Nickel-Catalyzed Electroreductive Cross-Coupling Reactions of Anhydrides and Alkyl Halides

Thesis by

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ABSTRACT

The formation of new carbon–carbon bonds is one of the most important transformations in organic chemistry due to its ability to build the backbone of organic molecules. Nickel-catalyzed reductive cross-coupling reactions have recently emerged as an efficient and powerful strategy for the creation of new carbon–carbon bonds. Furthermore, electrochemistry can be harnessed to overcome some of the challenges encountered in many of the reductive cross-coupling reactions in the literature. Herein, we discuss the development of a new electroreductive nickel-catalyzed cross-coupling of anhydrides with unactivated alkyl bromides in collaboration with Amgen to produce large amounts of substituted cyclobutene products.

TABLE OF CONTENTS

Acknowledgements……...iii

Abstract ……vi

Table of Contents…….vii

List of Abbreviations…….ix

1. Introduction…….1

2. Reductive Cross-Coupling Development……6

3. Product Functionalization and Preliminary Scope…….12

4. Progress Towards Asymmetry……...16

5. Conclusion and Future Directions……..18

6. Experimental Section…….19

7. References……..26

Appendix: *Relevant Spectra*……...28

LIST OF ABBREVIATIONS

BiOX	bi(oxazoline)
BOX	bis(oxazoline)
Bu	butyl
^{t}Bu	*tert*-butyl
^{13}C	carbon-13 isotope
°C	degrees celcius
calc'd	calculated
CAM	cerium ammonium molybdate
cat.	catalyst
cm^{-1}	wavenumber(s)
Cs_2CO_3	cesium carbonate
cod	1,5,-cyclooctadine
CPME	cyclopentyl methyl ether
δ	chemical shift in ppm
d	doublet
d	deutero

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMA	*N,N*-dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dtbpy	4,4’-di-*tert*-butyl-2,2’-bipyridine
ee	enantiomeric excess
equiv.	equivalent(s)
Et	ethyl
et al.	and other (Latin: *et alii*)
FI	field ionization
g	gram(s)
h	hour(s)
^{1}H	proton
HRMS	high resolution mass spectrometry
in situ	in the reaction mixture
IR	infrared spectroscopy
J	coupling constant

K_2CO_3	potassium carbonate
LiOAc	lithium acetate
m	multiplet
M	molar or molecular ion
Me	methyl
MeCN	acetonitrile
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
mol	(mole(s)
m/z	mass-to-charge ratio
Na_2CO_3	sodium carbonate
NaOAc	sodium acetate
NaO_2CH	sodium formate
n.d	not detected
Ni	nickel
NMP	*N*-methyl-2-pyrrolidone

OH	hydroxyl
Ph	phenyl
phen	1,10-phenanthroline
PHOX	phosphinooxazoline
PyOx	pyridine-oxazoline
q	quartet
R	alkyl group
RCC	reductive cross-coupling
s	singlet
SFC	supercritical fluid chromatography
t	triplet
TBABr	tetra-*n*-butylammonium bromide
TBACl	tetra-*n*-butylammonium chloride
TBAOAc	tetra-*n*-butylammonium acetate
$TBAPF_6$	tetra-*n*-butylammonium hexafluorophosphate
THF	tetrahydrofuran

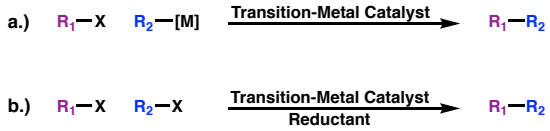
NICKEL-CATALYZED ELECTROREDUCTIVE CROSS-COUPLING REACTIONS OF ANHYDRIDES AND ALKYL HALIDES

1. INTRODUCTION

The formation of carbon–carbon bonds is one of the most important transformations in organic chemistry. Carbon–carbon bonds make up the backbones of organic molecules and the forging of these bonds is often the key to unlocking powerful syntheses of organic molecules. The development and use of transition-metal catalyzed cross-coupling reactions as a tool for carbon–carbon bond construction has been one of the most important recent advances in organic chemistry.[1-3] The importance of this work was highlighted by the Nobel Prize in Chemistry which was awarded to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki in 2010 for their contributions to palladium-catalyzed cross-coupling in organic synthesis.

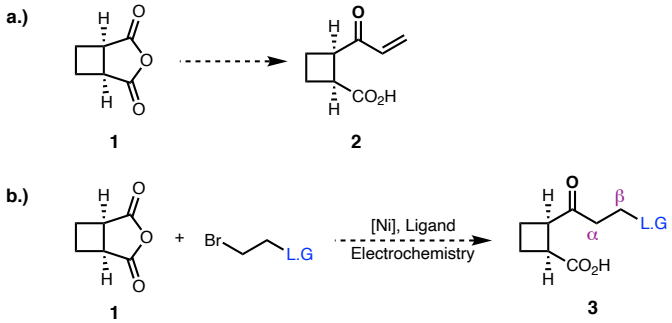
Transition-metal catalyzed cross-coupling reactions have traditionally (**Scheme 1.1a**) involved the use of a metal nucleophile and an electrophile as coupling partners. Reductive cross-coupling reactions (RCC) (**Scheme 1.1b**), which use two electrophiles as coupling partners in the presence of a reductant are not as well developed but can provide advantages over traditional cross-coupling reactions. The metal nucleophile in traditional cross coupling reactions, which must often be synthesized from a precursor, introduces several limitations such as the addition of steps in a synthesis, additional handling precautions, and limited functional group compatibility. In contrast, RCC often use organic halide fragments with wide commercial availability and greater functional group compatibility, making it a more direct approach for the coupling of organic fragments.

Scheme 1.1 *a.) Traditional cross-coupling reactions and b.) reductive cross-coupling reactions (X = Halide, Pseudohalide; R_1, R_2 = Alkyl, aryl, alkenyl; [M] = metal, metalloid)*



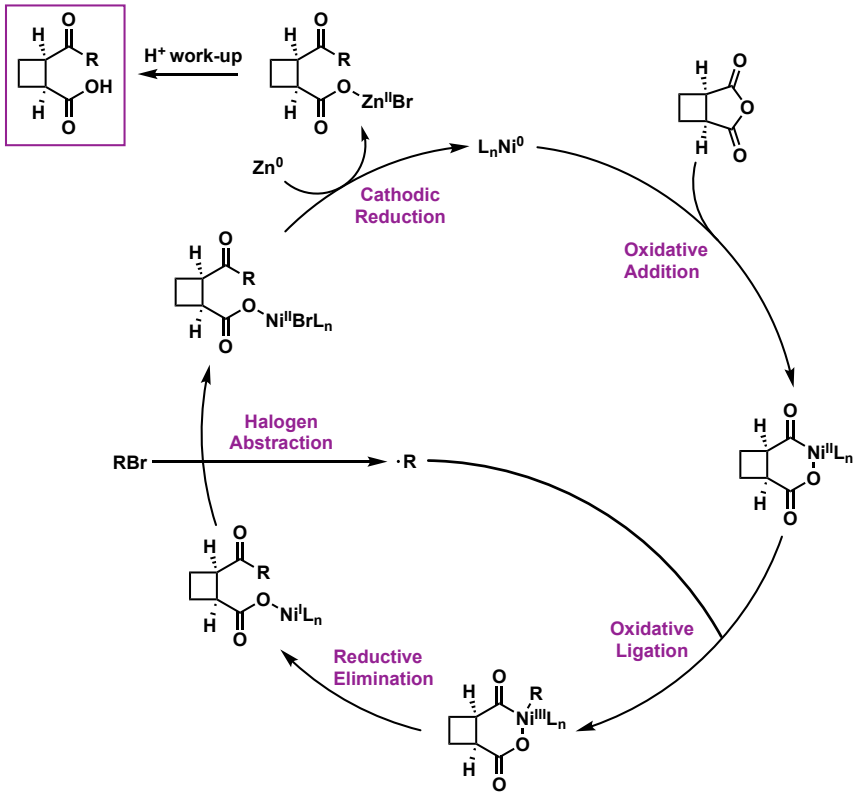
Amgen approached our group with an interest in developing a concise method for the synthesis of stereodefined substituted cyclobutanes such as **2** from cyclobutyl anhydride **1** (**Scheme 1.2a**). While the Amgen process team has developed a highly efficient one-step process to afford cyclobutyl anhydride **1** on multi kilogram scale, attempts to convert cyclobutyl anhydride **1** to target molecule **2** were unsuccessful.[4.] Our group proposed the use of a RCC approach to this transformation (**Scheme 1.2b**).

Scheme 1.2 *a.) Transformation of interest and b.) proposed RCC approach*



We hypothesized that this reaction would proceed by a chain radical mechanism as shown in **Figure 1.1**. In this cycle, oxidative addition proceeds with the anhydride first. The resulting nickel(II) intermediate is oxidatively ligated by an alkyl radical generated by halogen abstraction with the alkyl bromide to produce a nickel(III) intermediate. Upon reductive elimination at the cathode and workup with a proton source, the product is liberated and nickel(0) is regenerated.

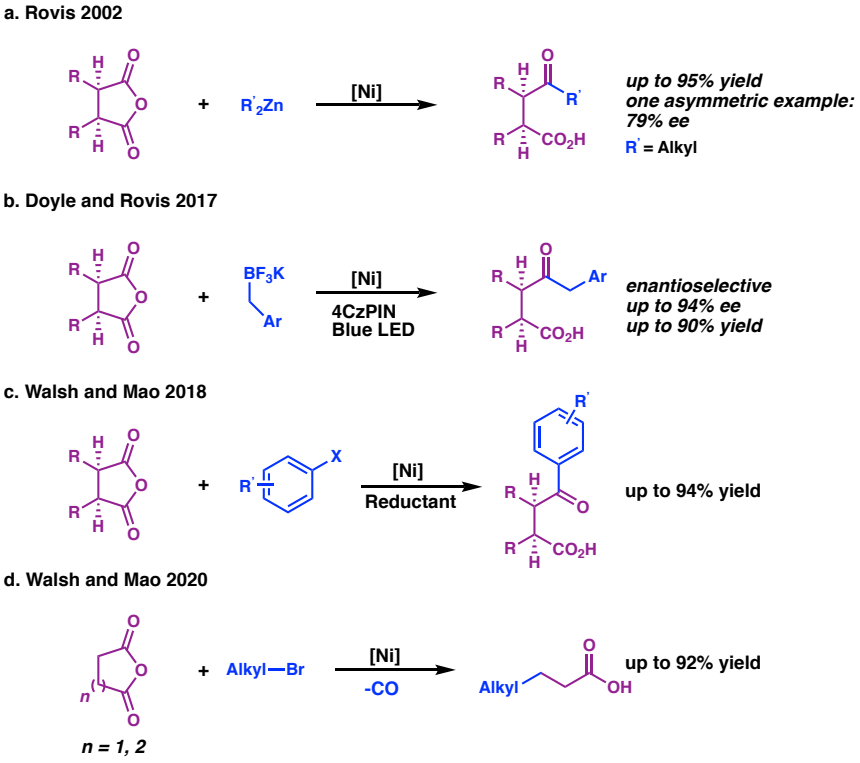
Figure 1.1 *Proposed catalytic cycle for RCC of cyclobutyl anhydride*



Prior to our development of a RCC approach for the desymmetrization of anhydrides, there have been multiple reports of anhydride desymmetrization in the literature. In 2002 Rovis reported the functionalization of anhydrides using organozinc nucleophiles in up to 95% yield. The use of a chiral phosphinooxazoline ligand allowed for the desymmetrization of a *meso*-anhydride in 85% yield and 79% ee (**Scheme 1.3a**).[5] Years later, Doyle and Rovis reported an enantioselective desymmetrization of *meso*-anhydrides in up to 90% yield and 94% ee using a dual nickel- and photoredox-catalyzed cross-coupling reaction (**Scheme 1.3b**).[6] In recent years, Walsh and Mao have reported the desymmetrization of cyclic *meso*-anhydrides with aryl halides in up to 94% yield using a RCC approach (**Scheme 1.3c**).[7] Most recently, Walsh and Mao reported the decarbonylative coupling of monocyclic anhydrides with unactivated alkyl halides in up to 92% yield (**Scheme**

1.3c).[8] However, there have been few examples of cross-coupling reactions involving cyclobutyl anhydride **1**. Furthermore, the reported examples of alkyl coupling partners did not contain the functionality needed to arrive at target compound **2**.

Scheme 1.3 *Nickel-catalyzed cross-coupling reactions of anhydrides*

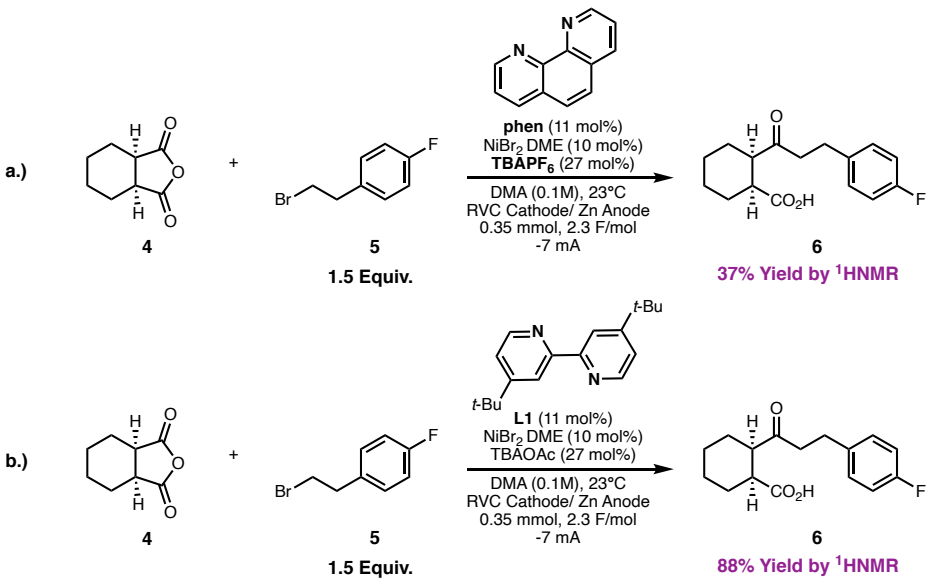


One of the primary challenges in RCC is achieving cross-selectivity.[9] The two electrophiles must have sufficiently different electronic properties such that one of the coupling partners selectively undergoes oxidative addition with the metal catalyst before the other to avoid significant homo-coupling. The direct coupling of two Csp^2 electrophiles such as an anhydride and an alkenyl halide may be difficult due to cross-selectivity. Using an alkyl bromide in place of an alkenyl halide could be more suitable for achieving cross-selectivity (**Scheme 1.2b**). The desired enone product **2** could then be unmasked by elimination of a beta leaving group installed on the alkyl coupling partner.

A second challenge in RCC is the use of superstoichiometric amounts of heterogeneous metal-powder reductants, which can introduce reproducibility issues due to sensitive stir rates, metal purity, and metal mesh size.[10-11] One approach to overcome these challenges is to leverage electrochemistry as the source of electrons, instead of terminal reductants like Zn^0 and Mn^0.[12] Furthermore, studying the mechanism of RCC systems can be challenging, since Ni^I and Ni^{III} species can be unstable and therefore difficult to isolate. This is another case where electrochemistry can be leveraged to study catalytically active species in situ to gain key mechanistic insight.[13] By developing an electroreductive nickel-catalyzed cross-coupling reaction, we aim to expand on the scope of current anhydride cross-coupling reactions in the literature and gain mechanistic insight into these reactions. Furthermore, we aim to leverage electrochemistry to avoid reproducibility issues associated with metal-dust reductants especially when the reaction is scaled up by the Amgen process team.

2. REDUCTIVE CROSS-COUPLING DEVELOPMENT

Scheme 2.1 *a. Cyclohexyl Anhydride RCC initial conditions and b. conditions after optimization*

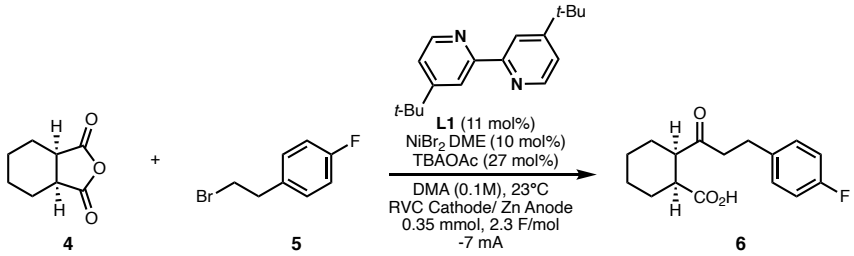


We began our optimization of the RCC of cyclobutyl anhydride **1** with important information gained from a similar RCC using cyclohexyl anhydride **4** that we were developing concurrently (**Scheme 2.1**). Initially, we were able to obtain cross-coupled product **6** in 37% yield by ^{1}HNMR using a phenanthroline ligand and tetrabutylammonium hexafluorophosphate electrolyte (**Scheme 2.1a**) and after focusing our efforts on the optimization of the ligand and electrolyte choice we were pleased to arrive at conditions that yielded cross-coupled product **6** in 88% yield by ^{1}HNMR (**Scheme 2.1b**). The reaction was run under constant current with an RVC cathode and Zn anode in an undivided cell, like other electrochemical RCC reactions in the literature.[12,15] An electron-rich bipyridine ligand **L1** with a coordinating tetrabutyl ammonium acetate electrolyte in an amide solvent were found to be optimal and afforded cross-coupled product **6** in 88% yield by ^{1}HNMR.

Control experiments on the RCC of cyclohexyl anhydride **4** with alkyl bromide **5** were conducted in order to confirm that the nickel catalyst was needed to promote reactivity. In the absence of nickel

(**Table 2.1**, Entry 2) and in the absence of ligand (**Table 2.1**, Entry 3), no product was detected by ^{1}HNMR, showing that the nickel catalyst plays an important role in the reaction. Furthermore, changing the catalyst loading from 10 mol% (**Table 2.1**, Entry 1) to 20 mol% resulted in no change in yield (**Table 2.1**, entry 4). Decreasing the catalyst loading to 5 mol % resulted in a decrease in yield (**Table 2.1**, entry 5) Changing the ratio of ligand to nickel from 11:10 to 20:10 resulted in a small decrease in yield (**Table 2.1**, entry 6).

Table 2.1 *Effects of Nickel and Ligand Loading on Reactivity*



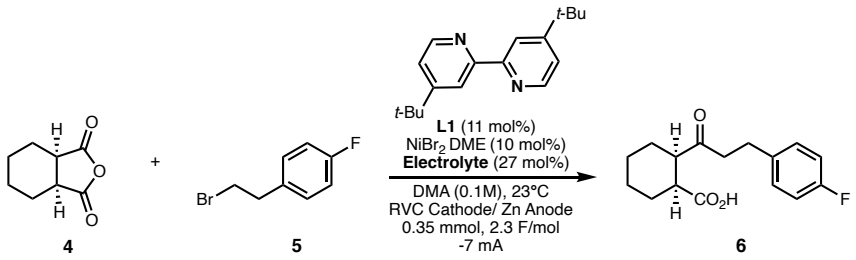
Entry	Deviation	% Yield[a]
1	None	88
2	No Nickel	n.d
3	No Ligand	n.d
4	20% Ni, 22% Ligand	88
5	5% Ni, 6% Ligand	75
6	20 mol% Ligand	83

a. Determined by ^{19}FNMR using CF_3PH as an external standard.

We were particularly interested in the effect of electrolyte loading and identity on our reaction. Doubling the electrolyte loading from 27 mol % (**Table 2.2**, Entry 1) to 54 mol % (**Table 2.2**, entry 2) resulted in a decrease in yield from 88% to 76%. Halving the electrolyte loading from 27 mol % to 13.5 mol % (**Table 2.2**, Entry 3) resulted in a large decrease in yield to 48%. Ammonium salt electrolytes containing coordinating anions such as halides (**Table 2.2**, Entries 4-6) performed comparably to the ammonium acetate electrolyte, with tetrabutylammonium iodide (**Table 2.2**, Entry 4) performing slightly worse at 75% yield. An ammonium salt electrolyte containing a non-

coordinating hexafluorophosphate anion resulted in a large decrease in yield to 49% yield (**Table 2.2**, Entry 7). This could suggest that the electrolyte could be serving a dual role as an additive. Although the mechanistic role of the electrolyte in our reaction has not yet been investigated, we have used additives such as sodium iodide in cross-coupling reactions developed in our lab.[15]

Table 2.2 *Effects of electrolyte type and loading*



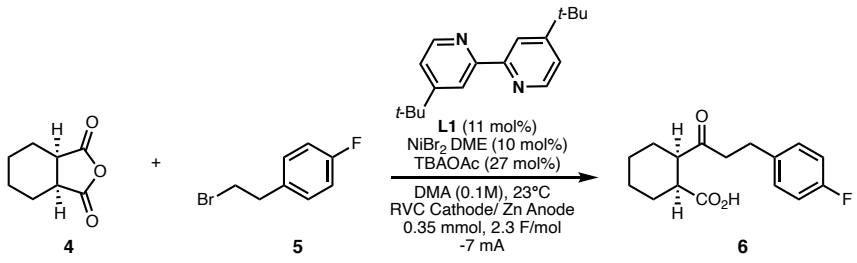
Entry	Electrolyte	% Yield[a]
1	TBAOAc (27 mol%)	88
2	TBAOAc (54 Mol %)	76
3	TBAOAc (13.5 Mol %)	48
4	TBAI	75
5	TBABr	86
6	TBACl	85
7	$TBAPF_6$	49
8	NaOAc	80
9	LiOAc	85
10	NaO_2CH	76

a. Determined by ^{19}FNMR using CF_3PH as an external standard.

We were also interested in increasing the concentration of the reaction to help us increase the yield while also generating more product with less solvent, which would be especially important when the Amgen team scales the reaction up. Increasing the concentration from 0.1 M (**Table 2.3**, Entry 1) to 0.3 M (**Table 2.3**, Entry 2) resulted in an increase in yield from 88% to 94%. Increasing the concentration farther to 0.45 M (**Table 2.3**, Entry 3) resulted in a comparable increase in yield to 94%. We though that decreasing equivalents of alkyl bromide was another way we could increase the efficiency of the reaction. Unfortunately, when the amount of alkyl bromide was reduced to 1.0 and 1.2 equivalents the yield dropped to 53% and 59%, respectively (**Table 2.3**, Entries 4-5). At

higher concentrations, using 1.2 equivalents of alkyl bromide still resulted in a decrease in yield (**Table 2.3**, Entries 6-7).

Table 2.3 *Concentration and Alkyl Halide Loading Optimization*



Entry	Deviation	% Yield[a]
1	None	88
2	0.3 M	94
3	0.45 M	93
4	1.0 Equiv. Alkyl-Br	53
5	1.2 Equiv. Alkyl-Br	59
6	0.3 M, 1.2 Alkyl-Br	81
7	0.45 M, 1.2 Alkyl-Br	82

a. Determined by ^{19}FNMR using CF_3PH as an external standard.

While ligand is another crucial component of the reaction, we did not extensively screen achiral ligands after quickly finding that bipyridine ligands allowed us to obtain significant amount of racemic cross-coupled product. The final goal of this project is to develop an asymmetric RCC, so most of our efforts to explore ligand space were focused on chiral ligand frameworks in both the cyclohexyl and the cyclobutyl anhydride systems.

After achieving high yields of cross-coupled product **6** from cyclohexyl anhydride **4**, we began to optimize on the cyclobutyl anhydride **1**. Similar optimal conditions with bipyridine ligand **L2** afforded cross-coupled product **3a** in 90% yield by ^{1}HNMR and 76% yield after isolation by flash column chromatography (**Scheme 2.2**).

Scheme 2.2 *Initial Cyclobutyl RCC Conditions*

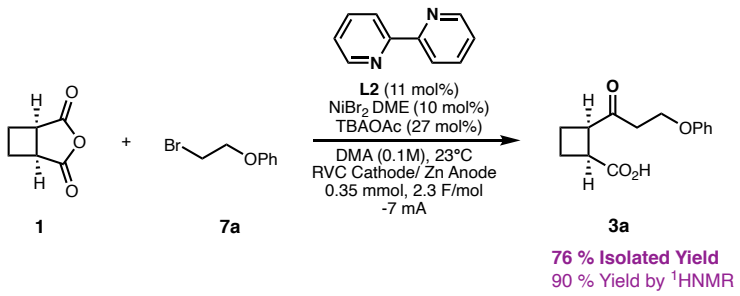
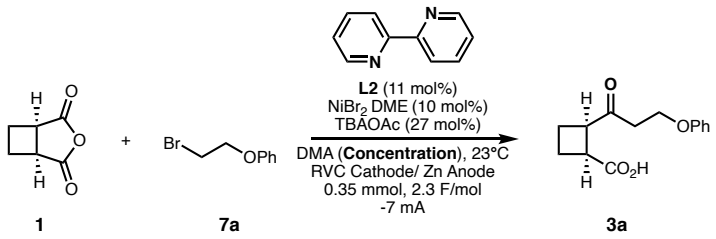


Table 2.4 *Concentration Optimization*



Entry	Concentration	% Yield[a]
1	0.1 M	88
2	0.3 M	55
3	0.5 M	63

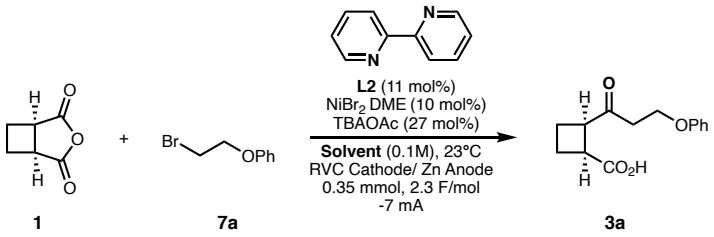
a. Determined by ^{1}HNMR using 2,3,4,5-Tetrachloronitrobenzene as an external standard.

In contrast to the trend observed in the coupling of cyclohexyl anhydride **4**, increasing the concentration of the coupling reaction of cyclobutyl anhydride **1** to 0.3 or 0.5 M resulted in a decrease in yield to 55% and 63%, respectively (**Table 2.4**, Entries 2-3).

One of the parameters in the cyclohexyl system that was not extensively investigated was solvent choice. We decided to screen a variety of polar aprotic solvents of interest to Amgen and found that amide solvents such as DMA and NMP were still optimal (**Table 2.5**, Entry 1 and 3). Using DMF (**Table 2.5**, Entry 2) and DMSO (**Table 2.5**, Entry 5) resulted in decreased the yield to 47% and 37%, and acetonitrile yielded only trace amounts of cross-coupled product (**Table 2.5**, Entry 4). Co-

mixtures of ethereal solvents and amide solvents were also evaluated (**Table 2.5**, Entries 6-8). Mixtures composed of primarily amide solvent performed slightly worse with CPME:NMP (1:2) resulting in a decrease to 84% yield and THF:NMP (1:2) resulting in a decrease to 81% yield (**Table 2.5**, Entries 9-10). While these mixed solvent systems performed slightly worse, we have found that ethereal cosolvents could be important in achieving selectivity in asymmetric reactions so these mixtures could be leveraged in our development of an asymmetric reaction.

Table 2.5 *Solvent optimization*

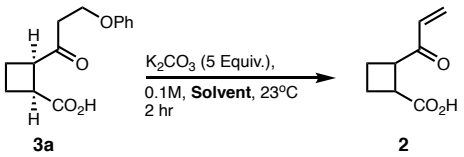


Entry	Solvent	% Yield[a]
1	DMA	88
2	DMF	47
3	NMP	92
4	MeCN	trace
5	DMSO	37
6	DME/DMF (14:1)	trace
7	CPME:DMA (2:1)	40
8	THF:DMA (2:1)	No Rxn[b]
9	CPME:NMP(1:2)	84
10	THF:NMP (1:2)	81

a. Determined by ^{1}HNMR using 2,3,4,5-Tetrachloronitrobenzene as an external standard.
b. Voltage of reaction spiked and exceeded electrasyn maximum voltage.

3. PRODUCT FUNCTIONALIZATION AND PRELIMINARY SCOPE

Table 3.1 *E1cB solvent optimization*



3a **2**

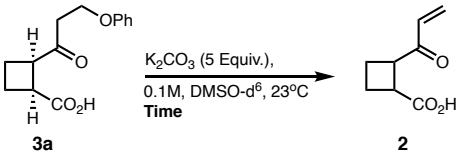
Entry	Solvent	% Yield[a]
1	DMSO	65
2	MeOH	trace
3	*t*-BuOH	38
4	MeCN	19
5	DMF	37

a. Determined by ^{1}HNMR using 2,3,4,5-Tetrachloronitrobenzene as an external standard.

With a procedure to generate **3a** in good yield, we began development of an E1cB protocol to generate target molecule **2**. Our initial conditions used DMSO as a solvent and 5 equivalents of K_2CO_3 (**Table 3.1**, Entry 1) and were able to obtain the target **2** in 65% yield. Switching the solvent to methanol resulted in only trace amounts of product with most of the starting material being converted to a side product that resulted from nucleophilic addition of methanol to the terminal enone (**Table 3.1**, Entry 2). Moving to a more hindered polar protic solvent like *tert*-Butanol, resulted in a decrease in yield to 38% when compared with DMSO (**Table 3.1**, Entry 3). Other polar aprotic solvents such as acetonitrile (**Table 3.1**, Entry 4) and DMF (**Table 3.1**, Entry 5) also resulted in a decrease in yield.

After establishing a procedure that could produce **2** in moderate yield, we were curious how reaction time was affecting yield. By running the E1cB reaction in deuterated DMSO, we found that after 2 hours the yield began to drop. We hypothesized that this was due to decomposition of the reactive enone **2**.

Table 3.2 *Time-course study of E1cB reaction*



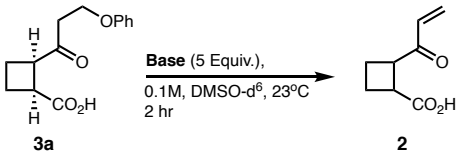
3a **2**

Entry	Time	% Yield[a]
1	1 hr	23
2	2 hr	58
3	3 hr	21

a. Determined by ^{1}HNMR using 2,3,4,5-Tetrachloronitrobenzene as an external standard.

After studying the effect of time on the reaction, we explored different carbonate bases. Switching to a smaller counter-ion such as sodium (**Table 3.3**, Entry 1), resulted in a decrease in yield to 18% when compared to potassium (**Table 3.3**, Entry 2). Switching to a larger counter-ion such as cesium (**Table 3.3**, Entry 3), resulted in no yield of target **2**. Additionally, using a bulky organic base such as DBU resulted in a decrease in yield to 35% (**Table 3.3**, Entry 4). From preliminary studies, we found that the use of K_2CO_3 with DMSO for 2 hours at room temperature was the best procedure for generating target **2** in moderate yield.

Table 3.3 *E1cB carbonate base screen*



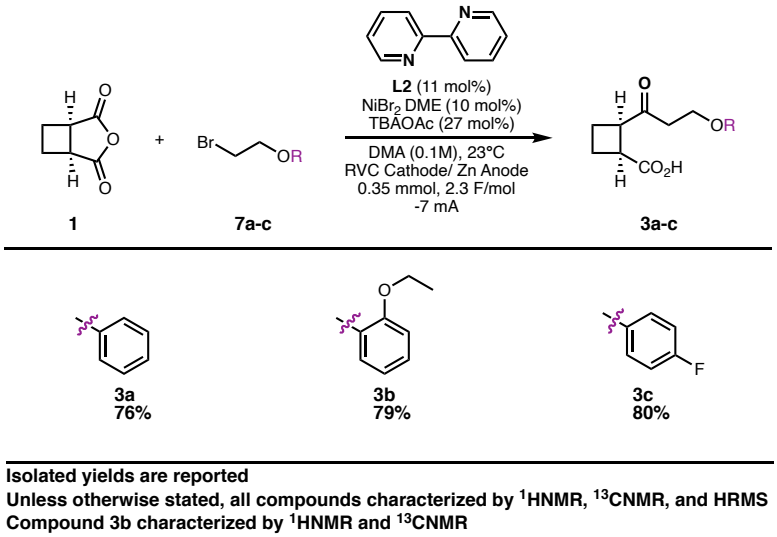
3a **2**

Entry	Base	% Yield[a]
1	Na_2CO_3	18
2	K_2CO_3	65
3	Cs_2CO_3	0
4	DBU	35

a. Determined by ^{1}HNMR using 2,3,4,5-Tetrachloronitrobenzene as an internal standard.

Once we could access **2** in moderate yield, we were curious in exploring the scope of both the reductive cross-coupling and E1cB reaction. We found that the addition of an electron donating ethoxy group to the arene and a weakly withdrawing halide to the arene was tolerated under the reaction conditions. Coupling anhydride **1** with halides **7a-c** yielded cross-coupled products **3a-c** in comparable yields (**Scheme 3.1**), with the substitution on the arene resulting in a small increase in yield.

Scheme 3.1 *Preliminary reductive cross-coupling scope*

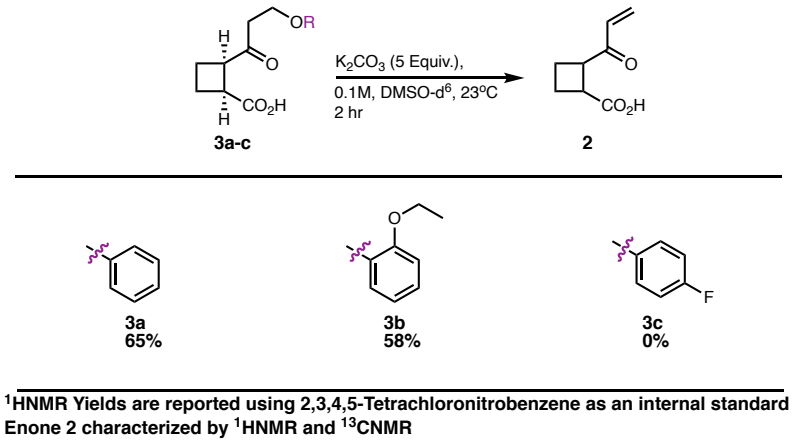


Isolated yields are reported
Unless otherwise stated, all compounds characterized by ^{1}HNMR, ^{13}CNMR, and HRMS
Compound 3b characterized by ^{1}HNMR and ^{13}CNMR

Subjecting **3a** and **3b** to the E1cB conditions (**Scheme 3.2**) yielded target enone **2** in moderate yields. Interestingly, when ketone **3c** was subjected to elimination conditions, no **2** was detected by ^{1}HNMR. We plan to expand the scope of the cross-coupling reaction to secondary bromides and bromides containing heteroatoms other than oxygen to observe how the resulting ketones would behave under elimination conditions. However, most of our efforts after obtaining a procedure to generate racemic target molecule **2** were focused on developing an asymmetric reaction. While a

chiral resolution could be used to obtain **2** as a single enantiomer, developing a procedure that allows for direct access to enantiopure material would be ideal.

Scheme 3.2 *E1cB leaving group effect*

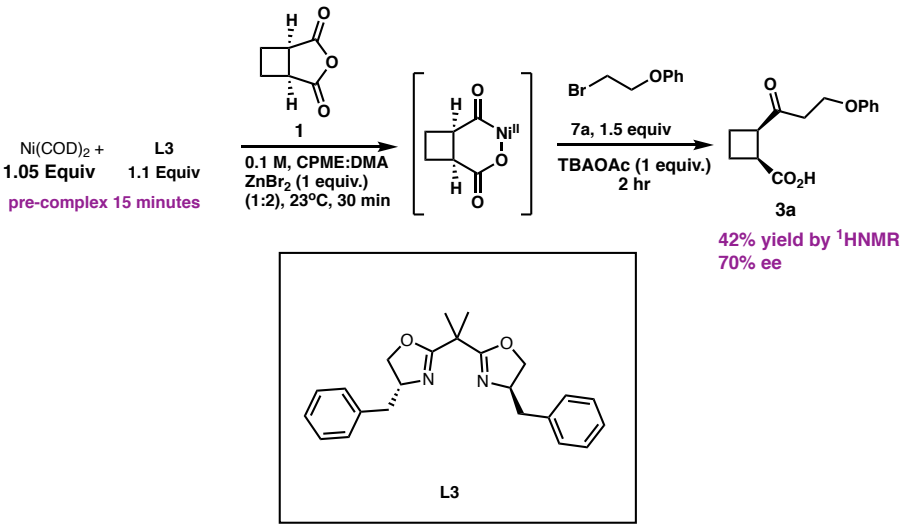


[1]HNMR Yields are reported using 2,3,4,5-Tetrachloronitrobenzene as an internal standard
Enone 2 characterized by [1]HNMR and [13]CNMR

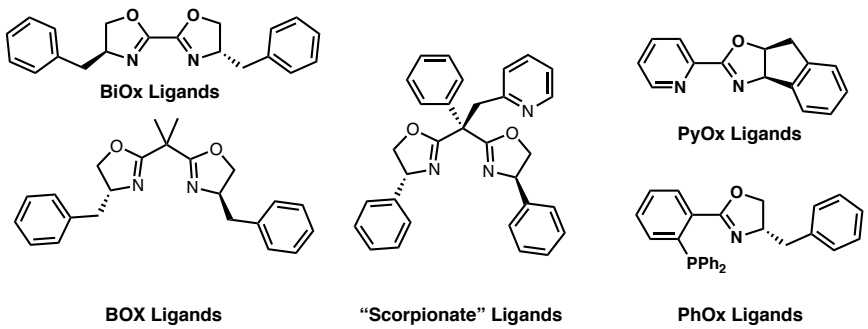
4. PROGRESS TOWARDS ASYMMETRY

After developing a sequence of reactions that could be used to generate racemic substituted cyclobutene **2** in moderate yields, we attempted to apply our reductive cross-coupling conditions with chiral ligands as proof-of-concept. Our initial attempts using the same conditions with different chiral ligand frameworks were unsuccessful. We were unable to produce more than trace amounts of compound **3** with chiral ligands. In order to decouple yield and selectivity, we conducted a series of stoichiometric experiments with chiral ligands (**Scheme 4.1**). We were pleased to observe that by using chiral BOX ligands like **L3** we were able to achieve moderate selectivity. We plan to improve this selectivity by developing new ligands in the BOX framework like the "scorpionate" ligands shown in **Scheme 4.2.** We also plan to screen different chiral ligand classes once we can obtain moderate yields of cross-coupled product in an asymmetric catalytic RCC system. A representative set of these ligands is shown in **Scheme 4.2**. We also plan to try using different substrates such as the α-chlorosilane shown in **Scheme 4.3**. One hypothesis for the lack of reactivity with chiral ligands is that the Nickel(I) complex is unable to initiate halide abstraction with less reactive electrophiles. Using an activated electrophile could be a way to test this hypothesis and potentially promote reactivity with chiral ligands.

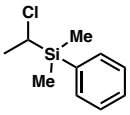
Scheme 4.1 *Proof of principle for asymmetric reductive cross-coupling*



Scheme 4.3 *Representative ligand classes of interest for an asymmetric catalytic RCC reaction*



Scheme 4.3 *Example of a potential activated secondary chloride substrate*



5. CONCLUSION AND FUTURE DIRECTIONS

In conclusion, we have developed a racemic nickel-catalyzed electroreductive cross-coupling reaction to access substituted cyclobutanes. Unactivated alkyl bromides can be coupled with cyclobutyl anhydrides to afford cross-coupled product in up to 80% isolated yield. These products can then be subjected to elimination conditions to access a terminal enone in up to 65% yield. Precedent for an asymmetric cross-coupling reaction has been established with stoichiometric experiments in the BOX ligand framework with cross-coupled product obtained in up to 68% ee. We plan to expand on the substrate scope of the racemic reaction and continue development of an asymmetric cross-coupling reaction.

6. EXPERIMENTAL SECTION

Note: At the time this section was compiled, characterization of reaction products was still in progress. Not all products that will appear in the final publication will have all of their characterization data available in this document.

GENERAL INFORMATION

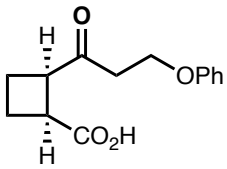
Unless otherwise stated, reactions were performed under a nitrogen atmosphere in a glovebox using dried solvents. Solvents, electrolytes, and ligands were purchased from Millipore Sigma. Nickel(II) bromide dimethoxyethane adduct ($NiBr_2$•dme) was purchased from Strem. Cyclobutane substrate 1 was sent to us by Amgen. Chemicals and reagents were stored in the glovebox and used as received unless otherwise stated. All electrochemical reactions were conducted using an IKA Electrasyn with electrodes purchased from IKA. Reactions were monitored by thin-layer chromatography (TLC) using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by ultraviolet (UV) light or with cerium ammonium molybdate or potassium permanganate staining. Flash column chromatography was performed as described by Still et al. (W. C. Still, M. Kahn, A. Mitra, J. Org. Chem. 1978, 43, 2923.) using silica gel (230- 400 mesh) purchased from Silicycle. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD with Prodigy cryoprobe (at 400 MHz and 101 MHz, respectively). NMR data is reported relative to internal CHCl3 (^{1}H, $\delta = 7.26$) and CDCl3 (^{13}C, $\delta = 77.0$). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired from the Caltech Mass Spectral Facility using field ionization (FI).

CROSS-COUPLING REACTIONS

General Procedure A: Racemic reaction on 0.35 mmol scale

In the glovebox, to a 5 mL oven-dried Electrasyn vial equipped with a 2-dram teflon-coated stir bar was added anhydride (1.0 equiv., 0.35 mmol), alkyl bromide (1.5 equiv., 0.53 mmol), TBAOAc (27 mol%, 0.09 mmol), ligand (11 mol%, 0.04 mmol), and $NiBr_2$•dme (10 mol%, 0.04 mmol). DMA (3.5 mL, 0.1 M) was added by syringe and the reaction solution was stirred until homogeneous. An Electrasyn cap equipped with an oven-dried RVC electrode (working) and a Zn anode (counter, cleaned by dipping in HCl and scuffing with 400 or 600 grit sandpaper) was attached to the Electrasyn vial. The Electrasyn vial was capped tightly with a rubber septum and brought out of the glovebox. Electrolysis was commenced using an IKA Electrasyn with constant current under positive N_2 (-7 mA, 0.45 mmol, 2.3 F/mol, 1000 rpm stir rate) and left until completion. Upon completion of electrolysis, the electrasyn cap was removed and the electrodes were rinsed with EtOAc into a 125 ml sep funnel. The RVC electrode was transferred to a 20 ml scint vial, which was filled with EtOAc then sonicated for 2 mins. The EtOAc was transferred to the sep funnel and the scint vial was filled with 3N HCl and sonicated for 2 mins. The HCl was transferred to the separatory funnel. The electrodes were washed with water (3x, do not collect) then with acetone (3x, leave full on the 3rd cleaning), and the vial was capped and left on the bench overnight. 20 mL 1M LiCl was added to the sep funnel, the phases were separated, and the aqueous phase was extracted with EtOAc (3x 20 ml, 80 ml total). The combined organic phases were washed with 1M LiCl (ca. 40 mL), dried over Na2SO4, and concentrated in vacuo. The crude material was then purified by silica gel column chromatography to afford the desired product (20 mL SiO2, 20% EA/1% AcOH/ 69% Hexane, UV/CAM/$KMnO_4$).

Characterization of Cross-Coupling Reaction Products:



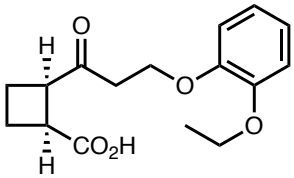
3a (DKC-01-185): Prepared from cis-cyclobutylanhydride (**1**, 44.1 mg, 0.35 mmol) and benzyl 2-bromoethyl ether **7a** according to General Procedure **A** with 2-2'-Bipyridal **L2** to produce **3a** in 76% yield as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.24 (m, 2H), 6.94 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.90 – 6.86 (m, 2H), 4.33 – 4.15 (m, 2H), 3.61 (tdd, *J* = 8.3, 5.2, 1.9 Hz, 1H), 3.51 – 3.38 (m, 1H), 2.97 – 2.80 (m, 2H), 2.47 – 1.98 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.70, 177.47, 129.56, 121.03, 114.62, 77.32, 62.87, 47.77, 40.69, 40.43, 21.89, 21.72.

FTIR (NaCl, thin film): 2952, 1708, 1600, 1496, 1243, 1243, 751, 690 cm^{-1}

HRMS (FI, *m/z*): calc'd for $C_{14}H_{16}O_4$ $[M]^+$: 248.1043; found: 248.1035.

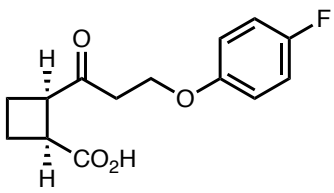


3b (DKC-01-177): Prepared from cis-cyclobutylanhydride (**1,** 44.1 mg, 0.35 mmol) and 2-(2-ethoxyphenoxy)ethylbromide (**7b**, 129 mg, 0.53 mmol) according to General Procedure **A** with 2-2'-Bipyridal **L2** to produce **3b** in 79% yield as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 – 6.85 (m, 4H), 4.47 – 4.37 (m, 1H), 4.20 – 3.99 (m, 3H), 3.71 – 3.58 (m, 1H), 3.54 (dddt, *J* = 9.8, 8.8, 6.4, 1.0 Hz, 1H), 3.17 – 3.00 (m, 1H), 2.70 (ddd, *J* = 17.3, 5.7, 4.0 Hz, 1H), 2.59 – 2.05 (m, 5H), 1.47 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.20, 176.26, 148.23, 121.24, 121.06, 113.09, 112.89, 64.64, 63.14, 47.63, 41.05, 40.37, 29.72, 21.18, 20.59, 14.70.

FTIR (NaCl, thin film): 2921, 1710, 1592, 1507, 1451, 1331, 1252, 1228, 1125, 1038, 743 cm^{-1}



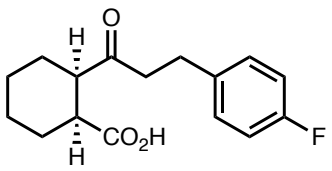
3c (DKC-01-164): Prepared from cis-cyclobutylanhydride (**1**, 44.1 mg, 0.35 mmol) and 1-(2-bromoethoxy-4-fluorobenzene) (**7c**, 115 mg, 0.53 mmol) according to General Procedure **A** with 2-2'-Bipyridal **L2** to produce **3c** in 80% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 – 6.90 (m, 1H), 6.82 (ddd, *J* = 9.2, 4.5, 2.6 Hz, 1H), 4.28 – 4.08 (m, 1H), 3.65 – 3.53 (m, 1H), 3.49 – 3.38 (m, 1H), 2.96 – 2.78 (m, 1H), 2.44 – 2.17 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.77, 115.93, 115.70, 115.62, 115.54, 77.23, 63.49, 47.65, 40.55, 40.36, 30.96, 21.80, 21.60.

FTIR (NaCl, thin film): 2944, 1709, 1505, 1205, 826 cm^{-1}

HRMS (FI, *m/z*): calc'd for $C_{14}H_{15}O_4F$ $[M]^+$: 266.0949; found: 266.0946.

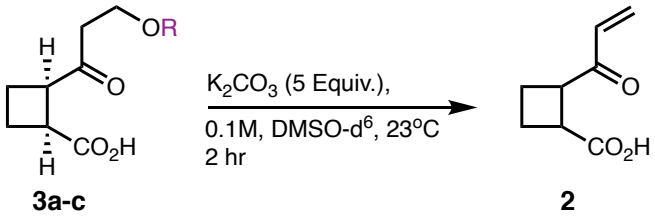


6 (AMS-05-100): Prepared from cis-cyclobutylanhydride (**1**, 44.1 mg, 0.35 mmol) and 1-(2-bromoethoxy-4-fluorobenzene) (**7c**, 115 mg, 0.53 mmol) according to General Procedure **A** with 2-2'-Bipyridal **L2** to produce **6** in up to 88% yield by ^{1}HNMR,

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 – 7.08 (m, 2H), 7.04 – 6.89 (m, 2H), 2.91 – 2.67 (m, 6H), 2.08 (ddd, *J* = 13.1, 9.5, 6.4 Hz, 1H), 2.02 – 1.90 (m, 1H), 1.80 (tq, *J* = 7.9, 4.6 Hz, 2H), 1.59 (tt, *J* = 11.1, 6.1 Hz, 1H), 1.39 (qd, *J* = 10.0, 5.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.55, 179.92, 162.56, 160.14, 136.98, 136.94, 129.82, 129.74, 115.24, 115.03, 49.42, 42.36, 41.85, 28.73, 25.98, 25.88, 23.93, 23.44.

Elimination Reactions:



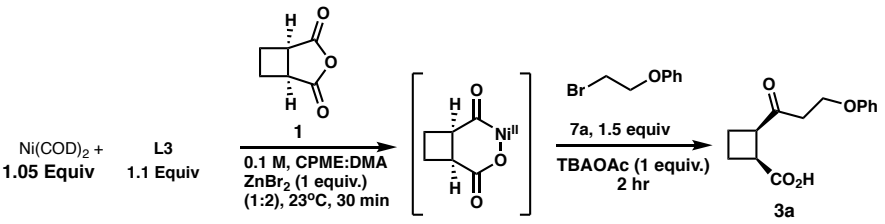
3a-c **2**

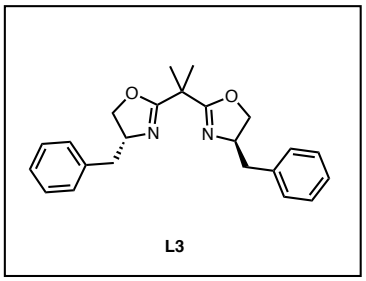
Outside of the glovebox, to a 2-dram oven-dried vial equipped equipped with a stir bar (ends of the stir-bar were shaved with a razor blade for even stirring) was added cross-coupled product **3a-c** (1 equiv., 0.1 mmol) and K_2CO_3 (5 equiv., 124 mg, 0.5 mmol, 5 equiv.). 5.0 mL DMSO-d_6 was then added (0.1 M) and the reaction was stirred at 1000 rpm for 2 hours. Reactions were typically monitored by ^{1}HNMR using 2,3,4,5-tetrachloronitrobenzene as an internal standard. After 2 hours, the reaction was diluted to 20 mL with EtOAc and added to a separatory funnel. 20 mL 3M HCl was added, and the organic layer was extracted. The organic layer was washed with water (4 x 20 mL) and then filtered over Na_2SO_4. The organic filtrate was then concentrated in vacuo. The crude material was purified by silica gel column chromatography (20 mL SiO2, 10% EA/90% Hexane, UV). Isolated yield TBD, small amounts were purified for NMR characterization and further characterization by Amgen.

^{1}H NMR (400 MHz, C_6D_6): δ 6.17 (dd, *J* = 17.7, 10.6 Hz, 1H), 5.99 (dd, *J* = 17.7, 1.2 Hz, 1H), 5.31 (dd, *J* = 10.6, 1.2 Hz, 1H), 3.66 – 3.45 (m, 2H), 2.21 – 1.97 (m, 1H), 1.96 – 1.63 (m, 3H).

^{13}C NMR (101 MHz, C_6D_6): δ 198.10, 175.87, 134.58, 44.92, 39.28, 29.87, 21.55, 21.06.

Stochiometric Enantioselective Reactions:

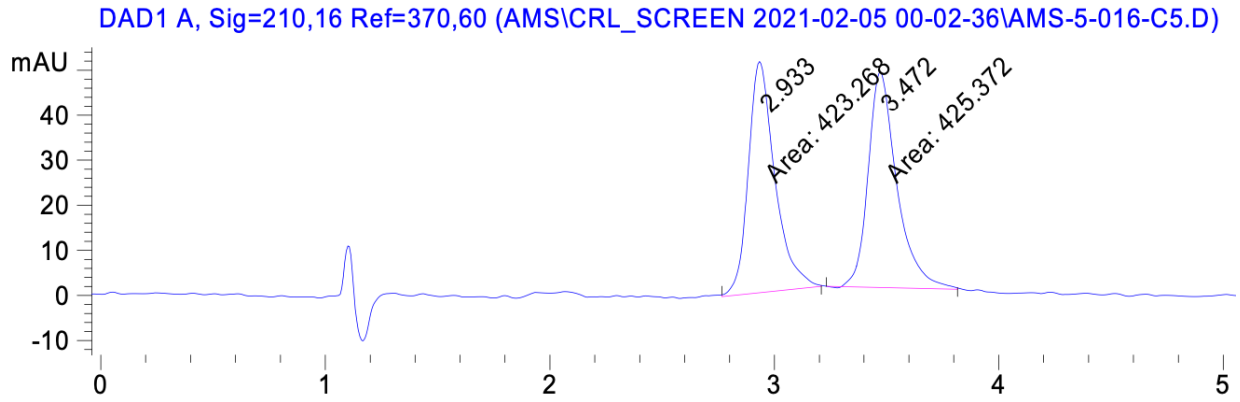




Inside of the glovebox, to an oven-dried 1-dram vial equipped with a stir-bar was added $Ni(COD)_2$ (28.9 mg, 1.05 equiv, 0.105 mmol) and **L3** (39.9 mg, 1.1 equiv., 0.11mmol) in 2 mL DMA:THF 3:7. The solution was stirred for 15 minutes inside of the glovebox at which point, **1** (12.6 mg, 1.0 equiv., 0.1 mmol) and $ZnBr_2$ (22.5 mg, 1.0 equiv., 0.1 mmol) was added to the reaction vial and stirred for an additional 30 minutes. After 30 minutes, alkyl bromide **7a** (30.2 mg, 1.5 equiv., 0.15 mmol) and TBAOAc (30.2 mg, 1.0 equiv., 0.1 mmol) was added to the vial and stirred for an additional 2 hours. After 2 hours, the reaction was diluted to 20 mL with EtOAc and transferred to a separatory funnel. 10 mL 1 M LiCl and 10 mL 1 M HCl were added to the separatory funnel. The aqueous layer was then extracted with EtOAc (3 x 15mL). The combined organics were then washed with 20 mL of 1 M LiCl and filtered over Na_2SO_4. The filtrate was concentrated in vacuo. The crude material was analyzed by ^{1}HNMR with 2,3,4,5-tetrachloronitrobenzene added as an external standard and the NMR yield was determined to be **42%**. The crude material was purified by silica gel column chromatography (20 mL SiO2, 20% EA/1% AcOH/ 69% Hexane, UV/CAM/$KMnO_4$) to yield a white powder.

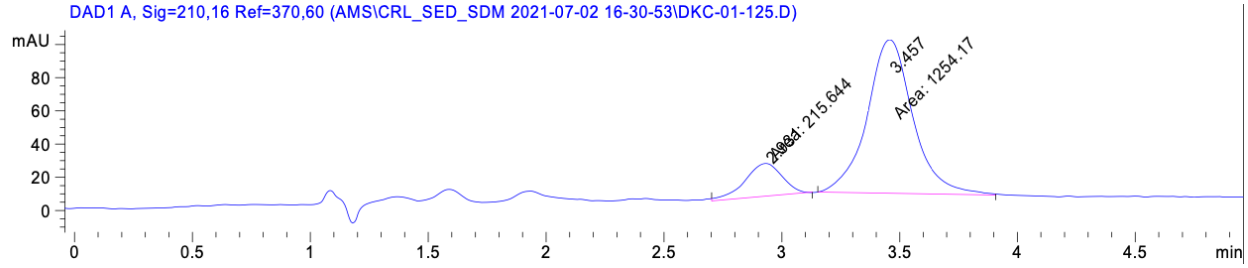
The enantiomeric excess of the purified material was determined to be **70%** by chiral SFC (AS-H, 2.5 mL/min, 25% IPA in CO_2, $\lambda = 210$ nm)

SFC Data for Racemic 3a



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.933	MM	0.1371	423.26770	51.45766	49.8760
2	3.472	MM	0.1478	425.37177	47.96597	50.1240

SFC Data for Enantioenriched 3a



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.931	MM	0.1817	215.64401	19.77772	14.6715
2	3.457	MM	0.2257	1254.17358	92.62733	85.3285

7. REFERENCES

1. Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. Enantioselective and Enantiospecific Transition-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents to Construct C-C Bonds. *Chem. Rev.* **2015**, *115*(17), 9587–9652.

2. Poremba, K. E.; Dibrell, S. E.; Reisman, S. E. Nickel-Catalyzed Enantioselective Reductive Cross-Coupling Reactions. *ACS Catal.* **2020**, *11*(15), 8237–8246.

3. Lucas, E. L.; Jarvo, E. R. Stereospecific and Stereoconvergent Cross-Couplings Between Alkyl Electrophiles. *Nat Rev Chem*, *1*, **2017**, 0065.

4. Beaver, M. G.; Zhang, E.–X.; Liu, Z.–Q.; Zheng, S.–Y.; Wang, B.; Lu, J.–P.; Tao, J.; Gonzalez, M.; Jones, S.; Tedrow, J. S. Development and Execution of a Production-Scale Continuous [2+2] Photocycloaddition. *Org. Process. Res. Dev.* **2020**, *24*, 2139–2146.

5. Bercot, E. A.; Rovis, T. A Mild and Efficient Catalytic Alkylative Monofunctionalization of Cyclic Anhydrides. *J. Am. Chem. Soc.* **2002**, *124*(2), 174–175.

6. Stache, E. E.; Rovis, T.; Doyle, A. G. Dual Nickel- and Photoredox-Catalyzed Enantioselective Desymmetrization of Cyclic *meso*-Anhydrides. *Angew. Chem. Int. Ed.* **2017**, *56*(13), 3679 – 3683.

7. Lin, T.; Mi, J.; Song, L.; Gan, J.; Luo, P.; Mao, J.; Walsh, P. J. Nickel-Catalyzed Desymmetrizing Cross-Electrophile Coupling of Cyclic *Meso*-Anhydrides

8. Lin, T.; Gu, Y.; Qian, P.; Guan, H.; Walsh, P. J.; Mao, J. Nickel-catalyzed reductive coupling of homoenolates and their higher homologues with unactivated alkyl bromides. *Nat. Commun.* **2020**, *11*, 5638.

9. Everson, D. A.; Weix, D. J. Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem.* **2014**, *79*(11), 4793–4798.

10. Yin, J.; Maguire, C. K.; Yasuda, N.; Brunskill, A. P.; Klapars, A. Impact of Lead Impurities in Zinc Dust on the Selective Reduction of a Dibromoimidazole Derivative. *Org. Process Res. Dev.* **2017**, *21*(1), 94–97.

11. Lin, Q.; Diao, T. Mechanism of Ni-Catalyzed Reductive 1,2-Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*(44), 17937–17948.

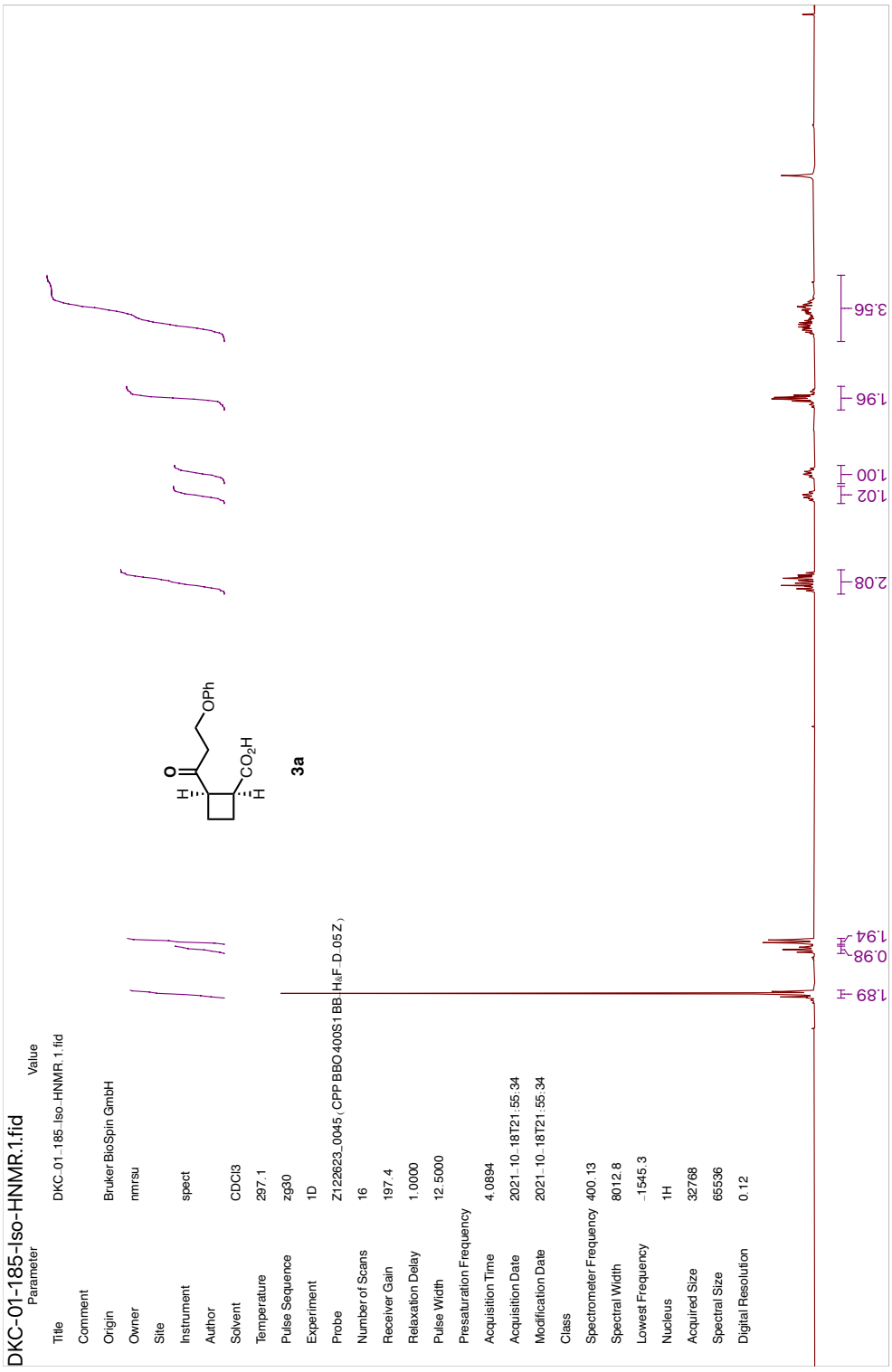
12. Delano, T. J.; Reisman, S. E. Enantioselective Electroreductive Coupling of Alkenyl and Benzyl Halides via Nickel Catalysis. *ACS Catal.***2019**, *9*(8), 6751–6754.

13. Lin, Q.; Fu, Y.; Diao, T. Monovalent Nickel-Mediated Radical Formation: A Concerted Halogen-Atom Dissociation Pathway Determined by Electroanalytical Studies. *J. Am. Chem. Soc.* **2021**, *143*(35), 14196–14206.

14. Perkins, R. J.; Pedro, D. J.; Hansen, E. C. Electrochemical Nickel Catalysis for Sp^2-Sp^3 Cross-Electrophile Coupling Reactions of Unactivated Alkyl Halides *Org. Lett*. **2017**, *19*, 3755–3758.

15. Cherney, A. H.; Reisman, S. E. Nickel-Catalyzed Asymmetric Reductive Cross-Coupling Between Vinyl and Benzyl Electrophiles. *J. Am. Chem. Soc*. **2014**, *136*, 14365−14368.

Appendix: Relevant Spectra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Title
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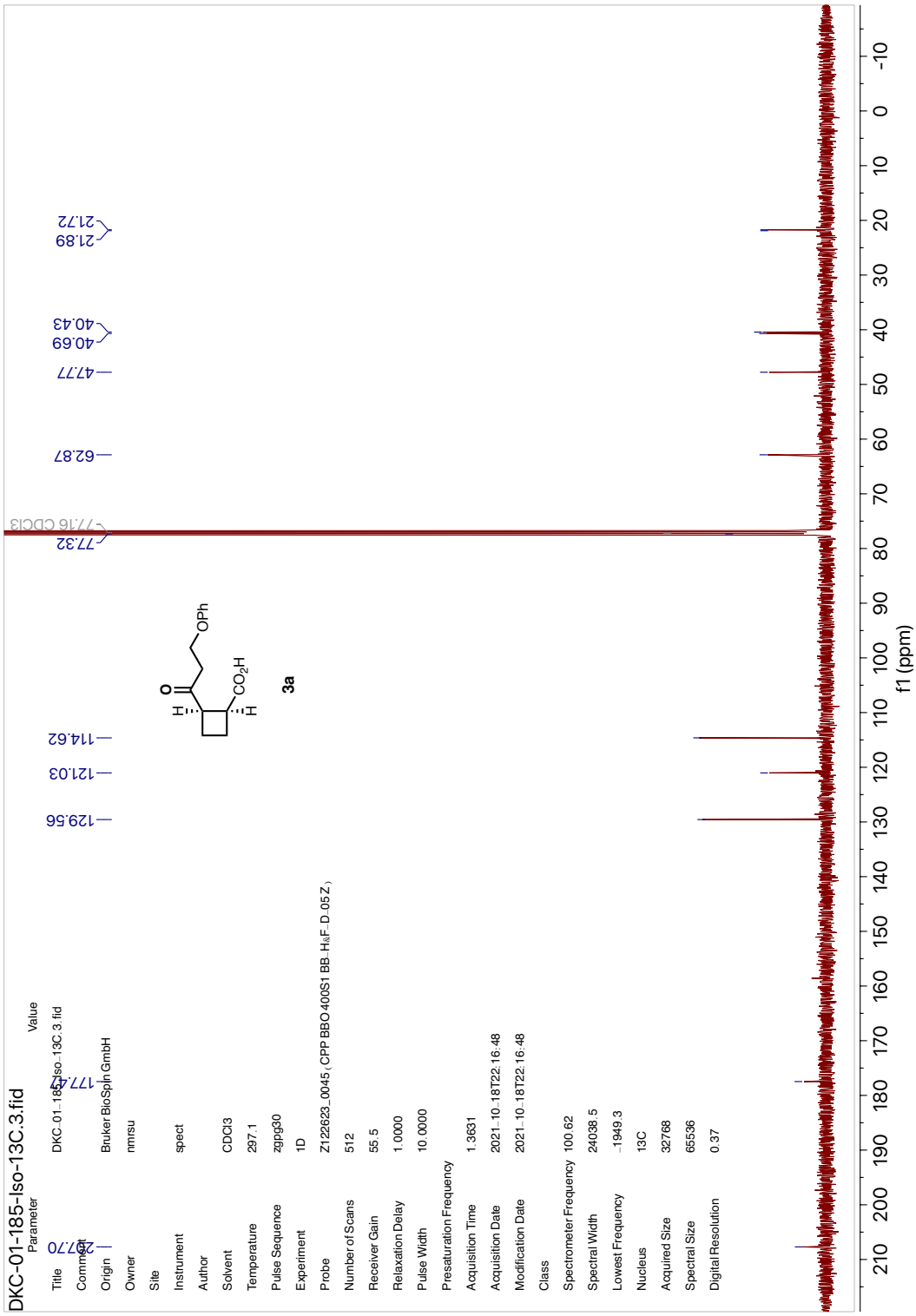
Comment
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Site
Instrument
spect
Author
Solvent
CDCl3
Temperature
297.1
Pulse Sequence
zg30
Experiment
1D
Probe
Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans
16
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
12.5000
Presaturation Frequency
Acquisition Time
4.0894
Acquisition Date
2021_10_18T21:55:34
Modification Date
2021_10_18T21:55:34
Class
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.3
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
Digital Resolution
0.12
OPh
CO2H
3a
1.89
0.98
1.94
2.08
1.02
1.00
1.96
3.56
f1 (ppm)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Value
Title
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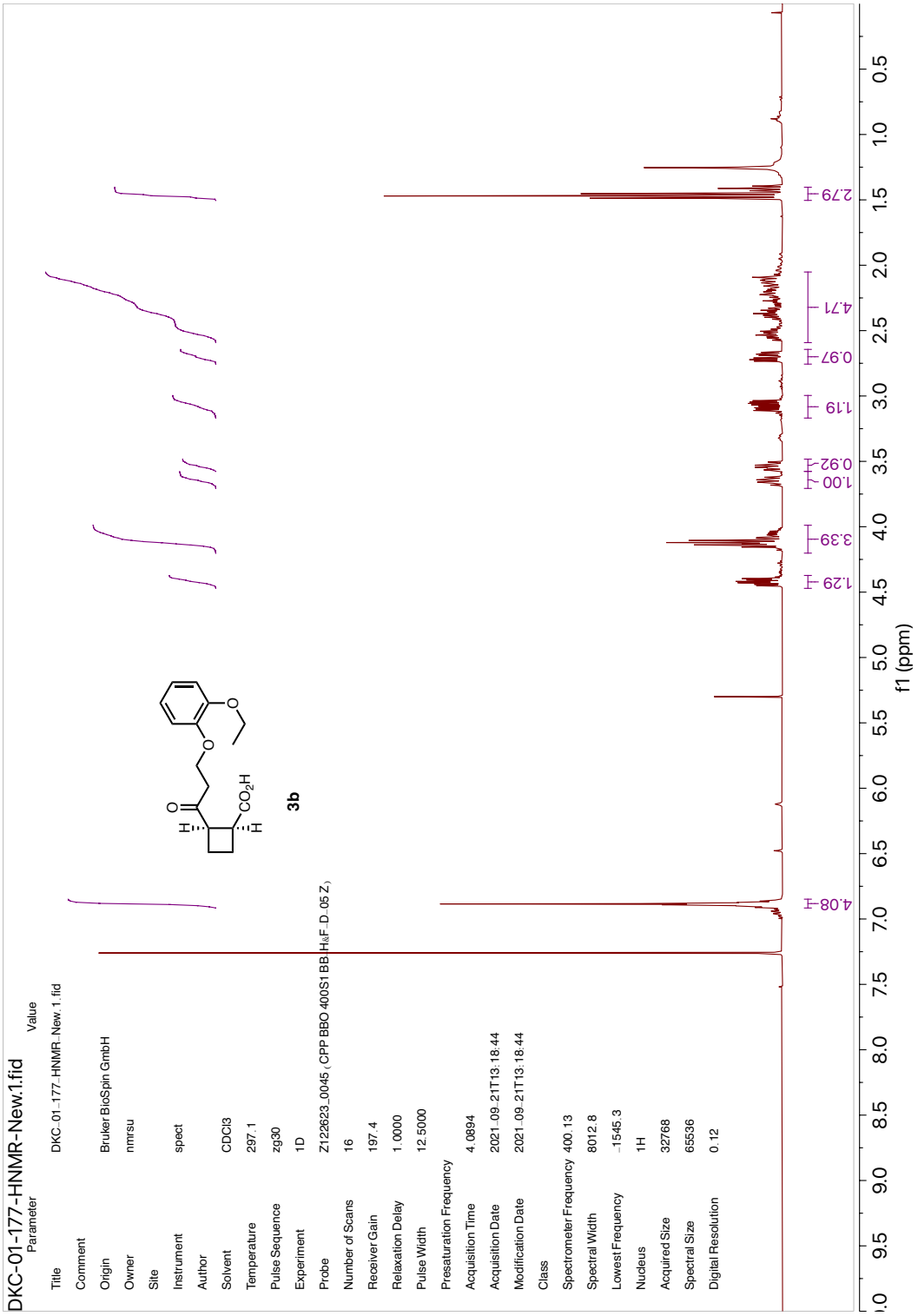
Comment
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Site
Instrument
spect
Author
Solvent
CDCl3
Temperature
297.1
Pulse Sequence
zgpg30
Experiment
1D
Probe
Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans
512
Receiver Gain
55.5
Relaxation Delay
1.0000
Pulse Width
10.0000
Presaturation Frequency
Acquisition Time
1.3631
Acquisition Date
2021-10-18T22:16:48
Modification Date
2021-10-18T22:16:48
Class
Spectrometer Frequency
100.62
Spectral Width
24038.5
Lowest Frequency
-1949.3
Nucleus
13C
Acquired Size
32768
Spectral Size
65536
Digital Resolution
0.37
197.70
177.47
129.56
121.03
114.62
77.32
77.16 CDCl3
62.87
47.77
40.69
40.43
21.89
21.72
OPh
CO2H
3a
f1 (ppm)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Title
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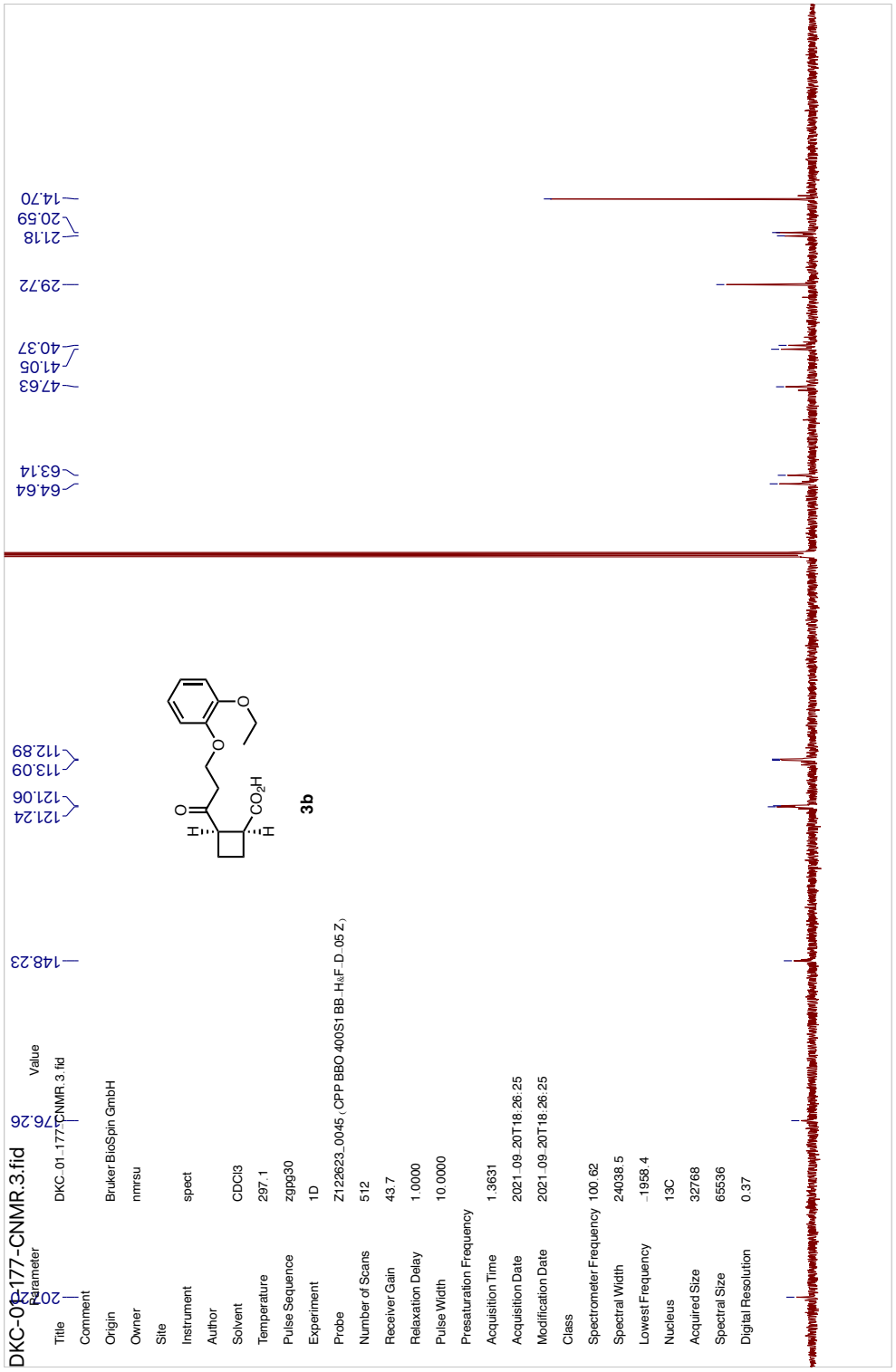
Comment
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Site
Instrument
spect
Author
Solvent
CDCl3
Temperature
297.1
Pulse Sequence
zg30
Experiment
1D
Probe
Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans
16
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
12.5000
Presaturation Frequency
Acquisition Time
4.0894
Acquisition Date
2021_09_21T13:18:44
Modification Date
2021_09_21T13:18:44
Class
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.3
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
Digital Resolution
0.12
3b
4.08
1.29
3.39
1.00
0.92
1.19
0.97
4.71
2.79
f1 (ppm)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Owner nmrsu
Site
Instrument spect
Author
Solvent CDCl3
Temperature 297.1
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 512
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Presaturation Frequency
Acquisition Time 1.3631
Acquisition Date 2021-09-20T18:26:25
Modification Date 2021-09-20T18:26:25
Class
Spectrometer Frequency 100.62
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Lowest Frequency -1958.4
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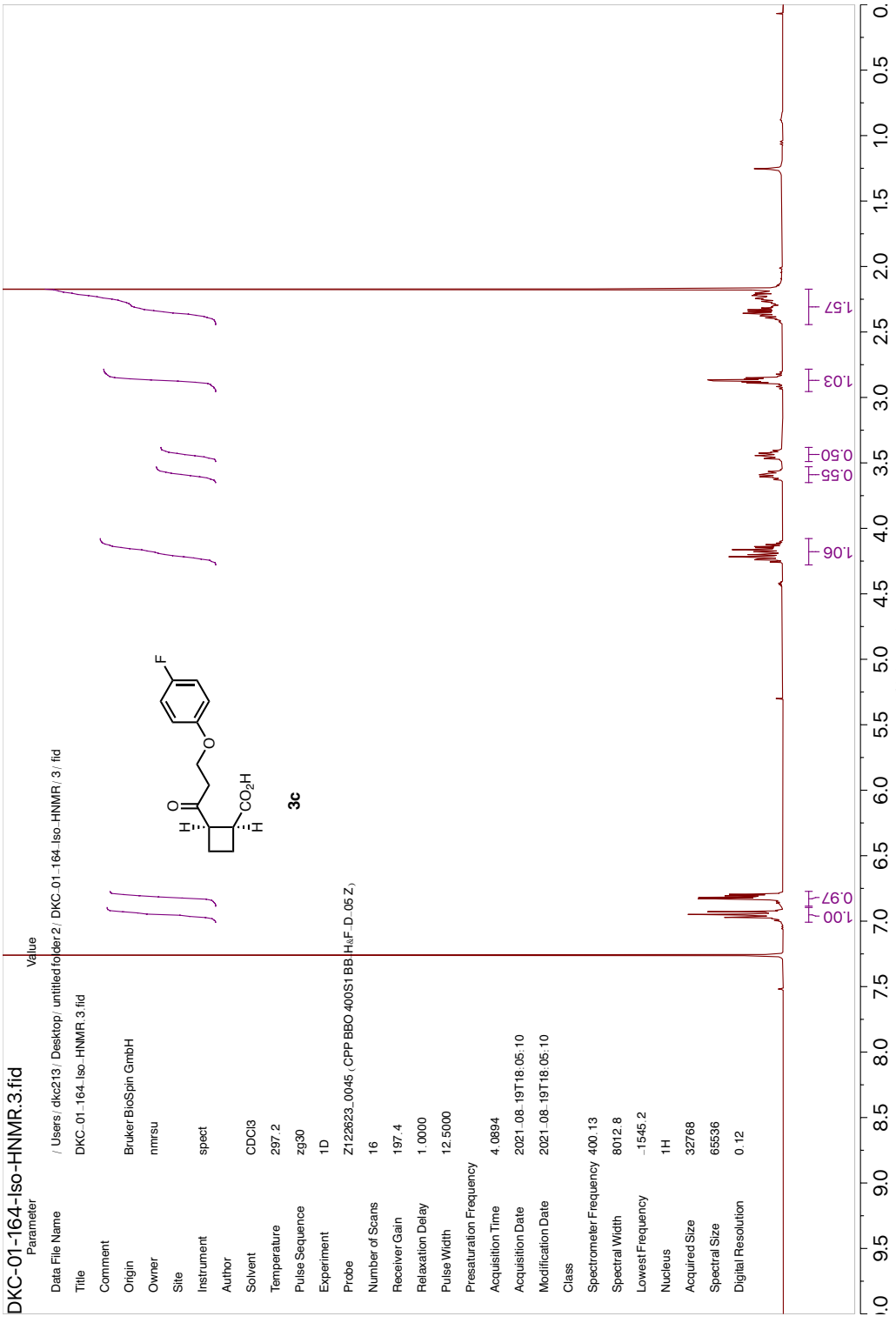
Spectral Size 65536
Digital Resolution 0.37
3b
f1 (ppm)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Comment
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Site
Instrument
spect
Author
Solvent
CDCl3
Temperature
297.2
Pulse Sequence
zg30
Experiment
1D
Probe
Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans
16
Receiver Gain
197.4
Relaxation Delay
1.0000
Pulse Width
12.5000
Presaturation Frequency
Acquisition Time
4.0894
Acquisition Date
2021_08_19T18:05:10
Modification Date
2021_08_19T18:05:10
Class
Spectrometer Frequency
400.13
Spectral Width
8012.8
Lowest Frequency
-1545.2
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
Digital Resolution
0.12
F
O
O
H
CO2H
H
3c
1.00
0.97
1.06
0.55
0.50
1.03
1.57
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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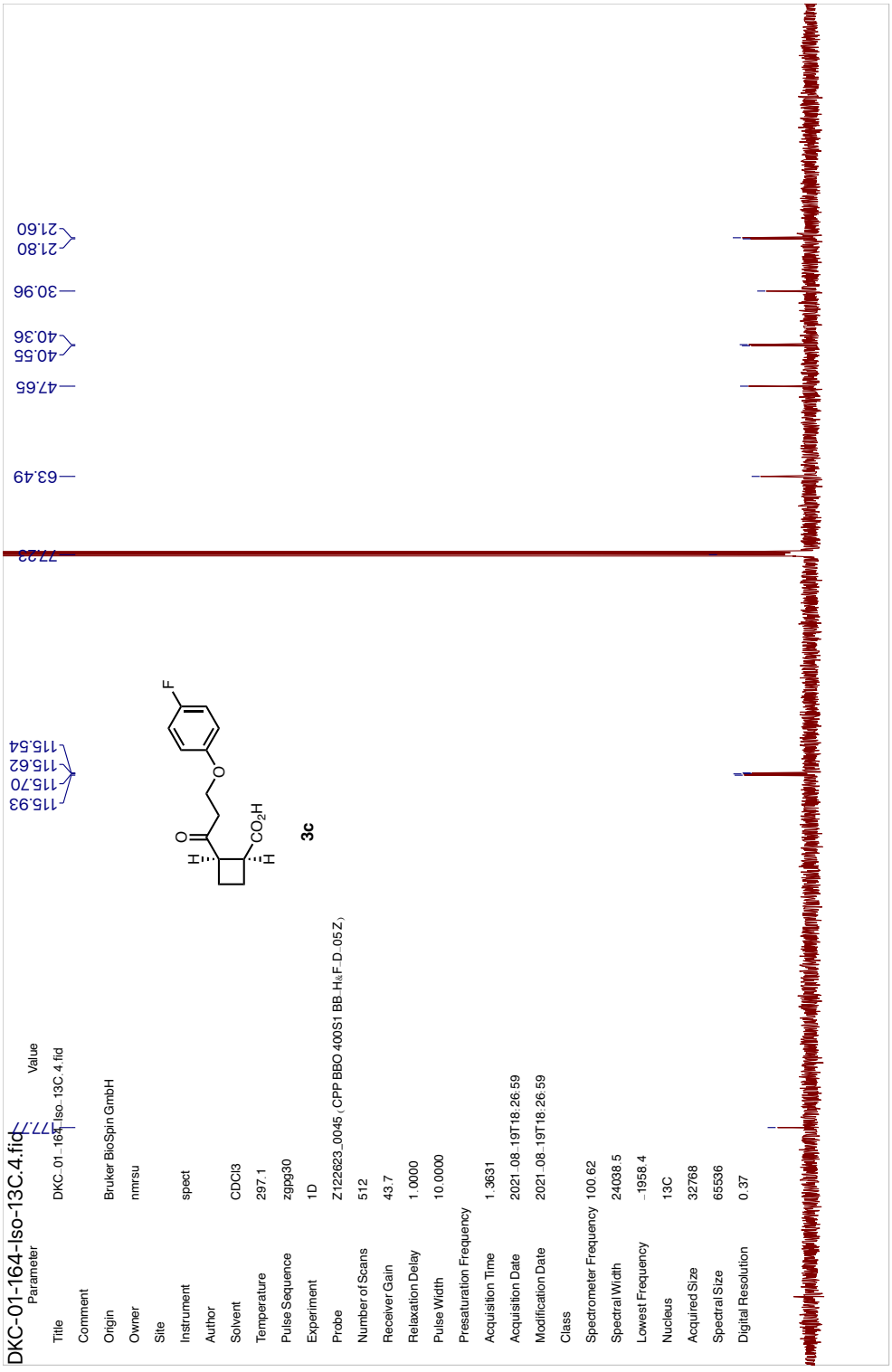
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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Title
DKC_01_164_Iso_13C_4.fid
Comment
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Site
Instrument
spect
Author
Solvent
CDCl3
Temperature
297.1
Pulse Sequence
zgpg30
Experiment
1D
Probe
Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans
512
Receiver Gain
43.7
Relaxation Delay
1.0000
Pulse Width
10.0000
Presaturation Frequency
Acquisition Time
1.3631
Acquisition Date
2021-08-19T18:26:59
Modification Date
2021-08-19T18:26:59
Class
Spectrometer Frequency
100.62
Spectral Width
24038.5
Lowest Frequency
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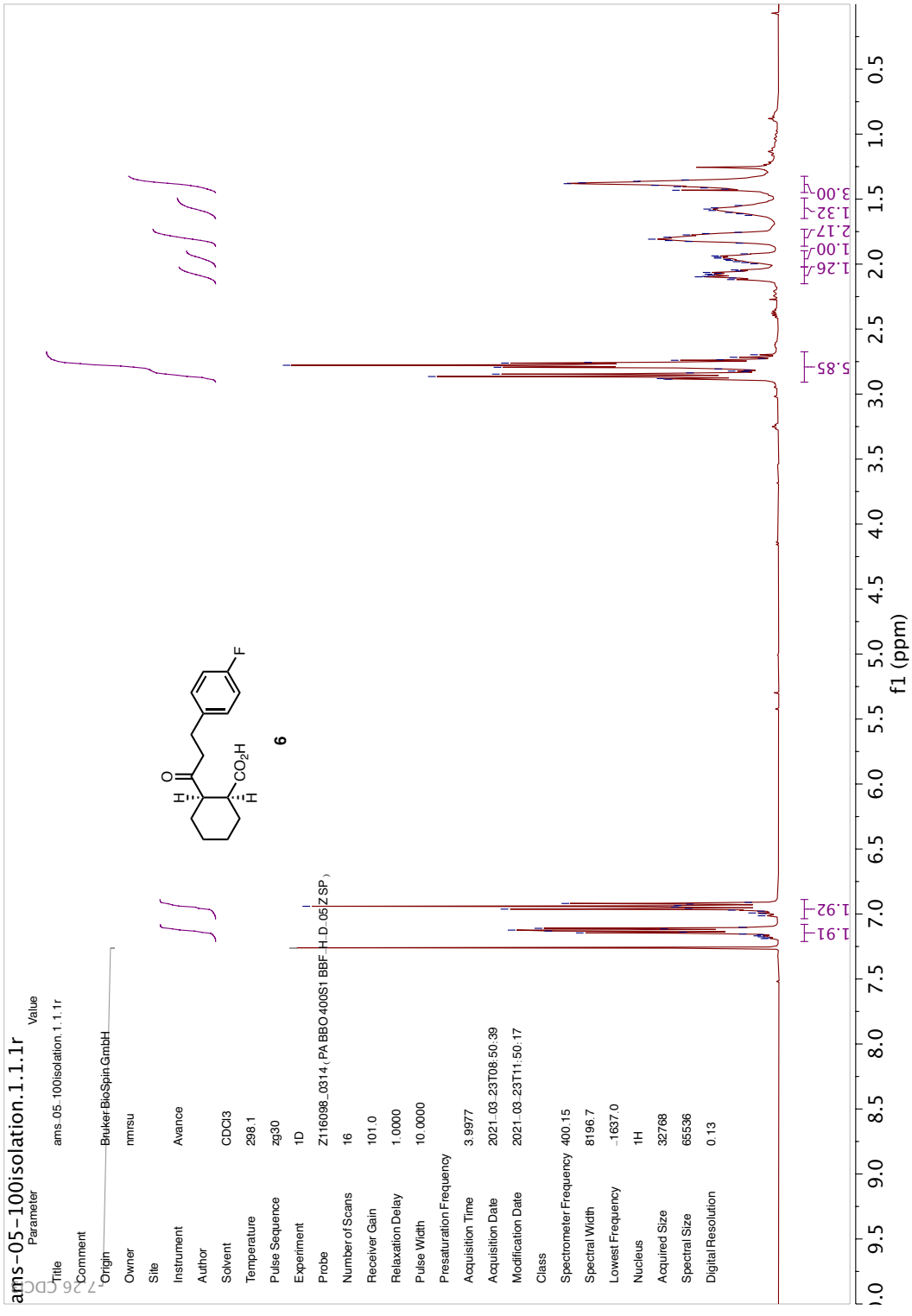
Nucleus
13C
Acquired Size
32768
Spectral Size
65536
Digital Resolution
0.37
3c
f1 (ppm)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ams_05_100isolation.1.1.1r
Comment
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Site
Instrument
Avance
Author
Solvent
CDCl3
Temperature
298.1
Pulse Sequence
zg30
Experiment
1D
Probe
Z116098_0314_(PA BBO 400S1 BBF H-D-05 Z SP)
Number of Scans
16
Receiver Gain
101.0
Relaxation Delay
1.0000
Pulse Width
10.0000
Presaturation Frequency
Acquisition Time
3.9977
Acquisition Date
2021_03_23T08:50:39
Modification Date
2021_03_23T11:50:17
Class
Spectrometer Frequency
400.15
Spectral Width
8196.7
Lowest Frequency
-1637.0
Nucleus
1H
Acquired Size
32768
Spectral Size
65536
Digital Resolution
0.13
CDCl3 7.26
6
O
H
CO2H
H
F
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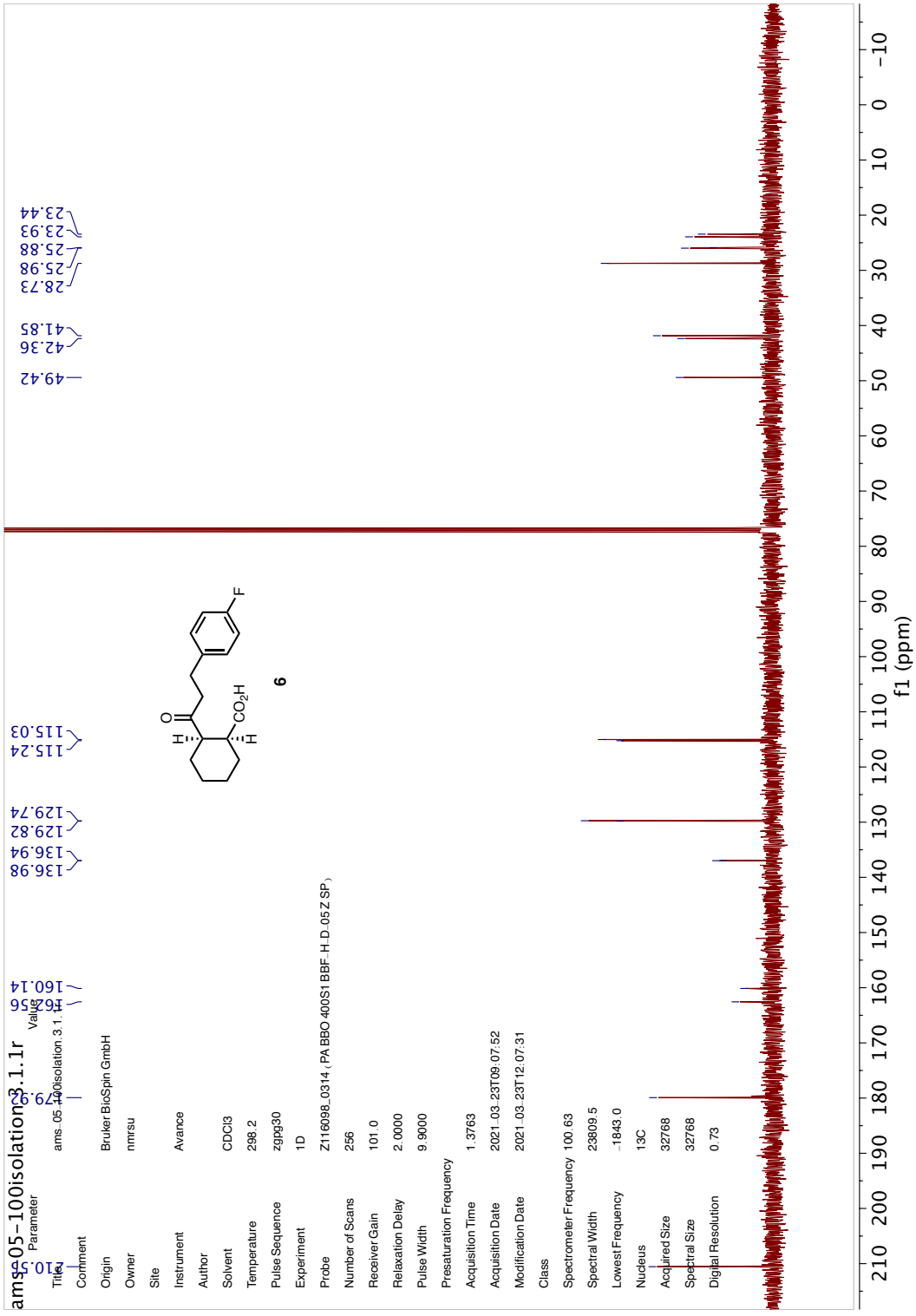
1.92
5.85
1.26
1.00
2.17
1.32
3.00
f1 (ppm)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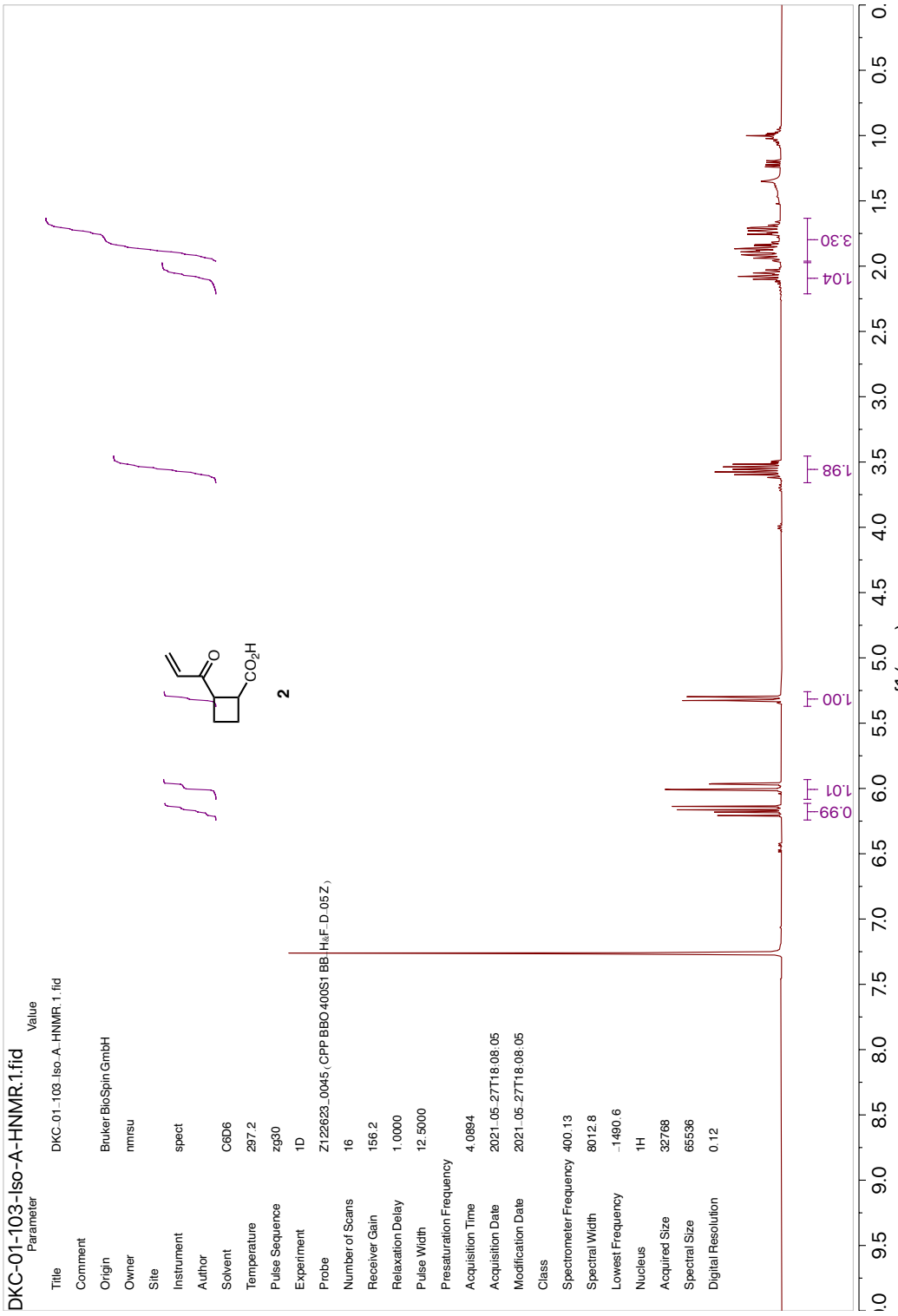
ams-05-100isolation-3.1.1r
Comment
Origin
Bruker BioSpin GmbH
Owner
nmrsu
Site
Instrument
Avance
Author
Solvent
CDCl3
Temperature
298.2
Pulse Sequence
zgpg30
Experiment
1D
Probe
Z116098_0314_(PA BBO 400S1 BBF-H-D-05Z SP)
Number of Scans
256
Receiver Gain
101.0
Relaxation Delay
2.0000
Pulse Width
9.9000
Presaturation Frequency
Acquisition Time
1.3763
Acquisition Date
2021-03-23T09:07:52
Modification Date
2021-03-23T12:07:31
Class
Spectrometer Frequency
100.63
Spectral Width
23809.5
Lowest Frequency
-1843.0
Nucleus
13C
Acquired Size
32768
Spectral Size
32768
Digital Resolution
0.73
210.51
179.67
162.56
160.14
136.98
136.94
129.82
129.74
115.24
115.03
49.42
42.36
41.85
28.73
25.98
25.88
23.93
23.44
O
H
CO2H
H
F
6
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)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Parameter Value
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Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Site
Instrument spect
Author
Solvent C6D6
Temperature 297.2
Pulse Sequence zg30
Experiment 1D
Probe Z122623_0045_CPP BBO 400S1 BB-H&F-D-05 Z
Number of Scans 16
Receiver Gain 156.2
Relaxation Delay 1.0000
Pulse Width 12.5000
Presaturation Frequency
Acquisition Time 4.0894
Acquisition Date 2021_05_27T18_08_05
Modification Date 2021_05_27T18_08_05
Class
Spectrometer Frequency 400.13
Spectral Width 8012.8
Lowest Frequency -1490.6
Nucleus 1H
Acquired Size 32768
Spectral Size 65536
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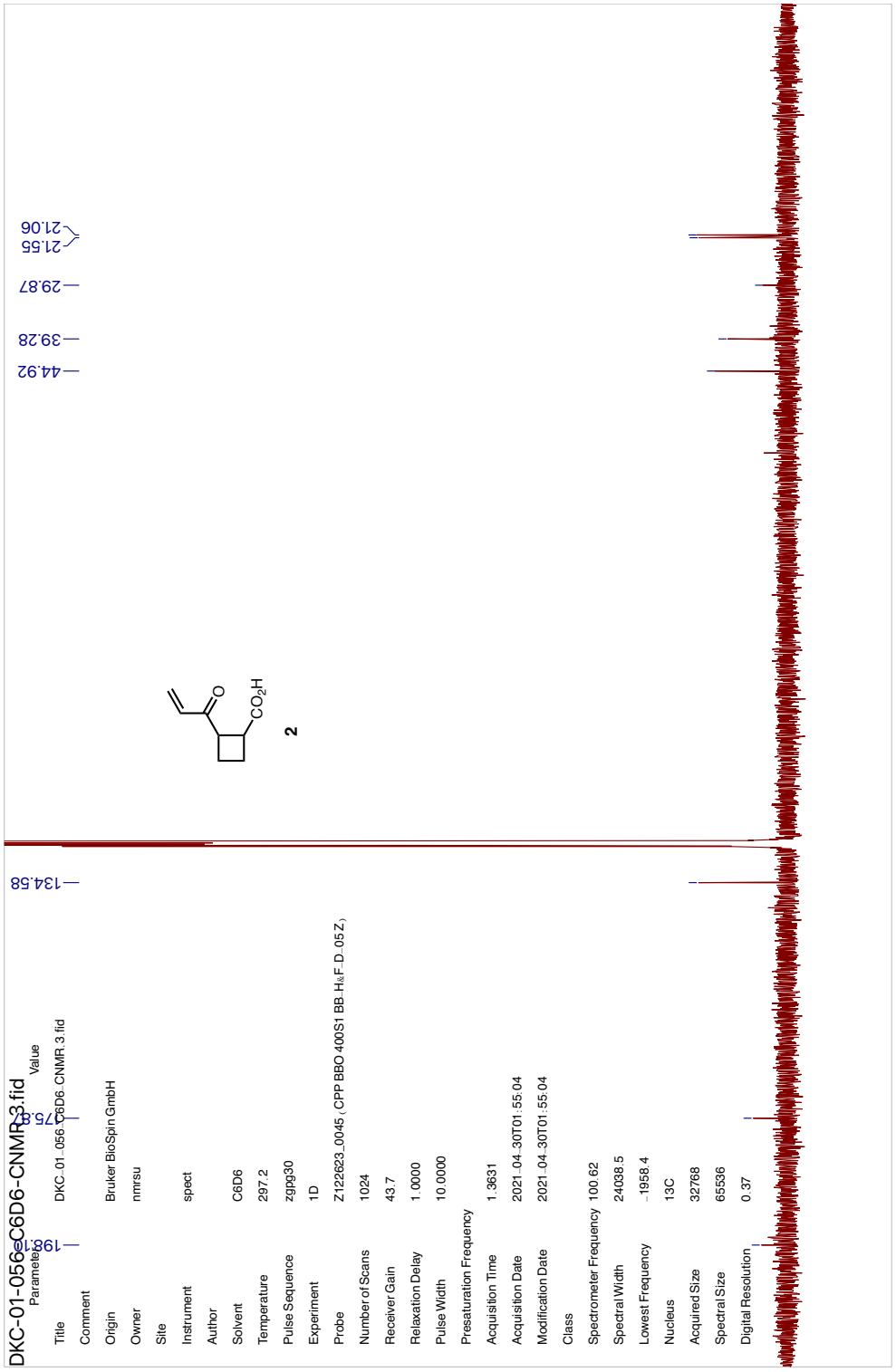
2
CO2H
O
0.99
1.01
1.00
1.98
1.04
3.30
f1 (ppm)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Parameter Value
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Comment
Origin Bruker BioSpin GmbH
Owner nmrsu
Site
Instrument spect
Author
Solvent C6D6
Temperature 297.2
Pulse Sequence zgpg30
Experiment 1D
Probe Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans 1024
Receiver Gain 43.7
Relaxation Delay 1.0000
Pulse Width 10.0000
Presaturation Frequency
Acquisition Time 1.3631
Acquisition Date 2021_04_30T01.55.04
Modification Date 2021_04_30T01.55.04
Class
Spectrometer Frequency 100.62
Spectral Width 24038.5
Lowest Frequency -1958.4
Nucleus 13C
Acquired Size 32768
Spectral Size 65536
Digital Resolution 0.37
198.10
175.81
134.58
44.92
39.28
29.87
21.55
21.06
O
CO2H
2
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)