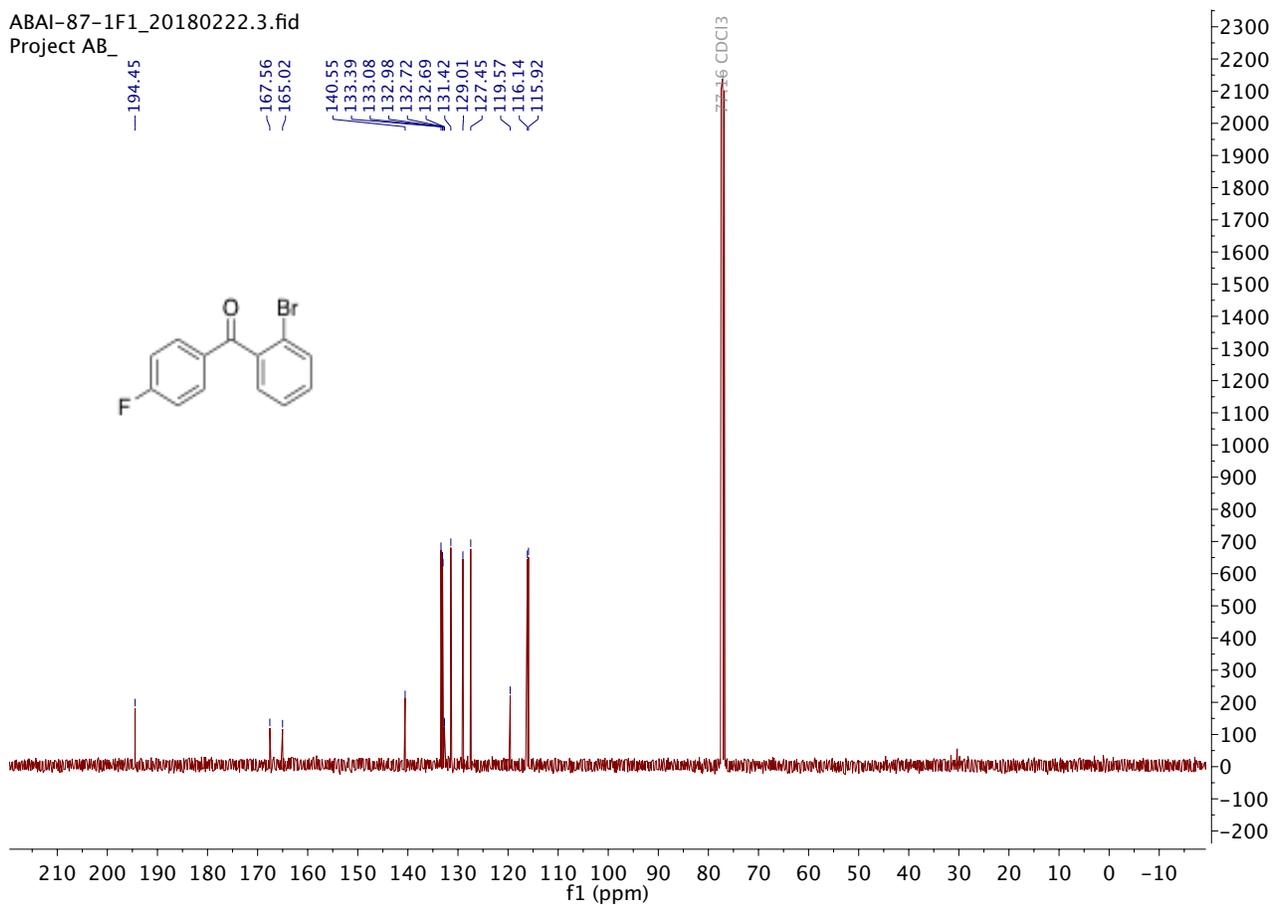
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

300.9630
C$_{13}$H$_8$O Br F Na = 300.9635
-0.4553 mmu

*2-**b**romophenyl 3-fluorophenyl methanone **5l***

abai−86−4f2_20180221.3.fid
Project AB_
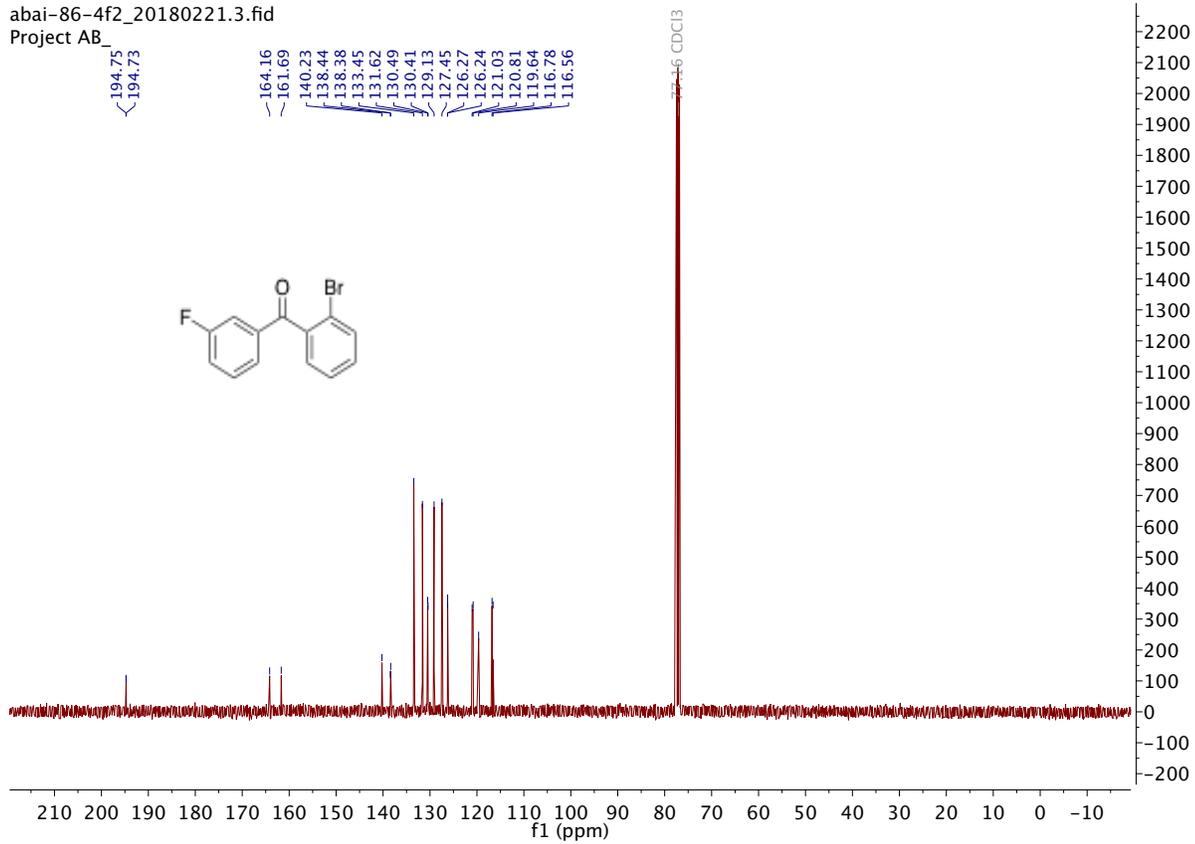
abai-86-4-f1_180618150932 #1-4 RT: 0.02-0.10 AV: 4 NL: 1
T: FTMS + p ESI Full ms [200.00-400.00]

300.9630
$C_{13} H_8 O Br F Na = 300.9635$
-0.4553 mmu
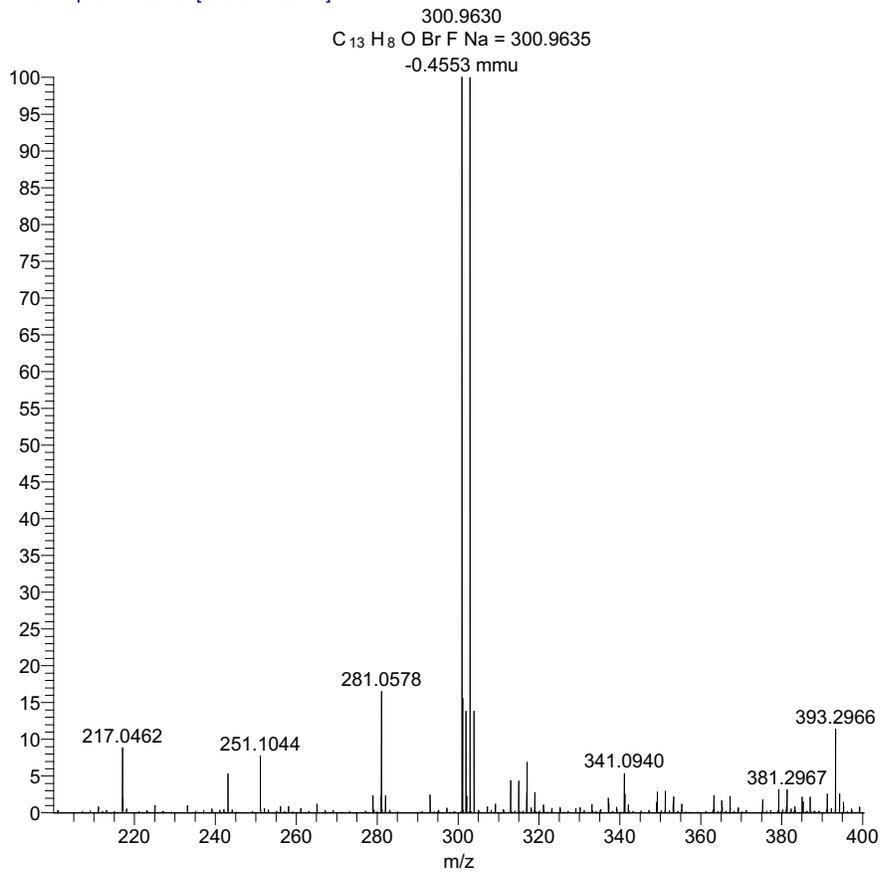
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

2-Bromophenyl 2-fluorophenyl methanone **5m**

abai–86-3_20180221.1.fid
Project AB_
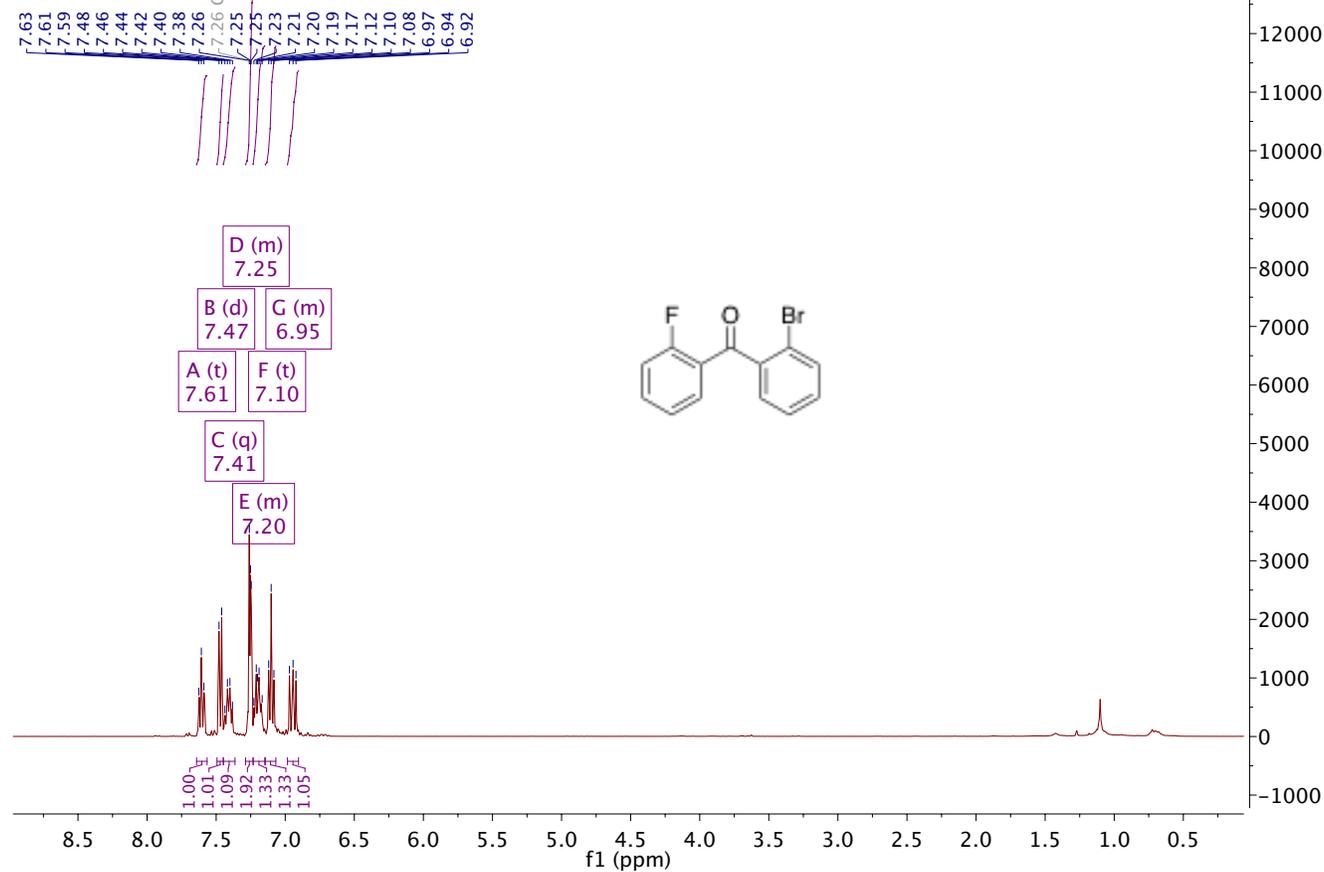
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Project AB_
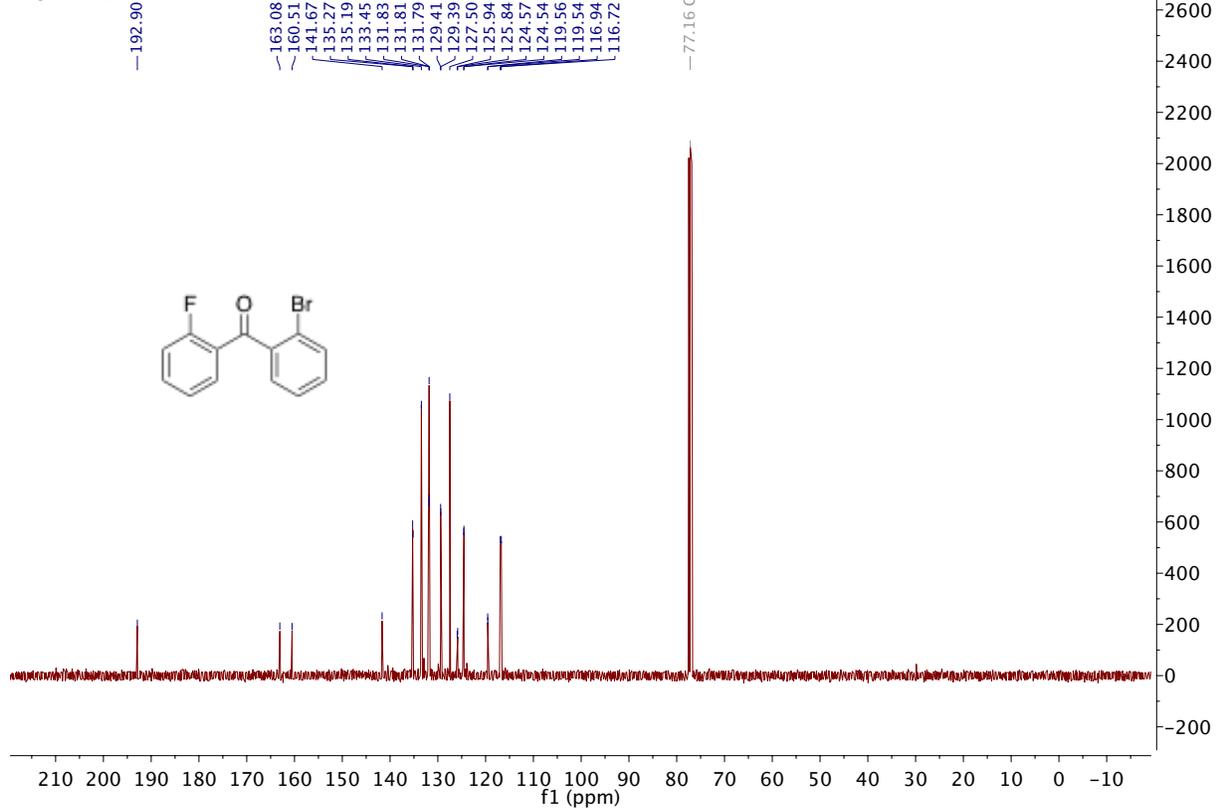
— 37 —

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

302.9608
$C_{13} H_8 O$ ^{81}Br F Na = 302.9614
-0.6759 mmu
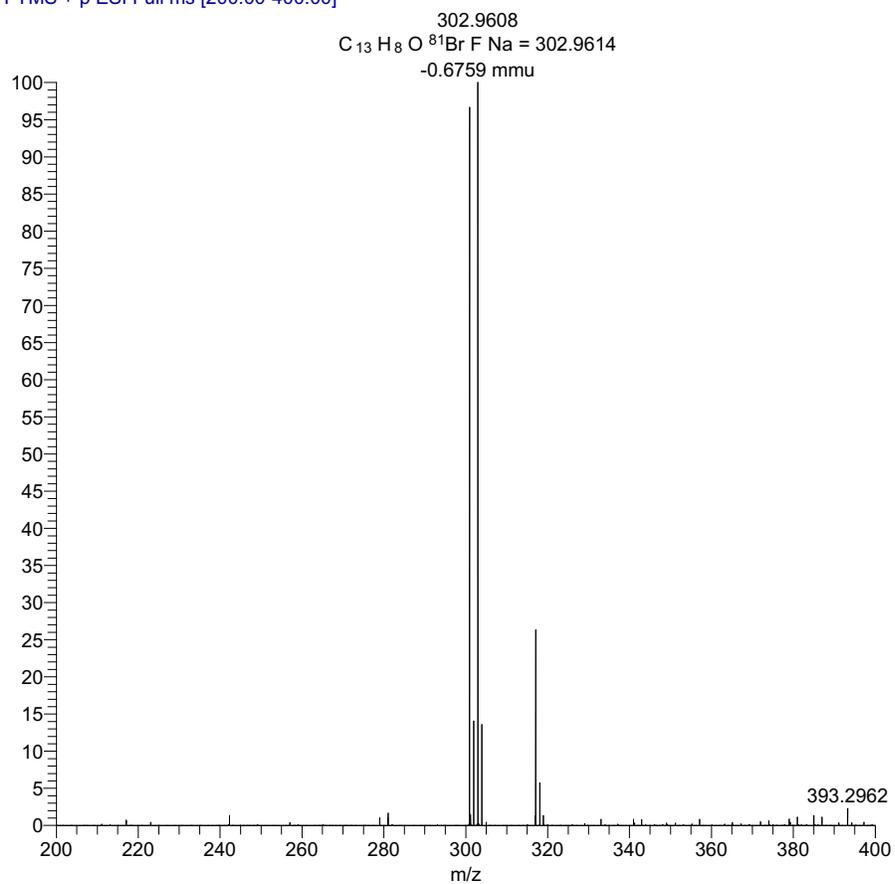
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

4.2 Spectra for butyl 2-benzoylbenzoate esters 2

Butyl 2-(4-methoxybenzoyl)benzoate 2a

abai–92–f2
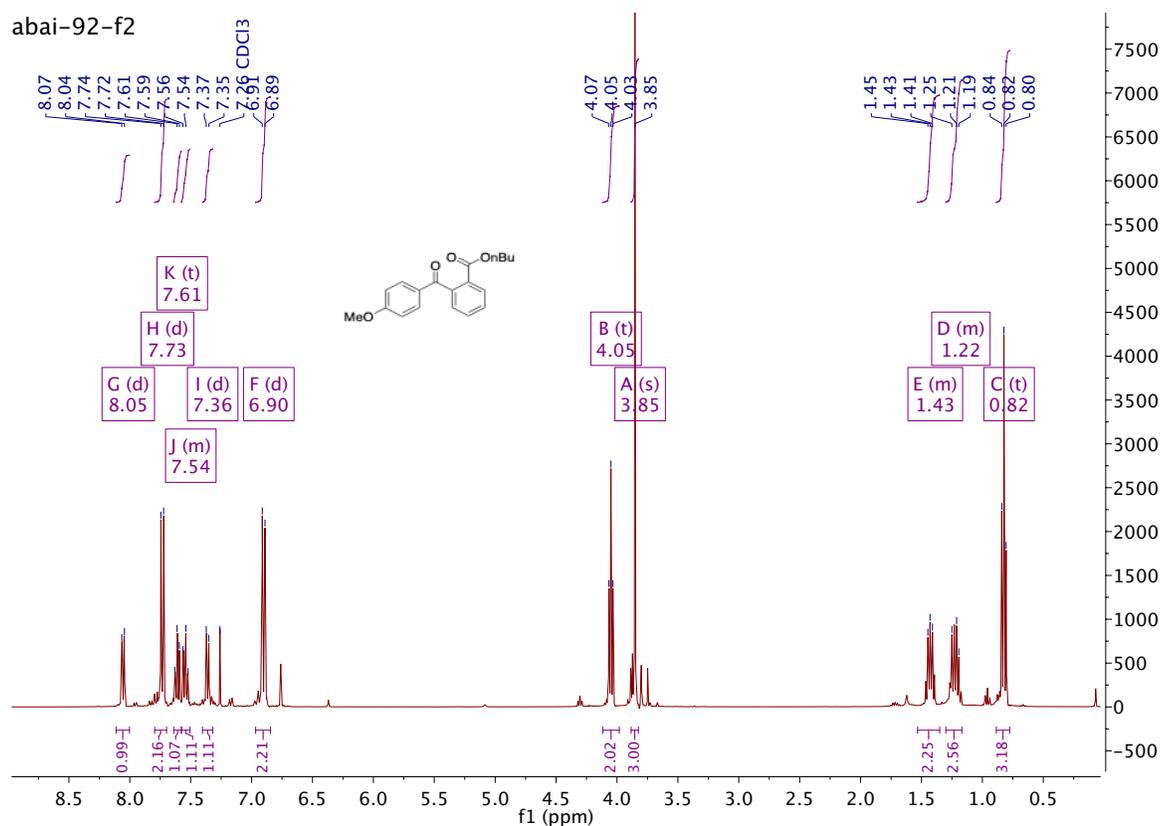
abai–92–f2
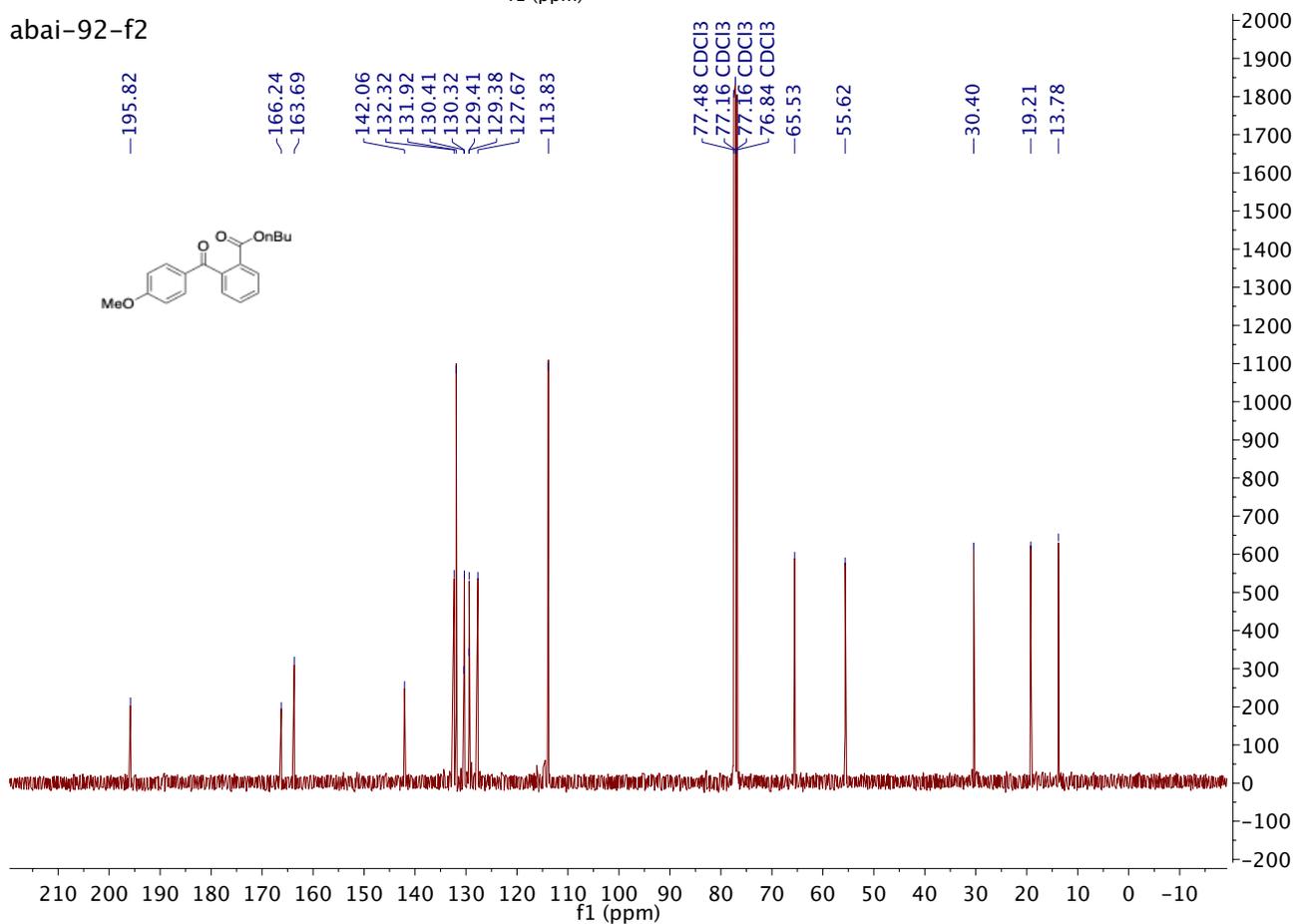
abai-112-6f3_190627172410 #1-4 RT: 0.01-0.10 AV: 4 NL: 5.01E7
T: FTMS + p ESI Full ms [150.00-500.00]

335.1260
C$_{19}$H$_{20}$O$_4$Na = 335.1254
0.6501 mmu

239.0706
C$_{15}$H$_{11}$O$_3$ = 239.0703
0.3556 mmu

488.1848

m/z
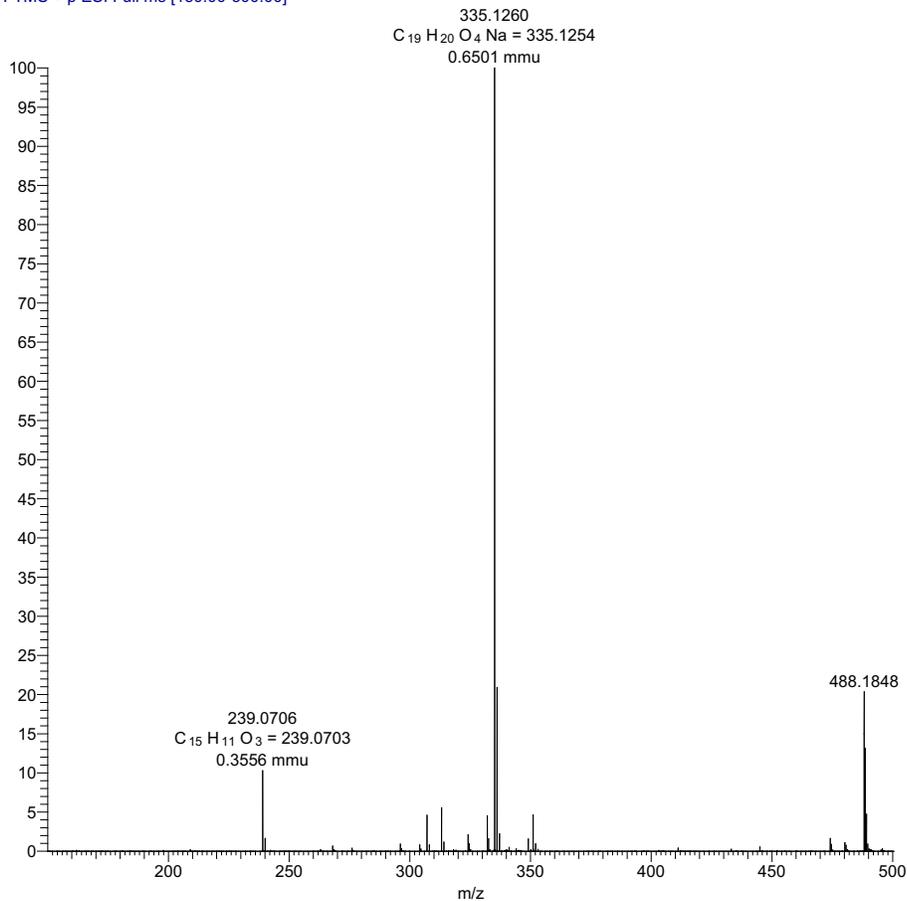
Butyl 2-(3-methoxybenzoyl)benzoate **2b**

abai–112–5f2
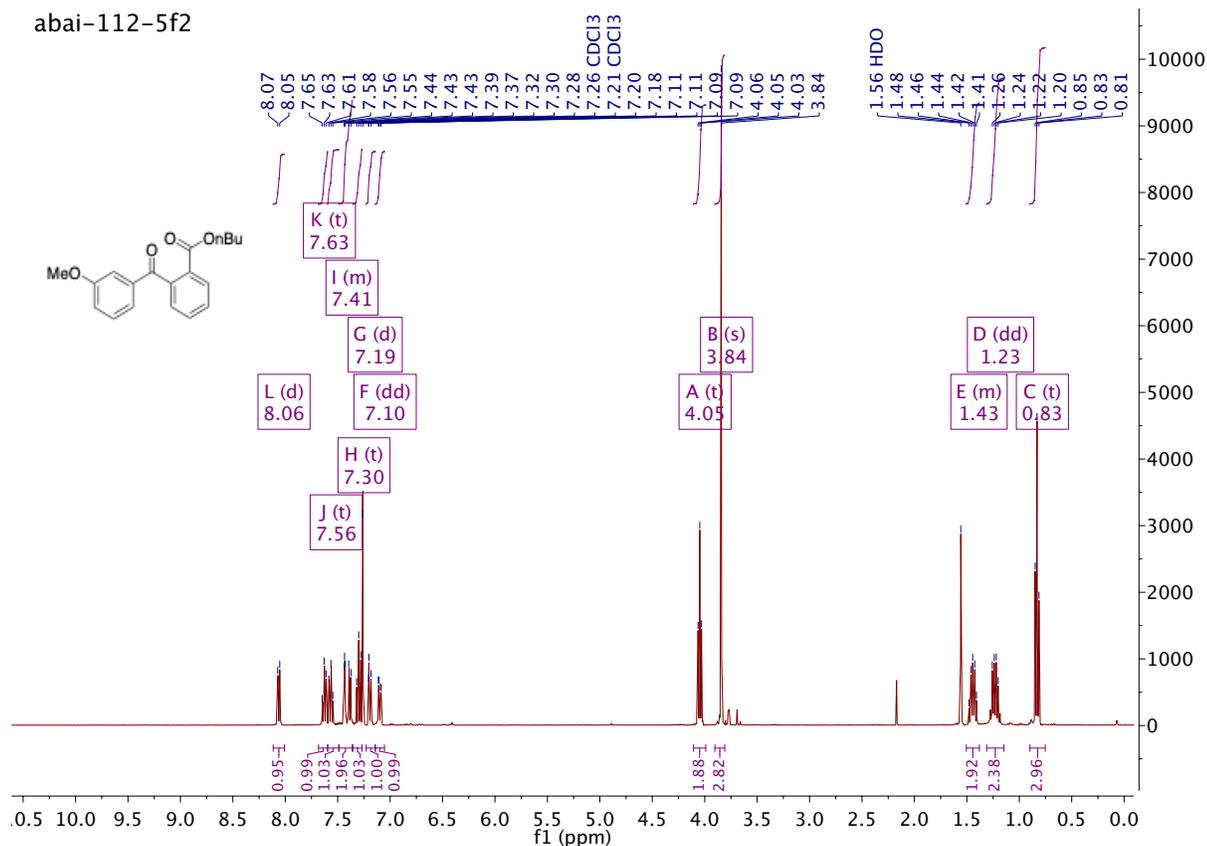
K (t)
7.63

I (m)
7.41

G (d)
7.19

B (s)
3.84

D (dd)
1.23

L (d)
8.06

F (dd)
7.10

A (t)
4.05

E (m)
1.43

C (t)
0.83

H (t)
7.30

J (t)
7.56

f1 (ppm)

abai-112-5f2

196.86
166.14
159.90
141.78
138.62
132.40
130.29
129.65
129.58
129.55
127.75
122.86
119.98
113.11
77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3
65.60
55.58
30.44
19.22
13.80
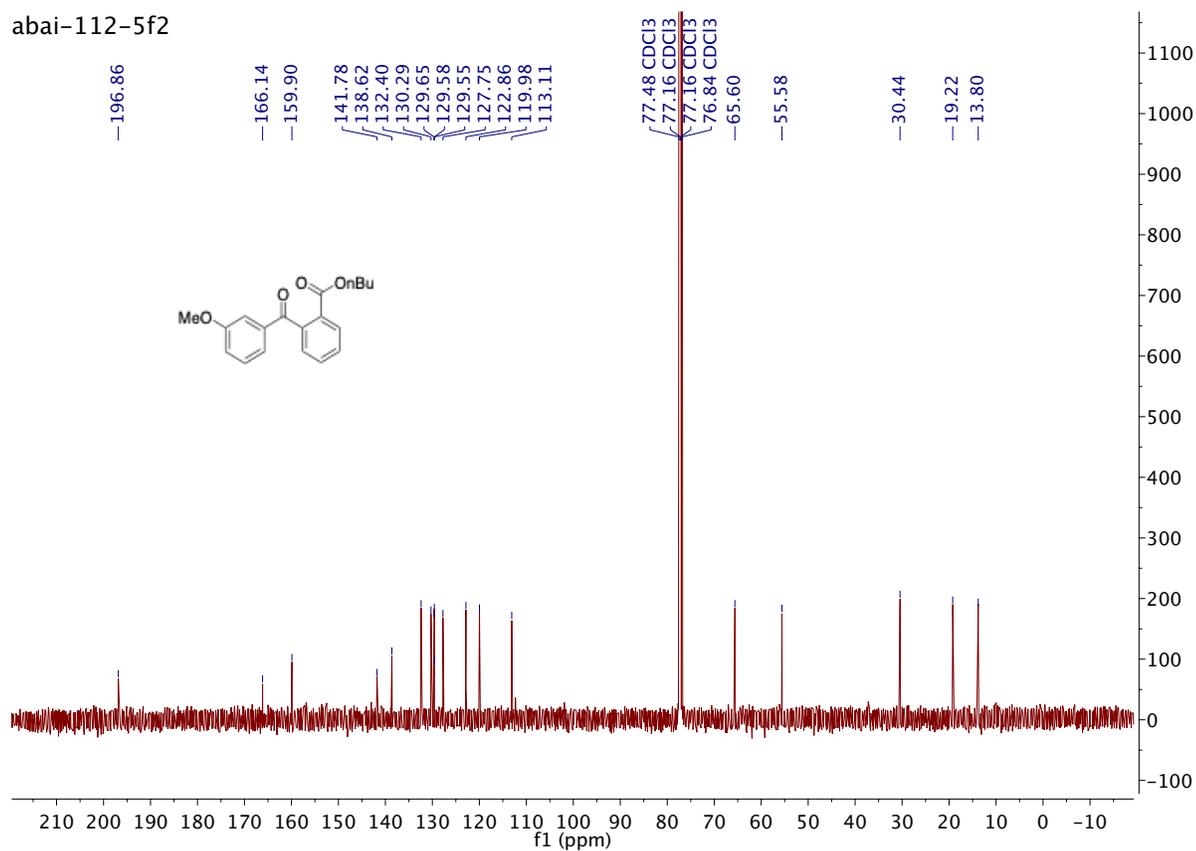
abai-112-5f2_190627172410 #1-5 RT: 0.00-0.11 AV: 5 NL: 4.27E7
T: FTMS + p ESI Full ms [150.00-500.00]

335.1260
$C_{19}H_{20}O_4Na = 335.1254$
0.6076 mmu

239.0705
$C_{15}H_{11}O_3 = 239.0703$
0.2749 mmu

488.1844
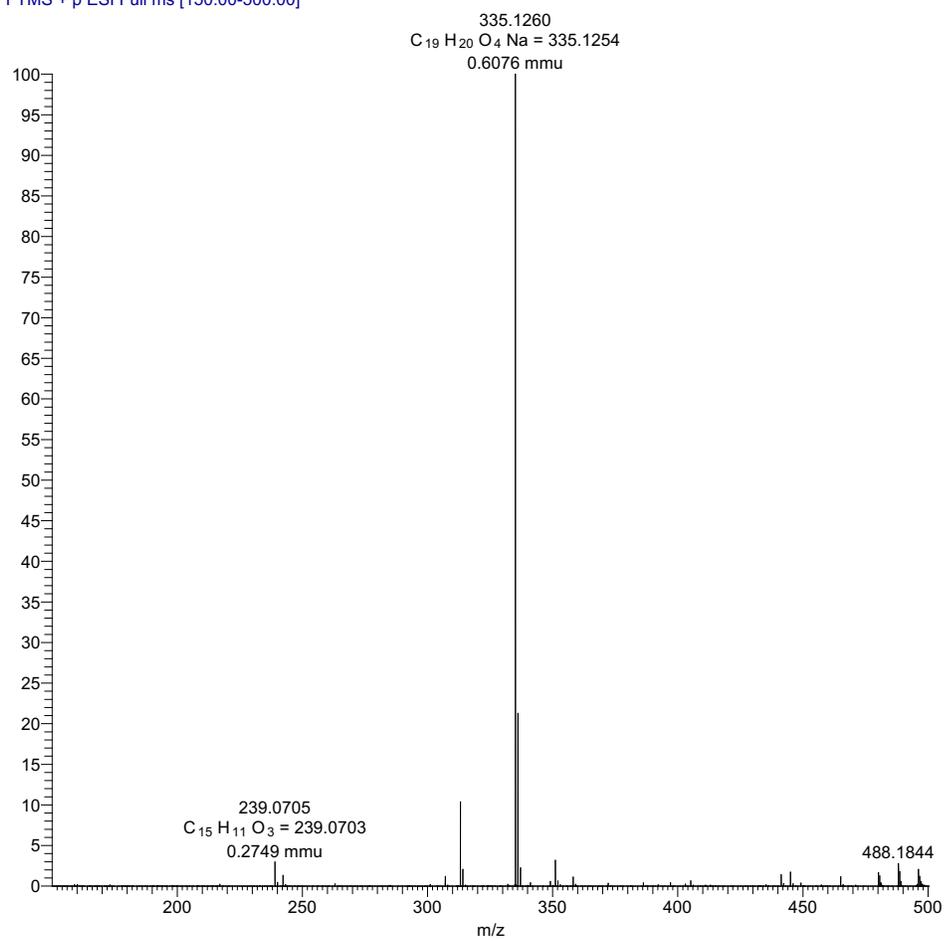
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

Butyl 2-(4-fluorobenzoyl)benzoate **2c**

abai−112−1f1
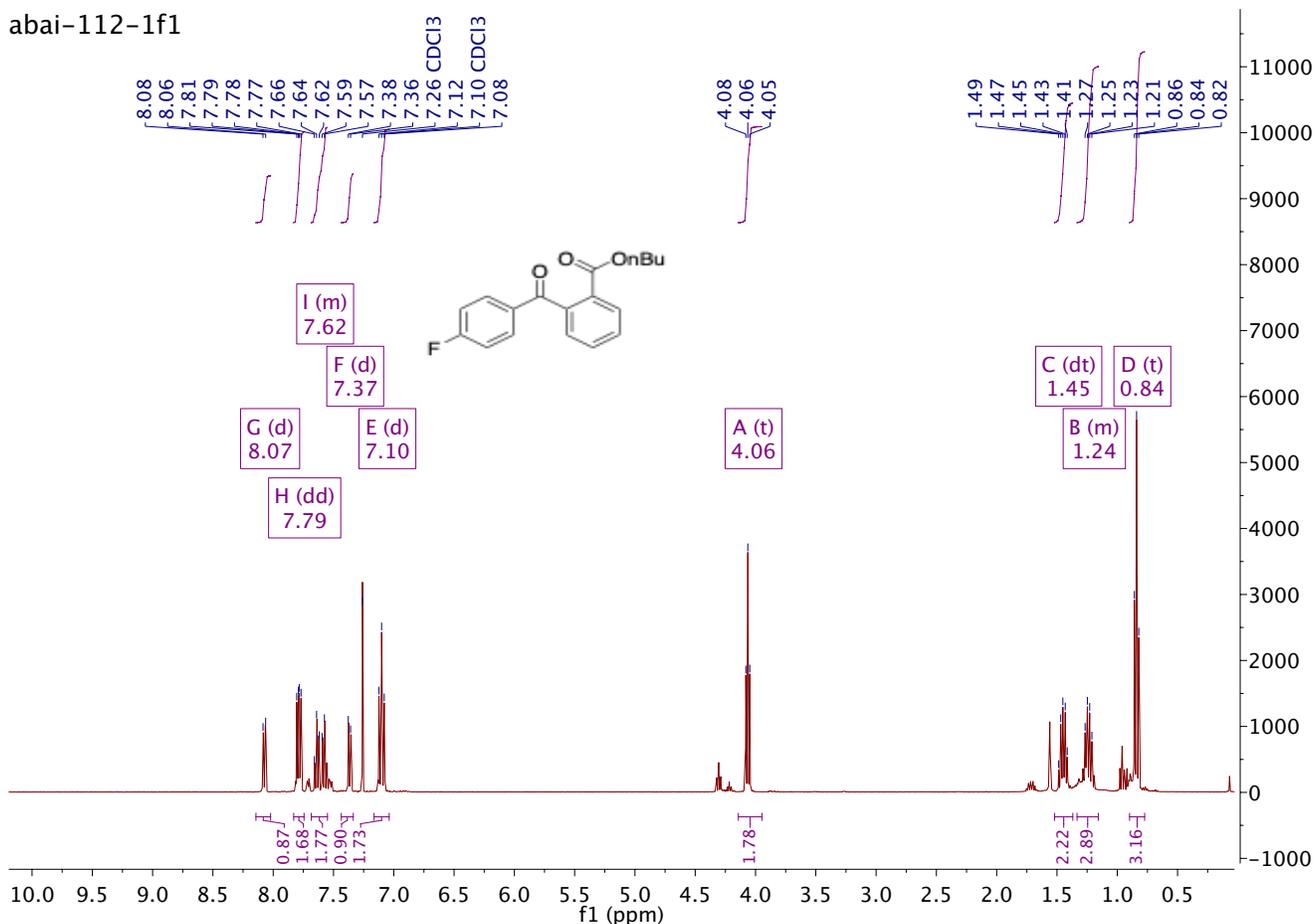
abai−112−1f1
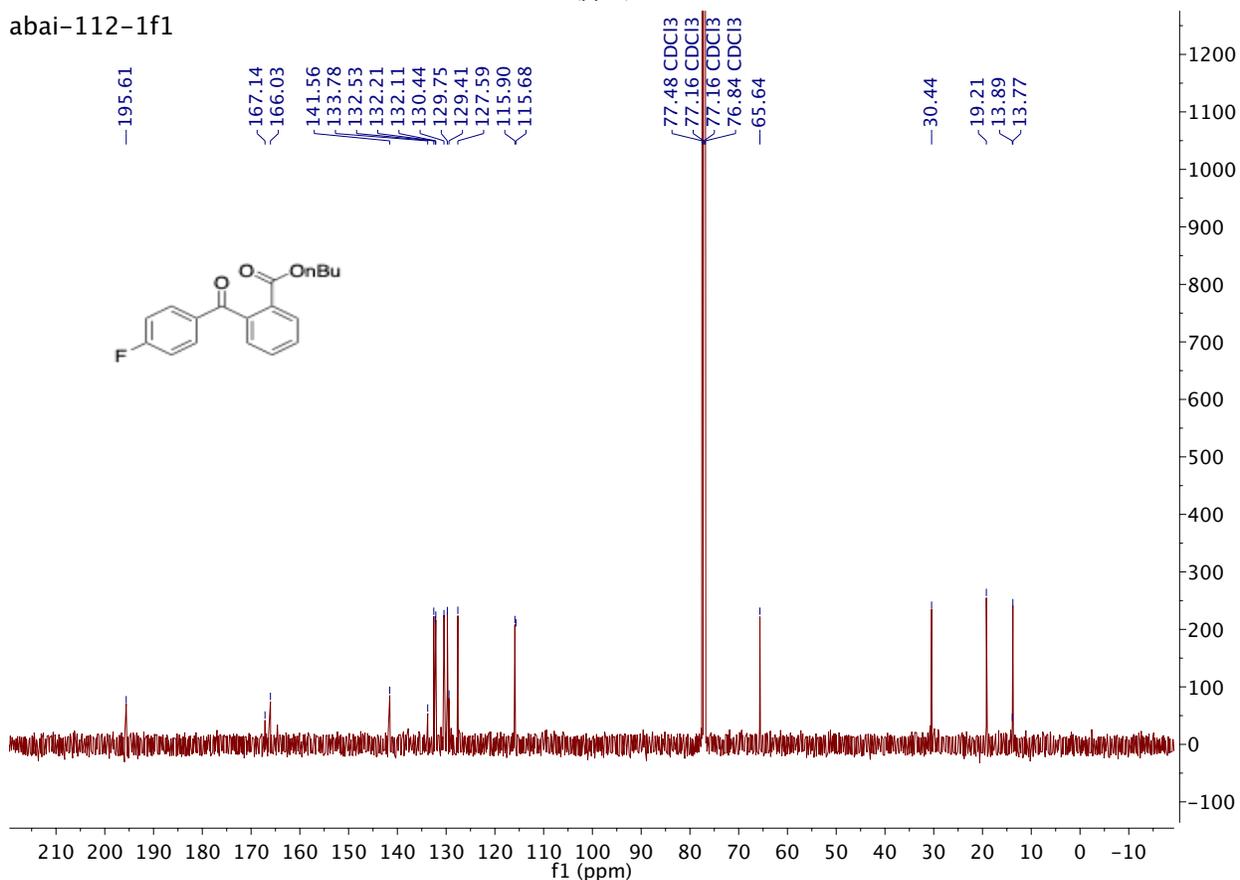
323.1059
$C_{18} H_{17} O_3 F Na = 323.1054$
0.4723 mmu

441.2971

m/z

*Butyl 2-(2-fluorobenzoyl)benzoate **2d***

ABAI–112–2F1
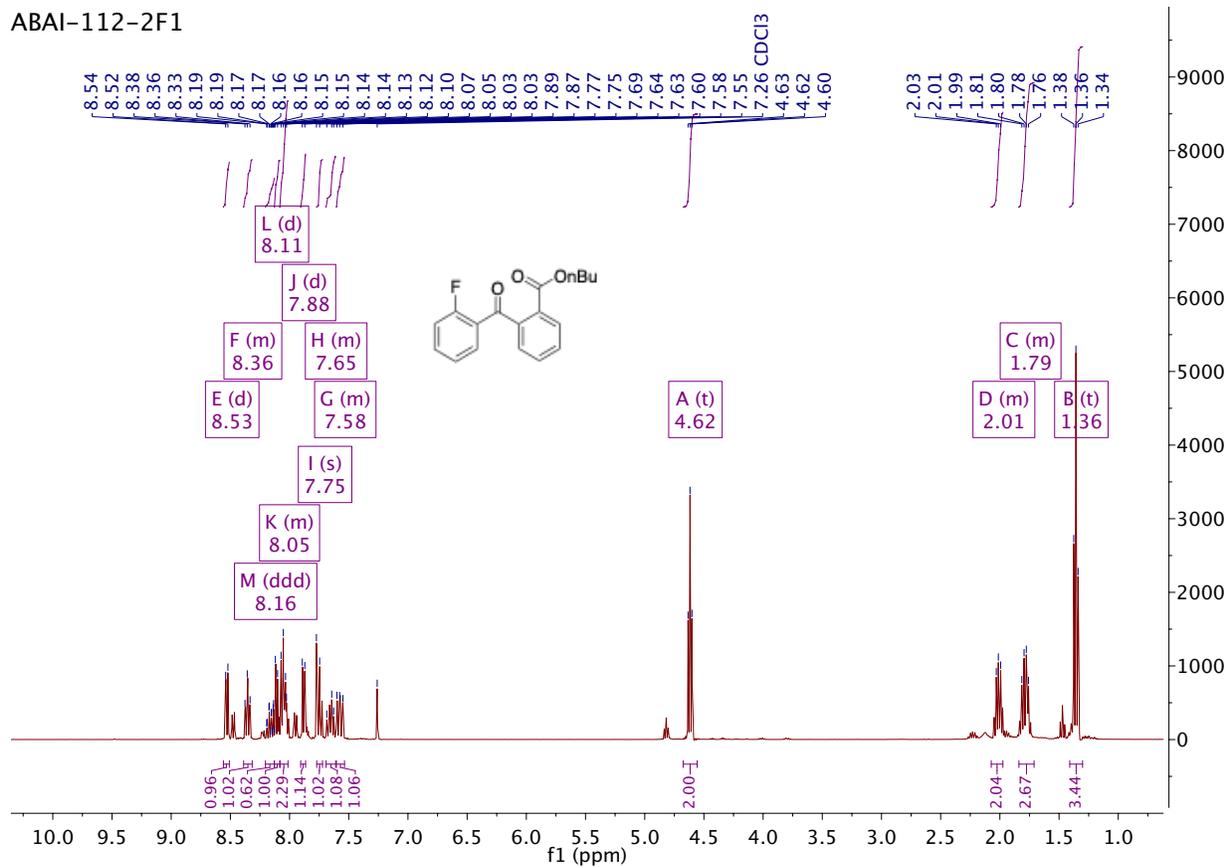
f1 (ppm)

– 43 –

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

ABAI–112–2F1

193.68
166.34
163.22
160.66
143.49
134.99
134.90
134.63
132.34
131.50
130.14
129.73
126.95
125.90
124.32
124.28
117.00
116.77
77.16 CDCl3
65.57
30.46
19.20
13.76

f1 (ppm)
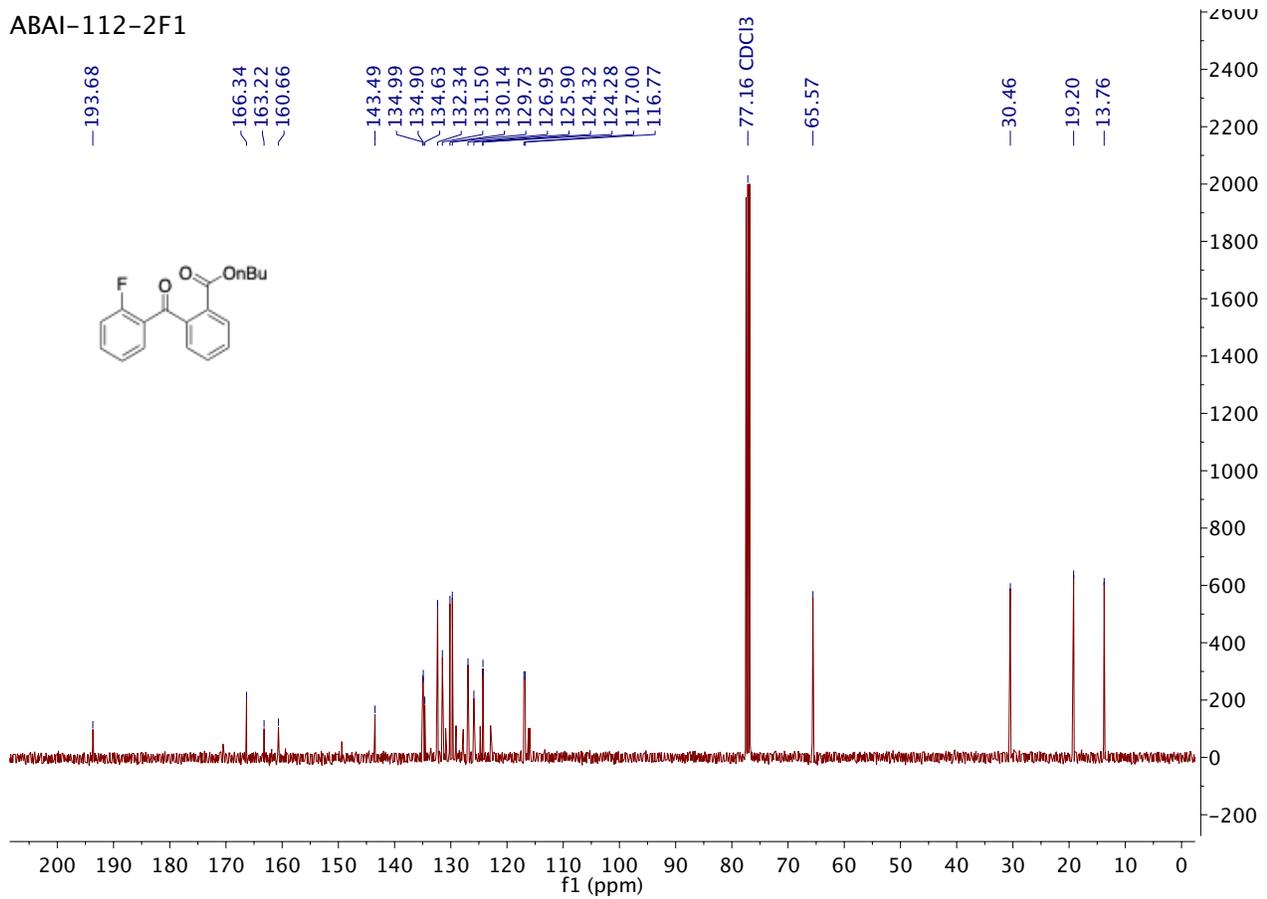
abai-112-2f1_190627172410 #1-5   RT: 0.01-0.12   AV: 5   NL: 3
T: FTMS + p ESI Full ms [150.00-500.00]

323.1058
$C_{18} H_{17} O_3 F Na = 323.1054$
0.4104 mmu

227.0503
$C_{14} H_8 O_2 F = 227.0503$
-0.0167 mmu

377.1722
$C_{22} H_{26} O_4 Na = 377.1723$
-0.1471 mmu

433.0208

441.2971

478.1406

m/z
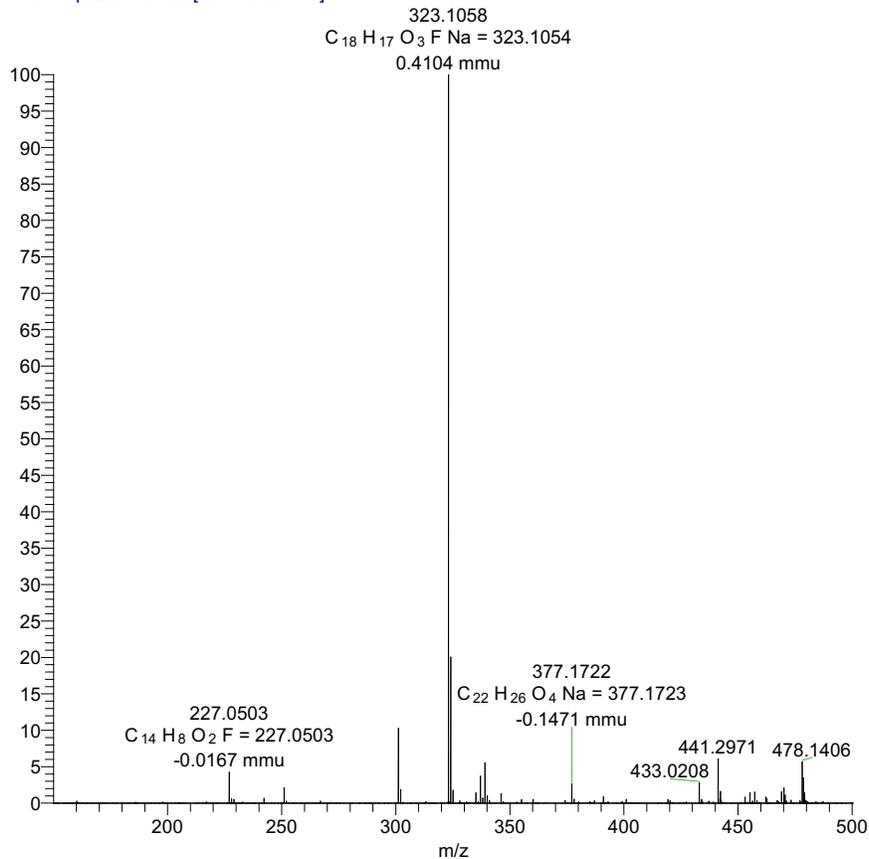
4.3 Spectra for methyl 2-benzoylbenzoate esters 2

Methyl 2-(4-methoxybenzoyl)benzoate **2aa**
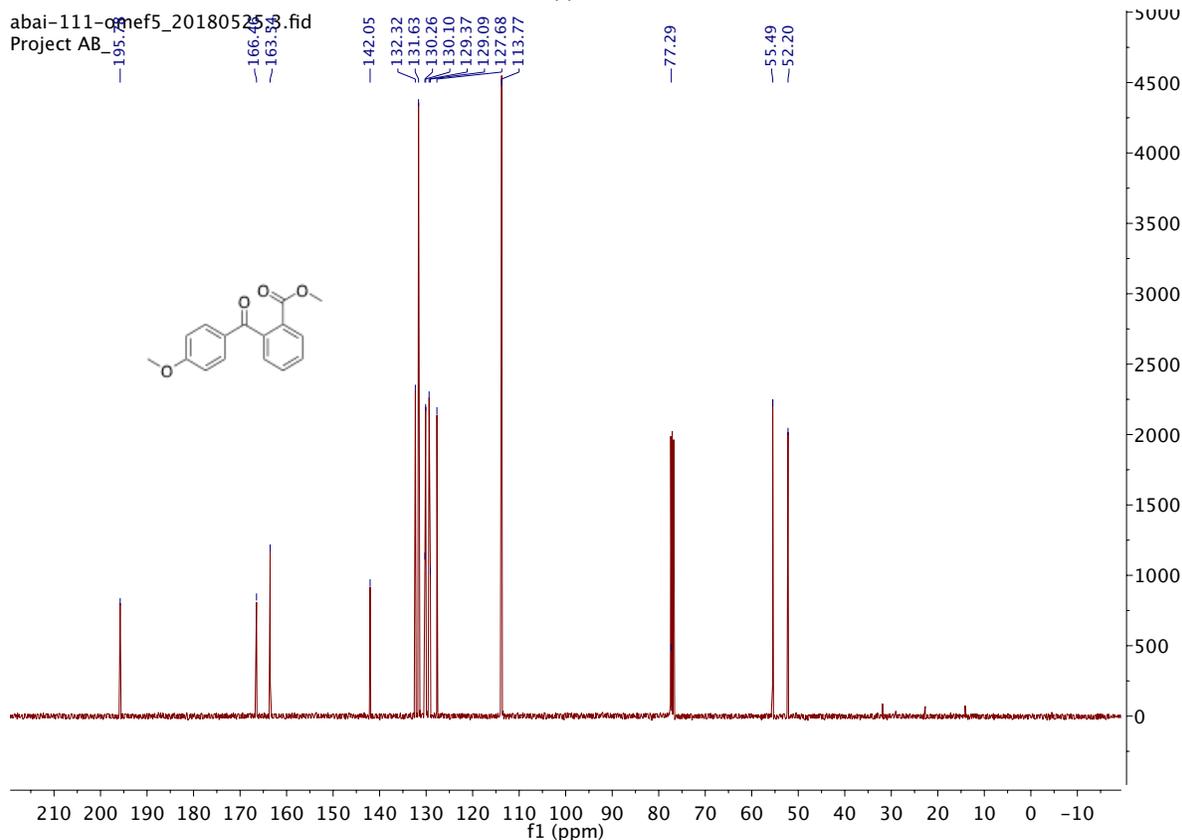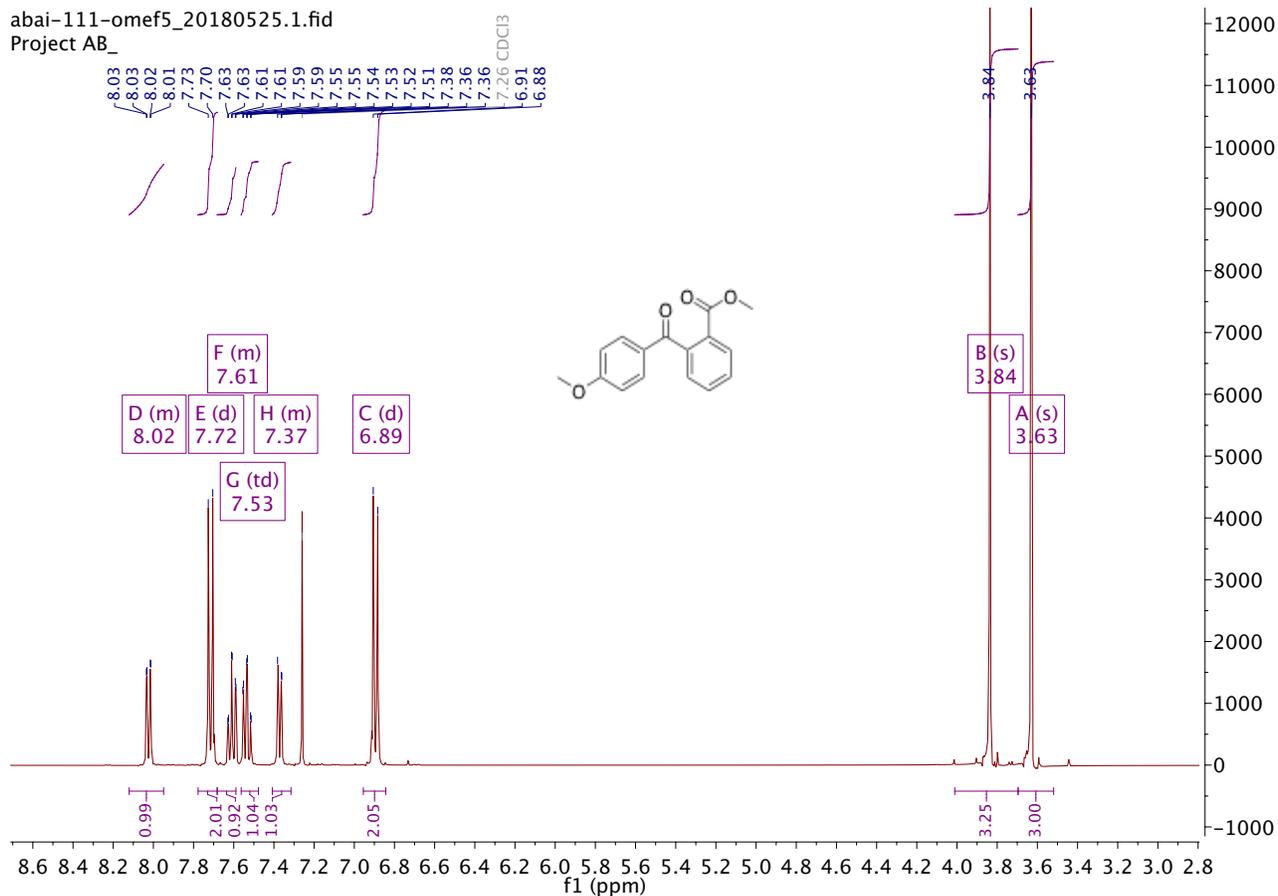
ABAI-111-1DF2_180618105745 #1-5   RT: 0.01-0.12   AV: 5   NI   .7
T: FTMS + p ESI Full ms [200.00-500.00]

293.0784
$C_{16} H_{14} O_4 Na = 293.0784$
-0.0800 mmu

239.0699
$C_{15} H_{11} O_3 = 239.0703$
-0.3783 mmu

425.1143

m/z
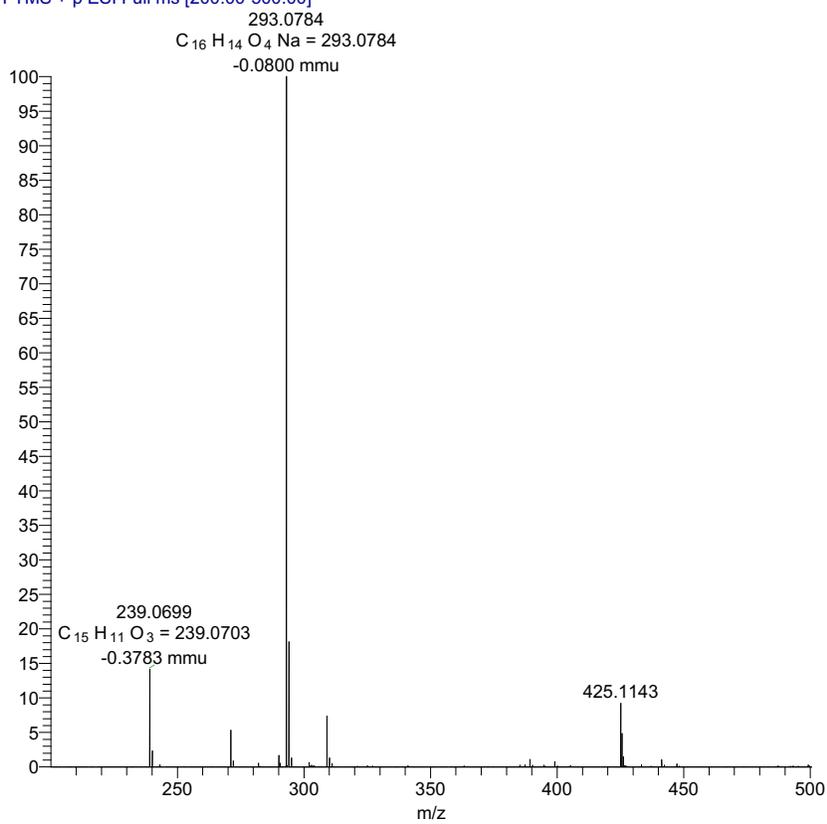
methyl 4'-methoxy-[1,1'-biphenyl]-2-carboxylate **B** *(from direct coupling).*

abai−111−df1
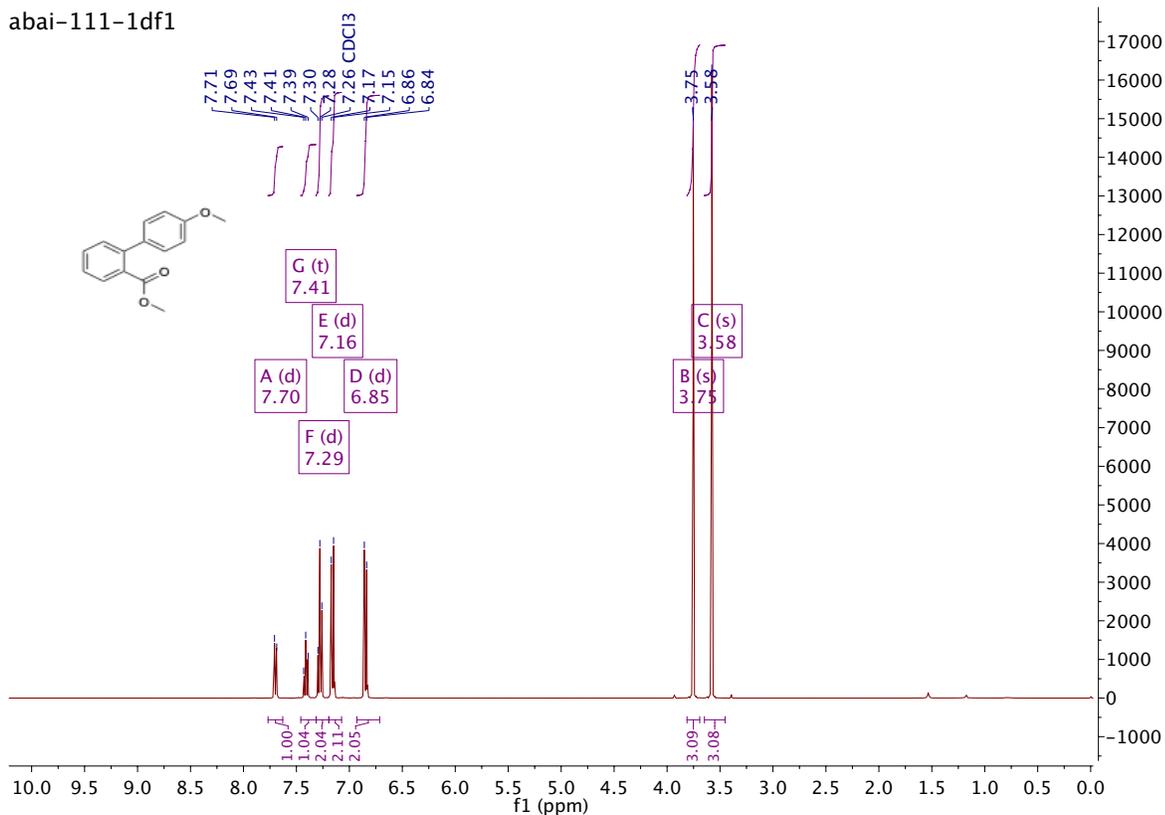
7.71
7.69
7.43
7.41
7.39
7.30
7.28
7.26 CDCl3
7.17
7.15
6.86
6.84

3.75
3.58

G (t)
7.41

E (d)
7.16

A (d)
7.70

D (d)
6.85

F (d)
7.29

C (s)
3.58

B (s)
3.75

1.00
1.04
2.04
2.11
2.05

3.09
3.08

f1 (ppm)

– 46 –

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.
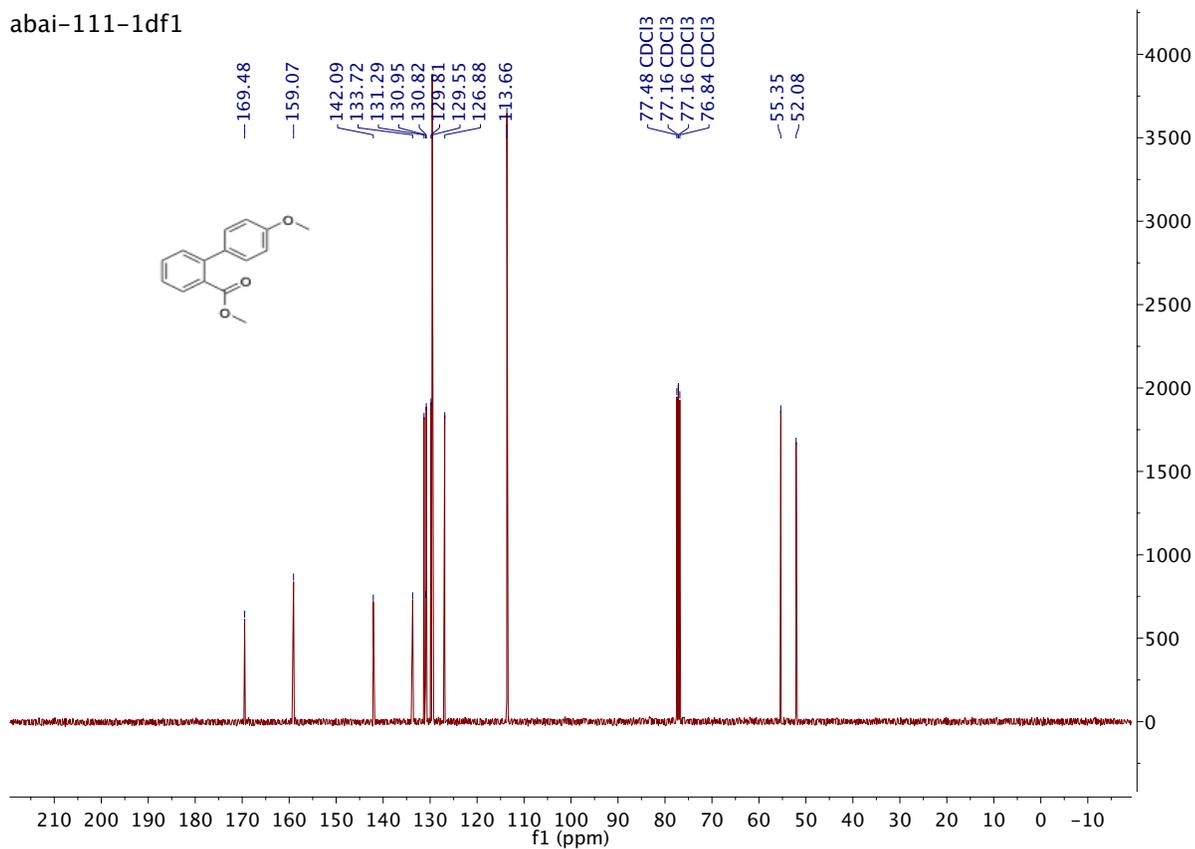
abai-111-1df1

Methyl 2-(3-methoxybenzoyl) benzoate *2ab*

abai-111-17f2_20180610.1.fid
Project AB_
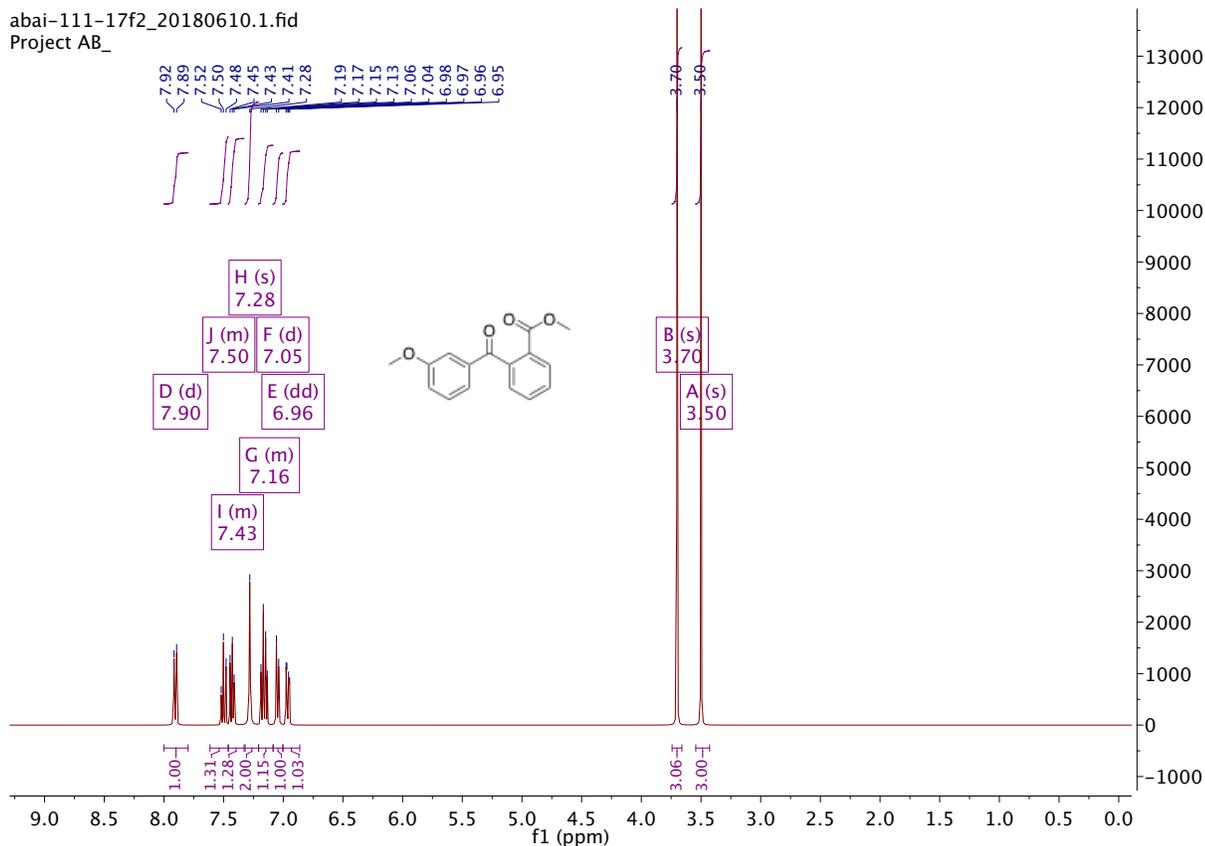
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

abai-111-17f2_20180610.3.fid
Project AB_
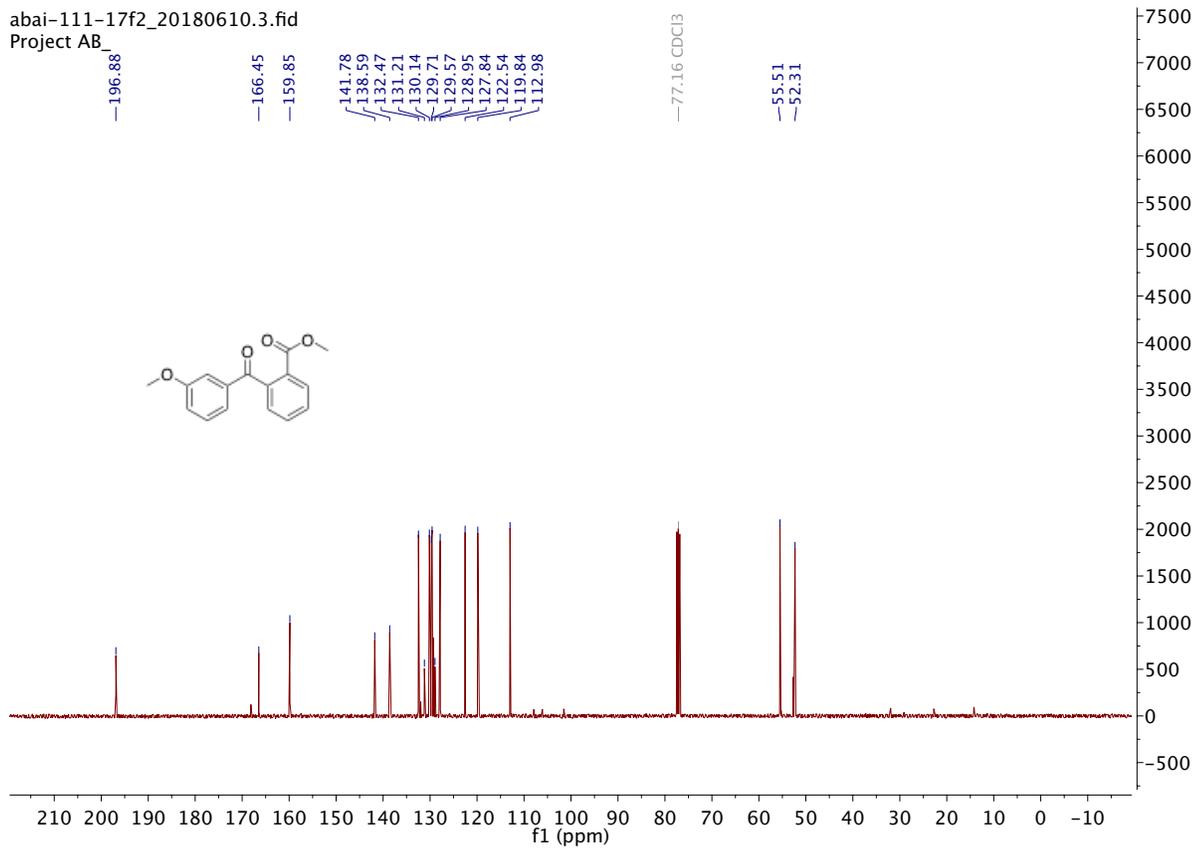
ABAI-111-17-F2 #1-4   RT: 0.02-0.11   AV: 4   NL: 6.66E7
T: FTMS + p ESI Full ms [200.00-500.00]
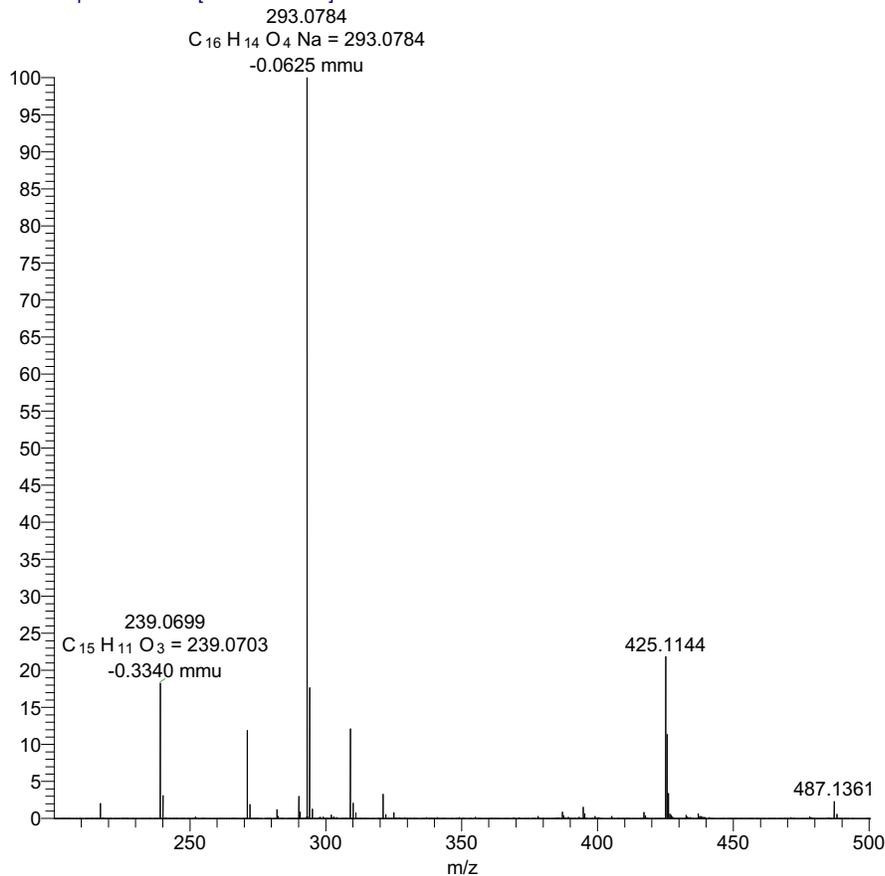
293.0784
$C_{16} H_{14} O_4 Na = 293.0784$
-0.0625 mmu

239.0699
$C_{15} H_{11} O_3 = 239.0703$
-0.3340 mmu

425.1144

487.1361

Methyl 2-(2-methoxybenzoyl)benzoate **2ac**

ABAI–111–3–F2_20180601.1.fid
Project AB_

I (t)
7.53

D (m)
7.71

F (t)
6.99

C (d)
7.87

G (d)
7.36

E (d)
6.90

H (m)
7.46

B (s)
3.57

A (s)
3.59
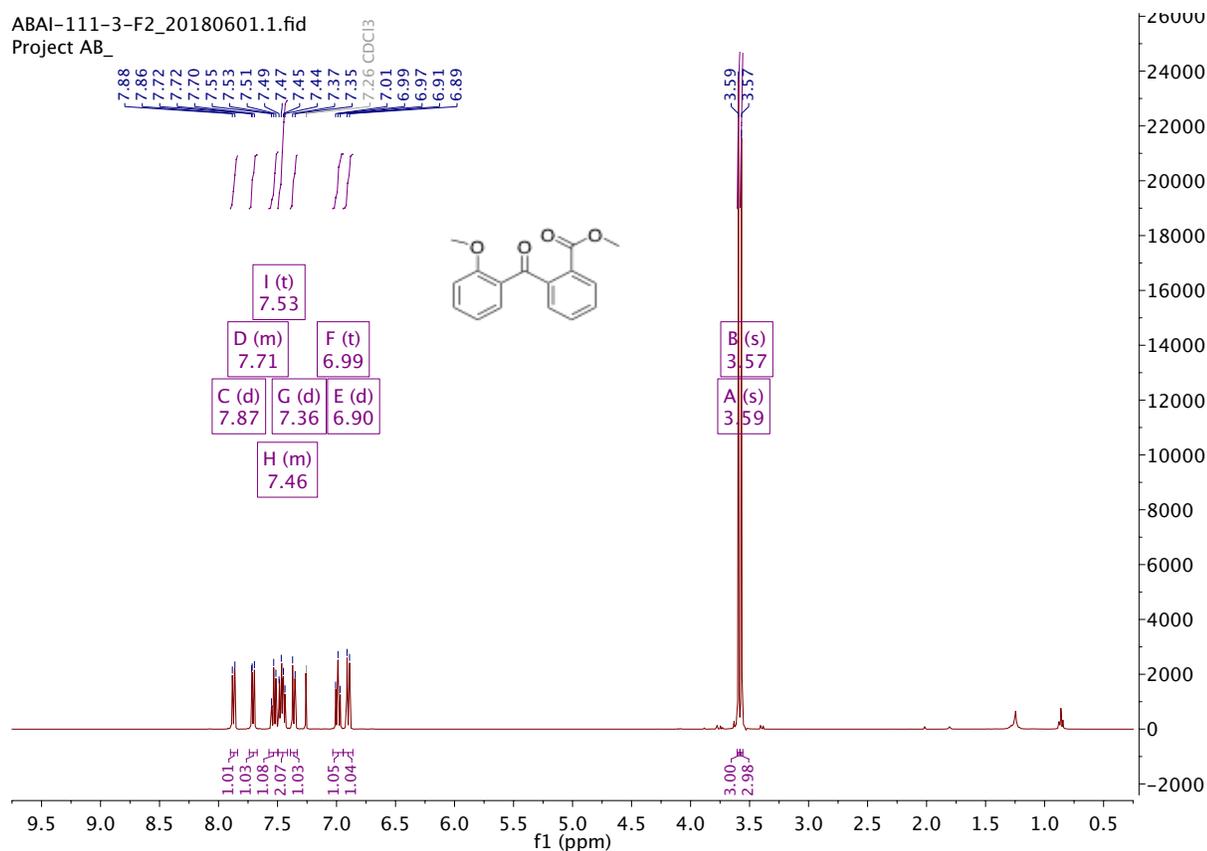
ABAI–111–3–F2_20180601.3.fid
Project AB_

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

293.0783
C$_{16}$H$_{14}$O$_4$Na = 293.0784
-0.1051 mmu

271.0965
C$_{16}$H$_{15}$O$_4$ = 271.0965
-0.0307 mmu

239.0700
C$_{15}$H$_{11}$O$_3$ = 239.0703
-0.3177 mmu

350.1385

Methyl 2-(4-(methylthio)benzoyl) benzoate **2ad**

abai–111–14f2_20180610.1.fid
Project AB_
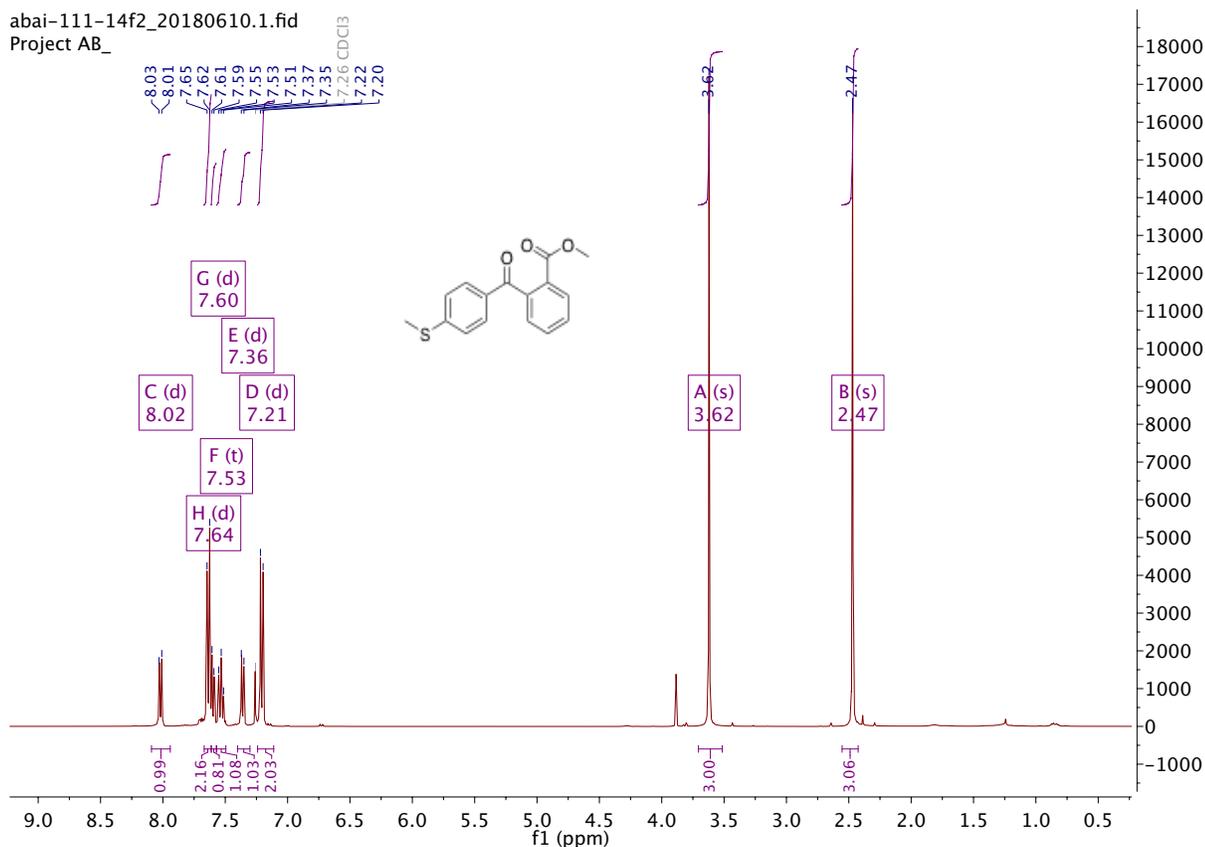
abai–111–14f2_20180610.3.fid
Project AB_
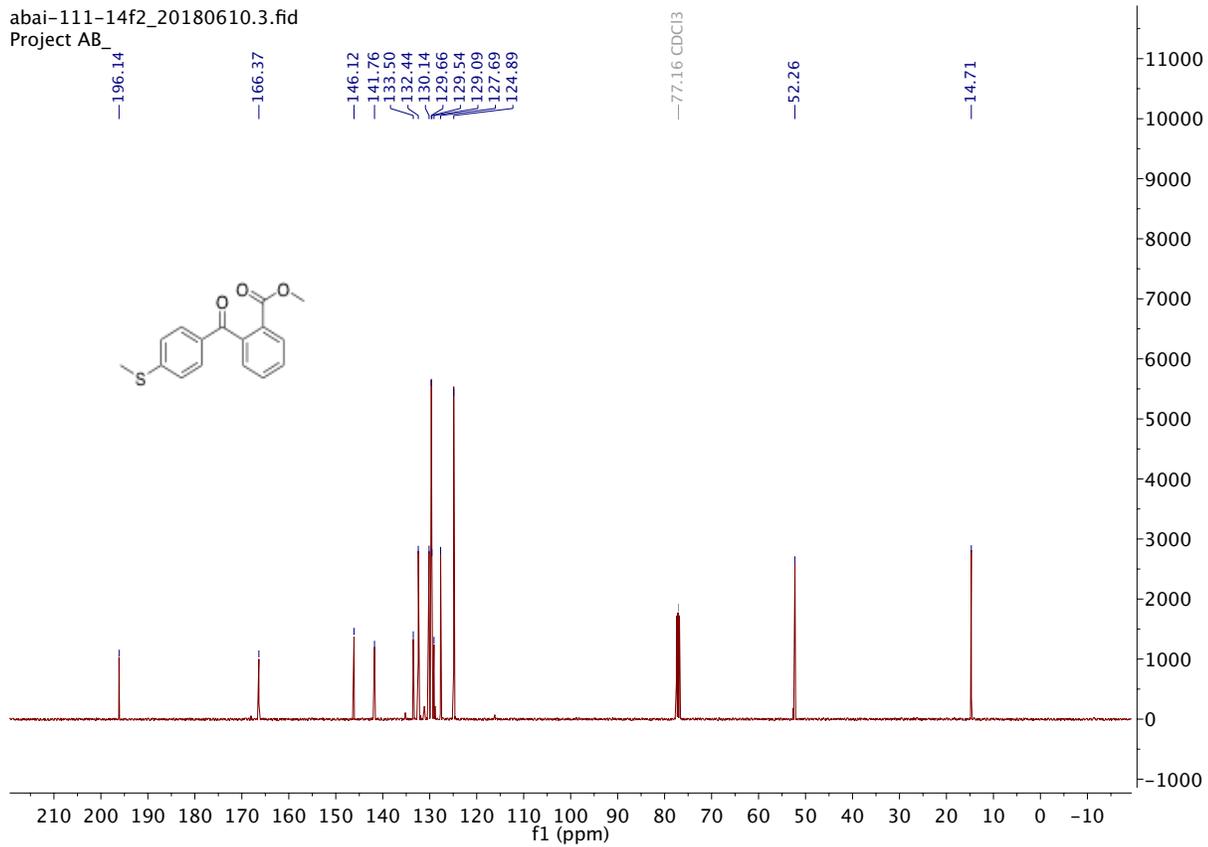
ABAI-111-14F2 #4   RT: 0.11   AV: 1   NL: 6.49E7
T: FTMS + p ESI Full ms [200.00-500.00]
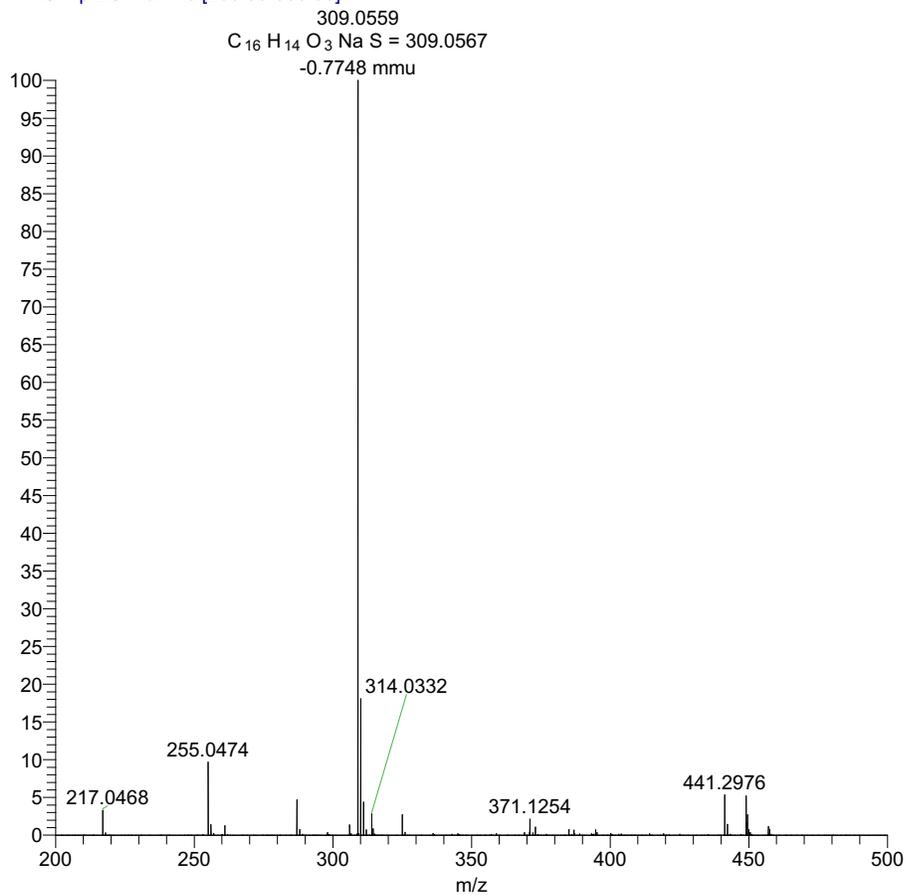
309.0559
$C_{16}H_{14}O_3NaS = 309.0567$
-0.7748 mmu

Methyl 2-(3-(methoxycarbonyl)benzoyl)benzoate **2ag**

abai-111-9-f3_20180618.1.fid
Project AB_
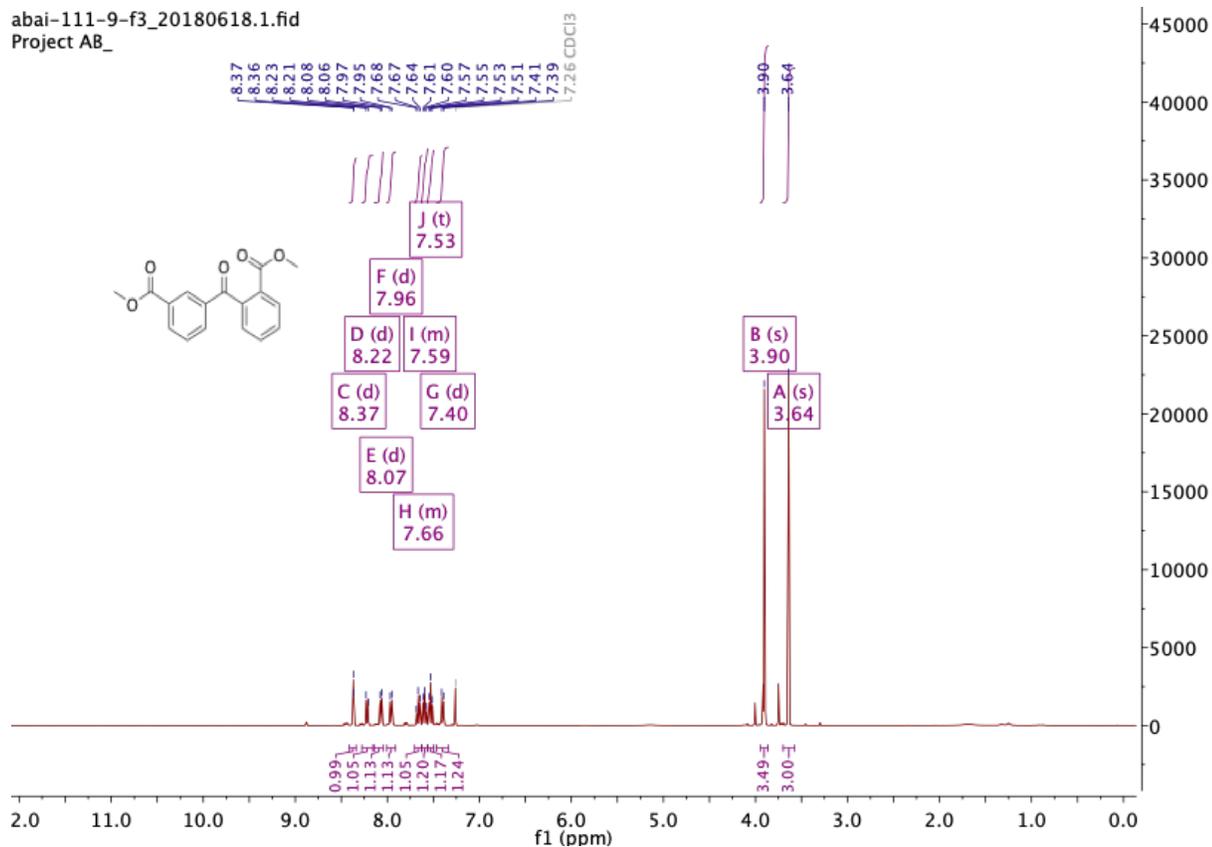
abai-111-9-f3_20180618.3.fid
Project AB_
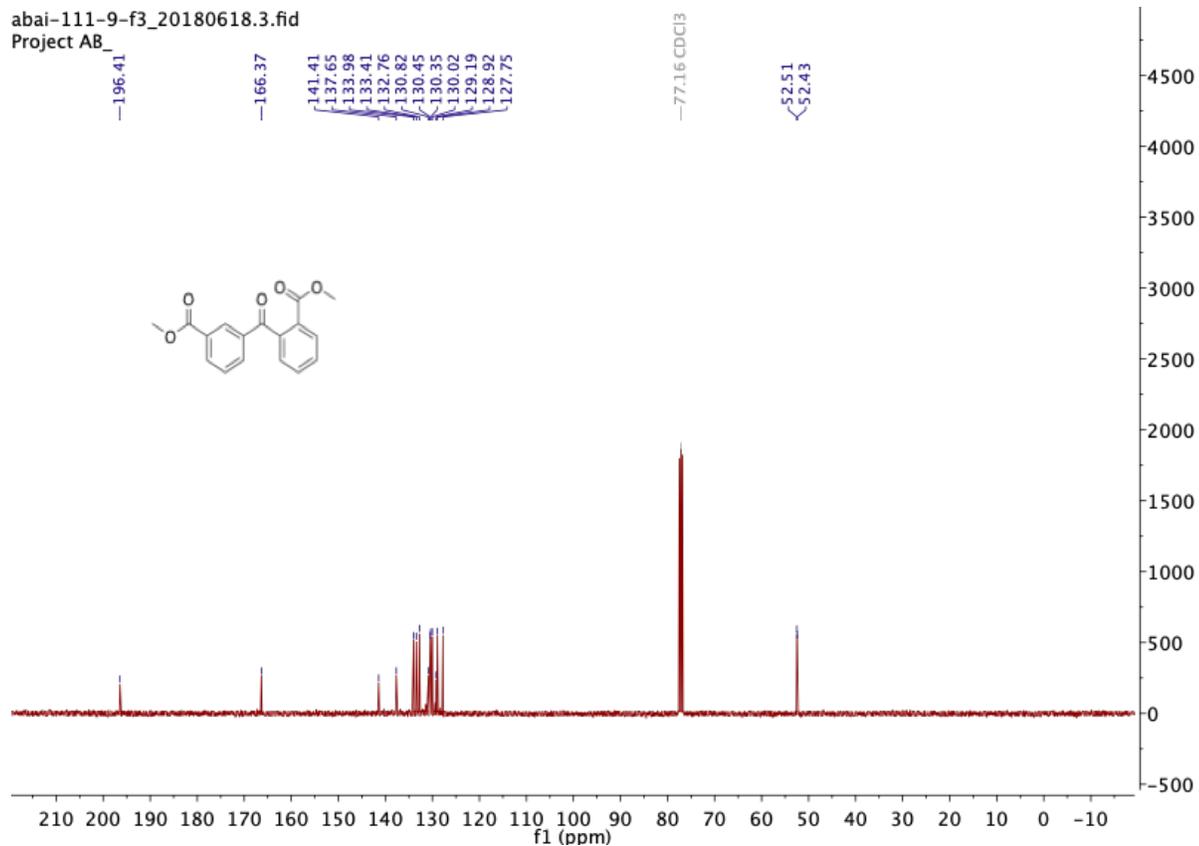
ABAI-111-9_180618122059 #1-5   RT: 0.01-0.13   AV: 5   NL: 3.
T: FTMS + p ESI Full ms [200.00-400.00]

Mass spectrum peaks: 321.0736 $C_{17}H_{14}O_5Na = 321.0733$, 0.2318 mmu; 299.0918 $C_{17}H_{15}O_5 = 299.0914$, 0.3688 mmu; 378.1336
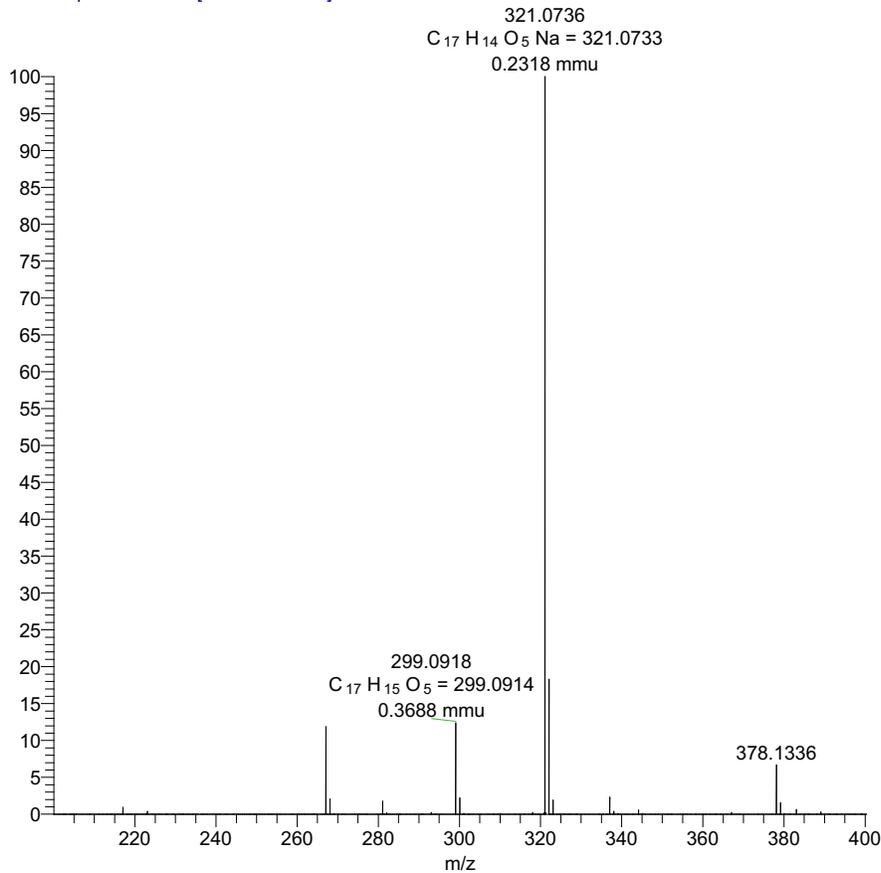
Dimethyl 2,2'-carbonyldibenzoate **2ah**

ABAI-111-12_20180606.1.fid
Project AB_
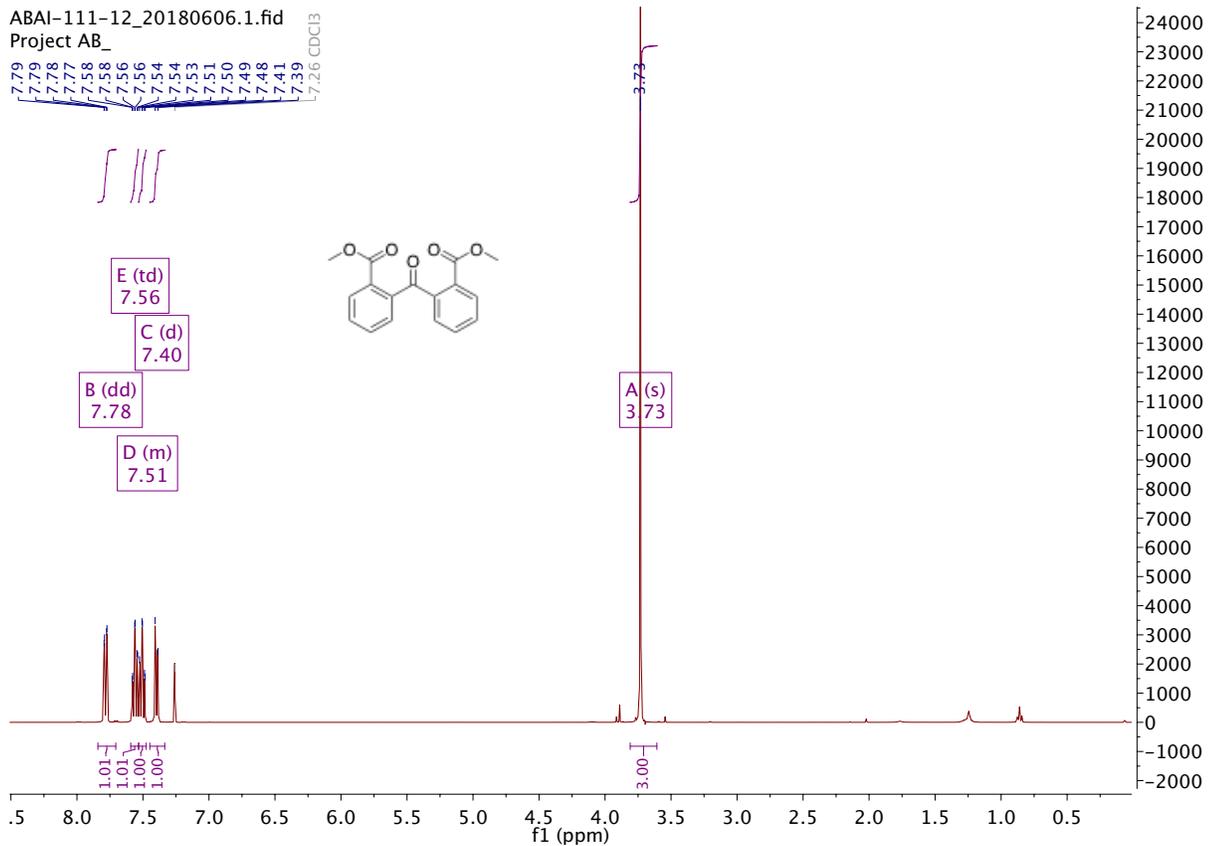
7.79, 7.79, 7.78, 7.77, 7.58, 7.58, 7.56, 7.56, 7.54, 7.54, 7.53, 7.51, 7.50, 7.49, 7.48, 7.41, 7.39, 7.26 CDCl3, 3.73

E (td) 7.56
C (d) 7.40
B (dd) 7.78
D (m) 7.51
A (s) 3.73

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

ABAI–111–12_20180606.3.fid
Project AB_

195.65
168.33
138.51
131.98
131.35
131.16
129.70
129.36
128.93
77.36
77.16 CDCl3
52.61

f1 (ppm)
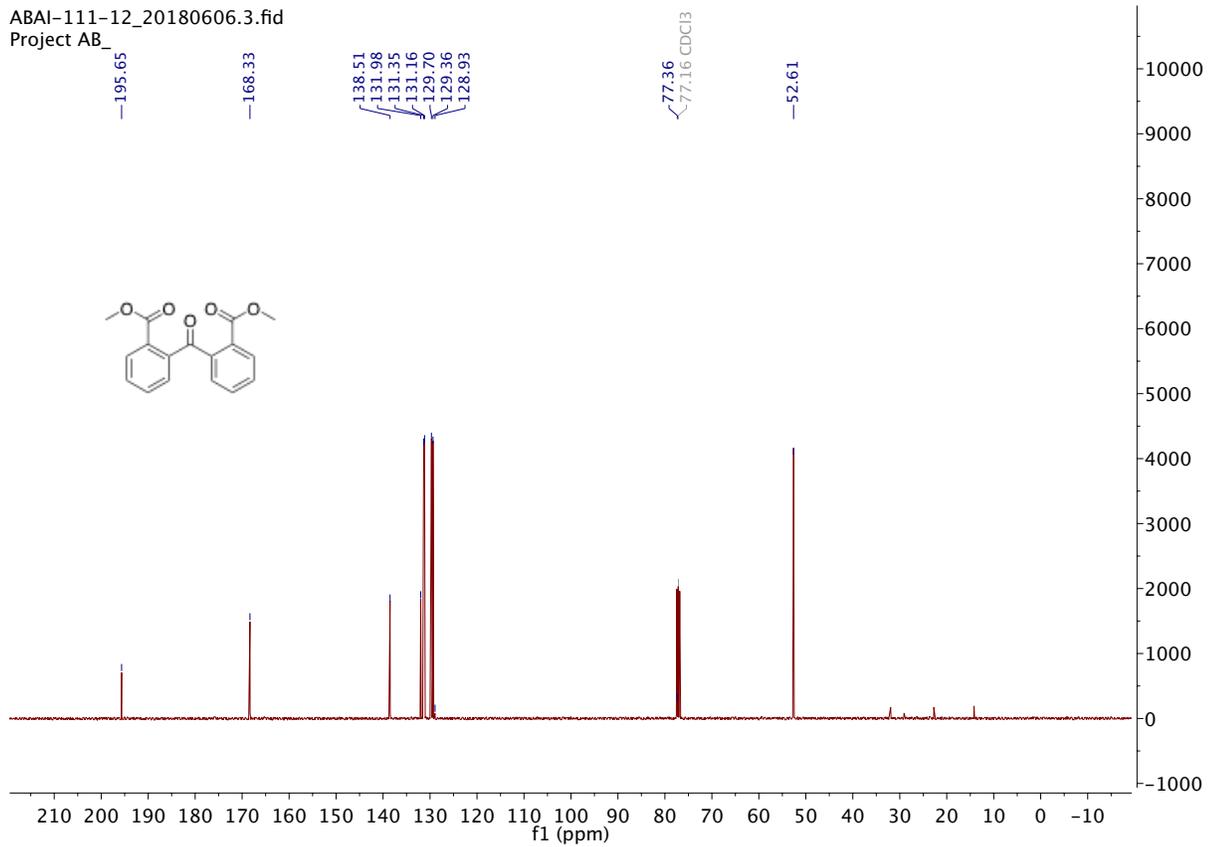
ABAI-111-7D-F2_180618115027 #1-4   RT: 0.02-0.11   AV: 4   N   E7
T: FTMS + p ESI Full ms [200.00-400.00]
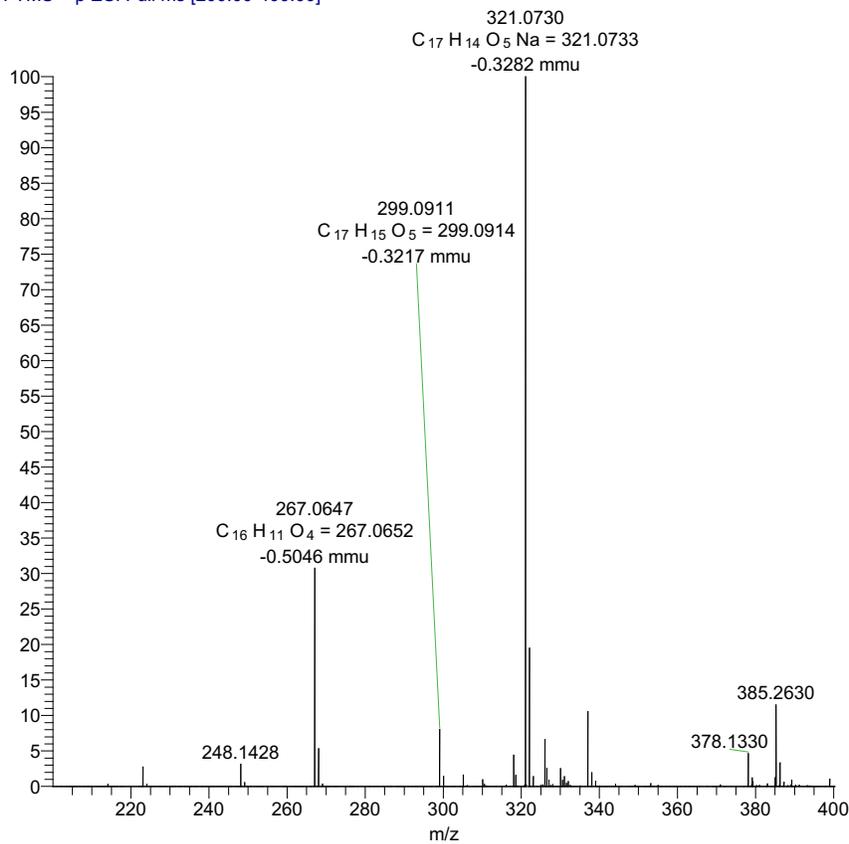
321.0730
C$_{17}$ H$_{14}$ O$_5$ Na = 321.0733
-0.3282 mmu

299.0911
C$_{17}$ H$_{15}$ O$_5$ = 299.0914
-0.3217 mmu

267.0647
C$_{16}$ H$_{11}$ O$_4$ = 267.0652
-0.5046 mmu

248.1428

385.2630

378.1330

m/z

Methyl 2-(4-cyanobenzoyl) benzoate **2ai**

ABAI–5DF2_20180613.1.fid
Project AB_

F (d)
7.73

D (m)
7.62

B (d)
8.08

C (d)
7.40

A (s)
3.67

E (d)
7.68

G (d)
7.83

f1 (ppm)

ABAI–5DF2_20180613.3.fid
Project AB_

f1 (ppm)
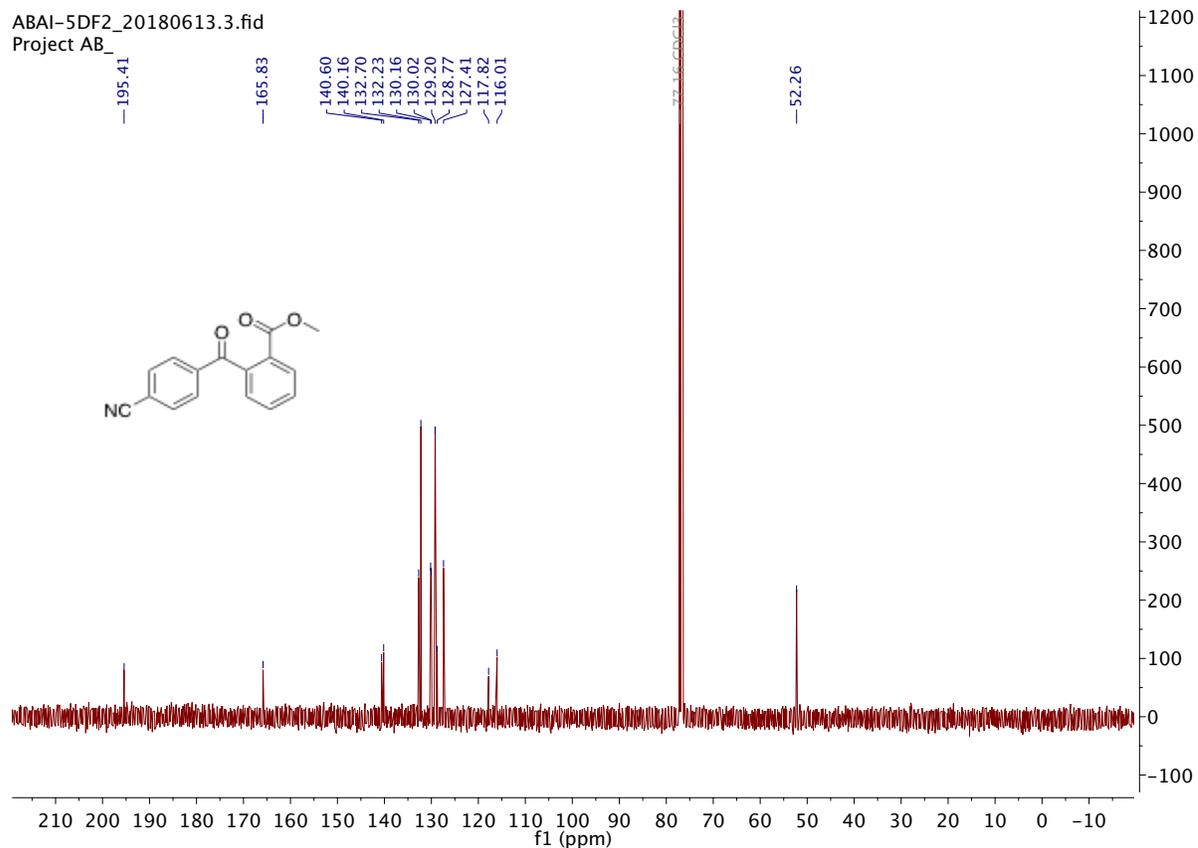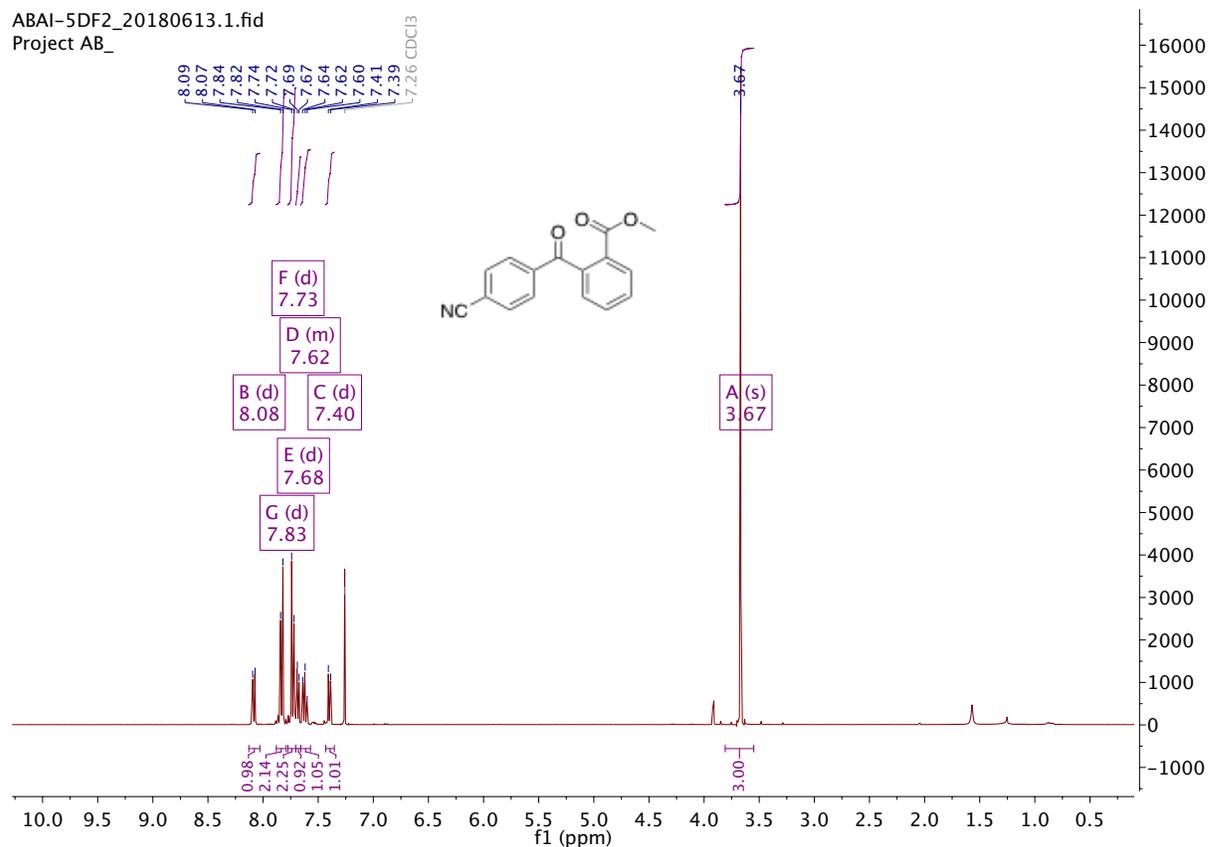
ABAI-111-5DF2_180618113446 #1-4   RT: 0.01-0.09   AV: 4   NI   6
T: FTMS + p ESI Full ms [200.00-400.00]

288.0630
$C_{16} H_{11} O_3 N$ Na = 288.0631
-0.1539 mmu

321.0732

266.0810
$C_{16} H_{12} O_3 N$ = 266.0812
-0.1847 mmu

217.0466

393.2733

293.0782

379.3107

337.0471   352.0790

m/z
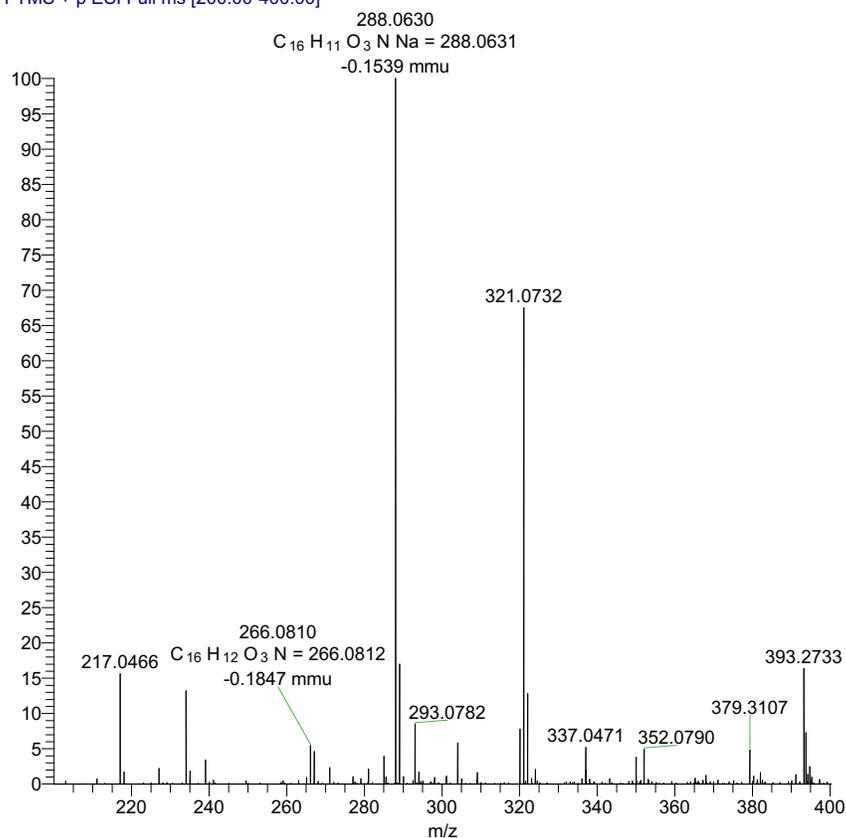
Methyl 2-(3-cyanobenzoyl) benzoate **2aj**

abai-111-4d_20180612.2.fid
Project AB_
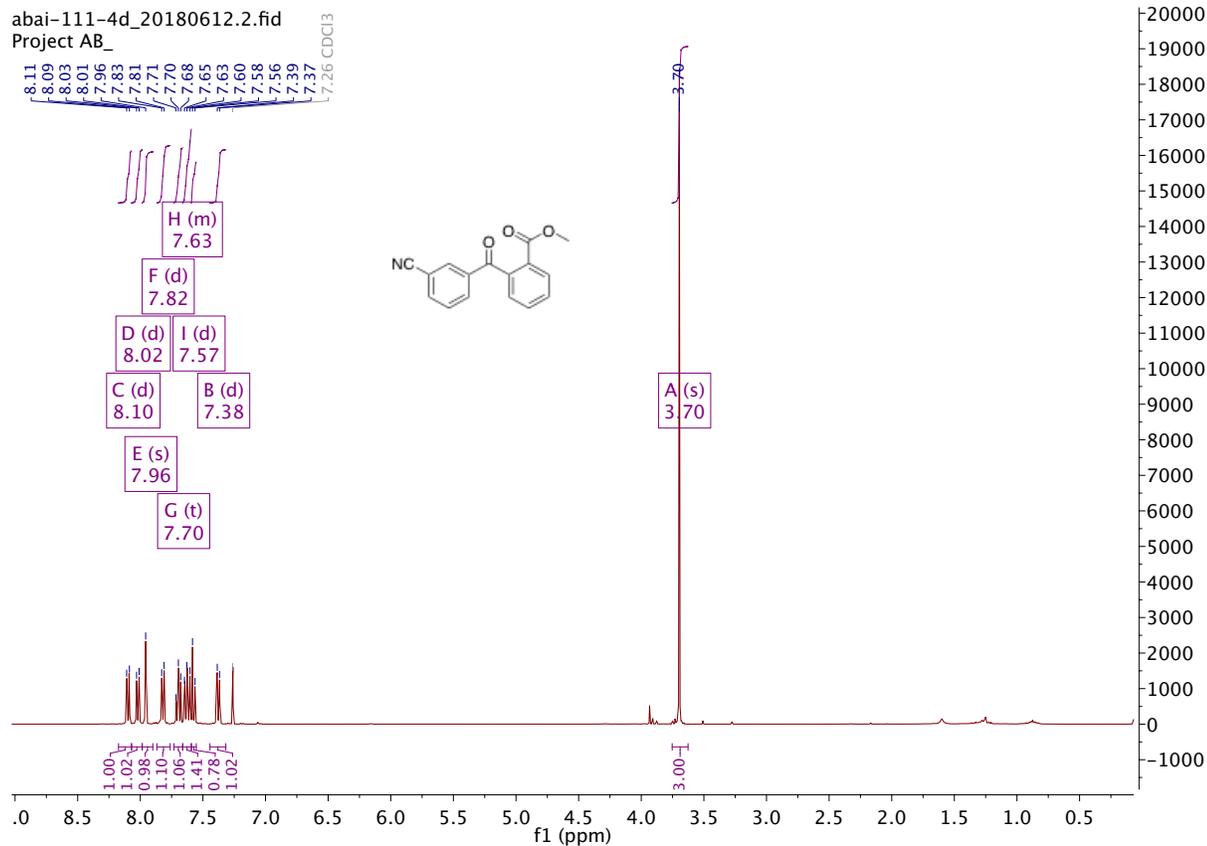
8.11
8.09
8.03
8.01
7.96
7.83
7.81
7.71
7.70
7.68
7.65
7.63
7.60
7.58
7.56
7.39
7.37
7.26 CDCl3

3.70

H (m)
7.63

F (d)
7.82

D (d)   I (d)
8.02   7.57

C (d)   B (d)
8.10   7.38

E (s)
7.96

G (t)
7.70

A (s)
3.70

1.00
1.02
0.98
1.10
1.06
1.41
0.78
1.02

3.00

f1 (ppm)

abai–111–4d_20180612.4.fid
Project AB_
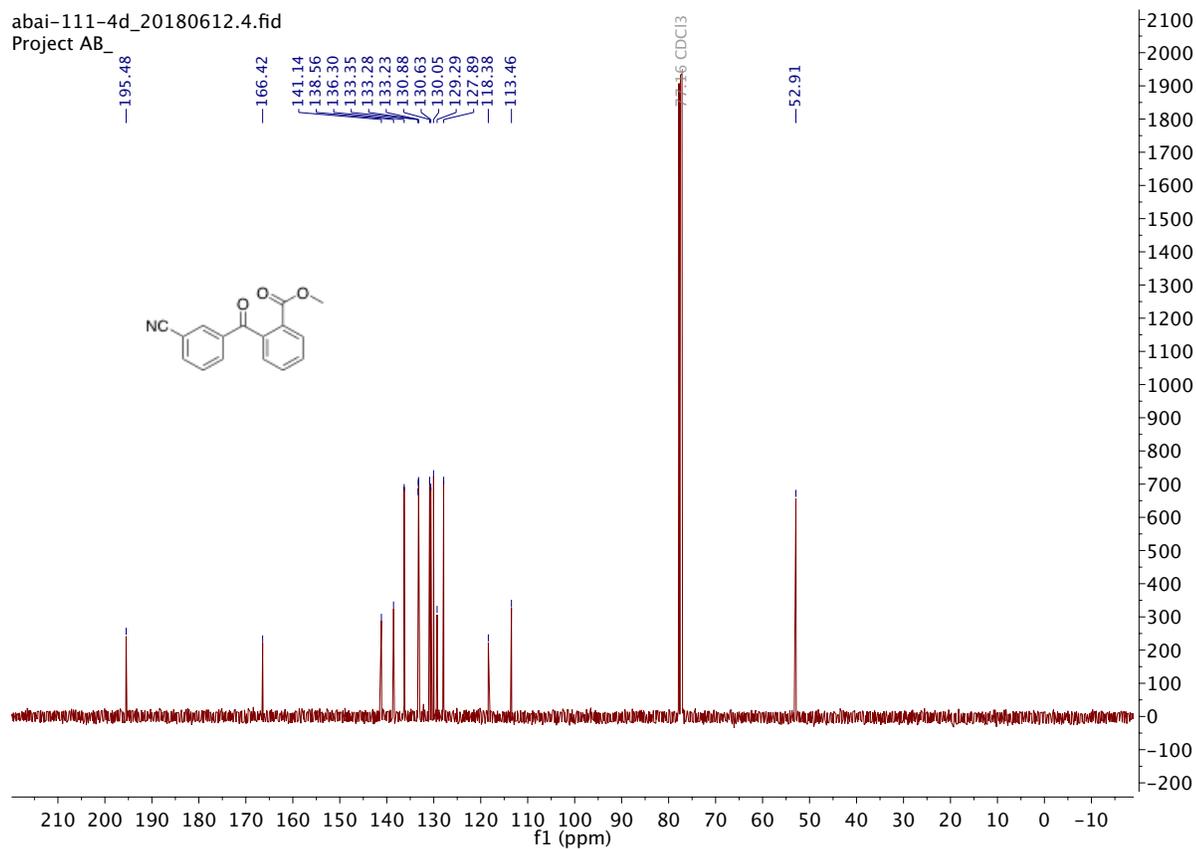
ABAI-111-4D-F2_180618113446 #1-4   RT: 0.02-0.10   AV: 4   N   Ξ7
T: FTMS + p ESI Full ms [200.00-400.00]
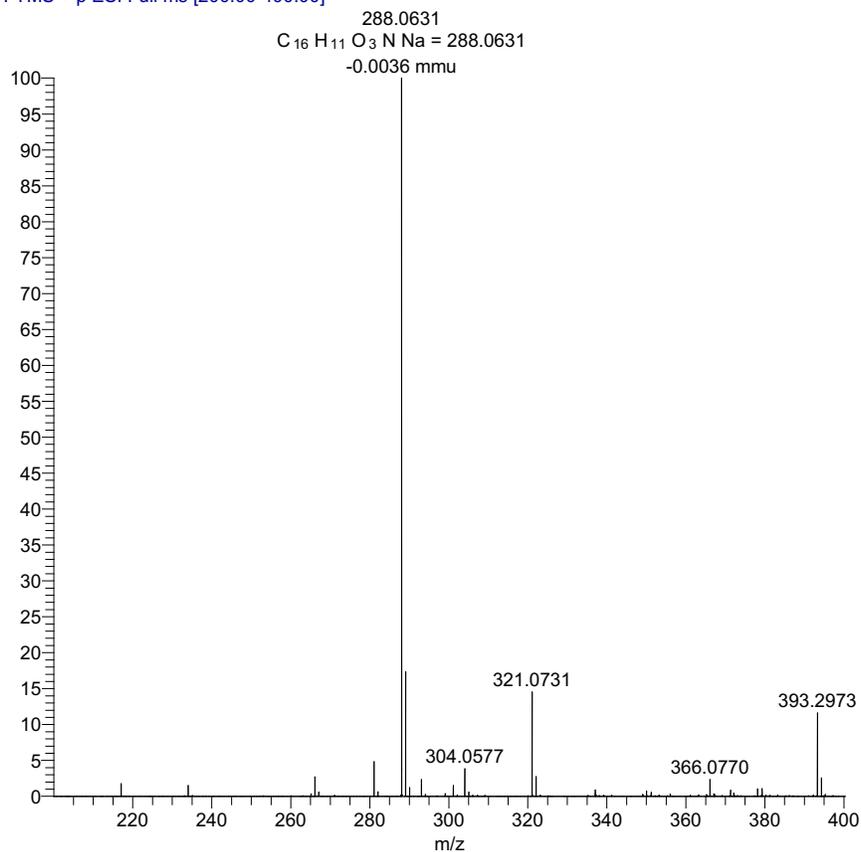
288.0631
C 16 H 11 O 3 N Na = 288.0631
-0.0036 mmu

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

Methyl 2-(4-fluorobenzoyl) benzoate **2ak**

abai–111–6d_20180612.2.fid
Project AB_

F (td)
7.64

D (d)
7.38

B (m)
8.05

C (m)
7.09

E (m)
7.57

G (dd)
7.77

A (s)
3.65
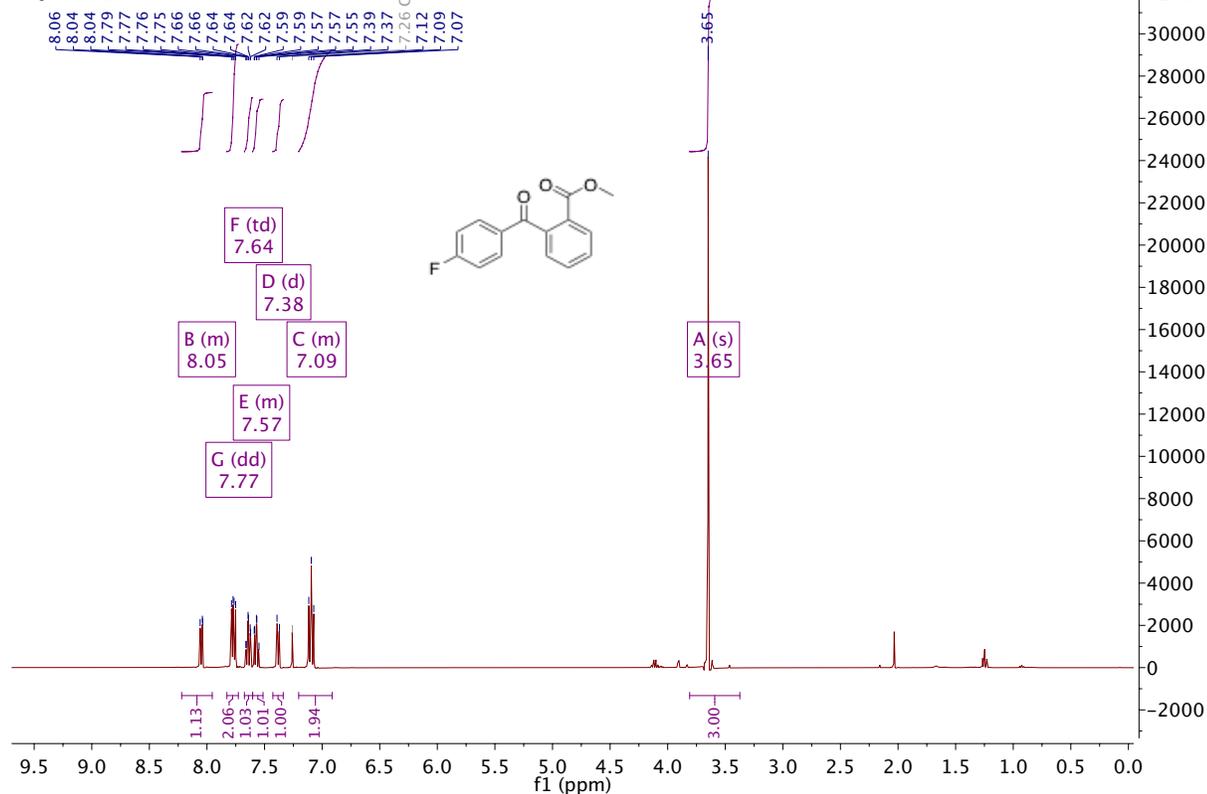
abai–111–6d_20180612.4.fid
Project AB_
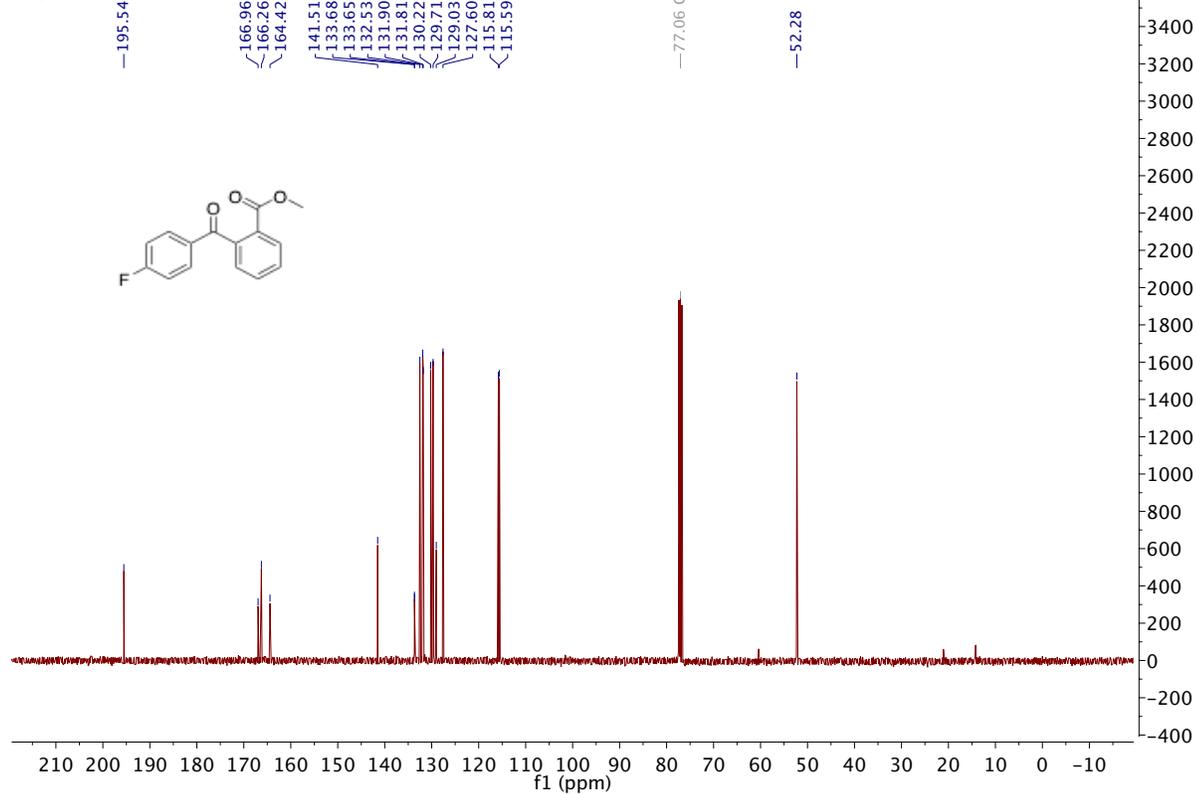
– 58 –

ABAI-111-6D-F2_180618113446 #1-4   RT: 0.02-0.11   AV: 4   N   Ξ7
T: FTMS + p ESI Full ms [200.00-400.00]

281.0586
$C_{15} H_{11} O_3 F Na = 281.0584$
0.1099 mmu

259.0765
$C_{15} H_{12} O_3 F = 259.0765$
0.0380 mmu

m/z

Methyl 2-(3-fluorobenzoyl) benzoate **2al**

abai–111–3d_20180612.2.fid
Project AB_
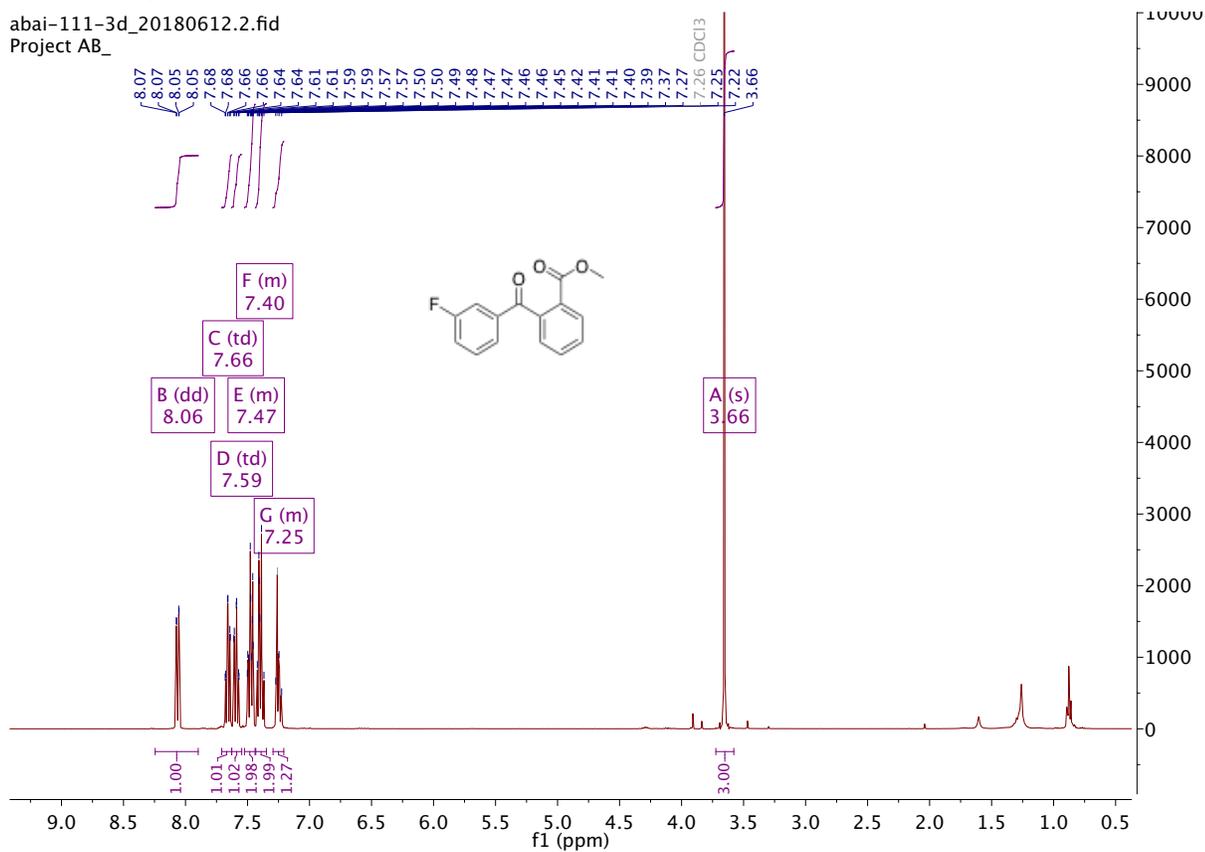
F (m)
7.40

C (td)
7.66

B (dd)
8.06

E (m)
7.47

D (td)
7.59

G (m)
7.25

A (s)
3.66

f1 (ppm)

abai–111–3d_20180612.4.fid
Project AB_

196.20
196.18
166.62
164.43
161.96
141.69
139.84
139.77
133.04
130.67
130.60
130.31
129.50
128.09
125.56
125.53
120.66
120.45
116.22
115.99
77.16 CDCl3
52.74
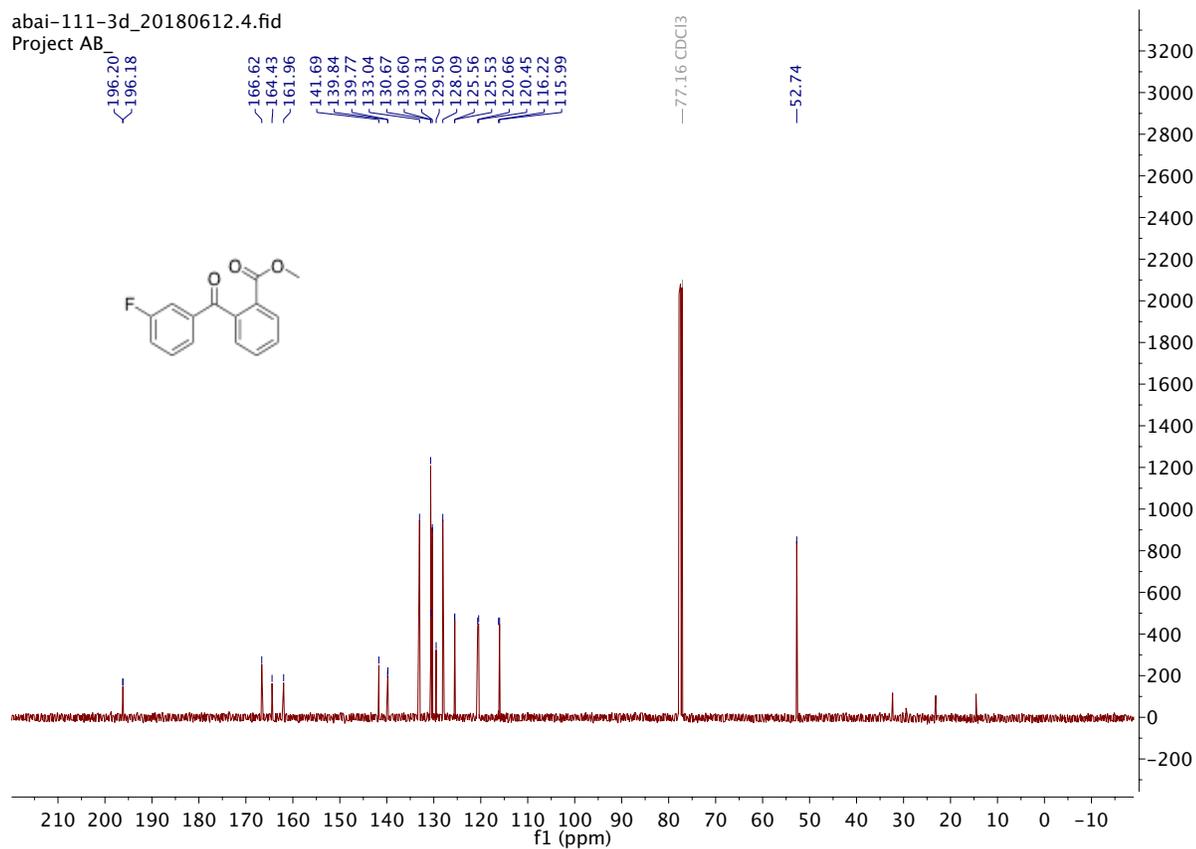
ABAI-111-3D_180618113446 #1-5   RT: 0.01-0.13   AV: 5   NL: 2
T: FTMS + p ESI Full ms [200.00-400.00]
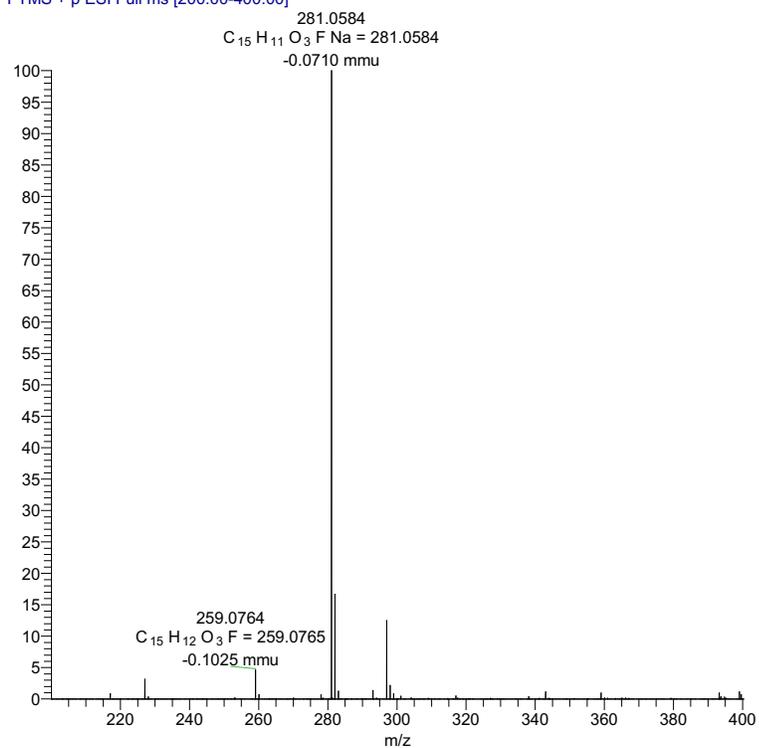
281.0584
C15 H11 O3 F Na = 281.0584
-0.0710 mmu

259.0764
C15 H12 O3 F = 259.0765
-0.1025 mmu

Methyl 2-(2-fluorobenzoyl) benzoate **2am**

ABAI–111–2DF2_20180610.1.fid
Project AB_
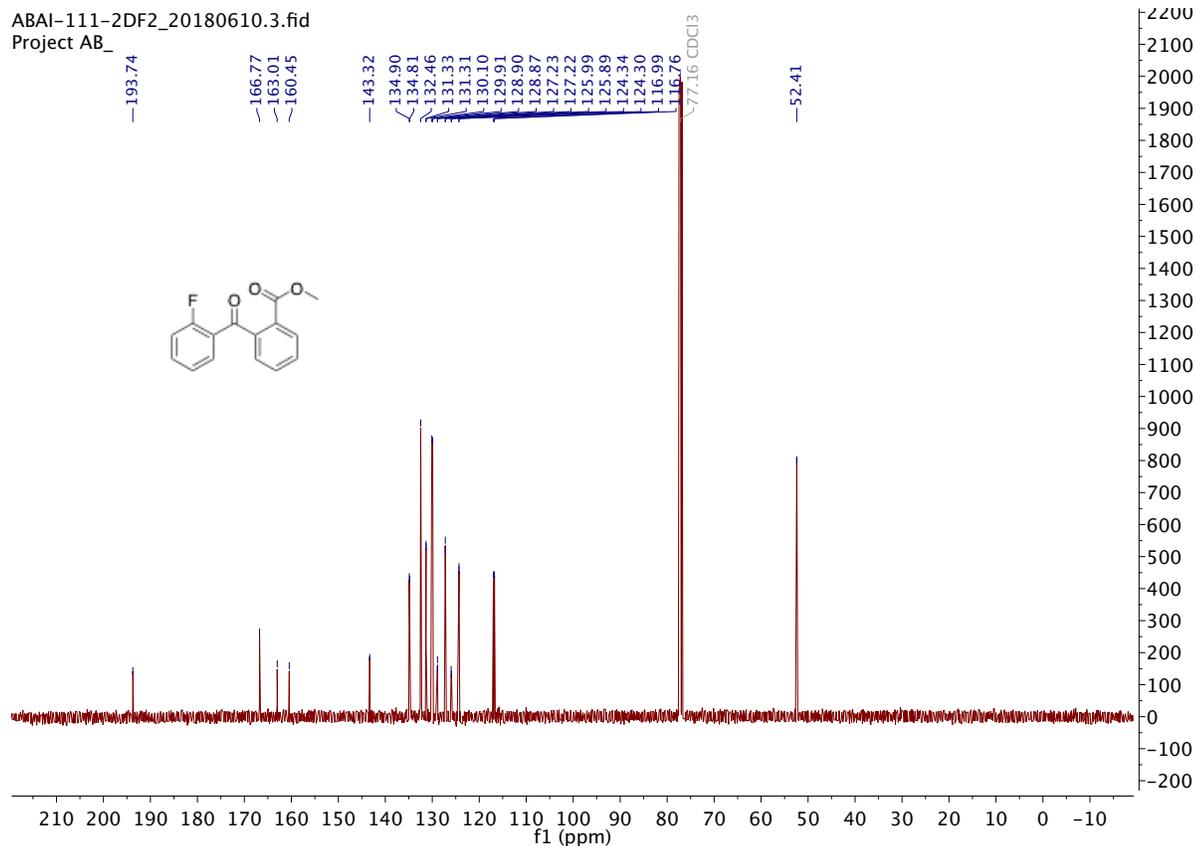
G (td)
7.65

C (td)
7.83

E (m)
7.27

B (dd)
8.02

D (m)
7.10

A (s)
3.72

F (m)
7.43

H (m)
7.58

ABAI–111–2DF2_20180610.3.fid
Project AB_

ABAI-111-2DF2 #1-4 RT: 0.01-0.10 AV: 4 NL: 3.70E7
T: FTMS + p ESI Full ms [200.00-500.00]

281.0583
C 15 H 11 O 3 F Na = 281.0584
-0.1194 mmu

373.0846   407.0846   415.0708

m/z
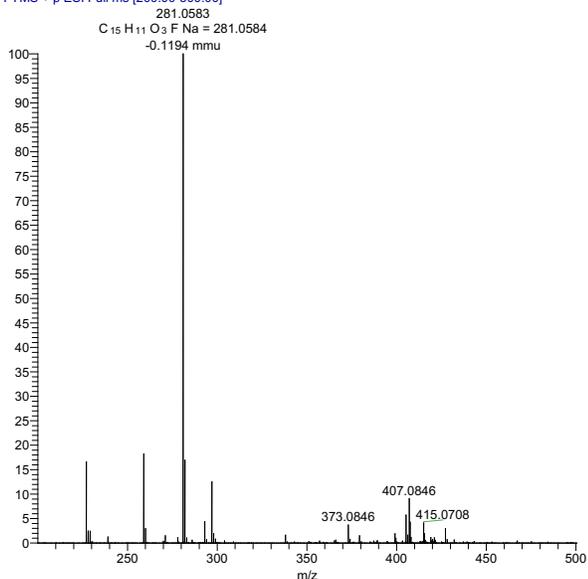
Methyl 2-(thiophene-2-carbonyl) benzoate **2an**

abai-76-2-f4.10.fid

8.03
8.01
7.65
7.63
7.61
7.58
7.56
7.55
7.54
7.46
7.44
7.35
7.34
7.33
7.26 CDCl3

3.67

F (d)
7.60

D (d)
7.45

B (d)   C (m)
8.02   7.34

E (m)
7.55

G (d)
7.64

A (s)
3.67

0.95
1.50
0.74
1.58
0.97
0.95

3.00

f1 (ppm)
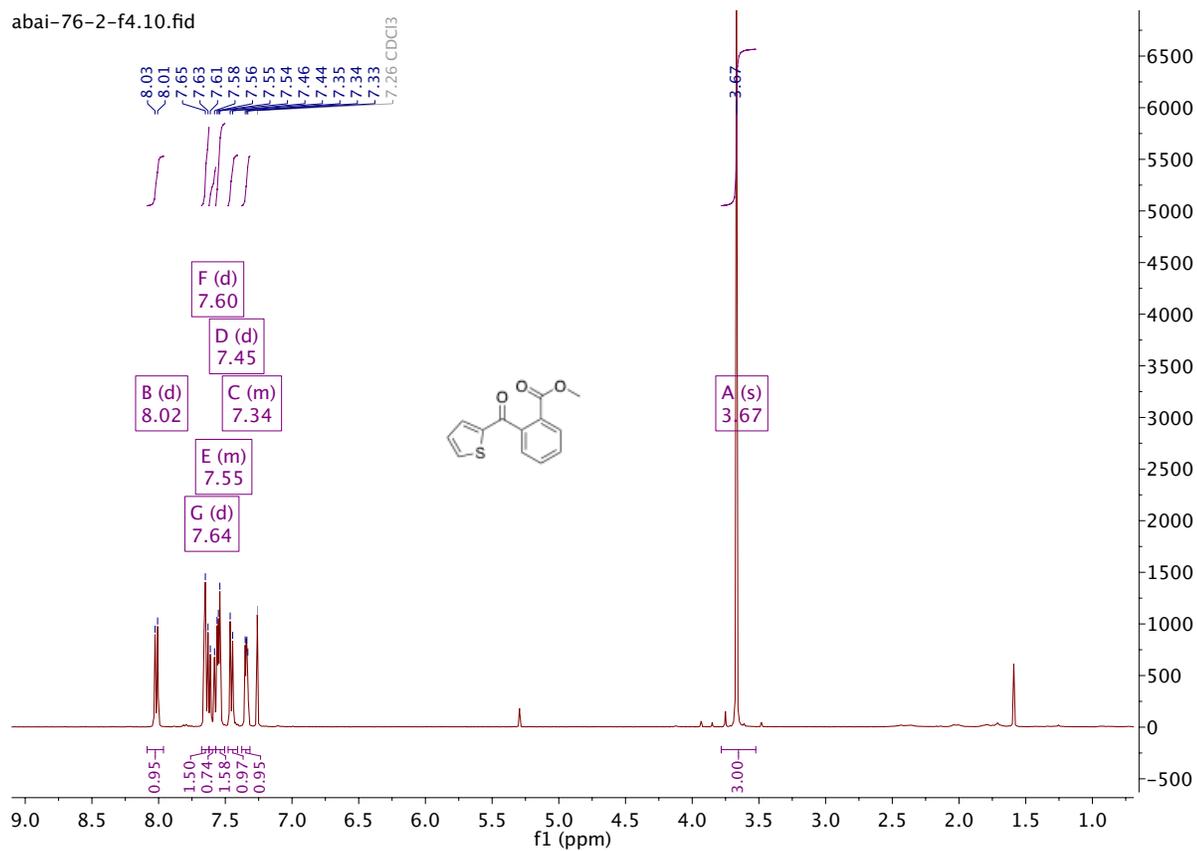
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

abai−76−2−f4.11.fid
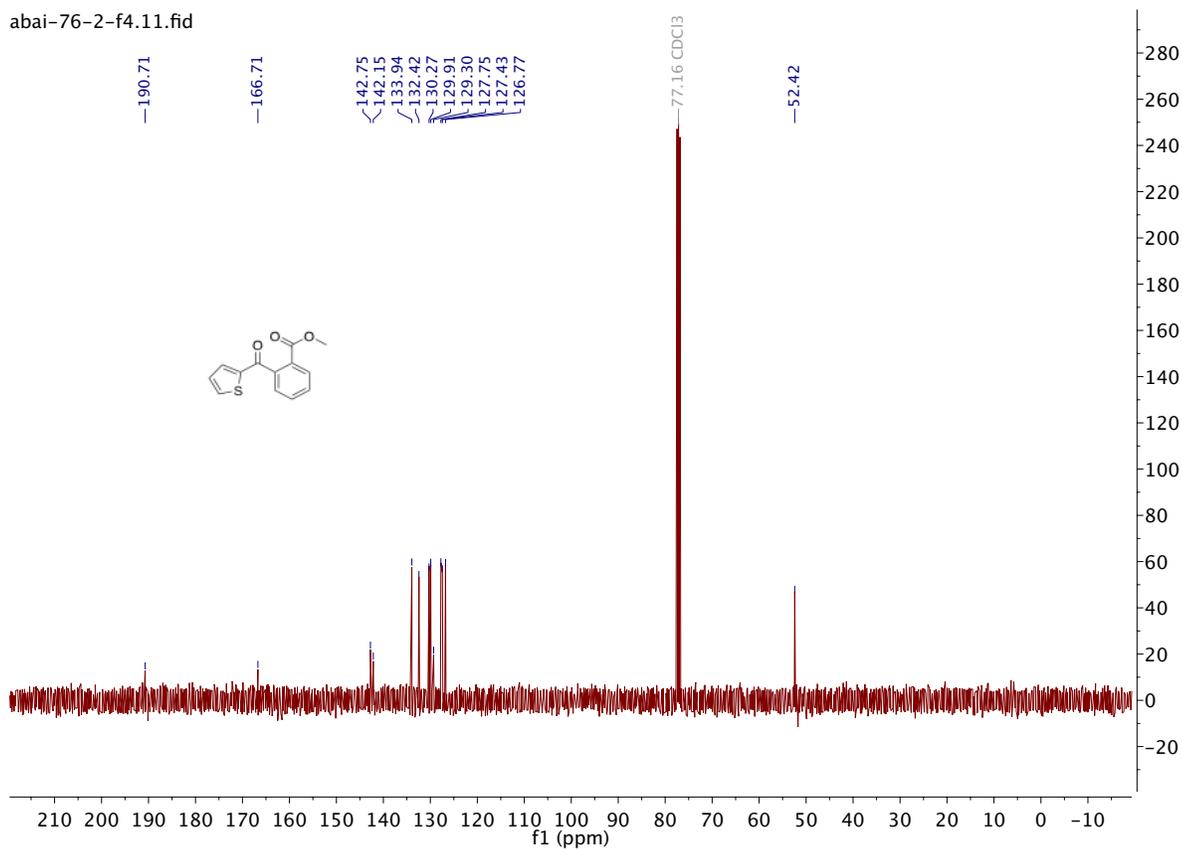
Methyl 2-(benzo[b]thiophene-2-carbonyl) benzoate *2ao*

ABAI−B1−F4
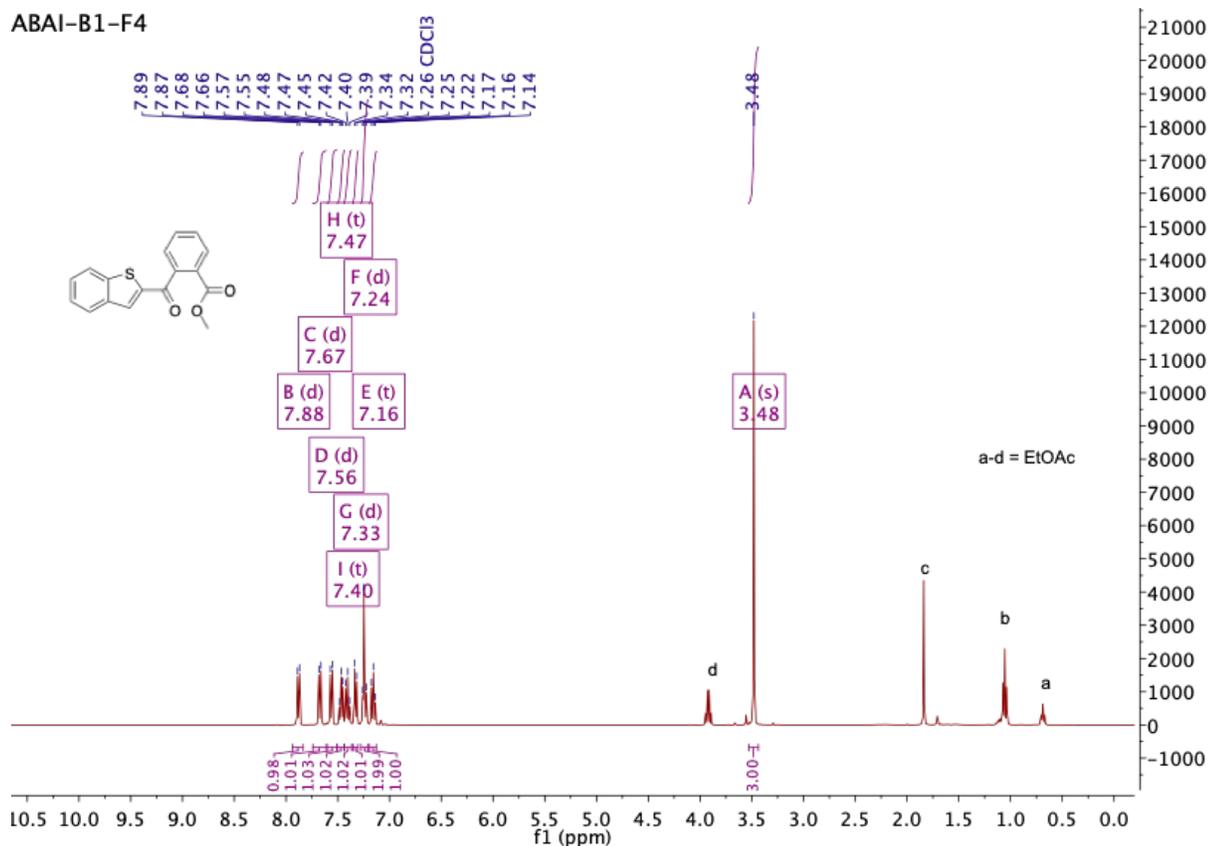
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

ABAI-B1-F4
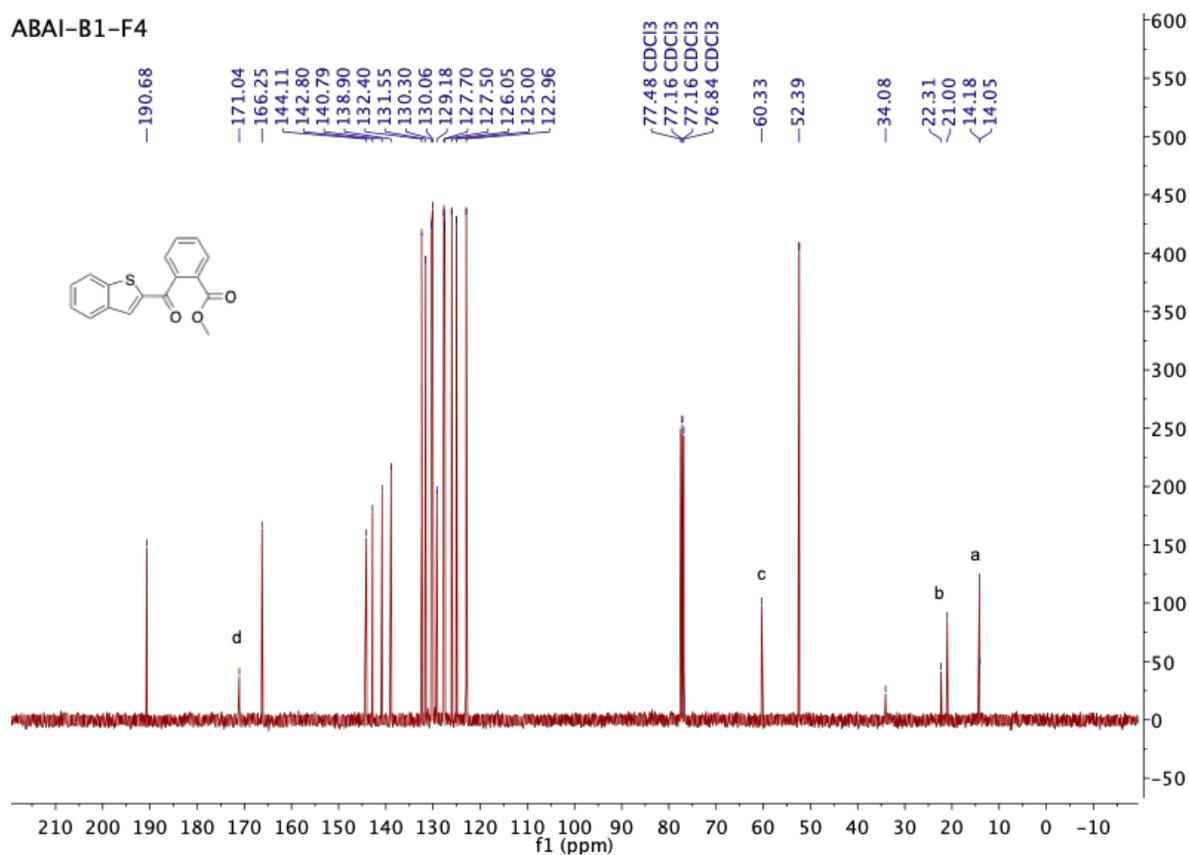
Methyl 5-fluoro-2-(4-methoxybenzoyl)benzoate *2ba*

abai-115-4-f2_20180921.1.fid
Project AB_
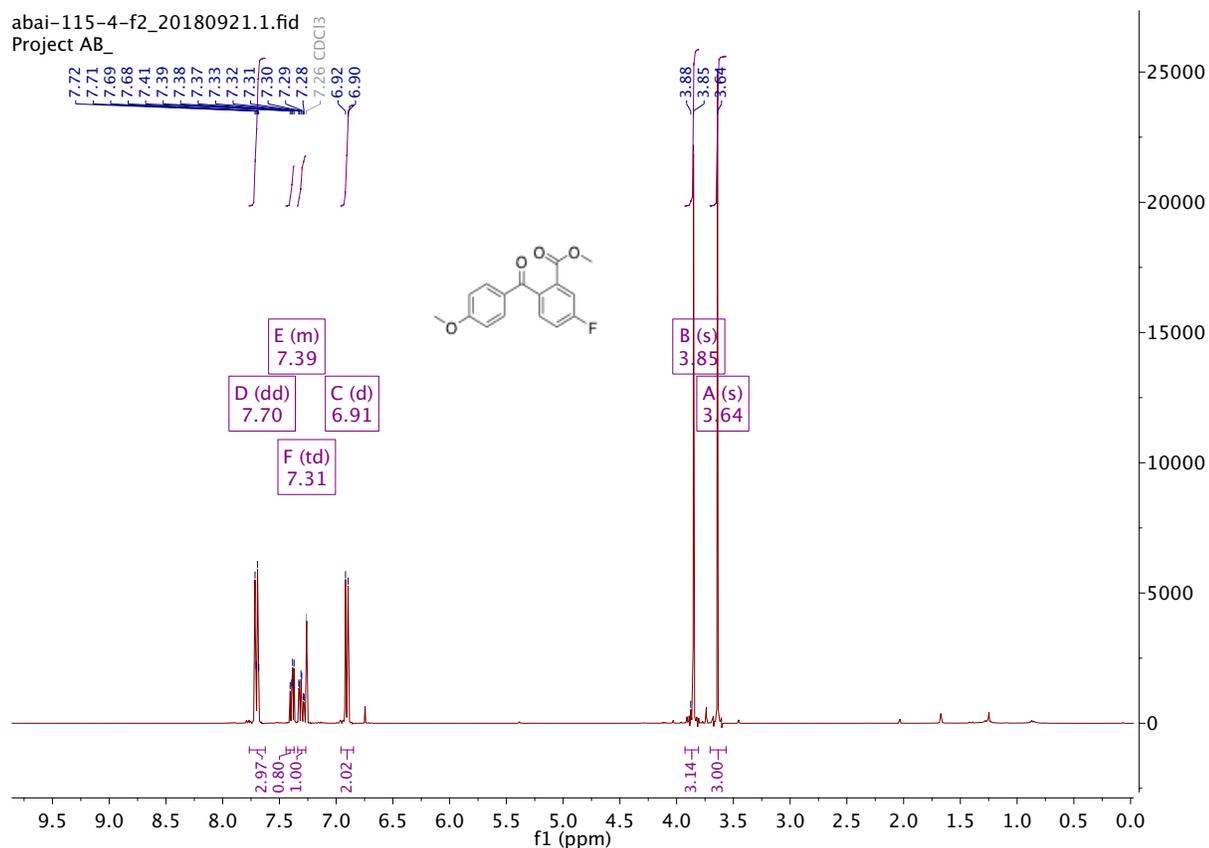
abai-115-4-f2_20180921.3.fid
Project AB_
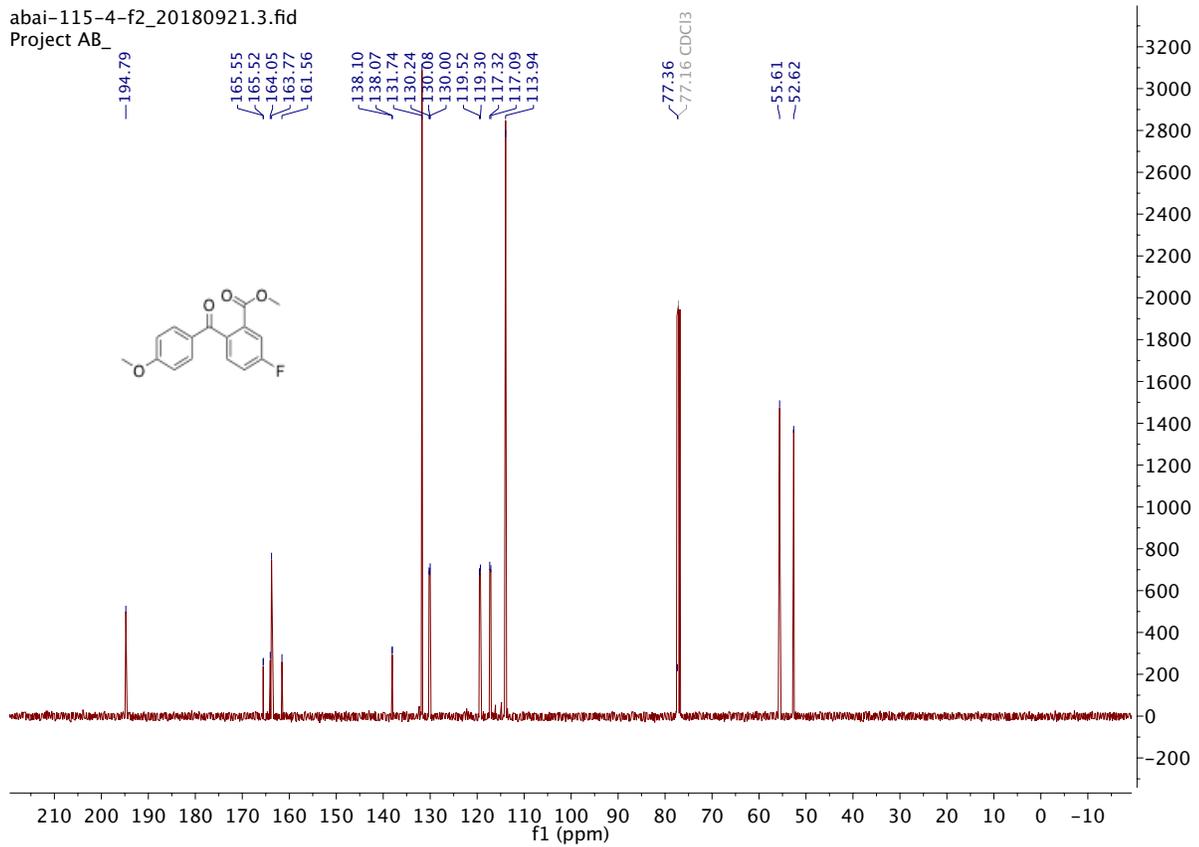
abai-115-4f2_181005104518 #1-5   RT: 0.01-0.12   AV: 5   NL: 6.61E7
T: FTMS + p ESI Full ms [200.00-500.00]
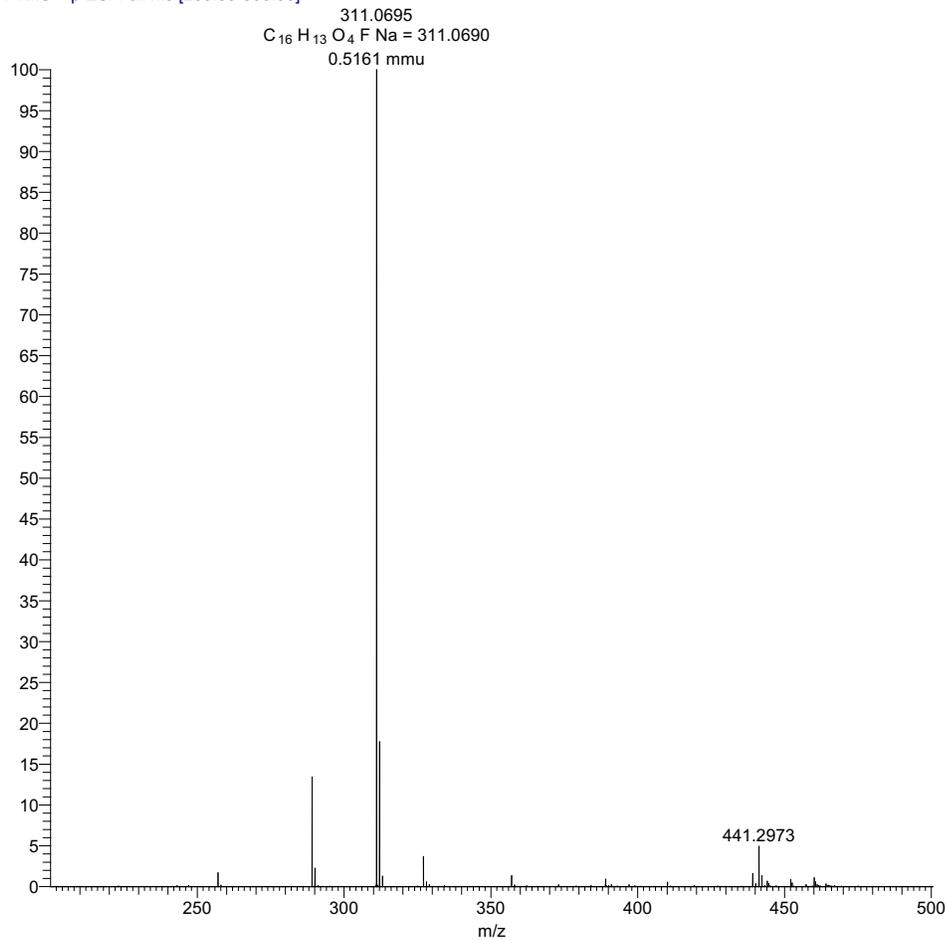
311.0695
$C_{16}H_{13}O_4FNa$ = 311.0690
0.5161 mmu

441.2973

Methyl 4-fluoro-2-(4-methoxybenzoyl)benzoate **2ca**

abai–115-8f2_20180925.1.fid
Project AB_
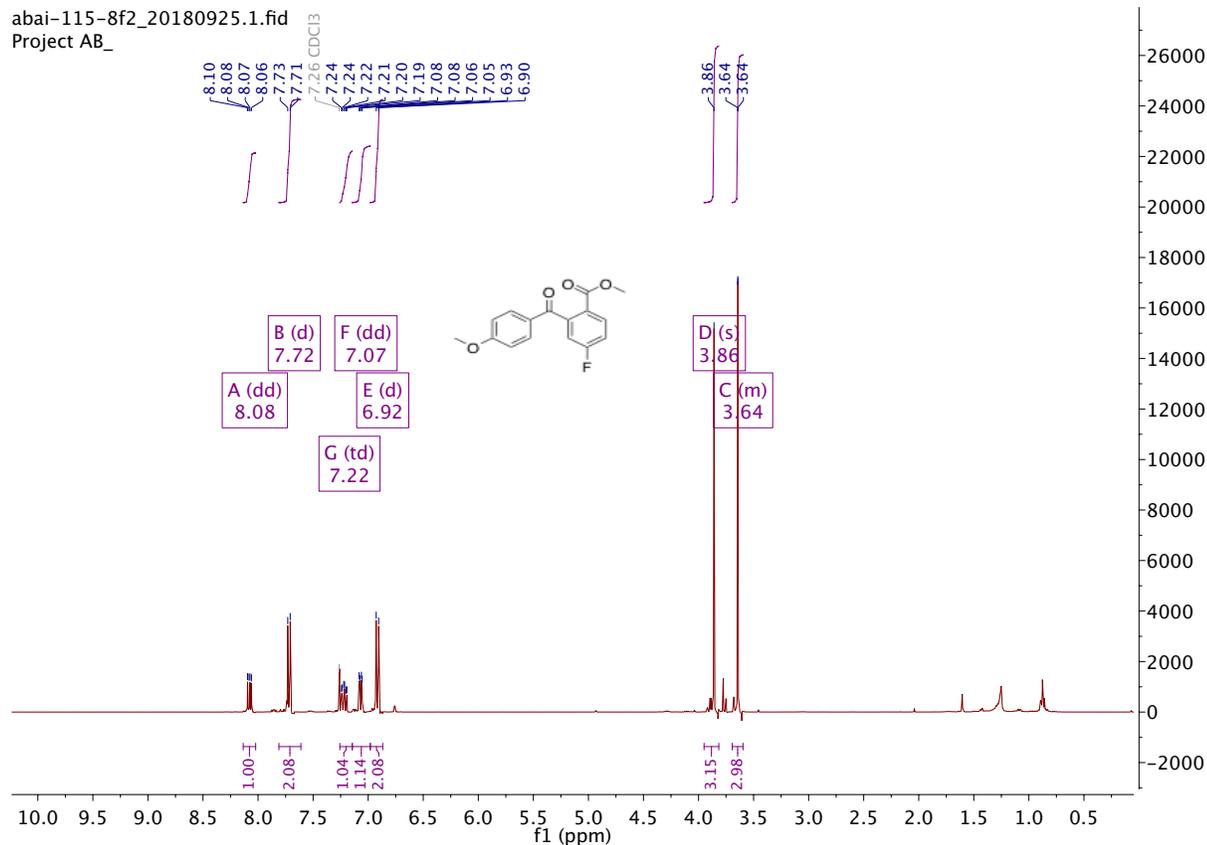
abai–115-8f2_20180925.3.fid
Project AB_

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

311.0695
$C_{16} H_{13} O_4 F Na = 311.0690$
0.5094 mmu

357.0547
$C_{25} H_9 O_3 = 357.0546$
0.0603 mmu

441.2974

257.0612
$C_{15} H_{10} O_3 F = 257.0608$
0.3249 mmu

457.3414

m/z

*Methyl 5-chloro-2-(4-methoxybenzoyl)benzoate **2da***

abai–115–2–f3_20180920.1.fid
Project AB_
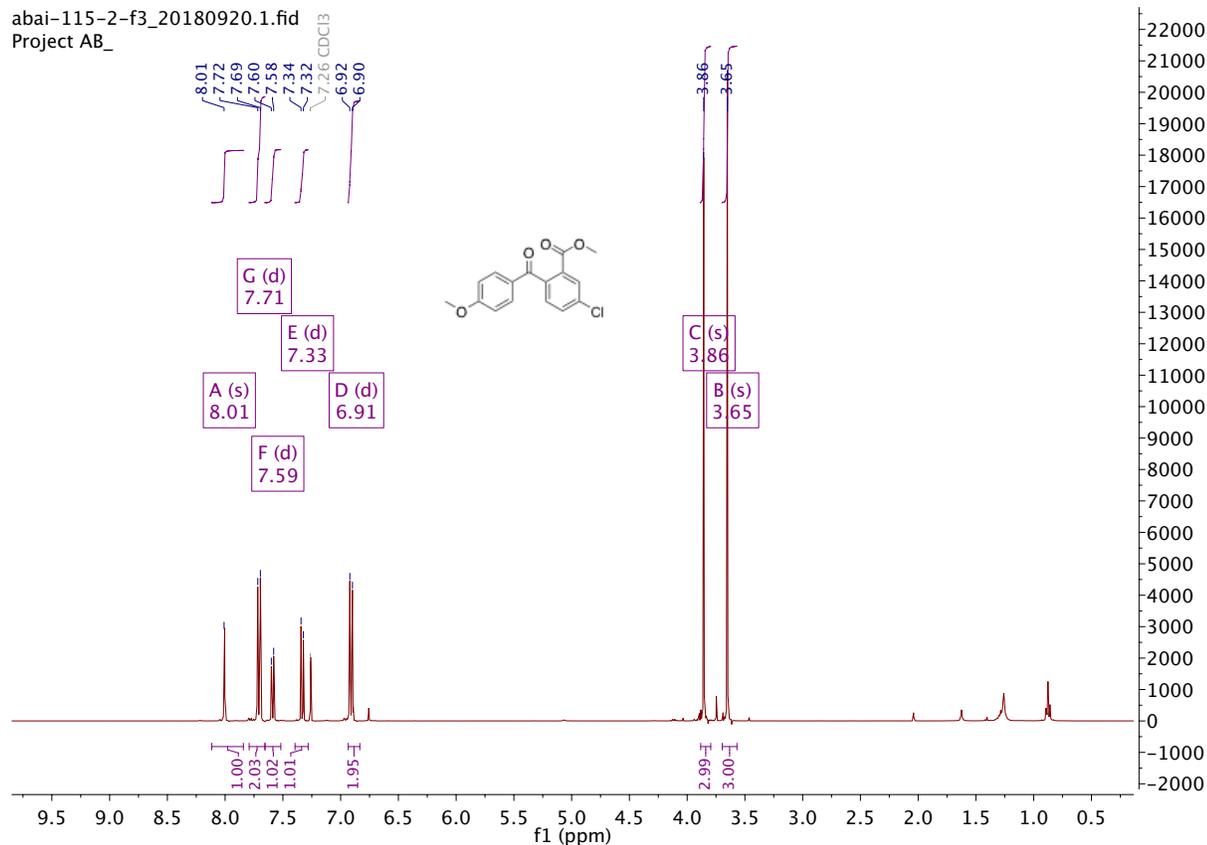
abai–115–2–f3_20180920.3.fid
Project AB_
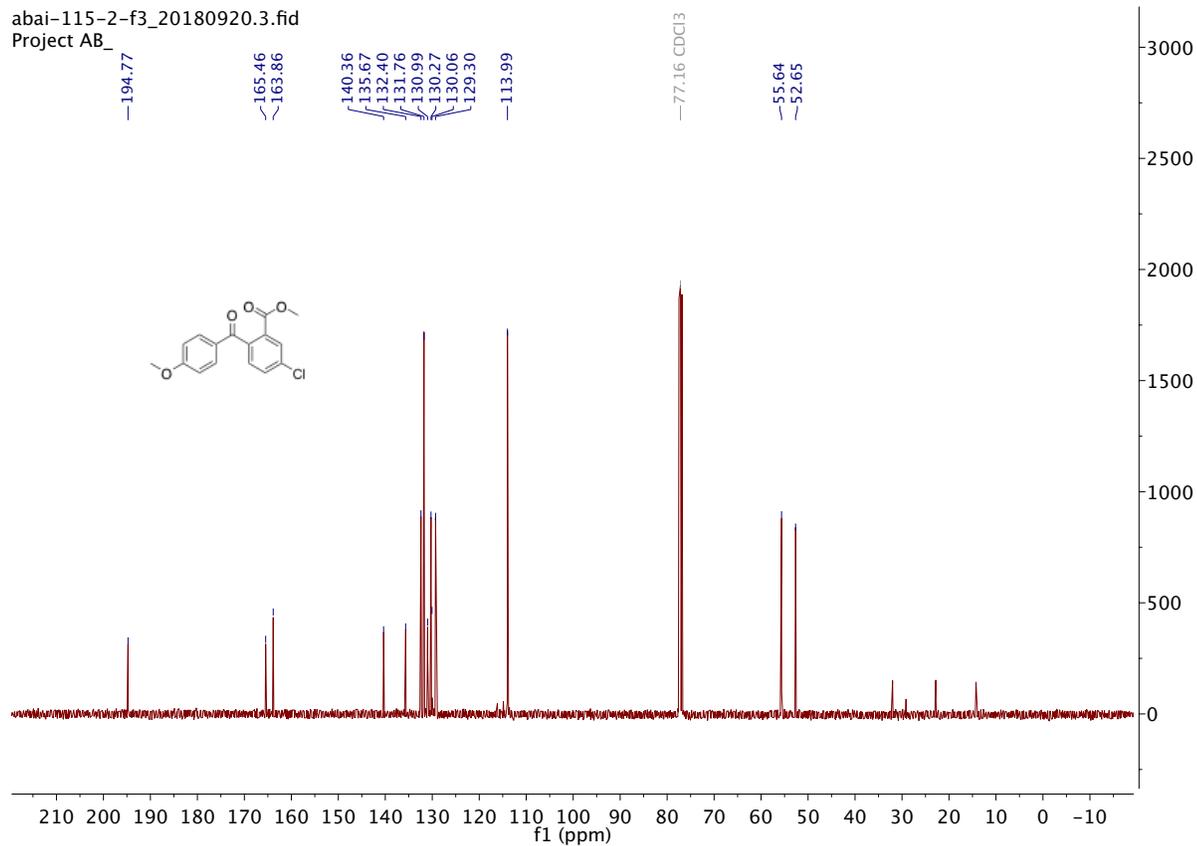
abai-115-2f3_181005104518 #1-5   RT: 0.02-0.13   AV: 5   NL: 3.24E7
T: FTMS + p ESI Full ms [200.00-500.00]

327.0401
C $_{16}$ H $_{13}$ O $_4$ Cl Na = 327.0395
0.6768 mmu

273.0317
C $_{15}$ H $_{10}$ O $_3$ Cl = 273.0313
0.3878 mmu

404.9824   441.2974   485.0411
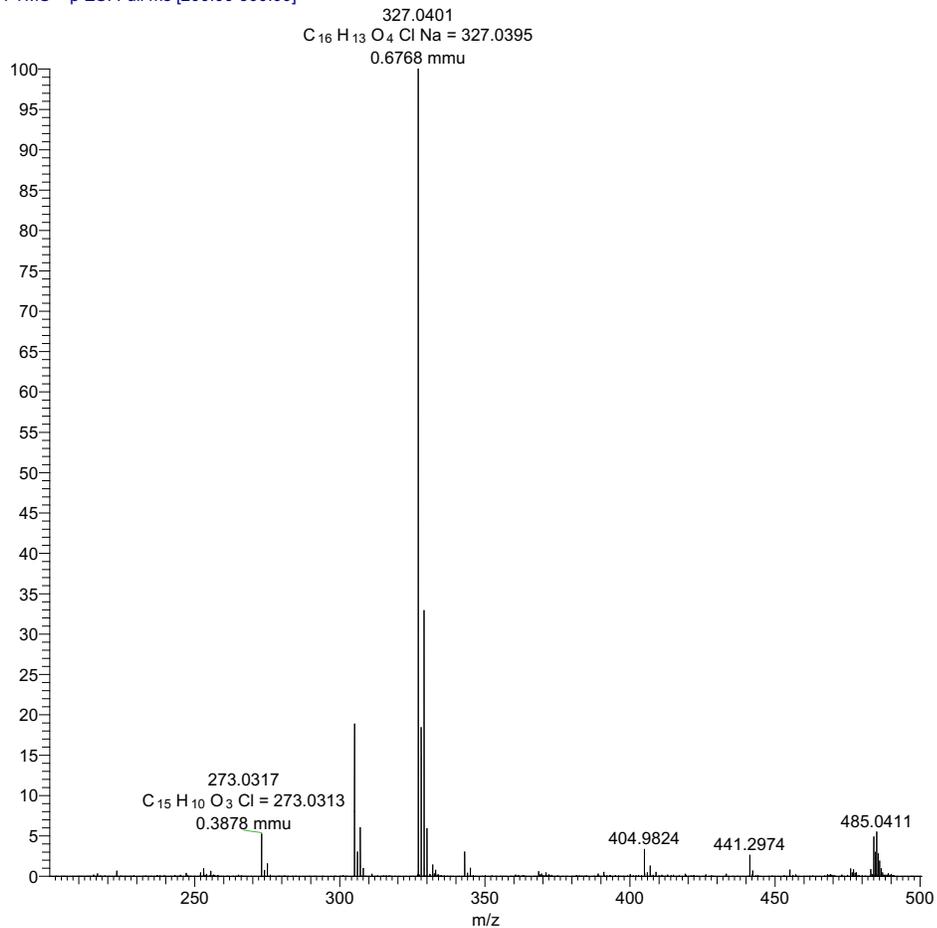
Methyl 4-chloro-2-(4-methoxybenzoyl)benzoate **2ea**

abai−115−6−f2_20180923.1.fid
Project AB_
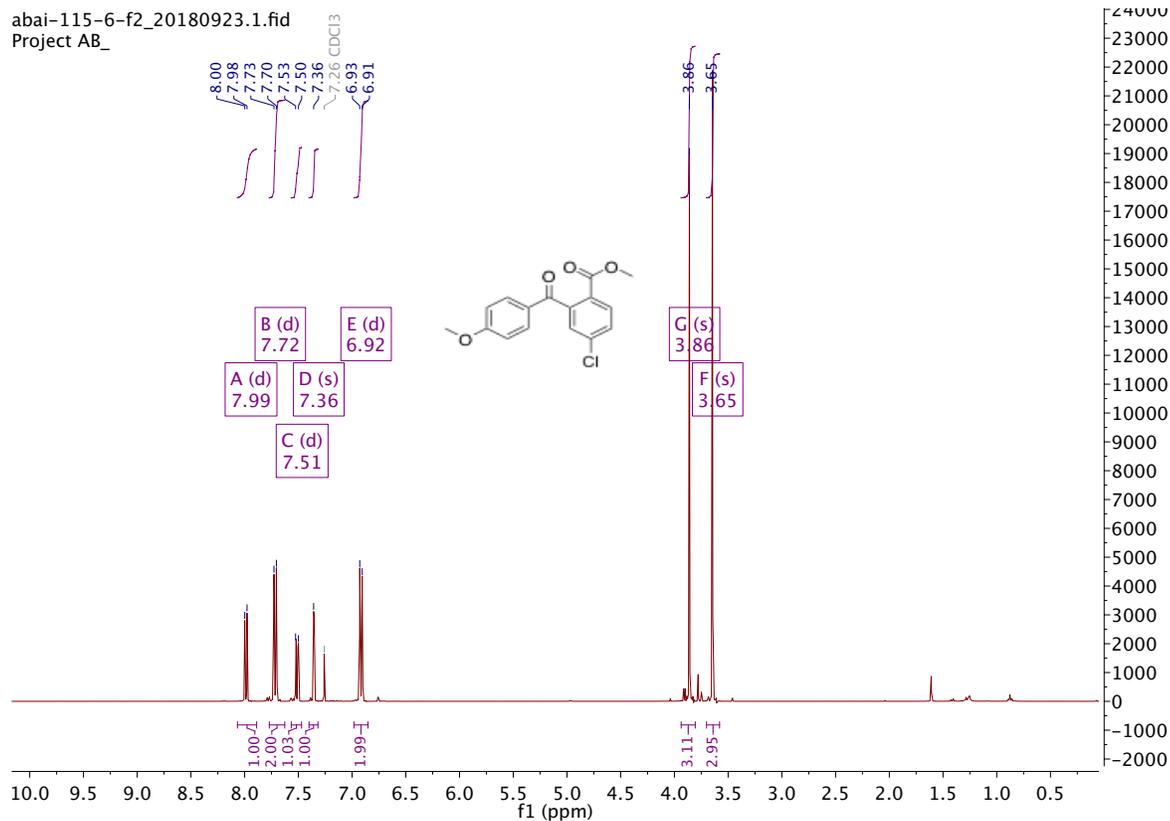
| B (d) | E (d) |
| 7.72 | 6.92 |

| A (d) | D (s) |
| 7.99 | 7.36 |

| C (d) |
| 7.51 |

| G (s) |
| 3.86 |

| F (s) |
| 3.65 |

abai–115–6–f2_20180923.3.fid
Project AB_
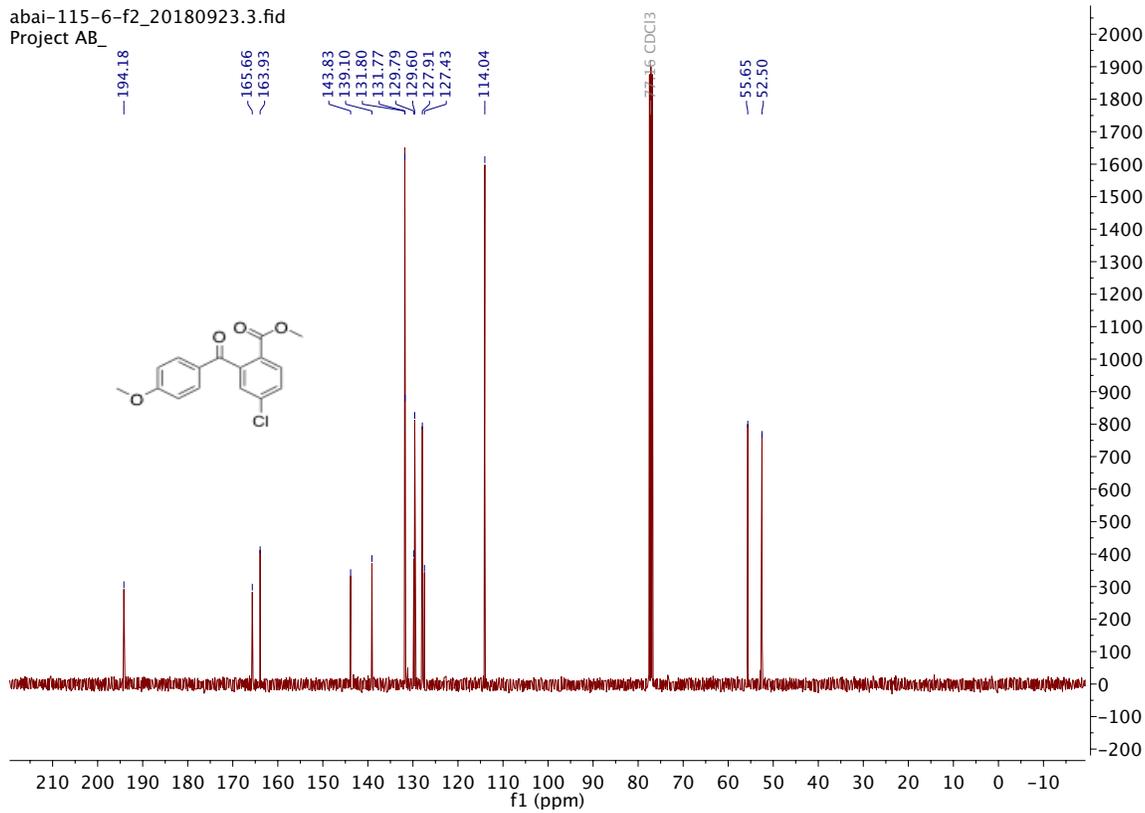
abai-115-6f2_181005161140 #1-4 RT: 0.02-0.10 AV: 4 NL: 2.18E7
T: FTMS + p ESI Full ms [200.00-500.00]
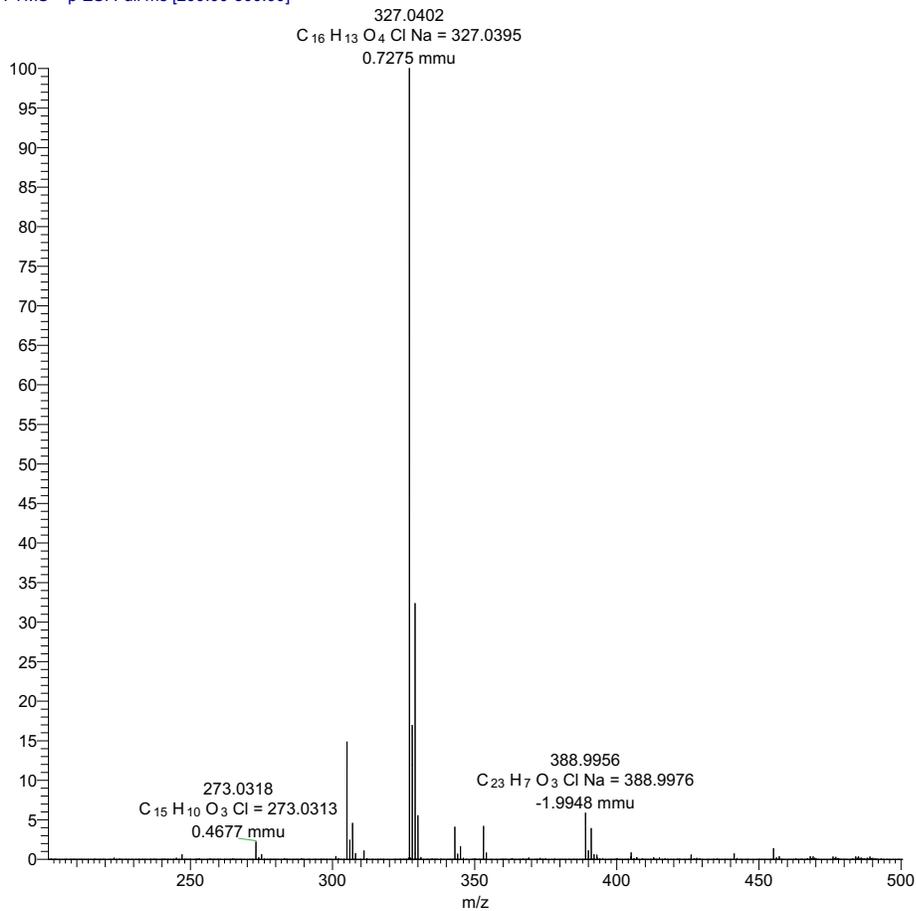
327.0402
$C_{16} H_{13} O_4 Cl Na = 327.0395$
0.7275 mmu

273.0318
$C_{15} H_{10} O_3 Cl = 273.0313$
0.4677 mmu

388.9956
$C_{23} H_7 O_3 Cl Na = 388.9976$
-1.9948 mmu

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

*Methyl 2-(4-methoxybenzoyl)-5-methylbenzoate **2fa***

abai–115–10–f3_20180928.1.fid
Project AB_

7.82
7.73
7.70
7.42
7.40
7.29
7.27
7.26 CDCl3
6.90
6.88

3.84
3.60

2.45

H (s)
7.82

E (d)
7.28

F (d)
7.41

D (d)
6.89

G (d)
7.72

C (s)
3.84

B (s)
3.60

A (s)
2.45

0.79
2.16
0.99
1.46
1.98

3.04
3.03

3.00

f1 (ppm)
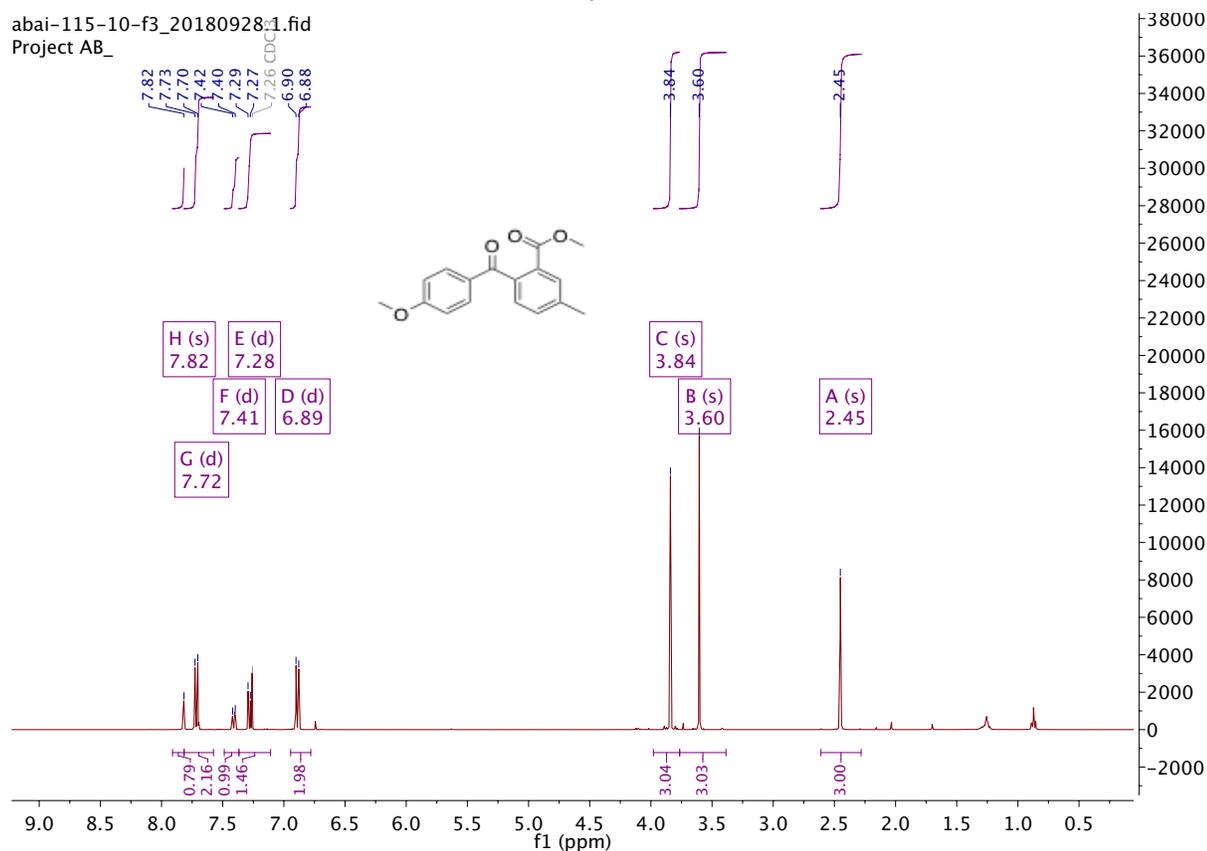
abai–115–10–f3_20180928.3.fid
Project AB_

196.00

166.89
163.52

139.81
139.18
132.93
131.68
130.61
129.42
127.98

113.79

77.36
77.16 CDCl3

55.56
52.23

21.30

f1 (ppm)

307.0947
C$_{17}$H$_{16}$O$_4$Na = 307.0941
0.6001 mmu

285.1130
C$_{17}$H$_{17}$O$_4$ = 285.1121
0.8250 mmu

253.0863
C$_{16}$H$_{13}$O$_3$ = 253.0859
0.4277 mmu

m/z
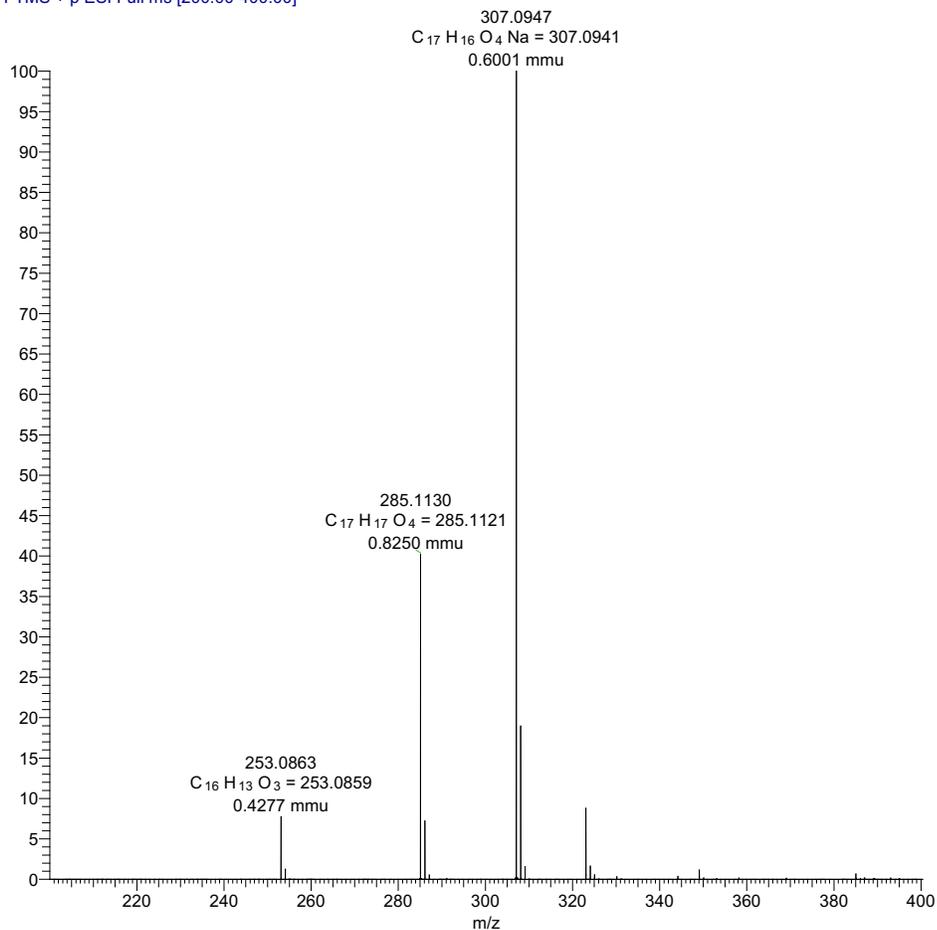
Methyl 2-(4-methoxybenzoyl)-3-methylbenzoate **2ga**

abai–115–7f1_20180925.1.fid
Project AB_
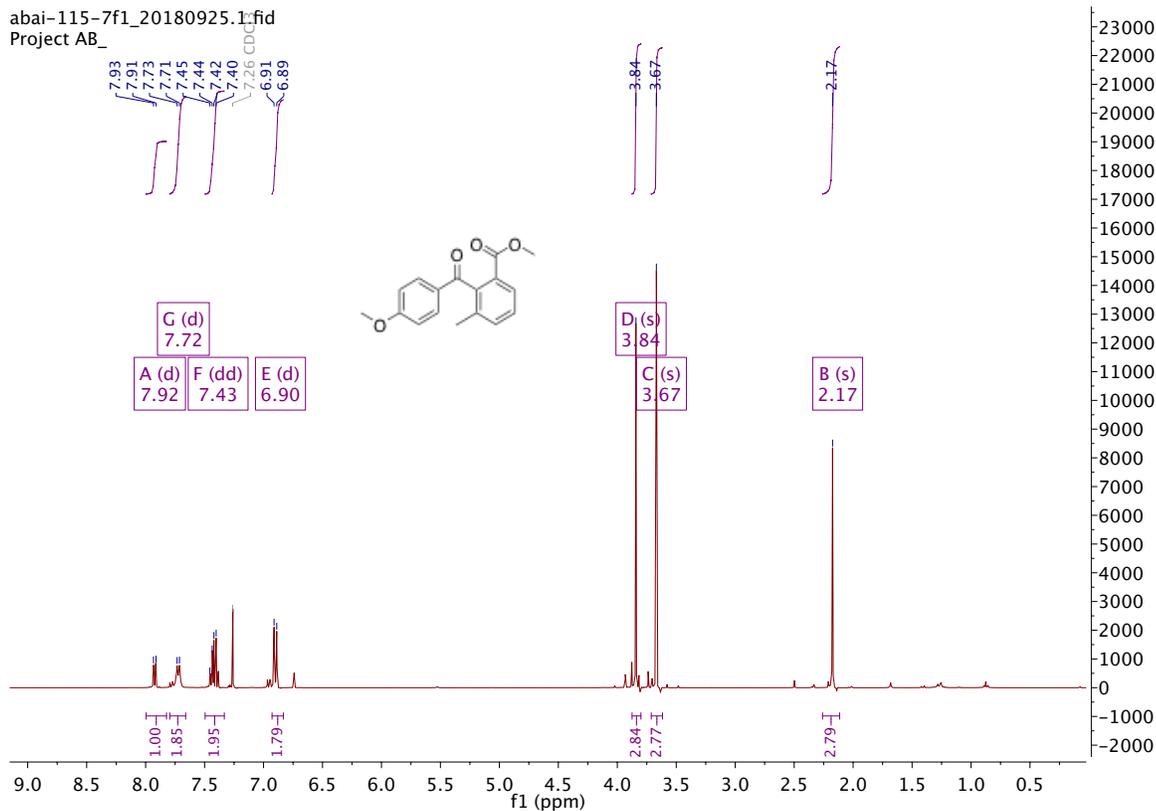
G (d)
7.72

A (d) F (dd) E (d)
7.92   7.43   6.90

D (s)
3.84

C (s)
3.67

B (s)
2.17

f1 (ppm)

abai-115-7f1_20180925.3.fid
Project AB_
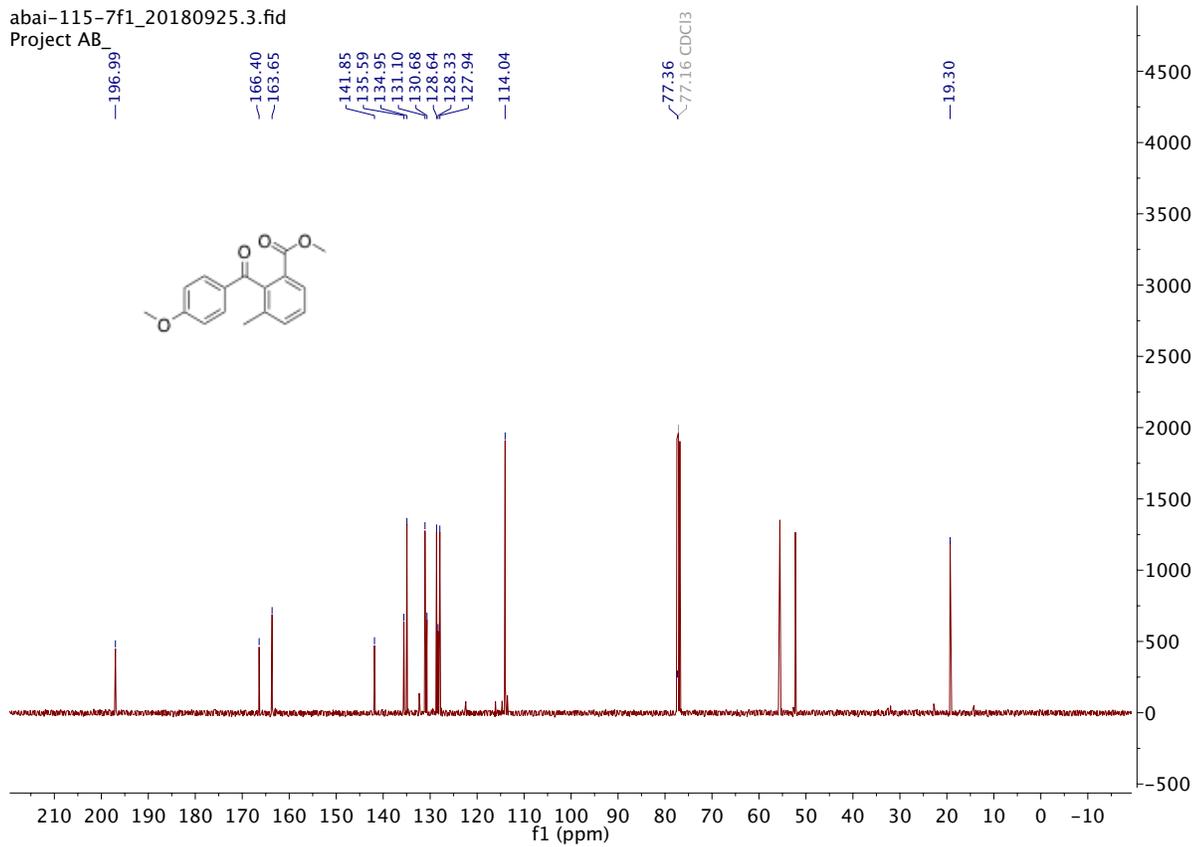
abai-115-7f1_181005161140 #1-5   RT: 0.01-0.12   AV: 5   NL: 6.95E7
T: FTMS + p ESI Full ms [200.00-500.00]
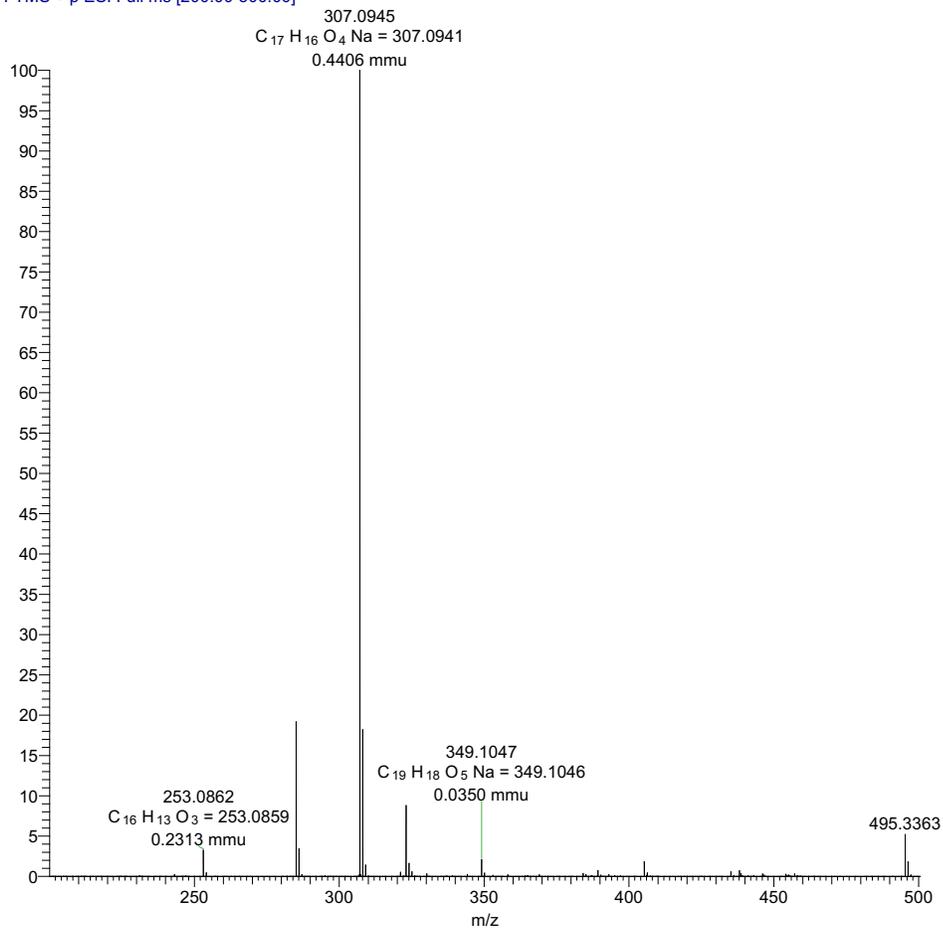
307.0945
$C_{17}H_{16}O_4Na = 307.0941$
0.4406 mmu

349.1047
$C_{19}H_{18}O_5Na = 349.1046$
0.0350 mmu

253.0862
$C_{16}H_{13}O_3 = 253.0859$
0.2313 mmu

495.3363

Methyl 4-methoxy-2-(4-methoxybenzoyl) benzoate **2ha**

abai–115–9–f2_20180923.1.fid
Project AB_
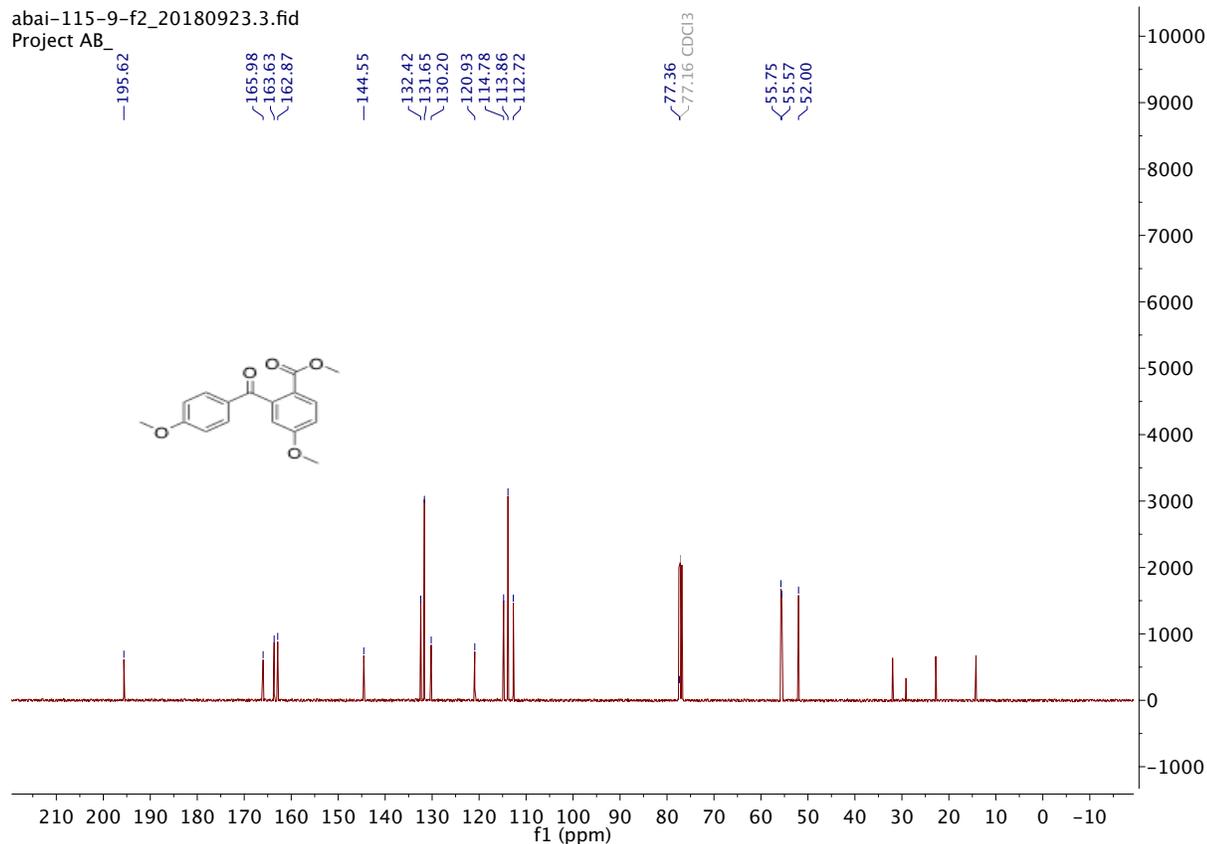
C (d) 7.73

A (d) 8.01

E (d) 6.89

D (s) 6.82

F (dd) 7.00

G (s) 3.84

B (s) 3.61

H (s) 3.85

abai–115–9–f2_20180923.3.fid
Project AB_

abai-115-9f2_181005163548 #1-4 RT: 0.02-0.11 AV: 4 NL: 1.01E7
T: FTMS + p ESI Full ms [200.00-400.00]

323.0894
C17 H16 O5 Na = 323.0890
0.3797 mmu

301.1076
C14 H18 O6 F = 301.1082
-0.5471 mmu

269.0811
C16 H13 O4 = 269.0808
0.2605 mmu

m/z
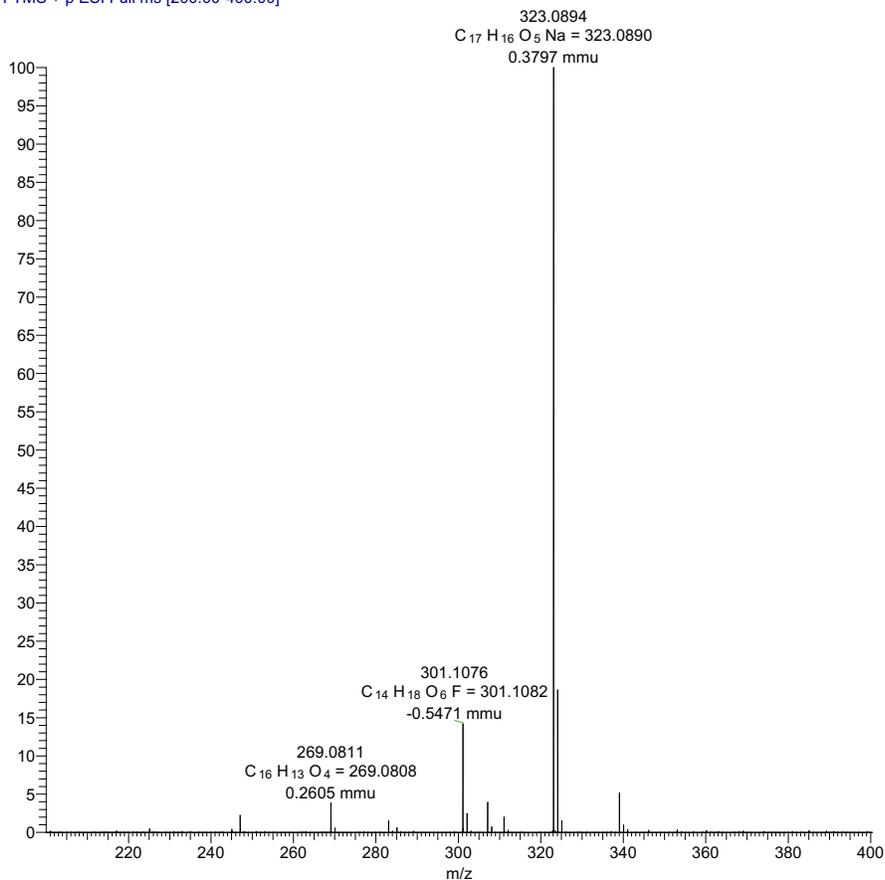
Methyl 2-(4-methoxybenzoyl)-5-methylbenzoate **2ia**

abai-115-5f1_20180921_1.fid
Project AB_
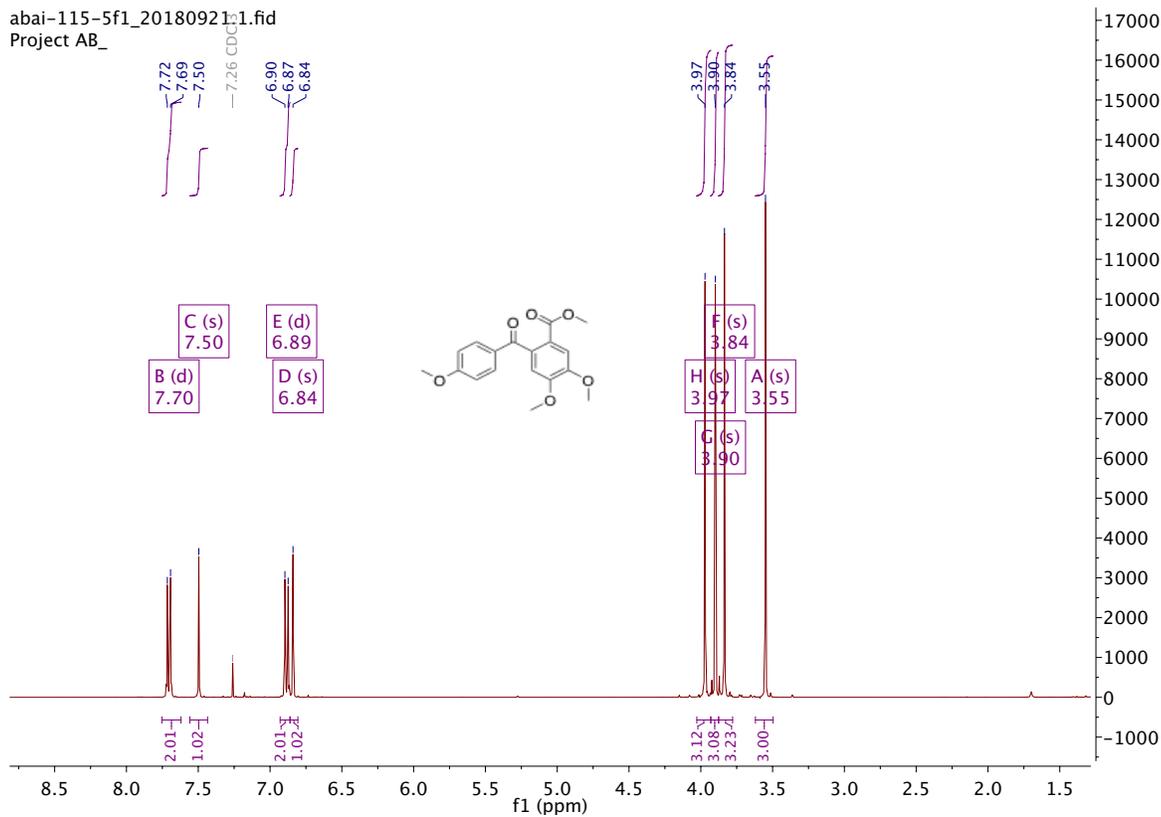
C (s) 7.50
B (d) 7.70
E (d) 6.89
D (s) 6.84
F (s) 3.84
H (s) 3.97
A (s) 3.55
G (s) 3.90

f1 (ppm)

abai-115-5f1_20180921.3.fid
Project AB_
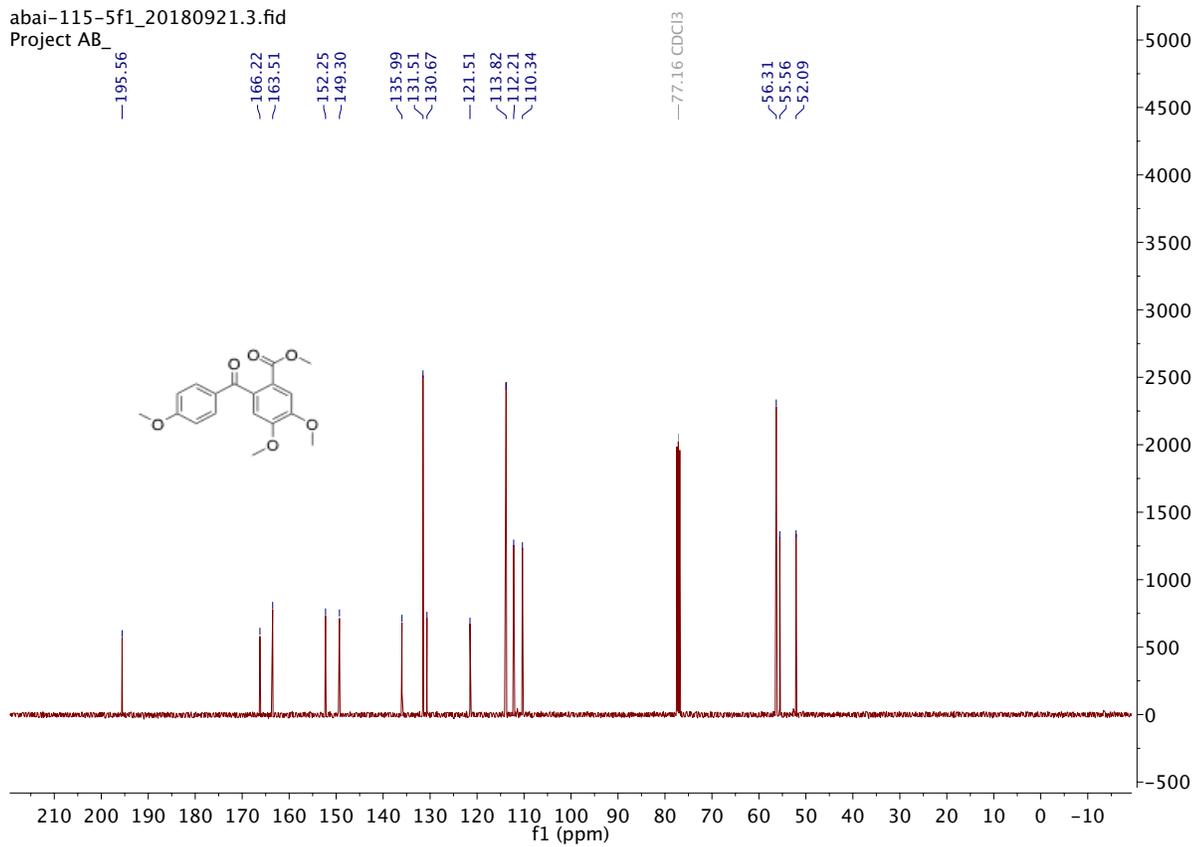
abai-115-5f1_181005161140 #1-5 RT: 0.02-0.13 AV: 5 NL: 1.10E7
T: FTMS + p ESI Full ms [200.00-500.00]

353.1001
C $_{18}$ H $_{18}$ O $_{6}$ Na = 353.0996
0.5167 mmu

311.0695
C $_{21}$ H $_{11}$ O $_{3}$ = 311.0703
-0.7882 mmu

277.0687
C $_{12}$ H $_{14}$ O $_{6}$ Na = 277.0683
0.4163 mmu
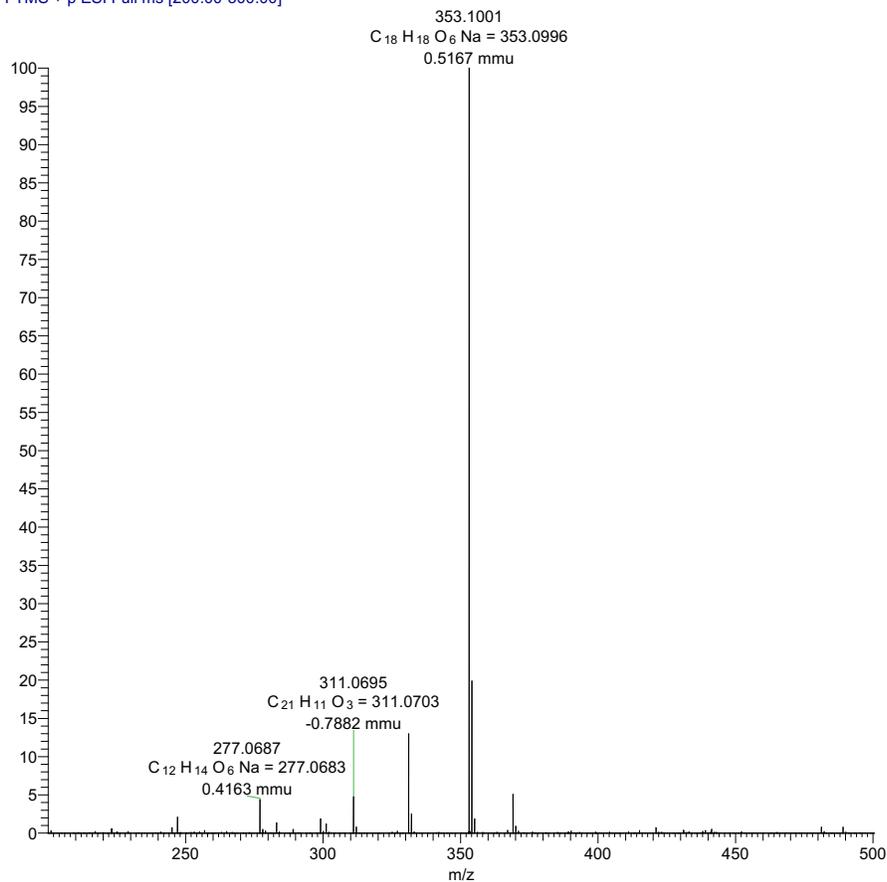
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

Methyl 5-fluoro-2-(2-methoxybenzoyl)benzoate **2bc**

ABAI–115–12–F2_20181003.1.fid
Project AB_

G (d)
7.41

H (m)   D (t)
7.49   7.02

F (d)   C (d)
7.39   6.92

J (dd)   E (td)
7.72   7.23

I (dd)
7.54

B (s)
3.61

A (s)
3.60

f1 (ppm)
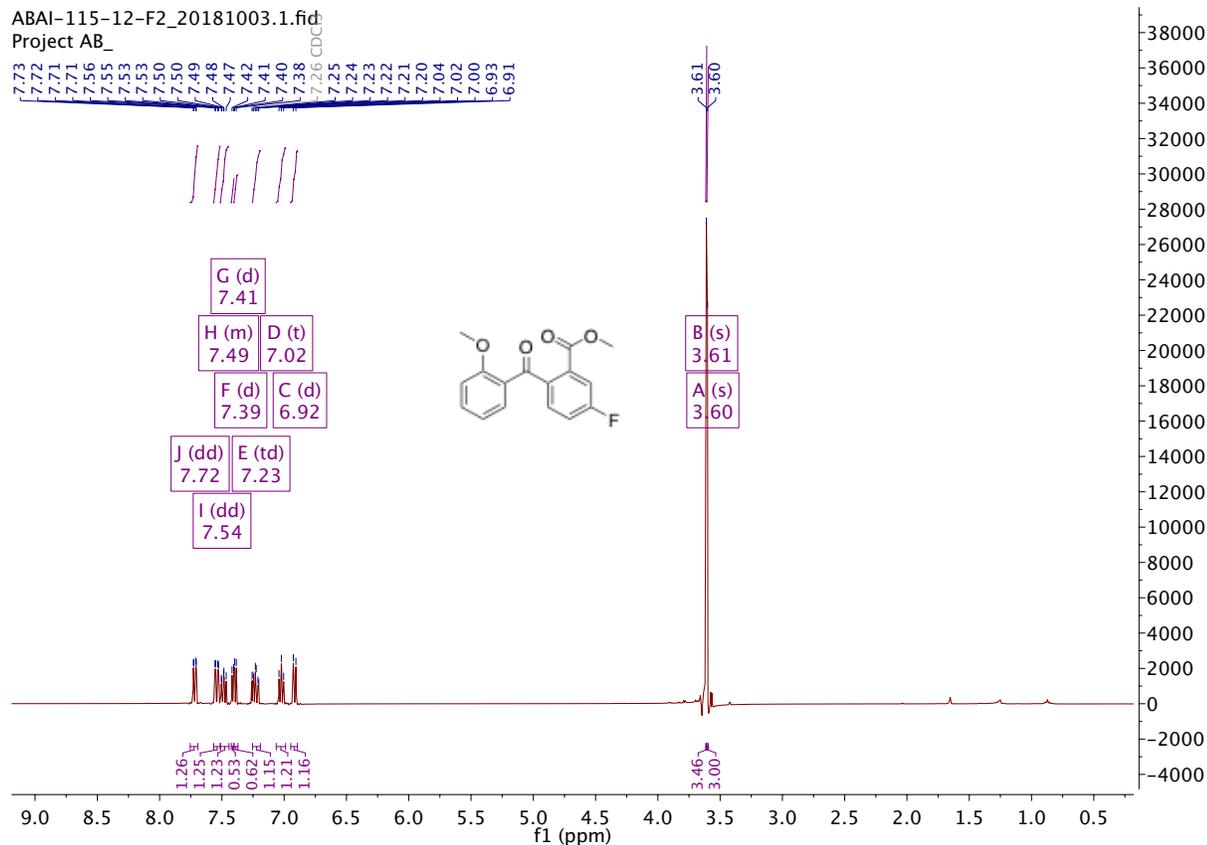
ABAI–115–12–F2_20181003.3.fid
Project AB_
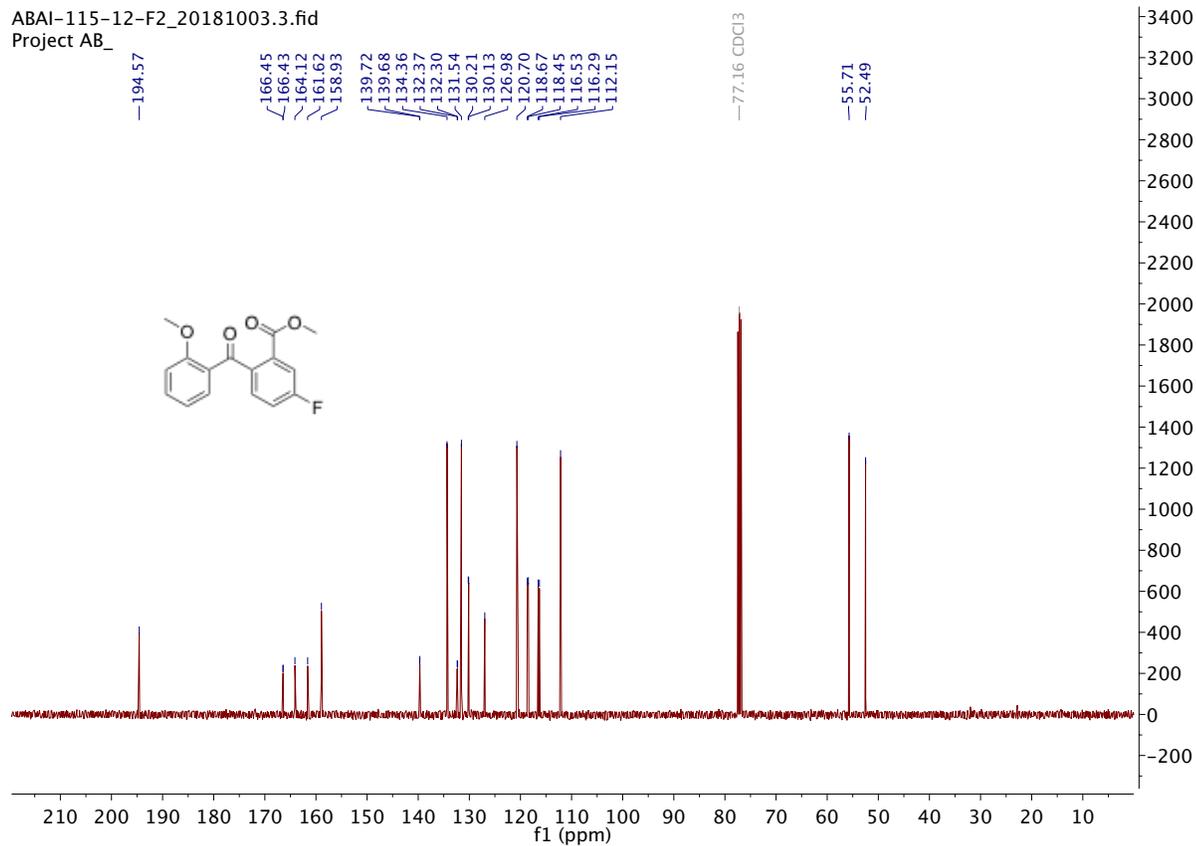
f1 (ppm)

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

abai-115-12-f2_181005163548 #1-4   RT: 0.01-0.10   AV: 4   NL: 4.68E7
T: FTMS + p ESI Full ms [200.00-400.00]

311.0693
C$_{16}$H$_{13}$O$_4$F Na = 311.0690
0.2498 mmu

289.0875
C$_{16}$H$_{14}$O$_4$F = 289.0871
0.3905 mmu

339.0637
C$_{17}$H$_{13}$O$_5$F Na = 339.0639
-0.1936 mmu

m/z
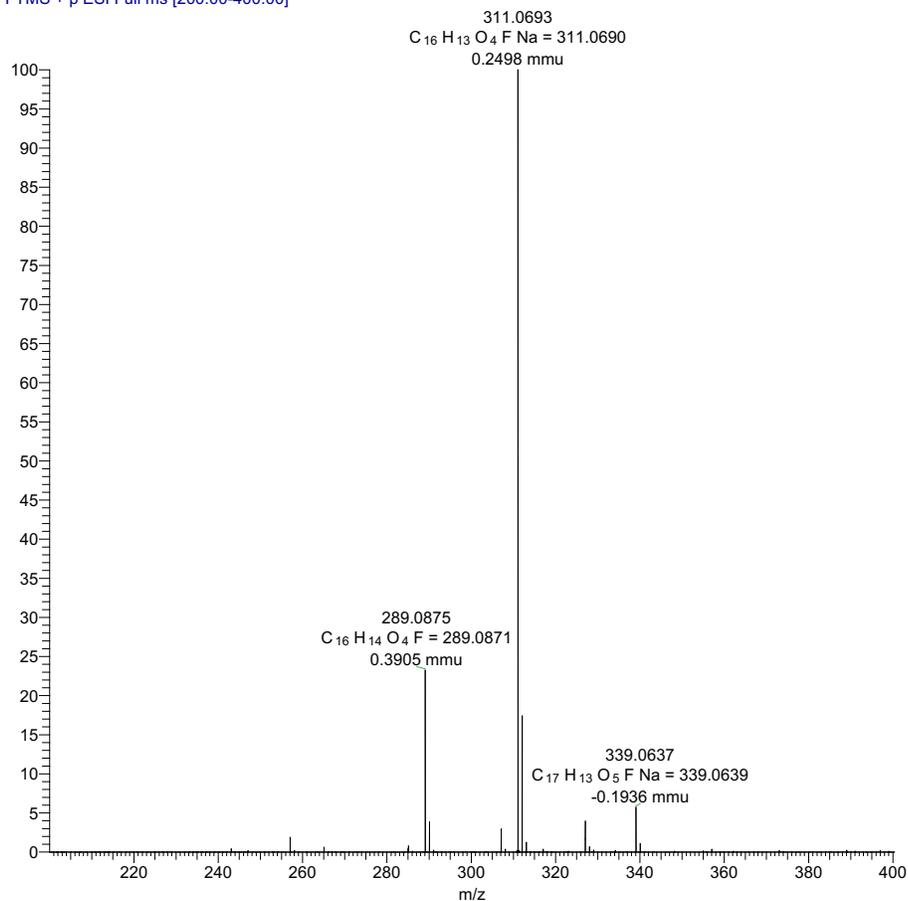
Methyl 5-fluoro-2-(2-(methoxycarbonyl)benzoyl)benzoate **2bh**

abai-115-11f2_20180928.1.fid
Project AB_
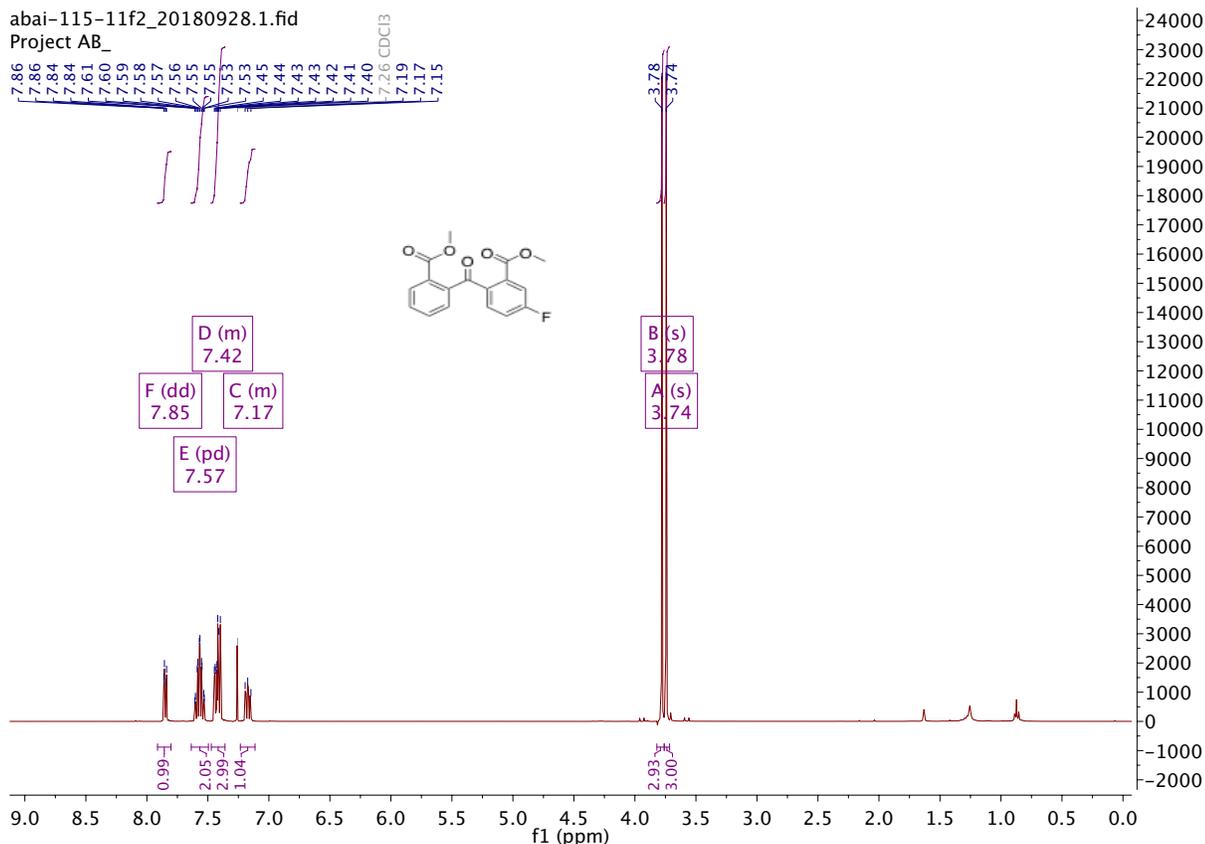
D (m)
7.42

F (dd)
7.85

C (m)
7.17

E (pd)
7.57

B (s)
3.78

A (s)
3.74

f1 (ppm)

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

abai-115-11f2_20180928.3.fid
Project AB_
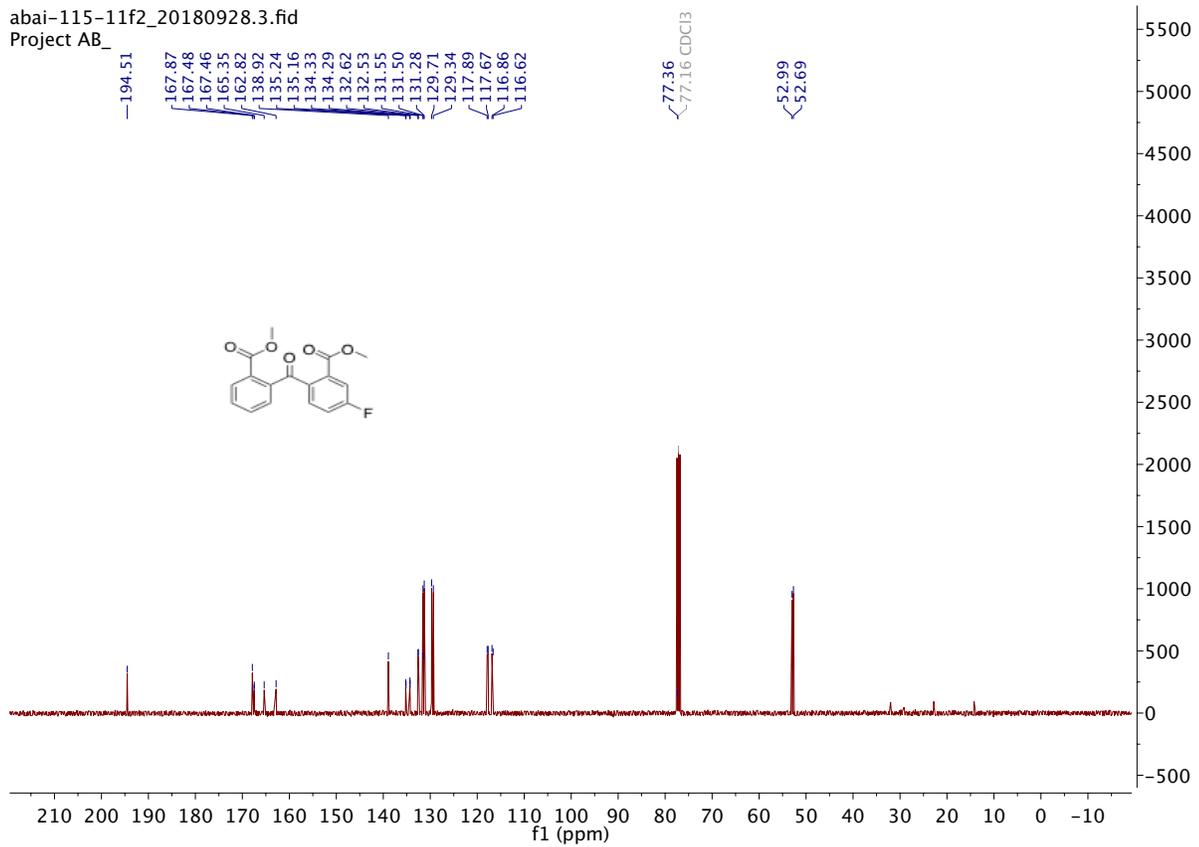
abai-115-11_181005163548 #1-4 RT: 0.02-0.11 AV: 4 NL: 3.76E7
T: FTMS + p ESI Full ms [200.00-400.00]
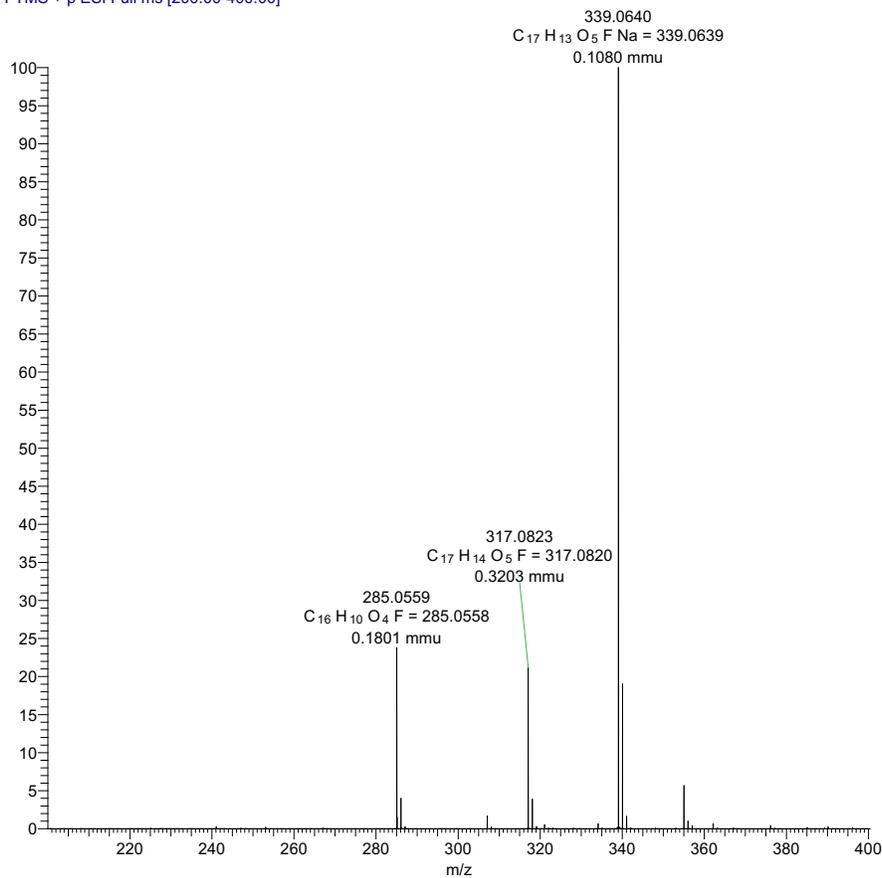
339.0640
$C_{17}H_{13}O_5FNa$ = 339.0639
0.1080 mmu

317.0823
$C_{17}H_{14}O_5F$ = 317.0820
0.3203 mmu

285.0559
$C_{16}H_{10}O_4F$ = 285.0558
0.1801 mmu

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

*Methyl 2-(2-naphthoyl)-4-methoxybenzoate **2hp***
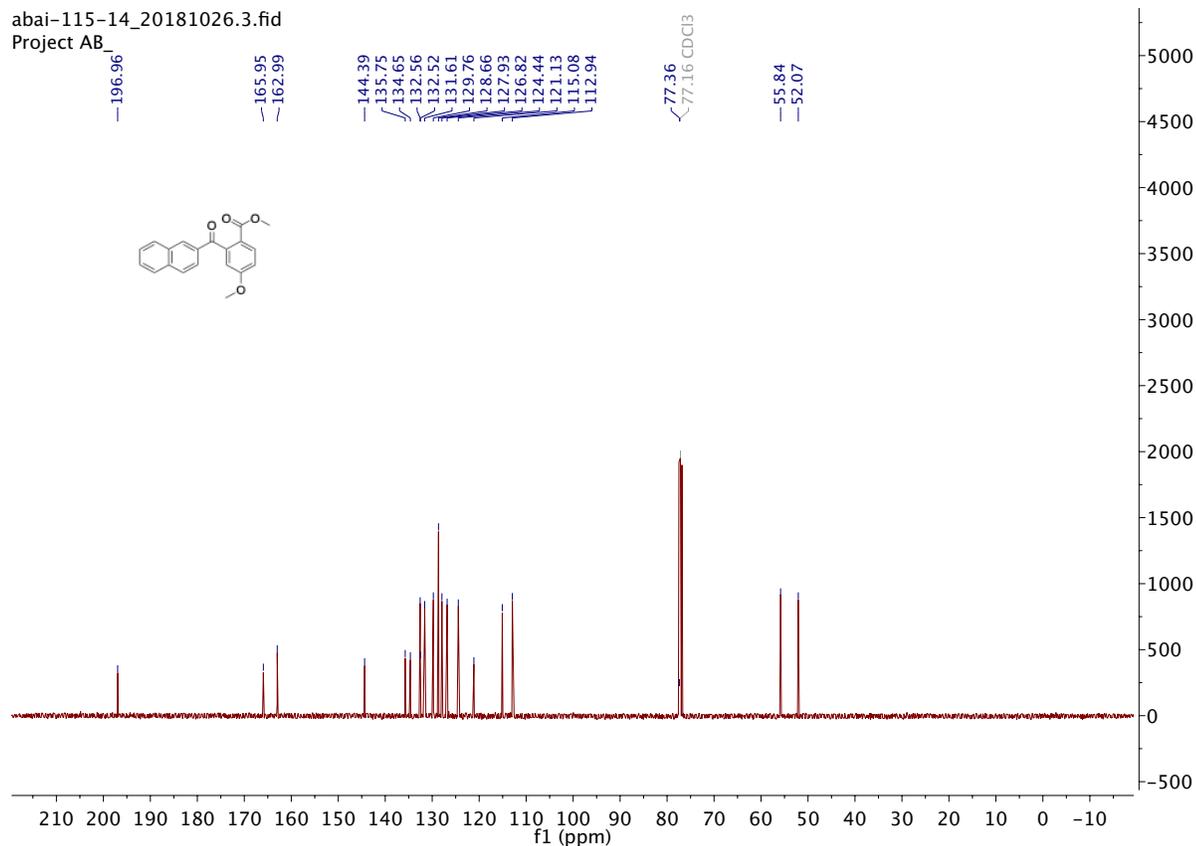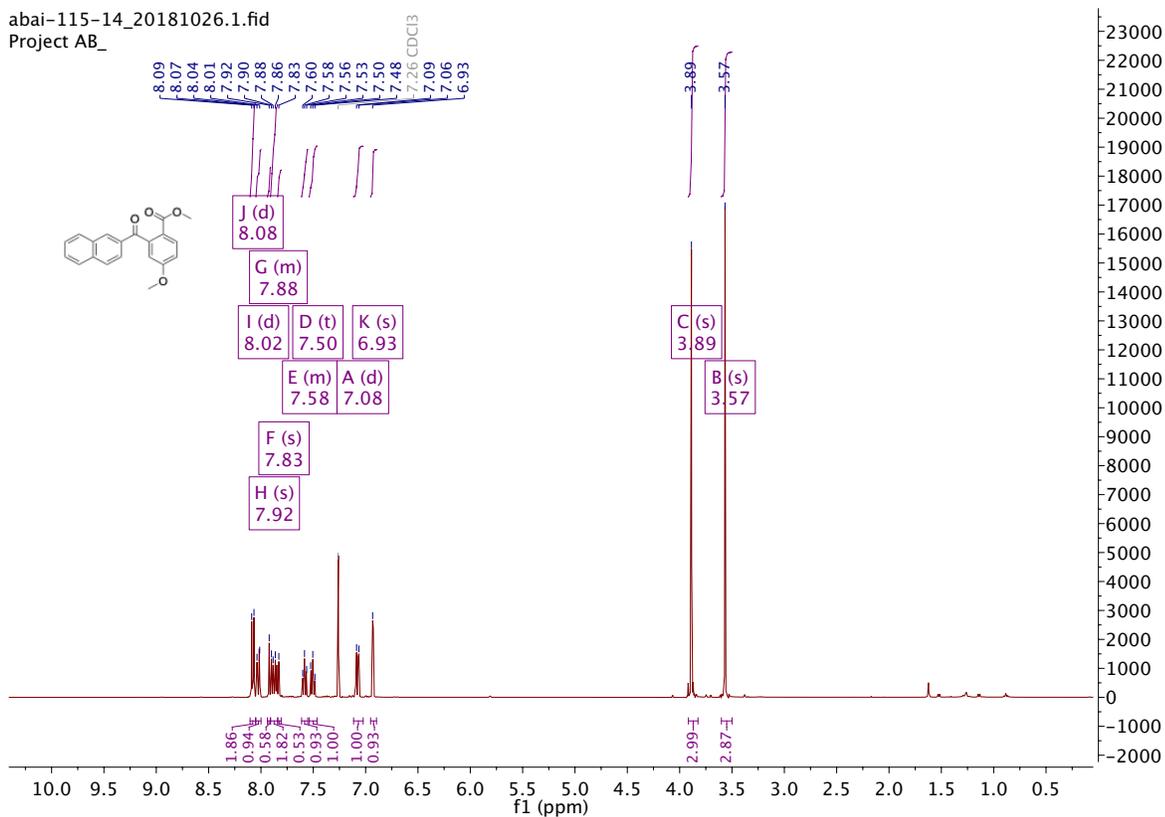
abai−115−14_20181026.1.fid
Project AB_

abai−115−14_20181026.3.fid
Project AB_

ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.
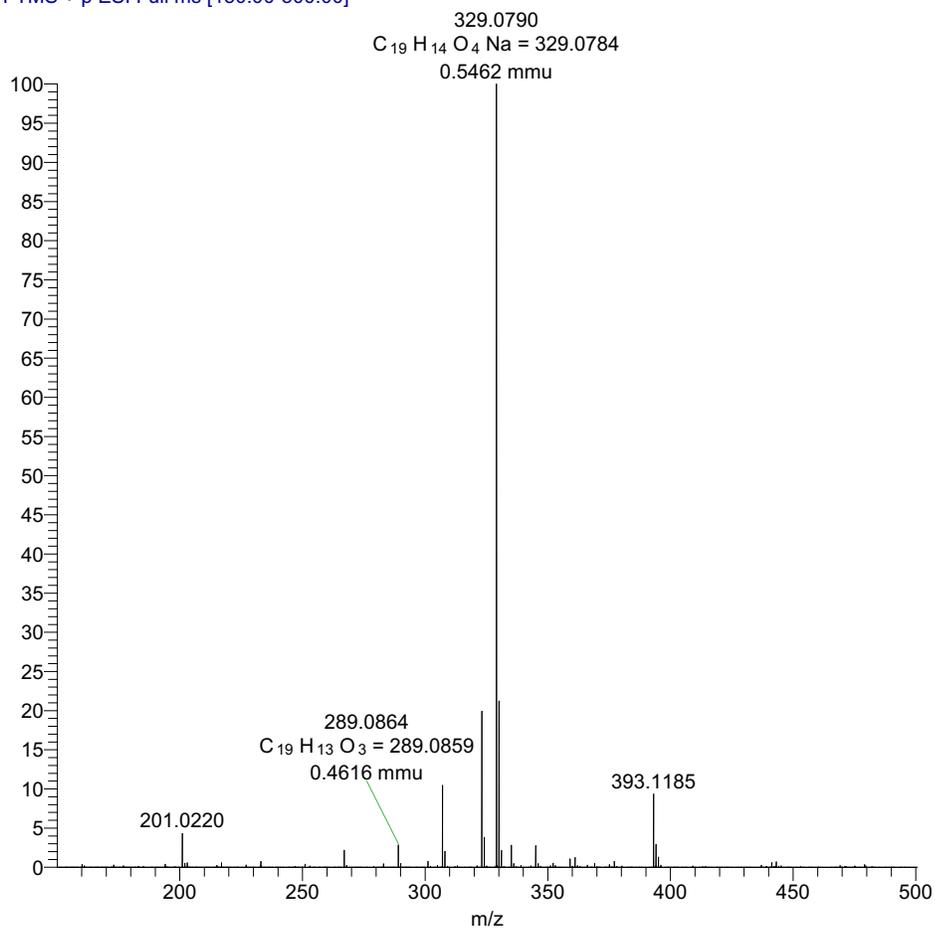
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

4.4 Spectra for products from control experiments for hydrocarbonylations (section 1.4).

abai−44−2−pure.10.fid
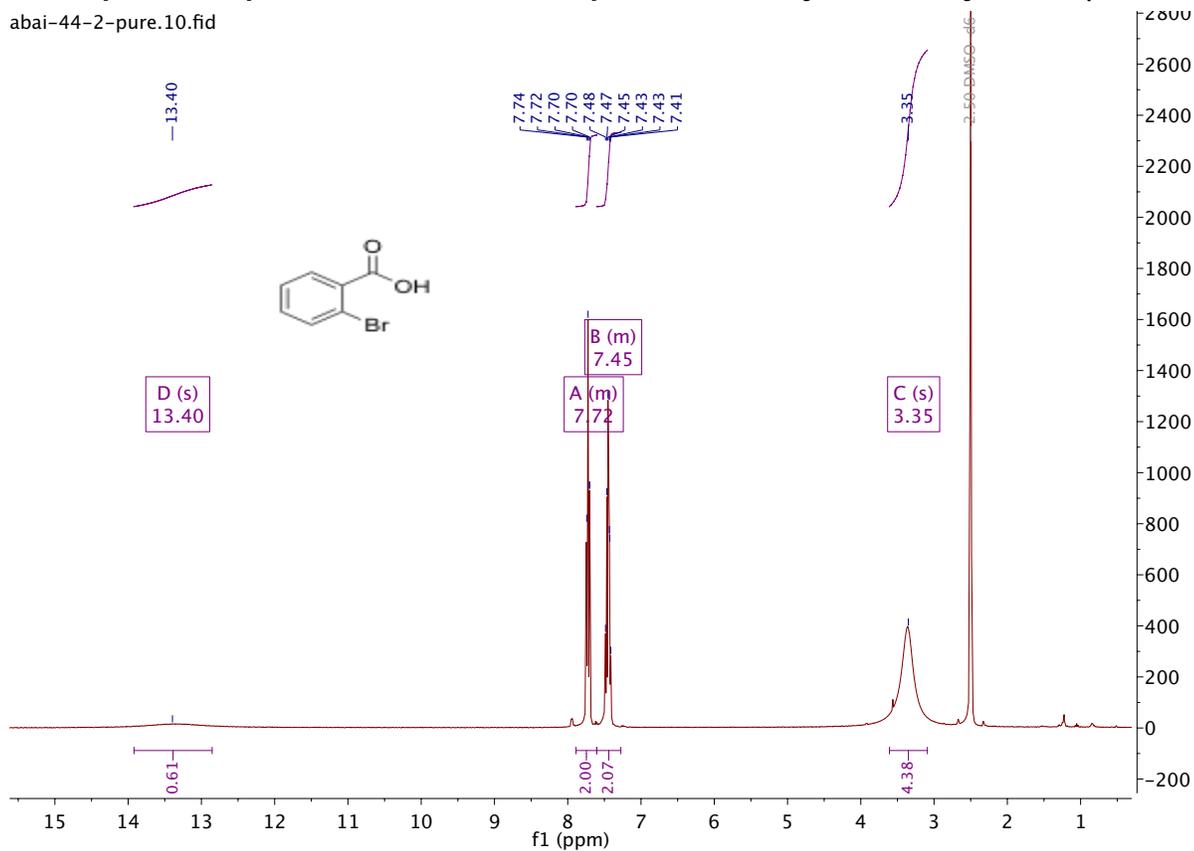
abai−44−1pure.10.fid
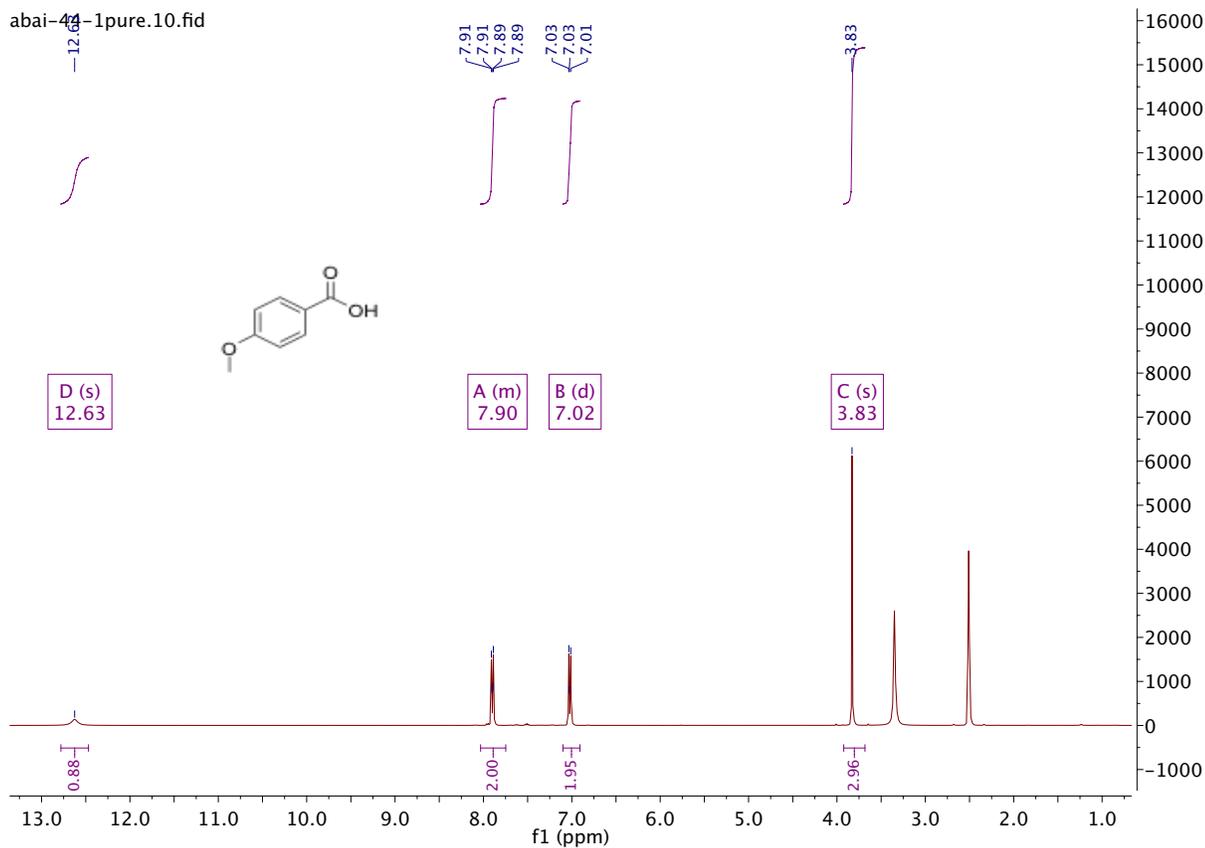
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

abai-44-1pure.11.fid
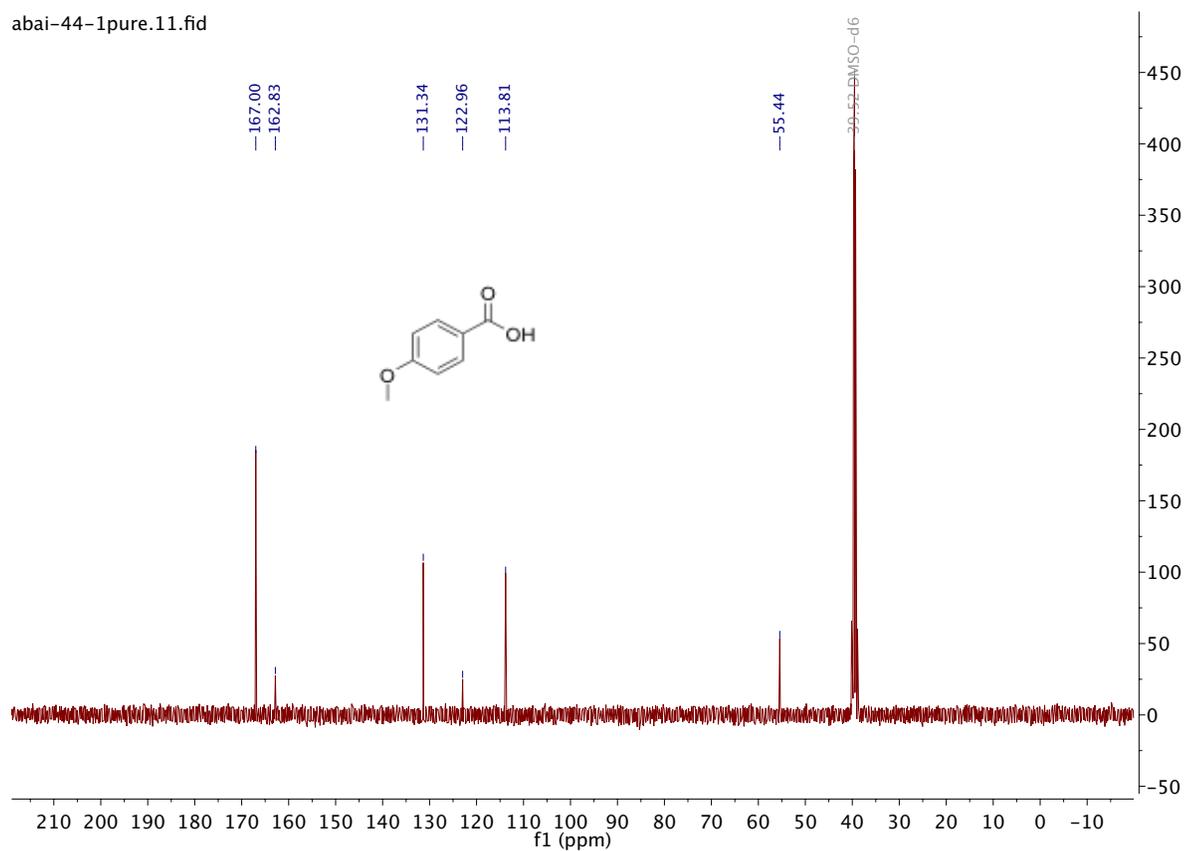
abai-59-orgapure.10.fid
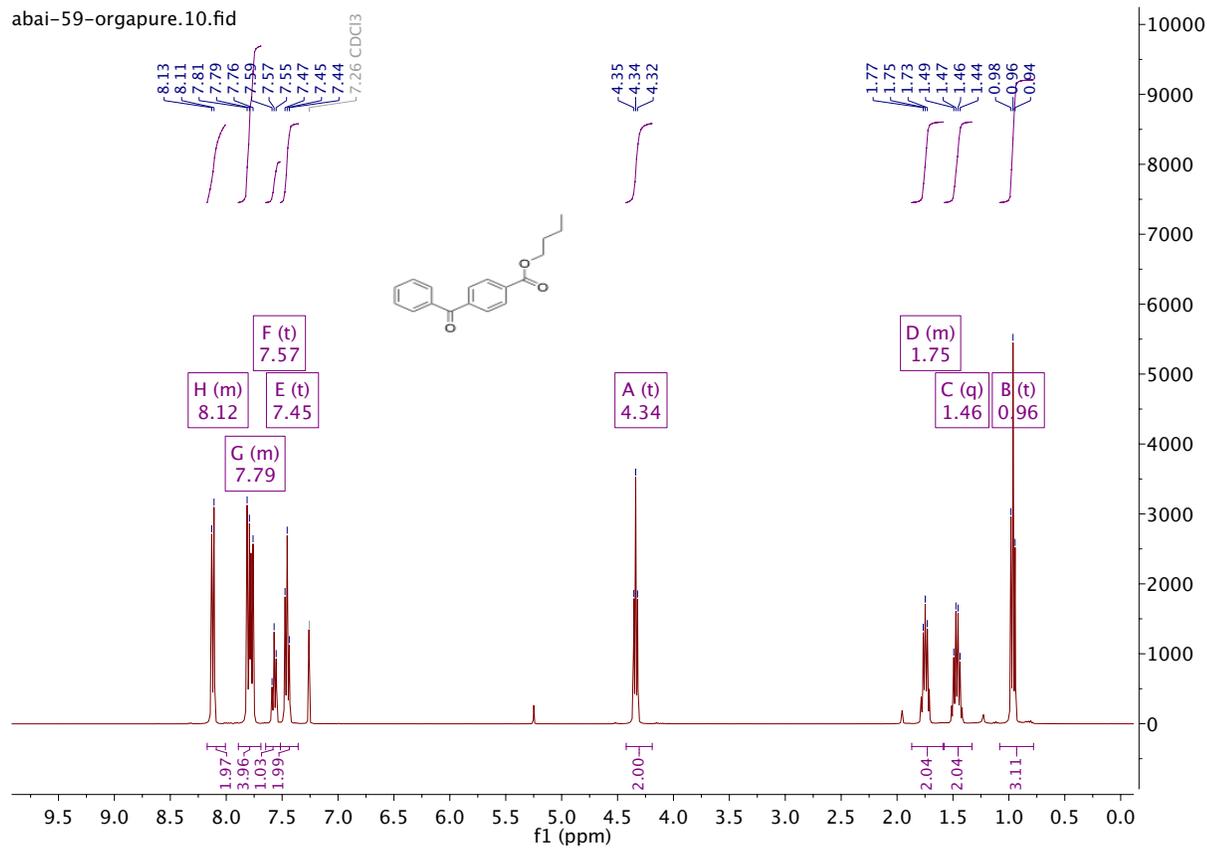
ESI : Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides.

abai–59–orgapure.11.fid
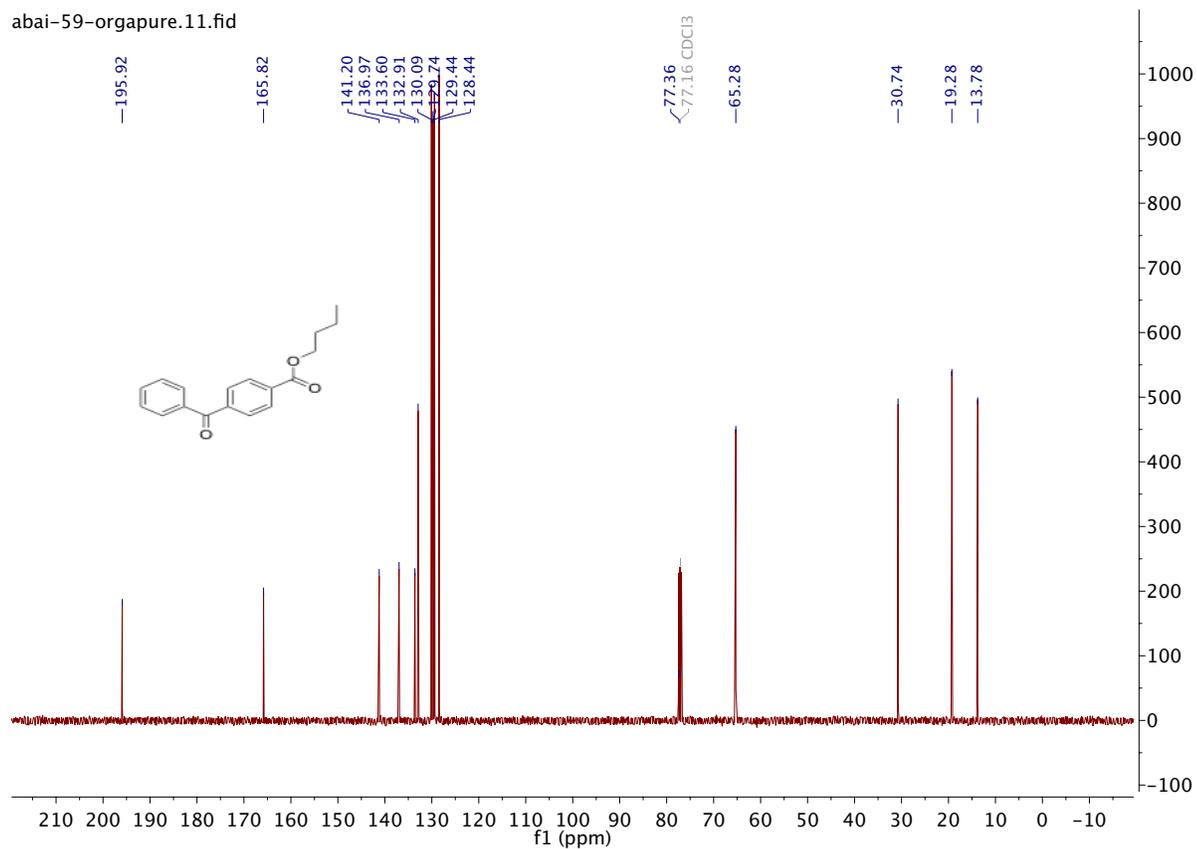
Paper III

Renewable Solvents for Pd-Catalyzed Carbonylations

Aya Ismael, Ashot Gevorgyan, Troels Skrydstrup, and Annette Bayer

Manuscript is submitted

Organic Process Research & Development

Renewable Solvents for Palladium-Catalyzed Carbonylation Reactions

Aya Ismael,[a] Ashot Gevorgyan,[a] Troels Skrydstrup,[b] and Annette Bayer[a]*

a. Department of Chemistry, Faculty of Science and Technology, UiT The Arctic University of Norway, N-9037 Tromsø, Norway; b. Carbon Dioxide Activation Center (CADIAC), Interdisciplinary Nanoscience Center (iNANO) and Department of Chemistry, Aarhus University, Gustav Wieds Vej 14, 8000 Aarhus C, Denmark.

TOC GRAPHIC:

α-Pinene
from Coniferous plants

(*R*)-(+)-Limonene
from waste citrus peels

Dimethyl carbonate
from CO₂
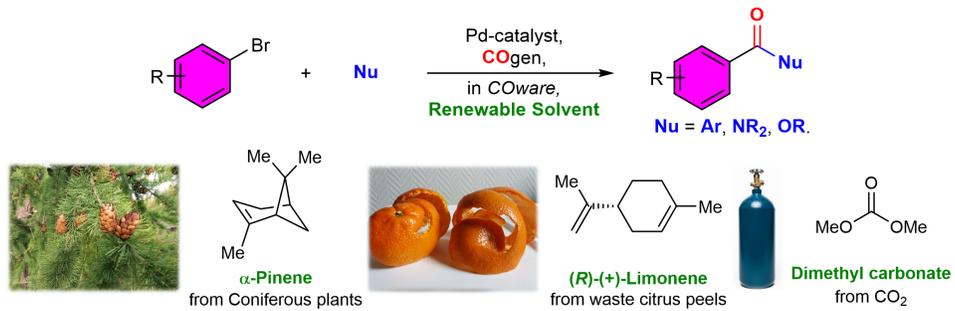
ABSTRACT: Solvents constitute the largest component for many chemical processes and substitution of non-renewable solvents is a long-standing goal for green chemistry. Here we show that Pd-catalyzed carbonylative couplings, such as carbonylative cross couplings, aminocarbonylations and alkoxycarbonylations, can be successfully realized using renewable solvents. The present research covers not only well-established renewable solvents, such as 2-methyltetrahydrofuran, limonene and dimethyl carbonate, but also recently introduced biomass-derived 1,1-diethoxyethane, isosorbide dimethyl ether, eucalyptol, rose oxide, γ-terpinene and α-pinene. The carbonylative coupling of boronic acids and aryl bromides works well in limonene. Aminocarbonylation gave excellent results in dimethyl carbonate, α-pinene and limonene, while alkoxycarbonylation was successful in 2-methyltetrahydrofuran, α-pinene, γ-terpinene and dimethyl carbonate. The developed renewable methodologies can be used for the synthesis of commercial drug Trimetozine and an analogue of Itopride.

INTRODUCTION

According to the development plan of the United Nations General Assembly "*Transforming Our World: The 2030 Agenda for Sustainable Development*" initiated in 2015, considerable efforts are needed over the coming decade to build a better and more sustainable future.[1] The realization of most of the aspects of "*The 2030 Agenda for Sustainable Development*" can be directly conditioned by sustainable innovations in chemical research.

Today, most of the industrial processes and particularly the pharmaceutical industry are largely based on the application of non-renewable solvents, which usually constitute over 80% of

materials needed for the production of the final ingredientes.[2] As a result, yearly manufacture of non-renewable and hazardous common organic solvents exceeds 20 million metric tons.[2d] A recent survey on the solvents used in the pharmaceutical industry for the period 1997 - 2012 revealed that the top 10 most frequently used solvents are dichloromethane, hexane, diisopropyl ether, 1,2-dimethoxyethane, 1,4-dioxane, 1,2-dichloroethane, diethyl ether, chloroform, diglyme and chlorobenzene.[3] This unsustainable practice can be addressed by the development and popularization of renewable and safe solvent candidates.

Liquids or low melting chemicals available from the valorization of biomass[4,5] as well as chemicals derived from the reduction of CO_2[6,7] have enormous potential to replace the common non-renewable solvents utilized in organic synthesis.[3] The most frequently used solvents available from biomass are polar protic ethanol, glycerol and its derivatives, and choline chloride-based deep eutectic solvents, polar aprotic 2-methyltetrahydrofuran (2MeTHF), cyrene and γ-valerolactone (GVL), as well as nonpolar limonene and *p*-cymene (Fig. 1).[4,5] Among CO_2-derived chemicals carbonates and ethers like dimethoxymethane (methylal) have attracted attention as solvents (Fig. 1).[6,7] Recently, we have shown that biomass-derived solvents such as nonpolar ethers (1,1-diethoxyethane (acetal), dimethyl isosorbide, eucalyptol, rose oxide) and terpenes (γ-terpinene and α-pinene) can be successfully used in Cu-catalyzed carboxylation reactions (Fig. 1).[51]
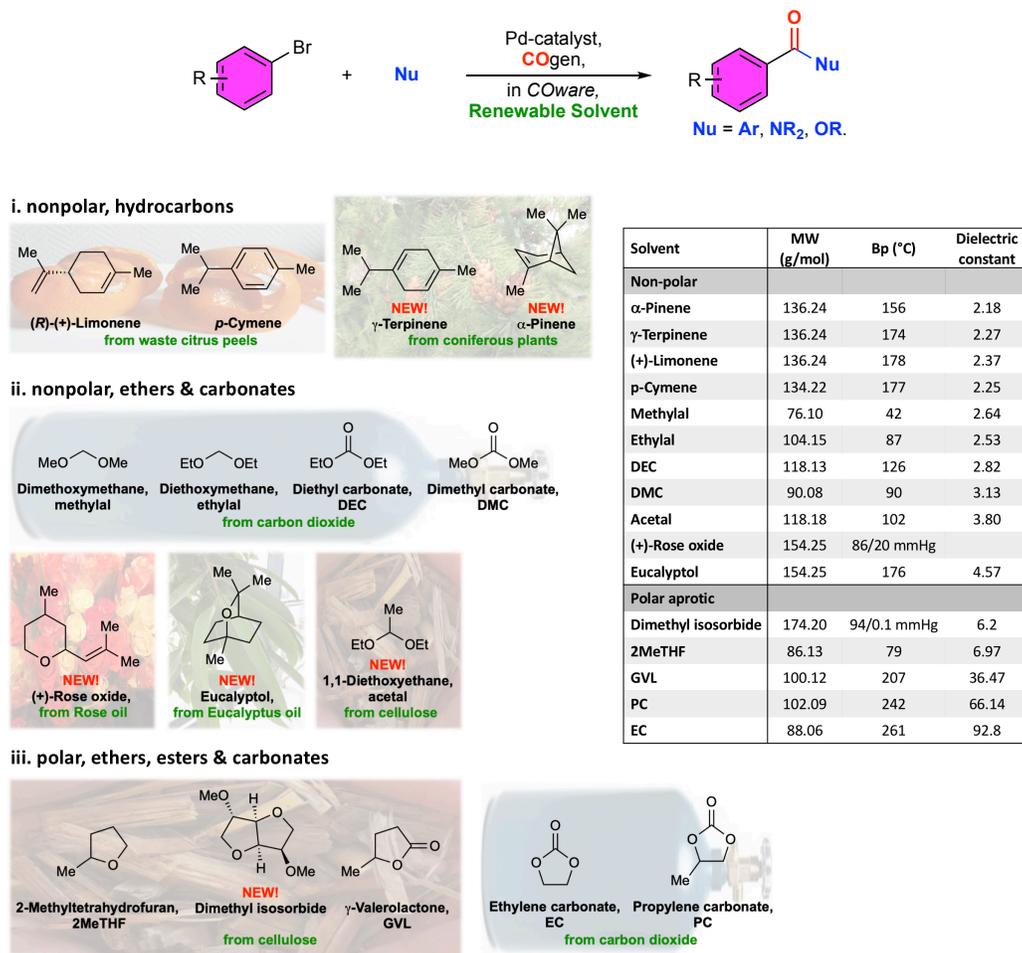
Figure 1. Overview of present work and renewable solvents used in the work (pictures taken by AG).

Solvent	MW (g/mol)	Bp (°C)	Dielectric constant
Non-polar			
α-Pinene	136.24	156	2.18
γ-Terpinene	136.24	174	2.27
(+)-Limonene	136.24	178	2.37
p-Cymene	134.22	177	2.25
Methylal	76.10	42	2.64
Ethylal	104.15	87	2.53
DEC	118.13	126	2.82
DMC	90.08	90	3.13
Acetal	118.18	102	3.80
(+)-Rose oxide	154.25	86/20 mmHg	
Eucalyptol	154.25	176	4.57
Polar aprotic			
Dimethyl isosorbide	174.20	94/0.1 mmHg	6.2
2MeTHF	86.13	79	6.97
GVL	100.12	207	36.47
PC	102.09	242	66.14
EC	88.06	261	92.8

A complete life cycle assessment (LCA) of the latter solvents is not available, but most of them are significantly less toxic compared to common organic solvents.[8] Low toxicity is particularly inherent to naturally occurring dimethyl isosorbide, GVL and eucalyptol, ethanol-derived diethoxyethane (acetal), as well as CO_2-derived diethyl carbonate (DEC), dimethyl carbonate (DMC) and methylal. Among others, these solvents are used in large quantities in the pharmaceutical and food industries as additives, antiseptic and flavoring agents.[9] There is no need to continue increasing the consumption of non-renewable solvents for processes where renewable solvents provide comparable outcome.

Renewable solvents have proven to be suitable for a variety of transformations including classical condensation reactions and transition-metal (TM)-catalyzed cross-couplings.[4-6] However, the use of renewable solvents as reaction media for carbonylative couplings with CO remain largely unexplored.[10,11] The fact that the Pd-catalyzed carbonylations have found numerous applications in modern drug discovery and isotopic labeling of pharmaceuticals[10d,e,g] makes the development of renewable methodologies for carbonylations a task of great significance. This work describe the use of newly introduced biomass-derived solvents (acetal, dimethyl isosorbide, γ-terpinene, α-pinene, eucalyptol, and rose oxide, Fig. 1), and previously studied renewable solvents (2MeTHF, GVL, limonene, *p*-cymene, DMC, DEC, ethylene carbonate (EC), propylene carbonate (PC), methylal and diethoxymethane (ethylal) Fig. 1) for Pd-catalyzed carbonylations.

RESULTS AND DISCUSSION

A range of renewable solvents were studied for carbonylative couplings of aryl bromides with arylboronic acids,[12] amines (aminocarbonylation)[13] and alcohols (alkoxycarbonylation) (Fig. 1).[14] We decided to focus on Pd-based catalytic systems that have proven to be versatile catalysts for carbonylative couplings.[11k,12-14] For safety reasons the reactions were conducted in two chamber reactors (COware) developed in the group of Skrydstrup, using stoichiometric quantities of CO generated *ex situ* from COgen (9-methyl-9*H*-fluorene-9-carbonyl chloride).[10e] The solvent´s polarity was approximated as nonpolar and polar based on their dielectric constant; a solvent was classified as polar if the dielectric constant was over 5 (Fig. 1, Table S1).

Carbonylative C-C couplings of aryl bromides and arylboronic acids

As a starting point, we analyzed the carbonylative coupling of 3-bromoanisole with *m*-tolylboronic acid (Chart 1). We focused on the catalytic system based on Pd(acac)$_2$ as catalyst precursor, and di(1-adamantyl)-*n*-butylphosphine hydroiodide (cataCXium AHI) as ligand,

originally developed in the group of Skrydstrup.[12g] The original protocol relied on cyclic diethanolamine esters of boronic acids (DABO boronates) or aryl trihydroxyborates as successful starting materials and used toluene/H$_2$O (10:1) or toluene as solvent.[12g] We initiated our work by developing a simplified protocol where the aryl trihydroxyborates was generated *in situ* from simple boronic acids by addition of 1M aqueous NaOH, thus preventing the external, up-front preparation of the organoboronate (see ESI, Table S1, entry 3).
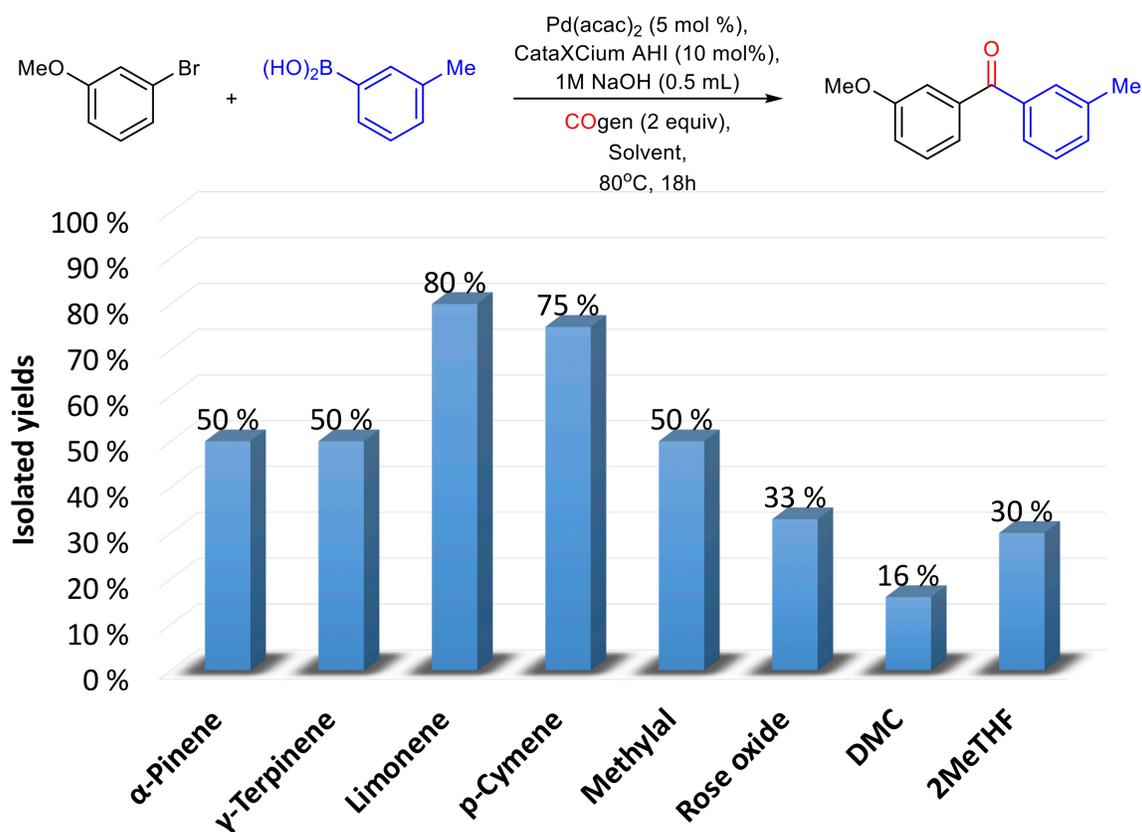
**Chart 1**. Screening of renewable solvents for carbonylative coupling of *m*-tolylboronic acid and 3-bromoanisole.

Using the modified protocol, we investigated the efficiency of various renewable solvents in the Pd-catalyzed carbonylative coupling of *m*-tolylboronic acid and 3-bromoanisole (Chart 1, see also Table S1 for a correlation of solvent polarity and yields). It has to be noted that the final reaction

media contained approx. 15% (v/v) of water in all cases due to the addition of aqueous NaOH. Our studies revealed that nonpolar ethers and carbonates (rose oxide, methylal, DMC) and polar ether 2MeTHF provide the carbonylation product in low to moderate yields (16-50%). In contrast, biomass-derived nonpolar hydrocarbons (limonene, *p*-cymene, γ-terpinene, α-pinene) gave consistently better yields with *p*-cymene and limonene being the best solvents (75% and 80% isolated yield, respectively); an observation that correlates well with the use of toluene or toluene/water as solvent in previous studies providing the corresponding product in 90% yield.[12g] Despite the fact that limonene possesses a terminal and an internal double bond, the Heck-type arylation of the solvent was not observed under the reaction conditions. Neither were related side products noted for reactions in rose oxide, γ-terpinene and α-pinene.

We proceeded to analyze the generality of the Pd-catalyzed carbonylative couplings in limonene as solvent (Scheme 1). Examination of a variety of aromatic boronic acids and aryl bromides indicated a good substrate scope. The yields varied from 71-95% for electron-rich (**3a**, **3c**, **3d**, **3e**, **3h**, **3i**), electron-deficient aryl (**3f**, **3g**) and heterocyclic boronic acids (**3j**, **3k**). The broad applicability of boronic acids is particularly interesting as the use of *in situ* generated aryl trihydroxyborates extended the substrate scope beyond the limitations associated with isolation of unstable trihydroxyborate salts.[12g] Similarly, both electron-rich (**3m**, 75%; **3o**, 79%) and electron-deficient (**3n**, 83%; **3p**, 83%) aryl bromides as well as heteroaryl bromides (**3l**, 91%) were successful in the carbonylative couplings. We observed a low yield only for 2-methoxycarbonyl-phenylboronic acid (**3b**, 40%), which may be due to steric hindrance or side reactions such as hydrolysis of the ester. Overall, the observed yields were at the same level as previously reported protocols using toluene as solvent,[12e,g] indicating that limonene is a renewable alternative for carbonylative couplings of boronic acids and aryl bromides.
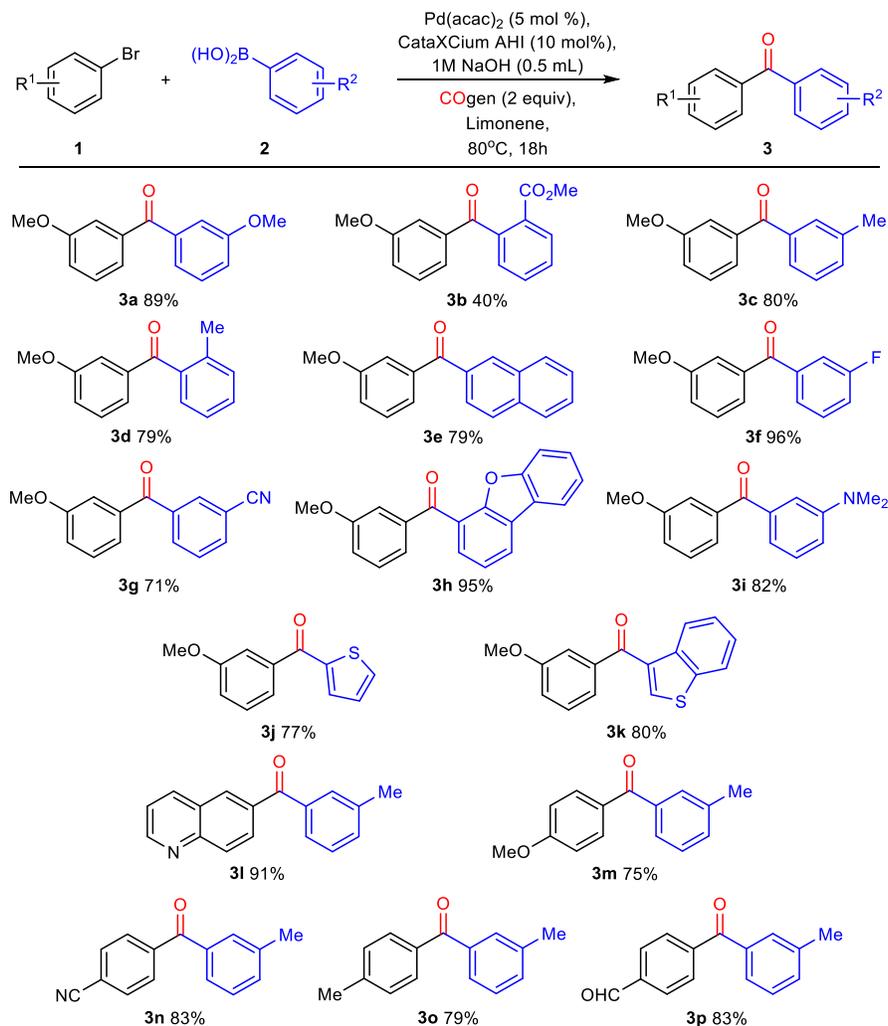
Scheme 1. Scope of carbonylative coupling of boronic acids and aryl bromides using the sustainable solvent limonene.

Aminocarbonylation of aryl bromides

Next, we examined the Pd-catalyzed aminocarbonylation reaction of aryl bromides. Here, we focused on the catalytic system developed in the group of Buchwald using Pd(OAc)$_2$ as Pd source, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene as ligand (XantPhos) and toluene as solvent.[14c] The Pd-catalyst was tested in renewable solvents on the model reaction of *N*-methylaniline with 4-bromobenzonitrile (Chart 2).
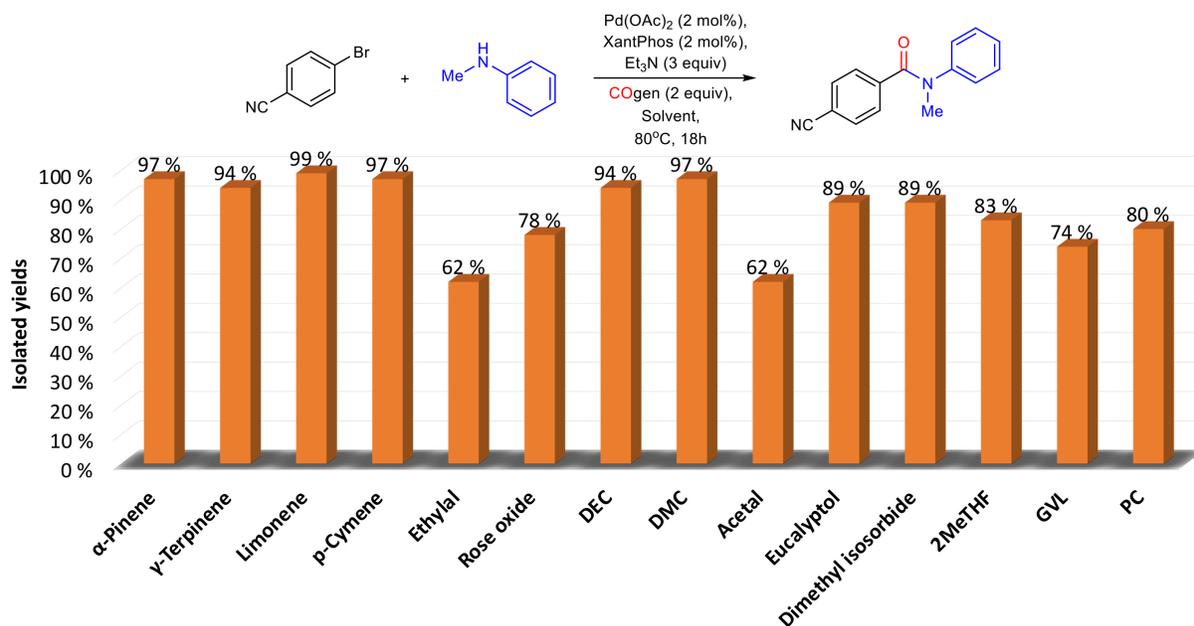
Chart 2. Screening of renewable solvents for aminocarbonylation with resulting isolated yields.

Our studies demonstrated that for this aminocarbonylation exceptional results can be obtained in most of the renewable solvents (Chart 2). As a general trend, all reactions in nonpolar hydrocarbons provided excellent yield (limonene, 99%; *p*-cymene, 97%; γ-terpinene, 94%; α-pinene; 97%); in good correlation with previous work being performed in toluene as solvent providing the product in 97% yield.[14c] Excellent yields were also obtained in nonpolar carbonates (DMC, 97%; DEC, 94%). Other solvents like polar carbonate PC and lactone GVL, and nonpolar and polar ethers (ethylal, acetal, rose oxide, eucalyptol, dimethyl isosorbide, 2MeTHF) were less efficient with yields ranging between 62-89%.

Noteworthy, under the conditions used for aminocarbonylation we did not observe side reactions like hydroamination or Mizoroki-Heck coupling for solvents possessing double bonds.

As several renewable solvents provided good yields, we screened the top three best solvents (DMC, α-pinene, limonene) for several aminocarbonylations (Scheme 2). These studies revealed that except for the products **5m** and **5n**, the best solvents DMC, α-pinene and limonene gave
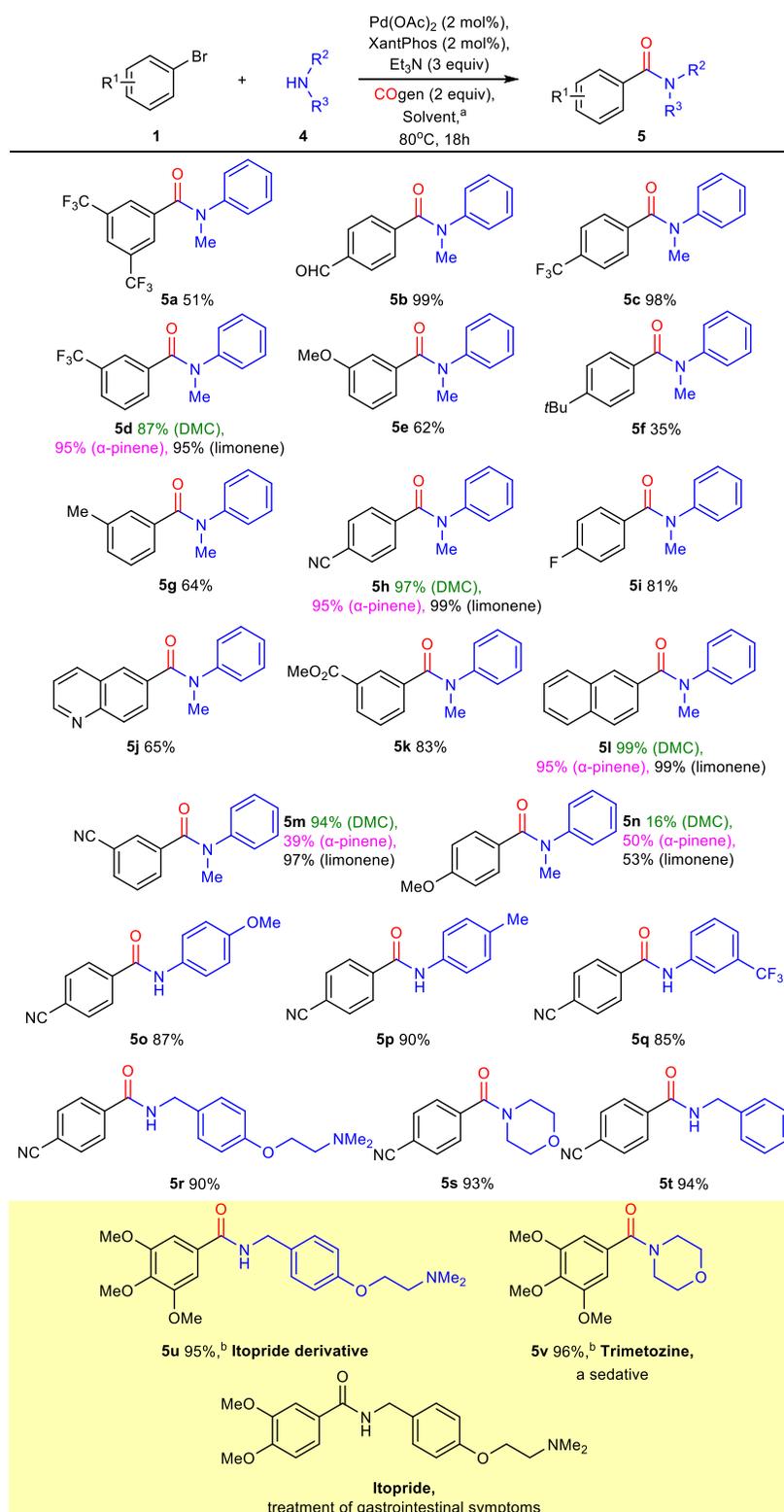
Scheme 2. Scope of aminocarbonylation of aryl bromides. [a] Unless otherwise mentioned, the reaction was performed in DMC. [b] XantPhos Pd G3 was used instead of Pd(OAc)2/XantPhos.

comparable results for several aminocarbonylations (**5d**, **5h**, **5l**). For the product **5m**, α-pinene (39%) turned out far less effective than other solvents, while for the product **5n**, DMC provided low yield (16%) (Scheme 2). For an extended analysis of the substrate scope, we therefore decided to focus on the use of DMC, as it is considerably less toxic and less expensive than the two other solvents.[15]

Reactions with variously substituted aryl bromides illustrated that many functional groups (CHO, CN, CO_2Me) were well tolerated. In general, aryl bromides with electron-withdrawing substituents provided corresponding aminocarbonylation products in good to quantitative yields (**5b**, 99%; **5c**, 98%; **5d**, 87%; **5h**, 97%; **5i**, 81%; **5k**, 83%; **5m** 94%), except for **5a** (51% yield). Electron-rich aryl bromides were less effective producing the corresponding amides from low to acceptable yields (**5e**, 62%; **5f**, 35%; **5g**, 64%; **5n**, 16%). However, the aminocarbonylation of electron-rich 3,4,5-trimethoxyphenyl bromide, using XantPhos Pd G3 as catalyst, provided the commercial drug Trimetozine (**5v**, 96% yield, a sedative) and an analogue of Itopride (**5u**, 95% yield, Itopride is used for treatment of gastrointestinal symptoms) in excellent yields.[13h] The reaction worked well also with fused systems like naphthalene (**5l**, 99%) and heterocycles (**5j**, 65%) (Scheme 2). Changes in the amine structure were tolerated well and both anilines with electron-donating and -withdrawing substituents, and primary and secondary aliphatic amines were successfully coupled with 4-bromobenzonitrile and CO (Scheme 2, **5o**, 87%; **5p**, 90%; **5q**, 85%; **5r**, 90%; **5s**, 93%; **5t**, 94%). Overall, the observed trends were in agreement with reports of aminocarbonylations performed in non-renewable solvents.[13,14c] The good yields and substrate scope indicate that renewable solvents like DMC, α-pinene and limonene can effectively replace 1,4-dioxane, toluene and THF frequently used in Pd-catalyzed aminocarbonylation reactions.[10b,13,14c]

Alkoxycarbonylation of arylbromides

Finally, we analyzed the potential adaptation of renewable solvents for Pd-catalyzed alkoxycarbonylation.[14] For the initial studies, we examined the alkoxycarbonylation of 2-bromonaphthalene with sodium *tert*-butoxide and CO using the catalytic system based on Pd(dba)$_2$ as catalyst precursor and 1,1′-bis(diisopropylphosphino)ferrocene (dippf) as ligand first reported by Skrydstrup and coworkers for alkoxycarbonylations in THF (Chart 3).[14f] The screening of renewable solvents showed that excellent results can be achieved also for the Pd-catalyzed alkoxycarbonylations (Chart 3).

Not surprisingly, the polar ether 2MeTHF (91% yield) was among the best solvents, as previous studies were performed in THF (88% yield).[14f] Interestingly, excellent yields of 93% were also obtained in some nonpolar hydrocarbons (γ-terpinene, α-pinene), while other nonpolar hydrocarbons (limonene, 56%), ethers (methylal, 45%; ethylal, 64%; acetal, 55%; rose oxide, 36%; eucalyptol, 82%), and carbonates (DEC, 45%) provided low to moderate yields. In nonpolar carbonate DMC, instead of *tert*-butoxycarbonylation, the product of methoxycarbonylation was isolated in 93% yield (Chart 3, Scheme 4). This was the only observation where the solvent was chemically transformed in the reaction. Similar transesterifications were not observed for the other carbonates (DEC, PC, EC). Polar solvents (dimethyl isosorbide, 30%; GVL, 64%; PC, 60%; EC, 30% yield) were less efficient.
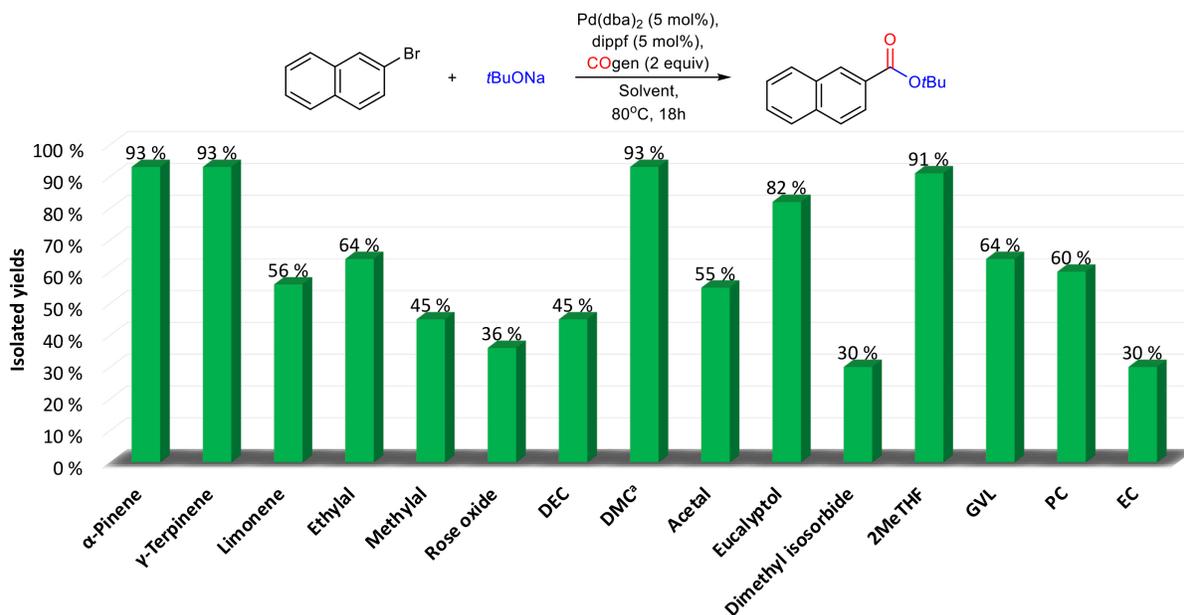
Chart 3. Screening of renewable solvents for alkoxycarbonylation with resulting isolated yields. [a] In DMC, methoxycarbonylation was observed.

As for aminocarbonylation, we screened the top three best solvents (2MeTHF, α-pinene and γ-terpinene) for alkoxycarbonylations of several substrates (Chart 3, Scheme 3). These studies revealed that the choice of solvent is dependent on the substrate. 2MeTHF was the best solvent for the products **7c** (52%) and **7d** (45%). The best yields of **7b** were seen in γ-terpinene (98%), whereas γ-terpinene was not a good reaction media for the product **7f** (44%). α-Pinene appeared to be the best solvent for the products **7a** (93%) and **7f** (51%) and in general showed good performance for most of the substrates.
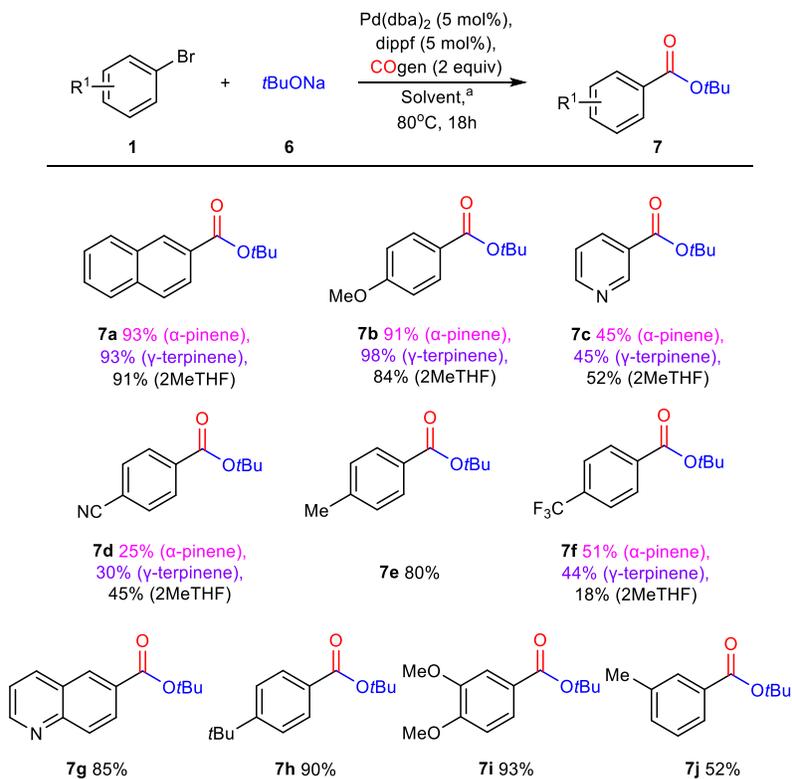
Scheme 3. Scope of *tert*-butoxycarbonylation of aryl bromides. [a] Unless otherwise mentioned, the reaction was performed in α-pinene.

The following investigation of the scope of *tert*-butoxycarbonylation in α-pinene as solvent showed that both electron-rich and -deficient aryl bromides can be effectively transformed into the corresponding products in moderate to good yields (Scheme 3). The best yields were observed for *tert*-butoxycarbonylation of electron-rich aryl bromides (**7a**, 93%; **7b**, 91%; **7e**, 80%; **7g**, 85%; **7h**, 90%; **7i**, 93%). It should be noted that aryl bromides possessing electron-withdrawing groups and electron-deficient 3-bromopyridine were less effective and gave products in moderate yields (**7c**, 45%; **7d**, 25%; **7f**, 51%). Similar observations were reported by Skrydstrup et al. for alkoxycarbonylations performed in THF.[14f] Overall, our studies indicate that for alkoxycarbonylations renewable solvent perform on the same level, and in some cases even better, than previously reported non-renewable solvents.[10,14] Renewable solvents such as 2MeTHF,

DMC, α-pinene and γ-terpinene can be useful alternatives for trimethylamine, hexafluoroisopropanol, THF, toluene and dimethyl sulfoxide frequently used for alkoxycarbonylation reactions.[14]

Studies on the alkoxycarbonylation in DMC.

In general, alkoxycarbonylation reactions rely on the use of bulky alcohols, phenols or corresponding alkoxides.[14] Alcohols possessing α-hydrogens have found limited applications due to the side processes associated with β-hydride elimination.[14b,d] Therefore, we had a closer look at the methoxycarbonylations observed in DMC. The scope of the reaction was briefly studied on a range of substituted aryl bromides (Scheme 4). The reaction gave good yields for electron-rich 4-bromoanisole (**8b** 90%) and 4-bromotoluene (**8d**, 80%), as well as for 2-bromonaphthalene (**8a**, 93%) and 6-bromoquinoline (**8e**, 93%). Moderate yields were observed for electron-deficient aryl bromides (**8c**, 58%). For most of the products in Scheme 4, traces of *tert*-butoxycarbonylation were seen along with the main methoxycarbonylation product.
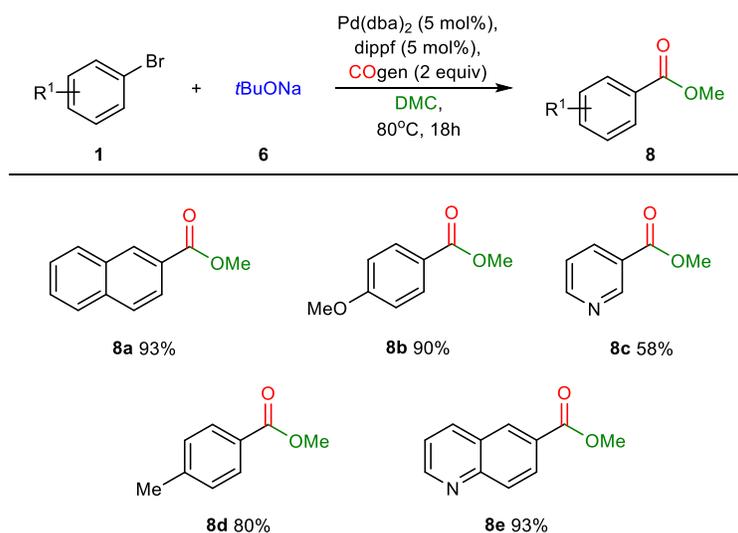
Scheme 4. Scope of methoxycarbonylation of aryl bromides.

To gain a better understanding of the mechanism of the observed methoxycarbonylation, we performed a set of control experiments (Scheme 5). The *tert*-butyl ester **7a** was transformed into corresponding methyl ester **8a** in quantitative yield when treated with NaO*t*Bu in DMC. The transesterification took place in presence and absence of the Pd-catalyst (Scheme 5, A, B). In addition, the Pd-catalyzed methoxycarbonylation of 2-bromonaphthalene with sodium methoxide in DMC provided the methoxycarbonylated product in 67% yield, while an equivalent experiment in α-pinene did not lead to methoxycarbonylation (Scheme 5, C). These findings indicate that two different reaction pathways may contribute to the formation of methoxycarbonylated products: (i) the Pd-catalyzed alkoxycarbonlyation with *tert*-butoxide followed by a transesterification with sodium methoxide generated *in situ* from the reaction of excess sodium *tert*-butoxide with DMC; and (ii) the Pd-catalyzed methoxycarbonylation with *in-situ* generated sodium methoxide.
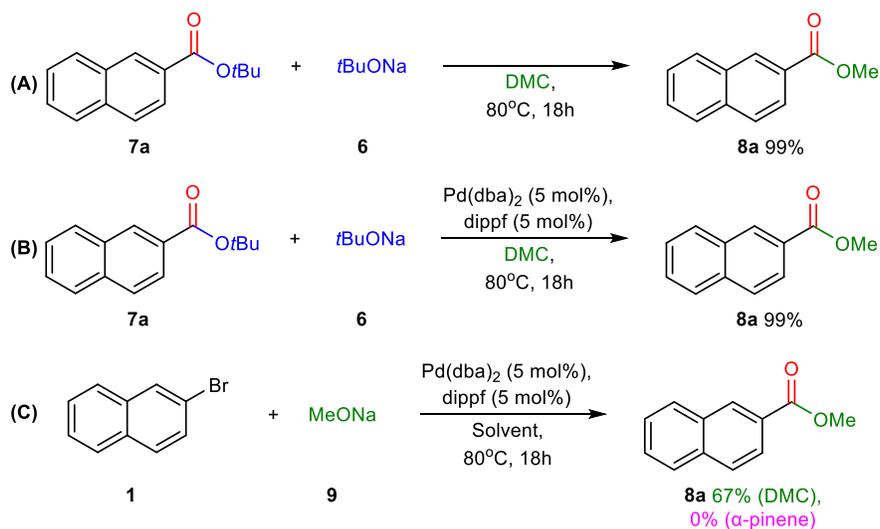
Scheme 5. Control experiments to elucidate the formation of methoxycarbonylated products.

CONCLUSIONS

We have shown that Pd-catalyzed carbonylative transformations can be conducted in biomass- and CO_2-derived solvents with exceptionally high efficiency. A vast array of renewable solvents was

analyzed for this purpose, including both well-established (2MeTHF, GVL, limonene, *p*-cymene, DMC, DEC, PC, EC) and recently introduced solvent candidates (acetal, dimethyl isosorbide, γ-terpinene, α-pinene, eucalyptol, rose oxide, methylal and ethylal). The work covered Pd-catalyzed carbonylative coupling of boronic acids and aryl bromides, aminocarbonylation and alkoxycarbonylation. For each of these transformations we have found several renewable solvents, which can successfully substitute traditional non-renewable solvents. For carbonylative coupling of boronic acids and aryl bromides the best results were observed in limonene and *p*-cymene. Aminocarbonylation worked well in DMC, α-pinene and limonene, whereas the best solvents for alkoxycarbonylation turned out to be 2MeTHF, α-pinene, γ-terpinene and DMC. Most of the known methodologies on alkoxycarbonylation are limited to bulky alkoxides and alcohols. We could show that this drawback can be overcome by the use of DMC, which lead to methoxycarbonylated products. Finally, yet importantly, aminocarbonylation in renewable solvents can be used for the production of commercial drug Trimetozine and an analogue of Itopride.

EXPERIMENTAL METHODS

General considerations.

Solvents used in the work are purchased from Sigma Aldrich if not otherwise stated. 2MeTHF (anhydrous, ≥99%, inhibitor-free, 673277-1L), methylal (absolute, over molecular sieve, ≥99.0%, 47676-250ML), ethylal (absolute, over molecular sieve, ≥99.0%, 47675-500ML-F), DMC (anhydrous, ≥99%, 517127-1L), DEC (anhydrous, ≥99%, 517135-1L), PC (anhydrous, 99.7%, 310328-1L) and EC (anhydrous, 99%, 676802-1L) were bought as anhydrous solvents equipped with a septa. Other renewable solvents were reagent grade; they were degassed, kept over activated molecular sieves (4 Å) at least a week before use and stored under Ar atmosphere. The purity of

the solvents used in the work were as follows: acetal (99%, inhibitor-free, A902-500ML); dimethyl isosorbide (98%, inhibitor-free, 247898-100G); GVL (99%, V403-500G); γ-terpinene (97%, 223190-100ML); α-pinene (98%, 147524-250ML); limonene (97%, 183164-100ML); *p*-cymene (99%, C121452-1L); eucalyptol (99%, inhibitor-free, C80601-500ML); rose oxide (97%, inhibitor-free, TCI, M2363-25G).

2MeTHF, acetal, dimethyl isosorbide, eucalyptol, rose oxide, methylal and ethylal are ethers and may form peroxides when stored under air. However, peroxide tests (test strips for peroxide, MQuant®, Supelco®, VWR/Merck 1.10081.0001) of freshly bought solvents did not show any noticeable levels of peroxides. Acetal, methylal and ethylal can be hydrolyzed in the presence of strong acids when heated. Under basic conditions, which are frequently used for the reactions involving organometallics, acetal, methylal and ethylal are stable. GVL, DMC, DEC, PC and EC can be hydrolyzed in the presence of strongly basic water solutions; under anhydrous conditions, they are stable. γ-Terpinene, limonene and eucalyptol can be converted to *p*-cymene when heated above 220°C.[4b] Overall, the examined renewable solvents appeared to be stable under the conditions used in this work. We have not observed the formation of side-products e.g. originating from hydrolysis of the carbonate, ethers and esters used as solvents in this work (an exception was alkoxycarbonylation in DMC). It should be noted that the oxidation products of terpenes can be allergens.[9]

The reactions were performed in the previously reported two-chamber system (COware with total volume 20 mL, ESI Fig. S1) under an argon atmosphere, and a glovebox was employed for weighing out the reagents.

Warning! Most of the reactions were performed in specialized glassware under pressure. The glassware should always be examined for damages before any manipulation. All laboratory safety

procedures must be followed strictly and the work with pressure tubes must be conducted behind a shield.

General procedure for Pd-catalyzed carbonylative coupling of boronic acids and aryl bromides (Scheme 1).

Chamber A was sequentially charged with aryl bromide (50 mg, 1.0 equiv), boronic acid (1.2 equiv), Pd(acac)$_2$ (5 mol%), cataCXium AHI (10 mol%), 1M NaOH (500 µl) and dry solvent (3 mL). The reaction mixtures consisted of an organic and an aqueous layer. Precipitation of palladium was not observed.

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (5 mol%), DIPEA (3 equiv) and 1,4-dioxane (3 mL). The two-chamber system was closed tightly with suitable caps and **Chamber B** was stirred at 80 ºC until the release of CO was stopped. This was followed by stirring of both chambers at 80 ºC for 18 hours. The resulting mixture of **Chamber A** was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane: EtOAc (9:1) eluent.

General procedure for Pd-catalyzed aminocarbonylation (Scheme 2).

Chamber A was sequentially charged with aryl bromide (50 mg, 1.0 equiv), corresponding amine (1.5 equiv), Pd(OAc)$_2$ (2 mol%), XantPhos (2 mol%), triethylamine (3 equiv) and dry solvent (3 mL). At the onset of the reaction, the mixture was homogeneous, while precipitation of palladium species (Pd-black) was observed during the course of the reaction both in conventional and renewable solvents.

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (5 mol%), 1,4-dioxane (3 mL) and DIPEA (3

equiv). Addition of DIPEA initialize the release of CO. The two-chamber system was closed tightly with suitable caps and stirred at 80 °C for 18 hours. The resulting mixture of **Chamber A** was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane : EtOAc (9:2) eluent.

General procedure for Pd-catalyzed alkoxycarbonylation (Scheme 3, 4).

Chamber A was sequentially charged with aryl bromide (50 mg, 1.0 equiv), tBuONa (1.5 equiv), Pd(dba)$_2$ (5 mol%), 1,1′-bis(diisopropylphosphino)ferrocene (dippf) (5 mol%) and corresponding dry solvent (3 mL). At the onset of the reaction, the mixture was homogeneous, while precipitation of palladium species was observed during the course of the reactions both in conventional and renewable solvents.

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (5 mol%), 1,4-dioxane (3 mL) and DIPEA (3 equiv). Addition of DIPEA initialize the release of CO. The two-chamber system was closed tightly with suitable caps and stirred at 80 °C for 18 hours. The resulting mixture of **Chamber A** was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane : EtOAc (9:1) eluent.

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

Detailed description of experiments and results, analytical and spectroscopic data (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): T.S. is co-owner of SyTracks A/S, which commercializes the two-chamber system (COware) and COgen.

ABBREVIATIONS

2MeTHF = 2-methyltetrahydrofuran; acetal = 1,1-diethoxyethane; COgen = 9-methyl-9*H*-fluorene-9-carbonyl chloride; COware = two chamber reactor; cataCXium AHI = di(1-adamantyl)-*n*-butylphosphine hydriodide; DMC = dimethyl carbonate; DEC = diethyl carbonate; DIPEA = N,N-diisopropylethylamine; dippf = 1,1′-bis(diisopropylphosphino)ferrocene; EtOAc = ethyl acetate; EC = ethylene carbonate; GVL = γ-valerolactone; LCA = life-cycle assessment; PC = propylene carbonate; Pd(acac)$_2$ = palladium(II) acetylacetonate; Pd(OAc)$_2$ = palladium(II) acetate; Pd(dba)$_2$ = bis(dibenzylideneacetone)palladium(0); TTBP•HBF$_4$ = tri-*tert*-butylphosphonium tetrafluoroborate; XantPhos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; XantPhos Pd G3 = [(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate.

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Supplementary Information

Renewable Solvents for Palladium-Catalyzed Carbonylation Reactions

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# 1.	General considerations

All chemicals and solvents were purchased from Sigma Aldrich and VWR and were used as received without further purification. Solvents were dried according to standard procedures on molecular sieves 4 Å.[1] Flash chromatography was carried out on silica gel 60 (230–400 mesh). NMR spectra were obtained on a Bruker Avance 400 MHz at 20°C. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dt = double triplet, m = multiplet), coupling constant (J, Hz) and integration. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak (CDCl$_3$: δH 7.26 and δC 77.16; Methanol-d$_4$: δH 3.31 and δC 49.00; Deuteriumoxid: δH 4.79; DMSO-d$_6$: δH 2.51 and δC 39.52). The raw data was analyzed with MestReNova (Version 10.0.2-15465). Positive ion electrospray ionization mass spectrometry was conducted on a Thermo electron LTQ Orbitrap XL spectrometer. The data was analyzed with Thermo Scientific Xcalibur software. Melting points were measured using Stuart SMP50 automatic melting point detector. Infrared spectra were recorded on a Agilent Cary 630 FT-IR spectrometer and absoptions are reported in wavenumber (cm^{-1}); s = strong, m = medium, w = weak.

Solvents used in the work were purchased from Sigma Aldrich if not otherwise stated. 2MeTHF (anhydrous, ≥99%, inhibitor-free, 673277-1L), methylal (absolute, over molecular sieve, ≥99.0%, 47676-250ML), ethylal (absolute, over molecular sieve, ≥99.0%, 47675-500ML-F), dimethylcarbonate (anhydrous, ≥99%, 517127-1L), diethylcarbonate (anhydrous, ≥99%, 517135-1L), propylene carbonate (anhydrous, 99.7%, 310328-1L) and ethylene carbonate (anhydrous, 99%, 676802-1L) were bought as anhydrous solvents equipped with a septa. Other renewable solvents were reagent grade; they were degassed, kept over activated molecular sieves (4 Å) at least for a week before use and stored under Ar atmosphere. The purity of the solvents used in the work were as follows: diethoxyethane (99%, inhibitor-free, A902-500ML); dimethyl isosorbide (98%, inhibitor-free, 247898-100G); GVL (99%, V403-500G); γ-terpinene (97%, 223190-100ML); α-pinene (98%, 147524-250ML); (R)-(+)-limonene (97%, 183164-100ML); p-cymene (99%, C121452-1L); eucalyptol (99%, inhibitor-free, C80601-500ML); (+)–rose oxide (97%, inhibitor-free, Chemtronica/TCI M2363-25G).

2MeTHF, acetal, dimethyl isosorbide, eucalyptol, rose oxide, methylal and ethylal are ethers and may form peroxides when stored under air; however, peroxide tests (Test strips for peroxide, MQuant®, Supelco®, VWR/Merck 1.10081.0001) of freshly bought solvents did not show any noticeable levels of peroxides. Acetal, methylal and ethylal can be hydrolyzed in the presence of strong acids when heated. Under basic conditions, which are frequently used for the reactions involving organometallics, acetal, methylal and ethylal are stable. GVL, DMC, DEC, PC and EC can be hydrolyzed in the presence of strongly basic water solutions; under anhydrous conditions, they are stable. γ-Terpinene, limonene and eucalyptol can be converted to p-cymene when heated above 220°C. Overall, the examined renewable solvents appeared to be stable under the conditions used in this work. It should be noted that the oxidation products of terpenes can be allergens.

The reactions were performed in the previously reported two-chamber system (COware with total volume of 20 mL, Fig. S1) under an argon atmosphere, and a glovebox was employed for weighing out the reagents.

Warning! Most of the reactions were performed in specialized glassware under pressure. The glassware should always be examined for damages before any manipulation. All laboratory safety procedures must be followed strictly and the work with pressure tubes must be conducted behind a shield.

2. The two-chamber system used in the work
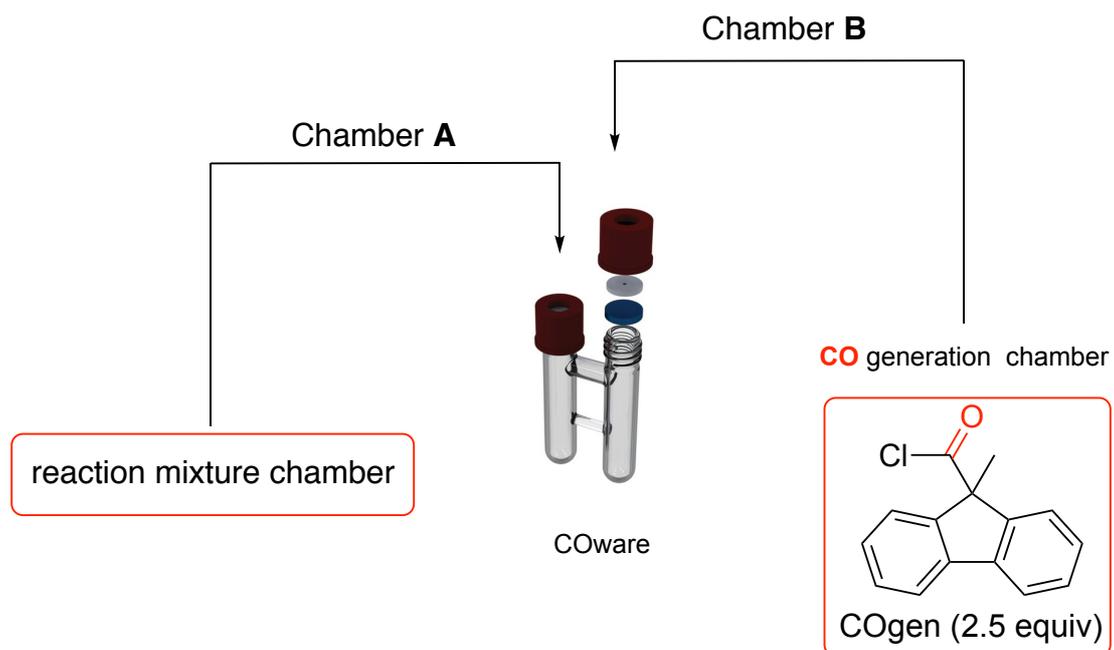
Fig. S1. The two-chamber system used in the work, and the CO generator (COgen).

# 3. Overview of solvents used in the study and their properties

Table S1. Overview of solvent properties and isolated yield from solvent screens. Solvents are organized by increasing dielectric constant.

Solvent	MW (g/mol)	Bp (°C)	Dielectric constant[1]	Compound class	C-C yield (%)	C-N yield (%)	C-O yield (%)
non-polar							
α-Pinene	136.24	156	2.18	hydrocarbon	50	97	93
γ-Terpinene	136.24	174	2.27[2]	hydrocarbon	50	94	93
(+)-Limonene	136.24	178	2.37	hydrocarbon	80	99	56
p-Cymene	134.22	177	2.25[3]	hydrocarbon	75	97	
Toluene	92.14	111	2.38	hydrocarbon	90[10]	97[11]	
Diethoxymethane (ethylal)	104.15	87	2.53[4]	ether		62	64
Dimethoxymethane (methylal)	76.10	42	2.64	ether	50		45
Diethylcarbonate (DEC)	118.13	126	2.82	carbonate		94	45
Dimethylcarbonate (DMC)	90.08	90	3.13[5]	carbonate	16	97	93*
1,1-Diethoxyethane (acetal)	118.18	102	3.80	ether		62	55
(+)-Rose oxide	154.25	86/20 mmHg		ether	33	78	36
Eucalyptol	154.25	176	4.57	ether		89	82
polar aprotic							
Dimethyl isosorbide (DMI)	174.20	94/0.1 mmHg	6.2[6]	ether		89	30
2-Methyltetrahydrofuran (2MeTHF)	86.13	79	6.97[7]	ether	30	83	91
Tetrahydrofuran (THF)	72.11	65	7.52	ether			88[12]
γ-Valerolactone (GVL)	100.12	207	36.47[8]	ester		74	64
Propylenecarbonate (PC)	102.09	242	66.14	carbonate		80	60
Ethylenecarbonate (EC)	88.06	261	92.8[9]	carbonate			30

* Yield of product corresponding to an overall methoxycarbonylation. [1] Values obtained from CRC Handbook of Chemistry and Physics (85th ed.) unless specified otherwise. T = 15 to 30 °C. [2] Value obtained from: Thomas, G. A.; Hawkins, J. E. *J. Am. Chem. Soc.* **1954**, *76* (19), 4856-4858. [3] Value obtained from: Altshuller, A. P., *J. Phys. Chem.* **1954**, *58* (5), 392-395. [4] Value obtained from: Philippe, R.; Piette, A. M., *Bull. Soc. Chim. Belg.* **1955**, *64*, 600-27. [5] Value obtained from: Rivas, M. A.; Pereira, S. M.; Banerji, N.; Iglesias, T. P., *J. Chem. Thermodyn.* **2004**, *36* (3), 183-191. [6] Value obtained from: Zia, H.; Ma, J. K. H.; O'Donnell, J. P.; Luzzi, L. A. *Pharm. Res.* **1991**, *8* (4), 502-504. [7] Value obtained from: Aycock, D. F. *Org. Process Res. Dev.* **2007**, *11* (1), 156-159. [8] Value obtained from: Aparicio, S.; Alcalde, R. *Phys. Chem. Chem. Phys.* **2009**, *11* (30), 6455-6467. [9] Value obtained from: Ding, M. S. *J. Electrochem. Soc.* **2003**, *150* (4), A455. [10] Bjerglund, K. M.; Skrydstrup, T.; Molander, G. A. *Org. Lett.* **2014**, *16*, 1888-1891. [11] Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102-7107. [12] Xin, Z.; Gogsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett.* **2012**, *14*, 284-287.

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4. Optimization of carbonylative Suzuki-Miyaura coupling with boronic acids

Table S2. Catalyst screening for the carbonylative coupling of boronic acids and 3-bromoanisole.
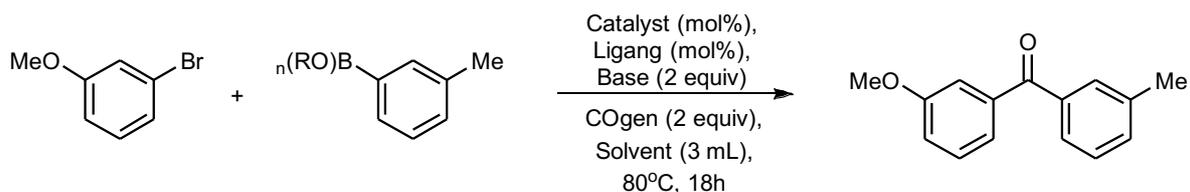
| Entry	Boronic acid derivative	Catalyst (mol%)	Ligand (mol%)	Base	Solvent	Isol. Yield (%)
1	Me—B(OH)$_2$	Pd(OAc)$_2$ (3)	IMes (4)	Cs$_2$CO$_3$	1,4-Dioxane	40
2[4]	Me—B(OH)$_3$Na	Pd(acac)$_2$ (5)	CataXCiumA.HI (10)	-	Toluene	83
3[4]	Me—B(O—NH)(O)	Pd(acac)$_2$ (5)	CataXCiumA.HI (10)	-	Toluene:H$_2$O (10:1)	45
4	Me—B(OH)$_2$	Pd(acac)$_2$ (5)	CataXCiumA.HI (10)	1M aq. NaOH	Toluene	82

The reagents were weighed in the glove box!

Chamber A was sequentially charged with 3-methoxybromobenzene (50 mg, 1.0 equiv), corresponding organoboronate (1.2 equiv), Pd-catalyst (3-5 mol%), ligand (4-10 mol%), base (0-2 equiv) and corresponding solvent (3 mL).

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (5 mol%), 1,4-dioxane (3 mL) and DIPEA (3 equiv). Addition of DIPEA initialize the release of CO. The two-chamber system was closed tightly with suitable caps and stirred at 80°C for 18 hours. The resulting mixture of **Chamber A** was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane : EtOAc (9:2) eluent.

5. Screening of solvents

5.1 Screening of solvents for carbonylative coupling of boronic acids and aryl halides.
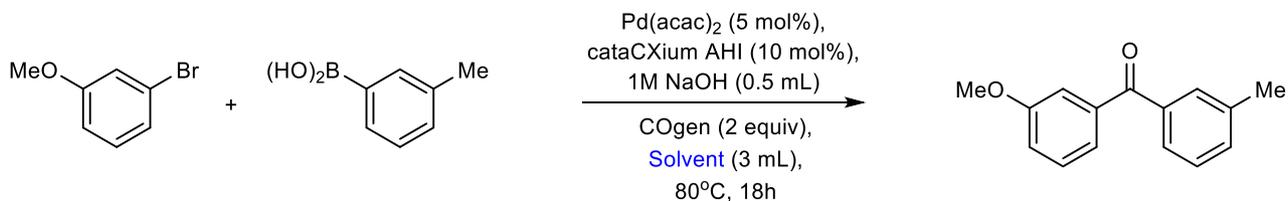
The reagents were weighed in the glove box!

Chamber A was sequentially charged with 3-methoxybromobenzene (50 mg, 1.0 equiv), *m*-tolylboronic acid (1.2 equiv), Pd(acac)$_2$ (5 mol%), cataCXium AHI (10 mol%), 1M NaOH (500 µl) and corresponding dry solvent (3 mL).

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (5 mol%), 1,4-dioxane (3 mL) and DIPEA (3 equiv). Addition of DIPEA initialize the release of CO. The two-chamber system was closed tightly with suitable caps and stirred at 80°C for 18 hours. The resulting mixture of **Chamber A** was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane : EtOAc (9:2) eluent.

5.2   Screening of solvents for the aminocarbonylation.

Chamber A was sequentially charged with 4-bromobenzonitrile (50 mg, 1.0 equiv), *N*-methylaniline (1.5 equiv), Pd(OAc)$_2$ (2 mol%), XantPhos (2 mol%), triethylamine (3 equiv) and corresponding dry solvent (3 mL).

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (5 mol%), 1,4-dioxane (3 mL) and DIPEA (3 equiv). Addition of DIPEA initialize the release of CO. The two-chamber system was closed tightly with suitable caps and stirred at 80°C for 18 hours. The resulting mixture of **Chamber A** was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane : EtOAc (9:2) eluent.

5.3   Screening of solvents for the alkoxycarbonylation.

Chamber A was sequentially charged with 2-bromonaphthalene (50 mg, 1.0 equiv), *t*BuONa (1.5 equiv), Pd(dba)$_2$ (5 mol%), 1,1'-bis(diisopropylphosphino)ferrocene (dippf) (5 mol%) and corresponding dry solvent (3 mL).

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (5 mol%), 1,4-dioxane (3 mL) and DIPEA (3 equiv). Addition of DIPEA initialize the release of CO. The two-chamber system was closed tightly with suitable caps and stirred at 80°C for 18 hours. The resulting mixture of **Chamber A** was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane : EtOAc (9:1) eluent.

6.   General procedures
The reagents were weighed in the glove box!

6.1   General procedure A: Carbonylative coupling of boronic acids and aryl halides.
Chamber A was sequentially charged with aryl bromide (50 mg, 1.0 equiv), boronic acid (1.2 equiv), Pd(acac)$_2$ (5 mol%), cataCXium AHI (10 mol%), 1M NaOH (500 µl) and dry solvent (3 mL).

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (5 mol%), DIPEA (3 equiv) and 1,4-dioxane (3 mL). The two-chamber system was closed tightly with suitable caps and **Chamber B** was stirred at 80°C until the release of CO was stopped. This was followed by stirring of both chambers at 80°C for 18 hours. The resulting mixture of **Chamber A** was

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filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane : EtOAc (9:1) eluent.

6.2   General procedure B: Aminocarbonylation.

Chamber A was sequentially charged with aryl bromide (50 mg, 1.0 equiv), corresponding amine (1.5 equiv), Pd(OAc)$_2$ (2 mol%), XantPhos (2 mol%), (in the case of **5u** and **5v** Pd(OAc)$_2$/XantPhos system was replaced by XantPhos Pd G3 (2 mol%)), triethylamine (3 equiv) and corresponding dry solvent (3 mL).

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (5 mol%), 1,4-dioxane (3 mL) and DIPEA (3 equiv). Addition of DIPEA initialize the release of CO. The two-chamber system was closed tightly with suitable caps and stirred at 80°C for 18 hours. The resulting mixture of **Chamber A** was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane : EtOAc (9:2) eluent.

6.3   General procedure C: Alkoxycarbonylation.

Chamber A was sequentially charged with aryl bromide (50 mg, 1.0 equiv), *t*BuONa (1.5 equiv), Pd(dba)$_2$ (5 mol%), 1,1'-bis(diisopropylphosphino)ferrocene (dippf) (5 mol%) and corresponding dry solvent (3 mL).

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (5 mol%), 1,4-dioxane (3 mL) and DIPEA (3 equiv). Addition of DIPEA initialize the release of CO. The two-chamber system was closed tightly with suitable caps and stirred at 80°C for 18 hours. The resulting mixture of **Chamber A** was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane : EtOAc (9:1) eluent.

7.   Control experiments on methoxycarbonylation.

Transesterification in the absence of Pd-catalyst

10 mL pressure vial was sequentially charged with *tert*-butyl 2-naphthoate (26 mg, 1.0 equiv), *t*BuONa (1.5 equiv) and dry DMC (3 mL). The pressure vial was closed tightly with suitable cap and stirred at 80°C for 18 hours. The resulting mixture was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane : EtOAc (9:1) eluent.

**Transesterification in the presence of Pd-catalyst**

10 mL pressure vial was sequentially charged with *tert*-butyl 2-naphthoate (26 mg, 1.0 equiv), *t*BuONa (1.5 equiv), Pd(dba)$_2$ (5 mol%), 1,1'-bis(diisopropylphosphino)ferrocene (dippf) (5 mol%) and dry DMC (3 mL). The pressure vial was closed tightly with suitable cap and stirred at 80°C for 18 hours. The resulting mixture was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane : EtOAc (9:1) eluent.

Pd-catalyzed methoxycarbonylation with sodium methoxide

Chamber A was sequentially charged with 2-bromonaphthalene (50 mg, 1.0 equiv), MeONa (1.5 equiv), Pd(dba)$_2$ (5 mol%), 1,1'-bis(diisopropylphosphino)ferrocene (dippf) (5 mol%) and dry DMC (3 mL).

Chamber B was sequentially charged with COgen (2 equiv), Pd(dba)$_2$ (5 mol%), tri-*tert*-butylphosphonium tetrafluoroborate (TTBP•HBF$_4$) (5 mol%), 1,4-dioxane (3 mL) and DIPEA (3 equiv). Addition of DIPEA initialize the release of CO. The two-chamber system was closed tightly with suitable caps and stirred at 80°C for 18 hours. The resulting mixture of **Chamber A** was filtered through celite and concentrated using a rotary evaporator. The crude was purified by column chromatography with heptane : EtOAc (9:1) eluent.

8. Characterisation of products
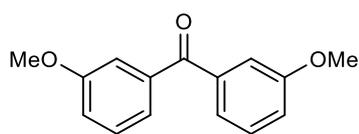
Bis(3-methoxyphenyl)methanone, 3a.[2] 1-Bromo-3-methoxybenzene (50 mg, 0.26 mmol) was reacted with (3-methoxyphenyl)boronic acid (48 mg, 0.32 mmol) according to the general procedure A to provide the product (57 mg, 89%) as red oil. **^{1}H NMR (400 MHz, CDCl₃):** δ = 7.24-7.20 (m, 6H), 7.00-6.99 (m, 2H), 3.72 (s, 6H). **^{13}C NMR (101 MHz, CDCl₃):** δ = 196.6, 159.9, 139.3, 129.6, 123.2, 119.2, 114.7, 55.8. **HRMS (ESI):** Calcd. for $C_{15}H_{14}O_3Na$ [M+Na]+ 265.0835; found 265.0837.
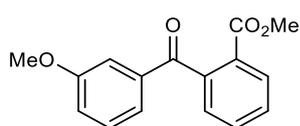
Methyl 2-(3-methoxybenzoyl)benzoate, 3b.[3] 1-Bromo-3-methoxybenzene (50 mg, 0.26 mmol) was reacted with (2-(methoxycarbonyl)phenyl)boronic acid (57 mg, 0.32 mmol) according to the general procedure A to provide the product (25 mg, 40%) as yellow oil. **^{1}H NMR (400 MHz, CDCl₃):** δ = 7.90 (d, J = 8.7 Hz, 1H), 7.61-7.46 (m, 1H), 7.46-7.33 (m, 1H), 7.28 (s, 2H), 7.21-7.08 (m, 1H), 7.05 (d, J = 7.7 Hz, 1H), 6.96 (dd, J = 8.7, 3.2 Hz, 1H), 3.70 (s, 3H), 3.50 (s, 3H). **^{13}C NMR (101 MHz, CDCl₃):** δ = 196.9, 166.5, 159.9, 141.8, 138.6, 132.5, 131.2, 130.1, 129.7, 129.6, 129.0, 127.8, 122.5, 119.8, 113.0, 55.5, 52.3. **HRMS (ESI):** Calcd. for $C_{16}H_{14}O_4Na$ [M+Na]+ 293.0784; found 293.0787.
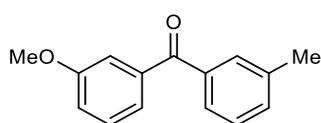
(3-Methoxyphenyl)(m-tolyl)methanone, 3c.[4] 1-Bromo-3-methoxybenzene (50 mg, 0.26 mmol) was reacted with *m*-tolylboronic acid (44 mg, 0.32 mmol) according to the general procedure A to provide the product (48 mg, 80%) as yellow oil. **^{1}H NMR (400 MHz, CDCl₃):** δ = 7.63 (s, 1H), 7.58 (d, J = 7.3 Hz, 1H), 7.43-7.29 (m, 5H), 7.14-7.11 (m, 1H), 3.85 (s, 3H), 2.41 (s, 3H). **^{13}C NMR (101 MHz, CDCl₃):** δ = 196.8, 159.6, 139.1, 138.2, 137.7, 133.3, 130.5, 129.2, 128.1, 127.4, 122.9, 118.8, 114.4, 55.5, 21.4. **HRMS (ESI):** Calcd. for $C_{15}H_{14}O_2Na$ [M+Na]+ 249.0886; found 249.0886.
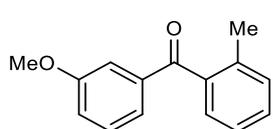
(3-Methoxyphenyl)(o-tolyl)methanone, 3d.[5] 1-Bromo-3-methoxybenzene (50 mg, 0.26 mmol) was reacted with *o*-tolylboronic acid (44 mg, 0.32 mmol) according to the general procedure A to provide the product (57 mg, 79%) as brown oil. **^{1}H NMR (400 MHz, CDCl₃):** δ = 7.47-7.46 (m, 1H), 7.45-7.40 (m, 1H), 7.38-7.36 (m, 1H), 7.35-7.33 (m, 1H), 7.32-7.31 (m, 2H), 7.30-7.28 (m, 1H), 7.18-7.15 (m, 1H), 3.88 (s, 3H), 2.38 (s, 3H). **^{13}C NMR (101 MHz, CDCl₃):** δ = 198.5, 159.8, 139.2, 138.7, 136.8, 131.1, 130.3, 129.5, 128.5, 125.3, 123.4, 119.9, 113.9, 55.5. **HRMS (ESI):** Calcd. for $C_{15}H_{14}O_2Na$ [M+Na]+ 249.0886; found 249.0886.
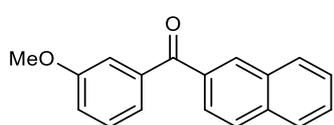
(3-Methoxyphenyl)(naphthalen-2-yl)methanone, 3e.[6] 1-Bromo-3-methoxybenzene (50 mg, 0.26 mmol) was reacted with naphthalen-2-ylboronic acid (55 mg, 0.32 mmol) according to the general procedure A to provide the product (53 mg, 79%) as yellow oil. **^{1}H NMR (400 MHz, CDCl₃):** δ = 8.29 (s, 1H), 7.94-7.5 (m, 2H), 7.94-7.88

(m, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.43-7.40 (m, 3H), 7.22-7.10 (m, 1H), 3.87 (s, 3H). **¹³C NMR (101 MHz, CDCl₃):** δ = 196.6, 159.7, 139.3, 135.4, 134.9, 132.3, 131.9, 129.5, 129.4, 128.4, 128.4, 127.9, 126.9, 125.9, 123.0, 118.9, 114.5, 55.6. **HRMS (ESI):** Calcd. for $C_{18}H_{14}O_2Na$ [M+Na]⁺ 285.0886; found 285.0889.
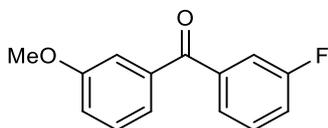
(3-Fluorophenyl)(3-methoxyphenyl)methanone, 3f.[7] 1-Bromo-3-methoxybenzene (50 mg, 0.26 mmol) was reacted with (3-fluorophenyl)boronic acid (44 mg, 0.32 mmol) according to the general procedure A to provide the product (59 mg, 96%) as yellow oil. **¹H NMR (400 MHz, CDCl₃):** δ = 7.58 (d, *J* = 7.7 Hz, 1H), 7.51-7.49 (m 1H), 7.48-7.43 (m, 1H), 7.41-7.37 (m, 1H), 7.35 (s, 1H), 7.33 (s, 1H), 7.32-7.27 (m, 1H), 7.15 (dd, *J* = 8.1, 3.7 Hz, 1H), 3.86 (s, 3H). **¹³C NMR (101 MHz, CDCl₃):** δ = 195.2 (d, *J* = 2.3Hz), 162.6 (d, *J* = 248.2 Hz), 159.8, 139.8 (d, *J* = 6.4 Hz), 138.5, 130.1 (d, *J* = 7.7 Hz), 129.5, 125.9 (d, *J* = 3.2 Hz), 122.9, 119.6 (d, *J* = 21.3 Hz), 119.3, 116.9 (d, *J* = 22.6 Hz), 114.4, 55.6. **HRMS (ESI):** Calcd. for $C_{14}H_{11}O_2FNa$ [M+Na]⁺ 253.0635; found 253.0637.
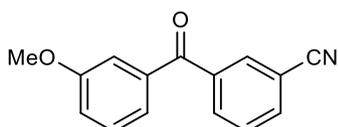

3-(3-Methoxybenzoyl)benzonitrile, 3g.[8] 1-Bromo-3-methoxybenzene (50 mg, 0.26 mmol) was reacted with (3-cyanophenyl)boronic acid (47 mg, 0.32 mmol) according to the general procedure A to provide the product (45 mg, 71%) as yellow oil. **¹H NMR (400 MHz, CDCl₃):** δ = 8.06 (s, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.32 (s, 1H), 7.28-7.25 (m, 1H), 7.18-7.15 (m, 1H), 3.86 (s, 3H). **¹³C NMR (101 MHz, CDCl₃):** δ = 194.3, 159.9, 138.8, 137.7, 135.4, 133.9, 133.5, 129.7, 129.5, 122.8, 119.7, 118.0, 114.4, 112.9, 55.6. **HRMS (ESI):** Calcd. for $C_{15}H_{12}NO_2$ [M+H]⁺ 238.0863; found 238.0882.
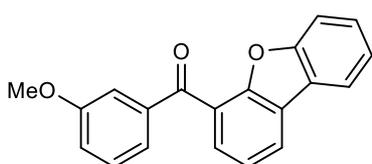
Dibenzo[b,d]furan-4-yl(3-methoxyphenyl)methanone, 3h. 1-Bromo-3-methoxybenzene (50 mg, 0.26 mmol) was reacted with dibenzo[*b,d*]furan-4-ylboronic acid (68 mg, 0.32 mmol) according to the general procedure A to provide the product (76 mg, 95%) as orange oil. **¹H NMR (400 MHz, CDCl₃):** δ = 8.15 (d, *J* = 8.8 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.52-7.51 (m, 1H), 7.49-7.45 (m, 1H), 7.44-7.43 (m, 1H), 7.42-7.41 (m, 1H), 7.40-7.35 (m, 2H), 7.18-7.16 (m, 1H), 3.86 (s, 3H). **¹³C NMR (101 MHz, CDCl₃):** δ = 193.8, 159.8, 156.5, 154.0, 139.1, 129.4, 128.7, 127.9, 125.7, 124.2, 123.5, 123.4, 123.3, 122.5, 120.8, 119.9, 114.2, 112.3, 55.6. **IR (ATR, cm⁻¹)** ν = 2959 (s), 2929 (s), 1873 (m), 1719 (s), 1614 (w), 1462 (w), 1369 (s), 1294 (s), 1261 (s), 1171 (s), 1123 (s), 780 (s). **HRMS (ESI):** Calcd. for $C_{20}H_{14}O_3Na$ [M+Na]⁺ 325.0835; found 325.0840.
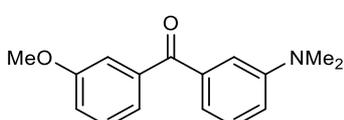
(3-(Dimethylamino)phenyl)(3-methoxyphenyl)methanone, 3i. 1-Bromo-3-methoxybenzene (50 mg, 0.26 mmol) was reacted with 3-((dimethylamino)phenyl)boronic acid (53 mg, 0.32 mmol) according to the

general procedure A to provide the product (56 mg, 82%) as yellow oil. **¹H NMR (400 MHz, CDCl₃):** δ = 7.30-7.27 (m, 3H), 7.24-7.14 (m, 1H), 7.09-7.08 (m, 1H), 7.04-6.99 (m, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.85-7.83 (m, 1H), 3.76 (s, 3H), 2.90 (s, 6H). **¹³C NMR (101 MHz, CDCl₃):** δ = 197.6, 159.7, 150.8, 139.7, 138.7, 129.5, 129.1, 123.3, 119.1, 119.1, 116.8, 114.8, 113.6, 55.9, 40.9. **HRMS (ESI):** Calcd. for $C_{16}H_{17}O_2NNa$ [M+Na]⁺ 278.1151; found 278.1156.
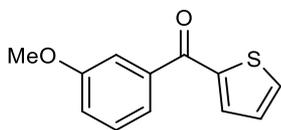
(3-Methoxyphenyl)(thiophen-3-yl)methanone, 3j.[9] 1-Bromo-3-methoxybenzene (50 mg, 0.26 mmol) was reacted with thiophen-2-ylboronic acid (41 mg, 0.32 mmol) according to the general procedure A to provide the product (45 mg, 77%) as orange oil. **¹H NMR (400 MHz, CDCl₃):** δ = 7.72 (d, J = 6.1 Hz, 1H), 7.67 (d, J = 4.9 Hz, 1H), 7.47-7.41 (m, 1H), 7.40-7.38 (m, 2H), 7.17-7.15 (m, 1H), 7.14-7.12 (m, 1H), 3.87 (s, 3H). **¹³C NMR (101 MHz, CDCl₃):** δ = 188.1, 159.7, 143.7, 139.6, 135.0, 134.4, 129.5, 128.1, 121.9, 118.8, 113.9, 55.6. **HRMS (ESI):** Calcd. for $C_{12}H_{10}O_2NaS$ [M+Na]⁺ 241.0294; found 241.0295.
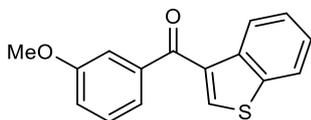
Benzo[b]thiophen-3-yl(3-methoxyphenyl)methanone, 3k. 1-Bromo-3-methoxybenzene (50 mg, 0.26 mmol) was reacted with benzo[b]thiophen-3-ylboronic acid (57 mg, 0.32 mmol) according to the general procedure A to provide the product (47 mg, 80%) as orange oil. **¹H NMR (400 MHz, CDCl₃):** δ 8.58 (d, J = 8.2 Hz, 1H), 8.02 (s, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.52 (t, J = 8.2 Hz, 1H), 7.47-7.43 (m, 1H), 7.40-7.42 (m, 2H), 7.17- 7.15 (m, 1H), 7.14-7.12 (m, 1H), 3.87 (s, 3H). **¹³C NMR (101 MHz, CDCl₃):** δ = 190.6, 159.8, 140.7, 140.1, 138.4, 137.5, 134.8, 129.5, 125.8, 125.7, 125.3, 122.4, 122.3, 118.8, 114.0, 55.6. **HRMS (ESI):** Calcd. for $C_{16}H_{12}O_2NaS$ [M+Na]⁺ 291.0450; found 291.0453.
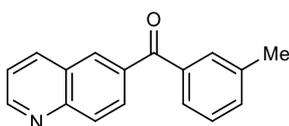
Quinolin-6-yl(m-tolyl)methanone, 3l. 6-Bromoquinoline (50 mg, 0.24 mmol) was reacted with m-tolylboronic acid (39 mg, 0.29 mmol) according to the general procedure A to provide the product (54 mg, 91%) as yellow oil. **¹H NMR (400 MHz, CDCl₃):** δ = 9.02 (d, J = 5.9 Hz, 1H), 8.25 (s, 1H), 8.22-8.21 (m, 1H), 8.19 (s, 1H), 8.15-8.13 (m, 1H), 7.67 (s, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.48 (dd, J = 8.3, 4.2 Hz, 1H), 7.41 (dt, J = 14.9, 7.6 Hz, 2H), 2.43 (s, 3H). **¹³C NMR (101 MHz, CDCl₃):** δ = 196.4, 152.6, 149.9, 138.5, 137.6, 137.5, 135.8, 133.6, 131.4, 130.6, 129.9, 129.7, 128.4, 127.5, 127.4, 122.1, 21.5. **HRMS (ESI):** Calcd. for $C_{17}H_{13}ONNa$ [M+Na]⁺ 270.0889; found 270.0893.
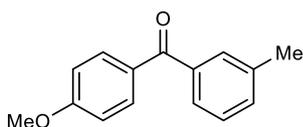
(4-Methoxyphenyl)(m-tolyl)methanone, 3m.[4] 1-Bromo-4-methoxybenzene (50 mg, 0.28 mmol) was reacted with m-tolylboronic acid (44 mg, 0.32 mmol) according to the general procedure A to provide the product (45 mg, 75%) as yellow oil. **¹H NMR (400 MHz, CDCl₃):** δ = 7.83 (d, J = 8.9 Hz, 2H), 7.58 (s, 1H), 7.53 (d, J = 7.0 Hz, 1H), 7.39-7.33 (m, 2H), 6.96 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H), 2.42 (s, 3H). **¹³C NMR (101 MHz, CDCl₃):** δ = 195.9, 163.3, 138.5, 138.2, 132.8, 132.7, 130.4, 130.3, 128.1, 127.1, 113.6, 55.6, 21.5. **HRMS (ESI):** Calcd. for $C_{15}H_{14}O_2Na$ [M+Na]⁺ 249.0886; found 249.0890.
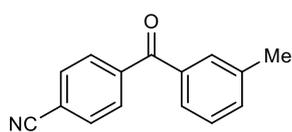
4-(3-Methylbenzoyl)benzonitrile, 3n.[10] 4-Bromobenzonitrile (50 mg, 0.27 mmol) was reacted with *m*-tolylboronic acid (45 mg, 0.33 mmol) according to the general procedure A to provide the product (50 mg, 83%) as white solid. Mp 118-121 °C. **^{1}H NMR (400 MHz, CDCl3):** δ = 7.86 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.60 (s, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.40-7.37 (m, 1H), 2.43 (s, 3H). **^{13}C NMR (101 MHz, CDCl3):** δ = 195.4, 141.5, 138.7, 136.5, 134.2, 132.3, 130.3, 128.6, 127.5, 118.2, 115.7, 21.5. **HRMS (ESI):** Calcd. for $C_{15}H_{12}ON$ [M+H]+ 222.0913; found 222.0914.
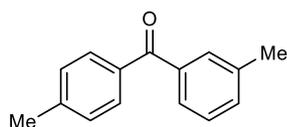
*m-Tolyl(p-tolyl)methanone, 3o.*[11] 1-Bromo-4-methylbenzene (50 mg, 0.29 mmol) was reacted with *m*-tolylboronic acid (48 mg, 0.35 mmol) according to the general procedure A to provide the product (48 mg, 79%) as yellow oil. **^{1}H NMR (400 MHz, CDCl3):** δ = 7.65 (d, *J* = 8.0 Hz, 2H), 7.54 (s, 1H), 7.50-7.48 (m, 1H), 7.34-7.28 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 2.37 (s, 3H), 2.35 (s, 3H). **^{13}C NMR (101 MHz, CDCl3):** δ = 196.8, 143.2, 138.1, 138.1, 135.1, 133.0, 130.4, 130.4, 129.0, 128.1, 127.3, 21.7, 21.5. **HRMS (ESI):** Calcd. for $C_{15}H_{14}ONa$ [M+Na]+ 233.0937; found 233.0938.
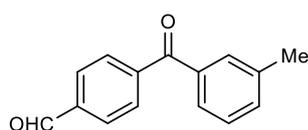
4-(3-Methylbenzoyl)benzaldehyde, 3p. 4-Bromobenzaldehyde (50 mg, 0.27 mmol) was reacted with *m*-tolylboronic acid (44 mg, 0.32 mmol) according to the general procedure A to provide the product (50 mg, 83%) as white solid. Mp 79-82 °C. **^{1}H NMR (400 MHz, CDCl3):** δ = 10.12 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 2H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.62 (s, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.39-7.35 (m, 1H), 2.42 (s, 3H). **^{13}C NMR (101 MHz, CDCl3):** δ = 196.1, 191.7, 142.8, 138.6, 136.9, 134.0, 130.4, 129.6, 128.4, 127.5, 21.5. **HRMS (ESI):** Calcd. for $C_{15}H_{13}O_2$ [M+H]+ 225.0910; found 225.0907.
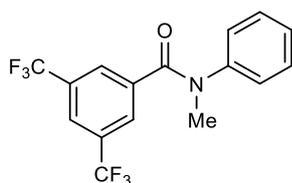
N-Methyl-N-phenyl-3,5-bis(trifluoromethyl)benzamide, 5a. 1-Bromo-3,5-bis(trifluoromethyl)benzene (50 mg, 29.5 µl, 0.17 mmol) was reacted with *N*-methyl aniline (28 µl, 0.26 mmol) according to the general procedure B to provide the product (30 mg, 51%) as white solid. Mp 85-88 °C. **^{1}H NMR (400 MHz, CDCl3):** δ = 7.73 (s, 3H), 7.30-7.27 (m, 2H), 7.24-7.20 (m, 1H), 7.04 (d, *J* = 7.4 Hz, 2H), 3.54 (s, 3H). **^{13}C NMR (101 MHz, CDCl3):** δ = 167.3, 143.9, 137.9, 131.3 (q, *J* = 33.6 Hz), 130.8, 129.9, 129.3, 127.8, 127.1, 124.3, 123.7-122.8 (m), 121.6, 118.9, 38.6. **HRMS (ESI):** Calcd. for $C_{16}H_{11}ONF_6Na$ [M+Na]+ 370.0637; found 370.0641.
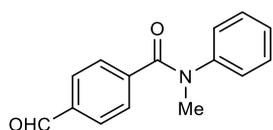
4-Formyl-N-methyl-N-phenylbenzamide, 5b.[12] 4-Bromobenzaldehyde (50 mg, 0.27 mmol) was reacted with *N*-methyl aniline (43 µl, 0.43 mmol) according to the general procedure B to provide the product (66 mg, 99%) as colourless oil. **^{1}H NMR (400 MHz, CDCl3):** δ = 9.90 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.22-7.18 (m, 2H), 7.15-7.12 (m, 1H), 7.02-7.00 (d, *J* = 7.5 Hz, 2H), 3.49 (s, 3H). **^{13}C NMR (101 MHz, CDCl3):** δ = 191.6, 169.4, 144.2, 141.8, 136.5, 129.4, 129.2, 129.1, 127.1, 127.0, 38.3. **HRMS (ESI):** Calcd. for $C_{15}H_{14}O_2N$ [M+H]+ 240.1019; found 240.1023.
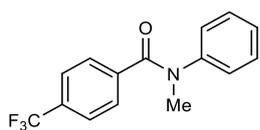
N-Methyl-N-phenyl-4-(trifluoromethyl)benzamide, 5c.[13] 4-Bromobenzotrifluoride (50 mg, 31.1 μl, 0.22 mmol) was reacted with *N*-methyl aniline (36 μl, 0.33 mmol) according to the general procedure B to provide the product (61 mg, 98%) as white solid. Mp 80-83 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.43-7.38 (m, 4H), 7.25-7.21 (m, 2H), 7.18-7.14 (m, 1H), 7.02 (d, *J* = 7.5 Hz, 2H), 3.50 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 169.2, 144.3, 139.6, 131.4 (q, *J* = 32.6 Hz), 129.5, 129.1, 127.8, 127.1, 127.0, 125.1, 124.9 (q, *J* = 3.8 Hz), 122.4, 119.7, 38.5. **HRMS (ESI):** Calcd. for C$_{15}$H$_{13}$ONF$_3$ [M+H]$^+$ 280.0944; found 280.0948.
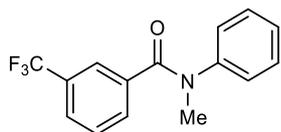
N-Methyl-N-phenyl-3-(trifluoromethyl)benzamide, 5d.[14] 3-Bromobenzotrifluoride (50 mg, 36 μl, 0.22 mmol) was reacted with *N*-methyl aniline (36 μl, 0.33 mmol) according to the general procedure B to provide the product (54 mg, 87%) as yellow oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.53 (s, 1H), 7.43 (t, *J* = 6.6 Hz, 2H), 7.24-7.22 (m, 1H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.15-7.12 (m, 1H), 7.00 (d, *J* = 7.6 Hz, 2H), 3.48 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 169.4, 144.4, 136.7, 132.0, 130.3 (q, *J* = 32.7 Hz), 129.8, 129.5, 128.4, 127.1, 127.0, 126.3 (q, *J* = 3.8 Hz), 125.9 (q, *J* = 3.8 Hz), 125.0, 122.3, 38.5. **HRMS (ESI):** Calcd. for C$_{15}$H$_{13}$ONF$_3$ [M+H]$^+$ 280.0944; found 280.0948.
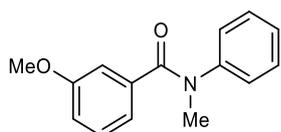
3-Methoxy-N-methyl-N-phenylbenzamide, 5e.[15] 1-Bromo-3-methoxybenzene (50 mg, 33.8 μ, 0.27 mmol) was reacted with *N*-methyl aniline (44 μl, 0.43 mmol) according to the general procedure B to provide the product (40 mg, 62%) as yellow oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.24-7.20 (m, 2H), 7.15-7.11 (m, 1H), 7.06-7.02 (m, 3H), 6.86 (s, 1H), 6.84-6.82 (m, 1H), 6.77-6.75 (m, 1H), 3.64 (s, 3H), 3.48 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 170.5, 159.0, 145.0, 137.2, 129.2, 128.8, 126.9, 126.6, 121.3, 116.1, 113.8, 55.3, 38.5. **HRMS (ESI):** Calcd. for C$_{15}$H$_{15}$O$_2$NNa [M+Na]$^+$ 264.0995; found 264.0997.
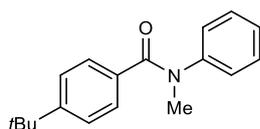
4-(tert-Butyl)-N-methyl-N-phenylbenzamide, 5f.[16] 1-Bromo-4-(*tert*-butyl)benzene (50 mg, 40.7 μl, 0.23 mmol) was reacted with *N*-methyl aniline (38 μl, 0.35 mmol) according to the general procedure B to provide the product (22 mg, 35%) as white solid. Mp 100-103 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.25-7.22 (m, 4H), 7.18 (s, 1H), 7.17-7.12 (m, 2H), 7.05 (d, *J* = 7.3 Hz, 2H), 3.49 (s, 3H), 1.22 (s, 9H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 170.7, 153.0, 145.3, 132.9, 129.2, 128.8, 127.0, 126.5, 124.7, 38.7, 34.8, 31.4, 31.2. **HRMS (ESI):** Calcd. for C$_{18}$H$_{21}$ONNa [M+Na]$^+$ 290.1515; found 290.1526.
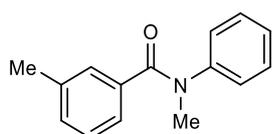
N,3-Dimethyl-N-phenylbenzamide, 5g.[17] 1-Bromo-3-methylbenzene (50 mg, 35.6 μl, 0.29 mmol) was reacted with *N*-methyl aniline (47 μl, 0.43 mmol) according to the general procedure B to provide the product (42 mg, 64%) as yellow oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.24-7.20 (m, 3H), 7.14-7.11 (m, 1H), 7.04-7.02 (m, 3H), 7.00-6.99 (m, 2H), 3.48 (s, 3H), 2.21 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 170.9, 145.1, 137.6, 135.9, 130.4, 129.5, 129.2, 127.5, 127.0, 126.5, 125.8, 38.5, 21.3. **HRMS (ESI):** Calcd. for C$_{15}$H$_{15}$ONNa [M+Na]$^+$ 248.1046; found 248.1050.
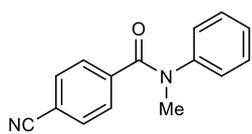
**4-Cyano-N-methyl-N-phenylbenzamide, 5h.**[18] 4-Bromobenzonitrile (50 mg, 0.27 mmol) was reacted with *N*-methyl aniline (45 µl, 0.43 mmol) according to the general procedure B to provide the product (63 mg, 97%) as colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.43 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.24-7.20 (m, 2H), 7.17-7.13 (m, 1H), 7.00-6.98 (d, *J* = 7.5 Hz, 2H), 3.47 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 168.3, 143.6, 140.0, 131.3, 129.2, 128.9, 126.9, 126.6, 117.8, 112.8, 38.0. **HRMS (ESI):** Calcd. for C$_{15}$H$_{13}$ON$_2$ [M+H]$^+$ 237.1022; found 237.1033.
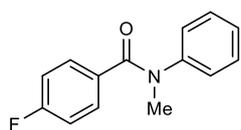
4-Fluoro-N-methyl-N-phenylbenzamide, 5i.[15] 1-Bromo-4-fluorobenzene (50 mg, 32 µl, 0.28 mmol) was reacted with *N*-methyl aniline (46.4 µl, 0.43 mmol) according to the general procedure B to provide the product (53 mg, 81%) as orange oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.32-7.30 (m, 2H), 7.28-7.22 (m, 2H), 7.18-7.15 (m, 1H), 7.03-7.02 (m, 2H), 6.84 (t, *J* = 8.7 Hz, 2H), 3.49 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 169.7, 163.3 (d, *J* = 250.2 Hz), 145.0, 132.0, 132.0, 131.2 (d, *J* = 8.6 Hz), 129.4, 127.0, 126.8, 114.9 (d, *J* = 21.8 Hz), 38.6. **HRMS (ESI):** Calcd. for C$_{14}$H$_{12}$ONFNa [M+Na]$^+$ 252.0795; found 252.0798.
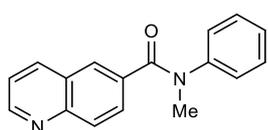
N-Methyl-N-phenylquinoline-6-carboxamide, 5j.[19] 6-Bromo-quinoline (50 mg, 32.5 µl, 0.24 mmol) was reacted with *N*-methyl aniline (39 µl, 0.35 mmol) according to the general procedure B to provide the product (41mg, 65%) as colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 8.88 (d, *J* = 5.9 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 7.88 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.36 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.22-7.18 (m, 2H), 7.13-7.12 (m, 1H), 7.08-7.06 (m, 2H), 3.56 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 169.9, 151.6, 148.3, 144.7, 136.8, 134.3, 129.5, 129.3, 129.3, 128.9, 127.5, 127.1, 126.9, 121.7, 38.7. **HRMS (ESI):** Calcd. for C$_{17}$H$_{14}$ON$_2$Na [M+Na]$^+$ 285.0998; found 285.1004.
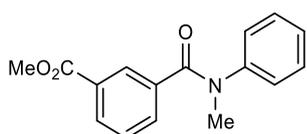
Methyl 3-(methyl(phenyl)carbamoyl)benzoate, 5k. Methyl 3-bromobenzoate (50 mg, 0.23 mmol) was reacted with *N*-methyl aniline (38 µl, 0.35 mmol) according to the general procedure B to provide the product (52 mg, 83%) as colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 8.00 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.22-7.18 (m, 2H), 7.15-7.11 (m, 2H), 7.03 (d, *J* = 7.4 Hz, 2H), 3.83 (s, 3H), 3.49 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 169.7, 166.3, 144.6, 136.4, 132.9, 130.7, 130.1, 129.9, 129.4, 128.0, 127.1, 126.9, 52.3, 38.5. **HRMS (ESI):** Calcd. for C$_{16}$H$_{15}$O$_3$NNa [M+Na]$^+$ 292.0944; found 292.0949.
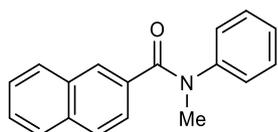
N-Methyl-N-phenyl-2-naphthamide, 5l.[17] 2-Bromonaphthalene (50 mg, 0.24 mmol) was reacted with *N*-methyl aniline (40 µl, 0.40 mmol) according to the general procedure B to provide the product (64 mg, 99%) as colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.91 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.47-7.40 (m, 2H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.21-7.17 (m, 2H), 7.12-7.07 (m, 3H), 3.56 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 170.3, 144.7, 133.3, 133.0, 132.1, 129.2, 129.0, 128.4, 127.3, 127.0, 126.9, 126.6, 126.2, 126.0, 125.2, 38.3. **HRMS (ESI):** Calcd. for C$_{18}$H$_{15}$ONNa [M+Na]$^+$ 284.1046; found 284.1051.
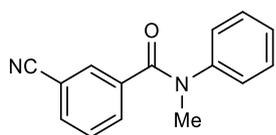
3-Cyano-N-methyl-N-phenylbenzamide, 5m. 3-Bromobenzonitrile (50 mg, 0.27 mmol) was reacted with *N*-methyl aniline (45 µl, 0.43 mmol) according to the general procedure B to provide the product (61 mg, 94%) as white solid. Mp 72-75 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.54 (s, 1H), 7.48-7.45 (m, 2H), 7.24-7.20 (m, 3H), 7.17-7.15 (m, 1H), 6.99 (d, *J* = 7.6 Hz, 2H), 3.46 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 168.2, 144.0, 137.3, 133.0, 132.9, 132.4, 129.6, 128.8, 127.4, 127.0, 118.1, 112.2, 38.5. **HRMS (ESI):** Calcd. for C$_{15}$H$_{13}$ON$_2$ [M+H]$^+$ 237.1022; found 237.1033.
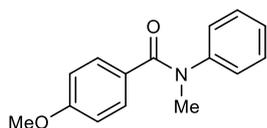
4-Methoxy-N-methyl-N-phenylbenzamide, 5n.[13] 1-Bromo-4-methoxybenzene (50 mg, 33.5 µl, 0.27 mmol) was reacted with *N*-methyl aniline (44 µl, 0.43 mmol) according to the general procedure B to provide the product (10 mg, 16%) as yellow oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.27-7.23 (m, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.64 (d, *J* = 8.9 Hz, 2H), 3.72 (s, 3H), 3.47 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 170.4, 160.7, 145.6, 131.0, 129.3, 128.1, 127.0, 126.4, 113.1, 55.3, 38.8. **HRMS (ESI):** Calcd. for C$_{15}$H$_{15}$O$_2$NNa [M+Na]$^+$ 264.0995; found 264.0997.
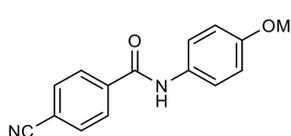
4-Cyano-N-(4-methoxyphenyl)benzamide, 5o.[20] 4-Bromobenzonitrile (50 mg, 0.27 mmol) was reacted with *p*-anisidine (50 mg, 0.41 mmol) according to the general procedure B to provide the product (60 mg, 87%) as white solid. Mp 157-160 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.96 (d, *J* = 8.4 Hz, 2H), 7.78-7.76 (m, 3H), 7.52 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 163.9, 157.2, 139.1, 132.7, 130.4, 127.9, 122.4, 118.1, 114.5, 55.7. **HRMS (ESI):** Calcd. for C$_{15}$H$_{12}$O$_2$N$_2$Na [M+Na]$^+$ 275.0791; found 275.0795.
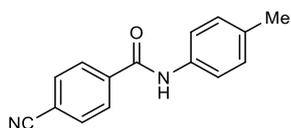
4-Cyano-N-(p-tolyl)benzamide, 5p.[21] 4-Bromobenzonitrile (50 mg, 0.27 mmol) was reacted with *p*-toluidine (44 mg, 0.41 mmol) according to the general procedure B to provide the product (60 mg, 90%) as white solid. Mp 178-180 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.96 (d, *J* = 8.2 Hz, 2H), 7.81 (bs, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 2.35 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 162.3, 139.1, 135.2, 134.8, 132.7, 129.9, 127.9, 120.6, 118.1, 115.5, 21.1. **HRMS (ESI):** Calcd. for C$_{15}$H$_{12}$ON$_2$ [M+Na]$^+$ 237.1022; found 237.1024.
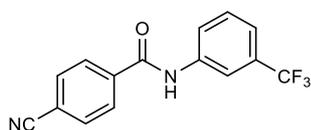
4-Cyano-N-(3-(trifluoromethyl)phenyl)benzamide, 5q. 4-Bromobenzonitrile (50 mg, 0.27 mmol) was reacted with 3-(trifluoromethyl)aniline (51.4 µl, 0.41 mmol) according to the general procedure B to provide the product (68 mg, 85%) as white solid. Mp 166-168 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 8.01 (m, 3H), 7.93 (s, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.47-7.44 (m, 1H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 164.2, 138.4, 137.9, 132.9, 131.8 (d, *J* = 32.7 Hz), 130.0, 127.9, 123.6, 121.9 (d, *J* = 3.7 Hz), 117.9, 117.3 (d, *J* = 4.0 Hz), 115.9. **HRMS (ESI):** Calcd. for C$_{15}$H$_8$OF$_3$N$_2$ [M-H]$^-$ 289.0594; found 289.0587.
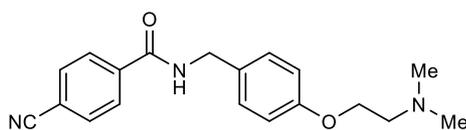
4-Cyano-N-(4-(2-(dimethylamino)ethoxy)benzyl)benzamide, 5r. 4-Bromobenzonitrile (50 mg, 0.27 mmol) was reacted with 2-(4-(aminomethyl)phenoxy)-*N,N*-dimethylethan-1-amine (80 mg, 0.41 mmol) according to the general procedure B to provide the product (80 mg, 90%) as white solid. Mp 109-112 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.87 (d, *J* = 8.5 Hz, 2H), 7.72-7.25 (d, *J* = 8.5 Hz, 2H), 7.25 (m, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.45 (bs, 1H), 4.57 (d, *J* = 5.5 Hz, 2H), 4.08 (t, *J* = 5.6 Hz, 2H), 2.78 (t, *J* = 5.6 Hz, 2H), 2.38 (s, 6H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 165.6, 158.6, 138.5, 132.6, 129.9, 129.5, 127.8, 118.1, 115.3, 115.1, 66.0, 58.2, 45.9, 44.1. **HRMS (ESI):** Calcd. for C$_{19}$H$_{22}$O$_2$N$_3$ [M+H]$^+$ 324.1707; found 324.1714.
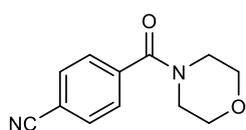
4-(Morpholine-4-carbonyl)benzonitrile, 5s.[22] 4-Bromobenzonitrile (50 mg, 0.27 mmol) was reacted with morpholine (36 µl, 0.41 mmol) according to the general procedure B to provide the product (55 mg, 93%) as white solid. Mp 143-145.6 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.70 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 3.75-3.60 (m, 6H), 3.41-3.35 (m, 2H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 165.8, 138.3, 137.7, 132.5, 128.9, 127.9, 127.9, 127.8, 118.1, 115.1, 44.3. **HRMS (ESI):** Calcd. for C$_{12}$H$_{12}$O$_2$N$_2$Na [M+Na]$^+$ 239.0791; found 239.0809.
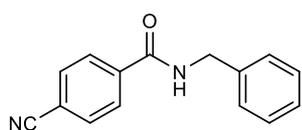
N-Benzyl-4-cyanobenzamide, 5t.[23] 4-Bromobenzonitrile (50 mg, 0.27 mmol) was reacted with phenylmethanamine (45 µl, 0.41 mmol) according to the general procedure B to provide the product (61 mg, 94%) as white solid. Mp 148-150 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.85 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.36-7.27 (m, 5H), 6.93 (bs, 1H), 4.59 (d, *J* = 5.7 Hz, 2H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 165.8, 138.3, 137.7, 132.5, 128.9, 127.9, 127.9, 127.8, 118.1, 115.1, 44.3. **HRMS (ESI):** Calcd. for C$_{15}$H$_{12}$ON$_2$Na [M+Na]$^+$ 259.0842; found 259.0841.
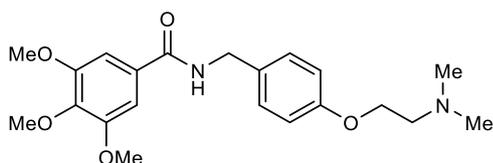
N-(4-(2-(Dimethylamino)ethoxy)benzyl)-3,4,5-trimethoxybenzamide, 5u. 5-Bromo-1,2,3-trimethoxybenzene (50 mg, 0.20 mmol) was reacted with 2-(4-(aminomethyl)phenoxy)-*N,N*-dimethylethan-1-amine (78 mg, 0.40 mmol) and XantPhos Pd G3 (38 mg, 2 mol%) according to the general procedure B to provide the product (75 mg, 95%) as white solid. Mp 105-108 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.22 (d, *J* = 8.6 Hz, 2H), 7.04 (s, 2H), 6.89 (bs, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.49 (d, *J* = 5.7 Hz, 2H), 4.07 (t, *J* = 5.5 Hz, 2H), 3.82 (s, 9H), 2.82 (t, *J* = 5.5 Hz, 2H), 2.39 (s, 6H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 167.0, 158.0, 153.1, 140.8, 130.9, 129.9, 129.3, 114.7, 104.6, 65.4, 60.9, 58.0, 56.6, 45.5, 43.6. **HRMS (ESI):** Calcd. for C$_{21}$H$_{29}$O$_5$N$_2$ [M+H]$^+$ 389.2071; found 389.2080.
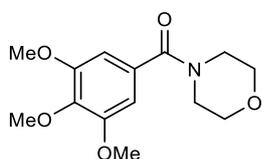
Morpholino(3,4,5-trimethoxyphenyl)methanone, 5v.[24] 5-Bromo-1,2,3-trimethoxybenzene (50 mg, 0.20 mmol) was reacted with morpholine (36 µl, 0.40 mmol) and XantPhos Pd G3 (38 mg, 2 mol%) according to the general procedure B to provide the product (55 mg, 96%) as white solid. Mp 116-118 °C. **^{1}H NMR (400 MHz,**

CDCl₃): δ = 6.59 (s, 2H), 3.84-3.82 (m, 10H), 3.65 (bs, 7H). **¹³C NMR (101 MHz, CDCl₃):** δ = 170.5, 153.7, 139.7, 131.0, 104.7, 67.3, 61.3, 56.6. **HRMS (ESI):** Calcd. for $C_{14}H_{19}O_5NNa$ [M+Na]⁺ 304.1155; found 304.1165.
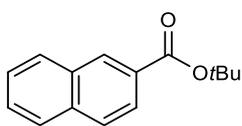
***tert*-Butyl 2-naphthoate, 7a.**[25] 2-Bromonaphthalen (50 mg, 0.24 mmol) was reacted with *t*BuONa (34 mg, 0.35 mmol) according to the general procedure C to provide the product (51 mg, 93%) as yellow oil. **¹H NMR (400 MHz, CDCl₃):** δ = 8.56 (s, 1H), 8.06-8.03 (m, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.87-7.85 (m, 2H), 7.62-7.47 (m, 2H), 1.67 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ = 166.0, 135.4, 132.6, 130.8, 129.4, 128.0, 128.0, 127.8, 126.6, 125.5, 81.2, 28.4. **HRMS (ESI):** Calcd. for $C_{15}H_{16}O_2Na$ [M+Na]⁺ 251.1043; found 251.1044.
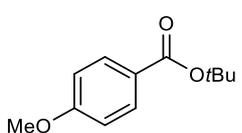
***tert*-Butyl 4-methoxybenzoate, 7b.**[25] 1-Bromo-4-methoxybenzene (50 mg, 33.5 μl, 0.27 mmol) was reacted with *t*BuONa (39 mg, 0.36 mmol) according to the general procedure C to provide the product (54 mg ,98%) as colourless oil. **¹H NMR (400 MHz, CDCl₃):** δ = 7.94 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 1.58 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ = 165.7, 163.1, 131.5, 124.6, 113.5, 80.6, 55.5, 28.4. **HRMS (ESI):** Calcd. for $C_{12}H_{16}O_3Na$ [M+Na]⁺ 231.0992; found 231.0988.
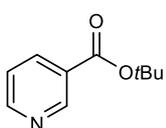
***tert*-Butyl nicotinate, 7c.**[25] 3-Bromopyridine (50mg, 30.5 μl, 0.32 mmol) was reacted with *t*BuONa (46 mg, 0.48 mmol) according to the general procedure C to provide the product (29 mg, 52%) as yellow oil. **¹H NMR (400 MHz, CDCl₃):** δ = 9.15 (s, 1H), 8.73-8.72 (m, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 7.45-7.30 (m, 1H), 1.59 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ = 164.5, 153.0, 151.0, 137.0, 127.9, 123.3, 82.2, 28.3. **HRMS (ESI):** Calcd. for $C_{10}H_{14}O_2N$ [M+H]⁺ 180.1019; found 180.1014.
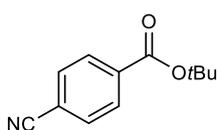
***tert*-Butyl 4-cyanobenzoate, 7d.**[25] 1-Bromo-4-benzonitrile (50mg, 0.27 mmol) was reacted with *t*BuONa (40 mg, 0.48 mmol) according to the general procedure C to provide the product (25 mg, 45%) as colourless oil. **¹H NMR (400 MHz, CDCl₃):** δ = 8.07 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 1.60 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ = 164.4, 136.3, 132.5, 130.4, 118.6, 116.3, 82.8, 28.5. **HRMS (ESI):** Calcd. for $C_{12}H_{13}O_2NNa$ [M+Na]⁺ 226.0838; found 226.0855.
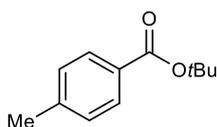
***tert*-Butyl 4-methylbenzoate, 7e.**[26] 1-Bromo-4-methylbenzene (50mg, 0.27 mmol) was reacted with *t*BuONa (42 mg, 0.43 mmol) according to the general procedure C to provide the product (50 mg, 80%) as yellow oil. **¹H NMR (101 MHz, CDCl₃):** δ = 7.88 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 2.39 (s, 3H), 1.59 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ = 166.3, 143.3, 129.9, 129.3, 81.1, 28.7, 22.0. **HRMS (ESI):** Calcd. for $C_{12}H_{16}O_2Na$ [M+Na]⁺ 215.1043; found 215.1038.
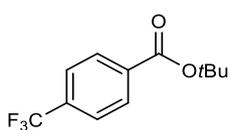
***tert*-butyl 4-(trifluoromethyl)benzoate, 7f.**[25] 4-Bromobenzotrifluoride (50 mg, 31.1 µl, 0.22 mmol) was reacted with tBuONa (40 mg, 0.48 mmol) according to the general procedure C to provide the product (28 mg, 51%) as yellow oil. **¹H NMR (101 MHz, CDCl₃):** δ 8.10 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H), 1.61 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ 164.6, 135.4, 134.1 (d, *J* = 32.5 Hz), 129.9, 125.8 − 124.5 (m), 82.1, 28.3. **HRMS (ESI):** Calcd. for $C_{12}H_{13}F_3O_2Na$ [M+Na]⁺ 269.0760; found 269.0756.
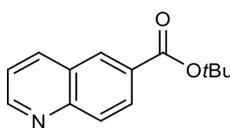
***tert*-Butyl quinoline-6-carboxylate, 7g.** 6-Bromoquinoline (50 mg, 0.24 mmol) was reacted with *t*BuONa (34 mg, 0.34 mmol) according to the general procedure C to provide the product (47 mg, 85%) as yellow oil. **¹H NMR (400 MHz, CDCl₃):** δ = 8.97-8.96 (m, 1H), 8.50 (s, 1H), 8.33-8.16 (m, 2H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 1.63 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ = 165.3, 152.3, 150.0, 137.4, 130.7, 130.1, 129.6, 129.2, 127.5, 121.8, 81.7, 28.3. **HRMS (ESI):** Calcd. for $C_{14}H_{15}O_2N$ [M+Na]⁺ 230.1176; found 230.1195.
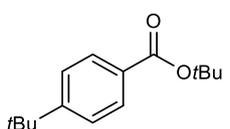
***tert*-Butyl 4-(tert-butyl)benzoate, 7h.**[25] 1-Bromo-4-(*tert*-butyl)benzene (50 mg, 0.23 mmol) was reacted with *t*BuONa (33 mg, 0.34 mmol) according to the general procedure C to provide the product (50 mg, 90%) as colourless oil. **¹H NMR (400 MHz, CDCl₃):** δ = 7.94 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 1.60 (s, 9H), 1.34 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ = 165.6, 155.8, 129.1, 124.9, 80.4, 34.8, 31.0, 28.0. **HRMS (ESI):** Calcd. for $C_{15}H_{22}O_2Na$ [M+Na]⁺ 257.1512; found 257.1537.
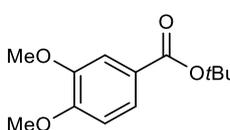
***tert*-Butyl 3,4-dimethoxybenzoate, 7i.**[25] 4-Bromo-1,2-dimethoxybenzene (50 mg, 0.23 mmol) was reacted with *t*BuONa (33 mg, 0.34 mmol) according to the general procedure C to provide the product (51 mg, 93%) as yellow oil. **¹H NMR (400 MHz, CDCl₃):** δ = 7.62-7.60 (m, 1H), 7.51-750 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 6H), 1.58 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ = 165.8, 152.7, 148.6, 124.7, 123.4, 112.0, 110.2, 80.8, 56.1, 28.4. **HRMS (ESI):** Calcd. for $C_{13}H_{18}O_4Na$ [M+Na]⁺ 261.1097; found 261.1095.
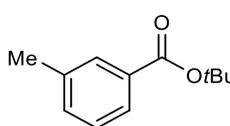
***tert*-Butyl 3-methylbenzoate, 7j.**[27] 1-Bromo-3-methylbenzene (50 mg, 35.6 µl, 0.27 mmol) was reacted with *t*BuONa (42 mg, 0.43 mmol) according to the general procedure C to provide the product (32 mg, 52%) as orange oil. **¹H NMR (400 MHz, CDCl₃):** δ = 7.80-7.78 (m, 2H), 7.34-7.28 (m, 2H), 2.39 (s, 3H), 1.60 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ = 166.1, 138.0, 133.3, 132.1, 130.1, 128.2, 126.7, 28.4, 21.4. **HRMS (ESI):** Calcd. for $C_{12}H_{16}O_2Na$ [M+Na]⁺ 215.1043; found 215.1037.
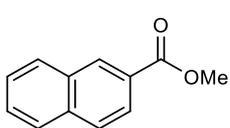
Methyl 2-naphthoate, 8a. 1-Bromo-4-methoxybenzene (50 mg, 33.5 µl, 0.27 mmol) was reacted with *t*BuONa (39 mg, 0.36 mmol) in dimethyl carbonate according to the general procedure C to provide the product (49 mg, 93%) as yellow oil. **¹H NMR (400 MHz, CDCl₃):** δ = 8.62 (s, 1H), 8.07 (d, *J* = 10.2 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.69-7.46 (m,

2H), 3.99 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 167.3, 135.6, 132.6, 131.2, 129.4, 128.3, 128.2, 127.9, 127.5, 126.7, 125.3, 52.3. **HRMS (ESI):** Calcd. for C$_{12}$H$_{10}$O$_2$Na [M+Na]$^+$ 209.0573; found 209.0566.
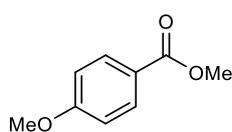
Methyl 4-methoxybenzoate, 8b.[28] 1-Bromo-4-methoxybenzene (50 mg, 33.5 μl, 0.27 mmol) was reacted with *t*BuONa (39 mg, 0.36 mmol) in dimethyl carbonate according to the general procedure C to provide the product (40 mg, 90%) as yellow oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.99 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 167.0, 163.4, 131.7, 122.7, 113.7, 55.5, 52.0. **HRMS (ESI):** Calcd. for C$_9$H$_{10}$O$_3$Na [M+H]$^+$ 167.0705; found 167.0717.
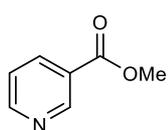
Methyl nicotinate, 8c.[29] 3-Bromopyridine (50 mg, 30.5 μl, 0.32 mmol) was reacted with *t*BuONa (46 mg, 0.48 mmol) in dimethyl carbonate according to the general procedure C to provide the product (25 mg, 58%) as orange oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 9.21 (s, 1H), 8.76 (s, 1H), 8.28 (d, *J* = 7.9 Hz, 1H), 7.38 (dd, *J* = 7.7, 4.9 Hz, 1H), 3.94 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 165.9, 153.5, 151.0, 137.1, 126.1, 123.4, 52.5. **HRMS (ESI):** Calcd. for C$_7$H$_8$O$_2$N [M+H]$^+$ 138.0550; found 138.0545.
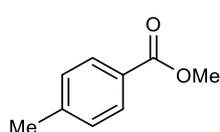
Methyl 4-methylbenzoate, 8d.[30] 1-Bromo-4-methylbenzene (50mg, 0.27 mmol) was reacted with *t*BuONa (42 mg, 0.43 mmol) in dimethyl carbonate according to the general procedure C to provide (35 mg, 80%) as colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.93 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 3.89 (s, 3H), 2.40 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 167.3, 143.7, 129.7, 129.2, 127.5, 52.0, 21.8. **HRMS (ESI):** Calcd. for C$_9$H$_{10}$O$_2$Na [M+H]$^+$ 151.0754; found 151.0757.
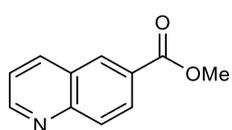
Methyl quinoline-6-carboxylate, 8e.[31] 6-Bromoquinoline (50 mg, 0.24 mmol) was reacted with *t*BuONa (34 mg, 0.34 mmol) in dimethyl carbonate according to the general procedure C to provide the product (42 mg, 93%) as white solid. Mp 80-82 °C. **^{1}H NMR (400 MHz, CDCl$_3$):** δ = 8.95-8.94 (m, 1H), 8.51 (s, 1H), 8.25-7.23 (m, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.10-8.08 (m, 1H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.94 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 166.6, 152.5, 150.1, 137.3, 131.0, 129.8, 128.9, 128.1, 127.4, 121.9, 52.5. **HRMS (ESI):** Calcd. for C$_{11}$H$_{10}$NO$_2$ [M+H]$^+$ 188.0706; found 188.0717.

9. References

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10.   Copies of spectra

Compound 3a
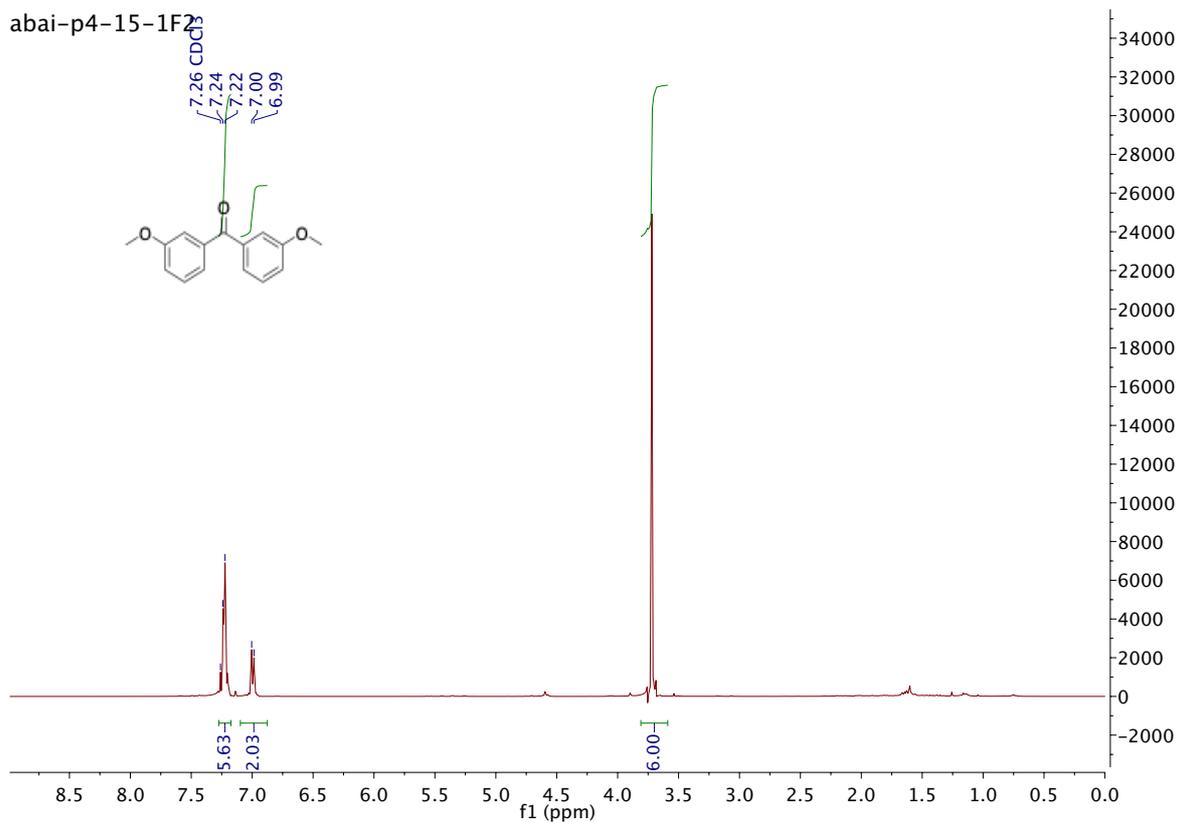
abai–p4–15–1F2

abai–p4–15–1F2

Compound 3b

7.92
7.89
7.52
7.50
7.48
7.45
7.43
7.41
7.28
7.19
7.17
7.15
7.13
7.06
7.04
6.98
6.97
6.96
6.95

3.70
3.50

13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000

1.00
1.31
1.28
2.00
1.15
1.00
1.03

3.06
3.00

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

196.88

166.45
159.85

141.78
138.59
132.47
131.21
130.14
129.71
129.57
128.95
128.84
127.84
122.54
119.84
112.98

77.16 CDCl3

55.51
52.31

7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

22

Compound 3c

7.63
7.59
7.57
7.40
7.38
7.37
7.37
7.35
7.34
7.32
7.26 CDCl3
7.11
7.11

3.85

−2.41

0.93
0.97
4.96
1.01

2.98

3.00

f1 (ppm)

−196.75

−159.62

139.13
138.20
137.72
133.27
130.49
129.24
128.13
127.41
122.91
118.83
114.37

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

−55.52

−21.43

f1 (ppm)

23

Compound 3d

abai-p4-15-6F2

7.46 7.45 7.43 7.41 7.39 7.38 7.36 7.35 7.34 7.33 7.32 7.30 7.29 7.27 7.17 7.16 7.15 7.14

0.93 1.21 1.27 1.83 0.73 0.97 0.94   3.06   3.00

f1 (ppm)

abai-p4-15-6F2

—198.48

—159.84

139.17 138.74 136.78 131.05 130.32 129.50 128.53 125.25 123.38 119.86 113.86

77.48 CDCl3 77.16 CDCl3 77.16 CDCl3 76.84 CDCl3

—55.54

f1 (ppm)
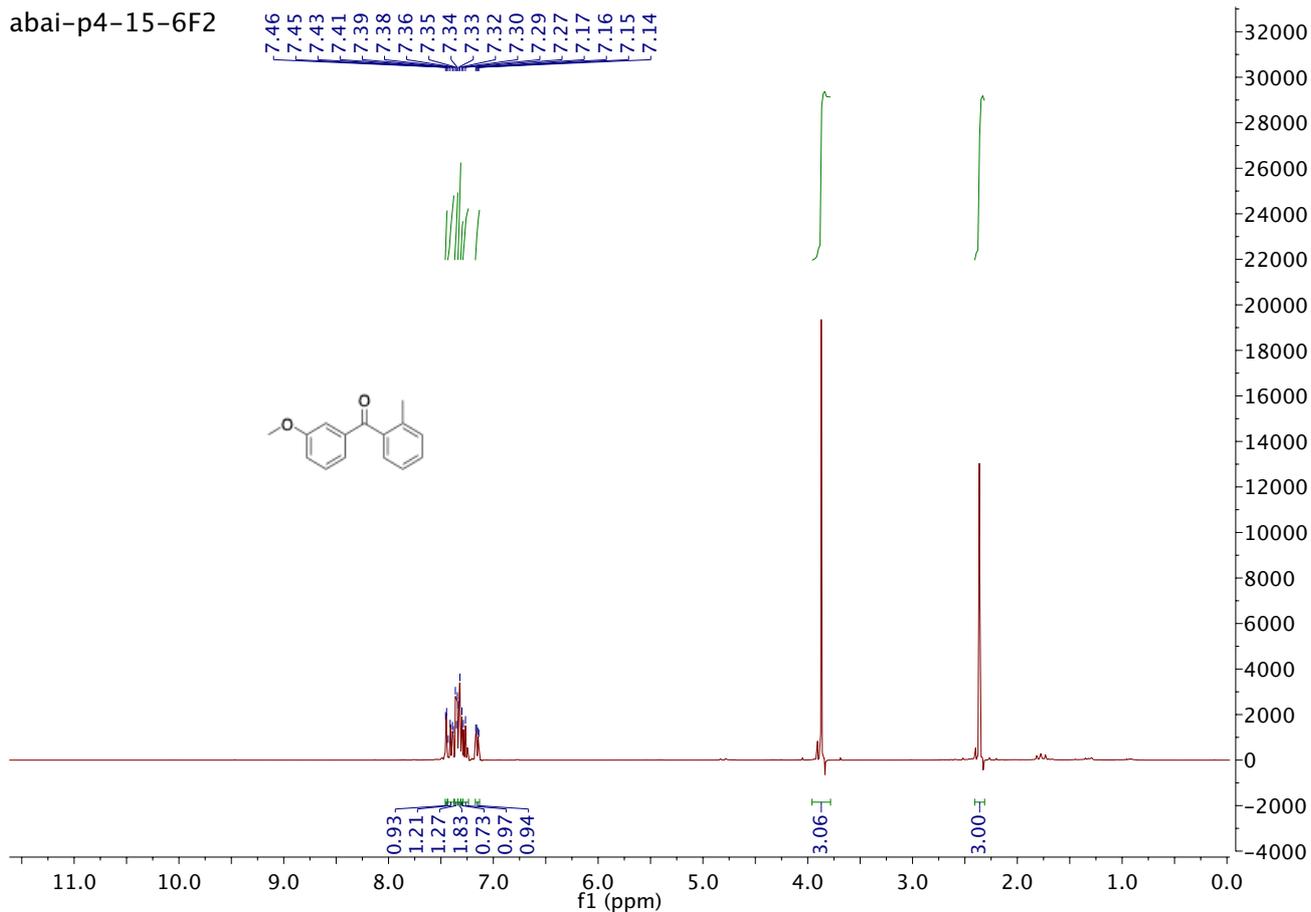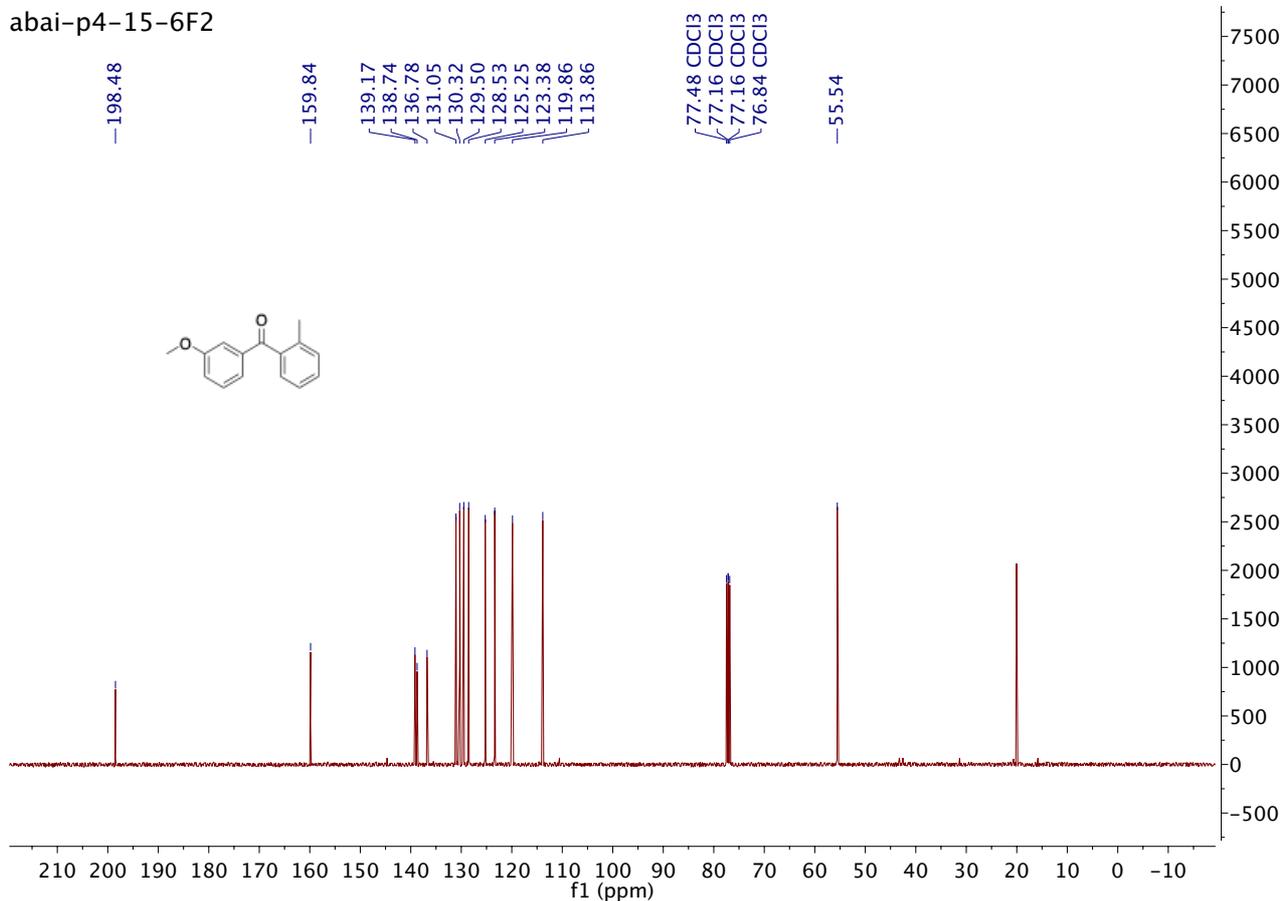
Compound 3e

abai-p4-15-8f2

8.29
7.95
7.93
7.91
7.90
7.63
7.61
7.59
7.57
7.55
7.53
7.43
7.42
7.26 CDCl3
7.19
7.18
7.18
7.17
7.17
7.16
7.16
7.15

3.87

0.95
1.77
2.07
1.01
1.01
2.92
0.98

3.00

f1 (ppm)

abai-p4-15-8f2

196.56

159.71
139.29
135.35
134.92
132.33
131.93
129.51
129.36
128.42
128.35
127.90
126.88
125.85
122.95
118.92
114.45

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

55.57

f1 (ppm)

25

Compound 3f

7.51
7.49
7.45
7.44
7.44
7.42
7.42
7.41
7.40
7.39
7.38
7.37
7.36
7.35
7.33
7.31
7.29
7.28
7.27
7.26 CDCl3
7.26
7.23
7.22
7.21
7.20
7.19
7.09
7.08
7.07
7.06

1.00
1.02
1.07
1.20
1.53
0.67
0.50
0.33
0.99

3.13

f1 (ppm)

195.16
195.14

163.80
161.34
159.77
139.83
139.76
138.42
130.09
130.01
129.46
125.92
125.89
122.89
119.64
119.42
119.29
116.94
116.72
114.41

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

55.60

f1 (ppm)

26

Compound 3g

27

Compound 3h

abai-p4-15-16f1

8.16
8.14
8.01
7.99
7.71
7.69
7.57
7.55
7.51
7.49
7.48
7.46
7.44
7.41
7.40
7.39
7.38
7.37
7.35
7.26 CDCl3
7.18
7.16

3.86

1.00
0.99
1.02
1.02
0.93
1.36
0.78
0.85
1.05
0.84
1.00

2.99

f1 (ppm)

abai-p4-15-16f1

193.84

159.81
156.53
153.98

139.09
129.44
128.73
127.91
125.72
124.23
123.45
123.40
123.29
122.51
120.78
119.91
114.15
112.30
77.48 CDCl3
77.36
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3
55.64

f1 (ppm)

Compound 3i

29
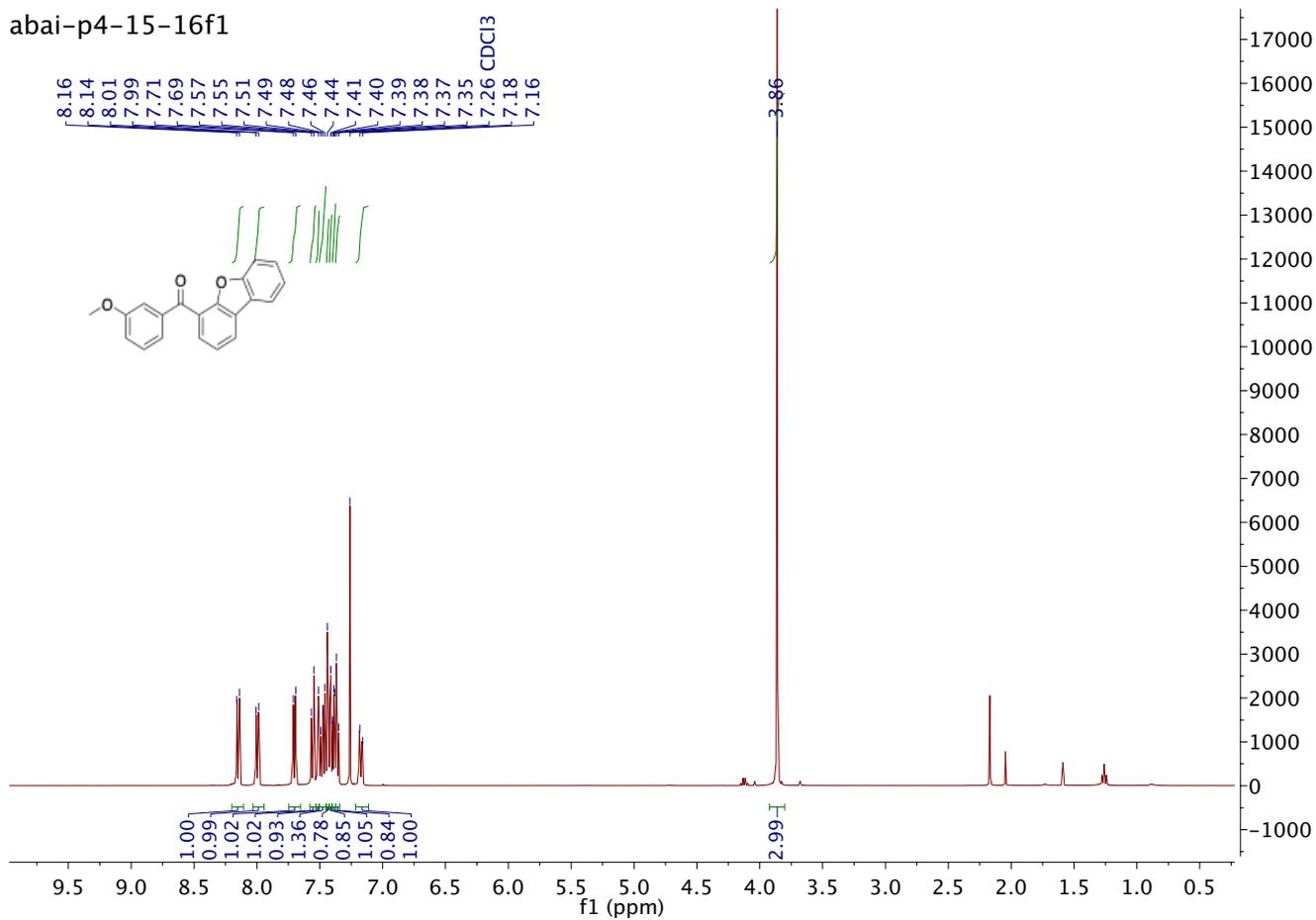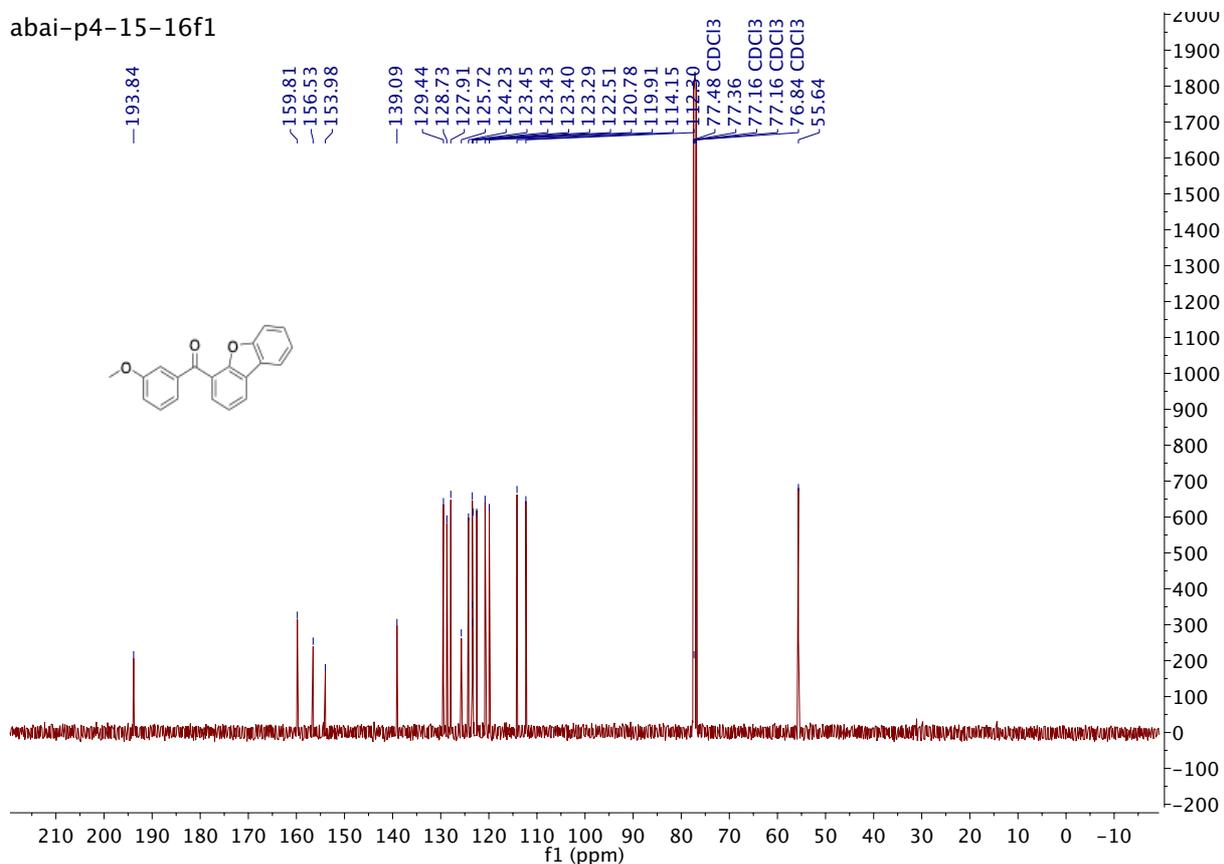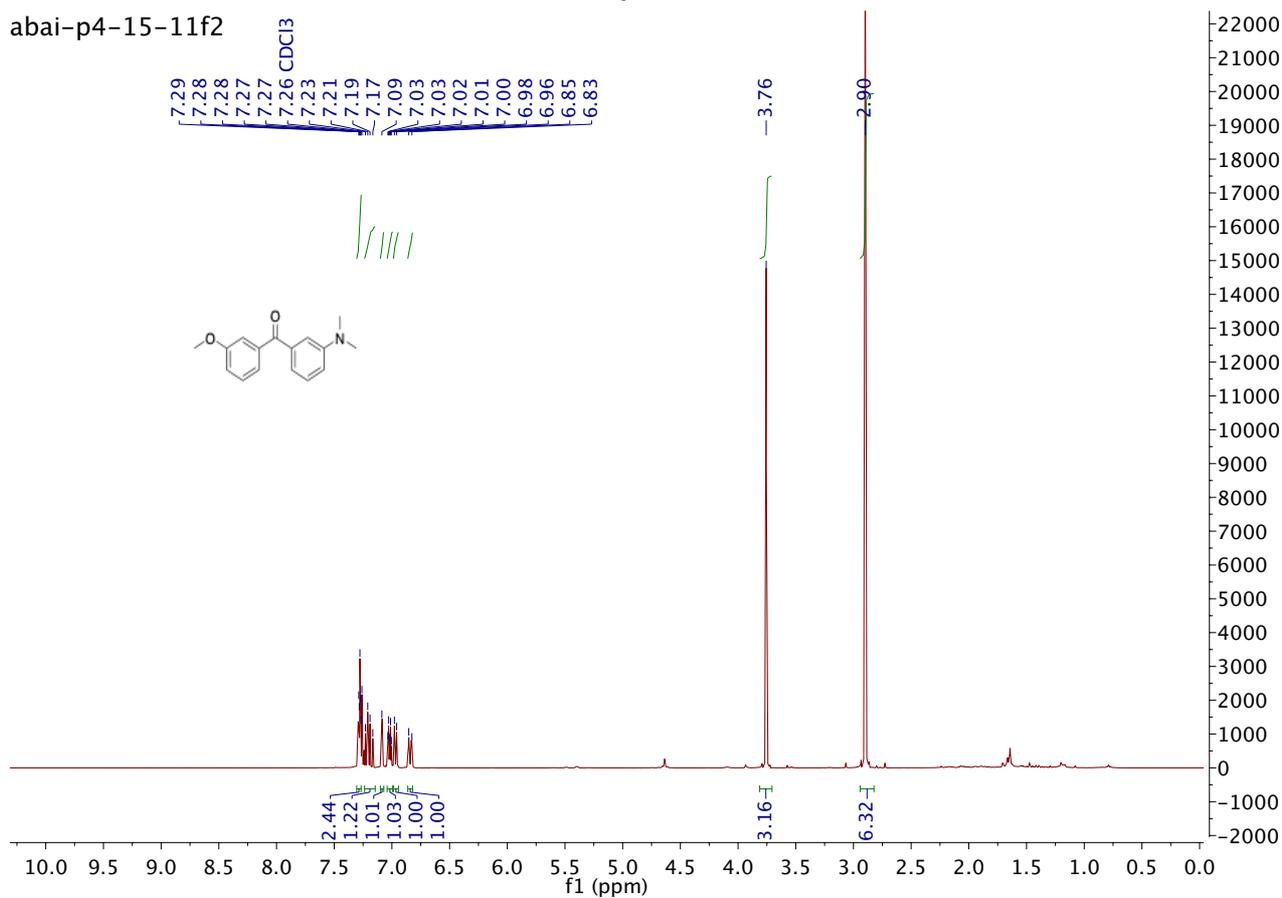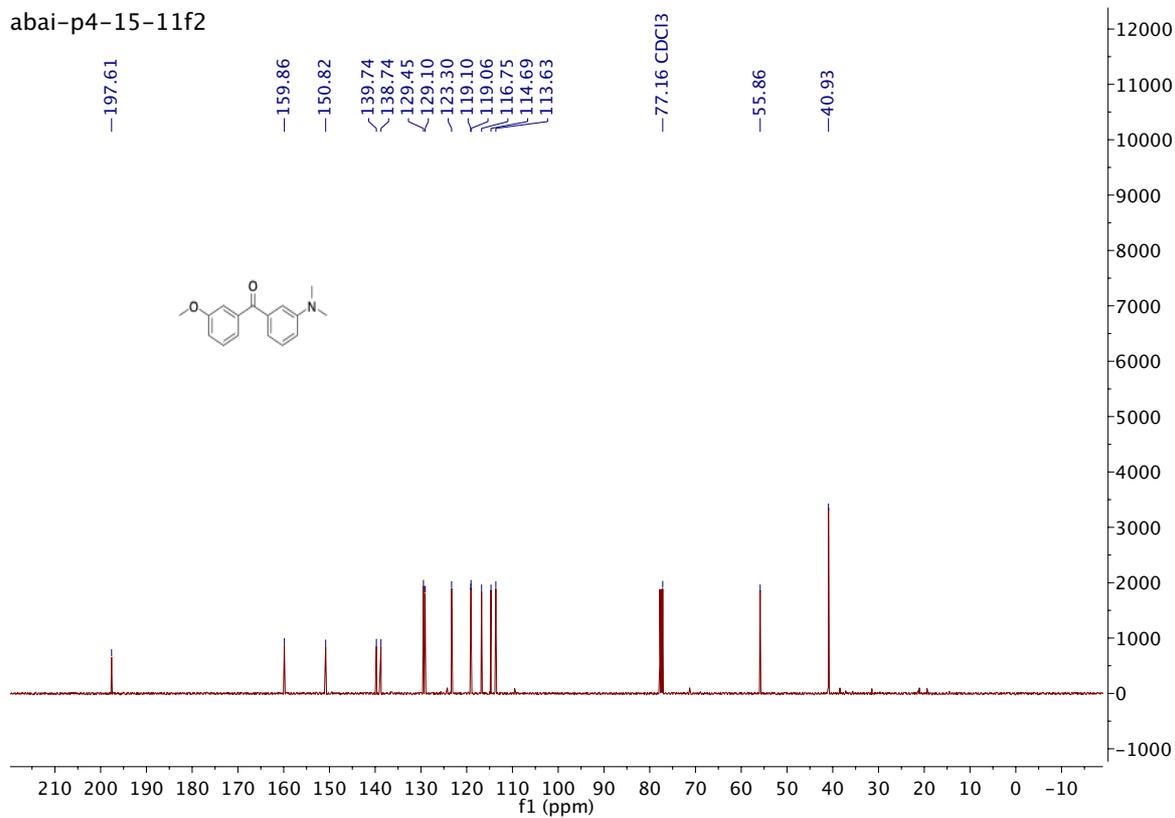
Compound 3j

abai–p4–15–9f1

7.73
7.71
7.68
7.67
7.44
7.42
7.40
7.38
7.26 CDCl3
7.26
7.16
7.15
7.12

3.87

0.98
0.95
0.93
0.77
1.08
0.98
0.90

3.00

f1 (ppm)

abai–p4–15–9f1

188.08

159.74

143.71
139.56
135.00
134.38
129.53
128.09
121.88
118.75
113.88

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

55.62

f1 (ppm)

30

Compound 3k

abai-p4-15-10

8.59
8.57
8.02
7.91
7.89
7.54
7.52
7.50
7.47
7.45
7.43
7.42
7.42
7.40
7.26 CDCl3
7.16
7.16
7.15
7.14
7.14
7.13
3.87

1.03
0.99
0.98
1.06
1.37
2.17
0.50
1.05
3.00

f1 (ppm)

abai-p4-15-10

190.63
159.76
140.66
140.10
138.41
137.50
134.82
129.48
125.76
125.66
125.26
122.43
122.26
118.76
114.03
77.48 CDCl3
77.36
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3
55.56

f1 (ppm)

31

Compound 3l

9.02
9.01
8.25
8.22
8.21
8.19
8.15
8.13
7.67
7.62
7.61
7.49
7.48
7.47
7.46
7.45
7.43
7.41
7.39
7.37
7.26 CDCl3

2.43

1.00
1.36
1.00
0.65
0.99
0.92
0.92
1.02
1.92

3.00

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

196.39

152.56
149.88
138.51
137.59
137.47
135.75
133.59
131.39
130.58
129.91
129.65
128.36
127.50
127.39
122.06

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

21.51

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

32

Compound 3m

7.84
7.82
7.58
7.54
7.52
7.39
7.36
7.26 CDCl3
6.97
6.95

3.89

2.42

1.93
0.97
0.98
1.99
2.01

3.00

3.06

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

—195.90

—163.29

138.45
138.18
132.77
132.66
130.44
130.30
128.11
127.11
113.64

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

—55.62

—21.51

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

33

Compound 3n

7.88
7.85
7.80
7.77
7.60
7.55
7.53
7.46
7.44
7.40
7.39
7.37
7.26 CDCl3

2.43

20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000

solvent
impurities

1.89
1.92
0.96
0.96
0.95
0.95

3.00

f1 (ppm)

−195.37

141.53
138.74
136.49
134.24
132.26
130.33
128.56
127.50
118.17
115.70

−77.16 CDCl3

−21.49

4000
3500
3000
2500
2000
1500
1000
500
0

f1 (ppm)

34

Compound 3o

7.66
7.64
7.54
7.50
7.48
7.33
7.31
7.30
7.28
7.26 CDCl3
7.22

2.37
2.35

1.96
0.94
0.98
2.12
1.97

3.00
2.82

f1 (ppm)

−196.77

143.21
138.14
138.07
135.12
133.01
130.44
130.37
129.02
128.10
127.29

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

21.74
21.45

f1 (ppm)

35

Compound 3p

10.12

8.00
7.98
7.91
7.89
7.62
7.57
7.55
7.44
7.42
7.39
7.35
7.26 CDCl3

2.42

1.01
1.94
1.91
0.95
0.97
0.98
0.80
3.00

f1 (ppm)

196.11
191.74

142.83
138.57
136.86
134.01
130.38
129.56
128.44
127.52

77.16 CDCl3

21.46

f1 (ppm)

36

Compound 5a

abai–p4–7–2f2

7.73
7.30
7.28
7.27
7.26 CDCl3
7.24
7.22
7.20
7.05
7.03

3.54

2.96
1.79
1.01
1.88

3.00

f1 (ppm)

abai–p4–7–2f2

167.30
143.86
137.86
131.80
131.46
131.13
130.79
129.86
129.26
127.76
127.10
124.27
123.37
123.33
123.29
121.56
118.85

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

38.62

f1 (ppm)

37

Compound 5b

Compound 5c

7.43
7.41
7.40
7.38
7.26 CDCl3
7.25
7.23
7.21
7.18
7.16
7.14
7.03
7.01

3.50

3.99
1.65
0.84
2.02

3.00

f1 (ppm)

169.24
144.31
139.56
131.86
131.53
131.21
130.89
129.51
129.09
127.81
127.13
127.00
125.10
124.92
124.89
124.85
124.81
122.40
119.69

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

38.47

f1 (ppm)

39

Compound 5d

abai-p4-7-1f2

7.53
7.45
7.43
7.42
7.26 CDCl3
7.24
7.22
7.21
7.19
7.15
7.13
7.00
6.99

3.48

0.98
2.01
1.20
1.64
1.03
2.00

3.14

abai-p4-7-1f2

169.04
144.39
136.73
132.02
130.46
130.13
129.50
128.36
127.13
127.04
126.37
126.34
126.30
126.26
125.99
125.95
125.92
125.88

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

38.50

Compound 5e

7.26 CDCl3
7.24
7.22
7.20
7.15
7.13
7.11
7.06
7.05
7.04
7.03
7.02
6.86
6.84
6.82
6.78
6.77
6.76
6.75

3.64
3.48

2.01
1.05
2.98
1.99
1.01

2.99
3.00

f1 (ppm)

170.46
158.98
145.00
137.16
129.24
128.83
126.88
126.61
121.30
116.14
113.75
77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3
55.26
38.50

f1 (ppm)

41

Compound 5f

abai-p4-7-16F2

7.26 CDCl3
7.24
7.23
7.22
7.21
7.18
7.16
7.14
7.06
7.04

3.49

1.22

3.80
1.25
1.52
1.91

3.00

9.05

f1 (ppm)

abai-p4-7-16F2

170.74

153.03

145.29

132.94
129.22
128.81
126.97
126.45
124.74

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

38.69
34.81
31.39
31.23

f1 (ppm)

42

Compound 5g

7.26 CDCl3
7.22
7.20
7.14
7.12
7.04
7.02
7.00
6.99

3.48

2.21

2.75
1.00
3.00
1.87

3.00

2.99

.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

170.94

145.07
137.62
135.93
130.41
129.52
129.17
127.52
126.96
126.51
125.83

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

38.49

21.32

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

43

Compound 5h

abai-p4-5-5

7.44 7.42 7.36 7.34 7.26 CDCl3 7.24 7.22 7.20 7.17 7.15 7.13 7.00 6.98

3.47

2.00 1.98 2.06 1.02 1.96

3.13

abai-p4-5-5

168.30

143.58 140.02 131.31 129.20 128.88 126.94 126.61 117.81 112.81

77.16 CDCl3 77.16 CDCl3 77.04 76.84 CDCl3 76.52 CDCl3

38.01

Compound 5i

abai-p4-7-4f2

abai-p4-7-4f2

45

Compound 5j

46

Compound 5k

abai–p4–7–14f2

8.00
7.90
7.88
7.44
7.42
7.26 CDCl3
7.23
7.21
7.19
7.15
7.13
7.04
7.02

3.83
3.49

0.99
1.00
1.03
2.99
1.03
2.00

3.01
3.00

f1 (ppm)

abai–p4–7–14f2

169.68
166.34
144.55
136.42
132.94
130.65
130.06
129.93
129.39
127.95
127.08
126.93

77.48 CDCl3
77.36
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

52.25

38.50

f1 (ppm)

47

Compound 5l

abai-p4-7-11F3

7.91 7.73 7.71 7.60 7.58 7.47 7.45 7.44 7.42 7.40 7.34 7.32 7.26 CDCl3 7.19 7.17 7.09 7.07

3.56

1.00 2.01 1.02 2.05 1.01 2.03 3.05

3.00

f1 (ppm)

abai-p4-7-11F3

170.62

144.97 133.59 133.33 132.45 129.47 129.28 128.67 127.63 127.29 127.17 126.96 126.56 126.35 125.56 77.48 CDCl3 77.36 77.16 CDCl3 77.16 CDCl3 76.84 CDCl3

38.62

f1 (ppm)

48

Compound 5m

7.54
7.54
7.48
7.46
7.45
7.26 CDCl3
7.24
7.22
7.20
7.17
7.15
7.00
6.98

3.46

0.98
1.95
3.16
0.95
1.99

3.00

f1 (ppm)

168.24
144.02
137.33
133.02
132.86
132.36
129.63
129.37
128.76
127.36
127.00
118.07
112.19

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

38.50

f1 (ppm)

49

Compound 5n

7.26 CDCl3
7.25
7.24
7.22
7.20
7.15
7.13
7.03
7.01
6.66
6.63

1.78
1.88
1.04
2.02
2.00

3.14
3.16

f1 (ppm)

170.39
160.71
145.59
131.02
129.31
128.09
126.98
126.40
113.09
77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3
55.32
38.75

f1 (ppm)

50

Compound 5o

abai-p4-8-1

7.97
7.95
7.78
7.76
7.54
7.51
7.26 CDCl3
6.93
6.90

3.82

2.03
2.96
1.98
2.09

3.00

f1 (ppm)

abai-p4-8-1

—163.89
—157.23
139.07
132.73
130.39
127.86
122.42
118.07
114.50

—77.16 CDCl3

—55.67

f1 (ppm)

51

Compound 5p

abai-p4-8-3

7.97
7.95
7.81
7.78
7.76
7.51
7.49
7.26 CDCl3
7.20
7.18

2.35

1.89
2.70
1.82
2.00

3.00

f1 (ppm)

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000

abai-p4-8-3

−162.32

139.11
135.18
134.82
132.74
129.87
127.88
120.59
118.06
115.46

77.16 CDCl3

−21.10

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

52

Compound 5q

abai-p4-8-2

8.00
7.98
7.93
7.87
7.85
7.81
7.79
7.54
7.52
7.50
7.46
7.44
7.26 CDCl3

2.95
1.03
1.09
1.93
1.10
1.00

abai-p4-8-2

164.18
138.40
137.94
132.88
131.98
131.65
129.97
127.94
123.55
121.91
117.91
117.25
115.93

77.16 CDCl3

53

Compound 5r

Compound 5s

7.71
7.69
7.50
7.48
7.26 CDCl3

3.75
3.60
3.41
3.35

2.00
2.00

6.10
2.02

f1 (ppm)

168.32

139.69
132.54
127.85

118.03
113.72

77.16 CDCl3
66.76

f1 (ppm)

55

Compound 5t

abai–p4–8–5F1

7.86
7.84
7.66
7.64
7.33
7.33
7.32
7.31
7.29
7.26 CDCl3
6.93

4.60
4.58

2.02
2.01
4.97
0.94

2.00

f1 (ppm)

abai–p4–8–5F1

—165.75

138.31
137.67
132.45
128.92
127.91
127.88
127.84
118.08
115.07

77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

—44.34

f1 (ppm)

56

Compound 5u

abai–p4–11–2f2

7.26 CDCl3
7.23
7.21
7.04
6.89
6.84
6.81

4.50
4.49
4.09
4.07
4.06
3.82

2.83
2.82
2.80
2.39

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
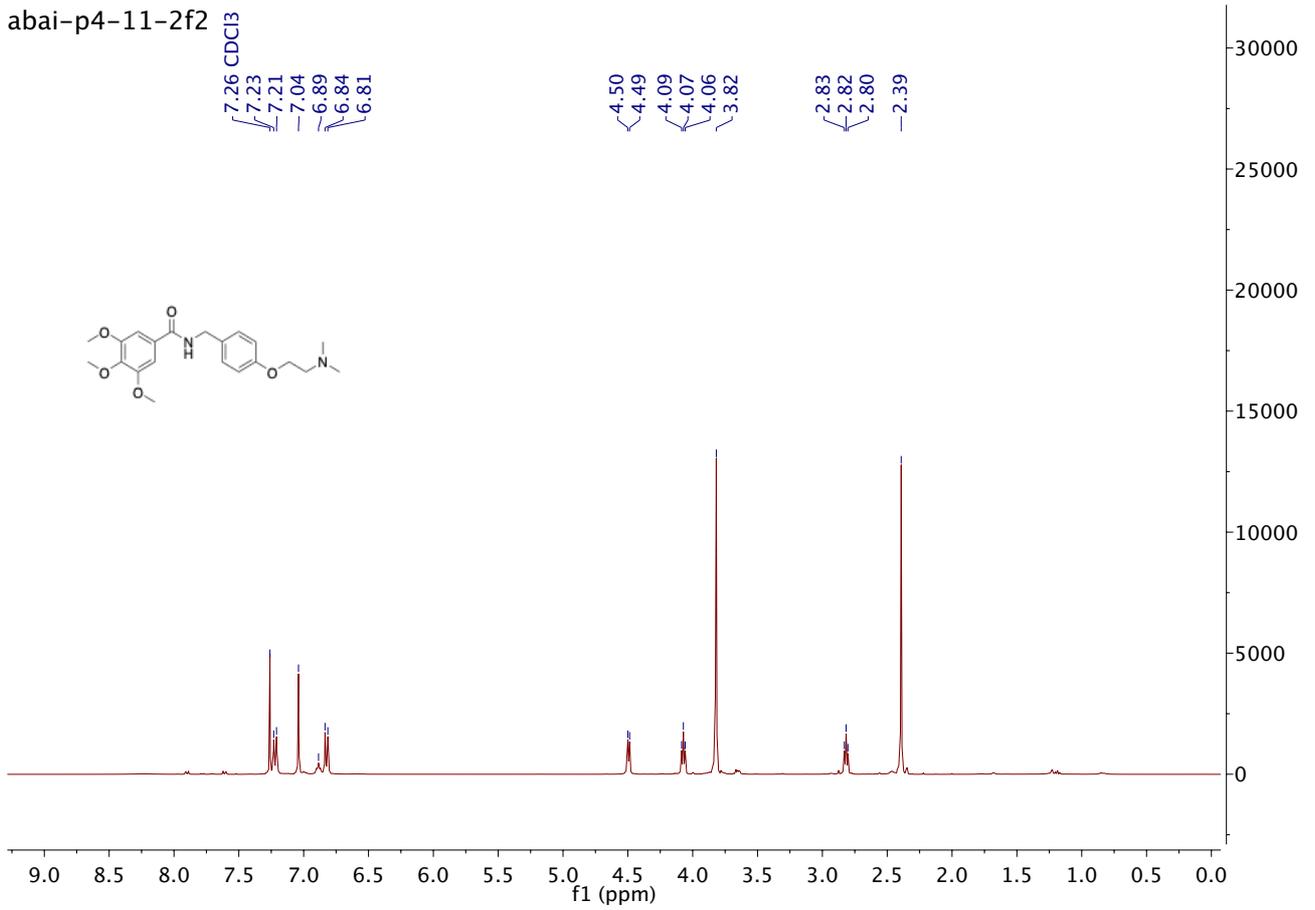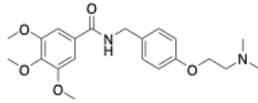
abai–p4–11–2f2

167.00
157.96
153.13
140.82
130.93
129.86
129.32
114.74
104.56
77.16 CDCl3
65.39
60.92
57.97
56.36
45.50
43.60

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

57

Compound 5v

−7.26 CDCl3
−6.59
3.84
3.82
3.65

2.01
9.84
7.02

f1 (ppm)

abai–p4–11–1

−170.52
−153.73
−139.69
−131.02
−104.74
−77.16 CDCl3
67.27
61.26
56.64

f1 (ppm)

58

Compound 7a

abai-p4-6-1

8.56
8.06
8.03
7.96
7.94
7.87
7.85
7.59
7.58
7.55
7.53
7.51
7.26 CDCl3

1.67

0.98
1.00
1.03
2.01
2.03
9.07

f1 (ppm)

abai-p4-6-1

166.04

135.42
132.63
130.75
129.39
128.03
128.01
127.82
126.57
125.45

81.24
77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

29.84
28.39

f1 (ppm)

59
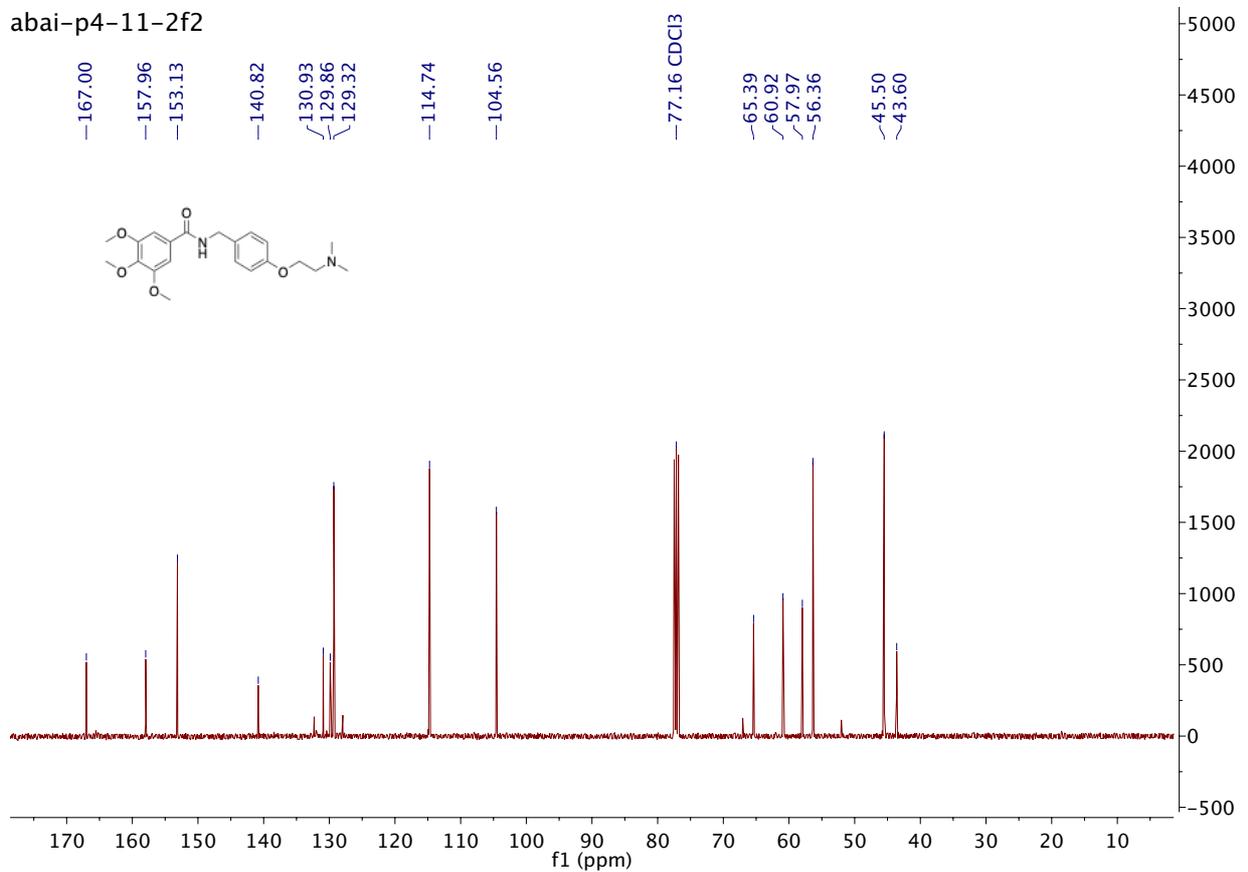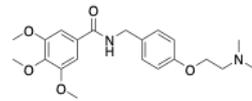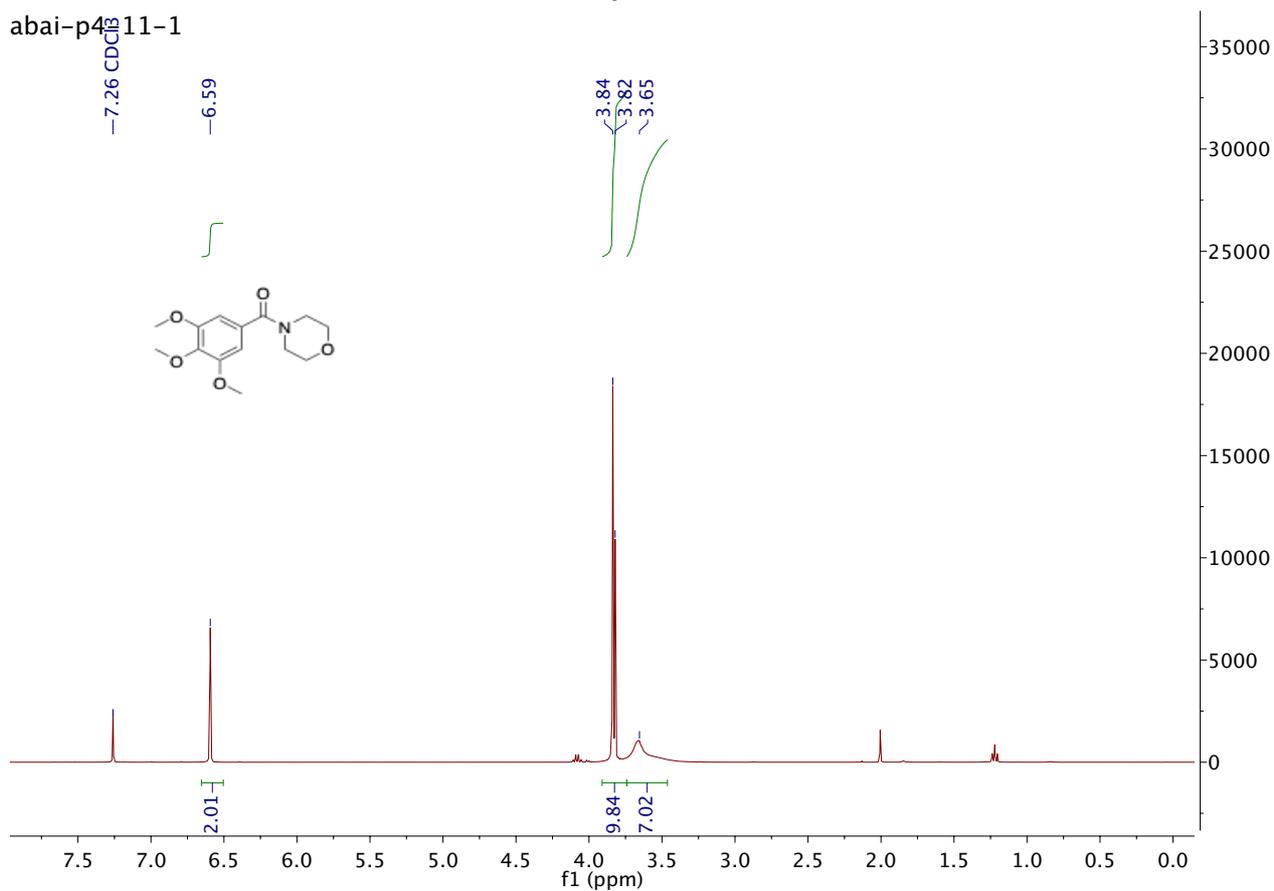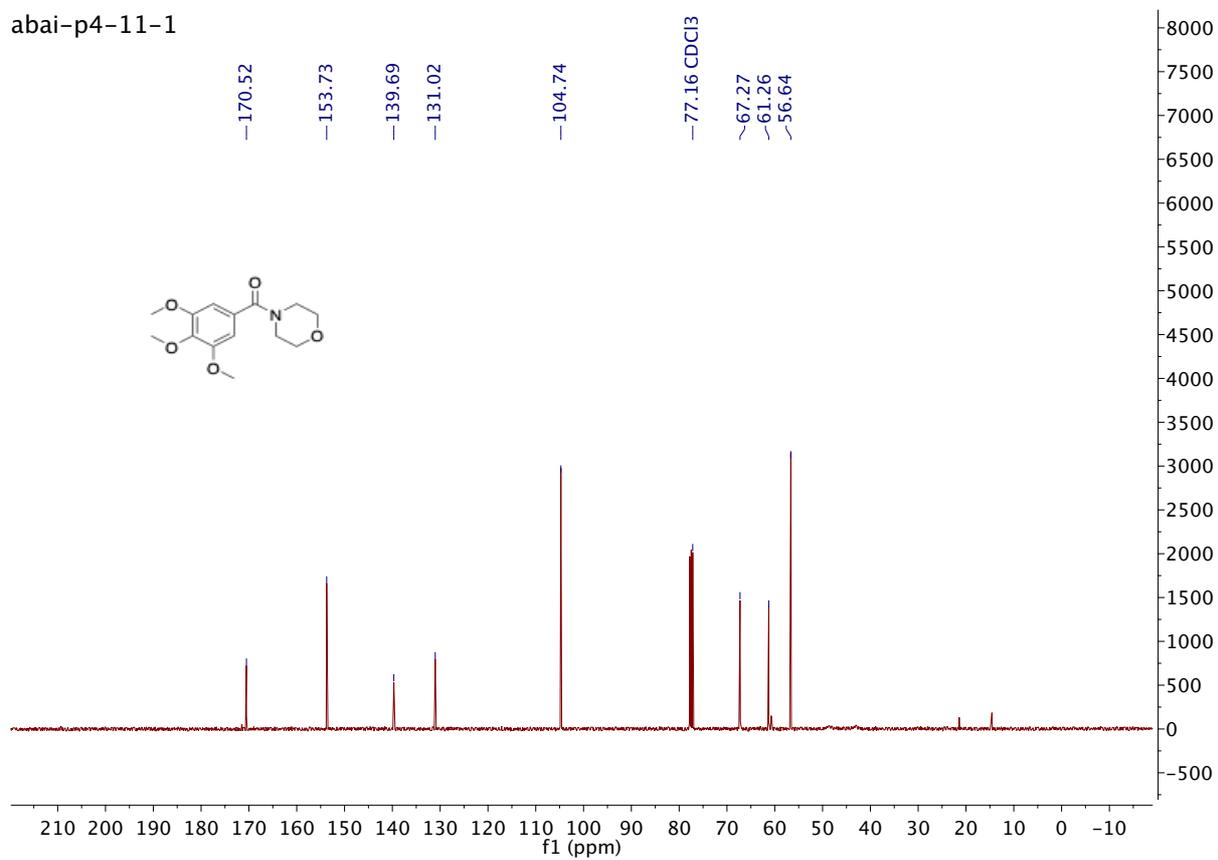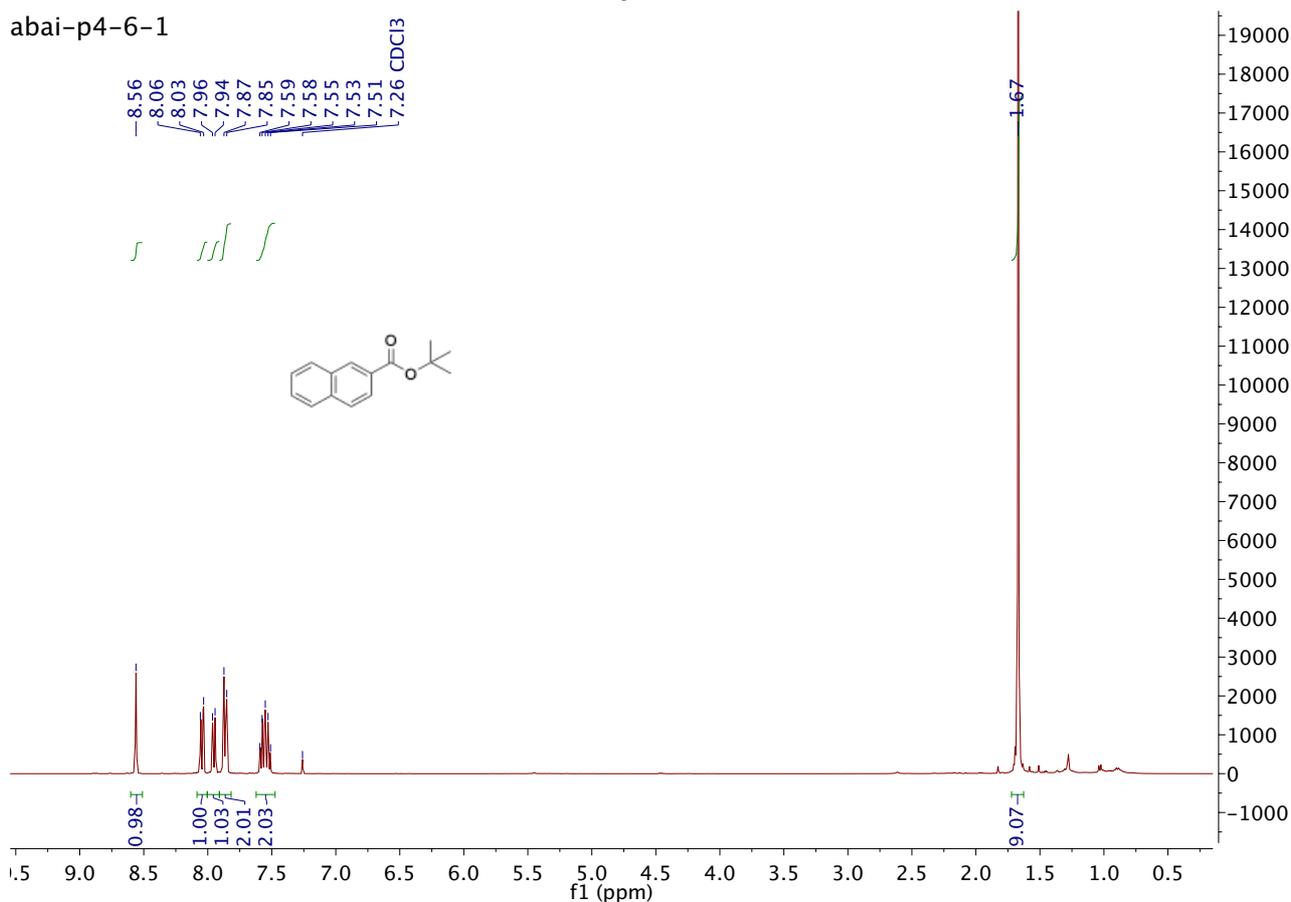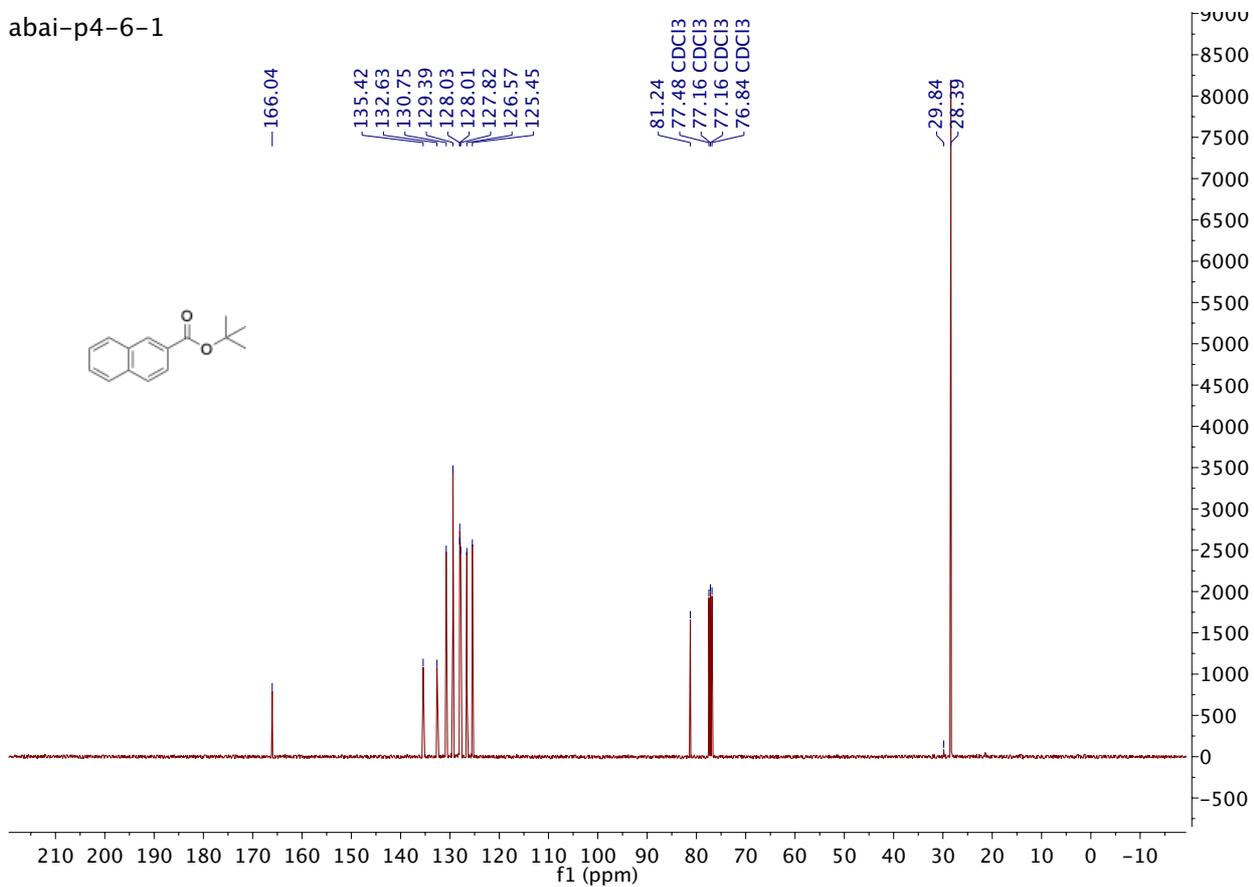
Compound 7b

abai–p4–6–2bf2

7.95
7.93
7.26 CDCl3
3.84
1.58

2.00
2.05
3.11
9.49

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3
f1 (ppm)

35000
30000
25000
20000
15000
10000
5000
0

abai–p4–6–2bf2

165.71
163.06
132.34
131.48
124.61
113.49
80.61
77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3
55.49
29.83
28.38

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500

60
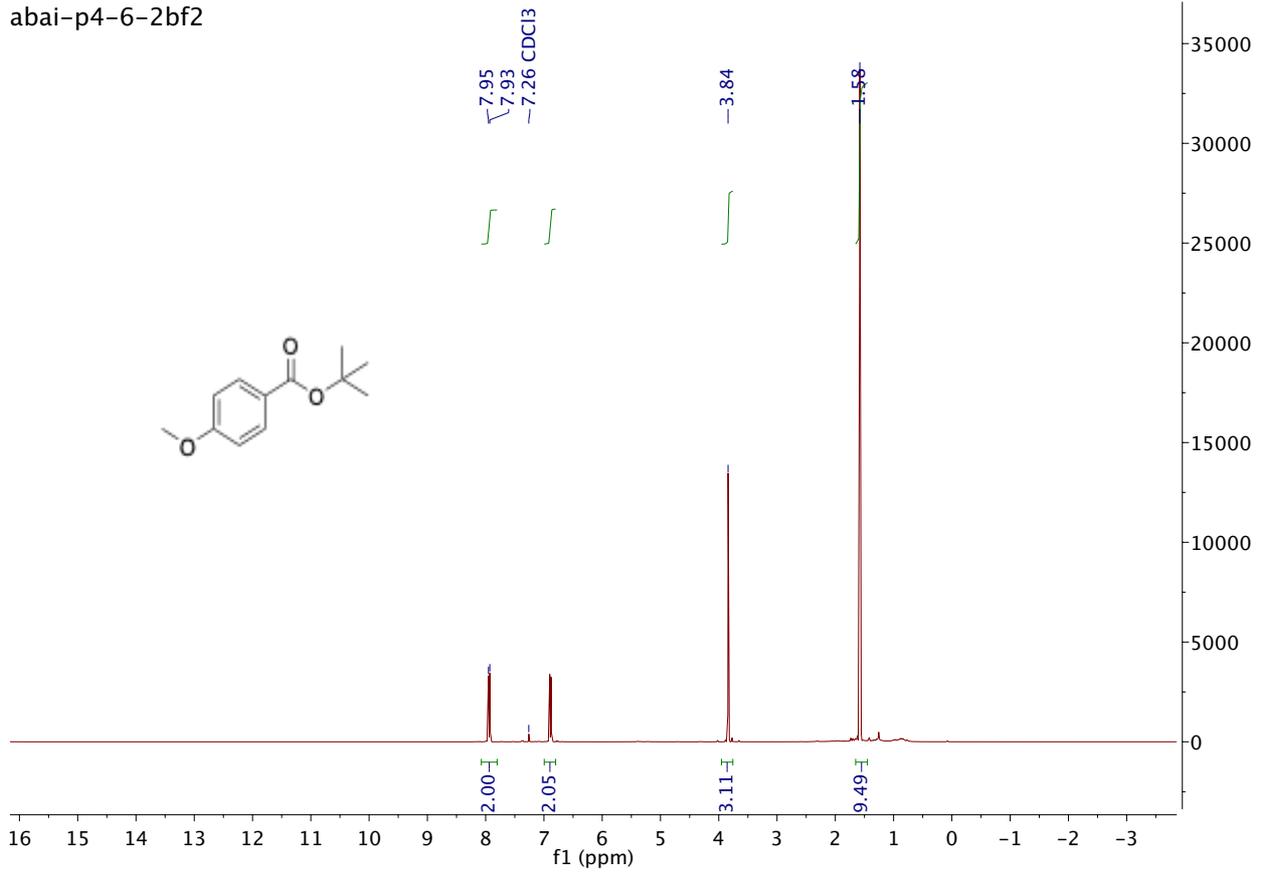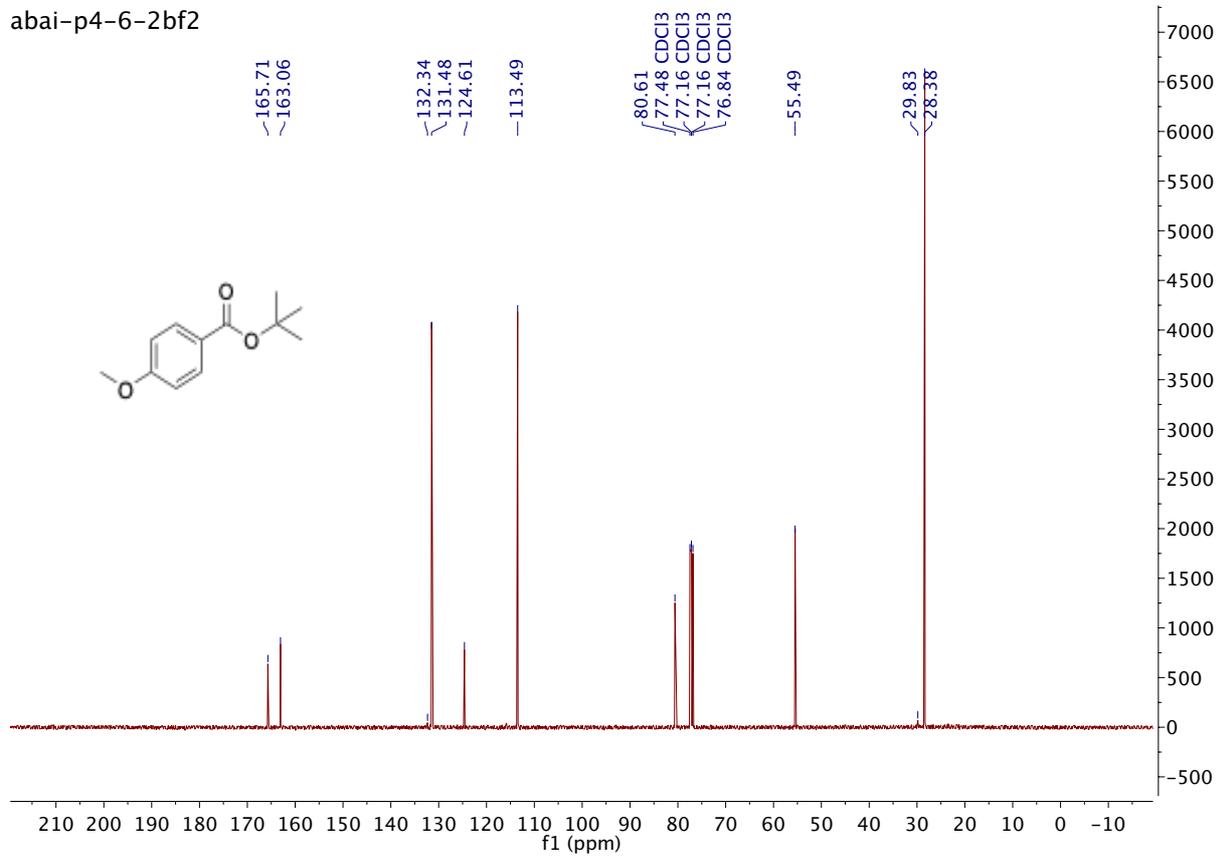
Compound 7c
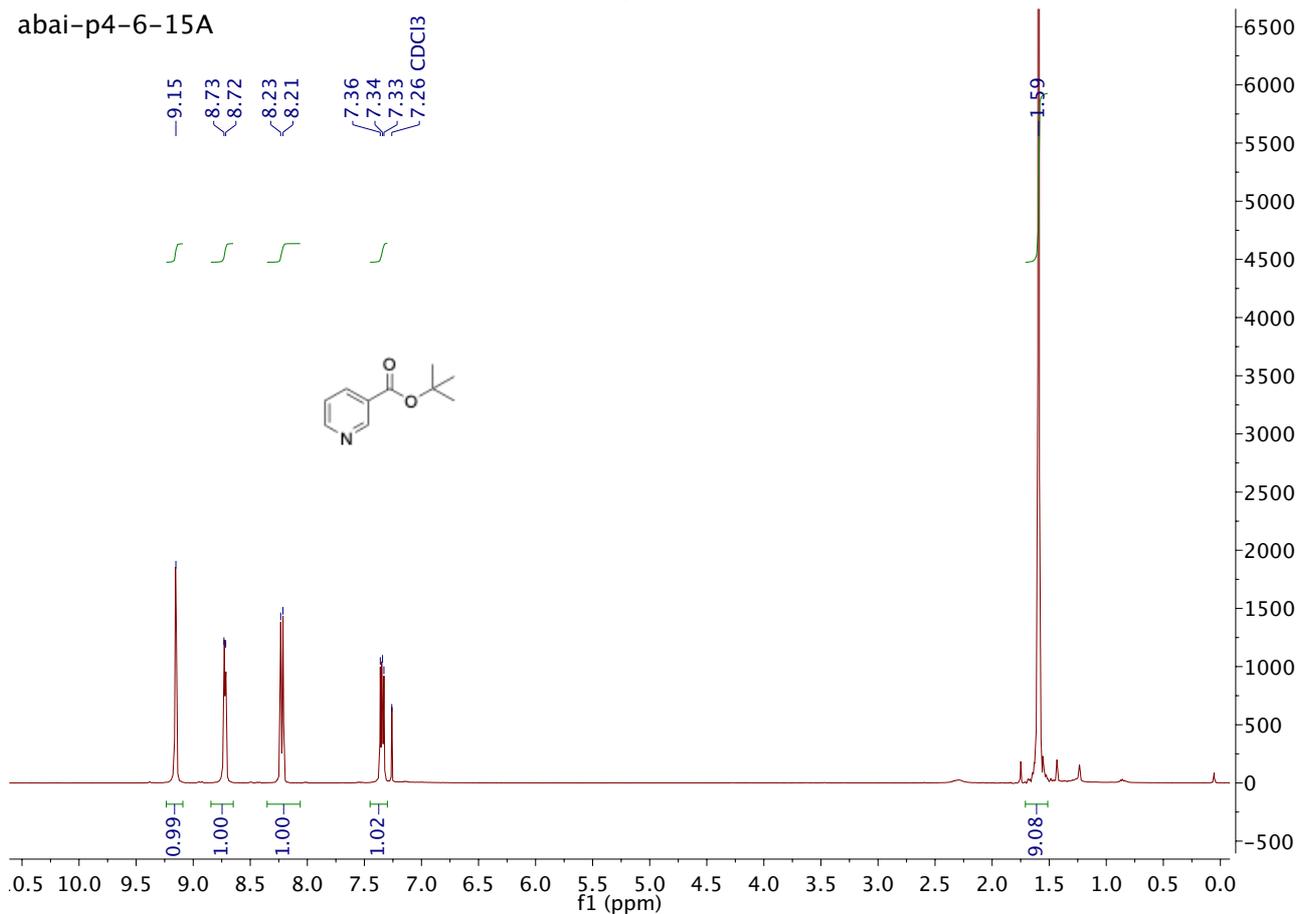
abai–p4–6–15A

abai–p4–6–15A
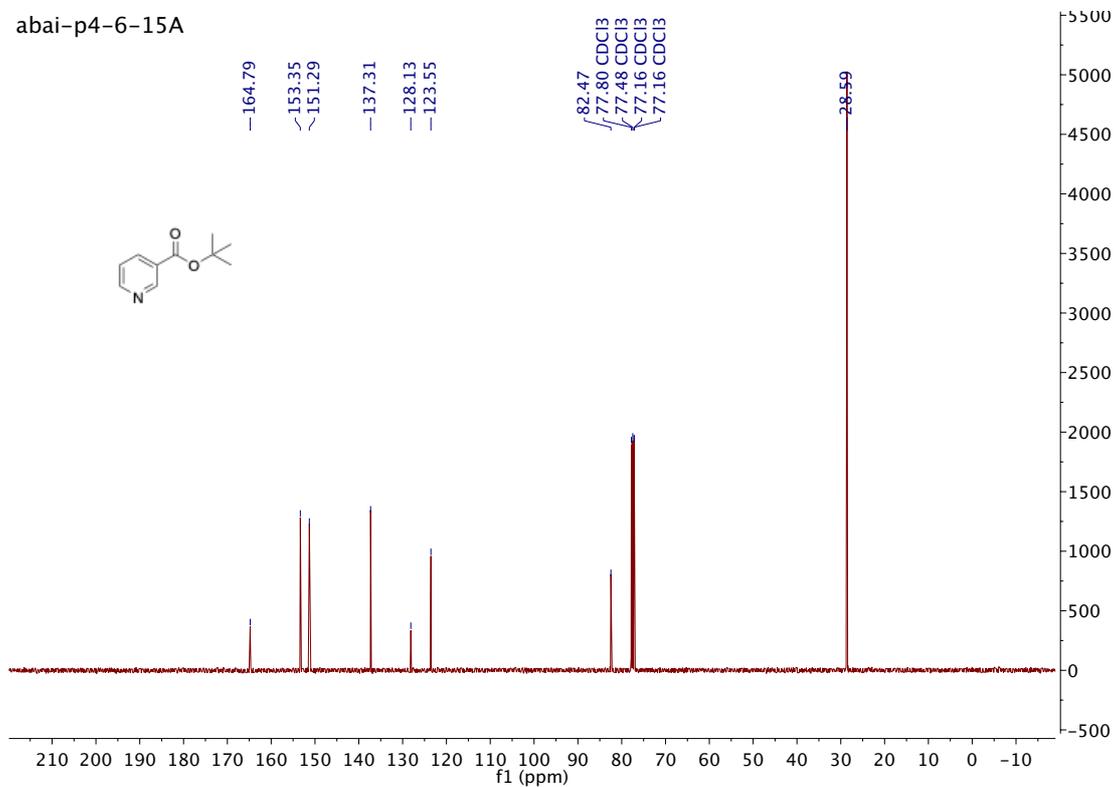
Compound 7d

abai–p4–11–2f2

8.09
8.06
7.72
7.70
—7.26 CDCl3

1.60

1.83
2.00
9.01

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

abai–p4–6–6

—164.42

136.28
132.49
130.37

118.60
116.29

82.82
—77.16 CDCl3

—28.53

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

62

Compound 7e

63

Compound 7f

8.11
8.09
7.69
7.67
7.26 CDCl3
1.61

2.00
2.09
8.81

f1 (ppm)

164.61
135.37
134.26
133.93
129.94
125.43
125.40
125.36
125.32
125.29
125.24
82.08
77.16 CDCl3
28.28

f1 (ppm)

64

Compound 7g

abai-p4-6-wf2

8.97
8.96
8.50
8.26
8.23
8.22
8.11
8.09
7.44
7.43
7.42
7.41
7.26 CDCl3

1.63

0.95
1.01
2.04
1.02
1.04

8.94

f1 (ppm)

abai-p4-6-wf2

—165.30

152.32
150.00

137.37
130.65
130.08
129.61
129.17
127.46
121.78

81.70
77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

28.32

f1 (ppm)

65

Compound 7h

abai–p4–6–YF2

7.95
7.93
7.45
7.43
7.26 CDCl3

1.60
1.34

2.02
2.04

9.15
9.10

f1 (ppm)

abai–p4–6–YF2

165.62
155.75
129.09
124.93
80.40
77.16 CDCl3
34.80
30.97
28.04

f1 (ppm)

66

Compound 7i

abai-p4-6-XF1

7.62
7.60
7.51
7.50
7.26 CDCl3
6.86
6.84
3.92
1.58

1.00
1.00
1.05
6.00
9.26

f1 (ppm)

abai-p4-6-XF1

165.76
152.68
148.60
124.70
123.37
112.01
110.19
80.84
77.16 CDCl3
56.12
28.37

f1 (ppm)

Compound 7j

abai-p4-6-3

7.80
7.78
7.34
7.32
7.31
7.30
7.28
7.26 CDCl3

−2.39

1.60

1.85
2.15

2.95
9.00

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

abai-p4-6-3

−166.12

138.04
133.28
132.09
130.08
128.21
126.68

80.99
77.48 CDCl3
77.16 CDCl3
77.16 CDCl3
76.84 CDCl3

−28.35
−21.43

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

68

Compound 8a

8.62
8.08
8.06
7.96
7.94
7.89
7.87
7.61
7.60
7.59
7.57
7.56
7.54
7.52

3.99

0.99
1.00
1.01
1.01
2.04
2.13

3.15

f1 (ppm)

167.33

135.60
132.58
131.15
129.44
128.32
128.24
127.85
127.49
126.72
125.32

52.32

f1 (ppm)

69

Compound 8b

abai-p4-12-1

70

Compound 8c

abai–p4–6–12–4F2
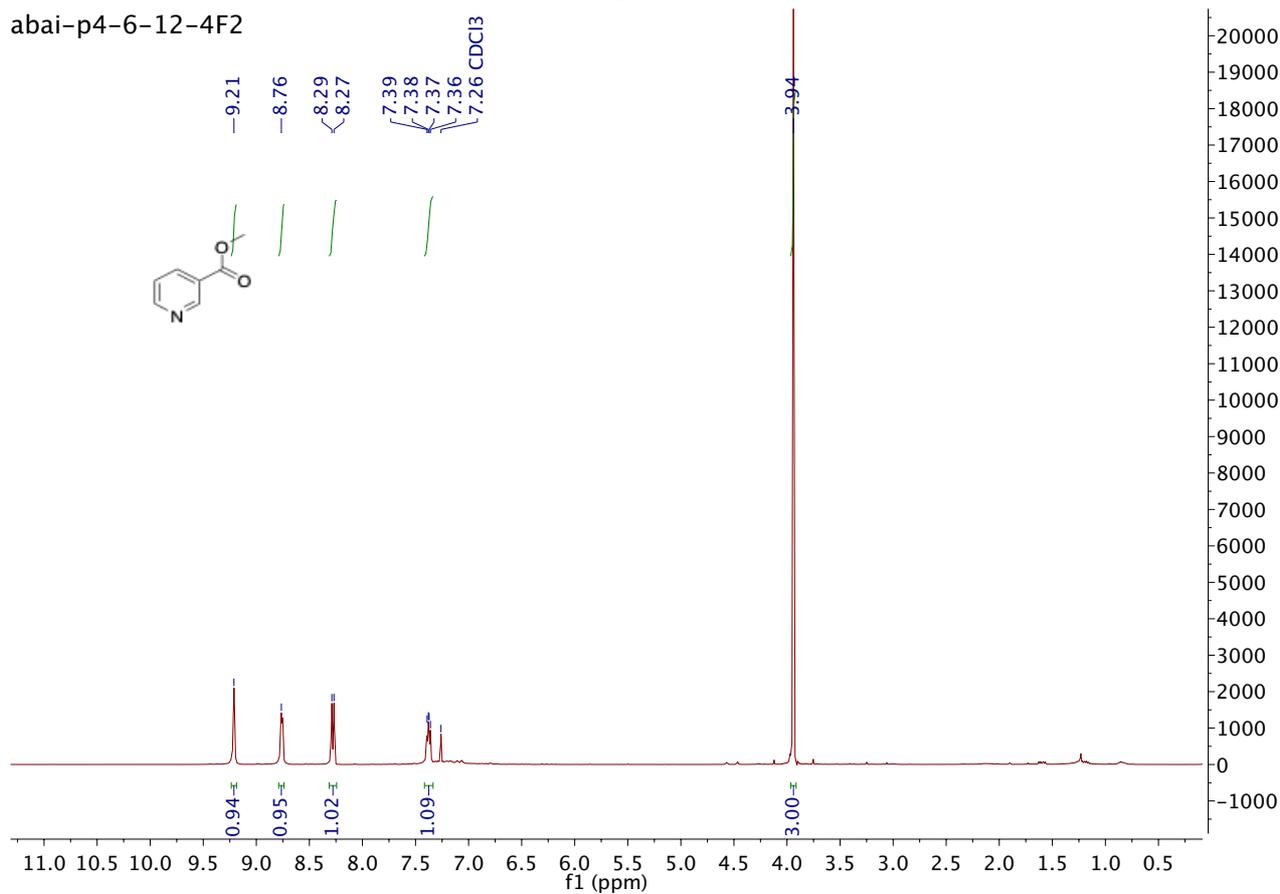
abai–p4–6–12–4F2

Compound 8d

7.94
7.92
7.26 CDCl3
7.24
7.22
3.89
2.40

2.03
1.99
3.03
3.09

f1 (ppm)

abai-p4-12-7F2

−167.29
−143.65
129.70
129.17
127.53
−77.16 CDCl3
−52.04
−21.75

f1 (ppm)

72

Compound 8e

abai-p4-12-5

8.95
8.95
8.94
8.94
8.51
8.25
8.23
8.19
8.17
8.10
8.08
7.41
7.40
7.39
7.38
7.26 CDCl3
3.94

0.98
0.97
2.01
1.02
1.00

3.02

26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
−2000

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3
f1 (ppm)

abai-p4-12-5

166.56
152.51
150.06
137.32
131.00
129.81
128.94
128.10
127.40
121.85
77.16 CDCl3
52.45

12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

73