Ruthenium-Catalyzed C-C Bond Formation via Functional-Group Directed C-H Bond Activation

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Abstract

Ruthenium-Catalyzed C-C Bond Formation via Functional-Group Directed C-H Bond Activation

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This thesis is an investigation on the formation of carbon-carbon (C-C) bonds in the presence of ruthenium catalyst.

In the first part of this thesis, oxidative dehydrogenative coupling reactions for carbon-carbon (C-C) bond formation are described. A ruthenium-catalyzed dimerization of 2-phenylpyridine derivatives is demonstrated to synthesize biaryls using iron(III) chloride as the terminal oxidant. In addition, the oxidative cross coupling of arenes and cycloalkanes is also illustrated, achieving a unique para-selectivity.

In the second part of the thesis, a ruthenium-catalyzed olefination via decarbonylative addition of aldehydes to terminal alkynes is described. Conjugated and isolated C=C bonds can be chemoselectively generated in two catalytic systems starting from aromatic and aliphatic aldehydes. The method provides an alternative synthesis of C=C bonds from direct C-H bond addition to triple bonds.

Résumé

Ruthenium-Catalyzed C-C Bond Formation via Functional-Group Directed C-H Bond Activation

Xiangyu Guo Superviseur: Prof. Chao-Jun Li

Université McGill

Cette thèse est le résultat de la recherche sur la formation de liaisons carbone-carbone (C-C), catalysé par le ruthénium.

La première partie de cette thèse expose les résultats sur la formation de liaison carbone-carbone (C-C) par la réaction de couplage oxydant par déshydrogénation. La synthèse de composés biaryl par l'utilisation d'un catalyseur de ruthénium a permis la dimérisation des dérivés de la 2-phénylpyridine en présence de chlorure de fer (III) comme oxydant terminal. En outre, l'oxydative cross-coupling entre arènes et cycloalcanes, a montrer une notable, para-sélectivité.

La seconde partie de cette thèse, décrit les résultats obtenue sur la réaction d'oléfination decarbonylative entre un aldéhyde et un alcyne vrai, catalyser par le ruthénium. En partant d'aldéhydes aromatiques ou aliphatiques et par l'utilisation de deux systèmes catalytiques, la synthèse chemioselective de double liaison C=C conjuguée ou isolée ont pu être réalisé. Cette réaction fournit ainsi, une intéressante alternative à la synthèse de doubles liaisons C=C par la directe addition de liaison C-H sur une triple liaison.

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Abbreviations

Ac	acetyl
acac	acetoacetonate
aq	aqueous
Ar	aryl
ArF	perfluoroaryl
BINOL	1,1’-bi-2-naphthol
bipy	2,2’-bipyridine
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BQ	*p*-benzoquinone
Bz	benzoyl
^{n}Bu	n-butyl
^{t}Bu	*tert*-butyl
C-C	carbon-carbon
CDC	cross-dehydrogenative coupling
CG	chelating groups
C-H	carbon-hydrogen
cod	cyclooctadiene
Cp	cyclopentadiene
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
Cy	cyclohexyl
p-cymene	1-methyl-4-(1-methylethyl)benzene
d	doublet (^{1}H NMR)
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DG	directing group
di	difunctionalization product
diglyme	bis(2-methoxyethyl) ether

DME	1,2-dimethoxyethane
DMF	N, N-dimethylformamide
DMSO	dimethylsulfoxide
DMAP	4-Dimethylaminopyridine
DPPA	diphenylphosphoryl azide
dppm	bis(diphenylphosphino)methane
dppe	bis(diphenylphosphino)ethane
dppp	bis(diphenylphosphino)propane
dppb	bis(diphenylphosphino)butane
dtbpy	2,6-di-*tert*-butyl-pyridine
eq.	equations
equiv	equivalents
EWG	electron-withdrawing group
FG	functional group
HBPin	Pinacolborane
HRMS	high resolution mass spectrometry
HPMV	heteropolymolybdovanadic acid $H_4PMo_{11}VO_{40}$
Hz	Hertz
imd	imidazole
ind	indenyl
IR	infrared spectroscopy
J	coupling constant
M	metal
m	multiplet (^{1}H NMR)
m-CPBA	meta-chloroperoxybenzoic acid
Me	methyl
NMR	nuclear magnetic resonance spectroscopy
NFSI	*N*-fluorobenzenesulfonimide
Nu	nucleophile
[O]	oxidant
o	ortho

OTf	trifluoromethanesulfonate
Oxone	potassium peroxymonosulfate
p	para
Ph	phenyl
Piv	pivaloyl
ppm	parts per million
^{i}Pr	isopropyl
Pyr	pyridine
q	quartet (^{1}H NMR)
rt	room temperature
s	singlet (^{1}H NMR)
TBHP	*tert*-butyl hydroperoxide
TBP	di-*tert*-butyl peroxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
T-HYDRO	*tert*-butyl hydroperoxide, 70 wt% in water
TIPS	triisopropylsilane
TLC	thin layer chromatography
TMS	tetramethylsilane
tpp	porphyrin
triphos	bis(2-diphenylphosphinoethyl)phenylphosphine
Ts	tosyl

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Part I.

Oxidative Dehydrogenative Coupling Reactions for C-C Bond Formation

Chapter 1 – Introduction to Oxidative Dehydrogenative Coupling Reactions

The Carbon-Carbon (C-C) bond is a principal functionality in organic chemistry, making the C-C bond formation reaction one of the most important reactions in organic synthesis.[1] Chemists are paying increasing attention to this area, and many new methodologies have been developed in the past years.

From the perspectives of operational simplicity, availability of starting materials, and atom economy, the need still exists for more efficient routes to accomplish C-C bond formations.[3] In recent decades, Professor Li and other researchers have made significant progress in the synthesis of C-C bonds. They showed that starting directly from two unfunctionalized C-H bonds, C-C bonds can be generated by cross-dehydrogenative coupling (CDC) under oxidative conditions.[2] This strategy is not only advantageous with respect to a reduction of byproduct formation, but also allows for a minimization of reaction steps. However, there are certain obstacles making this method quite challenging, such as the low activity of C-H bonds and selective functionalization of the desired C-H bond in the presence of all the others.

In this chapter, a concise review of intermolecular oxidative coupling reactions will be presented. The review will be focused on functionalization of arenes by introducing aryl groups and alkyl groups.

1.1 – Oxidative Dehydrogenative Coupling Reactions with Biaryl Bond Formation

The biaryl moiety is a common structural motif in natural products, agrochemicals, chiral ligands and pharmaceuticals.[4] The broadly applicable Ar-Ar bond synthetic methods include the coupling reactions (such as Suzuki, Stille, Negishi, Kumada, Hiyama, etc.) using a combination of an aryl halide (or pseudohalide) and an appropriate organometallic reagent (Figure 1a).[5] Transition metal-catalyzed C-H bond activation followed by C-C bond formation for direct arylation, has emerged as a powerful synthetic methodology in the past two decades (Figure 1b).[5c,6] Furthermore, an even more attractive approach would be the direct oxidative coupling of two unfunctionalized arenes or heteroarenes to give the corresponding biaryl product (Figure 1c). Because this strategy takes advantage of the C-H bonds as the only functionality, selectivity between different C-H bonds becomes an essential issue. In addition, controlling cross- or homo-coupling products in one-pot reactions also emerges as a big challenge.

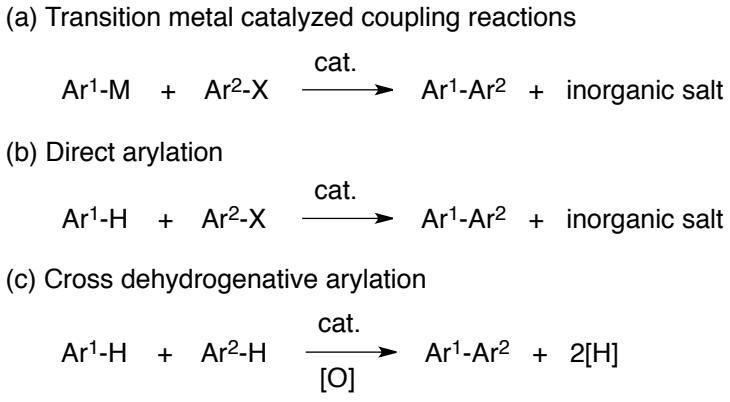
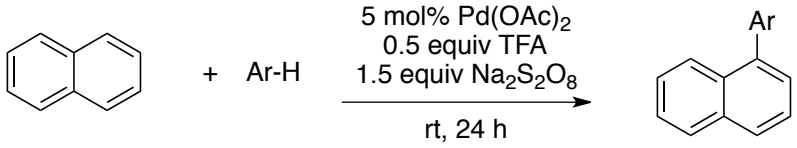


Figure 1. Catalytic strategies for the synthesis of biaryls via coupling reactions

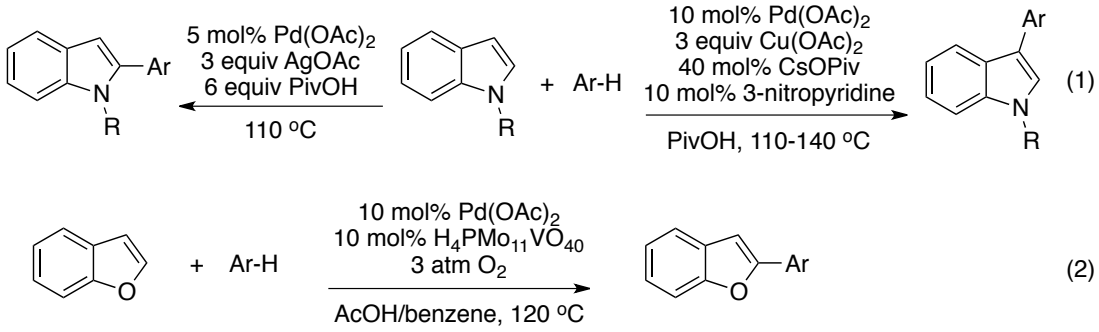
1.1.1 – Oxidative Cross-Dehydrogenative-Coupling Reactions between Arenes

Selectively functionalizing a desired aromatic C-H bond in an oxidative cross-coupling reaction is a major challenge. Selective functionalization could be accomplished with the direction of the distinct electron density of the C-H bonds. In 2006, Lu and co-workers pioneered the cross-coupling reaction of naphthalene and simple arenes using $K_2S_2O_8$ as the terminal oxidant (Scheme 1.1).[7] Reaction took place predominantly at the active α-position of naphthalenes.



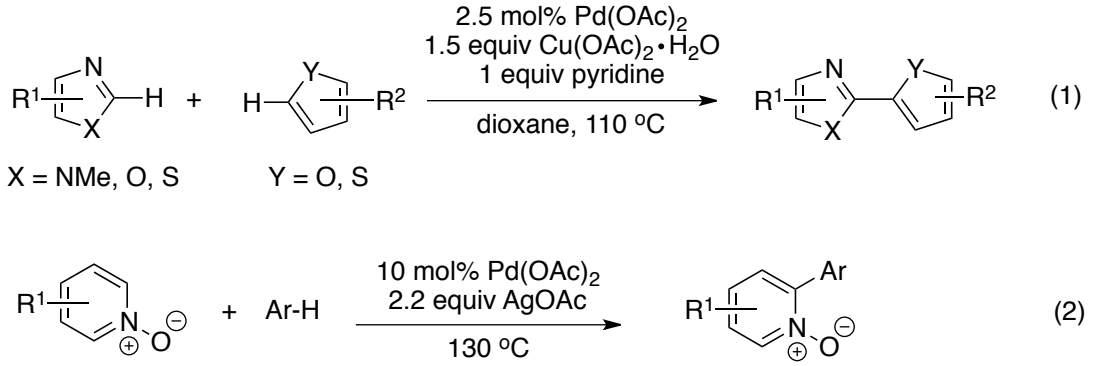
Scheme 1.1 Pd-catalyzed oxidative arylation of naphthalene.

Later on, Fagnou and co-workers published their work on the C3 arylation of N-acetylindoles with simple arenes.[8] On changing the oxidant from $Cu(OAc)_2$ to AgOAc, C2 selectivity was promoted (Scheme 1.2, Eq. 1).[9] Meanwhile, DeBoef and co-workers described similar cross-coupling reactions, functionalizing the C2 position of benzofurans using a catalytic amount of heteropolymolybdovanadic acid $H_4PMo_{11}VO_{40}$ (HPMV) together with O_2 as the oxidant (Scheme 1.2, Eq. 2).[10] Furthermore, they also expanded the reaction to indoles and explained the oxidant-controlled regioselectivity between C2 and C3 positions.[11]



Scheme 1.2 Pd-catalyzed oxidative arylation of protected indoles.

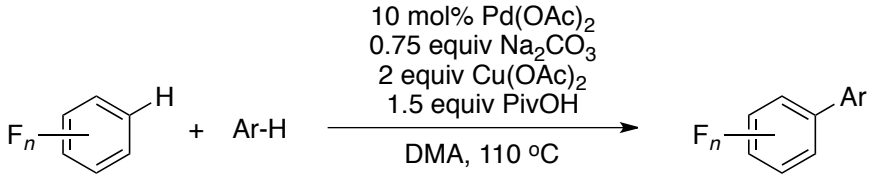
Hu and You published a report on the oxidative cross-coupling of *N*-heteroarenes with a variety of thiophenes or furans in the presence of a stoichiometric amout of $Cu(OAc)_2$ (Scheme 1.3, Eq. 1).[12] They also demonstrated that pyridine *N*-oxides could undergo the same coupling reaction. Chang and co-workers also revealed that simple arenes could react with pyridine *N*-oxides via a coupling reaction (Scheme 1.3, Eq. 2).[13]



Scheme 1.3 Pd-catalyzed oxidative 2-arylation of *N*-containing heteroarenes.

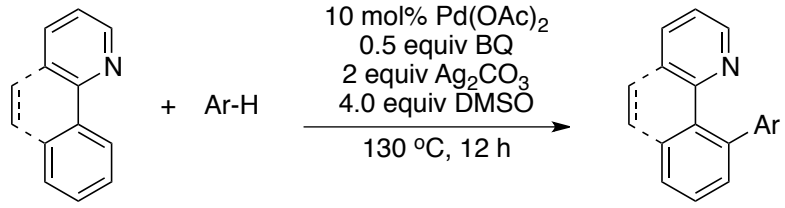
Perfluoroarenes were also applied to couple with benzene by Wei and Su, with $Pd(OAc)_2$ as the catalyst and $Cu(OAc)_2$ as the oxidant (Scheme 1.4).[14]

Concurrently, Zhang and co-workers developed the coupling reaction of perfluoroarenes with heteroarenes.[15]



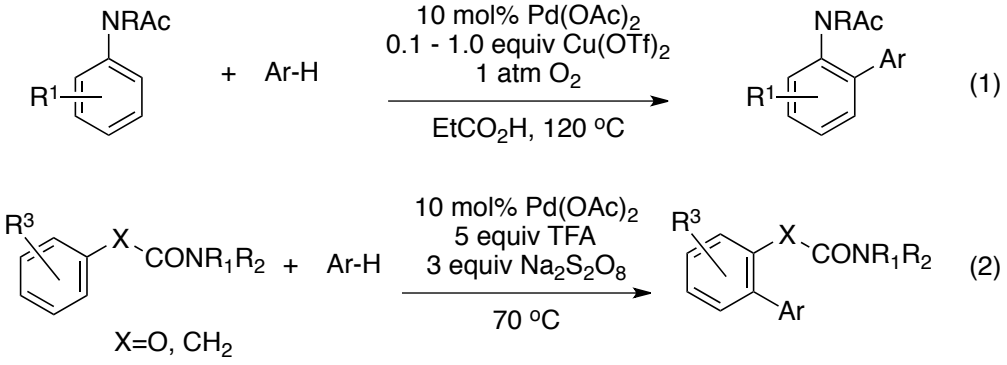
Scheme 1.4 Pd-catalyzed oxidative arylation of perfluoroarenes.

Another way to achieve good site selectivity is by using a chelation control mechanism. In 2007, Hull and Sanford achieved site selectivity by using a directing group via a chelation controled cyclopalladation mechanism.[16] Using Ag_2CO_3 as the oxidant, benzoquinolines and 2-arylpyridines could undergo a cross-coupling reaction with simple arenes (Scheme 1.5). The addition of DMSO inhibited the aggregation and precipitation of Pd^0. A mechanistic investigation revealed that the reaction underwent a Pd^0/Pd^{II} catalytic cycle and benzoquinone helped to promote the transformation.[17]



Scheme 1.5 Pd-catalyzed oxidation arylation of benzoquinolines and 2-phenylpyridines.

Other directing groups were also found effective for achieving excellent selectivity. Shi and co-workers reported arenes bearing an acetamido group could react with simple arenes smoothly, in the presence of $Cu(OTf)_2$ as a co-catalyst and O_2 as a green oxidant (Scheme 1.6, Eq. 1).[18] Buchwald and co-workers also used the same directing group for an oxidative coupling.[19] In their reaction, a copper salt was no longer needed, instead, trifluoroacetic acid (TFA) was added to facilitate the reaction. Sharing the structural similarity with anilides, *O*-phenylcarbamates and phenylacetamides were introduced to oxidative coupling reactions by Dong and co-workers, using inexpensive $Na_2S_2O_8$ as the oxidant (Scheme 1.6, Eq. 2).[20,21]



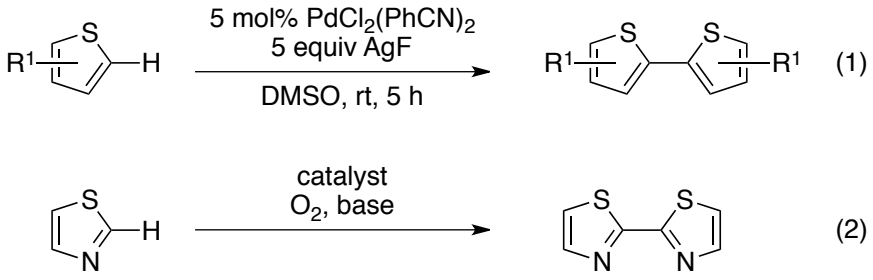
Scheme 1.6 Pd-catalyzed oxidative *ortho*-arylation.

1.1.2 – Oxidative Homo-Dehydrogenative-Coupling Reactions between Arenes

Homo-coupling biaryl products also have great significance in organic synthesis; many natural products have the core structure containing a symmetrical biaryl

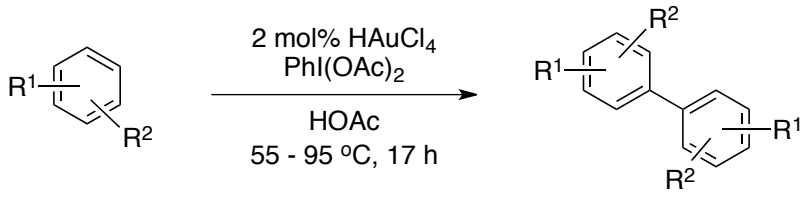
skeleton. van Helden and Verberg first described the palladium-mediated oxidative homo-coupling of benzene in 1965,[22] and the corresponding catalytic reaction was developed in 1973 by Iataaki and Yoshimoto: a palladium-catalyzed dehydrogenative coupling of arenes was accomplished with oxygen as terminal oxidant.[23] The oxidative dehydrogenative homo-coupling strategy was well developed since then, and the most recent work will be described here.

In 2004, Mori and co-workers demonstrated that *S*-heteroarenes dimerized in the presence of 5 mol% $PdCl_2(PhCN)_2$ and a silver salt as oxidant (Scheme 1.7, Eq. 1).[24] Later, Daugulis and others found that acidic arenes such as imidazole, triazole even perfluoroarenes could perform a Glaser-Hay type deprotonative dimerization under basic conditions and an oxygen atmosphere, catalyzed by transition metals such as $Cu(OAc)_2$, $NiCl_2$, $MnCl_2$, $CoCl_2$, and $FeCl_3$ (Scheme 1.7, Eq. 2).[25] In the absence of any base, $Cu(OAc)_2$ could also catalyze the azoles dimerization via a radical process promoted by molecular oxygen.[26]



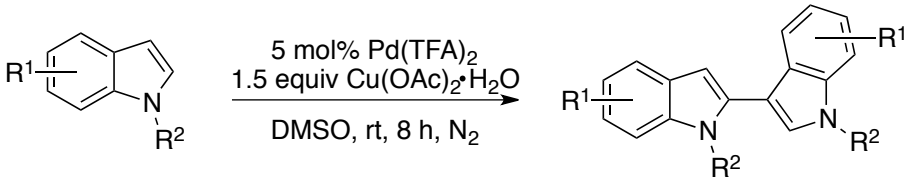
Scheme 1.7 Pd-catalyzed homo-coupling of heteroarenes.

Most recently, Tse and co-workers developed a gold-catalyzed system achieving the oxidative homo-coupling of non-activated arenes using $PhI(OAc)_2$ as the oxidant (Scheme 1.8).[27] A Friedel–Crafts type regioselectivity is observed in this reaction.



Scheme 1.8 Gold-catalyzed homo-coupling of non-activated arenes.

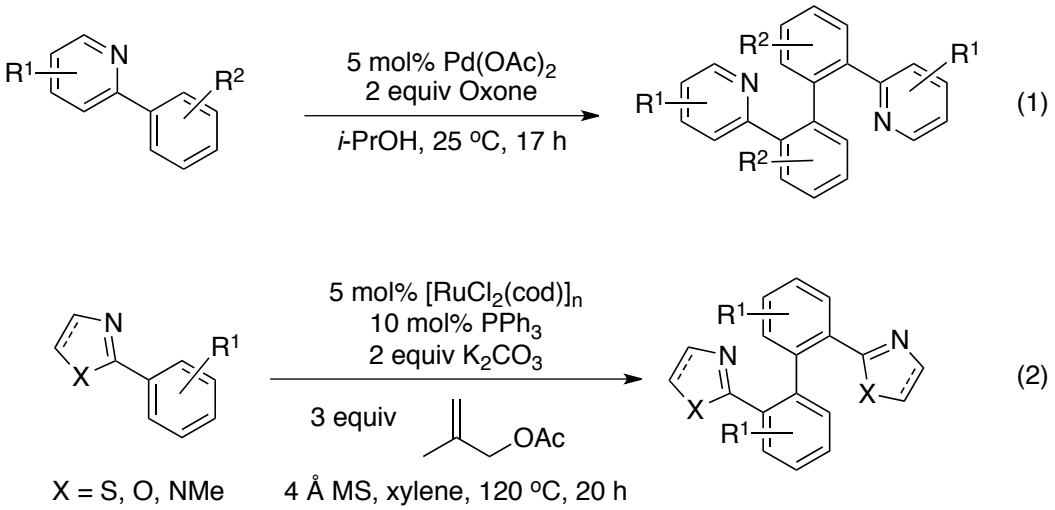
One unique example of heteroarene homo-coupling was reported by Zhang in 2010, where unsymmetrical coupling products were achieved.[28] This new protocol provides a facile route to 2,3'-biindolyls under very mild reaction conditions. Catalyzed by $Pd(TFA)_2$, C2 and C3 position of indoles was coupled in the presence of $Cu(OAc)_2$ hydrate in DMSO at room temperature (Scheme 1.9).



Scheme 1.9 Pd-catalyzed asymmetric homo-couling of indoles.

By installing a directing group, arenes could undergo a regioselective homo-coupling via chelation control. Sanford and co-workers reported a $Pd(OAc)_2$

catalyzed dimerization of 2-phenylpyridines at room temperature with oxone as a terminal oxidant (Scheme 1.10, Eq. 1).[29] Yu and co-workers discovered that the same reaction could be carried out with an *in situ* iodination followed by a Cu(II)/I_2 mediated Ullmann coupling to give the homodimerized product.[30] In 2008, Oi, Inoue and co-workers published the homo-coupling reaction of arenes bearing a *N*-directing group such as oxazolinyl, imidazolyl, thiazolyl groups, etc., catalyzed by a ruthenium complex in the presence of methallyl acetate as a hydrogen scavenger (Scheme 1.10, Eq. 2).[31]

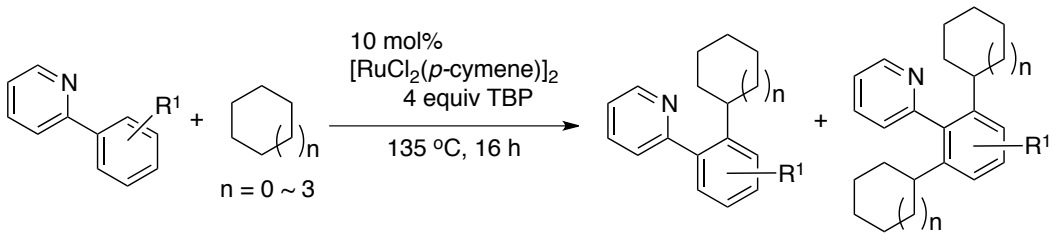


Scheme 1.10 Pd-catalyzed *N*-directed *ortho*-selective homo-coupling.

A hydroxyl group on an arene can also direct an *ortho* homo-coupling reaction. Dimerization of phenols and naphthols are well-know reactions[32] and are essential in the synthesis of ligands and natural products.[33] These reactions proceed via a radical mechanism, and are effectively catalyzed by iron and copper catalysts, using O_2 as the oxidant.[2e]

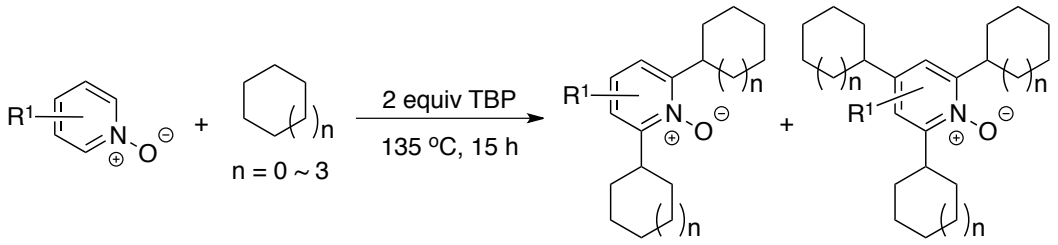
1.2 – Oxidative Cross-Dehydrogenative-Coupling Reactions of Arenes with Simple Alkanes

Using a simple alkane as a coupling partner in a CDC reaction is even more challenging, due to the Csp^3-H of alkanes being less active than the Csp-H of terminal alkynes or the Csp^2-H of aromatic arenes. Li and co-workers accomplished this task by taking advantage of the stability of alkyl radicals. They reported an oxidative coupling between cycloalkanes and arenes bearing a pyridyl directing group (Scheme 1.11).[34] With $[RuCl_2(p\text{-cymene})]_2$ as the catalyst, the reaction occurred exclusively on the phenyl rings of the 2-phenylpyridine derivatives, leading to both mono- and bis-alkylation products. Di-*tert*-butyl peroxide acted both as the oxidant and as the initiator to generate alkyl radicals.



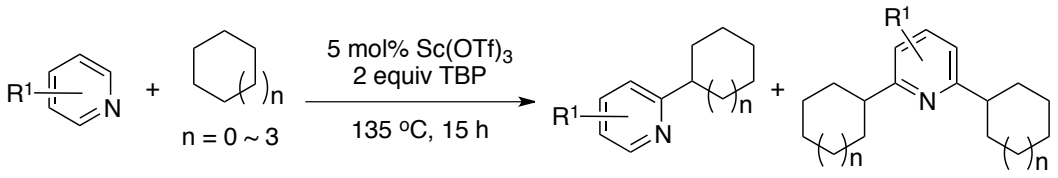
Scheme 1.11 Ru-catalyzed alkylation of 2-arylpyridines with cycloalkanes.

In another study, Itami, Li and co-workers illustrated a transition-metal-free system for the cross-coupling reactions of nitrogen heteroarenes and alkanes.[35] Alkyl radicals generated under the influence of di-*tert*-butyl peroxide were trapped by pyridine *N*-oxide derivatives to furnish the corresponding cross-coupling products (alkylated nitrogen heterocycles) in good yields (Scheme 1.12).



Scheme 1.12 Oxidative cross-coupling of pyridine *N*-oxides with cycloalkanes.

In contrast to the pyridine *N*-oxides, pyridines and quinolines remained inert under the same reaction conditions, due to the low activity of the C2-H bond on these heteroarene rings. Deng and Li overcame this obstacle by introducing a Lewis acid (LA) catalyst $Sc(OTf)_3$ to the system, thereby increasing the reactivity of pyridine derivatives similar to the use of pyridine *N*-oxide substrates (Scheme 1.13).[36] Interestingly, the alkylation of pyridine only occurred at the *ortho*-position of nitrogen, and no *para*-alkylation product was observed which is in sharp contrast to the pyridine *N*-oxide substrates.



Scheme 1.13 Lewis acid catalyzed alkylation of pyridines with cycloalkanes.

Chapter 2 – Ruthenium-Catalyzed Oxidative Homo-Coupling of 2-Arylpyridines

In the previous chapter, aryl carbon-carbon bond formation via an oxidative dehydrogenative coupling process was illustrated. Although powerful methodologies have been developed, exploring milder, easier and more efficient methods to build C-C bonds is still of great importance. Herein, a new protocol for the synthesis of biaryls via a ruthenium-catalyzed oxidative homo-coupling will be described.

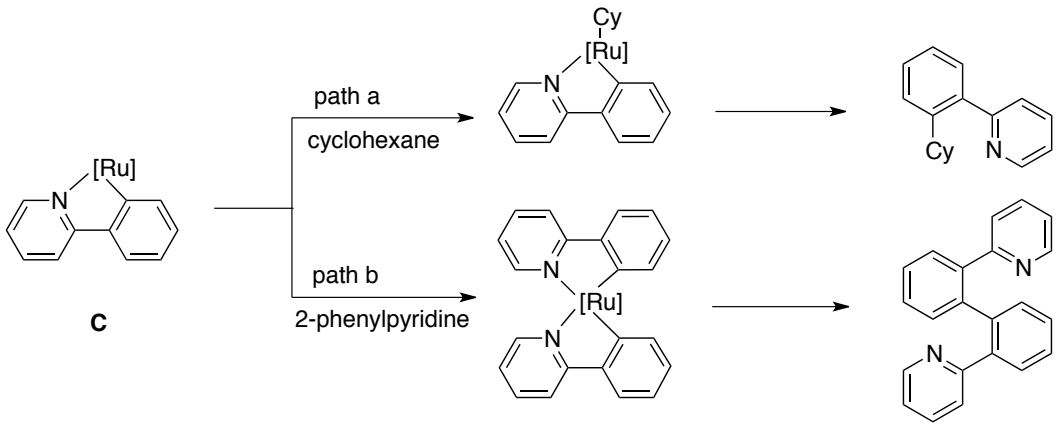
2.1 – Background

More recently, researchers have focused on finding new routes to execute similar C–H activation reactions for C-C bond formation by expanding the diversity of transition metal catalytic systems and replacing the sacrificial oxidants with more abundant and less expensive ones. In chapter 1, we pictured the strategies of oxidative homo-coupling reactions of arenes bearing a directing group.[1] However, these reactions still have limitations in their conditions. The oxidants in these protocols are either unstable or expensive, and excess oxidant was always required to guarantee the best conversion of the starting materials.

2.2 – Research Objective and Plan

Due to the limitation of previous methods in the oxidative homo-coupling reactions of arenes, we became interested in developing an improved system to facilitate the oxidative coupling while breaking through the limitations faced by most oxidative coupling protocols.

During our recent studies on the ruthenium-catalyzed Cross-Dehydrogenative-Coupling (CDC) of 2-phenylpyridines with cycloalkanes mediated by peroxides (Scheme 2.1 path a),[2] we observed a trace amount of the oxidative homo-coupling product of 2-phenylpyridine. We reasoned that in this competitive reaction, the intermediate **C** reacted with a second molecule of 2-phenylpyridine, which led to the homo-coupling product (Scheme 2.1, path b).



Scheme 2.1 Competitive reactions in the ruthenium-catalyzed coupling reaction of 2-phenylpyridines with cycloalkanes

In order to promote the homo-coupling reaction, we will focus our work on searching for the best combination of metal catalyst and oxidant. Different metal

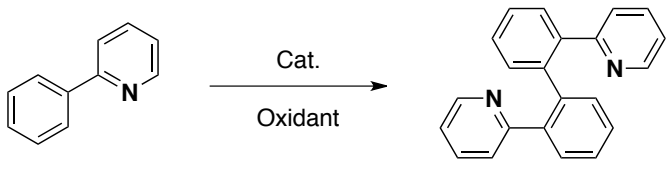
catalysts are to be tested to generate an efficient C-H activation and various oxidants will be examined to promote the regeneration of reactive catalyst.

2.3 –Results and Discussion

2.3.1 –Reaction Condition Screenings

With the research plan in hand, subsequently, various conditions regarding the ruthenium catalyst and the oxidant were examined to facilitate the formation of the designated homo-coupling product (Table 2.1).

Table 2.1 Reactions of 2-phenylpyridine **1a** under various conditions[a]



1a **2a**

entry	catalyst	oxidant (equiv)		solvent	temp(°C)	yield[b]
1	$RuCl_3$	$FeCl_3$	(1.0)	chlorobenzene	110	27
2	------	$FeCl_3$	(1.0)	chlorobenzene	110	0
3	$Ru_3(CO)_{12}$	$FeCl_3$	(1.0)	chlorobenzene	110	0
4	$Ru(acac)_3$	$FeCl_3$	(1.0)	chlorobenzene	110	60
5	$RuCl_2(PPh_3)_3$	$FeCl_3$	(1.0)	chlorobenzene	110	77
6	$[Ru(benzene)Cl_2]_2$	$FeCl_3$	(1.0)	chlorobenzene	110	59
7	$[Ru(p\text{-cymene})Cl_2]_2$	$FeCl_3$	(1.0)	chlorobenzene	110	84
8	$[Ru(p\text{-cymene})Cl_2]_2$	benzoquinone	(1.0)	chlorobenzene	110	43
9	$[Ru(p\text{-cymene})Cl_2]_2$	*t*BuOO*t*Bu	(1.0)	chlorobenzene	110	18

Table 2.1 Reactions of 2-phenylpyridine **1a** under various conditions[a] (continued)

entry	catalyst	oxidant (equiv)	solvent	temp(°C)	yield[b]
10	[Ru(*p*-cymene)Cl_2]$_2$	$FeCl_3$•$6H_2O$ (1.0)	chlorobenzene	110	66
11	[Ru(*p*-cymene)Cl_2]$_2$	$Fe(acac)_3$ (1.0)	chlorobenzene	110	trace
12	[Ru(*p*-cymene)Cl_2]$_2$	O_2 (1atm)	chlorobenzene	110	30
13	[Ru(*p*-cymene)Cl_2]$_2$	$FeCl_3$ (1.0)	chlorobenzene	130	87
14	[Ru(*p*-cymene)Cl_2]$_2$	$FeCl_3$ (1.0)	chlorobenzene	100	74
15	[Ru(*p*-cymene)Cl_2]$_2$	$FeCl_3$ (1.0)	anisole	110	68
16	[Ru(*p*-cymene)Cl_2]$_2$	$FeCl_3$ (1.0)	benzene	110	80
17	[Ru(*p*-cymene)Cl_2]$_2$	$FeCl_3$ (1.0)	toluene	110	81
18	[Ru(*p*-cymene)Cl_2]$_2$	$FeCl_3$ (1.0)	DCE	110	74
19	[Ru(*p*-cymene)Cl_2]$_2$	$FeCl_3$ (0.5)	chlorobenzene	110	72
20	[Ru(*p*-cymene)Cl_2]$_2$	$FeCl_3$ (0.8)	chlorobenzene	110	87

[a]Conditions: **1a** (0.5 mmol), catalyst (0.0125 mmol), solvent (1 mL), $FeCl_3$ (1.0 equiv = 0.5 mmol), 16h in air unless otherwise noted. [b]^{1}H NMR yields were examined using nitromethane as internal standard.

It was found that using $FeCl_3$, instead of peroxide, as the stoichiometric oxidant increased the product yield to 27% (Table 2.1, entry 1). No reaction was observed in the absence of the ruthenium catalyst (Table 2.1, entry 2). Other ruthenium catalysts were also examined (Table 2.1, entries 3-7). Whereas $Ru_3(CO)_{12}$ was inactive, the use of $Ru(acac)_3$, $RuCl_2(PPh_3)_3$, and [Ru(benzene)Cl_2]$_2$ increased the product yield to 60%, 77%, and 59%, respectively. The combination of [Ru(*p*-cymene)Cl_2]$_2$ with $FeCl_3$ gave 84% yield of the desired product (Table 2.1, entry 7). Other oxidants were also examined (Table 2.1, entries 8-12), and all led to lower product yields. The solvents were also investigated (Table 2.1, entries 13-18). Reasonable yields can also be obtained when conducting the reaction in other common solvents such as toluene, benzene and anisole. Although higher

temperature did not promote the reaction much, a lower reaction temperature resulted in a lower yield (Table 2.1, entries 7, 13 and 14).

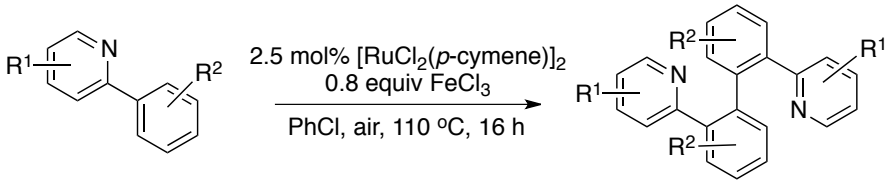
Decreasing the amount of the $FeCl_3$ to 50 mol% decreased the yield (Table 2.1, entry 19); however, more oxidant did not help the reaction either (compare entries 7 and 20). It was proposed that, with more $FeCl_3$ added, the nitrogen atom in 2-phenylpyridine was coordinated to the iron, which prevented its coordination to the ruthenium, thus reduced the efficiency of the C-H activation. Interestingly, when only 0.8 equiv of $FeCl_3$ was used, an 87% yield was obtained rather than the expected 80% (the highest theoretical yield). This unexpected "higher" yield was most likely due to the fact that the reaction was conducted under air and O_2 (in the air) functioned as an extra oxidant (Table 2.1, entries 12 and 20). Thus, we optimized the best conditions being 2.5 mol% $[Ru(p\text{-cymene})Cl_2]_2$ with 0.8 equiv of $FeCl_3$ in chlorobenzene at 110 ^oC under air for 16 h, giving the product in 87% NMR yield (Table 2.1, entry 20).

2.3.2 – Scope of the Ruthenium-Catalyzed Oxidative Homo-coupling Reaction

With the optimized reaction conditions in hand, 2-aryl pyridines bearing different substituents were subjected to this reaction condition (Table 2.2). No significant change was observed with 4-phenylphenylpyridine (compare entries 1 and 2). Electronic effects of the phenyl ring of the substrates did not have a great impact

on the reaction (Table 2.2, entries 1-7). Substrates with halide substituents proceeded equally well in this reaction (Table 2.2, entries 5 and 6).

Table 2.2 Substrate scope of ruthenium-catalyzed homo-coupling of substituted 2-arylpyridines[a]



1 **2**

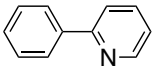
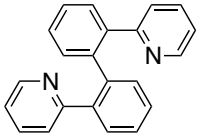
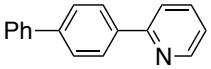
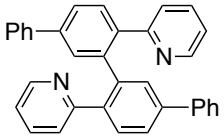
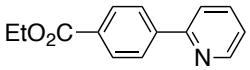
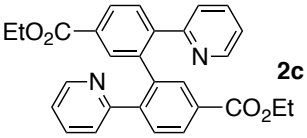
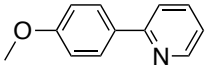
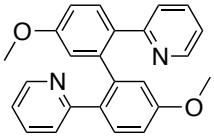
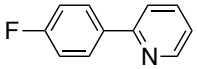
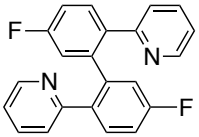
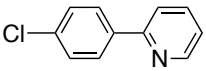
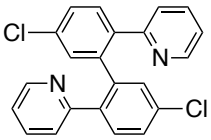
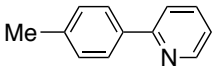
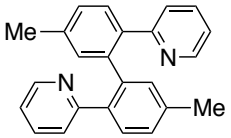
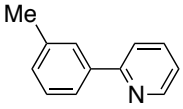
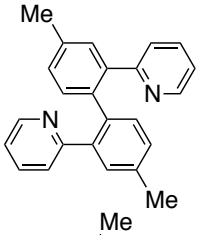
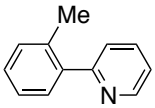
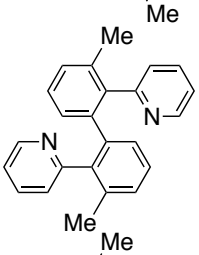
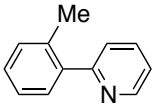
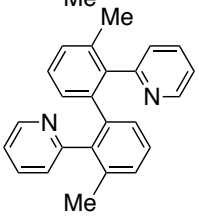
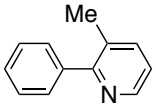
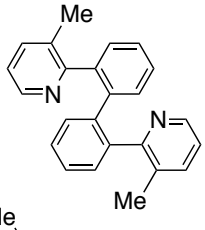
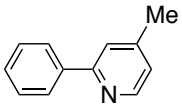
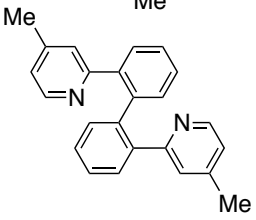
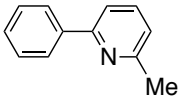
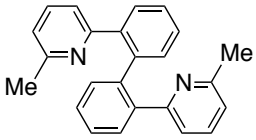
entry	substrate	product		isolated yield(%)
1			**2a**	84
2			**2b**	80
3			**2c**	67
4			**2d**	54
5			**2e**	71
6			**2f**	42

Table 2.2 Substrate scope of ruthenium-catalyzed homo-coupling of substituted 2-arylpyridines[a] (continued)

entry	substrate	product		isolated yield(%)
7			**2g**	74
8			**2h**	78
9			**2i**	12
10			**2i**	30[b]
11			**2j**	65
12			**2k**	66
13			**2l**	0

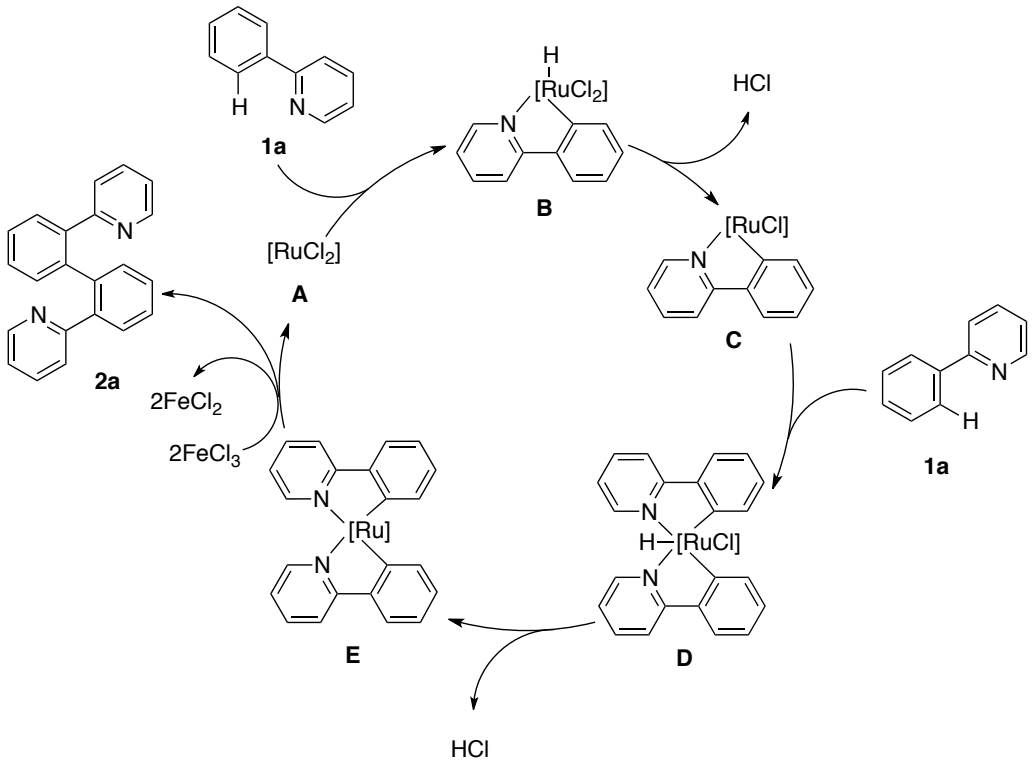
[a]Conditions: **1** (0.5 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.0125 mmol), $FeCl_3$ (0.4 mmol), chlorobenzene (1 mL), 16h in air unless otherwise noted. [b] 48h.

The position of substituents on both rings also played an important role in this reaction. A good yield was obtained with 2-(4-methylphenyl)pyridine (Table 2.2, entry 7). In the presence of two potential reaction sites on the phenyl ring of 2-(3-methylphenyl)pyridine, the reaction took place regioselectively at the less hindered C–H bond (Table 2.2, entry 8). However, when the methyl group on the phenyl ring was changed from *para*- or *meta*-substituted to *ortho*-substituted, the yield decreased dramatically. This is mainly due to the increased steric repulsion between the methyl group and the hydrogen atom on C3 position on the pyridine ring during the nitrogen-directed C-H activation process in 2-(2-methylphenyl)pyridine (Table 2.2, entries 9 and 10).

The reaction also proceeded well when changing the substituents on the pyridine ring. When methyl group was at 3- or 4- sites, reasonable yields were also obtained (Table 2.2, entries 11 and 12). However, the substrate with the methyl group at the 2-position of the pyridine ring could not undergo this reaction, which could also be explained by the steric effect in which the methyl group next to the nitrogen atom blocked its coordination to ruthenium (Table 2.2, entry 13).

2.3.3 – Proposed Mechanism of the Ruthenium-Catalyzed Oxidative Homo-coupling Reaction

To elucidate the formation of the coupling product, a tentative mechanism to rationalize the product formation is illustrated in Scheme 2.2. First the active ruthenium species **A** reacts with 2-phenylpyridine **1a** (and other arenes) by a chelation-directed C-H activation to generate intermediate **B**.[3] With the release of HCl via a reductive-elimination, intermediate **C** is formed.[1a,4] Subsequently, a second 2-phenylpyridine **1a** reacts with intermediate **C** and undergoes the same process forming intermediate **E**. Finally, reductive-elimination affords the oxidative coupling product, and ruthenium catalyst **A** is regenerated via oxidation by $FeCl_3$.



Scheme 2.2 Proposed mechanism for the ruthenium-catalyzed dimerization of 2-arylpyridine

2.4 – Conclusion

In summary, we have developed a homo-coupling of 2-arylpyridines by using ruthenium complex as the catalyst and $FeCl_3$ as the oxidant to generate biaryl compounds efficiently and regioselectively. The reaction proceeded well for a range of different substrates. A tentative mechanism for this reaction was also proposed.

Further work on this chemistry can be focused on testing different directing groups in this reaction, which will provide more synthetic applications. On the other hand, heteroatom arenes can also be examined in this chemistry to expand the reaction scope.

2.5 – Contributions

The reaction was first discovered by Dr. Guojun Deng and he did initial condition screening. I did further condition screening based on his work, as well as studied the scope screening and characterized the products. The paper was written by me and modified by Prof. Chao-Jun Li.

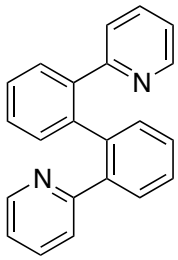
2.6 – Experimental Section

General Information Relating to All Experimental Procedures

Unless otherwise noted, all chemicals were obtained from commercial suppliers and used as received. All reactions were carried out under an atmosphere of air at ambient temperature unless otherwise stated. All work-up and purification procedures were carried out with reagent-grade solvents. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm) or Sorbent Silica Gel 60 F_{254} plates. The developed TLC plate was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh) or SORBENT silica gel 30-60 μm. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian MERCURY plus-300 spectrometer (^{1}H 270 MHz, ^{13}C 75 MHz) spectrometer or a Varian MERCURY plus-400 spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz). Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to $CDCl_3$ (δ 7.26 ppm). Chemical shifts for ^{13}C NMR are expressed in parts ppm relative to $CDCl_3$ (δ 77.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. HRMS were made by McGill University.

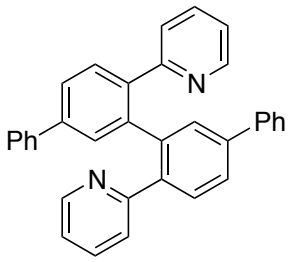
Typical procedure for 2-phenylpyridine homo-coupling: An oven-dried reaction vessel was charged with {[Ru(p-cymene)Cl_2]$_2$} (7.6 mg, 0.0125 mmol), 2-phenylpyridine (**1a**, 77.5 mg, 0.5 mmol), $FeCl_3$ (65 mg, 0.4 mmol), and chlorobenzene (1.0 mL). The reaction vessel was then sealed and the resulting

solution was stirred at 110 ^{o}C for 16 h. After cooling to room temperature, triethylamine (1.0 mL) and dichloromethane (1.0 mL) were added to the mixture and the resulting solution was stirred at room temperature for 30 min. Then the resulting mixture was filtered through a short silica gel plug in a filter by using dichloromethane as the eluent. The volatiles were removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate=1:1) to give **2a** (65 mg, 84%) as a yellow solid.



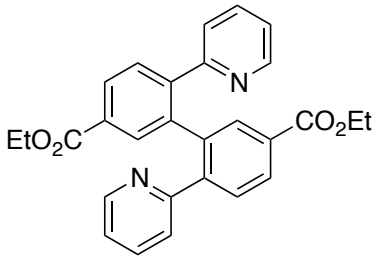
2,2'-Di(pyridin-2-yl)-1,1'-biphenyl (2a)

2a was prepared from **1a** (77.5 mg, 0.5 mmol), {[Ru(p-cymene)Cl_2]$_2$} (7.6 mg, 0.0125 mmol) and $FeCl_3$ (65 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=1:1, Rf=0.3) to afford **2a** as a yellow solid (65.0 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* =4.8 Hz, 2H), 7.53 – 7.56 (m, 2H), 7.32–7.44 (m, 8H), 7.01 – 7.05 (m, 2H), 6.78 (d, *J*=7.8 Hz, 2H),; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 148.8, 139.7, 139.5, 135.1, 131.2, 129.9, 128.5, 127.6, 124.3, 121.1. (Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047.)



4',6''-Di(pyridin-2-yl)-1,1':3',1'':3'',1'''-quaterphenyl (2b)

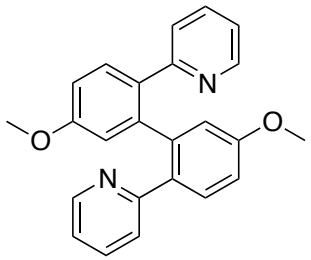
2b was prepared from **1b** (115.5 mg, 0.5 mmol), {[Ru(p-cymene)Cl_2]$_2$} (7.6 mg, 0.0125 mmol) and $FeCl_3$ (65 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=1:1, Rf=0.2) to afford **2b** as a brown solid (92.5 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (dq, *J* = 4.8, 0.9 Hz, 2H), 7.76 (d, *J* = 0.9 Hz, 2H), 7.66 – 7.74 (m, 8H), 7.47 (t, *J* = 7.8 Hz, 4H), 7.38 (m, 4H), 7.05 (qd, *J* = 4.8, 1.2 Hz, 2H), 6.90 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 149.0, 141.2, 140.0, 138.8, 135.2, 130.6, 129.8, 128.8, 127.5, 127.0, 126.4, 124.4, 121.2. IR (neat): 3050, 1584, 1566, 1460, 757, 693, 482, 467 ν cm^{-1}. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{34}H_{24}N_2$, 460.19322; found, 460.19395.



Diethyl 6,6'-di(pyridin-2-yl)-[1,1'-biphenyl]-3,3'-dicarboxylate (2c)

2c was prepared from **1c** (113.5 mg, 0.5 mmol), {[Ru(p-cymene)Cl_2]$_2$} (7.6 mg, 0.0125 mmol) and $FeCl_3$ (65 mg, 0.4 mmol) following the above general

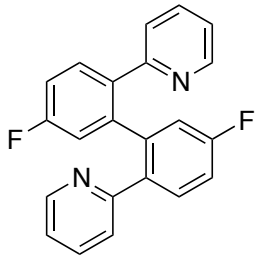
procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=1:1, Rf=0.2) to afford **2c** as a brown solid (76.0 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (dt, *J* = 4.8, 0.9 Hz, 2H), 8.15 (d, *J* = 1.8 Hz, 2H), 8.04 (dq, *J* = 7.5, 0.6 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.28 (td, *J* = 7.8, 1.8 Hz, 2H), 6.97 – 7.01 (m, 2H), 6.65 (dd, *J* = 8.1, 0.6 Hz, 2H), 4.38 (q, *J* = 1.2 Hz, 4H), 1.37 (t, *J* = 1.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 156.5, 149.0, 143.7, 139.0, 135.3, 132.2, 130.5, 130.0, 129.0, 124.1, 121.6, 61.0, 14.2. IR (neat): 2983, 1708, 1586, 473, 433 ν cm^{-1}.HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{28}H_{24}N_2O_4$, 452.17236; found, 452.17361.



2,2'-(5,5'-dimethoxy-[1,1'-biphenyl]-2,2'-diyl)dipyridine (2d)

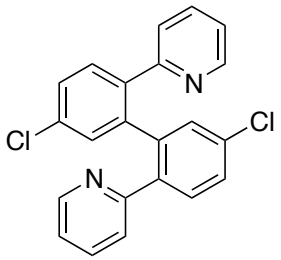
2d was prepared from **1d** (92.5 mg, 0.5 mmol), {[Ru(p-cymene)Cl_2]$_2$} (7.6 mg, 0.0125 mmol) and $FeCl_3$ (65 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=1:2, Rf=0.2) to afford **2d** as a yellow solid (50.0 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (dq, *J* = 4.8, 0.9 Hz, 2H), 7.49 (dd, *J* = 6.6, 2.7 Hz, 2H), 7.29 (td, *J* = 7.8, 1.8 Hz, 2H), 6.93 – 6.98 (m, 6H), 6.72 (d, *J* = 7.8 Hz, 2H), 3.81 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 157.5, 148.7, 141.0, 135.1, 132.6, 131.4, 124.1, 120.7, 116.0, 113.5, 55.2. IR (neat): 2953, 2833, 1606,

1566, 1461, 505, 488, 466 ν cm^{-1}. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{24}H_{20}N_2O_2$, 368.15215; found, 368.15248.



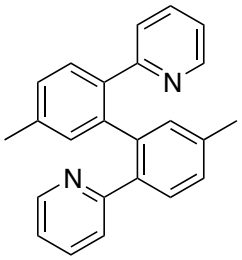
2,2'-(5,5'-difluoro-[1,1'-biphenyl]-2,2'-diyl)dipyridine (2e)

2e was prepared from **1e** (86.5 mg, 0.5 mmol), {[Ru(p-cymene)Cl_2]$_2$} (7.6 mg, 0.0125 mmol) and $FeCl_3$ (65 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=1:1, Rf=0.2) to afford **2e** as a brown solid (61.1 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (dq, J = 5.1, 0.9 Hz, 2H), 7.48 – 7.53 (m, 2H), 7.36 (td, J = 7.8, 1.8 Hz, 2H), 7.01 – 7.14 (m, 6H), 6.76 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (d, $J_{C\text{-}F}$= 247.3 Hz), 156.7, 149.0 140.8 (d, $J_{C\text{-}F}$= 6.3 Hz), 136.0, 135.4, 132.0 (d, $J_{C\text{-}F}$= 7.4 Hz), 124.1, 121.4, 117.7 (d, $J_{C\text{-}F}$= 21.4 Hz), 115.0 (d, $J_{C\text{-}F}$= 20.5 Hz). IR (neat): 3053, 1605, 1584, 1460, 1425, 496, 466, 417 ν cm^{-1}. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{22}H_{14}N_2F_2$, 344.11190; found, 344.11251.



2,2'-(5,5'-dichloro-[1,1'-biphenyl]-2,2'-diyl)dipyridine (2f)

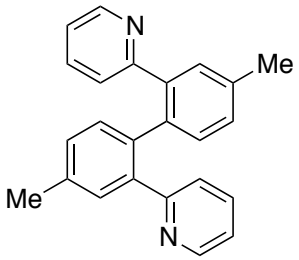
2f was prepared from **1f** (94.8 mg, 0.5 mmol), {[Ru(p-cymene)Cl_2]$_2$} (7.6 mg, 0.0125 mmol) and $FeCl_3$ (65 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=1:2, Rf=0.5) to afford **2f** as a brown solid (39.6 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (dq, *J* = 5.1, 0.9 Hz, 2H), 7.32 – 7.46 (m, 8H), 7.03 (qd, *J* = 5.1, 0.9 Hz, 2H), 6.70 (dt, *J* = 7.8, 0.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 149.0, 140.1, 138.2, 135.5, 134.5, 131.5, 130.7, 128.3, 124.1, 121.5. IR (neat): 3039, 1585, 1462, 1425, 781, 745, 488, 473, 442 ν cm^{-1}. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{22}H_{14}N_2Cl_2$, 376.05273; found, 376.05340.



2,2'-(5,5'-dimethyl-[1,1'-biphenyl]-2,2'-diyl)dipyridine (2g)

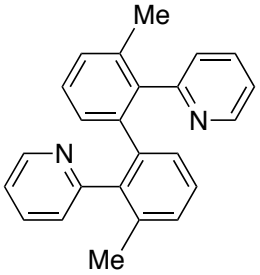
2g was prepared from **1g** (84.5 mg, 0.5 mmol), {[Ru(p-cymene)Cl_2]$_2$} (7.6 mg, 0.0125 mmol) and $FeCl_3$ (65 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2,

hexane/ethyl acetate=1:2, Rf=0.3) to afford **2g** as a brown solid (62.5 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (dq, *J* = 5.0, 0.9 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.28 (m, 4H), 7.21 (dt, *J* = 7.8, 0.9 Hz, 2H), 6.96 (qd, *J* = 4.8, 1.2 Hz, 2H), 6.66 (dd, *J* = 8.1, 0.9 Hz, 2H), 2.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 148.7, 139.6, 138.3, 137.0, 135.0, 131.8, 129.8, 128.4, 124.2, 120.8, 21.2. (Chen, X.; Dobereiner, G.; Hao, X.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Tetrahedron* **2009**, *65*, 3085.)



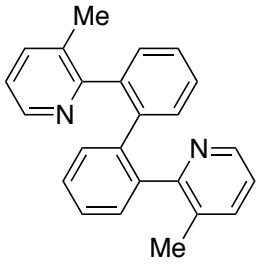
2,2'-(4,4'-dimethyl-[1,1'-biphenyl]-2,2'-diyl)dipyridine (2h)

2h was prepared from **1h** (84.5 mg, 0.5 mmol), {[Ru(p-cymene)Cl_2]$_2$} (7.6 mg, 0.0125 mmol) and $FeCl_3$ (65 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=1:2, Rf=0.5) to afford **2h** as a brown solid (65.4 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, *J* = 4.5Hz, 2H), 7.22 – 7.34 (m, 8H), 6.98 (qd, *J* = 4.8, 0.9 Hz, 2H), 6.72 (d, *J* = 8.1 Hz, 2H), 2.38 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 148.7, 139.5, 137.3, 136.6, 135.0, 131.2, 130.5, 129.3, 124.3, 120.9, 20.9. IR (neat): 2995, 1585, 1566, 1460, 757, 693, 482, 467 ν cm^{-1}. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{24}H_{20}N_2$, 336.16204; found, 336.16265.



2,2'-(3,3'-dimethyl-[1,1'-biphenyl]-2,2'-diyl)dipyridine (2i)

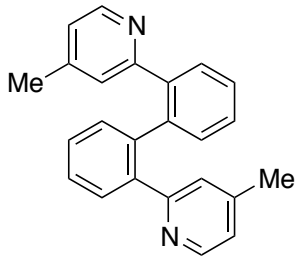
2i was prepared from **1i** (84.5 mg, 0.5 mmol), {[Ru(p-cymene)Cl_2]$_2$} (7.6 mg, 0.0125 mmol) and $FeCl_3$ (65 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=1:2, Rf=0.4) to afford **2i** as a brown solid (25.5 mg, 30%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J = 4.8 Hz, 2H), 7.35 – 7.52 (m, 4H), 7.16 (dq, J = 7.2, 0.8 Hz, 2H), 7.10 (d, J = 7.6 Hz, 2H), 7.00 (t, J = 7.2 Hz, 2H), 6.68 (d, J = 7.2 Hz, 2H), 2.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 149.3, 140.7, 140.6, 136.4, 135.2, 129.5, 129.0, 125.9, 125.2, 122.1, 18.9. IR (neat): 2990, 1586, 1566, 1463, 1440, 760, 696, 480, 458 ν cm^{-1}. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{24}H_{20}N_2$, 336.16139; found, 336.16265.



2,2'-bis(3-methylpyridin-2-yl)-1,1'-biphenyl (2j)

2j was prepared from **1j** (84.5 mg, 0.5 mmol), {[Ru(p-cymene)Cl_2]$_2$} (7.6 mg, 0.0125 mmol) and $FeCl_3$ (65 mg, 0.4 mmol) following the above general

procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=1:2, Rf=0.4) to afford **2j** as a white solid (55.1 mg, 66%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.16 (s, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.08 – 7.25 (m, 10H), 1.86 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 146.1, 140.1, 139.4, 137.7, 137.5, 131.7, 130.3, 127.4, 126.7, 121.5, 19.3. (Chen, X.; Dobereiner, G.; Hao, X.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Tetrahedron* **2009**, *65*, 3085.)



2,2'-bis(4-methylpyridin-2-yl)-1,1'-biphenyl (2k)

2k was prepared from **1k** (84.5 mg, 0.5 mmol), {[Ru(p-cymene)Cl_2]$_2$} (7.6 mg, 0.0125 mmol) and $FeCl_3$ (65 mg, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=1:2, Rf=0.3) to afford **2k** as a white solid (55.3 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J =5.1Hz, 2H), 7.34 – 7.49 (m, 8H), 6.82 (dd, J = 4.5, 0.6 Hz, 2H), 6.49 (d, J = 0.6 Hz, 2H), 6.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 148.5, 146.0, 140.1, 139.8, 131.1, 129.6, 128.2, 127.4, 125.3, 122.0, 20.9. IR (neat): 3038, 1600, 1544, 1463, 1432, 830, 776, 755, 465, 444 ν cm^{-1}. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{24}H_{20}N_2$, 336.16204; found, 336.16265.

Chapter 3 – Ruthenium-Catalyzed Para-Selective Oxidative Cross-Coupling of Arenes and Cycloalkanes

In Chapter 1, we described the functionalization reactions of aromatic rings with carbon-carbon (C-C) bond formation, involving arylation and alkylation of arenes. One key issue in these reactions is the controlled functionalization of carbon-hydrogen (C-H) bonds regioselectively in the presence of all others. In this chapter, we will focus on the regioselectivity of C-H bond functionalization reactions of benzene derivatives and will illustrate a *para*-selective oxidative cross-coupling reaction of arenes and cycloalkanes.

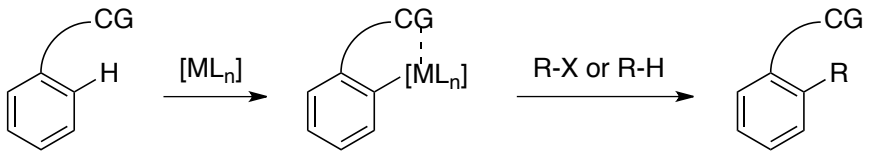
3.1 – Introduction to the Regioselectivity of C-H Bond Functionalization of Benzene Derivatives

Regiocontrolled functionalization of aromatic rings has been an important subject throughout the history of organic chemistry because of the vital role of aromatic compounds in materials, fine chemicals, and biological compounds. There has been much effort in recent years toward the development of methodologies to introduce functional groups regioselectively on aromatic rings.

The Friedel-Crafts-type[1] electrophilic substitution of arenes constitutes a key pillar of classical synthetic chemistry, leading to *ortho*- and *para*-aryl C-C bonds with electron-rich aromatic compounds, but frequently, they are not highly

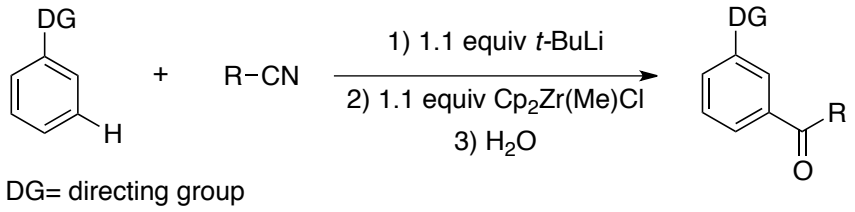
regioselective. Fries rearrangement[2] is another typical electrophilic reaction, which generates the same selectivity, but in all instances, only esters can be used with stable acyl components that can withstand the harsh conditions of the Fries rearrangement.

Direct *ortho*-lithiation is a powerful technique for the construction of 1,2-disubstituted aromatic compounds due to a wide variety of functional groups, which can serve as directing groups.[3] Most recently, chelation-controlled transition-metal-catalyzed C-H activation cross-couplings have merged as milestones of modern achievements in creating alternatives, furnishing *ortho*-functionalized products regioselectively (Scheme 3.1).[4] We are not going into details here as many examples were given in chapter 1.



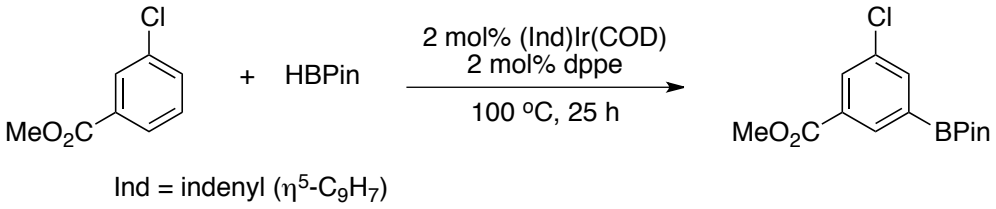
Scheme 3.1 Chelating groups (CG) directed *ortho*-functionalization

Meta-functionalization of C-H bonds is more difficult compared to the *ortho*-selectivity. In 1998, Buchwald and co-workers pioneered this field by taking advantage of an *ortho*-lithiation procedure combined with zirconocene-benzyne chemistry (Scheme 3.2).[5] 3-Acyl-1-substituted benzene derivatives were obtained by acidic hydrolysis of the azazirconacycle intermediates which resulted from the coupling of a nitrile with a zirconocene-benzyne complex.



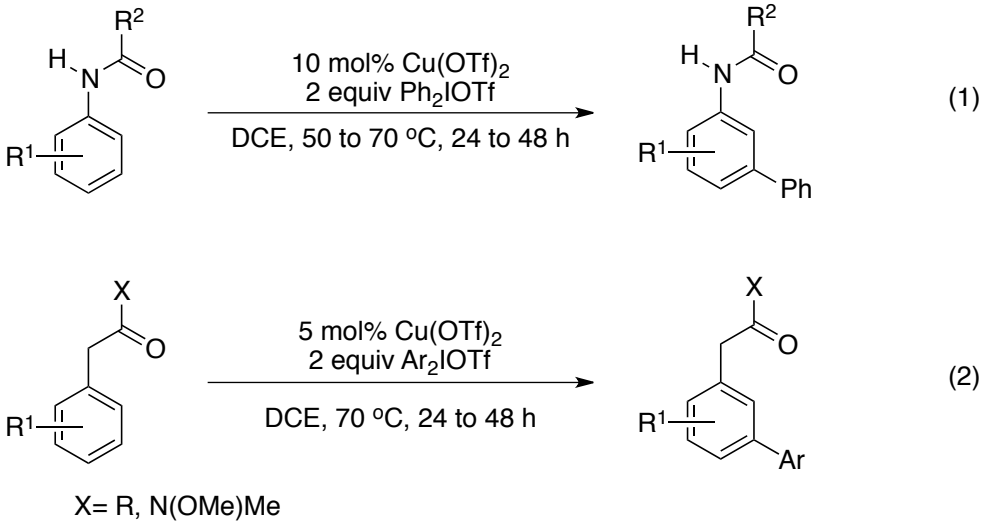
Scheme 3.2 *Meta*-acylation of 1-substituted benzene derivatives

Later, Smith and co-workers reported an iridium-catalyzed *meta*-borylation enabling the direct synthesis of arylboron compounds from aromatic hydrocarbons and pinacolboranes under neat conditions (Scheme 3.3).[6] Concurrently, the same type of iridium-catalyzed C-H borylation was independently discovered by Ishiyama, Miyaura and Hartwig.[7] Due to the active feature of arylboronic acid derivatives, the product of this reaction could be used as an intermediate in two continuous steps to furnish a variety of 5-functionalized 1,3-disubstituted benzene derivatives. Many papers have been published by Smith, Maleczka and Hartwig, involving the formation of arylboronic acids,[8] trifluoroborates,[8] halobenzenes,[9] phenols,[10,12] biaryl ether,[12] aminoaryl boronate esters,[11] and arylamines.[12]

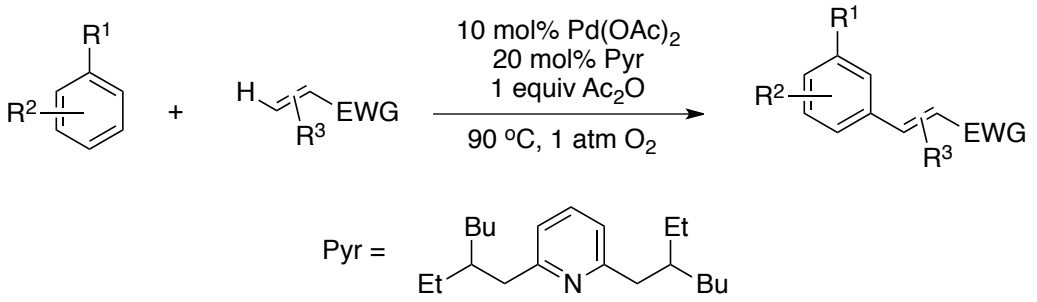


Scheme 3.3 Synthesis of arylboron compounds via iridium-catalyzed *meta*-borylation

Gaunt and Phipps described the development of a copper-catalyzed arylation reaction that selectively substituted phenyl electrophiles at the aromatic carbon–hydrogen sites meta to an amido substituent (Scheme 3.4, Eq. 1).[13] Later in 2011, they successfully applied this strategy to α-arylacetamides and α-arylketones (Scheme 3.4, Eq. 2).[14] Interestingly, they discovered a metal-free arylation process at a higher temperature,[14] which denied their previous hypothesized 2,3-anti–oxy-cupration mechanism.[13]



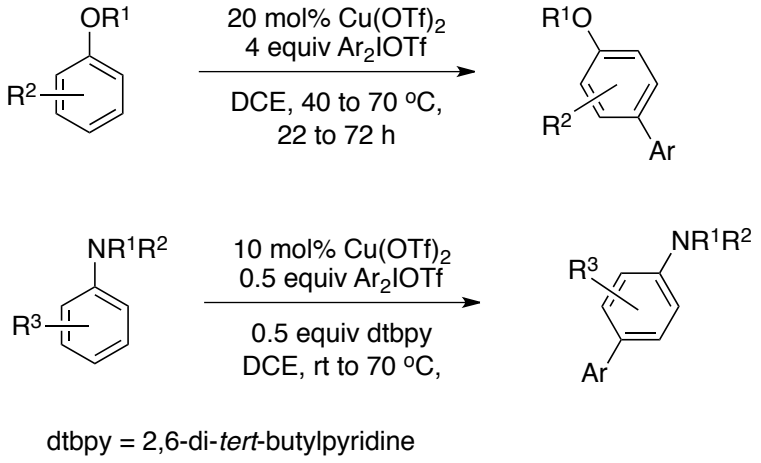
Scheme 3.4 Copper-catalyzed *meta*-arylation of anilides and α-aryl carbonyl compounds



Scheme 3.5 Pd-catalyzed *meta*-alkenylation of electron-deficient arenes

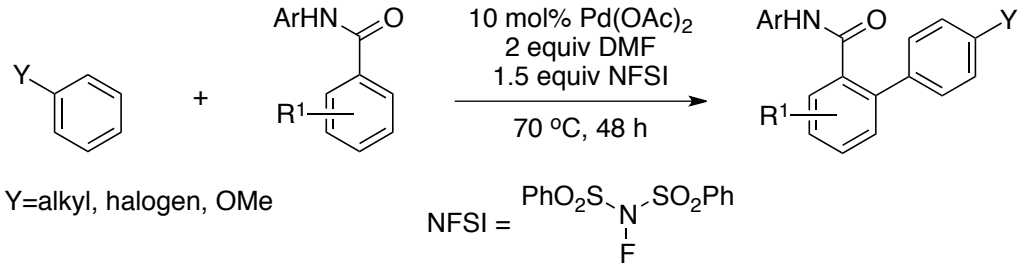
The first example of a *meta*-selective olefination process of highly electron-deficient arenes was demonstrated by Yu and co-workers (Scheme 3.5).[15] Bulky pyridine ligands were chosen for this transformation, promoting the oxidation of Pd(0) and weakening the Pd-N bond to facilitate the coordination of the substrates. Oxidative alkenylation occured regioselectively due to enhanced acidity of the C-H bonds meta to the electron-withdrawing groups.

Regarding to the catalytic *para*-selective C-H bond functionalization of benzene derivatives, most recently, Gaunt and co-workers published their work on *para*-selective arylation of aniline and phenol derivatives (Scheme 3.6).[16] This copper-catalyzed Friedel-Crafts-type strategy precluded the need for prefunctionalization of the nucleophilic arene components and represented a significant advance in direct arylation methodology to form valuable biaryl bonds.



Scheme 3.6 Copper-catalyzed *para*-arylation of aniline and phenol derivatives

Yu and co-workers also contributed to this area. Very recently during our study, they developed a palladium-catalyzed highly *para*-selective C-H/C-H coupling of benzamides with monosubstituted arenes using an F^+ reagent as a bystanding oxidant (Scheme 3.7).[17] The combination of an acidic amide directing group for the first C-H activation step and a bystanding F^+ oxidant for the second C-H activation step is crucial for high *para*-selectivity.



Scheme 3.7 Pd-catalyzed *para*-coupling of benzamides with monosubstituted arenes

3.2 – Ruthenium-Catalyzed Para-Selective Oxidative Cross-Coupling of Arenes and Cycloalkanes

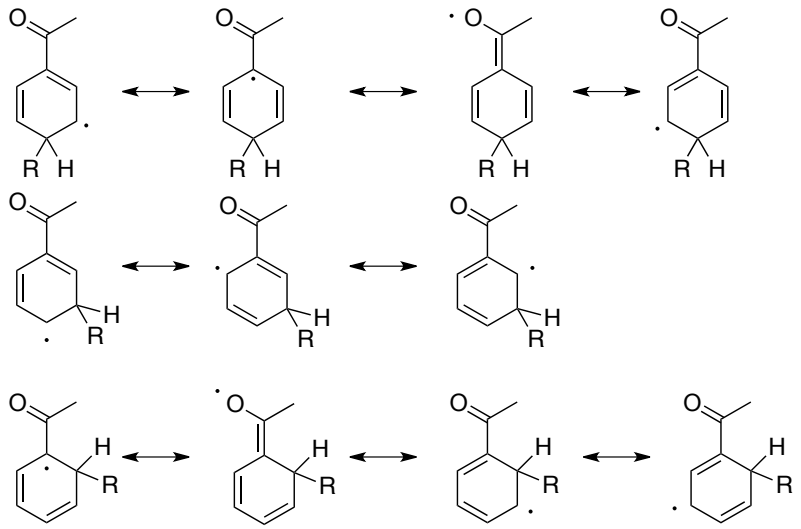
3.2.1 – Background

Achieving a regioselective C-H functionalization of mono-substituted arene substrates is a fundamental challenge from the viewpoint of synthetic applications. Although many methodologies have been developed in the last few decades, most of them featured an *ortho*-functionalization, while only a few achieved *meta*-selectivity and even less produced para products. In the first part of this chapter, we displayed the reactions reported by Gaunt[16] and Yu,[17] however, these reactions only provided a route to the *para*-arylation of arene substrates, and the *para*-alkylation of arene substrates remains unexplored. On the other hand, the formation of a carbon-carbon (C-C) bond directly from carbon-hydrogen (C-H) bonds via an oxidative cross-coupling has proven to be the most advanced method to reduce the total synthetic steps and byproduct. Our group demonstrated that simple alkanes could undergo an oxidative cross-coupling process with arenes.[18]

3.2.2 – Research Objective and Plan

The objective of this chapter is to develop a novel methodology in direct *para*-selective alkylation via an oxidative cross-dehydrogenative coupling (CDC) of benzene derivatives with cycloalkanes.

Based on the knowledge from previous reports, mechanistic insights on the radical nature inspired us to take advantage of stabilizing the resonance of a radical-charactered intermediate by both electron-donating and electron-withdrawing groups through FMO interactions,[19,20] thereby leading to selective *para*-functionalization (Scheme 3.8).



Scheme 3.8 Intermediate resonance structure of a radical (R•) addition to an acyl benzene

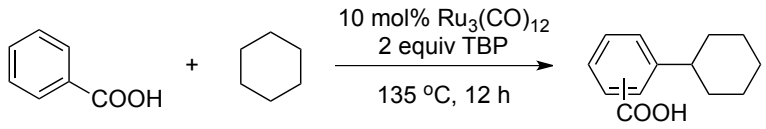
As the reaction will most likely undergo a radical process, peroxides will be used as both the radical initiator and the oxidant. We propose that acyl benzene derivatives are best candidate for this reaction as reasoned in Scheme 3.8. Low-valent metal catalysts will also be tested to see if they can facilitate the reaction, as low-valent metal complexes are found to be good acceptors for radicals and can stabilize the radical intermediate. Different additives and ligands will also be applied to help stabilize the intermediate.

3.2.3 – Results and Discussion

3.2.3.1 – Reaction Condition Screenings

To test our hypothesis of the *para*-selective oxidative cross-coupling reaction, we chose benzoic acid and cyclohexane as the standard substrates for the optimization of the reaction conditions (Table 3.1). Di-*tert*-butyl peroxide (TBP) was used as an external oxidant in this reaction. We found that the desired product **5a** could be generated without any catalyst in a trace amount. When 10 mol% $Ru_3(CO)_{12}$ was added to the system, 35% yield of the desired product **5a** could be obtained (Table 3.1, entry 1). Subsequently, we focused our efforts on changing the ligands. Sulfinyl groups were found to be good ligands for this reaction (Table 3.1, entries 2 and 3). Phosphine ligands gave similar results, except dppb (bis(diphenylphosphino)butane) and binap (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) achieving 75% and 60% yields, respectively (Table 3.1, entries 4 – 13). Dppb oxide gave a similar yield to dppb; and it was found that dppb (^{31}PNMR $\delta = -15.0$) was oxidized to dppb oxide (^{31}PNMR $\delta = 33.1$) after 3h during the course of the reaction based on a phosphorus NMR while the product yield was less than 10%. Therefore, it appears that the real ligand in this reaction is dppb oxide. Either a higher or lower temperature did not improve the yield (Table 3.1, entries 14 and 15).

Table 3.1 Optimization of reaction conditions of cross-coupling of benzene derivatives with cycloalkanes [a]



3a (0.2 mmol) **4a** ~9 equiv **5a**

entry	additives	% NMR yield
1	none	35
2	10 mol% $Na(OAc)_2$ + 10 mol%DMSO	45
3	5 mol% 1,2-bis(phenylsulfinyl)ethane	55
4	10 mol% Ph_3P	50
5	10 mol% nBu_3P	35
6	5 mol% dppm	52
7	5 mol% dppe	53
8	5 mol% dppp	53
9	5 mol% dppb	75
10	5 mol% dppb oxide	75
11	5 mol% binap	60
12	5 mol% 1,2-bis(diphenylphosphino)benzene	41
13	3 mol% $(Ph_2PCH_2CH_2)_2PPh$	38
14	5 mol% dppb	38[b]
15	5 mol% dppb	70[c]
16	5 mol% dppb	77[d]
17	5 mol% dppb	61[e]
18	2.5 mol% dppb	53[f]
19	10 mol% dppb	48
20	2.5 mol% dppb	55

[a]Conditions: **3a** (0.2 mmol), **4a** (0.2 mL, ~9 equiv), 10 mol% $Ru_3(CO)_{12}$ (0.007 mmol), 2 equiv TBP (di-*tert*-butyl peroxide), 135 °C, 12 h under air, NMR yields were examined using nitromethane as internal standard; [b]120 °C; [c]150 °C; [d]4 equiv TBP; [e]1 equiv TBP; [f]5 mol% $Ru_3(CO)_{12}$.

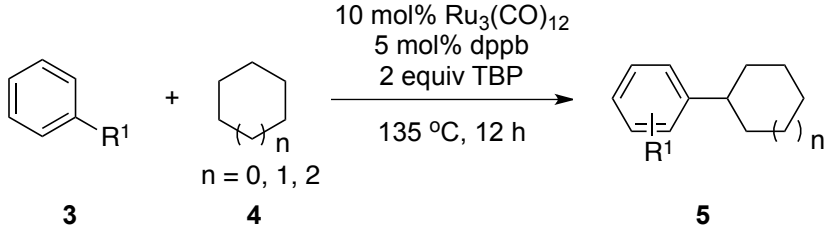
Increasing the loading of TBP to 4 equiv only increased the yield slightly, while lowering the amount of TBP used in this reaction reduced the yield (Table 3.1,

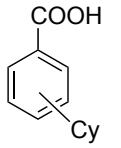
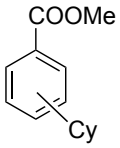
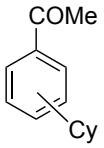
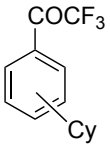
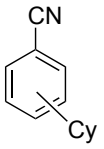
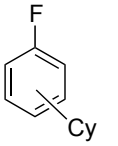
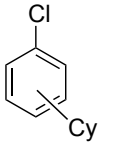
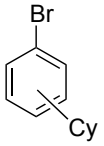
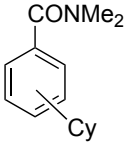
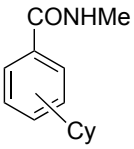
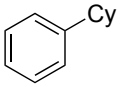
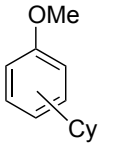
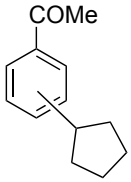
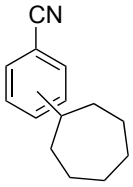
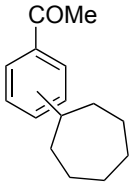
entries 16 and 17). Thus, further studies used 2 equiv oxidant. Other oxidants such as TBHP, dicumyl peroxide, benzoic peroxyanhydride and *tert*-butyl benzoperoxoate gave much lower yields (not shown). The product yield dropped to 53% with a reduced loading of the catalyst and ligand (Table 3.1, entry 18). Using either more or less ligand decreased the product yield (Table 3.1, entries 19 and 20). Thus, we chose 10 mol% $Ru_3(CO)_{12}$ together with 5 mol% dppb and 2 equiv TBP at 135 ^oC for 12h under air as our standard conditions.

3.2.3.2 – Scope of the Ruthenium-Catalyzed Para-Selective Oxidative Cross-Coupling of Arenes and Cycloalkanes

With the optimized conditions in hand, other benzene derivatives and cycloalkanes were investigated (Table 3.2). The reaction proceeded efficiently for a wide range of benzene derivatives. Electron-withdrawing groups were found to be efficient for this reaction. Other than benzoic acid, methyl benzoate worked similarly well and gave a 70% isolated yield (**5b**). Acetophenone, 2,2,2-trifloroacetophenone and cyanobenzene achieved much higher yields (**5c** 83%, **5d** 95% and **5e** 90%).

Table 3.2 Scope of cross-coupling of benzene derivatives with cycloalkanes[a-d]

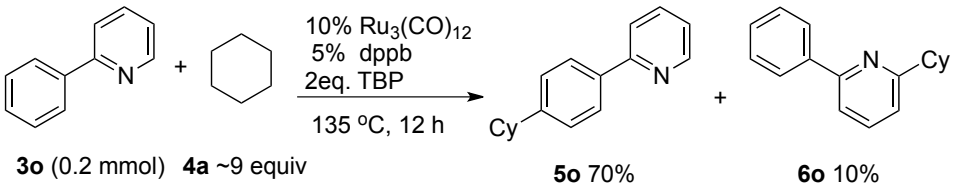


 **5a** 71% 92% para	 **5b** 70% 95% para	 **5c** 83% 96% para	 **5d** 95% 94% para	 **5e** 90% 45% para 42% ortho 13% meta
 **5f** 46%[e,f] 52% para 36% ortho 12% meta	 **5g** 75% 51% para 40% ortho 9% meta	 **5h** 72% 76% para 18% ortho 6% meta	 **5i** 45% 85% para	 **5j** 50% 91% para
 **5k** 45%[e,f]	 **5l** 47% 60% para 30% ortho 10% meta	 **5m** 26%	 **5n** 82% 50% para 44% ortho 13% meta	 **5w** 41% 95% para

[a]Conditions: **3** (0.2 mmol), **4** (0.2 mL), 10 mol% $Ru_3(CO)_{12}$ (0.007 mmol), 5 mol% dppb, 2 equiv TBP (di-*tert*-butyl peroxide), 135 ^oC, 12 h under air; yield was given as a total yield of mixtures of *ortho*/*meta*/*para*-products; [b]Regioselectivity ratio determined by GC-MS; [c]Cy= cyclohexyl; [d]Isolated, otherwise noted; [e]determined by ^1H NMR yield; [f]72 h.

Halobenzenes also reacted with cyclohexanes in good yields (**5g** 75% and **5h** 72%) with the halogen group untouched. Fluorobenzene gave a moderate yield, possibly due to the low boiling point of fluorobenzene (84 ^oC) and only a trace amount may be present in the catalytic mixture (**5f**). Iodobenzene gave a complicated mixture. Amides were also effective, albeit giving moderate yields (**5i** 45% and **5j** 50%). A free N-H bond can be tolerated without any protection during the reaction (**5j**). It is interesting to note that even unfunctionalized

benzene can be used for this reaction (**5k** 45%). The reaction of benzene ring bearing electron-donating groups such as methoxyl group gave **5l** with moderate yields. Other cycloalkanes are also effective in this reaction. The ring size of alkanes had a dramatic influence on the reaction: while cyclopentane gave a much lower yield (**5m**) cycloheptane gave a similar result compared with cyclohexane (**5n** 82%, **5w** 41%). In all these reactions, only trace amounts (about 5%) of the disubstituted products were observed.

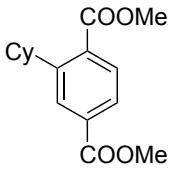
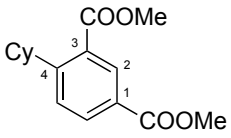
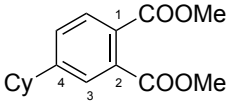
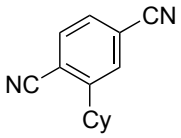
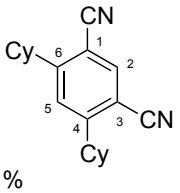
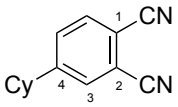


Scheme 3.9 Reaction of 2-phenylpyridine with cyclohexane (separated yields)

The reaction proceeded predominately at the *para*-position in all cases for mono-substituted benzene derivatives (see **5a** to **5d**, **5i, 5j** and **5w**). However, for benzene derivatives with a halogen or alkoxy substitutent (see **5e** to **5h**, **5l**) the amount of *ortho*-products was increased.

Interestingly, when the commonly used 2-phenylpyridine was tested in this reaction, we found that the coupling took place exclusively at the *para*-position (>99%) (Scheme 3.9). A small amount of product due to the reaction of the pyridine ring was also observed.

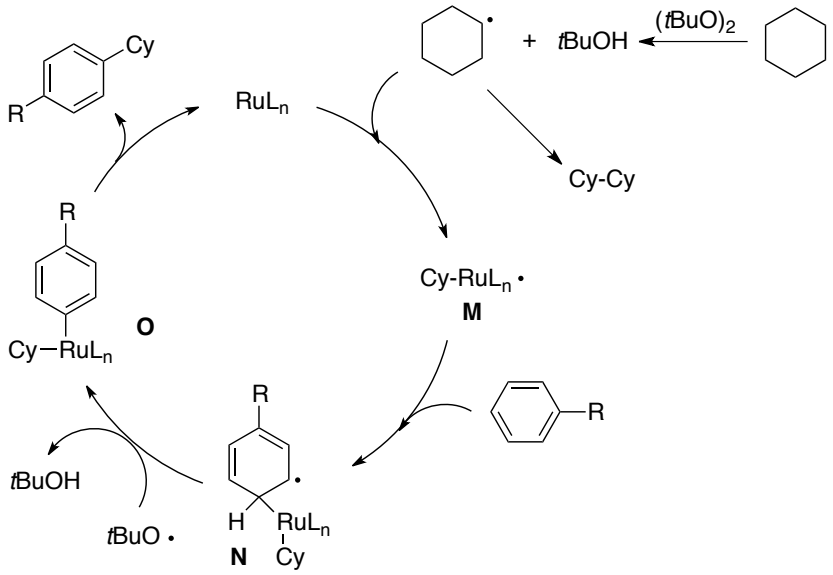
Table 3.3 Cross-coupling of disubstituted benzene derivatives with cyclohexanes[a,c,d]

 **5p** 39%	 **5q** 67% (4-substituted 95%) (disubstituted **7q** 15%[b])	 **5r** 80% (4-substituted >95%[e])
 **5s** 70% (disubstituted **7s** 20%)	 **7t** 81% (4,6-disubstituted >95%[e]) (mono-substituted **5t** 12%[b])	 **5u** 82% (4-substituted 77% 3-substituted 23%[e])

[a]Conditions: **3** (0.2 mmol), **4** (0.2 mL, ~9 equiv), 10 mol% $Ru_3(CO)_{12}$ (0.007 mmol), 5 mol% dppb, 2 equiv TBP (di-*tert*-butyl peroxide), 135 [o]C, 12 h under air; [b]determined by GC-MS; [c]Cy= cyclohexyl; [d]yields are separated yield, if not other noted; [e]determined by [1]HNMR.

Disubstituted benzene derivatives were also examined (Table 3.3). As methyl benzoate has a very high *para*-selectivity, dimethyl terephthalate only gave a low yield (39%) at the *ortho*-position because of the inaccessibility of the *para*-position (**5p**). By making the *para*-position available, excellent yields of the corresponding products were obtained. (80% to 93%). With the less selective but stronger activating cyano group, 1,3-dicyanobenzene generated dicyclohexyl substituted product **7t** as the major product with an 81% yield.

3.2.3.3 – Mechanism Discussion



Scheme 3.10 Proposed mechanism for benzene derivatives alkylation

A kinetic isotope study revealed that the reaction showed no-isotope effect, with a k_H/k_D=1.00, when chlorobenzene and chlorobenzene-d_5 were used as the substrates. These results suggested that the reaction most likely proceeds via a radical mechanism (Scheme 3.10). After the cyclohexyl radical was generated, it reacted with the ruthenium catalyst to form a radical comlpex **M**, which added to the benzene ring yielding the intermediate **N**. A *tert*-butoxide radical removed the hydrogen radical to re-aromatize the benzene ring giving intermediate **O**. A reductive elimination regenerated the ruthenium catalyst and yielded the product.

3.2.4 – Conclusion

In summary, we have developed a novel direct *para*-selective oxidative cross-coupling of benzene derivatives with cycloalkanes catalyzed by ruthenium. A wide range of arenes with electron-withdrawing substituents was functionalized directly with simple cycloalkanes in high *para*-selectivity; arenes with electron-donating groups was mainly *para*-functionalized. The reaction overwhelmed the effect of strongly ortho-directing of chelating substituents. Notably, benzoic acid can be used directly.

As an initial work on this project, we succeeded in the *para*-alkylation of arenes with cycloalkanes. Other radical species such as Grignard reagent can also be tested to install a specific functional group onto the *para*-position of the benzene derivatives. Instead of using peroxides as the radical initiator, other method such as light to generate radical will also be examined. Meanwhile, a second-generation catalytic system is still needed to improve the *para*-selectivity for substrates such as halobenzenes.

3.2.5 – Contribution

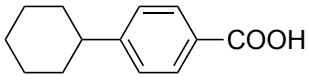
I designed and conducted all the experiments (condition screening, scope screening, products isolation and characterization). The paper was written by me and modified by Porf. Chao-Jun Li.

3.2.6 – Experimental Section

General Information Relating to All Experimental Procedures

Unless otherwise noted, all chemicals were obtained from commercial suppliers and used as received. All reactions were carried out under an atmosphere of air at ambient temperature unless otherwise stated. All work-up and purification procedures were carried out with reagent-grade solvents. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm) or Sorbent Silica Gel 60 F_{254} plates. The developed TLC plate was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh) or SORBENT silica gel 30-60 μm. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian MERCURY plus-300 spectrometer (^{1}H 300 MHz, ^{13}C 75 MHz) spectrometer or a Varian MERCURY plus-400 spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz) or a Varian MERCURY plus-500 spectrometer (^{1}H 500 MHz, ^{13}C 125 MHz). Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Chemical shifts for ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: δ 77.0 ppm). Data are reported as following: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. HRMS were made by McGill University.

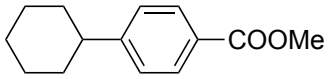
Typical procedure for 4-cyclohexylbenzoic acid synthesis: An oven-dried reaction vessel was charged with $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), benzoic acid (24.4 mg, 0.2 mmol), cyclohexane (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) under air (1 atm). The reaction vessel was then sealed, covered with aluminum foil, and the resulting solution was stirred at 135 ^oC for 12 h. Then, the resulting mixture was cooled to room temperature, filtered through a short silica gel plug eluted with ethyl acetate. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (SiO_2, hexane: ethyl acetate = 40:1) to give **5a** (mixture of *ortho*-, *meta*-, *para*-substituted isomers) (29.0 mg, 71%) as a white solid.



4-cyclohexylbenzoic acid (5a)

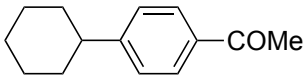
5a was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3a** (24.4 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=40:1, Rf=0.3) to afford **5a** (mixture of *ortho*-, *meta*-, *para*-substituted isomers) as a white solid (29.0 mg, 71%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J*= 7.6 Hz, 0.12H), 8.03 (d, *J*= 8.0 Hz, 1.58H), 7.92 – 7.97 (m, 0.30H), 7.45 – 7.50 (m, 0.30H), 7.39 (d, *J*= 7.6 Hz, 0.10H), 7.31 (d, *J*= 8 Hz, 1.58H), 2.58 (s, 1H), 1.88 (s, 4H), 1.77 (d, *J*= 12.4, 1H), 1.36 – 1.49 (m, 4H), 1.23

– 1.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 154.5, 130.4, 127.0, 126.8, 44.8, 34.3, 34.1, 26.8, 26.7, 26.0. (Wang, H.; Liu, J.; Deng, Y.; Min, T.; Yu, G.; Wu, X.; Yang, Z.; Lei, A. *Chem. Eur. J.* **2009**, *15*, 1499.)



methyl 4-cyclohexylbenzoate (5b)

5b was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3b** (27.2 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.3) to afford **5a** (mixture of *ortho*-, *meta*-, *para*-substituted isomers) as a white solid (30.5 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.97 (m, 1.80H), 7.84 – 7.90 (m, 0.20H), 7.32 – 7.40 (m, 0.20H), 7.27 (d, *J*= 7.6 Hz, 1.80H), 3.89 (s, 3H), 2.55 (s, 1H), 1.86 (s, 4H), 1.76 (d, *J*= 12.0 Hz, 1H), 1.34 – 1.47 (m, 4H), 1.26 – 1.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 153.4, 129.6, 127.7, 126.8, 51.9, 44.6, 34.3, 34.1, 26.7, 26.0. (Nasyr, I. A.; Zavgorodnii, S. V. *Ukrainskii Khimicheskii Zhurnal* (Russian Edition) **1964**, *30*, 862.)



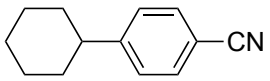
1-(4-cyclohexylphenyl)ethanone (5c)

5c was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3c** (24.0 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.2) to afford **5c** (mixture of *ortho*-, *meta*-, *para*-substituted isomers) as a white solid (33.5 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J*= 7.6 Hz, 1.80H), 7.76 – 7.81 (m, 0.20H), 7.35 – 7.46 (m, 0.20H), 7.29 (d, *J*= 8.0 Hz, 1.80H), 2.58 – 2.60 (m, 4H), 1.86 (s, 4H), 1.76 (d, *J*= 12.4 Hz, 1H), 1.35 – 1.48 (m, 4H), 1.25 – 1.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 153.7, 135.0, 131.8, 128.5, 127.0, 126.6, 126.1, 44.6, 34.3, 34.1, 26.8, 26.7, 26.5, 26.0. (AIST: Integrated Spectral Database System of Organic Compounds. (Japan))

1-(4-cyclohexylphenyl)-2,2,2-trifluoroethanone (5d)

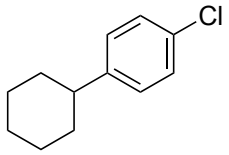
5d was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3d** (34.8 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.3) to afford **5d** (mixture of *ortho*-, *meta*-, *para*-substituted isomers) as colorless liquid (48.6 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J*= 4.5 Hz, 2H), 7.37 (t, *J*= 4.0 Hz, 2H), 2.60 (s, 1H), 1.88 (s, 4H), 1.78 (d, *J*= 12.5 Hz, 1H), 1.42 – 1.48 (m, 4H), 1.26 – 1.29 (m, 1H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 180.1 (q, *J*= 34.25 Hz), 156.7, 134.3, 130.4, 130.4, 129.1, 129.0, 128.4, 128.1, 127.7, 127.6, 116.8 (q, *J*= 289.75 Hz), 44.9, 44.4, 34.2, 33.9, 32.8, 31.1, 30.0, 26.7, 26.6, 25.9, 25.5, 23.8, 23.6. (Zhao, M.; Yang, X. *Huadong Ligong Daxue Xuebao* **1999**, *25*, 431.)



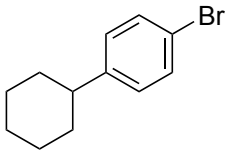
4-cyclohexylbenzonitrile (5e)

5e was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3e** (20.6 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.3) to afford **5e** (mixture of *ortho*-, *meta*-, *para*-substituted isomers) as colorless liquid (33.3 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.61 (m, 1.80H), 7.43 – 7.49 (m, 0.20H), 7.37 (t, *J*= 7.5 Hz, 0.20H), 7.30 (d, *J*= 8.5 Hz, 1.80H), 2.98 (s, 0.10H), 2.55 (s, 0.90H), 1.86 (d, *J*= 8.0 Hz, 4H), 1.77 (d, *J*= 12.0 Hz, 1H), 1.38 – 1.48 (m, 4H), 1.25 – 1.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 132.9, 132.2, 131.6, 130.5, 129.6, 127.7, 126.5, 126.2, 119.2, 109.6, 44.8, 34.6, 34.1, 34.0, 33.7, 26.6, 25.9. (Itou, T.; Yoshimi, Y.; Morita, T.; Tokunaga, Y.; Hatanaka, M. *Tetrahedron* **2008**, *65*, 263.)



1-chloro-4-cyclohexylbenzene (5g)

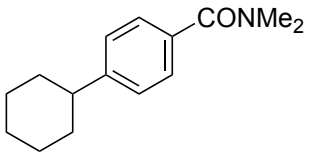
5g was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3g** (22.5 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.9) to afford **5g** (mixture of *ortho*-, *meta*-, *para*-substituted isomers) as colorless liquid (29.2 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J*= 1.0, 8.0 Hz, 0.40H), 7.19 – 7.27 (m, 2.10H), 7.07 – 7.16 (m, 1.50H), 3.02 (td, *J*= 3.0, 11.5 Hz, 0.40H), 2.46 – 2.48 (m, 0.60H), 1.84 – 1.90 (m, 4H), 1.77 (t, *J*= 13.0 Hz, 1H), 1.34 – 1.49 (m, 4H), 1.23 – 1.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 146.5, 144.8, 134.0, 133.5, 129.5, 129.4, 128.3, 128.2,127.2, 127.0, 126.8, 126.8, 125.9, 125.1, 44.3, 44.0, 40.5, 34.4, 34.3, 33.1, 26.8, 26.8, 26.7, 26.2, 26.0, 26.0. (Coxon, J. M.; Schuyt, H. A.; Steel, P. J. *Aust. J. Chem.* **1980**, *33*, 1863.)



1-bromo-4-cyclohexylbenzene (5h)

5h was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3h** (31.4 mg, 0.2 mmol), **4a** (0.2 mL,

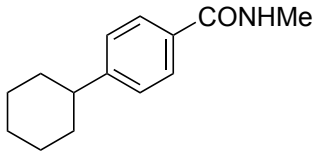
~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.9) to afford **5g** (mixture of *ortho*-, *meta*-, *para*-substituted isomers) as colorless liquid (34.4 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.54 (m, 0.40H), 7.39 – 7.41 (m, 0.40H), 7.36 (s, 0.40H), 7.30 (dt, *J*= 2.0, 7.0 Hz, 0.40H), 7.24 – 7.27 (m, 0.80H), 7.19 – 7.17 (m, 0.80H), 7.07 – 7.10 (m, 0.40H), 7.01 – 7.05 (m, 0.40H), 2.97 (tt, *J*= 3.0, 12.0 Hz, 0.40H), 2.44 – 2.49 (m, 0.60H), 1.84 – 1.91 (m, 4H), 1.50 – 1.80 (m, 1H), 1.34 – 1.50 (m, 4H), 1.23 – 1.33 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 147.0, 146.3, 132.8, 131.3, 130.0, 129.8, 128.8, 128.6, 127.5, 127.3, 127.2, 125.5, 124.4, 122.4, 44.3, 44.0, 43.2, 34.3, 34.3, 33.2, 26.8, 26.7, 26.2, 26.0. (Kaufmann, M.; Gisler, M.; Leumann, C. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3810.)



4-cyclohexyl-*N*,*N*-dimethylbenzamide (5i)

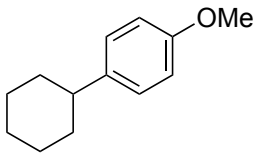
5i was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3i** (29.8 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=2:1, Rf=0.3) to afford **5i** (mixture of *ortho*-, *meta*-, *para*-substituted isomers) as a brown solid (20.8 mg, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J*= 8.5 Hz, 0.30H), 7.33 – 7.34 (m, 1.70H), 7.21 – 7.26 (m, 2H),

3.10 (s, 3H), 2.99 – 3.00 (m, 3H), 2.49 – 2.53 (m, 1H), 1.85 (s, 4H), 1.75 (d, *J*= 11.5 Hz, 1H), 1.34 – 1.45 (m, 4H), 1.23 – 1.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 151.7, 149.7, 133.7, 128.0, 127.2, 127.0, 126.8, 126.7, 125.5, 124.4, 44.4, 39.7, 35.4, 34.3, 34.3, 34.2, 26.8, 26.7, 26.1, 26.0; HRMS ESI (m/z): $[MH]^+$ calcd for $C_{15}H_{22}NO$, 232.16959; found, 232.16925.



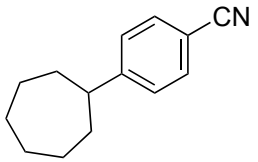
4-cyclohexyl-*N*-methylbenzamide (5j)

5j was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3j** (27.0 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=2:1, Rf=0.2) to afford **5j** (*para*-substituted product) as a white solid (21.7 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J*= 8.0 Hz, 2H), 7.25 (d, *J*= 8.5 Hz, 2H), 6.13 (s, 1H), 3.00 (d, *J*= 4.5 Hz, 3H), 2.54 (s, 1H), 1.85 (s, 4H), 1.75 (d, *J*= 12.5 Hz, 1H), 1.35 – 1.46 (m, 4H), 1.25 – 1.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 151.7, 132.1, 127.0, 126.8, 44.5, 34.2, 26.8, 26.7, 26.0; IR (neat): 3317, 2925, 2849, 1634, 1609, 1536, 1494, 1304, 665, 629, 551, 428, 415, 407ν cm^{-1}. HRMS ESI (m/z): $[MH]^+$ calcd for $C_{14}H_{20}NO$, 218.15394; found, 218.15387.



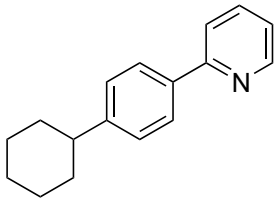
1-cyclohexyl-4-methoxybenzene (5l)

5l was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3l** (21.6 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.6) to afford **5g** (mixture of *ortho*-, *meta*-, *para*-substituted isomers) as colorless liquid (17.9 mg, 47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (dd, *J*= 2.0, 7.0 Hz, 0.90H), 7.16 (td, *J*= 1.5, 7.5 Hz, 0.90H), 7.09 (t, *J*= 7.5 Hz, 0.10H), 7.04 (d, *J*= 2.0 Hz, 0.10H), 6.99 (dd, *J*= 2.0, 8.5 Hz, 0.10H), 6.91 – 6.94 (m, 0.90H), 6.85 (d, *J*= 8.0 Hz, 0.90H), 6.77 – 6.79 (m, 0.10H), 3.83 (s, 2.70H), 3.80 (s, 0.30H), 2.93 – 2.99 (m, 0.90H), 2.44 – 2.46 (m, 0.10H), 1.81 – 1.84 (m, 4H), 1.74 – 1.77 (m, 1H), 1.34 – 1.47 (m, 4H), 1.22 – 1.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 136.2, 126.5, 126.4, 120.5, 110.3, 55.4, 36.7, 34.8, 33.3, 33.2, 27.1, 27.1, 27.0, 26.5, 26.4. (Cahiez, G.; Chaboche, C.; Duplais, C.; Moyeux, A. *Org. Lett.* **2009**, *11*, 3176.)



4-cycloheptylbenzonitrile (5n)

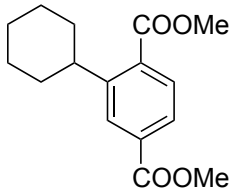
5n was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3e** (20.6 mg, 0.2 mmol), **4b** (0.2 mL, ~1.7 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.3) to afford **5n** (mixture of *ortho*-, *meta*-, *para*-substituted isomers) as colorless liquid (32.6 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J*= 8.0 Hz, 1.60H), 7.41 – 7.47 (m, 0.40H), 7.26 – 7.28 (m, 2H), 3.13 (s, 0.10H), 2.69 – 2.71 (m, 0.90H), 1.80 – 1.88 (m, 4H), 1.66 – 1.69 (m, 2H), 1.53 – 1.63 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 132.2, 127.5, 119.2, 109.3, 47.1, 36.5, 36.4, 27.8, 27.1; HRMS ESI (m/z): $[MH]^+$ calcd for $C_{14}H_{18}N$, 200.14338; found, 200.14343.



2-(4-cyclohexylphenyl)pyridine (5o)

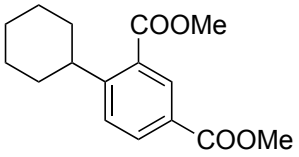
5o was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3o** (20.6 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.2) to afford **5o** (*para*-substituted product) as a white solid (33.2 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J*= 1.5 Hz, 1H), 7.97 (d, *J*= 7.5 Hz, 2H), 7.65 (d, *J*= 8.0 Hz, 1H), 7.58 (dd, *J*= 2.5, 8.0

Hz, 1H), 7.46 (t, *J*= 7.5 Hz, 2H), 7.39 (t, *J*= 7.5 Hz, 1H), 2.55 – 2.60 (m, 1H), 1.87 – 1.93 (m, 4H), 1.78 (d, *J*= 13.0 Hz, 1H), 1.39 – 1.50 (m, 4H), 1.25 – 1.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 148.7, 141.4, 139.5,134.9, 128.7, 128.5, 126.7, 120.2, 41.7, 34.1, 26.7, 26.0; IR (neat): 2922, 2849, 2361, 1590, 1588, 1472, 1445, 836, 742, 694, 491, 472, 449 ν cm^{-1}. HRMS ESI (m/z): $[MH]^+$ calcd for $C_{17}H_{20}N$, 238.15903; found, 238.15859.



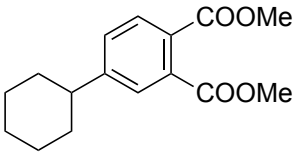
dimethyl 2-cyclohexylterephthalate (5p)

5p was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3p** (38.8 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.7) to afford **5p** as a white solid (21.5 mg, 39%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.85 (d, *J*= 8.0 Hz, 1H), 7.73 (d, *J*= 8.0 Hz, 1H), 3.91 (s, 3H), 3.92 (s, 3H), 3.22 – 3.27 (m, 1H), 1.85 (s, 4H), 1.76 (d, *J*= 13.0 Hz, 1H), 1.38 – 1.51 (m, 4H), 1.27 – 1.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 166.5, 148.6, 134.2, 132.6, 129.7, 128.1, 126.4, 52.3, 52.2, 40.3, 34.2, 26.8, 26.1; IR (neat): 2925, 2848, 2358, 1721, 1433, 1243, 1223, 750, 503 ν cm^{-1}. HRMS ESI (m/z): $[MH]^+$ calcd for $C_{16}H_{21}O_4$, 277.14344; found, 277.14357.



dimethyl 4-cyclohexylisophthalate (5q)

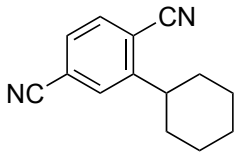
5q was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3q** (38.8 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.7) to afford **5q** (mixture of 2-, 4-, 5-substituted isomers) as a white solid (37.0 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 0.10H), 8.39 (d, *J*= 1.5 Hz, 0.90H), 8.06 – 8.08 (m, 1H), 7.45 (d, *J*= 8.5 Hz, 1H), 3.90 – 3.92 (m, 6H), 3.35 – 3.39 (m, 0.90H), 2.58 – 2.63 (m, 0.10H), 1.84 (t, *J*= 8.5 Hz, 4H), 1.76 (d, *J*= 13.0 Hz, 1H), 1.35 – 1.47 (m, 4H), 1.24 – 1.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 167.5, 166.3, 153.9, 148.8, 132.4, 131.3, 130.5, 130.1, 128.3, 127.4, 127.1, 52.2, 52.2, 52.1, 44.2, 40.4, 34.1, 34.1, 26.8, 26.3, 26.1, 25.9; HRMS ESI (m/z): $[MH]^+$ calcd for $C_{16}H_{21}O_4$, 277.14344; found, 277.14357.



dimethyl 4-cyclohexylphthalate (5r)

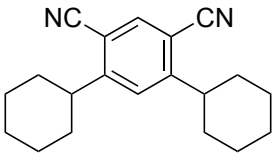
5r was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3r** (38.8 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the

above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.6) to afford **5r** as colorless liquid (44.2 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J*= 13.0 Hz, 1H), 7.50 (d, *J*= 1.5 Hz, 1H), 7.35 (dd, *J*= 1.5, 7.5 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.56 (td, d, *J*= 3.0, 12.5 Hz, 1H), 1.85 (s, 4H), 1.74 (d, *J*= 12.5 Hz, 1H), 1.34 – 1.45 (m, 4H), 1.21 – 1.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 167.8, 151.9, 132.6, 129.3, 129.2, 128.7, 127.1, 52.5, 52.4, 44.4, 34.0, 26.6, 25.9; IR (neat): 2924, 2850, 1723, 1606, 1434, 1289, 1197, 1124, 1070, 770, 500, 488, 436 ν cm^{-1}. HRMS ESI (m/z): $[MH]^+$ calcd for $C_{16}H_{21}O_4$, 277.14344; found, 277.14357.



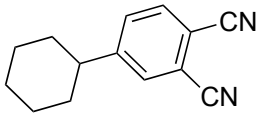
2-cyclohexylterephthalonitrile (5s)

5s was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3s** (25.6 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.7) to afford **5s** as a white solid (29.4 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J*= 8.0 Hz, 1H), 7.65 (s, 1H), 7.56 (d, *J*= 8.0 Hz, 1H), 2.99 – 3.03 (m, 1H), 1.89 – 1.92 (m, 4H), 1.81 (d, *J*= 13.0 Hz, 1H), 1.39 – 1.52 (m, 4H), 1.25 – 1.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 133.4, 130.4, 129.6, 117.5, 116.7, 116.4, 116.2, 42.6, 33.4, 26.3, 25.6; HRMS ESI (m/z): $[MNa]^+$ calcd for $C_{14}H_{14}N_2Na$, 233.10492; found, 233.10534.



4,6-dicyclohexylisophthalonitrile (7t)

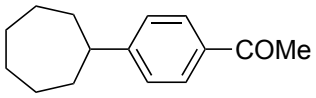
7t was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3t** (25.6 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.8) to afford **7t** (mixture of 4,6-disubstituted and 2,4-disubstituted isomers) as a white solid (34.0 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 0.70 H), 7.74 (d, *J*= 13.0 Hz, 0.30H), 7.35 (s, 0.70H), 7.31 (d, *J*= 8.5 Hz, 0.30H), 3.31 (tt, *J*= 3.5, 12.5 Hz, 0.15H), 3.07 (tt, *J*= 3.0, 11.5 Hz, 0.15H), 2.99 (td, *J*= 3.0, 11.5 Hz, 1.40H), 2.22 (m, 0.30H), 1.89 – 1.91 (m, 8H), 1.80 (t, *J*= 14.0 Hz, 2H), 1.39 – 1.52 (m, 8H), 1.25 – 1.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 154.3, 137.1, 125.0, 124.8, 116.4, 110.6, 44.7, 43.2, 33.4, 33.3, 30.4, 26.6, 26.4, 26.3, 25.7, 25.7, 25.2; HRMS ESI (m/z): $[MH]^+$ calcd for $C_{20}H_{25}N_2$, 293.20123; found, 293.20130.



4-cyclohexylphthalonitrile (5u)

5u was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3u** (25.6 mg, 0.2 mmol), **4a** (0.2 mL, ~1.8 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography

(SiO_2, hexane/ethyl acetate=6:1, Rf=0.3) to afford **5u** (mixture of 3-, 4-substituted isomers) as a white solid (34.4 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*= 8.5 Hz, 0.88H), 7.64 – 7.65 (m, 1.12H), 7.56 (dd, *J*= 1.5, 8.0 Hz, 1H), 3.01 – 3.06 (m, 0.12H), 2.56 – 2.62 (m, 0.88H), 1.87 – 1.88 (m, 4H), 1.78 (d, *J*= 12.0 Hz, 1H), 1.35 – 1.47 (m, 4H), 1.24 – 1.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 133.5, 133.0, 132.1, 131.8, 130.9, 130.9, 115.8, 115.6, 115.6, 113.0, 44.4, 43.0, 33.7, 33.4, 26.3, 25.6, 25.6; IR (neat): 3045, 2926, 2855, 2229, 1605, 1491, 1455, 1406, 837, 505, 493, 428 ν cm^{-1}. HRMS ESI (m/z): $[MNa]^+$ calcd for $C_{14}H_{14}N_2Na$, 233.10492; found, 233.10534.



1-(4-cycloheptylphenyl)ethanone (5w)

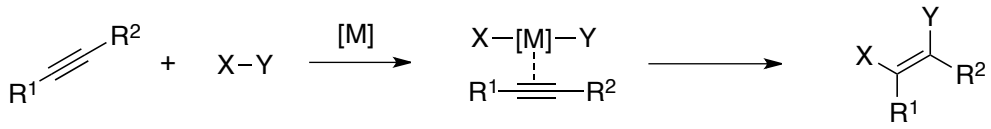
5w was prepared from dppb (bis(diphenylphosphino) butane) (4.3 mg, 0.01 mmol), $Ru_3(CO)_{12}$ (4.3 mg, 0.007 mmol), **3c** (24.0 mg, 0.2 mmol), **4b** (0.2 mL, ~1.7 mmol) and TBP (di-*tert*-butyl peroxide) (74 μL, 0.4 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=6:1, Rf=0.3) to afford **5w** (*para*-substituted product) as clear liquid (17.7 mg, 41%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.88 (m, 2H), 7.26 – 7.29 (m, 2H), 2.70 – 2.74 (m, 1H), 2.57 (s, 3H), 1.88 – 1.90 (m, 2H), 1.70 – 1.82 (m, 2H), 1.54 – 1.70 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 155.5, 134.8, 128.6, 126.9, 47.0, 36.4, 27.8, 27.2, 26.5. IR (neat): 3342, 2922, 2848, 1676, 1606, 1414, 1363, 1262, 822, 594, 472, 462, 411 ν cm^{-1}. HRMS ESI (m/z): $[MH]^+$ calcd for $C_{15}H_{21}O$, 217.15869; found, 217.15803.

Part II.

Ruthenium-Catalyzed Olefination via Decarbonylative Addition of Aldehydes to Terminal Alkynes

Chapter 4 –Introduction to the Olefination via Decarbonylative Strategies

The C=C bond is one of the most important and fundamental motifs in organic chemistry, and the synthesis of C=C bonds has been the focus of organic chemistry for over a century.[1] Many methodologies have been developed in this area, and among these, addition reactions of X–Y bonds (X and Y represent any element or functional group) to alkynes proceed with 100% atom efficiency and are thus more compatible with the principles of green chemistry.[2,3] Furthermore, metal catalysis has merged as a powerful method for addition to alkynes. The insertion of the alkyne triple bond into the X-Y linkage is facilitated by the oxidative addition of X-Y bond to the metal catalyst and alkenes are generated via a reductive elimination (Scheme 4.1).



Scheme 4.1 Olefin synthesis via addition of an X-Y bond to a triple bond

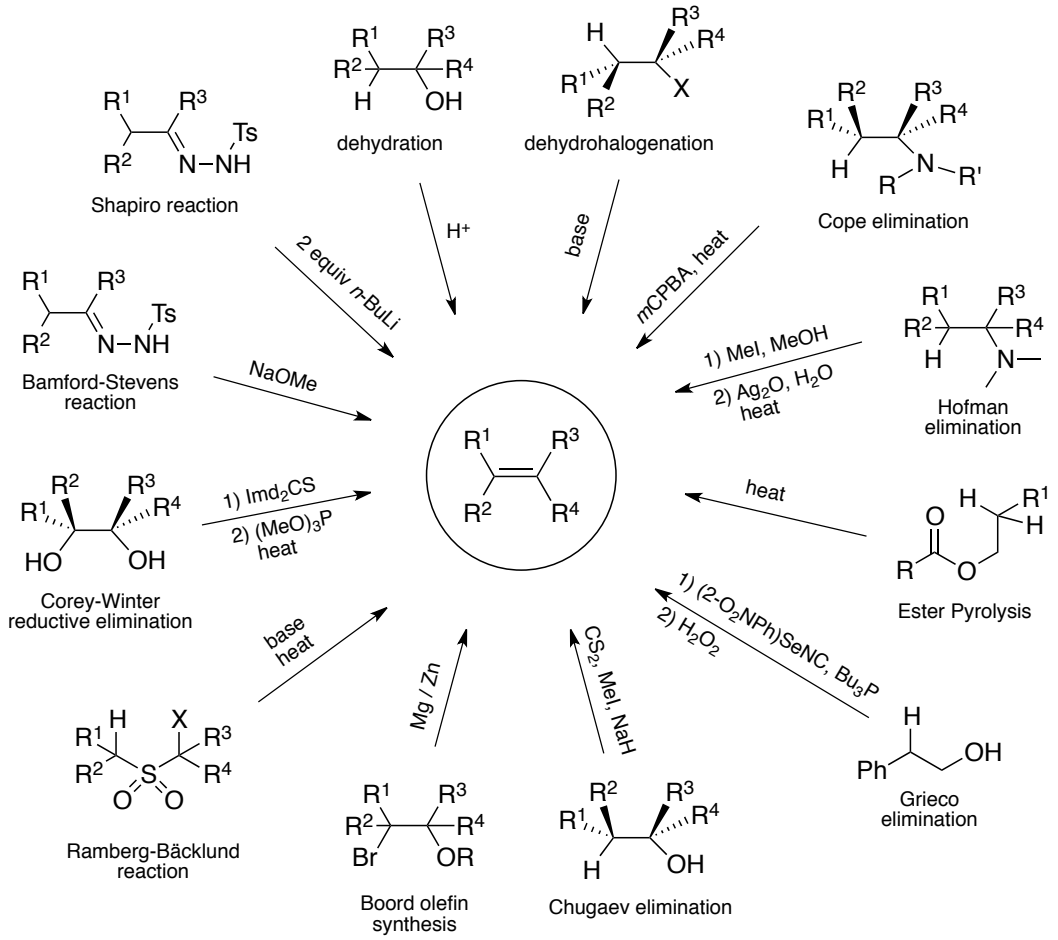
On the other hand, addition of C-H bond to alkynes generates alkenes and new C-C bonds at the same time, which is attractive but challenging. It shows high efficiency in atom economy, but the low reactivity of C-H bonds makes addition to alkynes much more difficult. Although transition-metal-catalyzed C-H activation converted this concept into reality,[4] only specific substrates could be used in such methodology and a more general method is still required. However,

instead of addition of R-H bonds directly to alkynes, starting from an aldehyde R-CHO could be alternative. After an oxidative addition and a corresponding decarbonylation process, a R-M-H complex can be generated and finally undergo an addition reaction of the R-H bond to an alkyne. CO is the only byproduct in the reaction, and the availability of various aldehydes in Nature guarantees broad potential applications with this method.

In this chapter, we will demonstrate selected examples on aldehyde decarbonylation reactions and synthesis of isolated C=C bonds will be briefly described.

4.1 – Introduction to C=C Bond Synthesis

Many methods have been developed throughout the history of organic chemistry regarding to the synthesis of C=C bonds, and elimination of two substitutes on C-C single bond to yield C=C bond is the most fundamental one. Based on the mechanism, elimination reactions can be cataloged into E1, E2 and E1cB reactions.[5] Leaving groups have great impacts on the reaction mechanism, regioselectivity and reaction conditions (Scheme 4.2). Alkyl halides go through a dehydrohalogenation and generate the more substituted alkenes (Zaitsev's rule). An α-halo sulfone can be converted into an alkene in the presence of a base with extrusion of sulfur dioxide via Ramberg-Bäcklund Reaction.[6]

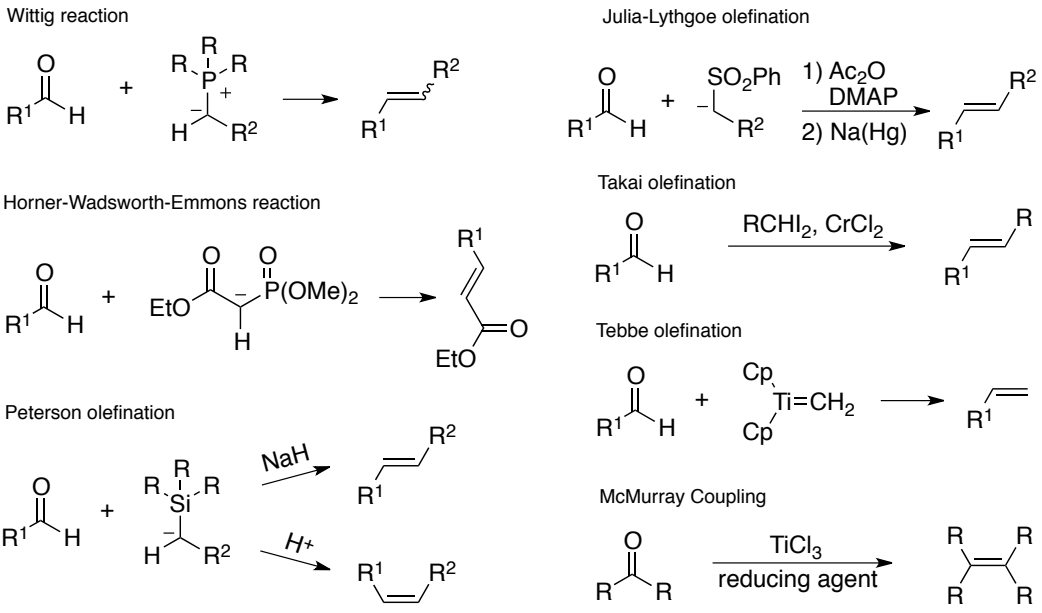


Scheme 4.2 Alkene synthesis via elimination reactions with different leaving groups

Alcohols can undergo a dehydration to form alkenes, in which case water is lost via the E1 mechanism. Alcohols may also be converted to a better leaving group which can undergo a milder *syn*-elimination such as the Chugaev elimination[7] and the Grieco elimination.[8] Related reactions include eliminations by β-haloethers (the Boord olefin synthesis[5,9]) and esters (ester pyrolysis[5]). Diols can be transformed into the corresponding olefins by sequential treatment with 1,1'-

thiocarbonyldiimidazole and trimethylphosphite (Corey-Winter reductive elimination[10]).

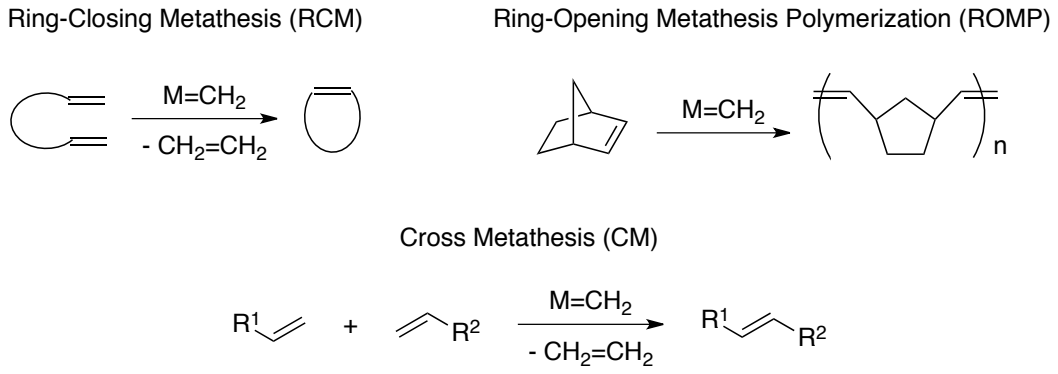
The amine or ammonia is not a suitable leaving group, so the amine is first either alkylated (the Hoffmann elimination[5]) or oxidized to an amine oxide (the Cope reaction[11]) to render a smooth elimination. With a tosylhydrazone as the leaving group, the alkenes can be generated via either the Shapiro reaction[12] (assisted by alkyl lithium or Grignard reagents), or the Bamford-Stevens reaction[13,12c] (assisted by NaOMe, LiH, NaH, $NaNH_2$, etc.).



Scheme 4.3 Olefination from carbonyl compounds

Carbonyl compounds play an important role in the synthesis of C=C bonds (Scheme 4.3). The Wittig reaction[14] involves construction of a new carbon-carbon double bond by coupling of a carbonyl compound (aldehyde or ketone) and a

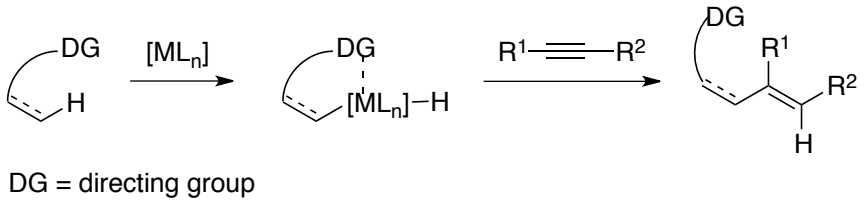
nucleophile (carbanion). The Horner-Wadsworth-Emmons reaction[15] is developed based on the Wittig reaction with stabilized phosphorus ylides (phosphonate carbanions) leading to olefins with excellent *E*-selectivity. The Peterson olefination[16] uses a silicon-based reagent and allows for the selectivity between *E*- or *Z*-products. The Julia-Lythgoe olefination[17] uses the carbanion generated from a phenyl sulfone to form the *E*-product. The Takai olefination[18] based on an organochromium intermediate also delivers *E*-product. The Tebbe olefination[19] uses a titanium compound for the synthesis of methylene compounds. Starting from carbonyl compounds alone, alkenes can also be generated using Ti metal reduction (the McMurry reaction[20]).



Scheme 4.4 Important classes of olefin metathesis

Olefin metathesis[21] provides an alternative for alkene synthesis by exchange with other alkenes (Scheme 4.4). Frequently, loss of ethylene gas is used to drive the reaction towards the desired product. In many cases, a mixture of geometric isomers is obtained, but the reaction tolerates many functional groups. The method is particularly effective for the preparation of cyclic alkenes.

Alkyne addition reactions are useful methods for the stereoselective synthesis of disubstituted alkenes. Hydrogenation of alkynes can lead to *cis*-alkenes in the presence of Lindlar' catalyst[22] or form *trans*-alkenes treating with sodium metal in liquid ammonia.[23] Hydrometalation or carbometalation of alkynes can generate vinyl metallic compounds (e.g. hydroalumination,[24] carboalumination,[25] carbocupration,[26] hydrozirconation,[27] and hydroboration[28]), and in a follow-up step, the sensitive metal group is replaced by an electrophile to build carbon-carbon bonds or carbon-heteroatom bonds.



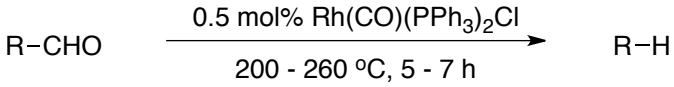
Scheme 4.5 Alkenylation via transition-metal-catalyzed C−H addition to C−C triple bonds

Other than these methods, a simplified alternative is the alkenylation through C−H addition to C−C triple bonds, which represent the simplest atom-economical reactions (Scheme 4.5).[4] These reactions require pre-installed directing groups for activation of the designated C-H bond. However, most reactions use aromatic sp^2 C−H bonds, while there have been only limited examples of sp^3 C−H bond functionalization in which alkynes were used as an addition partner.[4h-4i]

4.2 – Introduction to the Decarbonylative Reactions of Aldehydes

The removal of formyl functionalities, known as the decarbonylation of aldehydes, RCHO → RH + CO, is a very useful and thermodynamically downhill organic reaction that is normally carried out with the help of transition metal complexes, mainly involving Ru(II), Rh(I) and Ir(I) species. It is one of the essential protocols in synthetic chemistry, and has been applied broadly in the total syntheses of natural products.[29]

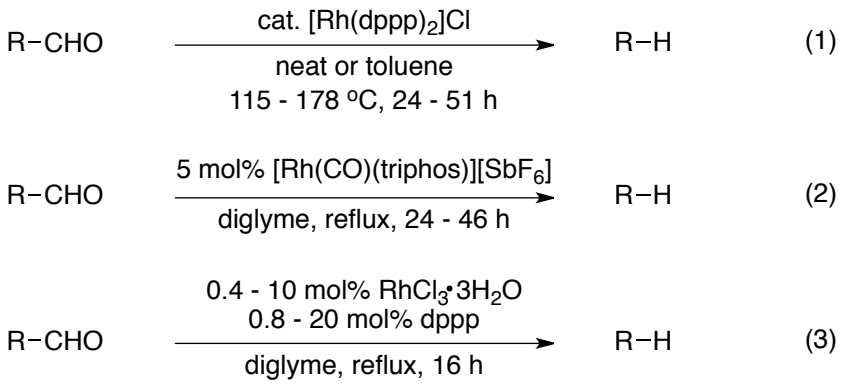
Aldehyde decarbonylation was first discovered as a stoichiometric reaction by Tsuji and Ohno in 1965, using a stoichiometric amount of Wilkinson's complex, $RhCl(PPh_3)_3$.[30] Three years later in 1968, this method was developed into a catalytic process by the same authors.[31] The carbonyl group was removed from aldehydes with 0.5 mol% of $Rh(CO)(PPh_3)_2Cl$ (Scheme 4.6). High temperature was required because the intermediate Rh-CO species generated in the reaction was stable (up to 200 ^oC) and incapable of engaging in further decarbonylation cycles. They also revealed that $PdCl_2$ could work as a catalyst for such a process.



Scheme 4.6 Rhodium-catalyzed decarbonylation of aldehydes

The high temperature restricted the application of decarbonylation due to some side reactions. To overcome this problem, In 1978, Doughty and Pignolet

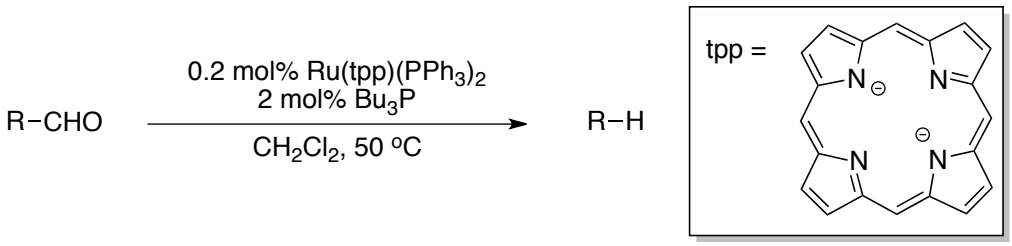
demonstrated that rhodium complexes with bidentate phosphines were much more active catalysts towards the decarbonylation reactions due to the decreasing of Rh-CO π-back-bonding (Scheme 4.7, Eq. 1).[32] Since then, rhodium catalysts with chelating phosphines have been extensively studied and applied in organic synthesis as a mature method.[29,33,34,35] Crabtree, Rheingold and co-workers used rhodium complex with a triophos ligand (triphos = bis(2-diphenylphosphinoethyl)phenylphosphine) for aldehyde decarbonylation at temperatures approaching 100 ^{o}C (Scheme 4.7, Eq. 2).[33] The limitation of this method is that the catalyst is not easy to prepare. More recently in 2006, Madsen and co-workers reported the $RhCl_3 \bullet 3H_2O$-catalyzed decarbonylation of various aldehydes in refluxing diglyme with dppp as ligand (dppp = bis(diphenylphosphino)propane) (Scheme 4.7, Eq. 3).[34]



Scheme 4.7 Phosphine chelated rhodium complexes catalyzed decarbonylation

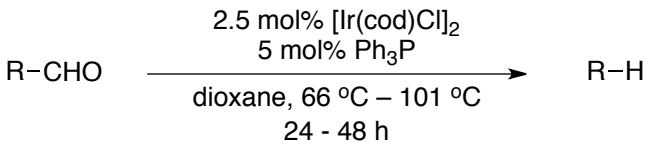
Ruthenium catalysts are rarely applied in aldehyde decarbonylation reactions,[36,37,38,43c] however, they showed good activities. James, Dolphin and co-workers found that ruthenium(II) porphyrin complexes could accomplish an

efficient decarbonylation of aldehydes under mild conditions (Scheme 4.8).[38] *n*-Bu_3P was added in the system, as the authors argued that P(*n*-Bu)$_3$ is much more effective than PPh_3 for displacement of coordinated CO on the ruthenium catalyst.



Scheme 4.8 Ru-catalyzed decarbonylation of aldehydes

Other than rhodium and ruthenium, iridium was also found effective in aldehyde decarbonylation.[36,39,40,43g,43h] Tsuji and co-workers presented their work on a highly active iridium catalyst system that realized the efficient catalytic decarbonylation of aldehydes at lower temperatures (66 °C – 101 °C) (Scheme 4.9).[40] A simple combination of commercially available $[IrCl(cod)]_2$ (cod = 1,5-cyclooctadiene) and an easily accessible phosphine such as PPh_3 or P(*n*-Bu)$_3$ provides a highly active and practical catalyst system.

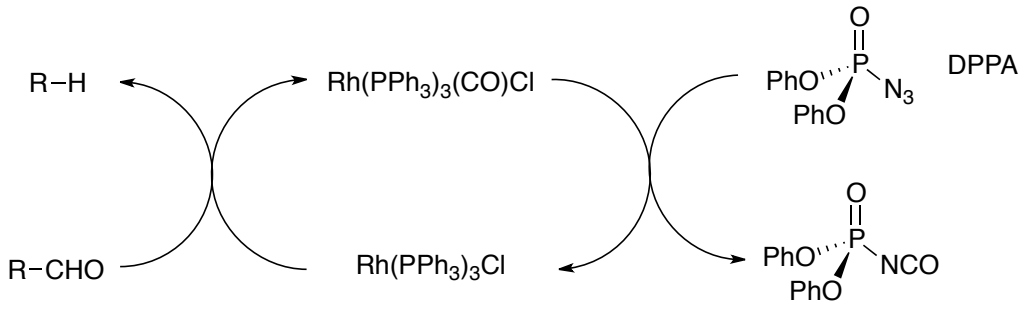


Scheme 4.9 Ir-catalyzed decarbonylation of aldehydes

Aldehyde decarbonylation can also be carried out by enzymes, which are the so-called aldehyde decarbonylase (AD). Biochemical studies of alkane biosynthesis focused mostly on natural metabolic systems, and many decarbonylation processes of long-chain fatty aldehydes to the corresponding alkanes were developed.[41]

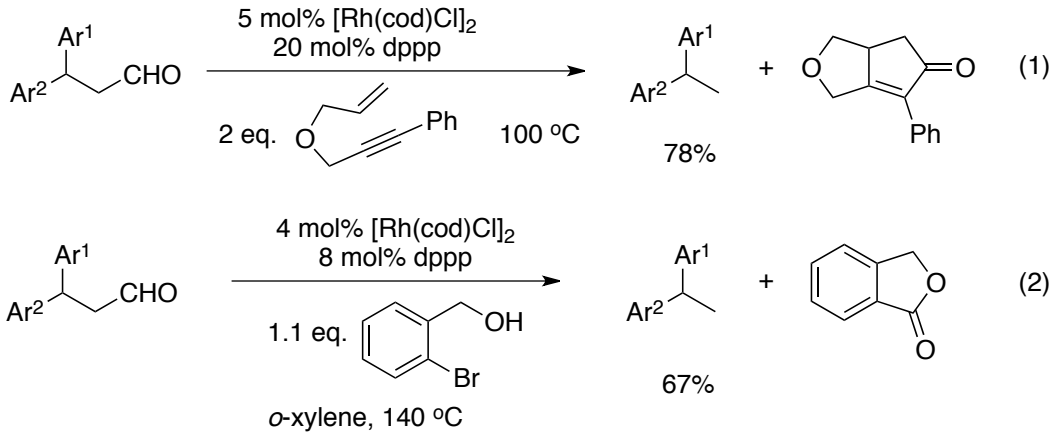
The loss of the evolved CO ligand to regenerate the active catalyst is a key issue in completing the catalytic cycle of transition-metal-catalyzed aldehyde decarbonylation. Despite much effort, forcing conditions such as elevated temperature are always required for catalyzed aldehyde decarbonylation, or a stoichiometric amount metal complex is used to guarantee a full conversion. Thus, many methods such as addition of CO-trapping agents were applied to improve the catalyst performance and reaction efficiency.

One approach to solve this problem was described by O'Connor and Ma.[42] They showed that in the presence of a stoichiometric amount of diphenylphosphoryl azide (DPPA), aldehyde decarbonylation could be achieved at room temperature. CO ligand was abstracted from rhodium by DPPA with the formation of diphenylphosphoryl isocyanate, and a catalytically active rhodium complex with empty coordinate site was regenerated (Scheme 4.10). One limitation of this method is that only primary aldehydes can be applied.



Scheme 4.10 DPPA promoted rhodium catalyzed decarbonylation of aldehydes

The removal of carbonyl ligand on transition metals could also be accomplished by combination with other reactions that required a CO source as a trap for CO. Morimoto/ Kakiuchi and Shibata independently reported Pauson−Khand-type reactions by using aldehydes as a source of carbon monoxide (Scheme 4.11, Eq. 1).[43,44] Rh, Ru, and Ir were all found effective for such processes. Another approach was contributed by Morimoto and co-workers.[44,45] They reported a rhodium-catalyzed carbonylative cyclization of organic halides with tethered nucleophiles by using aldehydes as a substitute for carbon monoxide (Scheme 4.11, Eq. 2). These reactions involved the decarbonylation of aldehydes by transition metal catalysts, and the successive carbonylative cyclizations of organic halides or enynes utilized the metal carbonyl that is formed in situ. In addition, Carreira and co-workers demonstrated that an N_2 stream could also help to remove the CO from the system.[44] With these methods, the equilibrium of aldehyde decaronylation reactions was driven forward to a complete.



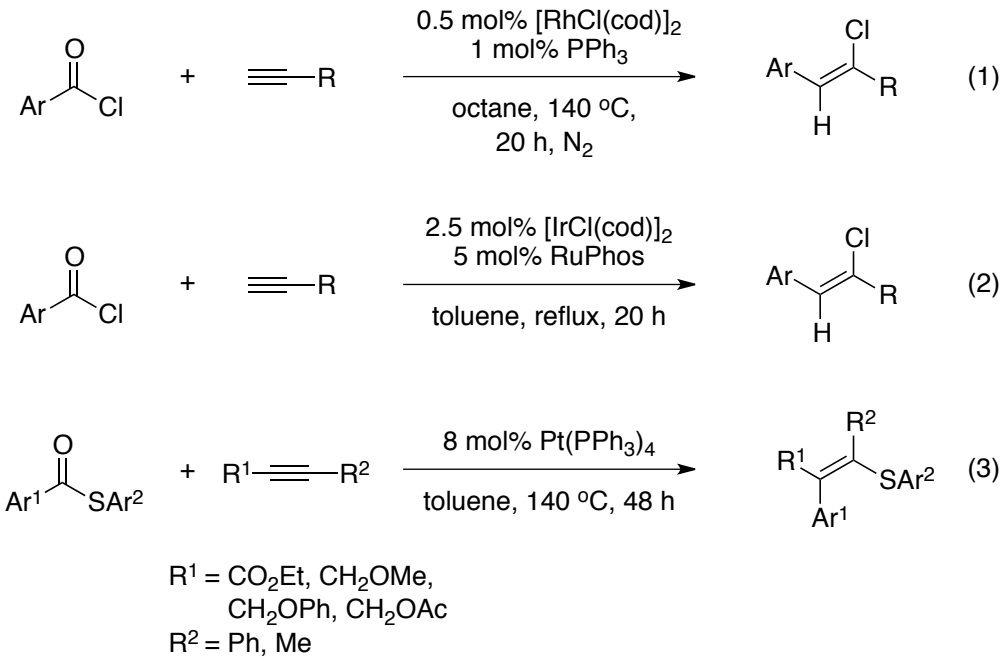
Scheme 4.11 Chemical traps for CO lead to catalytic decarbonylation[20]

Chapter 5 – Ruthenium-Catalyzed Olefination via Decarbonylative Addition of Aromatic Aldehydes to Terminal Alkynes

In chapter 4, we discussed the C=C bond formation reactions as well as the aldehyde decarbonylation reactions. In this chapter, a decarbonylative addition reaction, which is the combination of the two strategies, will be demonstrated, showing a novel method for C=C bonds synthesis.

5.1 – Background

The decarbonylative addition of reactive carbonyl compounds to alkynes provides a pathway to the synthesis of C=C bonds. Miura and co-workers demonstrated that aroyl chlorides could add across alkynes to yield vinyl chloride derivatives in the presence of a catalytic amount of $[RhCl(cod)]_2$ and PPh_3 (Scheme 5.1, Eq. 1).[1a] Most recently in 2009, Tsuji and co-workers achieved the same decarbonylative addition reaction by using iridium complex and RuPhos as the catalytic system (Scheme 5.1, Eq. 2).[1b] Pt-catalyzed thioesters C-S bond insertion could also lead to a decarbonylative process, which further underwent an addition reaction to unsymmetrical internal alkynes and generated the corresponding arylthiolation products (Scheme 5.1, Eq. 3).[2] However, only heteroatom-substituted olefins can be generated in these reactions.



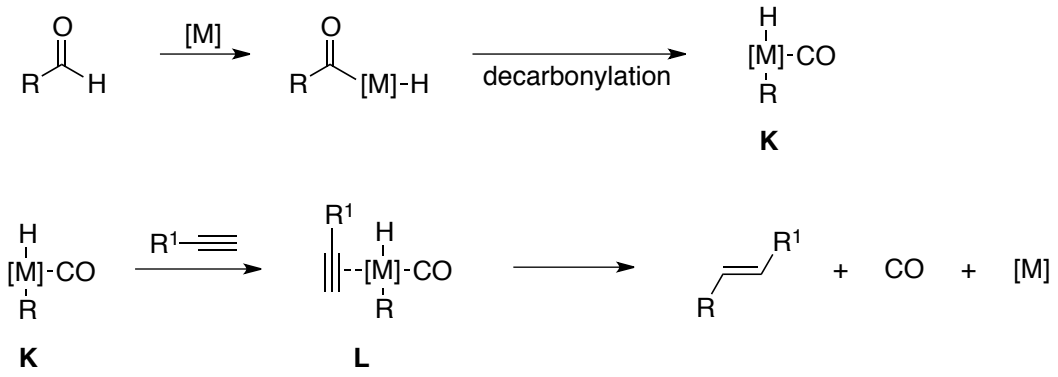
Scheme 5.1 Decarbonylative addition of carbonyl containing compounds to alkynes

5.2 – Research Objective and Plan

In order to explore a novel strategy for olefin synthesis, we would like to develop a decarbonylative addition reaction of aldehydes to alkynes for synthesizing C=C bonds, in which the carbonyl group works as a directing group and can be removed simultaneously.

The direct addition of a C-H bond to an alkyne to generate the olefin is the most atom-economical and efficient way. Although some reactions of this type were developed,[3] the substrate scope was quite limited and a pre-functionalized directing group was required.

On the other hand, the decarbonylation reaction of aldehyde can generate the same intermediate in-situ, which is alkyl/aryl metal hydride **K** (Scheme 5.2). With the addition of alkynes in the system, an alkyne can coordinate to the intermediate **K** giving the intermediate **L**, which can give the simple olefin as the product after an insertion and a following elimination.



Scheme 5.2 Proposed pathway for decarbonylative addition reactions

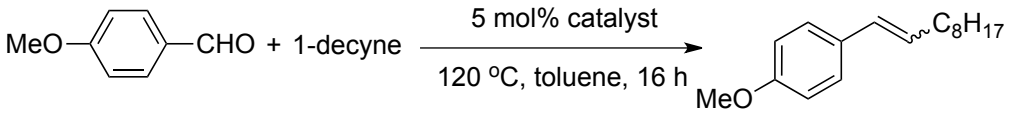
The feasibility of the decarbonylative addition reaction is briefly illustrated in Scheme 5.2, and we then consider the possible catalyst for this reaction. Rhodium, ruthenium and iridium complexes, which are found to be effective in aldehyde decarbonylation reactions, will be tested in the first step to check if the designated product could be generated. Ligands and additives will be examined as well.

5.3 –Results and Discussion

5.3.1 –Reaction Condition Screenings

Various conditions concerning the catalysts and the additives were examined to optimize the formation of this decarbonylative addition product. We first tested various catalysts such as $PdCl_2$, $PtCl_2$, $RhCl_3$, and $RuCl_3$ and found no reaction was observed under the same reaction conditions, while a trace amount of the desired product was observed with $HIrCl_6$. However, interestingly water was found to be beneficial to the reaction: the use of 5 mol% $RuCl_3 \cdot 3H_2O$ as catalyst generated the decarbonylative addition product in a 19% yield (Table 5.1).

Table 5.1 Effect of different ruthenium catalysts on the decarbonylative addition[a]



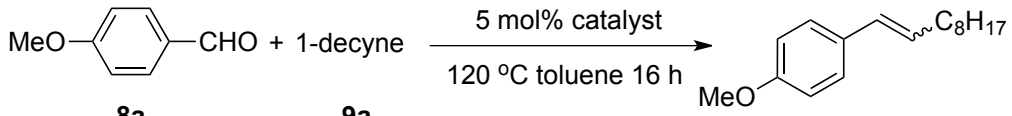
8a 0.2 mmol **9a** 0.8 mmol **10a**

entry	catalyst	additive	% NMR yield
1	$RuCp_2$	4μL H_2O	0
2	$RuCp_2$		0
3	$[RuCl_2(benzene)]_2$	4μL H_2O	14
4	$[RuCl_2(benzene)]_2$		0
5	$RuCl_2(PPh_3)_3$	4μL H_2O	0
6	$RuCl_2(PPh_3)_3$		0
7	$Ru(Cp)Cl(Ph_3P)_2$	4μL H_2O	0
8	$Ru(Cp)Cl(Ph_3P)_2$		0
9	$[(COD)RuCl_2]_n$	4μL H_2O	35
10	$[(COD)RuCl_2]_n$		0
11	$Ru(acac)_2$	4μL H_2O	0
12	$Ru(acac)_2$		0
13	$RuCl_3$	4μL H_2O	19
14	$RuCl_3$		0
15	$RuCl_3 \cdot 3H_2O$		19

[a]**8a** (0.2 mmol), **9a** (0.8 mmol), catalyst 5 mol% based on Ru, toluene (1 mL), 120 ^{o}C, 16 h under argon, ^{1}H NMR yields were examined using nitromethane as internal standard.

We then further examined commonly used ruthenium catalysts with or without water. By the using 5 mol% $[Ru(COD)Cl_2]_n$ together with 4 μL water, the designated product could be generated in 35% yield (Table 5.1, entry 9). We also tried different ruthenium cationic catalysts to further investigate whether the reaction can proceed smoothly to yield the designated product (Table 5.2). However, no better yields were achieved under these conditions comparing to the use of $[Ru(COD)Cl_2]_n$ (35%, Table 5.1, entry 9). We examined the combination of $[Ru(COD)Cl_2]_n$ with AgOTf as well, and found only reduced product yields were obtained (Table 5.3).

Table 5.2 Effect of cationic ruthenium catalysts on the decarbonylative addition

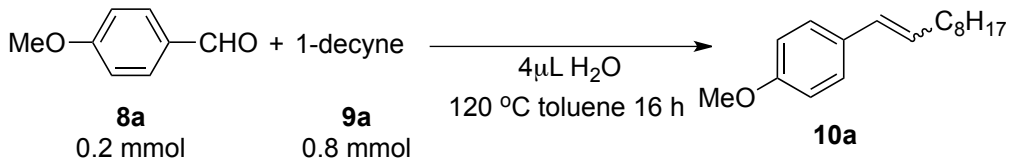


8a 0.2 mmol **9a** 0.8 mmol **10a**

entry	catalyst	% NMR yield[a]	% NMR yield[a,b]
1	$[Ru(bpy)_2(4\text{-}DMAP)_2](PF_6)_2$	0	0
2	$[Ru(bpy)_2(5\text{-}Clphen)](PF_6)$	0	0
3	$[Ru(COD)](OTf)_2$	5	11
4	$[Ru(COD)](BF_4)_2$[c]	0	0
5	$[Ru(COD)](PF_6)_2$[c]	trace	2
6	$[Ru(\rho\text{-cymene})](BF_4)_2$[c]	0	0
7	$Ru(BF_4)_3$[c]	0	0
8	$Ru(PF_6)_3$[c]	0	0
9	$Ru(OTf)_3$[c]	0	5

[a]^{1}H NMR yields were examined using nitromethane as internal standard; [b]with 4 μL H_2O added; [c]the catalyst was generated *in situ* in 0.5 mL toluene at r.t.; then aldehyde, alkyne (and water) were added to the resulting mixture, followed by the addition of another 0.5 mL toluene, and then the temperature was rised to 120 ^oC.

Table 5.3 Effect of AgOTf on the decarbonylative addition



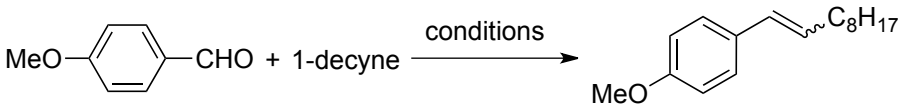
8a 0.2 mmol **9a** 0.8 mmol **10a**

entry	% $[Ru(COD)Cl_2]_n$	% AgOTf[a]	% NMR yield[b]
1	5	5	17
2	5	10	11
3	5	15	10
4	0	5	0

[a]AgOTf and $[Ru(COD)Cl_2]_n$ were first stirred in 0.5 mL toluene for 1 h at r.t.; then the aldehyde, alkyne and water were added to the resulting mixture, and another 0.5 mL toluene was added, and the temperature was rised to 120 ^oC; [b1]H NMR yields were examined using nitromethane as internal standard

Different ligands and additives were also examined to improve the yield; however, the addition of various ligands reduced the yield (Table 5.4, entries 1 – 5). Other than adding water directly, we also examined complex hydrates as an alternative source of water and found that the addition of 30 mol% $CuCl_2 \cdot 2H_2O$ increased the product yield to 48% (Table 5.4, entry 6).

Table 5.4 Optimization of the decarbonylative addition reaction conditions[a]



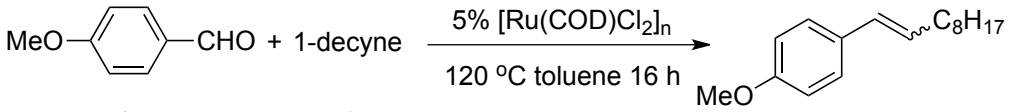
8a **9a** **10a**

entry	% catalyst	% additive or ligand	% NMR yield[b]
1	5% $[Ru(COD)Cl_2]_n$	10% dppp + 4 μL H_2O	22
2	5% $[Ru(COD)Cl_2]_n$	10% dppe + 4 μL H_2O	11
3	5% $[Ru(COD)Cl_2]_n$	10% Ph_3P + 4 μL H_2O	23
4	5% $[Ru(COD)Cl_2]_n$	10% $((F_3C)_2CH)_3P$ + 4 μL H_2O	11
5	5% $[Ru(COD)Cl_2]_n$	50% 1, 5 - COD + 4 μL H_2O	6
6	5% $[Ru(COD)Cl_2]_n$	30% $CuCl_2$ hydrate	48
7	5% $[Ru(COD)Cl_2]_n$	5 equiv LiCl	16
8	5% $[Ru(COD)Cl_2]_n$	30% $CuCl_2$ hydrate + 5 equiv LiCl	59
9	10% $[Ru(COD)Cl_2]_n$	30% $CuCl_2$ hydrate + 5 equiv LiCl	83
10	10% $[Ru(COD)Cl_2]_n$	30% $CuCl_2$ hydrate + 5 equiv LiCl	65[c]
11	10% $[Ru(COD)Cl_2]_n$	30% $CuCl_2$ hydrate + 5 equiv LiCl	48[d]
12	10% $[Ru(COD)Cl_2]_n$	30% $CuCl_2$ hydrate + 5 equiv LiCl	NR[e]
13	10% $[Ru(COD)Cl_2]_n$	30% $CuCl_2$ hydrate + 5 equiv LiCl	72[f]
14	10% $[Ru(COD)Cl_2]_n$	30% $CuCl_2$ hydrate + 5 equiv LiCl	70[g]
15	10% $[Ru(COD)Cl_2]_n$	30% $CuCl_2$ hydrate + 5 equiv LiCl	50[h]

[a]Conditions: **8a** (0.2 mmol), **9a** (0.8 mmol), toluene (1 mL), 120 ^oC, 16 h under argon, unless otherwise noted; [b]determined by ^1H NMR of the crude reaction mixture, using nitromethane as internal standard; [c]in anisole; [d]in diglyme; [e]in water; [f]130 ^oC; [g]110 ^oC; [h]in air.

Based on this discovery, we applied different copper salts (hydrate) into the reaction system (Table 5.5). Interestingly, $CuCl_2$ improved the yield to 37% in an anhydrous condition and CuF_2 as well as $CuBr_2$ could also achieve the reaction to some extent (Table 5.5, entries 11 – 13). We speculated that chloride ion might serve as a weak coordinating ligand that could facilitate the reaction by stabilizing the catalyst. Indeed, in the presence of 5 equiv LiCl, the product could still be generated in 16% yield without adding water or $CuCl_2 \cdot 2H_2O$ (Table 5.4, entry 7).

Table 5.5 Effect of various copper complexes on the decarbonylative addition



8a 0.2 mmol **9a** 0.8 mmol **10a**

entry	additive	% conversion[a]	% NMR yield
1	5% CuCl + 4 μL H_2O	26	19
2	15% $CuSO_4 \cdot 5H_2O$	25	15
3	15% $Cu_2(CN)_2$ + 4 μL H_2O	2	0
4	15% $Cu(acac)_2$ + 4 μL H_2O	13	0
5	15% $Cu(OAc)_2 \cdot H_2O$	4	2
6	15% $Cu(NO_3)_2 \cdot H_2O$	9	0
7	15% $Cu(ClO_4)_2 \cdot 6H_2O$	32	3
8	15% $Cu(OCOCF_3)_2 \cdot H_2O$	5	0
9	15% $Cu(OH)_2$ + 4 μL H_2O	4	0
10	15% $Cu(OMe)_2$ + 4 μL H_2O	19	0
11	15% $CuBr_2$	20	trace
12	15% CuF_2	34	31
13	15% $CuCl_2$	50	37
14	30% $CuCl_2$ hydrate	50	40[b]
15	15% CuCl + 4 μL H_2O	30	12[b]

[a]consumed amount of the aldehyde, determined by crude ^{1}H NMR, using nitromethane as internal standard; [b]in air

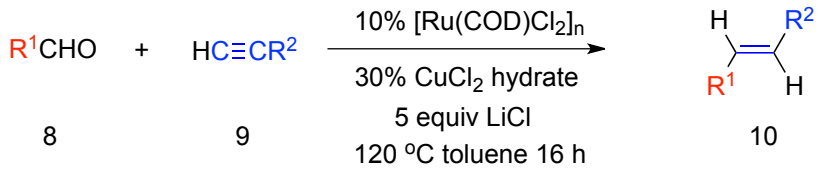
A combination of the catalyst, $CuCl_2 \cdot 2H_2O$ and LiCl was examined: an 83% yield of the desired product was achieved with 10 mol% catalyst together with $CuCl_2 \cdot 2H_2O$ and LiCl (Table 5.4, entry 9). The reaction temperature and solvents were also examined (Table 5.4, entries 10–14). The yield was reduced to 50%, when the reaction was conducted under air (Table 5.4, entry 15). Although a small amount of water was beneficial to the reaction, no product was generated when the reaction was conducted in water (Table 5.4, entry 12). When D_2O, instead of

H_2O, was added, no deuterated product was detected and a similar yield (32%) was obtained. We reasoned that water was not involved in the catalytic cycle and a trace amount of water could help the chloride ion to disperse in the reaction system and coordinate to the metal catalyst whereas too much water would quench the reaction.

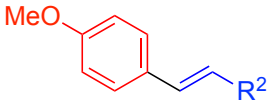
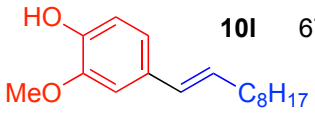
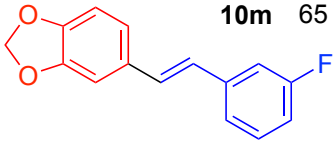
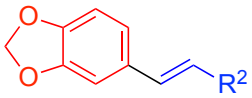
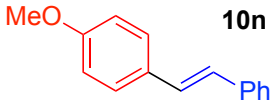
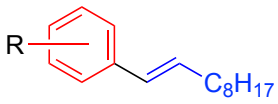
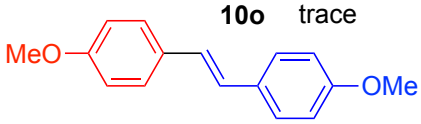
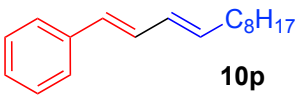
5.3.2 – Scope of the Ruthenium-Catalyzed Decarbonylative Addition of Aromatic Aldehydes to Terminal Alkynes

With the optimized reaction conditions in hand, different substrates were investigated using this reaction (Table 5.6). The reaction worked well for aromatic aldehydes. Electronic effect played an important role in this reaction. Aromatic aldehydes with more electron-donating groups on the phenyl ring gave much better yields than those with electron-withdrawing groups (Table 5.6). The yield decreased when an ester group was the substituent (**10k**). Other substrates (aldehyde and alkyne) containing ester groups such as methyl 4-formylbenzoate, methyl propiolate and propargyl propionate also gave low yields, and the corresponding acid, resulted from the decomposition of the ester, was found after the reaction.

Table 5.6 Substrate scope of decarbonylative addition reaction[a]



8 9 10

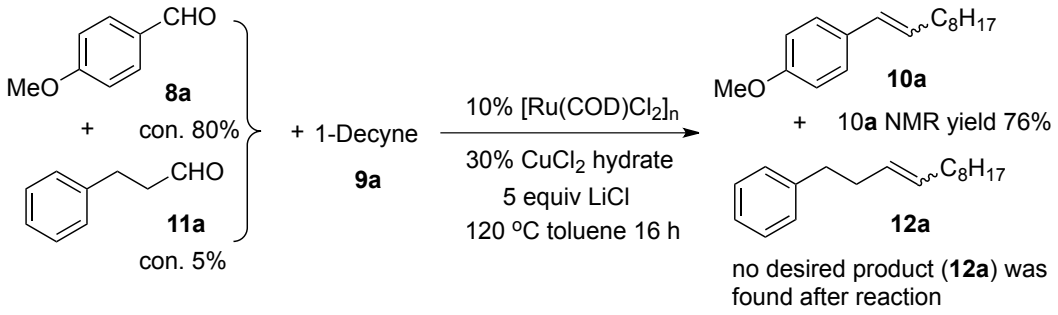
product	isolated yield[c] [%]	E/Z	product	isolated yield[c] [%]	E/Z
				**10l** 67	2:1
10a (R^2=C_8H_{17})	75	6:1			
10b (R^2=C_4H_9)	70[b]	3.5:1			
10c (R^2=$C_{12}H_{25}$)	72	6:1		**10m** 65	1.2:1
					
10d (R^2=C_8H_{17})	79	3:1		**10n** 64	1.1:1
10e (R^2=C_4H_9)	72[b]	3:1			
				**10o** trace	N/A
10f (R=2-OMe)	68	2:1			
10g (R=3-OMe)	40	3:1			
10h (R=4-Me)	60	4:1			
10i (R=4-C_6H_5)	62	4:1		**10p** 62	2.5:1
10j (R=4-Br)	35	2.3:1			
10k (R=4-OCOMe)	25	4:1			

[a]Conditions: **8** (0.2 mmol), **9** (0.8 mmol), toluene (1 mL), 120 °C, 16 h under argon, unless otherwise noted; [b]150 °C; [c]total yield of both E and Z isomers, E/Z ratio determined by ^{1}H NMR.

An unprotected hydroxyl group could also be tolerated by the reaction (**10l**). Both aromatic and aliphatic alkynes can be used as the alkyne substrates. Phenylacetylenes bearing electron-withdrawing groups gave better yields than those having electron-donating groups (**10l**–**10n**). It is worth noting that a conjugated aldehyde could also participate in the reaction, generating a 1,3-

butadiene product (**10p**). *Trans*-alkenes were generated as major products in all cases, and aliphatic alkynes showed better stereoselectivity than aromatic alkynes (Table 5.6). No product was obtained when the terminal alkynes were replaced with internal alkynes such as 2-hexyne and diphenylethyne.

Aliphatic aldehydes failed to react under the current catalytic system, which provides an interesting chemoselectivity. A competition experiment with both aromatic and aliphatic aldehydes led to the olefination product corresponding exclusively to the reaction of aromatic aldehyde (Scheme 5.3).



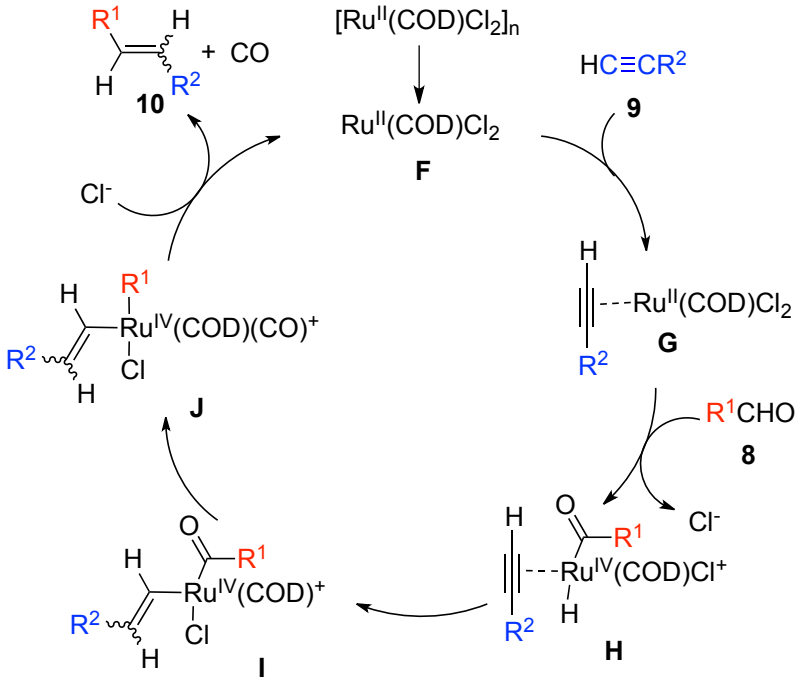
Conditions: **8a** (0.2 mmol), **11a** (0.2 mmol), **9a** (0.8 mmol), conversion and yield were determined by ^{1}H NMR.

Scheme 5.3 One-pot competing reaction between aromatic and aliphatic aldehydes

5.3.3 – Proposed Mechanism of the Ruthenium-Catalyzed Decarbonylative Addition of Aromatic Aldehydes to Terminal Alkynes

A tentative mechanism to rationalize the decarbonylative addition reaction is illustrated in Scheme 5.4. The catalyst polymer first formed the monomer **F**, which coordinated with the alkyne to generate intermediate **G**. A control

experiment showed that no corresponding decarbonylative product was formed in the absence of alkyne. An oxidative addition with the aldehyde generated intermediate **H**, which subsequently underwent a fast alkyne insertion to form vinyl intermediate **I**. Then the acyl group on the metal decarbonylated to give the intermediate **J**, and finally, a reductive-elimination afforded the decarbonylative addition product and CO, and regenerated the active ruthenium complex **F**. IR study of the reaction residue revealed that ruthenium carbonyl complex was formed after the reaction (ν_{CO}=1989 cm^{-1}), which led to the termination of the catalytic cycle.



Scheme 5.4 A tentative mechanism for the Ru-catalyzed decarbonylative addition

The chloride ion may serve as a weak coordinating ligand shuttle to facilitate these steps. Although alkyne insertion into metal-hydride bonds commonly

undergoes a *syn*-addition, *cis*- and *trans*-products were obtained in this reaction. We speculated that copper salt might serve as a co-catalyst which affect the stereochemistry of the triple bond insertion.

5.4 – Conclusion

In summary, we have developed a novel method of olefination using aldehydes and alkynes via a decarbonylative addition. Various substrates were examined and a strong electronic effect and high chemoselectivity between aromatic and aliphatic aldehydes were observed in this reaction.

Although *E*-products are preferred in this reaction, the selectivity is away from excellent; thus further work will include the improvement of the *E*/*Z*-selectivity. Besides, more mechanistic work is also required to investigate the catalytic process of the decarbonylative addition and the role of $CuCl_2$. Intramolecular reaction will be tested as well, which generates a cyclic ring to expand the reaction application.

5.5 – Contribution

I designed and conducted all the experiments (condition screening, scope screening and products characterization). The paper was written by me and

modified by Prof. Chao-Jun Li. The reaction conditions and the yields were double checked by Dr. Jun Wang.

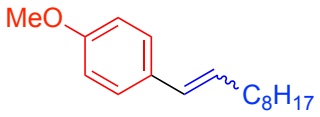
5.6 – Experimental Section

General Information Relating to All Experimental Procedures

Unless otherwise noted, all chemicals were obtained from commercial suppliers and used as received. All reactions were carried out under an atmosphere of air at ambient temperature unless otherwise stated. All work-up and purification procedures were carried out with reagent-grade solvents. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm) or Sorbent Silica Gel 60 F_{254} plates. The developed TLC plate was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh) or SORBENT silica gel 30-60 μm. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian MERCURY plus-300 spectrometer (^{1}H 300 MHz, ^{13}C 75 MHz) spectrometer or a Varian MERCURY plus-400 spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz) or a Varian MERCURY plus-500 spectrometer (^{1}H 500 MHz, ^{13}C 125 MHz). Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Chemical shifts for ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the

internal standard ($CDCl_3$: δ 77.0 ppm). Data are reported as following: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. HRMS were made by McGill University. IR spectra were recorded by a Nexus 670 Avator FTIR spectrometer.

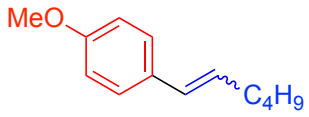
Typical procedure for 1-(dec-1-en-1-yl)-4-methoxybenzene synthesis: An oven-dried reaction vessel was charged with $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and *p*-anisaldehyde (24 μL, 0.2 mmol), 1-decyne (144 μL, 0.8 mmol) toluene (1.0 mL) under argon (1 atm). The reaction vessel was then sealed and the resulting solution was stirred at 120 ^oC for 16 h. Then, the resulting mixture was cooled to room temperature, filtered through a short silica gel plug eluted with dichloromethane. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (SiO_2, hexane/ ethyl acetate=100:1) to give **10a** (mixture of E/Z isomers) (37 mg, 75%) as colorless liquid.



1-(dec-1-en-1-yl)-4-methoxybenzene (10a)

10a was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8a** (24 μL, 0.2 mmol), **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by

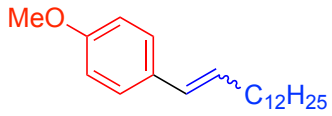
column chromatography (SiO_2, hexane/ethyl acetate=100:1, Rf=0.6) to afford **10a** (mixture of E/Z isomers) as colorless liquid (37 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.31 (m, 2H), 6.82 – 6.90 (m, 2H), 6.31 – 6.36 (m, 1H), 6.04 – 6.14 (m, 0.85H), 5.51 – 5.60 (m, 0.15H), 3.81 – 3.82 (m, 3H), 2.19 (q, *J* = 6.6 Hz, 2H), 1.46 (t, *J* = 6.9 Hz, 2H), 1.29 – 1.31 (m, 10H), 0.90 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 130.8, 129.1, 129.0, 127.0, 113.9, 55.2, 33.0, 31.9, 29.5, 29.5, 29.3, 29.2, 22.7, 14.1. (Alacid, E.; Nájera C. *J. Org. Chem.* **2009**, *74*, 2321)



1-(hex-1-en-1-yl)-4-methoxybenzene (10b)

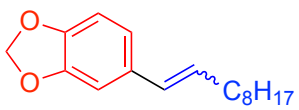
10b was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8a** (24 μL, 0.2 mmol), **9b** (65.7 mg, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=100:1, Rf=0.6) to afford **10b** (mixture of E/Z isomers) as yellow liquid (27 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.30 (m, 2H), 6.81 – 6.90 (m, 2H), 6.30 – 6.35 (m, 1H), 6.03 – 6.13 (m, 0.78H), 5.53 – 5.61 (m, 0.22H), 3.80 – 3.81 (m, 3H), 2.32 (qd, *J* = 7.2, 1.8 Hz, 0.48H), 2.19 (qd, *J* = 6.9, 1.2 Hz, 1.52H), 1.32 – 1.47 (m, 4H), 0.92 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 158.1, 131.7, 130.8, 129.9, 129.0, 129.0, 128.0, 127.0, 113.9, 113.5, 55.3, 55.2, 32.7, 32.2, 31.7, 28.3, 22.4,

22.3, 14.0. (Cahiez, G.; Gager, O.; Lecomte, F. *Org. Lett.* **2008**, *10*, 5255; Zhao, H.; Wang, Y.; Sha, J.; Shenga, S.; Cai, M. *Tetrahedron* **2008**, *64*, 7517)



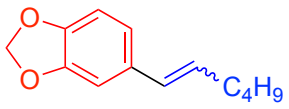
1-methoxy-4-(tetradec-1-en-1-yl)benzene (10c)

10c was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8a** (24 μL, 0.2 mmol), **9c** (155.5 mg, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=100:1, Rf=0.7) to afford **10c** (mixture of E/Z isomers) as yellow solid (44 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.30 (m, 2H), 6.81 – 6.90 (m, 2H), 6.30 – 6.35 (m, 1H), 6.04 – 6.13 (m, 0.85H), 5.50 – 5.62 (m, 0.15H), 3.80 – 3.82 (m, 3H), 2.32 (qd, *J* = 6.9, 1.8 Hz, 0.29H), 2.18 (qd, *J* = 6.9, 1.5 Hz, 1.71H), 1.52 (t, *J* = 6.6 Hz, 2H), 1.27 (br, 18H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 158.1, 131.8, 130.8, 129.9, 129.3, 129.1, 128.9, 128.0, 126.9, 113.9, 113.5, 55.3, 33.0, 31.9, 30.0, 29.7, 29.6, 29.5, 29.5, 29.4, 29.2, 28.7, 22.7, 14.1; MS(EI) m/z (%) 302, 287, 274, 259, 245, 231, 217, 203, 189, 173, 161, 147(100), 134, 121, 111, 103, 91, 77, 65, 55; HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{21}H_{34}O$, 302.25962; found, 302.26016.



5-(dec-1-en-1-yl)benzo[*d*][1,3]dioxole (10d)

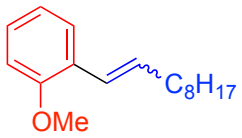
10d was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8d** (30.2 mg, 0.2 mmol), **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=40:1, Rf=0.5) to afford **10d** (mixture of E/Z isomers) as yellow liquid (41 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 – 6.90 (m, 1H), 6.72 – 6.81 (m, 2H), 6.26 – 6.33 (m, 1H), 6.06 (dt, *J* = 15.6, 6.9 Hz, 0.75H), 5.93 – 5.95 (m, 2H), 5.53 – 5.61 (m, 0.25H), 2.30 (qd, *J* = 7.2, 1.8 Hz, 0.51H), 2.18 (qd, *J* = 6.9, 1.2 Hz, 1.49H), 1.45 (t, *J* = 6.6 Hz, 2H), 1.28 – 1.29 (m, 10H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 147.3, 146.5, 146.0, 132.5, 132.2, 132.0, 129.5, 129.2, 128.2, 122.4, 120.1, 109.0, 108.2, 108.0, 105.3, 100.9, 32.9, 31.9, 30.0, 29.5, 29.5, 29.4, 29.3, 29.2, 28.6, 22.7, 14.1. (Trinnaman, L.; Da Costa, N. C.; Dewis, M. L.; John, T. V. *Special Publication - Royal Society of Chemistry* **2005**, *300*, 93)



5-(hex-1-en-1-yl)benzo[*d*][1,3]dioxole (10e)

10e was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8d** (30.2 mg, 0.2 mmol), **9b** (65.7 mg, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=40:1, Rf=0.5) to afford

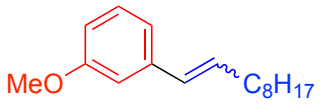
10e (mixture of E/Z isomers) as brown liquid (29 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (m, 1H), 6.71 – 6.80 (m, 2H), 6.26 – 6.31 (m, 1H), 6.05 (dt, *J* = 15.6, 6.9 Hz, 0.75H), 5.93 – 5.95 (m, 2H), 5.52 – 5.61 (m, 0.25H), 2.27 – 2.35 (m, 0.34H), 2.14 – 2.21 (m, 1.66H), 1.32 – 1.46 (m, 4H), 0.92 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 146.5, 132.5, 132.1, 129.5, 129.2, 128.2, 122.4, 120.1, 109.0, 108.2, 108.0, 105.4, 100.9, 32.6, 32.2, 31.6, 28.3, 22.4, 22.3, 14.0. (Witiak, D. T.; Williams, D. R.; Kakodkar, S. V. *J. Org. Chem.* **1974**, *39*, 1242)



1-(dec-1-en-1-yl)-2-methoxybenzene (10f)

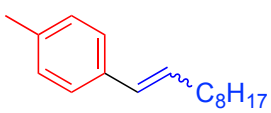
10f was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8f** (27.2 mg, 0.2 mmol), **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.3) to afford **10f** (mixture of E/Z isomers) as yellow liquid (33 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.5, 1.8 Hz, 0.56H), 7.16 – 7.23 (m, 1.15H), 6.84 – 6.96 (m, 2H), 6.71 (d, *J* = 15.9 Hz, 0.61H), 6.51 (d, *J* =11.7 Hz, 0.39H), 6.22 (dt, *J* = 15.9, 6.9 Hz, 0.61H), 5.74 (dt, *J* = 11.7, 7.2 Hz, 0.39H), 3.84 – 3.85 (m, 3H), 2.19 – 2.29 (m, 2H), 1.41 – 1.50 (m, 2H), 1.26 – 1.28 (m, 10H), 0.86 – 0.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 156.2, 133.1, 132.0, 130.0, 127.9, 127.7, 127.0, 126.5, 126.3, 124.1, 123.9, 120.6, 119.9, 110.7, 110.3, 55.4, 55.4, 33.5,

31.9, 31.9, 29.9, 29.5, 29.5, 29.4, 29.3, 28.7, 22.7, 14.1; MS(EI) m/z (%) 246, 232, 218, 203, 189, 181, 175, 167, 161, 153, 147(100), 141, 134, 128, 121, 115, 108, 102, 91, 83, 77, 71, 65, 55; HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{17}H_{26}O$, 246.19837; found, 246.19918.



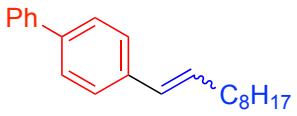
1-(dec-1-en-1-yl)-3-methoxybenzene (10g)

10g was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8g** (27.2 mg, 0.2 mmol), **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.5) to afford **10g** (mixture of E/Z isomers) as yellow liquid (20 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 – 7.28 (m, 1H), 6.73 – 6.96 (m, 3H), 6.33 – 6.40 (m, 1H), 6.18 – 6.27 (m, 0.75H), 5.67 (dt, *J* = 11.7, 7.2 Hz, 0.25H), 3.82 (s, 3H), 2.33 (qd, *J* = 7.2, 1.8 Hz, 0.55H), 2.20 (qd, *J* = 6.9, 0.9 Hz, 1.45H), 1.42 – 1.49 (m, 2H), 1.28 – 1.30 (m, 10H), 0.86 – 0.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 139.4, 133.6, 131.6, 129.5, 129.4, 129.0, 128.5, 121.3, 118.6, 114.3, 112.3, 111.9, 111.2, 55.2, 33.0, 31.9, 31.9, 30.0, 29.5, 29.3, 29.3, 29.2, 28.7, 22.7, 14.1. (Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424)



1-(dec-1-en-1-yl)-4-methylbenzene (10h)

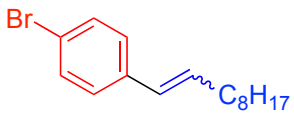
10h was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8h** (24.0 mg, 0.2 mmol), **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.4) to afford **10h** (mixture of E/Z isomers) as white liquid (28 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 – 7.28 (m, 4H), 6.32 – 6.39 (m, 1H), 6.12 – 6.22 (m, 0.80H), 5.62 (dt, *J* = 10.8, 7.5 Hz, 0.20H), 2.31 – 2.34 (m, 3.38H), 2.19 (qd, *J* = 6.9, 0.9 Hz, 1.62H), 1.41 – 1.46 (m, 2H), 1.28 – 1.30 (m, 10H), 0.86 – 0.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 135.1, 132.6, 130.2, 129.4, 129.1, 128.8, 128.6, 128.4, 125.8, 33.0, 31.9, 30.0, 29.5, 29.4, 29.4, 29.3,29.2, 28.7, 22.7, 21.1, 14.1. (Huang, X.; Sun, A.-M. *Synth. Commun.* **1998**, *28*, 773)



4-(dec-1-en-1-yl)-1,1'-biphenyl (10i)

10i was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8i** (36.4 mg, 0.2 mmol), **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.6) to afford **10i** (mixture of E/Z isomers) as white solid (36 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.64 (m, 4H), 7.31 – 7.47 (m, 5H), 6.40 – 6.45 (m, 1H), 6.24 – 6.33 (m, 0.81H), 5.71 (dt, *J* = 11.7, 7.2 Hz, 0.19H), 2.35 – 2.43 (m, 0.48H), 2.21 –

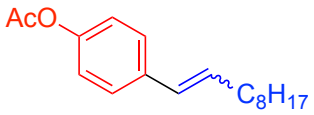
2.28 (m, 1.52H), 1.47 – 1.51 (m, 2H), 1.30 (br, 10H), 0.88 – 0.92 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 139.5, 139.1, 137.0, 133.6, 131.5, 129.2, 128.7, 128.2, 127.2, 127.1, 127.0, 126.9, 126.8, 126.3, 33.1, 31.9, 30.0, 29.5, 29.4, 29.3, 29.3, 28.8, 22.7, 14.1; MS(EI) m/z (%) 292, 264, 249, 235, 221, 205, 193(100), 180, 167, 152, 139, 128, 115, 102, 91, 77, 69, 55; HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{22}H_{28}$, 292.21910; found, 292.21971.



1-bromo-4-(dec-1-en-1-yl)benzene (10j)

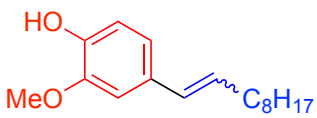
10j was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8j** (37.0 mg, 0.2 mmol), **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.5) to afford **10j** (mixture of E/Z isomers) as white liquid (21 mg, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.46 (m, 2H), 7.12 – 7.21 (m, 2H), 6.28 – 6.34 (m, 1H), 6.16 – 6.26 (m, 0.70H), 5.69 (dt, *J* = 11.7, 7.2 Hz, 0.30H), 2.15 – 2.31 (m, 2H), 1.41 – 1.48 (m, 2H), 1.28 (br, 10H), 0.88 (t, *J* = 4.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 134.1, 132.2, 131.5, 131.2, 130.3, 128.5, 127.5, 127.4, 120.3, 33.0, 31.9, 31.8, 31.8, 29.8, 29.5, 29.4, 29.3, 29.3, 29.2, 28.6, 22.7, 14.1; MS(EI) m/z (%) 294, 268, 254, 238, 223, 211, 195, 182(100), 169, 158, 149, 141, 129, 116, 103, 91, 77, 69, 55; HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{16}H_{23}{}^{79}Br$,

294.09831; found, 294.09705; $[M+H]^+$ calcd for $C_{16}H_{23}{}^{81}Br$, 296.09627; found, 296.09565.



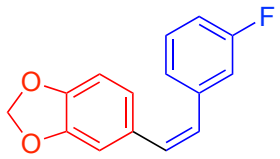
4-(dec-1-en-1-yl)phenyl acetate (10k)

10k was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8k** (32.8 mg, 0.2 mmol), **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.3) to afford **10k** (mixture of E/Z isomers) as brown liquid (14 mg, 25%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.36 (m, 2H), 6.98 – 7.06 (m, 2H), 6.32 – 6.38 (m, 1H), 6.12 – 6.22 (m, 0.81H), 5.62 – 5.70 (m, 0.19H), 2.30 (s, 0.45H), 2.29 (s, 2.55H), 2.15 – 2.22 (m, 2H), 1.43 – 1.45 (m, 2H), 1.27 (br, 10H), 0.86 – 0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 149.3, 143.4, 135.8, 133.5, 131.6, 129.7, 128.7, 127.7, 126.8, 121.5, 121.1, 99.8, 33.0, 31.9, 29.9, 29.5, 29.3, 29.3, 29.2, 28.6, 22.7, 21.1, 14.1; MS(EI) m/z (%) 274, 232, 218, 204, 189, 175, 161, 147, 133(100), 120, 107, 91, 77, 65, 55; HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{18}H_{26}O_2$, 274.19328; found, 274.19304.



4-(dec-1-en-1-yl)-2-methoxyphenol (10l)

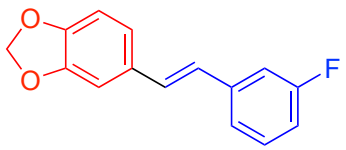
10l was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8l** (30.4 mg, 0.2 mmol), **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.2) to afford **10l** (mixture of E/Z isomers) as brown liquid (36 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 – 6.90 (m, 3H), 6.27 – 6.34 (m, 1H), 6.06 (dt, *J* = 15.6, 6.9 Hz, 0.66H), 5.53 – 5.61 (m, 1.34H), 3.90 (s, 2H), 3.89 (s, 1H), 2.32 (qd, *J* = 7.2, 1.5 Hz, 0.68H), 2.14 – 2.21 (m, 1.32H), 1.41 – 1.47 (m, 2H), 1.28 (br, 10H), 0.86 – 0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 144.7, 144.2, 131.7, 130.6, 130.2, 129.3, 129.0, 128.4, 121.9, 119.4, 114.3, 114.0, 111.3, 107.8, 55.8, 33.0, 31.9, 31.8, 30.0, 29.5, 29.4, 29.3, 29.2, 28.7, 22.7, 14.1; MS(EI) m/z (%) 262, 163, 150, 138, 131(100), 124, 115, 103, 91, 77, 65, 55; HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{17}H_{26}O_2$, 262.19328; found, 262.19316.



(*Z*)-5-(3-fluorostyryl)benzo[*d*][1,3]dioxole (10ma)

10ma was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8d** (30.2 mg, 0.2 mmol), **9m** (96.0 mg, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.6) to afford **10ma** (Z isomer) as yellow liquid (14 mg, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ

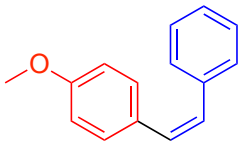
7.17 – 7.26 (m, 2H), 6.86 – 7.05 (m, 4H), 6.69 – 6.75 (m, 2H), 6.50 (q, J = 12.3 Hz, 2H), 5.93 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (d, $J_{C\text{-}F}$= 243.9 Hz), 147.1 (d, $J_{C\text{-}F}$= 43.3 Hz), 139.5 (d, $J_{C\text{-}F}$= 7.7Hz), 130.9, 130.6, 129.8, 129.7, 127.9 (d, $J_{C\text{-}F}$= 2.3 Hz), 124.6 (d, $J_{C\text{-}F}$= 2.6 Hz), 123.0, 115.5 (d, $J_{C\text{-}F}$= 21.3 Hz), 113.9 (d, $J_{C\text{-}F}$= 21.1 Hz), 108.8, 108.3, 101.0; MS(EI) m/z (%) 242(100), 228, 222, 211, 196, 183, 177, 171, 165, 157, 146, 139, 133, 126, 120, 113, 107, 98, 92, 81, 75, 69, 63, 57, 51; IR (neat): 2895, 1608, 1578, 1502, 1486, 1443, 1238, 1038, 780, 478, 464 ν cm^{-1}. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{15}H_{11}O_2F$, 242.07431; found, 242.07498.



(*E*)-5-(3-fluorostyryl)benzo[*d*][1,3]dioxole (10mb)

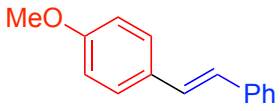
10mb was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8d** (30.2 mg, 0.2 mmol), **9m** (96.0 mg, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.5) to afford **10mb** (E isomer) as yellow solid (17 mg, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 – 7.34 (m, 3H), 7.05 – 7.06 (m, 1H), 6.86 – 7.00 (m, 4H), 6.79 – 6.82 (m, 1H), 5.99 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (d, $J_{C\text{-}F}$= 243.6 Hz), 147.9 (d, $J_{C\text{-}F}$= 43.3 Hz), 139.8 (d, $J_{C\text{-}F}$= 7.7 Hz), 131.3, 130.1, 130.0, 129.7, 125.7 (d, $J_{C\text{-}F}$= 2.6 Hz), 122.2 (d, $J_{C\text{-}F}$= 2.9 Hz), 121.8, 114.1 (d, $J_{C\text{-}F}$= 21.4 Hz), 112.5 (d, $J_{C\text{-}F}$= 21.6 Hz), 108.4, 105.6, 101.2; MS(EI) m/z (%) 242(100), 228, 222, 211,

196, 183, 177, 171, 165, 157, 146, 139, 133, 126, 120, 113, 107, 98, 92, 81, 75, 69, 63, 57, 51; IR (neat): 2900, 2359, 1607, 1578, 1498, 1486, 1443, 789, 682, 488, 471, 416 ν cm^{-1}. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{15}H_{11}O_2F$, 242.07431; found, 242.07498.



(*Z*)-1-methoxy-4-styrylbenzene (10na)

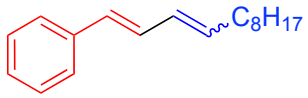
10nb was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8a** (24 μL, 0.2 mmol), **9n** (81.6 mg, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.5) to afford **10na** (Z isomer) as yellow liquid (13 mg, 31%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 – 7.27 (m, 7H), 6.74 – 6.77 (m, 2H), 6.52 – 6.53 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 137.6, 130.1, 129.7, 129.7, 128.8, 128.7, 128.2, 126.9, 113.5, 55.2. (Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Tetrahedron* **2006**, *62*, 7521)



(*E*)-1-methoxy-4-styrylbenzene (10nb)

10nb was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8a** (24 μL, 0.2 mmol), **9n** (81.6

mg, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.5) to afford **10nb** (E isomer) as yellow solid (14 mg, 33%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.51 (m, 4H), 7.32 – 7.37 (m, 2H), 7.21 – 7.26 (m, 1H), 7.00 – 7.11 (m, 2H), 6.89 – 6.95 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 137.6, 130.1, 128.6, 128.2, 127.7, 127.2, 126.6, 126.2, 114.1, 55.3. (Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Tetrahedron* **2006**, *62*, 7521)



(1*E*)-dodeca-1,3-dien-1-ylbenzene (10p)

10p was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2 \cdot 2H_2O$ (10.2 mg, 0.06 mmol), LiCl (42.5 mg, 5 equiv.), and **8p** (25.2 μL, 0.2 mmol), **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.5) to afford **10p** (mixture of E/Z isomers) as white solid (30 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 – 7.43 (m, 5H), 7.02 – 7.11 (m, 0.32H), 6.72 – 6.80 (m, 0.68H), 6.41 – 6.55 (m, 1H), 6.12 – 6.25 (m, 1H), 5.78 – 5.88 (m, 0.68H), 5.49 – 5.58 (m, 0.32H), 2.25 – 2.32 (m, 0.57H), 2.11 – 2.17 (m, 1.43H), 1.42 (br, 2H), 1.28 (br, 2H), 0.86 – 0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 136.1, 133.4, 131.9, 130.4, 129.8, 129.5, 128.6, 128.5, 128.5, 127.3, 127.0, 126.3, 126.1, 124.5, 32.9, 31.9, 29.7, 29.5, 29.3, 29.3, 29.2, 28.0, 22.7, 14.1. (Lemhadri, M.; Battace, A.; Berthiol, F.; Zair, T.; Doucet, H.; Santelli, M. *Synthesis* **2008**, *7*, 1142)

Chapter 6 – Ruthenium-Catalyzed Olefination via Decarbonylative Addition of Aliphatic Aldehydes to Terminal Alkynes

In chapter 5, we displayed the decarbonylative addition reaction of aldehydes to terminal alkynes; however, this chemistry was limited to only aromatic aldehydes. In this chapter, a decarbonylative addition reaction to terminal alkynes, which uses aliphatic aldehydes as the starting material, will be disclosed.

6.1 – Background

In the previous chapter, we reported an olefination strategy *via* a ruthenium-catalyzed decarbonylative addition reaction of aldehydes to alkynes, suggesting a new method for C=C formation.[1] However, the first generation catalyst was limited to only aromatic aldehydes. On the other hand, non-styrenyl alkenes are the structural feature of a wide range of chemical products such as insect pheromones (Figure 2), which are greatly important in the agriculture industry.

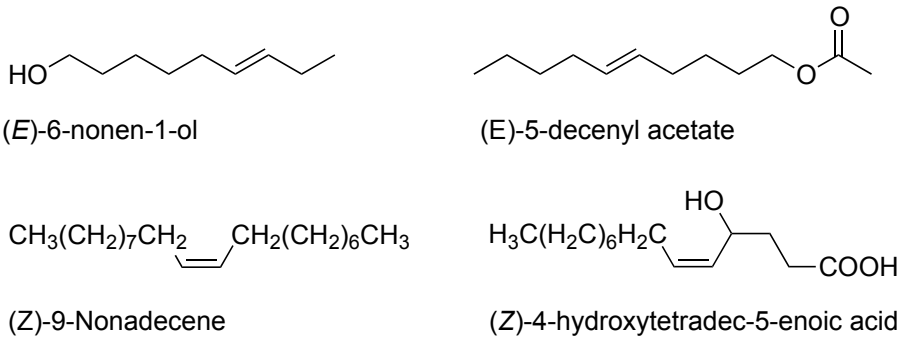


Figure 2. Examples of insect pheromones

A simple and direct generation of non-styrenyl alkenes from readily available basic functionalities will be highly desirable in alkene synthesis. We have demonstrated that direct addition of C-H bonds to alkynes is the most efficient and atom-economical reaction for alkene synthesis. However, there are limited studies that have been reported in regarding of this area.[2] The difficulty in this chemistry lies in that the activation energy of sp^3 C-H bond is much higher than sp^2 C-H bond, and a directing group, which is hard to remove after the synthesis, is required to introduce a regioselective C-H activation.

6.2 – Research Objective and Plan

With the success in aromatic aldehyde decarbonylative addition, we would like to develop a new catalytic system, with which a highly efficient decarbonylative addition of simple aliphatic aldehydes to terminal alkynes will be achieved to give isolated alkenes, and the directing group, carbonyl functionality, will be removed after the reaction simultaneously.

The success in aromatic aldehyde decarbonylative addition provided the evidence that such a catalytic cycle is feasible; however, the catalytic system only limits to aromatic aldehydes. We reason that this chemo-selectivity is due to the fact that aromatic aldehydes are more reactive than aliphatic aldehydes in both C-H activation and decarbonylation steps. Thus, to apply this strategy to aliphatic aldehydes, we can enhance the reactivity of the catalyst towards C-H activation or

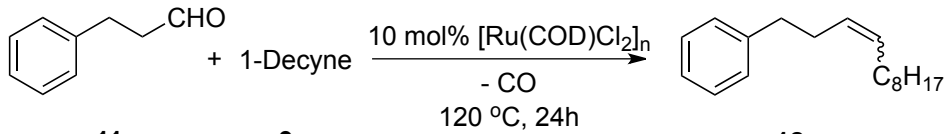
decarbonylation. The addition of ligands can be a suitable choice. We postulated that a bulky ligand is necessary to form a stabilized catalyst center while still maintaining free coordination sites for the decarbonylation and additions. Meanwhile, by the addition of electron-deficient ligands, the electron-density of transition metal catalysts will decrease, and as a consequence, the π-backbonding between metal center and CO will be reduced. This will make the CO easy to release from the catalyst to regenerate the active catalyst, which will facilitate the decarbonylation as well. In general, the investigation on aliphatic decarbonylative addition will mainly focus on ligands screening.

6.3 –Results and Discussion

6.3.1 –Reaction Condition Screenings

We chose hydrocinnamaldehyde (**11a**) and 1-decyne (**9a**) as the standard substrates for the optimization of the reaction conditions. Under our previously reported conditions for aromatic compounds, no reaction was observed (Table 6.1, entry 1). Triisopropyl phosphite and tri(2,4,6-trismethoxyphenly)phosphine were found to be effective in this reaction, producing the desired compound (**12a**) in 52% and 70% yield respectively; whereas no products or low yields were obtained with other ligands (Table 6.1, entries 3–9).

Table 6.1 Decarbonylative aldehyde-alkyne addition reactions under various conditions[a]



11a **9a** **12a**

entry	additive (equiv.)	ligand (equiv)	solvent	% yield[b]
1	$CuCl_2 \cdot 2H_2O$ (0.3)	—	toluene	0[c]
2	—	—	toluene	0
3	$CuCl_2$ (0.3)	—	toluene	0
4	$CuCl_2$ (0.3)	$(tBu)_3P$ (0.2)	toluene	0
5	$CuCl_2$ (0.3)	$(iPrO)_3P$ (0.2)	toluene	52
6	$CuCl_2$ (0.3)	Cy_3P (0.2)	toluene	0
7	$CuCl_2$ (0.3)	$(Me_2N)_3P$ (0.2)	toluene	0
8	$CuCl_2$ (0.3)	Ph_3P (0.2)	toluene	5
9	$CuCl_2$ (0.3)	L (0.2)	toluene	70[d]
10	$CuCl_2$ (0.3)	L (0.3)	toluene	23
11	$CuCl_2$ (0.3)	L (0.1)	toluene	38
12	—	L (0.2)	toluene	0
13	$CuCl_2$ (0.2)	L (0.2)	toluene	27
14	$CuCl_2$ (0.5)	L (0.2)	toluene	44
15	**$CuCl_2$ (0.3)**	**L (0.2)**	**CH_2Cl_2+toluene**	**95[e]**
16	$CuCl_2$ (0.3)	L (0.2)	CH_2Cl_2+toluene	trace[f]
17	$CuCl_2$ (0.3)	L (0.2)	dioxane	55
18	$CuCl_2$ (0.3)	L (0.2)	DCE	0
19	$CuCl_2$ (0.3)	L (0.2)	CH_2Cl_2+toluene	36[e,g]
20	$CuCl_2$ (0.3)	L (0.2)	CH_2Cl_2+toluene	trace[e,h]

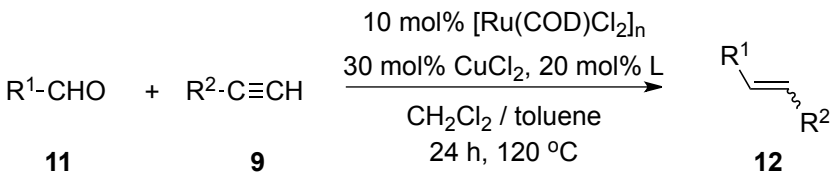
[a]Conditions: the reaction was pre-stired with 10 mol% $[Ru(COD)Cl_2]_n$, 30 mol% $CuCl_2$, 20 mol% ligand in 0.2 mL solvent under argon at r.t. for 24 h, then **11a** (0.2 mmol), **9a** (0.8 mmol), solvent (0.8 mL) was added under argon, heated to 120 °C for 24 h; [b]determined by ^{1}HNMR of the crude reaction mixture, using $MeNO_2$ as the internal standard; [c]5 equiv LiCl was added; [d]L = tri(2,4,6-trismethoxylphenly) phosphine [e]0.2 mL CH_2Cl_2 was added first at r.t. 0.8 mL toluene was added when heated to 120 °C; [f]without pre-stir; [g]150 °C; [h]100 °C.

When more ligand was used, the yield dropped dramatically to 23% possibly due to dwindling of free-coordination sites for decarbonylation to occur; on the other hand, less amount of ligand led to an unstabilized catalyst, which also reduced the yield to 38% (Table 6.1, entries 10 and 11). Copper chloride was also found to be essential in the reaction (Table 6.1, entries 12–14). Interestingly, pre-stirring was found to be essential for the reaction: only a trace amount of the product could be formed when all the chemicals were added at the same time and heated directly to 120 ^{o}C (Table 6.1, entry 16). A black residue was noticeably formed during the pre-stirring in toluene; however, we could not characterize this unkown compound/mixture. Different solvents were examined to facilitate the formation of the active catalyst in situ by dissolving the residue, and it was found that a combination of methylene chloride (0.2 mL) and toluene (0.8 mL) gave the best yield at 120 ^{o}C (Table 6.1, entries 15–18). Either an increase or a decrease in the reaction temperature decreased the product yield (Table 6.1, entries 19 and 20).

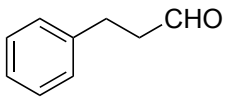
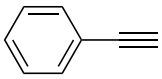
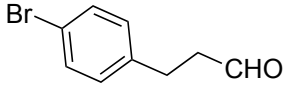
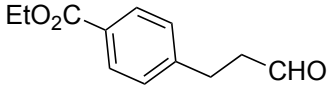
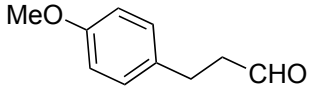
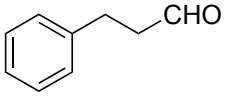
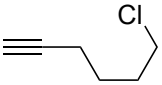
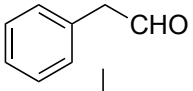
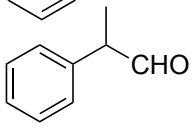
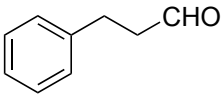
6.3.2 – Scope of the Ruthenium-Catalyzed Decarbonylative Addition of Aliphatic Aldehydes to Terminal Alkynes

With the optimized conditions, we then examined the scope of this reaction (Table 6.2). The reaction worked well for various aliphatic aldehydes and alkynes. Excellent yields could be obtained for aliphatic alkynes with a high boiling point (Table 6.2, entries 1 and 2), while 1-hexyne gave a 75% yield (Table 6.2, entry 3).

Table 6.2 Substrate scope of the decarbonylative aldehyde-alkyne addition reaction[a]



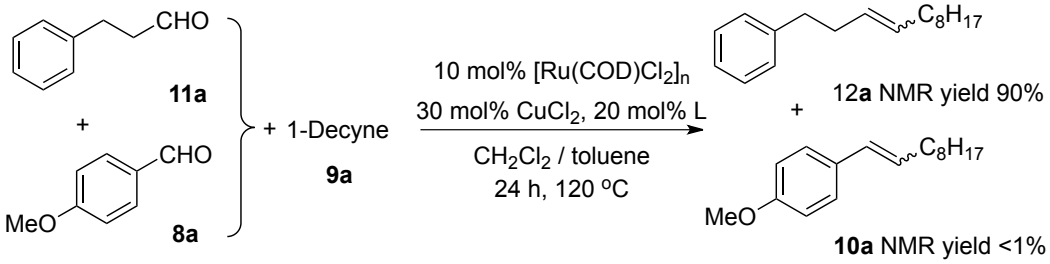
11 **9** **12**

entry	aldehyde	alkyne	product	yield[b] [%]	E/Z[c]
1		1-decyne	**12a**	90%	1 : 1.5
2		1-tetradecyne	**12b**	85%	1 : 1.3
3		1-hexyne	**12c**	75%	1 : 1.2
4	$CH_3(CH_2)_8CHO$		**12d**	50%	1.5 : 1
5	$CH_3(CH_2)_4CHO$		**12e**	44%	1.5 : 1
6		1-decyne	**12f**	90%	1 : 2.1
7		1-decyne	**12g**	91%	1 : 1
8		1-decyne	**12h**	92%	1 : 1.3
9			**12i**	88%	1 : 1
10		1-decyne	**12j**	60%	1 : 1.1
11		1-hexyne	**12k**	45%	1 : 1.3
12			no reaction		

[a]Conditions: the reaction was pre-stired with 10 mol% $[Ru(COD)Cl_2]_n$, 30 mol% $CuCl_2$, 20 mol% tri(2,4,6-trismethoxylphenyl) phosphine in 0.2 mL CH_2Cl_2 under argon at r.t. for 24 h, then aldehyde **11** (0.2 mmol), alkyne **9** (0.8 mmol), toluene (0.8 mL) was added

under argon, heated to 120 °C for 24 h; [b]Total isolated yield of both the E and Z isomers; [c]the E/Z ratio was determined by ^{13}C NMR analysis.

Aromatic alkynes also worked in this reaction system, but only gave moderate yield (Table 6.2, entries 4 and 5). Functional groups, such as halides, ester and methoxyl group, could well be tolerated by the reaction (Table 6.2, entries 6–9), and all of these substrates gave excellent yields of the olefination products. Phenylacetaldehyde derivatives led to a moderate yield (Table 6.2, entries 10 and 11), which is possibly due to the increased steric hindrance on the reacting carbon centers. Triisopropylsilyl acetylene also failed to react under these catalytic conditions (Table 6.2, entry 12), most likely due to steric effect.



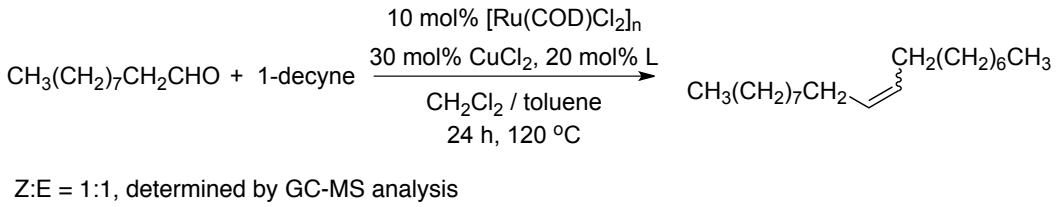
Conditions: **11a** (0.2 mmol), **8a** (0.2 mmol), **9a** (0.8 mmol), $[Ru(COD)Cl_2]_n$ 0.02 mmol, conversions and yields were determined by ^1H NMR.

Scheme 6.1 One-pot competing reaction between aliphatic and aromatic aldehydes

To further explore this complete switch of chemoselectivity, we ran a competition experiment involving both aliphatic and aromatic aldehydes. In a sharp contrast to our previous reports, aromatic aldehydes remain virtually unreactive under the present conditions. The product (**12a**) generated from aliphatic aldehyde was

formed in a 90% NMR yield, while less than 1% of corresponding aromatic alkene was observed (Scheme 6.1), which provided an exclusive chemoselectivity.

As a simple test of the potential utility of this novel olefination reaction, we applied this reaction in the synthesis of (Z)-9-nonadecene, an extract of sex pheromone glands of female *Sabulodes caberata Guenée*.[3] The reaction provided the alkene in a 55% NMR yield in one step, albeit as a mixture of Z:E isomers (Scheme 6.2).



Scheme 6.2 Synthesis of (Z)-9-nonadecenea

6.3.3 – Mechanism Discussion

The decarbonylative addition reaction of aliphatic aldehydes to terminal alkynes is expected to undergo the same mechanism as that with aromatic aldehydes. However, as a bulky ligand (tri(2,4,6-trismethoxylphenyl) phosphine) is used in the reaction, the aryl acyl group, which is from aromatic aldehyde C-H activation, can hardly undergo a decarbonylation reaction because the steric effect prevent the aryl group getting close to the metal comparing to that from an aliphatic aldehyde.

This effect is demonstrated by the reduced yields with product **12a** (90%), **12j** (60%), **12k** (45%), **10a** (<1%), when the substituent group is getting bigger. One the other hand, an electron-deficient and bulky ligand also promotes the reaction by facilitating both decarbonylation and release of CO. The two effects lead to the result that only aliphatic aldehydes are reactive in this reaction, and aromatic aldehydes stay inert, which completely switch the chemo-selectivity.

6.4 – Conclusion

In summary, we have discovered a novel method of C=C double bond formation, specifically for aliphatic aldehydes and alkynes via a decarbonylative addition reaction. Different functionalized substrates were examined, and good to excellent yields were obtained. An unprecedented complete switch of aromatic-aliphatic selectivity was observed.

As electron-deficient and bulky ligands are crucial for this reaction, modification of the ligands can be a good way to promote the yield and to test our mechanistic hypothesis towards the chemo-selectivity. The modification can be done in two aspects: one is to install e-withdrawing groups on the phenyl ring of the ligands making the ligands even more electron-poor; the other one is to make the ligand more bulky by changing the substituents on the phenyl ring. We also observed

that the *E*/*Z*-selectivity is not high in this reaction, more work is required to the improvement of the selectivity.

6.5 – Contribution

I designed and conducted all the experiments (condition screening, scope screening and products characterization). The paper was written by me and modified by Prof. Chao-Jun Li. The reaction conditions and the yields were double checked by Dr. Jun Wang.

6.6 – Experimental Section

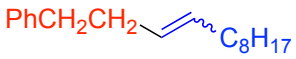
General Information Relating to All Experimental Procedures

Unless otherwise noted, all chemicals were obtained from commercial suppliers and used as received. All reactions were carried out under an atmosphere of air at ambient temperature unless otherwise stated. All work-up and purification procedures were carried out with reagent-grade solvents. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm) or Sorbent Silica Gel 60 F_{254} plates. The developed TLC plate was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh) or SORBENT silica gel 30-60 μm. Nuclear magnetic resonance (NMR)

spectra were recorded on a Varian MERCURY plus-300 spectrometer (^{1}H 300 MHz, ^{13}C 75 MHz) spectrometer or a Varian MERCURY plus-400 spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz) or a Varian MERCURY plus-500 spectrometer (^{1}H 500 MHz, ^{13}C 125 MHz). Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Chemical shifts for ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: δ 77.0 ppm). Data are reported as following: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. HRMS were made by McGill University. IR spectra were recorded by a Nexus 670 Avator FTIR spectrometer.

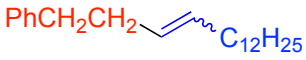
Typical procedure for dodec-3-enylbenzene synthesis: An oven-dried reaction vessel was charged with $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2$ (8.1 mg, 0.06 mmol), tri(2,4,6-trismethoxylphenyl) phosphine (21.2 mg, 0.04 mmol.), and CH_2Cl_2 (0.2 mL) under argon (1 atm). The reaction vessel was then sealed and the resulting solution was stirred at room temperature for 24 h. Then, to the resulting mixture, hydrocinnamaldehyde (26.4 μL, 0.2 mmol), 1-decyne (144 μL, 0.8 mmol) toluene (0.8 mL) were added and the resulting solution was stirred at 120 ^{o}C for 24 h. Then, the resulting mixture was cooled to room temperature, filtered through a short silica gel plug eluted with dichloromethane. The volatiles were

removed *in vacuo* and the residue was purified by column chromatography (SiO_2, hexane) to give **12a** (mixture of E/Z isomers) (43.9 mg, 90%) as colorless liquid.



dodec-3-en-1-ylbenzene (12a)

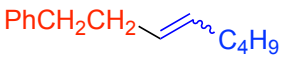
12a was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2$ (8.1 mg, 0.06 mmol), tri(2,4,6-trismethoxylphenyl) phosphine (21.2 mg, 0.04 mmol.), **11a** (26.4 μL, 0.2 mmol), and **9b** (65.7 mg, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane, Rf=0.6) to afford **12a** (mixture of E/Z isomers) as colorless liquid (43.9 mg, 90%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.30 (m, 2H), 7.18 – 7.21 (m, 3H), 5.38 – 5.45 (m, 2H), 2.67 (td, J = 3.2, 8.0 Hz, 2H), 2.30 – 2.38 (m, 2H), 1.97 (s, 2H), 1.26 (s, 12H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 131.2, 130.8, 129.2, 128.6, 128.4, 128.2, 128.2, 125.7, 125.7, 36.2, 36.0, 34.5, 32.6, 31.9, 29.6, 29.5, 29.5, 29.3, 29.2, 29.1, 27.2, 22.7, 14.1; HRMS ESI (m/z): $[M]^+$ calcd for $C_{18}H_{28}$, 244.21910; found, 244.21375.



hexadec-3-en-1-ylbenzene (12b)

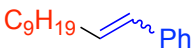
12b was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2$ (8.1 mg, 0.06 mmol), tri(2,4,6-trismethoxylphenyl) phosphine (21.2 mg, 0.04 mmol.), **11a** (26.4 μL, 0.2 mmol), and **9c** (155.5 mg, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane,

Rf=0.6) to afford **12b** (mixture of E/Z isomers) as colorless liquid (51 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.30 (m, 2H), 7.18 – 7.20 (m, 3H), 5.37 – 5.45 (m, 2H), 2.66 (td, *J* = 3.2, 8.0 Hz, 2H), 2.30 – 2.38 (m, 2H), 2.18 (s, 2H), 1.26 (s, 2H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.2, 130.8, 129.2, 128.6, 128.4, 128.2, 128.2, 125.7, 125.6, 36.2, 36.0, 34.5, 32.6, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 27.2, 22.7, 14.1; HRMS ESI (m/z): $[M]^+$ calcd for $C_{22}H_{36}$, 300.28170; found, 300.27648.



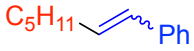
oct-3-en-1-ylbenzene (12c)

12c was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2$ (8.1 mg, 0.06 mmol), tri(2,4,6-trismethoxylphenyl) phosphine (21.2 mg, 0.04 mmol.), **11a** (26.4 μL, 0.2 mmol), and **9b** (65.7 mg, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane, Rf=0.6) to afford **12c** (mixture of E/Z isomers) as colorless liquid (28.2 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.32 (m, 2H), 7.12 – 7.21 (m, 3H), 5.38 – 5.46 (m, 2H), 2.66 (td, *J* = 2.1, 7.8 Hz, 2H), 2.27 – 2.40 (m, 2H), 1.96 – 2.02 (m, 2H), 1.25 – 1.36 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 142.1, 131.1, 130.7, 129.3, 128.6, 128.5, 128.4, 128.2, 128.2, 125.7, 125.6, 36.2, 36.0, 34.5, 32.2, 31.8, 31.7, 29.2, 26.9, 22.3, 22.1, 14.0, 14.0 (Ukaji, Y.; Yoshida, A.; Fujisawa, T. *Chemistry Letters* **1990**, *1*, 157).



undec-1-en-1-ylbenzene (12d)

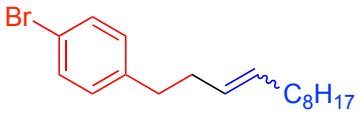
12d was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2$ (8.1 mg, 0.06 mmol), tri(2,4,6-trismethoxylphenyl) phosphine (21.2 mg, 0.04 mmol.), **11d** (31.2 mg, 0.2 mmol), and **9n** (81.6 mg, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=40:1, Rf=0.7) to afford **12d** (mixture of E/Z isomers) as colorless liquid (28.5 mg, 62%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 – 7.32 (m, 5H), 6.31 – 6.39 (m, 1H), 6.14 – 6.24 (m, 0.6H), 5.63 (dt, *J* = 6.9, 12.0 Hz, 0.4H), 2.29 (q, *J* = 7.2 Hz, 0.8H), 2.17 (q, *J* = 7.2 Hz, 1.2H), 1.39 – 1.43 (m, 2H), 1.24 (s, 12H), 0.85 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.3, 131.3, 129.6, 128.7, 128.6, 128.4, 128.1, 126.7, 126.4, 125.9, 33.0, 31.9, 30.0, 29.5, 29.4, 29.3, 29.3, 29.2, 28.6, 22.7, 14.1 (Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130,* 11270).



hept-1-en-1-ylbenzene (12e)

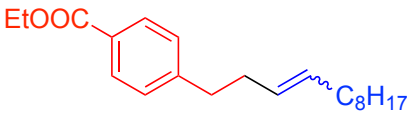
12e was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2$ (8.1 mg, 0.06 mmol), tri(2,4,6-trismethoxylphenyl) phosphine (21.2 mg, 0.04 mmol.), **11e** (20.0 mg, 0.2 mmol), and **9n** (81.6 mg, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=40:1, Rf=0.6) to afford **12e** (mixture of E/Z isomers) as colorless liquid (20.1 mg, 58%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.36 (m, 5H), 6.36 – 6.42 (m, 1H), 6.23 (dt, *J* = 6.8, 16.0 Hz, 0.6H), 5.67 (dt, *J* = 7.2, 11.6

Hz, 0.4H), 2.33 (qd, J = 1.6, 7.6 Hz, 0.8H), 2.20 (q, J = 7.2 Hz, 1.2H), 1.44 – 1.49 (m, 2H), 1.26 – 1.35 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 133.3, 131.3, 129.7, 128.7, 128.6, 128.5, 128.1, 126.7, 126.4, 125.9, 33.0, 31.6, 31.4, 29.7, 29.1, 28.6, 22.6, 14.1, 14.0 (Hu, Y.; Yu, J.; Yang, S.; Wang, J.-X.; Yin, Y., *Synthetic Communications* **1999**, *29*, 11 57).



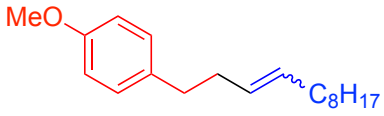
1-bromo-4-(dodec-3-en-1-yl)benzene (12f)

12f was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2$ (8.1 mg, 0.06 mmol), tri(2,4,6-trismethoxylphenyl) phosphine (21.2 mg, 0.04 mmol.), **11f** (42.4 mg, 0.2 mmol), and **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.4) to afford **12f** (mixture of E/Z isomers) as colorless liquid (28.2 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.39 (m, 2H), 7.03 – 7.06 (m, 2H), 5.32 – 5.41 (m, 2H), 2.60 (t, J = 7.5 Hz, 2H), 2.22 – 2.34 (m, 2H), 1.92 – 1.95 (m, 2H), 1.24 – 1.26 (m, 12H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 131.2, 131.2, 131.1, 130.3, 128.1, 119.4, 35.4, 31.9, 31.8, 29.6, 29.5, 29.3, 29.3, 29.1, 29.1, 29.1, 28.9, 28.8, 28.3, 27.2, 22.7, 22.6, 19.2, 14.1; HRMS ESI (m/z): $[M]^+$ calcd for $C_{18}H_{27}Br$, 323.12961; found, 323.11916.



ethyl 4-(dodec-3-en-1-yl)benzoate (12g)

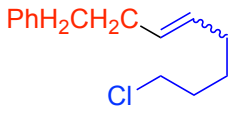
12g was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2$ (8.1 mg, 0.06 mmol), tri(2,4,6-trismethoxylphenyl) phosphine (21.2 mg, 0.04 mmol.), **11g** (41.2 mg, 0.2 mmol), and **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.3) to afford **12g** (mixture of E/Z isomers) as yellow liquid (57.5 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.96 (m, 2H), 7.21 – 7.25 (m, 2H), 5.34 – 5.42 (m, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 2.70 (td, *J* = 2.4, 7.5 Hz, 2H), 2.27 – 2.39 (m, 2H), 1.93 – 1.95 (m, 2H), 1.38 (t, *J* = 6.9 Hz, 3H), 1.23 – 1.24 (m, 12H), 0.87 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 147.5, 131.6, 131.2, 129.5, 128.7, 128.5, 128.0, 60.7, 36.1, 36.0, 34.1, 32.5, 31.9, 29.6, 29.5, 29.3, 29.1, 28.8, 27.2, 22.7, 14.3, 14.1; HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{21}H_{33}O_2$, 317.24856; found, 317.24751.



1-(dodec-3-en-1-yl)-4-methoxybenzene (12h)

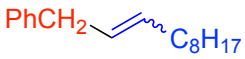
12h was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2$ (8.1 mg, 0.06 mmol), tri(2,4,6-trismethoxylphenyl) phosphine (21.2 mg, 0.04 mmol.), **11h** (32.8 mg, 0.2 mmol), and **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.8) to afford **12h** (mixture of E/Z isomers) as yellow liquid (50.4 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 – 7.13 (m, 2H), 6.82 – 6.84

(m, 2H), 5.38 – 5.44 (m, 2H), 3.79 (s, 3H), 2.59 – 2.63 (m, 2H), 2.27 – 2.35 (m, 2H), 1.97 – 1.99 (m, 2H), 1.27 (m, 12H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 157.6, 134.3, 134.2, 131.1, 130.7, 129.3, 129.3, 129.3, 128.7, 113.6, 113.6, 55.2, 35.2, 35.1, 34.7, 32.6, 31.9, 31.9, 29.6, 29.5, 29.5, 29.5, 29.4, 29.3, 29.1, 27.2, 22.7, 14.1; HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{19}H_{31}O$, 275.23670; found, 275.23694.



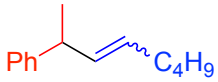
(8-chlorooct-3-en-1-yl)benzene (12i)

12i was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2$ (8.1 mg, 0.06 mmol), tri(2,4,6-trismethoxylphenyl) phosphine (21.2 mg, 0.04 mmol.), **11a** (26.4 μL, 0.2 mmol), and **9i** (93.2 mg, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.7) to afford **12i** (mixture of E/Z isomers) as colorless liquid (39.2 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.29 (m, 2H), 7.14 – 7.18 (m, 3H), 5.30 – 5.49 (m, 2H), 3.49 (q, J = 6.6 Hz, 2H), 2.62 – 2.68 (m, 2H), 2.26 – 2.37 (m, 2H), 1.95 – 2.02 (m, 2H), 1.65 – 1.76 (m, 2H), 1.37 – 1.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 142.0, 130.2, 130.1, 129.7, 129.4, 128.5, 128.2, 128.2, 125.8, 125.7, 45.0, 45.0, 36.0, 35.9, 34.4, 32.1, 31.9, 31.7, 29.2, 26.7, 26.6, 26.4; HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{19}Cl$, 222.11261; found, 222.11673.



undec-2-en-1-ylbenzene (12j)

12j was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2$ (8.1 mg, 0.06 mmol), tri(2,4,6-trismethoxylphenyl) phosphine (21.2 mg, 0.04 mmol.), **11j** (24.0 mg, 0.2 mmol), and **9a** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.8) to afford **12j** (mixture of E/Z isomers) as colorless liquid (27.6 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.30 (m, 2H), 7.19 – 7.20 (m, 3H), 5.49 – 5.59 (m, 2H), 3.40 (d, *J* = 6.0 Hz, 1H), 3.33 (d, *J* = 6.0 Hz, 1H), 2.15 (q, *J* = 6.4. Hz, 1H), 2.02 (d, *J* = 6.4 Hz, 1H), 1.37 – 1.40 (m, 2H), 1.27 (s, 10H), 0.88 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 132.2, 131.0, 128.6, 128.5, 128.4, 128.3, 128.3, 127.9, 125.8 , 125.8, 39.1, 33.5, 32.5, 31.9, 29.7, 29.5, 29.5, 29.3, 29.3, 29.2, 27.2, 22.7, 14.1 (Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130,* 11270).



oct-3-en-2-ylbenzene (12k)

12k was prepared from $[Ru(COD)Cl_2]_n$ (5.6 mg, 0.02 mmol), $CuCl_2$ (8.1 mg, 0.06 mmol), tri(2,4,6-trismethoxylphenyl) phosphine (21.2 mg, 0.04 mmol.), **11k** (26.8 mg, 0.2 mmol), and **9b** (144 μL, 0.8 mmol) following the above general procedure. The mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate=20:1, Rf=0.6) to afford **12k** (mixture of E/Z isomers) as colorless liquid

(20.7 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.33 (m, 2H), 7.14 – 7.22 (m, 3H), 5.42 – 5.61 (m, 2H), 3.72 (q, *J* = 8.7 Hz, 0.56H), 3.41 – 3.43 (m, 0.44H), 1.95 – 2.01 (m, 2H), 1.24 – 1.39 (m, 7H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 142.0, 131.5, 131.2, 129.0, 128.8, 128.4, 128.3, 128.2, 126.0, 125.7, 38.9, 34.3, 33.2, 32.0, 31.8, 28.3, 27.6, 22.4, 22.1, 14.0, 14.0 (Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, Y.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 4897).

Conclusions and Claims to Original Knowledge

Through the ruthenium-catalyzed activation of carbon-hydrogen (C-H) bonds, we have developed a series of carbon-carbon (C-C) bond formation reactions, featuring the generation of functionalized arenes and alkenes.

An oxidative dehydrogenative homo-coupling of 2-arylpyridine derivatives has been developed by using ruthenium complex as catalyst. Comparing to the previously reported methods, the oxidant ($FeCl_3$) that we used in this reaction is inexpensive and more stable.

A ruthenium-catalyzed oxidative dehydrogenative cross-coupling of benzene derivatives and cycloalkanes has been demonstrated. This method provided an easy access to the introduction of alkyl groups to benzene ring selectively at *para*-postion. Many functional groups can be tolerated under the reaction conditions, and especially electron withdrawing group led to a high selectivity.

An olefination via decarbonylative addition of aldehydes to terminal alkynes has been disclosed. Conjugated and isolated alkenes could be generated correspondingly from aromatic aldehydes and aliphatic aldehydes. This method provided an important approach to alkene synthesis by avoiding the use of forcing conditions and thus many functional groups can be tolerated.

During the course of this thesis, the following articles were published:

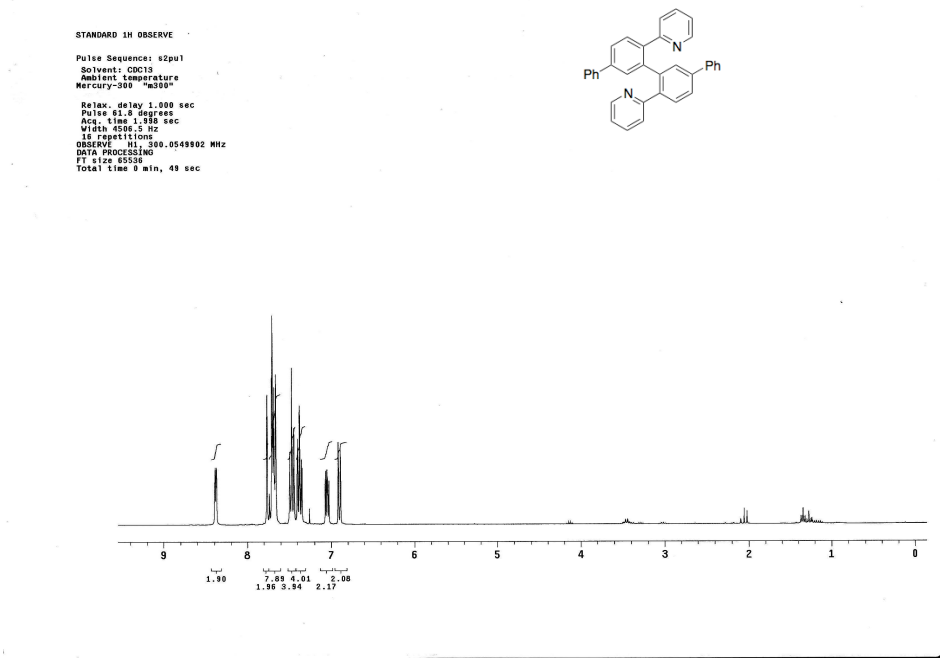
1. Guo, X.; Li, C.-J. "Ruthenium-Catalyzed Para-Selective Oxidative Cross-Coupling of Arenes and Cycloalkanes", *Org. Lett.* **2011**, *13*, 4977-4979
2. Guo, X.; Wang, J.; Li, C.-J. "Ru-Catalyzed Decarbonylative Addition of Aliphatic Aldehydes to Terminal Alkynes", *Org. Lett.* **2010**, *12*, 3176-3178
3. Guo, X.; Wang, J.; Li, C.-J. "An Olefination via Ruthenium-Catalyzed Decarbonylative Addition of Aldehydes to Terminal Alkynes", *J. Am. Chem. Soc.* **2009**, *131*, 15092-15093.
4. Guo, X.; Deng, G.; Li, C.-J. "Ruthenium-Catalyzed Oxidative Homo-Coupling of 2-Arylpyridines", *Adv. Synth. Catal.* **2009**, *351*, 2071-2074.
5. Yang, L.; Zeng, T.; Shuai, Q.; Guo, X.; Li, C.-J. " Phosphine Ligand Triggered Oxidative Decarbonylative Homocoupling of Aromatic Aldehydes: Selectively Generating Biaryls and Diarylketones", *Chem. Commun.* **2011**, *47*, 2161-2163.
6. Shuai, Q; Yang, L; Guo, X.; Basle, O; Li, C.-J. "Rhodium-Catalyzed Oxidative C−H Arylation of 2-Arylpyridine Derivatives via Decarbonylation of Aromatic Aldehydes", *J. Am. Chem. Soc.* **2010**, *132*, 12212-12213.
7. Yang, L; Guo, X.; Li, C.-J. "The First Decarbonylative Coupling of Aldehydes and Norbornenes Catalyzed by Rhodium", *Adv. Synth. Catal.* **2010**, *352*, 2899-2904.
8. Wang, J; Guo, X.; Li, C.-J. "Iridium as a General Catalyst for the Decarbonylative Addition of Aldehydes to Alkynes", *J. Organomet. Chem.* **2010**, *696*, 211-215.

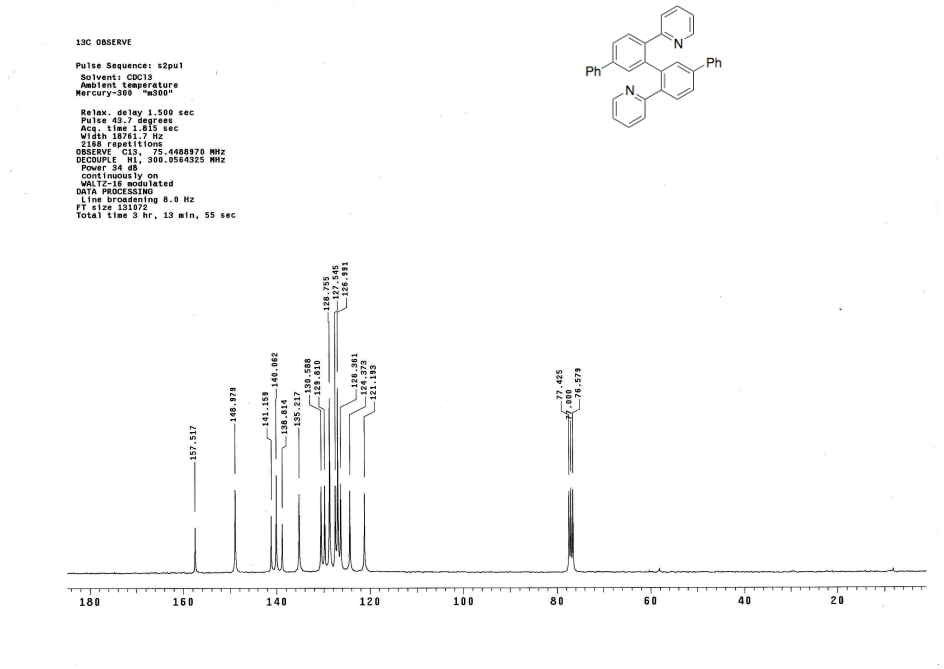
9. Yang, L; Correia, C. A.; Guo, X.; Li, C.-J. " A Novel Catalytic Decarbonylative Heck-type Reaction and Conjugate Addition of Aldehydes to Unsaturated Carbonyl Compounds ", *Tetrahedron Lett.* **2010**, *51*, 5486-5489.

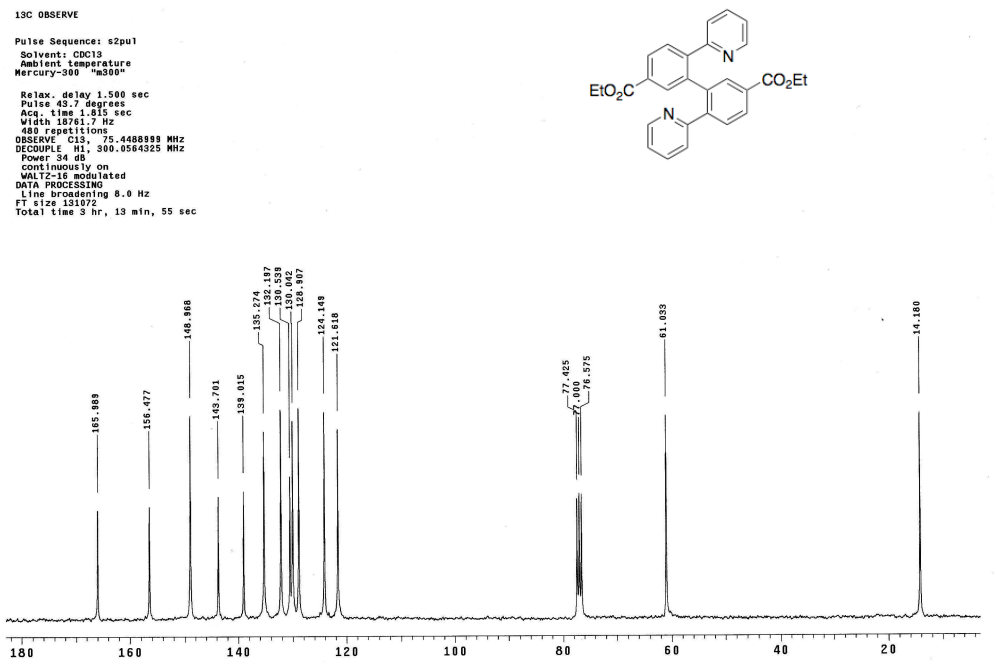
Appendix

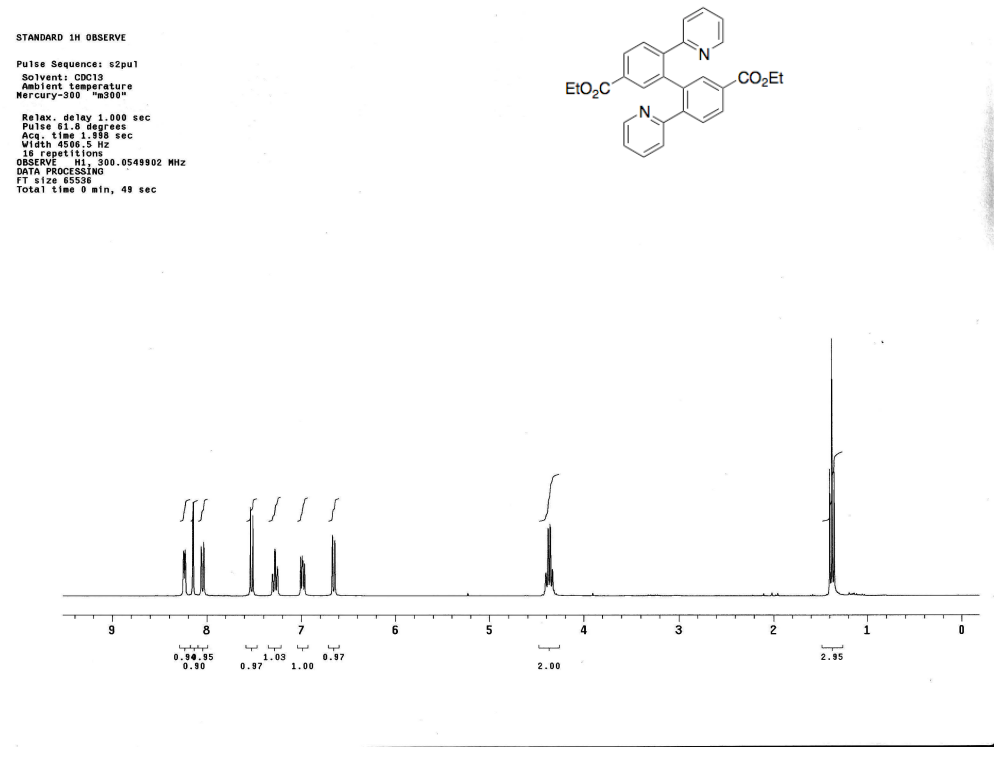
^{13}C NMR and ^{1}H NMR spectrums

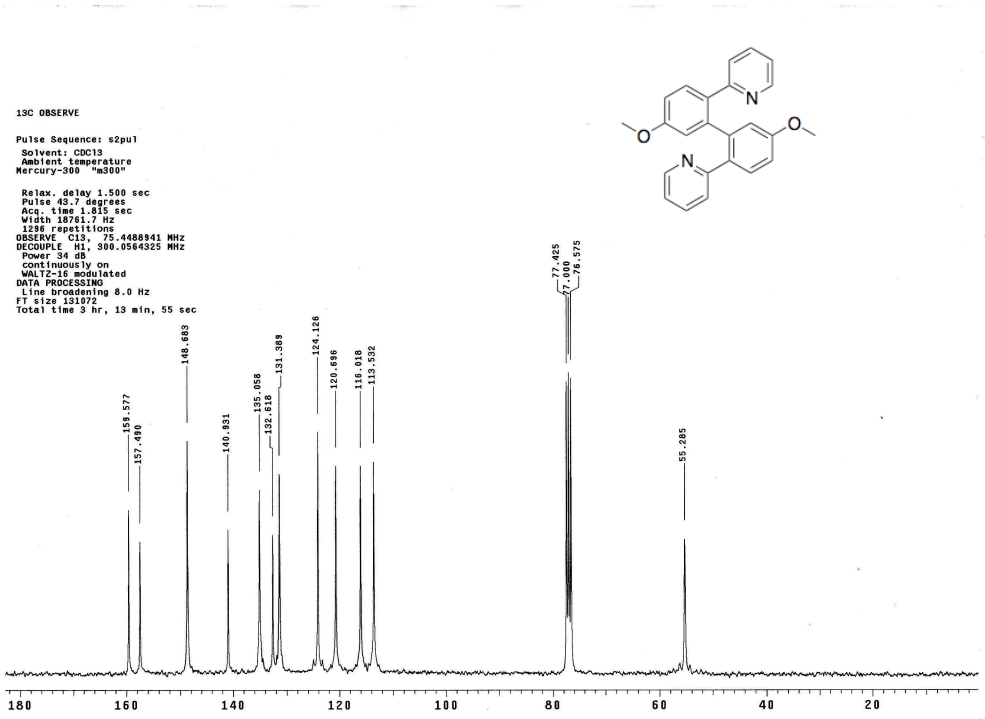
NMR spectrums for chapter 2

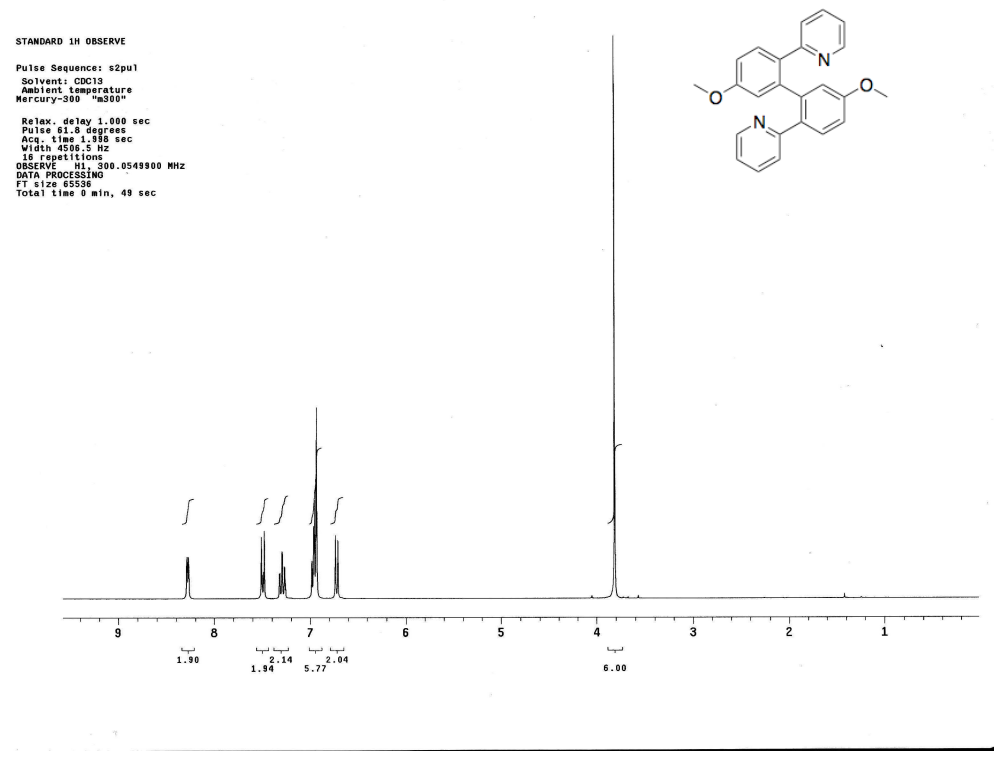


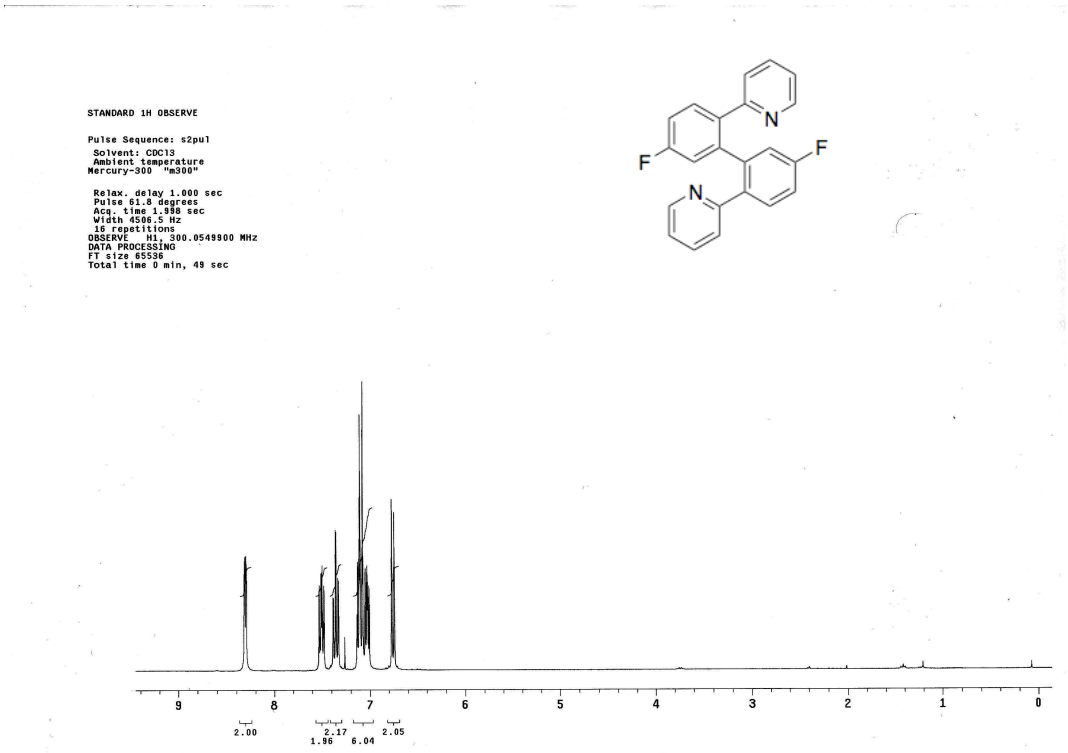


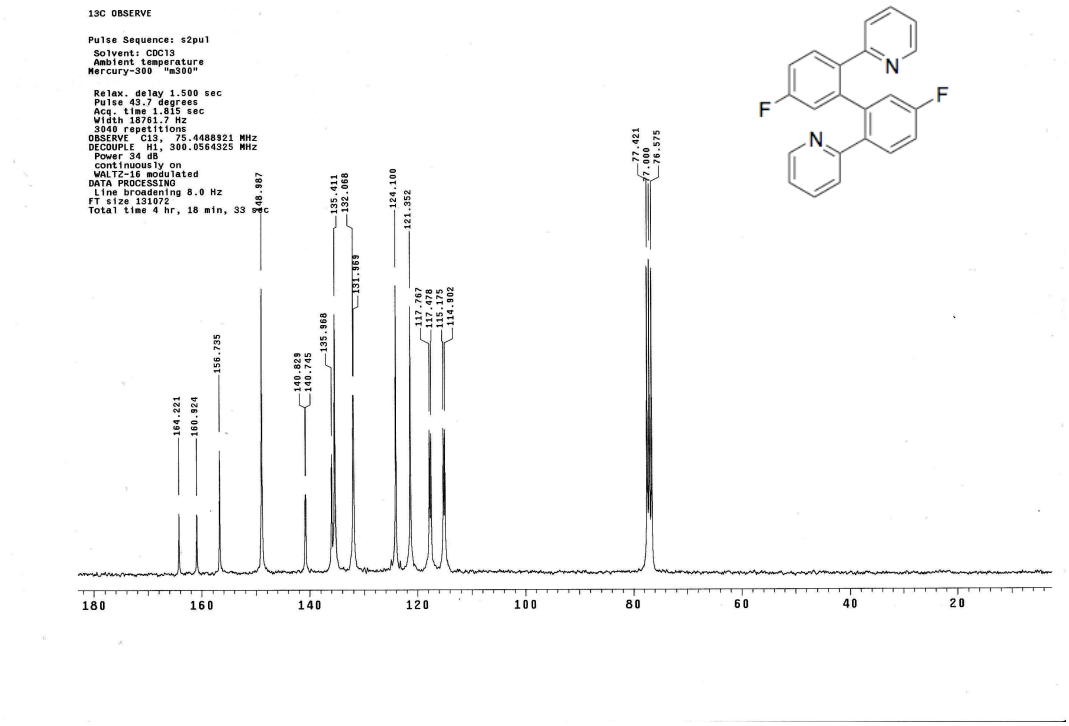

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 43.7 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
480 repetitions
OBSERVE C13, 75.4488899 MHz
DECOUPLE H1, 300.0564325 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 8.0 Hz
FT size 131072
Total time 3 hr, 13 min, 55 sec
EtO2C
CO2Et
N
N
165.989
156.477
148.868
143.701
139.015
135.274
132.187
130.539
130.003
128.907
124.148
121.618
77.425
77.000
76.575
61.033
14.180
180
160
140
120
100
80
60
40
20


STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 61.8 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.0549902 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 49 sec
EtO2C
CO2Et
N
N
9
8
7
6
5
4
3
2
1
0
0.90
0.95
0.97
1.03
1.00
0.97
2.00
2.95


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 43.7 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1296 repetitions
OBSERVE C13, 75.4488941 MHz
DECOUPLE H1, 300.0564325 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 8.0 Hz
FT size 131072
Total time 3 hr, 13 min, 55 sec
159.577
157.490
148.683
140.931
135.058
132.618
131.388
124.126
120.696
116.018
113.532
77.425
77.000
76.575
55.265
180
160
140
120
100
80
60
40
20
N
O
O
N


STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 81.8 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 49 sec
9
8
7
6
5
4
3
2
1
1.90
2.14
1.84
5.77
2.04
6.00
N
O
O
N

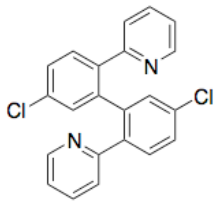

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 61.8 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 49 sec
F
N
N
F
9
8
7
6
5
4
3
2
1
0
2.00
2.17
1.96
6.04
2.05

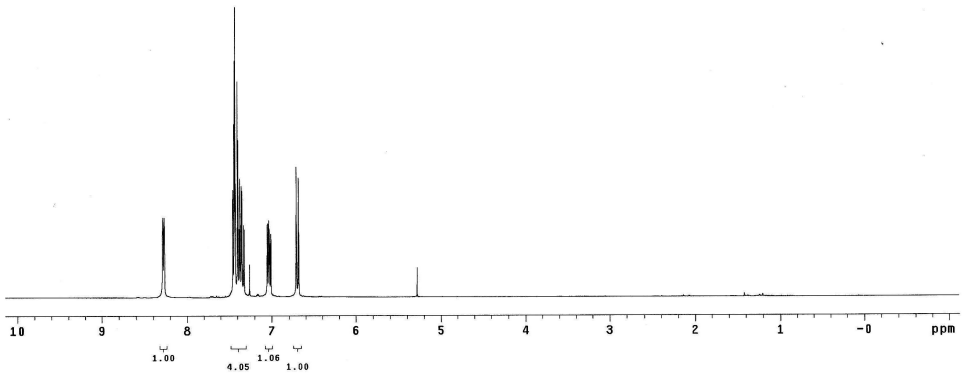

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 43.7 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
3040 repetitions
OBSERVE C13, 75.4488921 MHz
DECOUPLE H1, 300.0564325 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 8.0 Hz
FT size 131072
Total time 4 hr, 18 min, 33 sec
164.221
160.924
156.735
148.987
140.829
140.745
135.968
135.411
132.068
131.369
124.100
121.352
117.787
117.478
115.175
114.902
77.421
77.000
76.575
N
F
N
F
180
160
140
120
100
80
60
40
20

519-s-1

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"

Relax. delay 1.000 sec
Pulse 61.8 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 49 sec

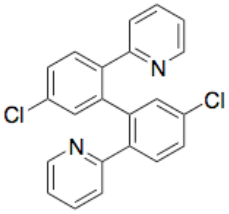


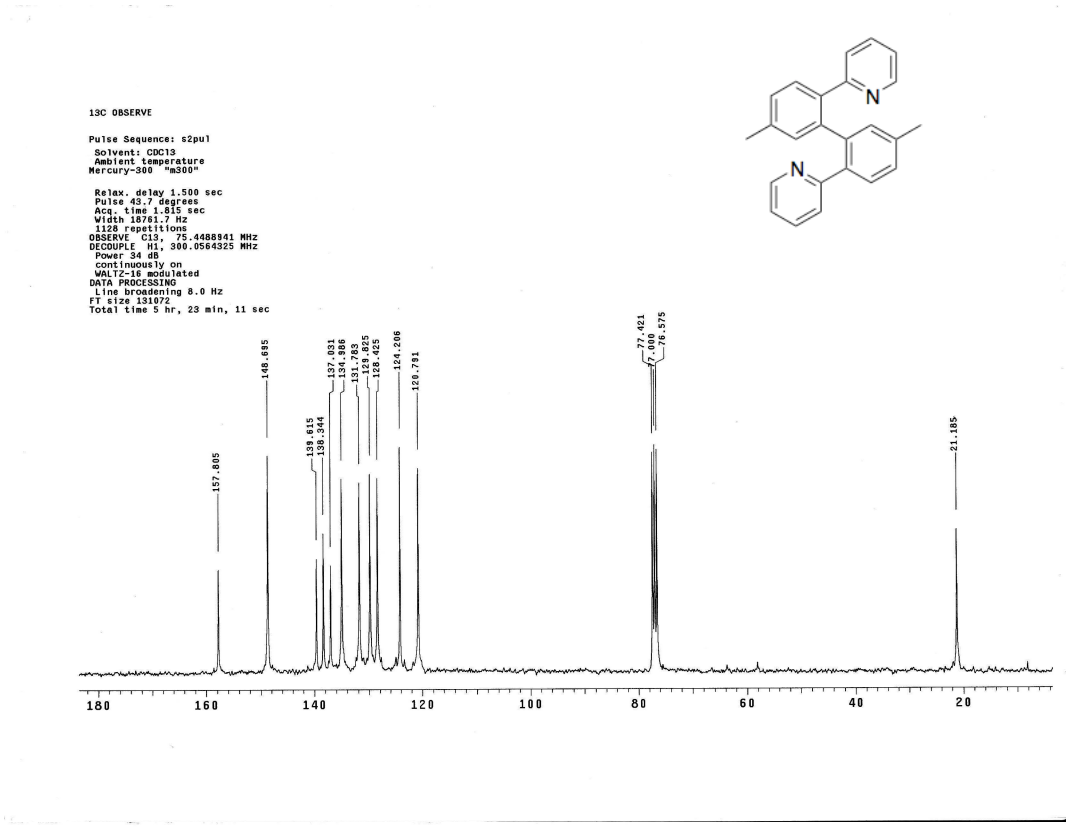


STANDARD 1H OBSERVE

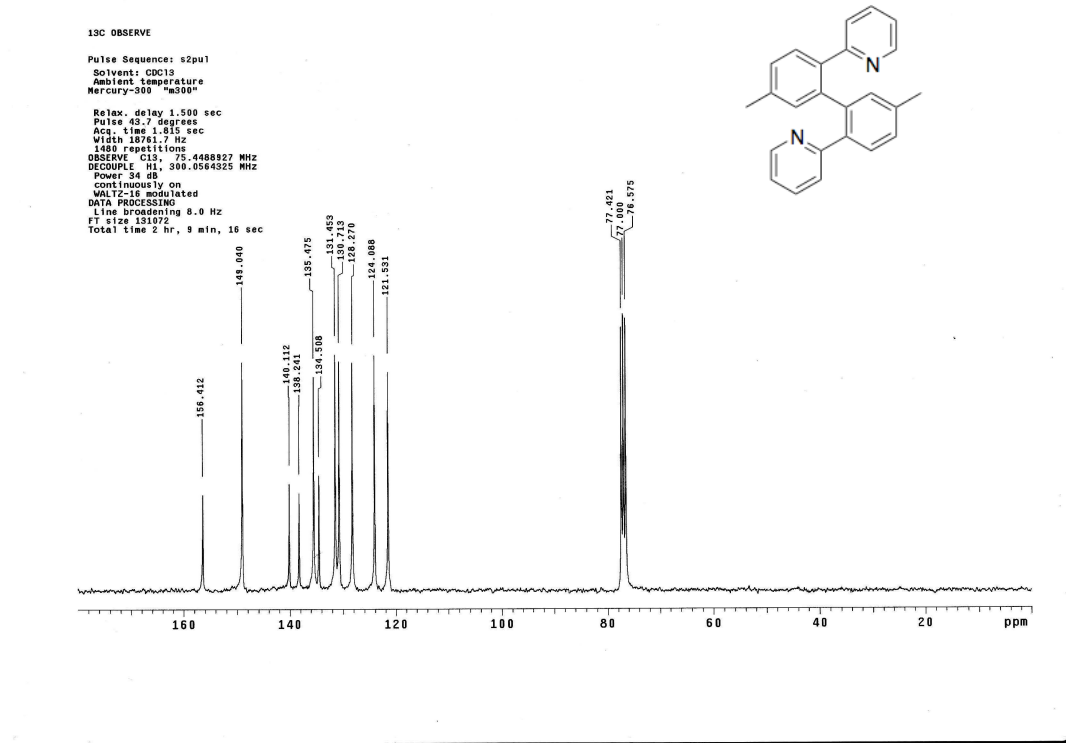
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"

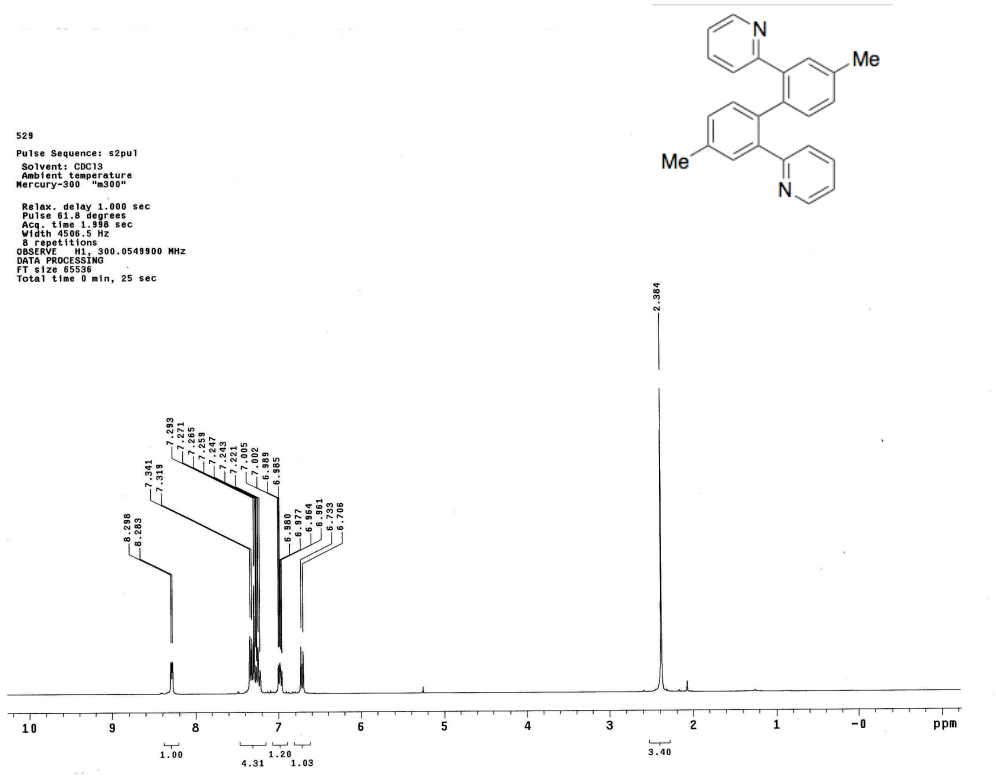
Relax. delay 1.000 sec
Pulse 61.8 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 0 sec

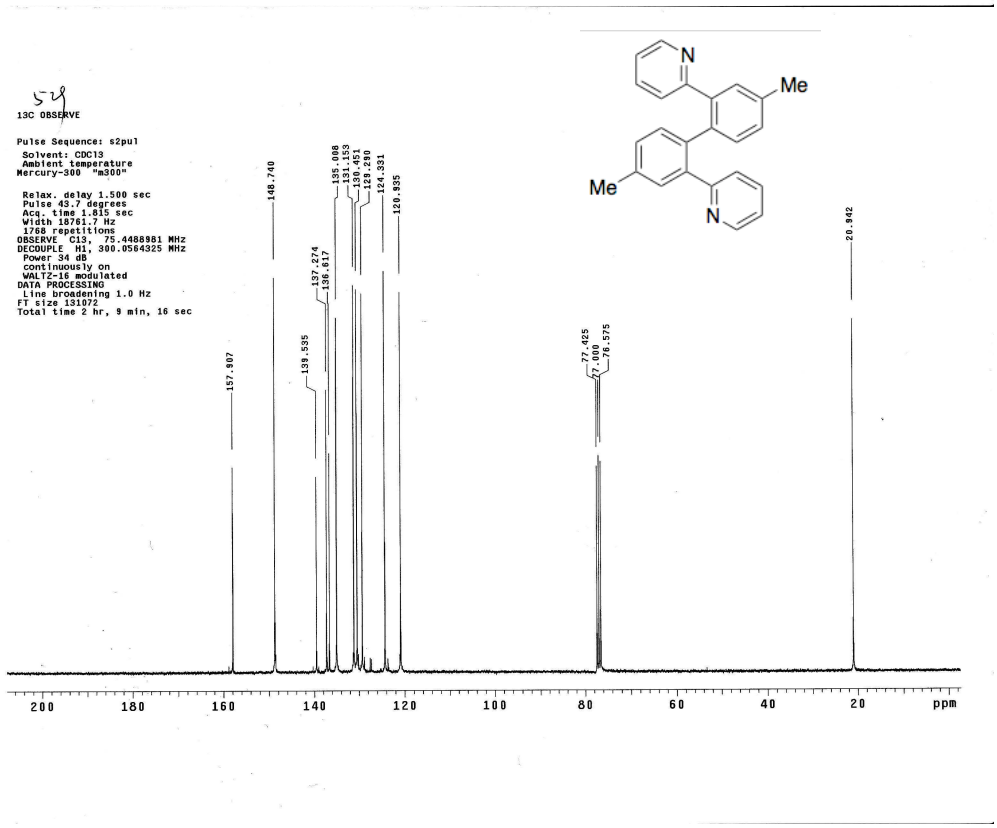


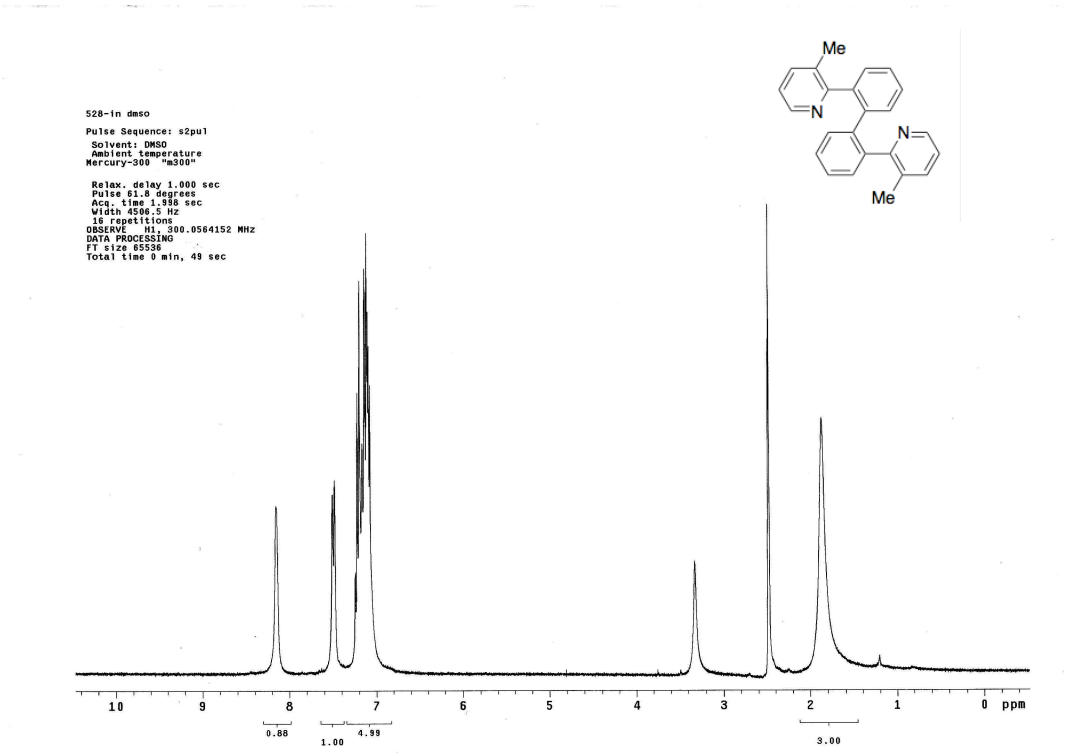

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 43.7 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1128 repetitions
OBSERVE C13, 75.4488941 MHz
DECOUPLE H1, 300.0564325 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 8.0 Hz
FT size 131072
Total time 5 hr, 23 min, 11 sec
157.805
148.695
139.615
138.344
137.031
134.986
131.783
129.825
128.425
124.206
120.791
77.421
77.000
76.575
21.185
180
160
140
120
100
80
60
40
20

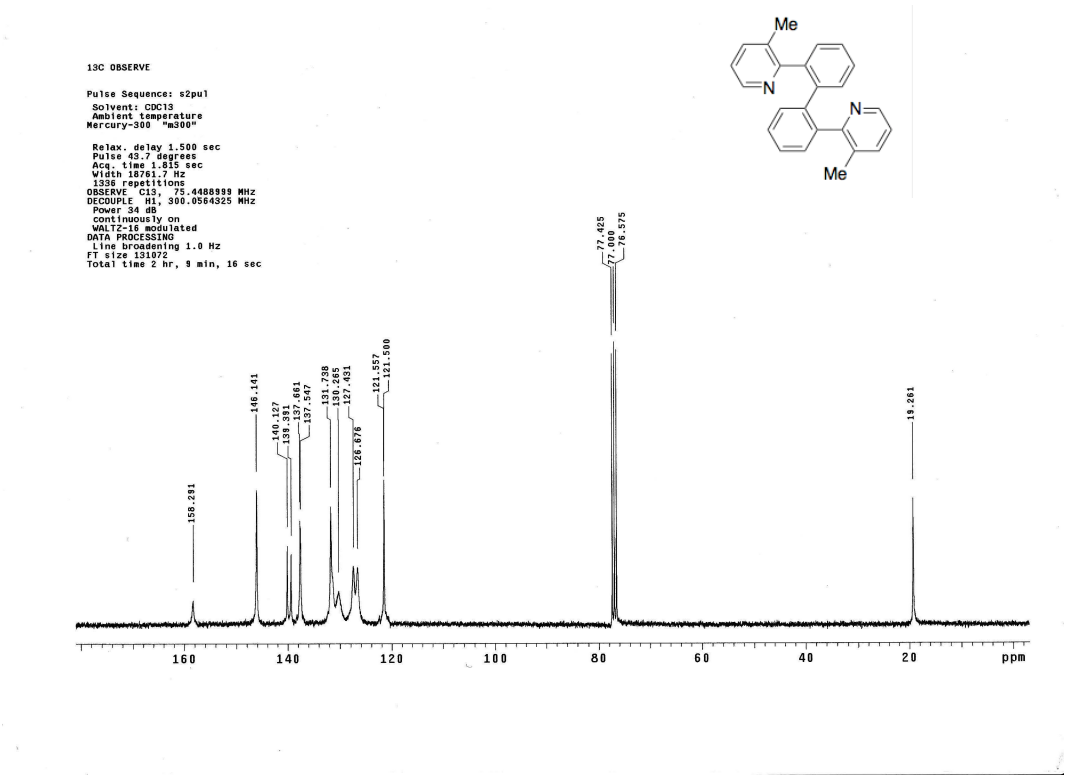
519

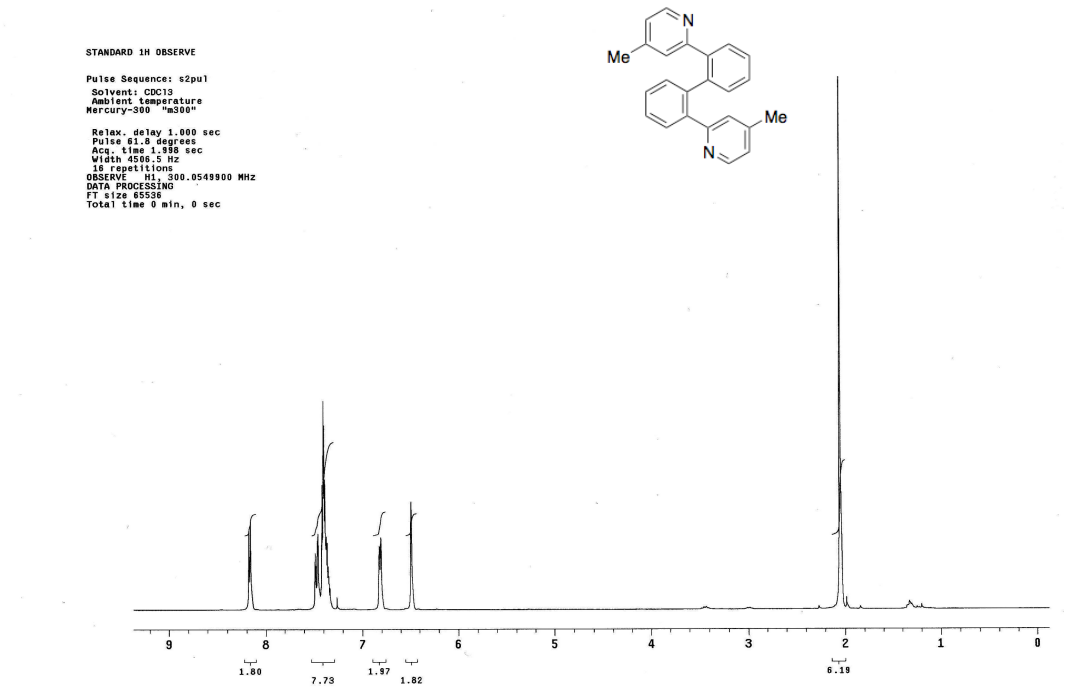

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 43.7 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1480 repetitions
OBSERVE C13, 75.4488927 MHz
DECOUPLE H1, 300.0564325 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 8.0 Hz
FT size 131072
Total time 2 hr, 9 min, 16 sec
156.412
148.040
140.112
138.241
135.475
134.508
131.453
130.713
128.270
124.088
121.531
77.421
77.000
76.575
160
140
120
100
80
60
40
20
ppm

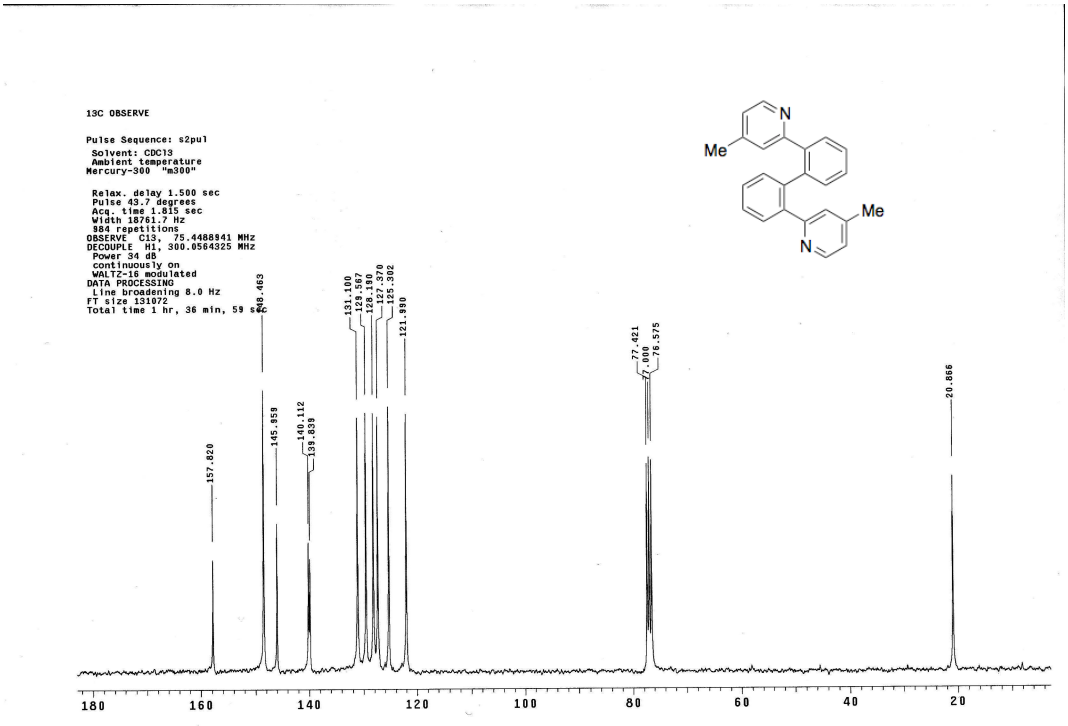

529
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 61.8 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
8 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 25 sec
N
Me
Me
N
2.384
7.293
7.271
7.265
7.259
7.247
7.243
7.201
7.005
7.002
6.989
6.985
7.341
7.319
8.288
8.283
6.980
6.877
6.864
6.861
6.703
6.700
10
9
8
7
6
5
4
3
2
1
-0
ppm
1.00
4.31
1.20
1.03
3.40


529
13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 43.7 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1768 repetitions
OBSERVE C13, 75.4488981 MHz
DECOUPLE H1, 300.0564325 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 2 hr, 9 min, 16 sec
N
Me
Me
N
157.807
148.740
139.535
137.274
136.817
135.008
133.155
130.451
128.290
124.331
120.935
77.425
77.000
76.575
20.942
200
180
160
140
120
100
80
60
40
20
ppm

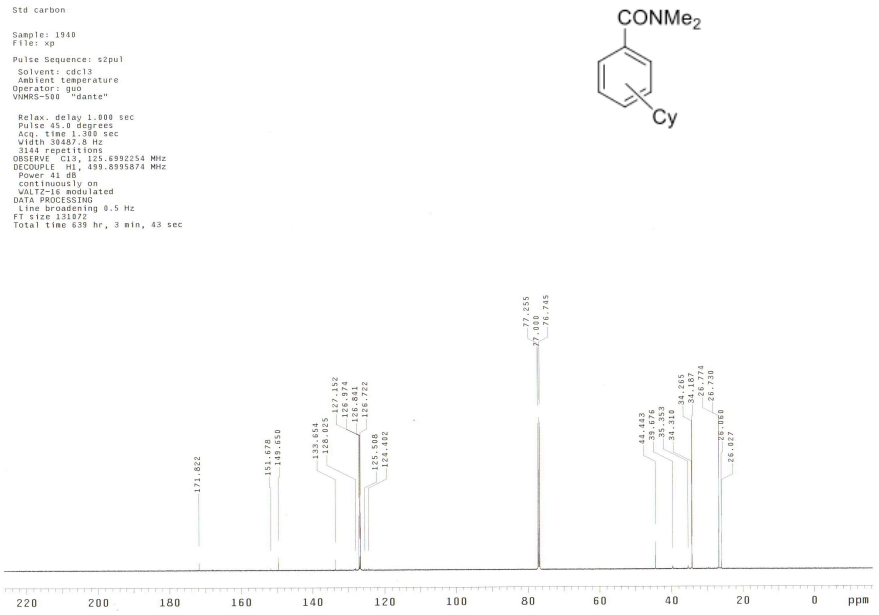

528-in dmso
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 61.8 degrees
Acq. time 1.898 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.0564152 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 49 sec
Me
N
N
Me
10
9
8
7
6
5
4
3
2
1
0 ppm
0.88
1.00
4.99
3.00

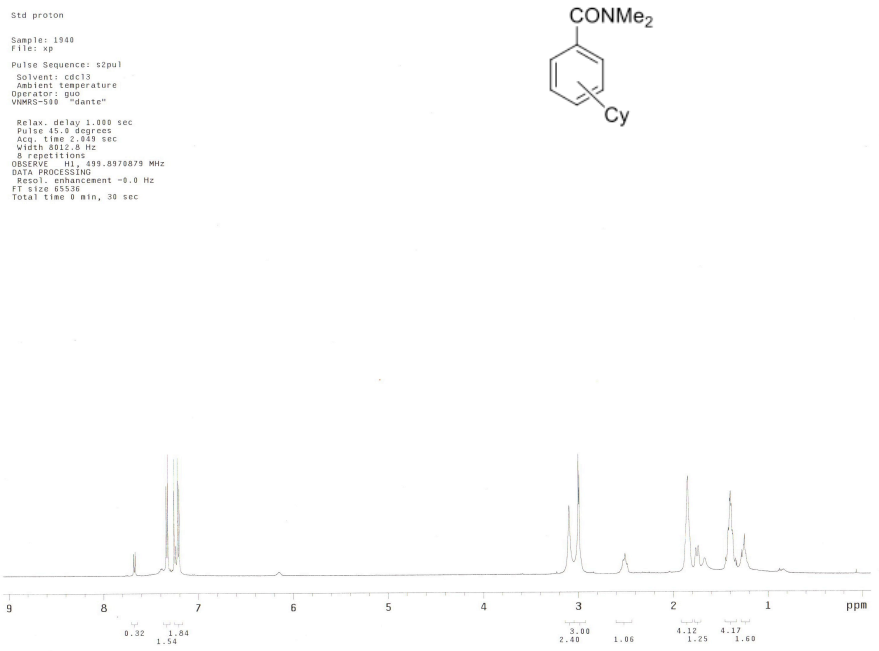

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 43.7 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1336 repetitions
OBSERVE C13, 75.4488999 MHz
DECOUPLE H1, 300.0564325 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 2 hr, 9 min, 16 sec
Me
N
N
Me
158.291
146.141
140.107
138.381
137.661
137.547
131.738
130.265
127.431
126.676
121.557
121.500
77.425
77.000
76.575
19.261
160
140
120
100
80
60
40
20
ppm

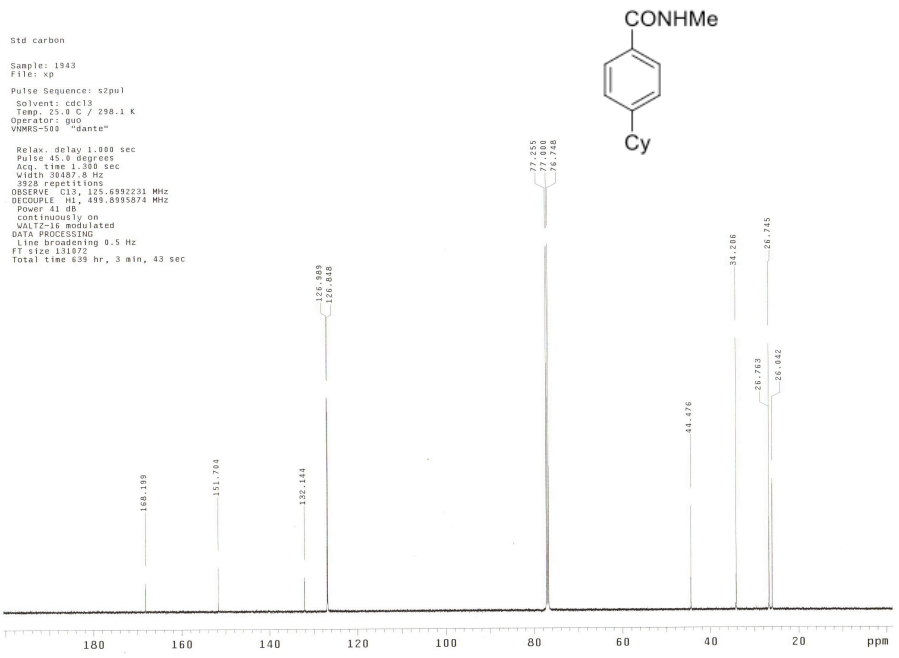

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 61.8 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 0 sec
N
Me
Me
N
9
8
7
6
5
4
3
2
1
0
1.80
7.78
1.97
1.82
6.19

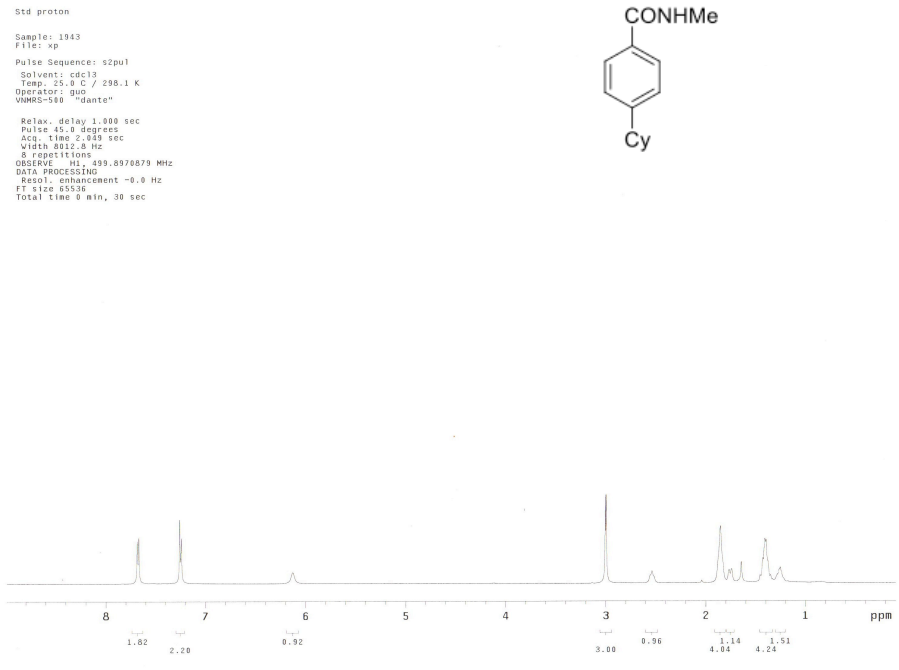

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 43.7 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
884 repetitions
OBSERVE C13, 75.4488941 MHz
DECOUPLE H1, 300.0564325 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 8.0 Hz
FT size 131072
Total time 1 hr, 36 min, 59 sec
N
Me
Me
N
157.820
148.463
145.558
140.112
139.839
131.100
129.197
128.180
127.370
125.302
121.990
77.421
77.000
76.575
20.866
180
160
140
120
100
80
60
40
20

NMR spectrums for chapter 3






Std carbon
Sample: 1943
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
3928 repetitions
OBSERVE C13, 125.6992231 MHz
DECOUPLE H1, 499.8995874 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 639 hr, 3 min, 43 sec
CONHMe
Cy
77.255
77.000
76.748
126.989
126.848
34.206
26.745
26.763
26.442
44.476
168.199
151.704
132.144
180
160
140
120
100
80
60
40
20
ppm

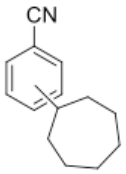

Std proton
Sample: 1943
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8970879 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
CONHMe
Cy
8
7
6
5
4
3
2
1
ppm
1.82
2.20
0.92
3.00
0.96
1.14
4.04
1.51
4.24

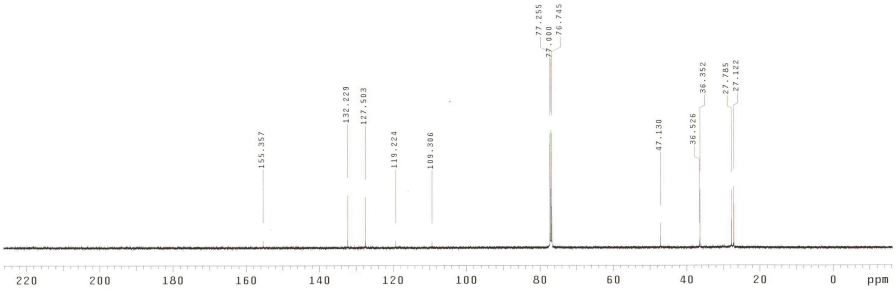
Std carbon

Sample: 1994
File: xp

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 24.0 C / 297.1 K
Operator: guo
VNMRS-500 "dante"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.300 sec
 Width 30487.8 Hz
 1216 repetitions
OBSERVE C13, 125.6952231 MHz
DECOUPLE H1, 499.8955874 MHz
 Power 41 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 131072
Total time 639 hr, 3 min, 43 sec



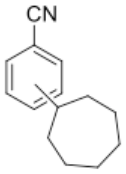


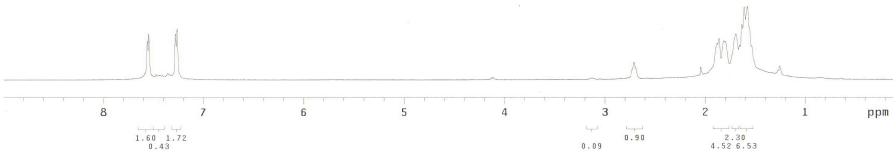
Std proton

Sample: 1994
File: home/guo/vnmrsys/data/1994h.fid

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 24.0 C / 297.1 K
Operator: guo
File: 1994h
VNMRS-500 "dante"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 8012.8 Hz
 8 repetitions
OBSERVE H1, 499.8970879 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec



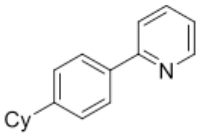


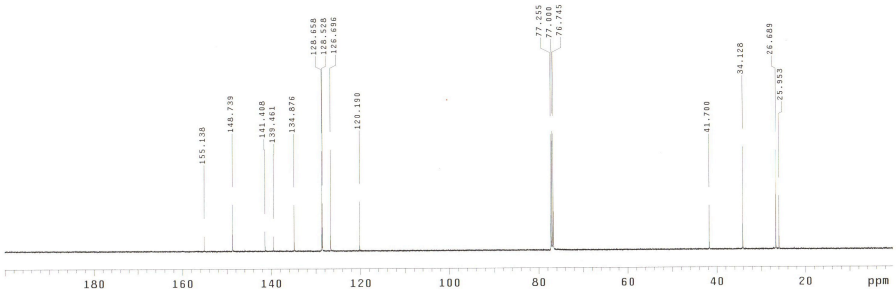
Std carbon

Sample: 2001-2
File: xp

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: guo
VNMRS-500 "dante"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.300 sec
 Width 30487.8 Hz
 2624 repetitions
OBSERVE C13, 125.6952240 MHz
DECOUPLE H1, 499.8995874 MHz
 Power 41 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 131072
Total time 639 hr, 3 min, 43 sec



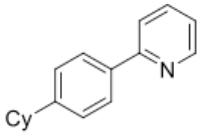


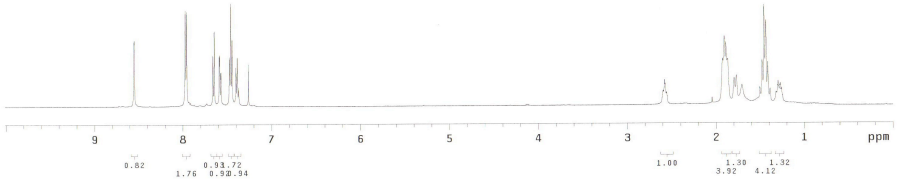
Std proton

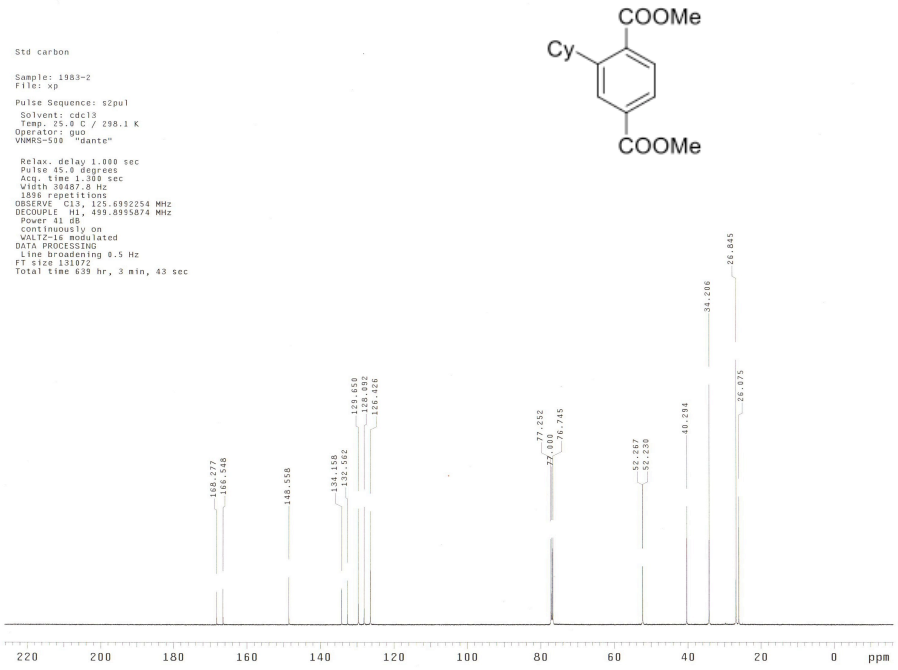
Sample: 2001-2
File: xp

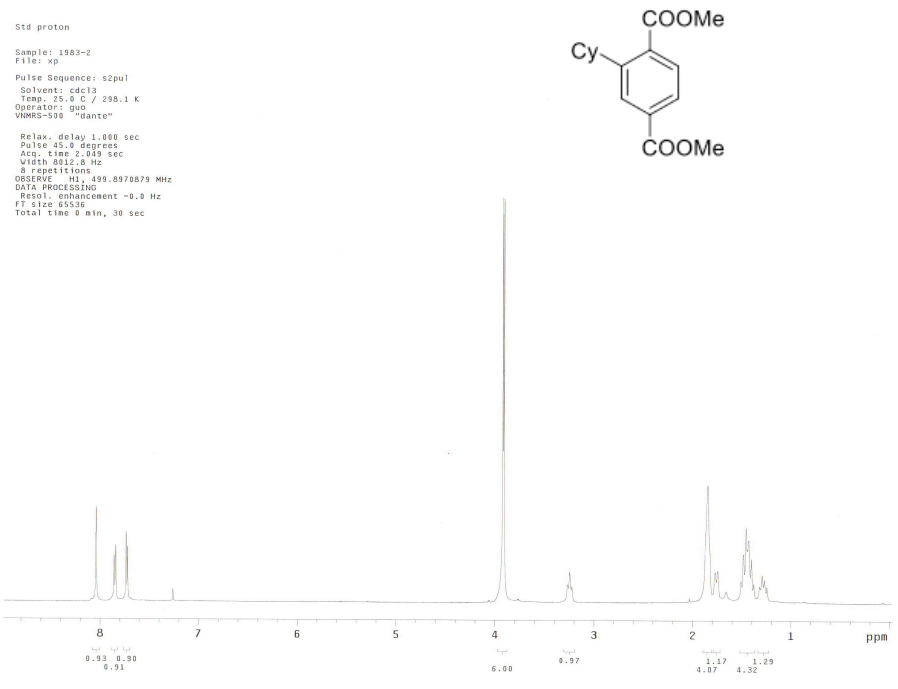
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: guo
VNMRS-500 "dante"

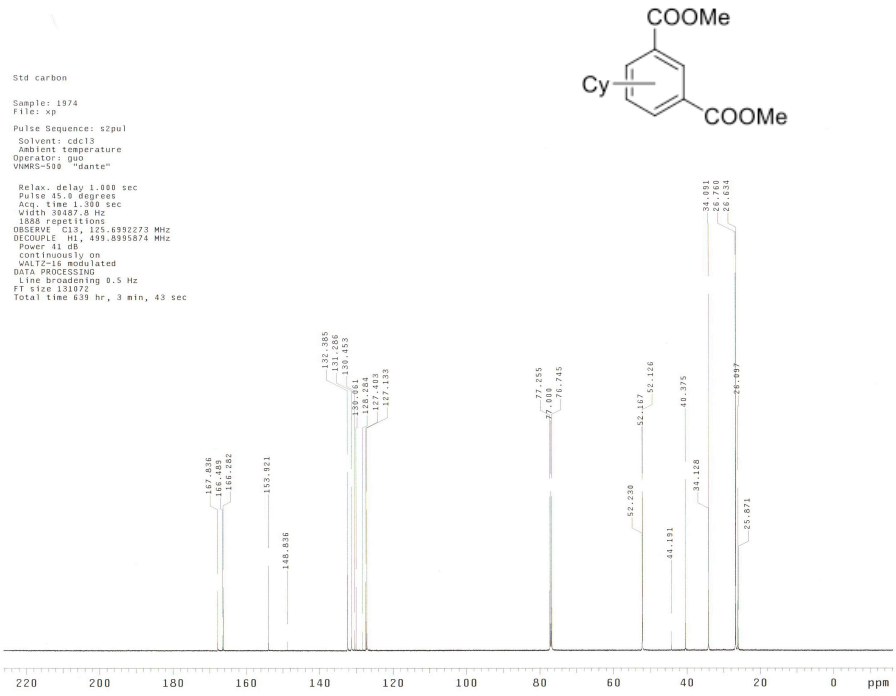
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 8012.8 Hz
 8 repetitions
OBSERVE H1, 499.8970879 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

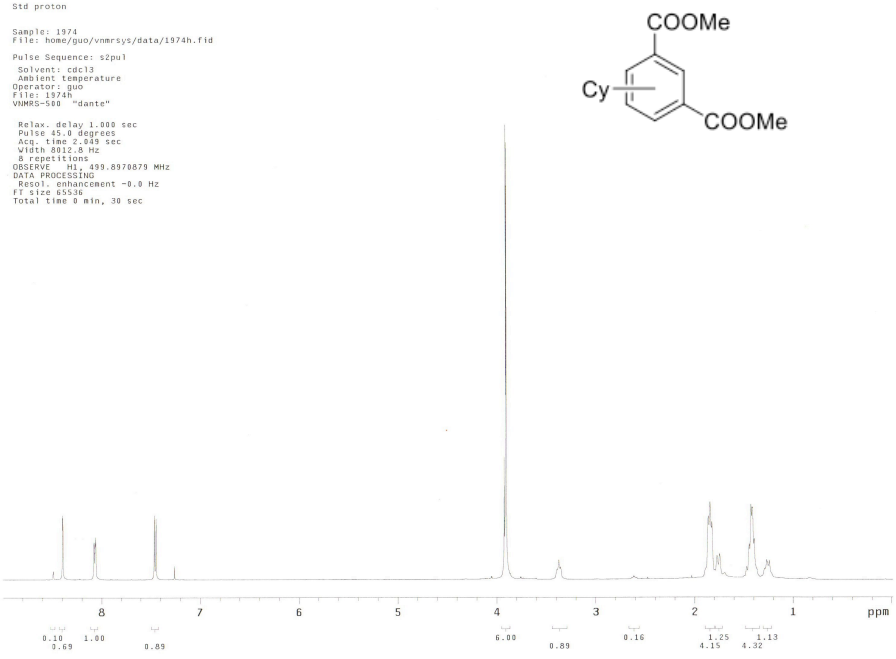


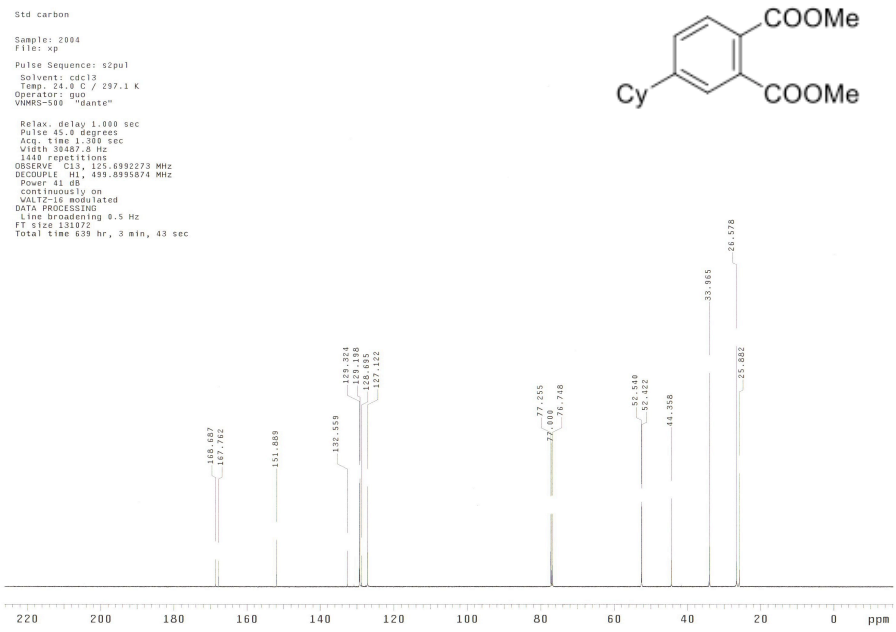


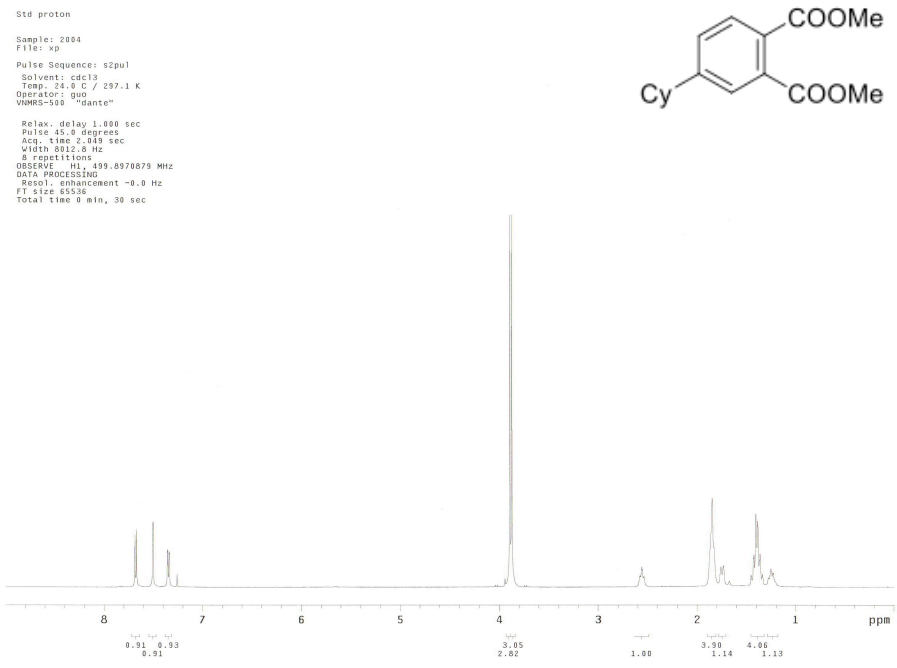

Std carbon
Sample: 1983-2
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
1896 repetitions
OBSERVE C13, 125.6952254 MHz
DECOUPLE H1, 499.8995874 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 639 hr, 3 min, 43 sec
COOMe
Cy
COOMe
168.277
166.548
148.558
134.158
132.562
129.659
128.832
128.426
77.252
77.000
76.745
52.267
52.230
40.294
34.206
26.845
26.075
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Std proton
Sample: 1983-2
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8970879 MHz
DATA PROCESSING
Resol. enhancement -0.8 Hz
FT size 65536
Total time 0 min, 30 sec
COOMe
Cy
COOMe
8
7
6
5
4
3
2
1
ppm
0.93
0.90
0.91
6.00
0.97
1.17
4.07
1.29
4.32


COOMe
Cy
COOMe
Std carbon
Sample: 1974
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.380 sec
Width 30487.8 Hz
1888 repetitions
OBSERVE C13, 125.6992273 MHz
DECOUPLE H1, 499.8995874 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 639 hr, 3 min, 43 sec
167.836
166.885
166.282
153.921
148.836
132.385
131.286
130.458
130.061
128.284
127.418
127.193
77.255
77.000
76.745
52.167
52.126
52.230
44.191
40.375
34.128
34.091
26.760
26.634
26.497
25.871
220
200
180
160
140
120
100
80
60
40
20
0
ppm


COOMe
Cy
COOMe
Std proton
Sample: 1974
File: home/guo/vnmrsys/data/1974h.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: guo
File: 1974h
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8970879 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
8
7
6
5
4
3
2
1
ppm
0.10
0.69
1.00
0.89
6.00
0.89
0.16
1.25
4.15
1.13
4.32


Std carbon
Sample: 2004
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
1440 repetitions
OBSERVE C13, 125.6992273 MHz
DECOUPLE H1, 499.8995874 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 639 hr, 3 min, 43 sec
COOMe
Cy
COOMe
168.687
167.762
151.869
132.559
129.324
129.198
128.695
127.122
77.255
77.000
76.748
52.540
52.422
44.358
33.965
26.578
25.882
220
200
180
160
140
120
100
80
60
40
20
0
ppm

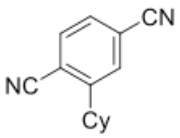

Std proton
Sample: 2004
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 24.0 C / 297.1 K
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8970879 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
COOMe
Cy
COOMe
8
7
6
5
4
3
2
1
ppm
0.91
0.93
0.91
3.05
2.82
1.00
3.90
1.14
4.06
1.13

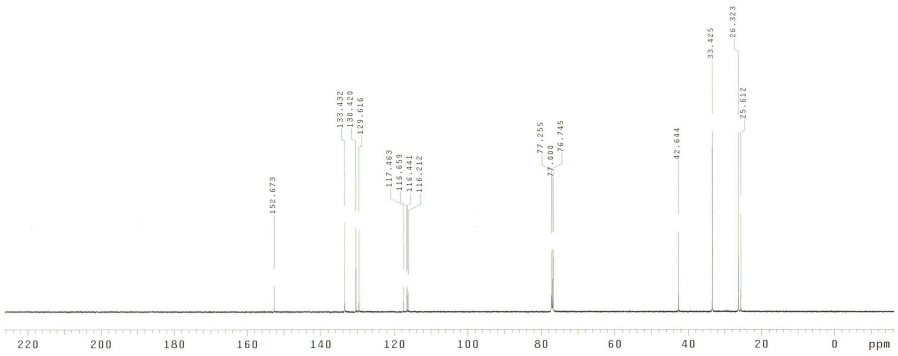
Std carbon

Sample: 2008-3
File: xp

Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: guo
VNMRS-500 "dante"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.380 sec
Width 30487.8 Hz
648 repetitions
OBSERVE C13, 125.6992259 MHz
DECOUPLE H1, 499.8995874 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 6390 hr, 37 min, 6 sec



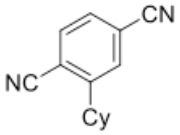


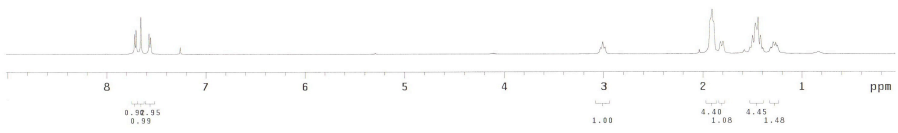
Std proton

Sample: 2008-3
File: xp

Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: guo
VNMRS-500 "dante"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8970879 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec



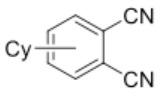


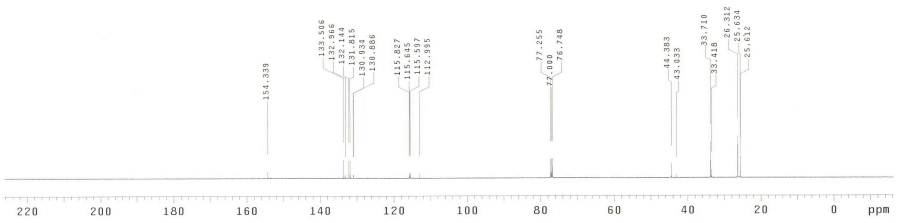
Std carbon

Sample: 2010-2
File: xp

Pulse Sequence: s2pul
 Solvent: cdcl3
 Ambient temperature
Operator: guo
VNMRS-500 "dante"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.380 sec
 Width 30487.8 Hz
 944 repetitions
OBSERVE C13, 125.6992263 MHz
DECOUPLE H1, 499.8995874 MHz
 Power 41 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 131072
Total time 63906 hr, 10 min, 56 sec



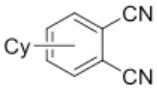


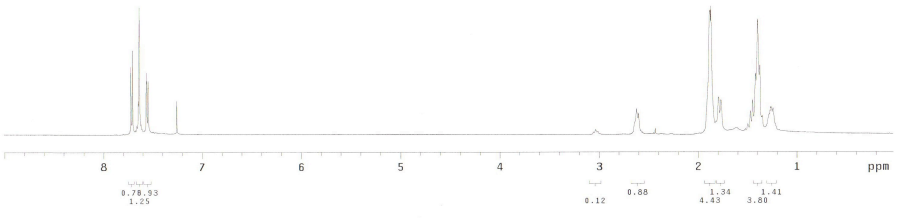
Std proton

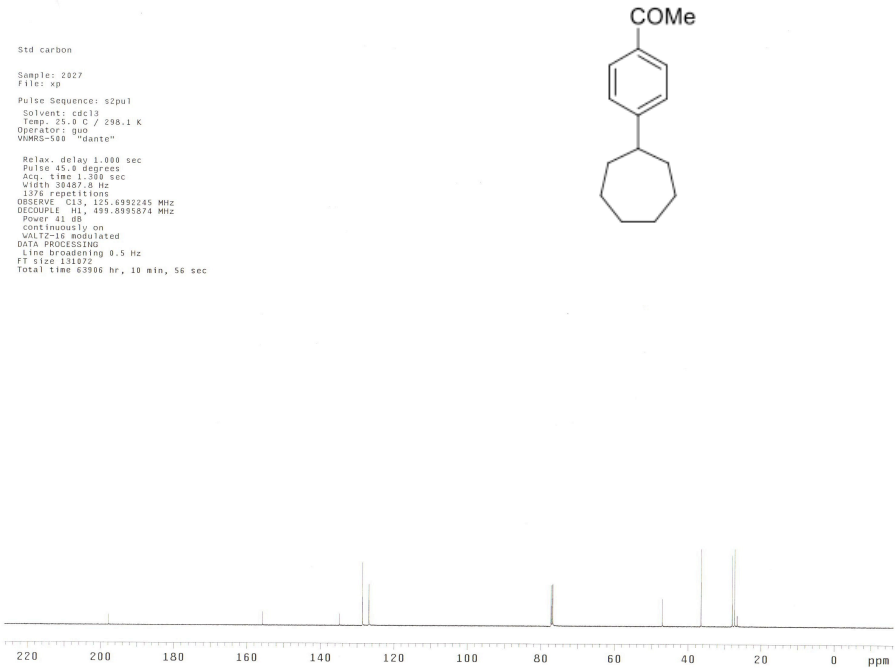
Sample: 2010-2
File: xp

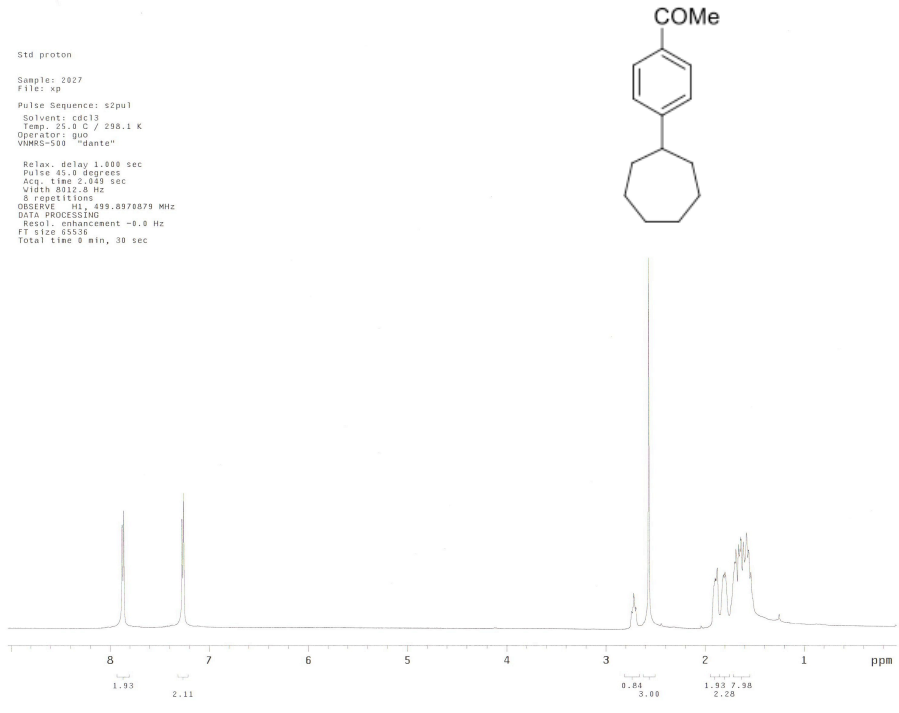
Pulse Sequence: s2pul
 Solvent: cdcl3
 Ambient temperature
Operator: guo
VNMRS-500 "dante"

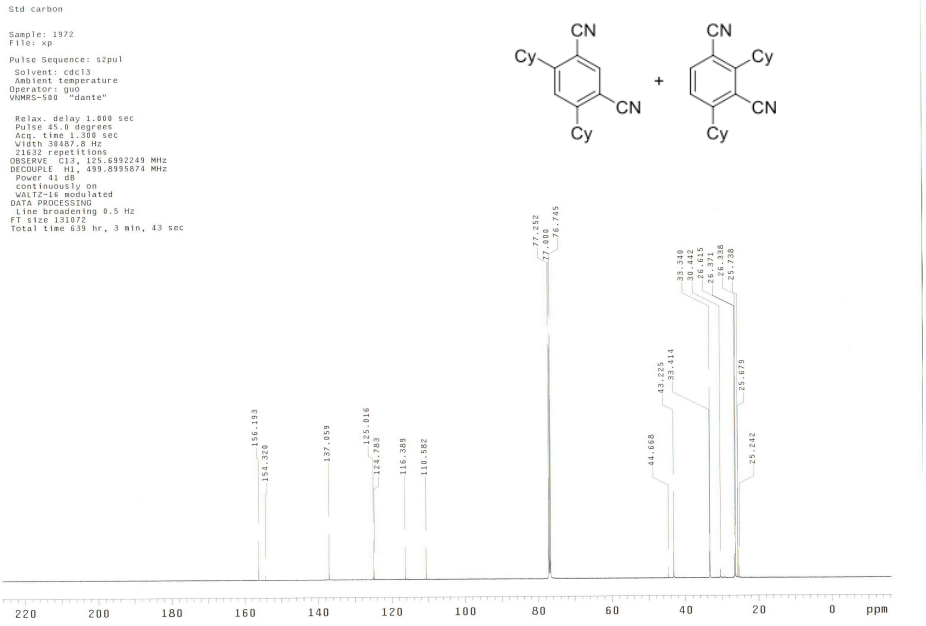
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 8012.8 Hz
 8 repetitions
OBSERVE H1, 499.8970879 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 8 min, 30 sec

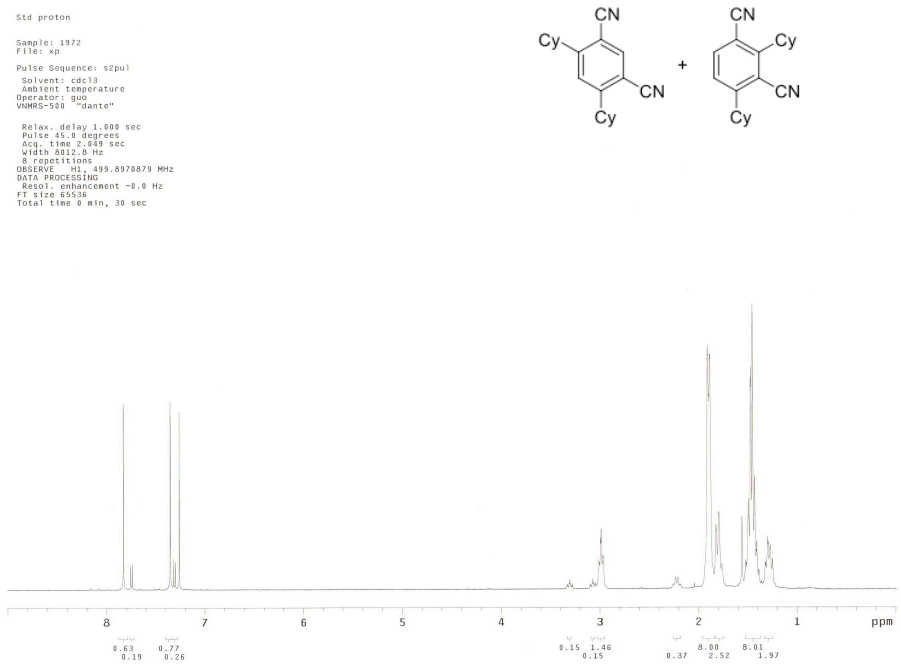




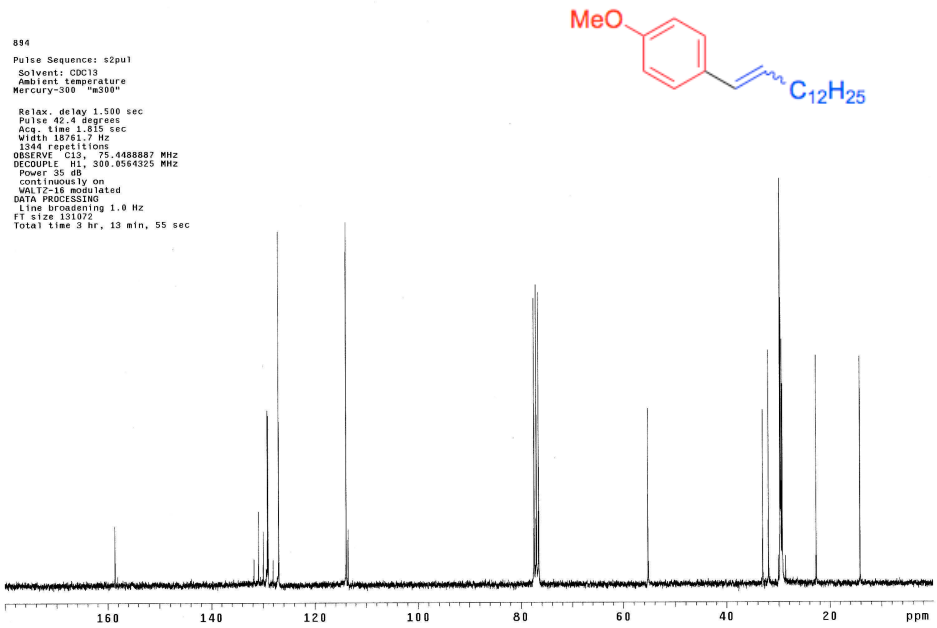

Std carbon
Sample: 2027
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.380 sec
Width 38487.8 Hz
1376 repetitions
OBSERVE C13, 125.6992245 MHz
DECOUPLE H1, 499.8995874 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 63906 hr, 10 min, 56 sec
COMe
220
200
180
160
140
120
100
80
60
40
20
0
ppm

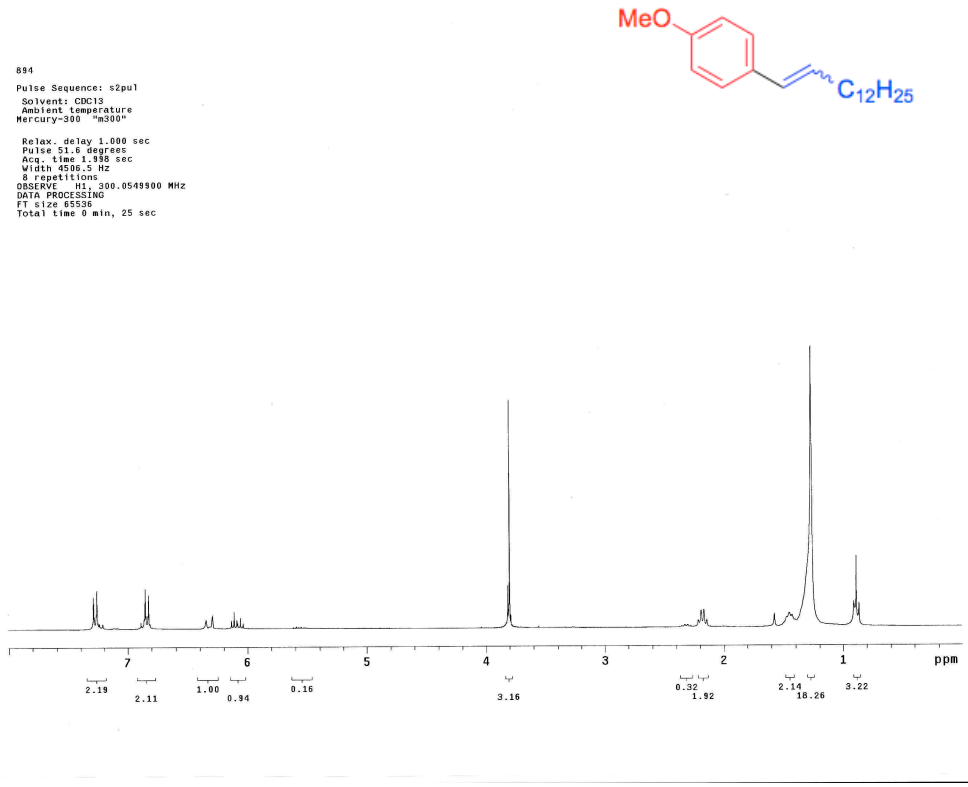

Std proton
Sample: 2027
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8970879 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
COMe
8
7
6
5
4
3
2
1
ppm
1.93
2.11
0.84
3.00
1.93 7.98
2.28


Std carbon
Sample: 1972
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
21632 repetitions
OBSERVE C13, 125.6992249 MHz
DECOUPLE H1, 499.8995874 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 639 hr, 3 min, 43 sec
CN
Cy
CN
Cy
+
CN
Cy
CN
Cy
77.262
77.001
76.745
33.348
30.442
26.415
26.371
26.336
25.738
43.225
39.414
25.679
44.668
25.242
156.193
154.320
137.059
125.018
124.785
116.389
110.582
220
200
180
160
140
120
100
80
60
40
20
0
ppm

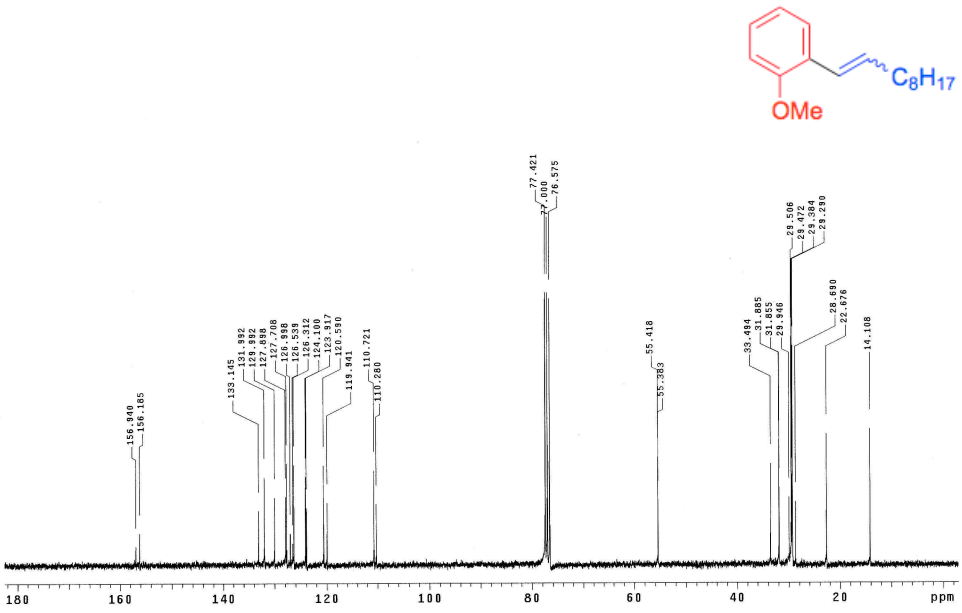

Std proton
Sample: 1972
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8970879 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
CN
Cy
CN
Cy
+
CN
Cy
CN
Cy
8
7
6
5
4
3
2
1
ppm
0.63
0.19
0.77
0.26
0.15
1.46
0.15
0.37
8.00
2.52
8.01
1.97

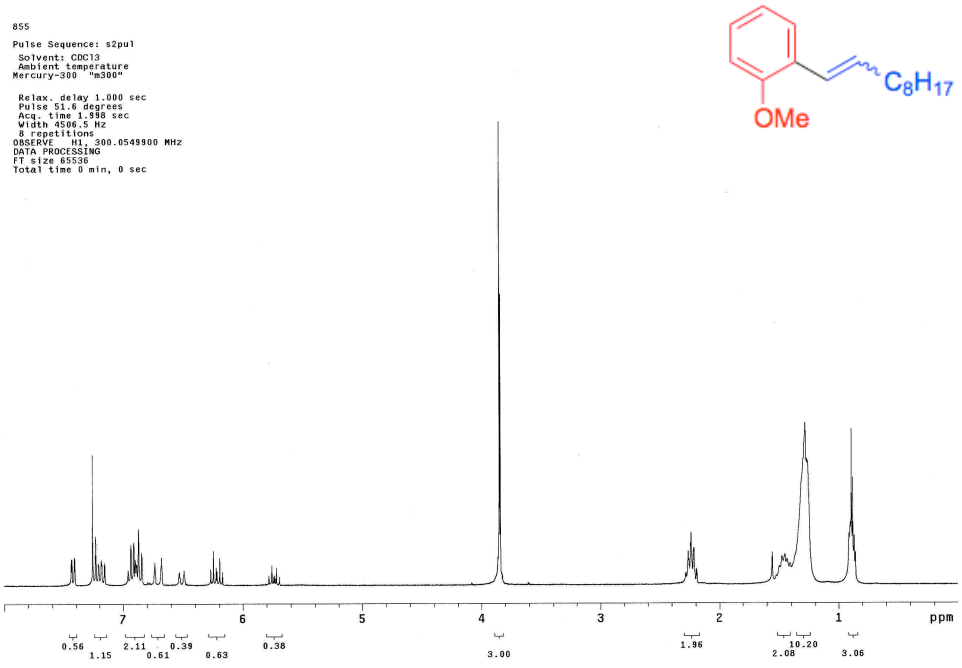
NMR spectrums for chapter 5

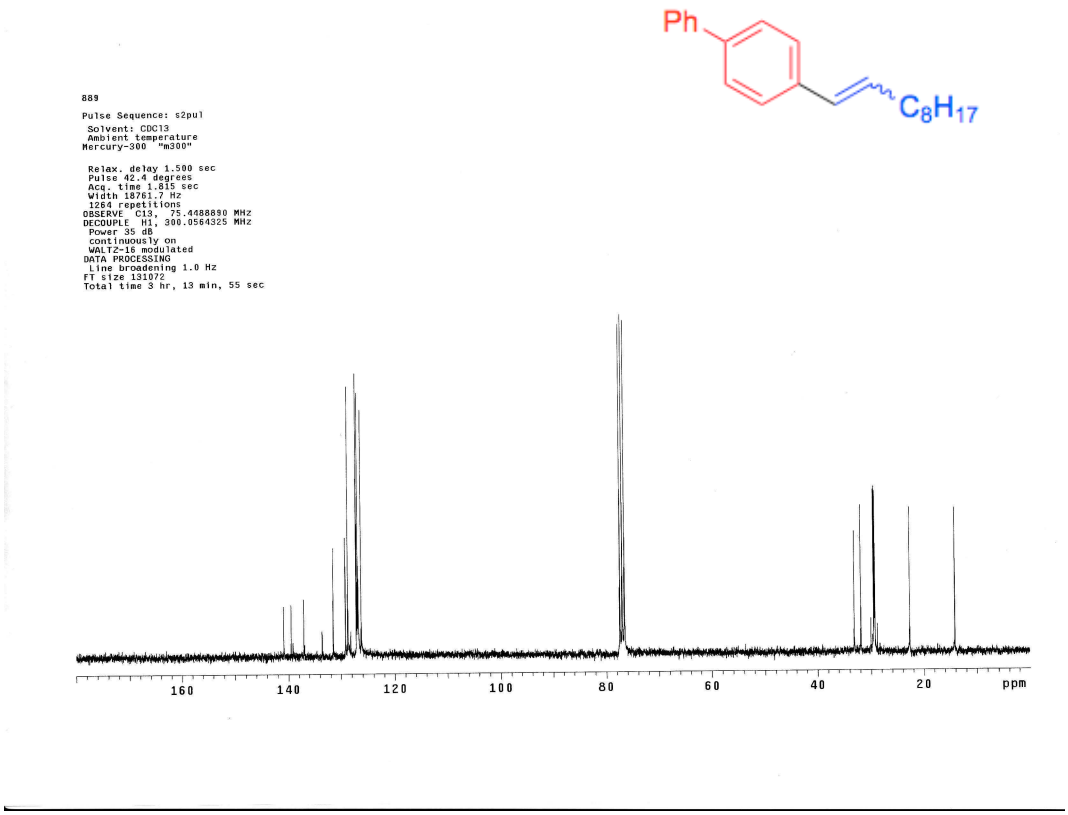


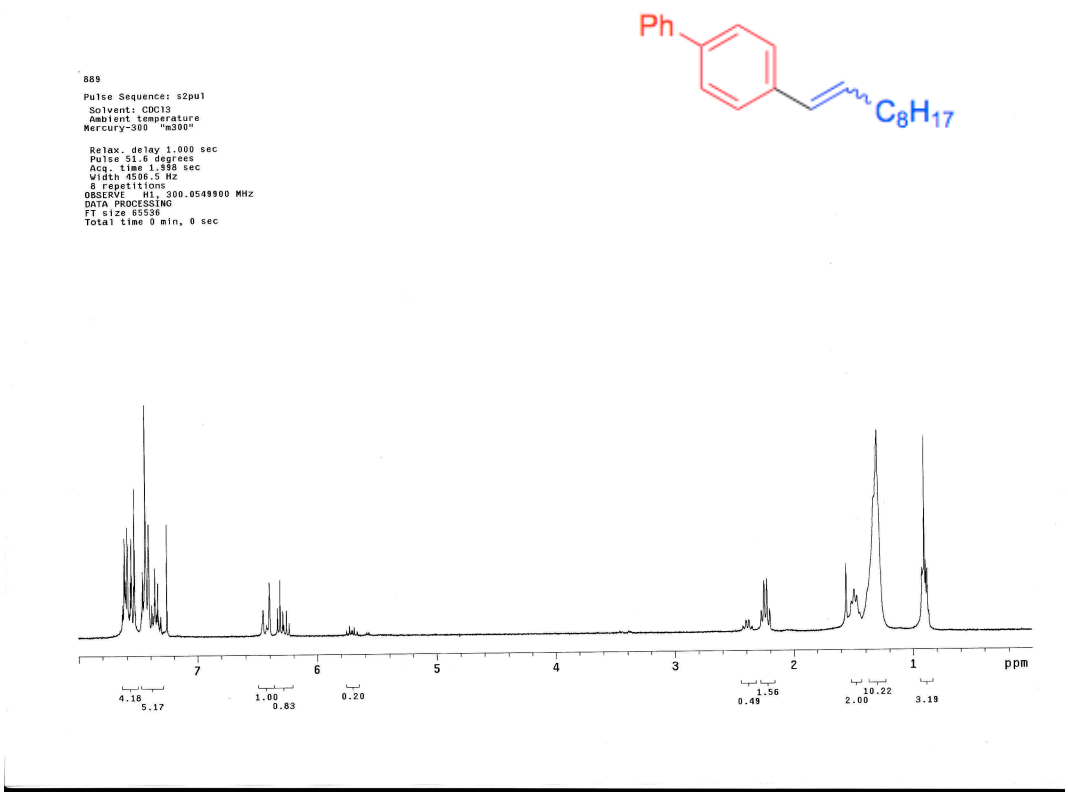


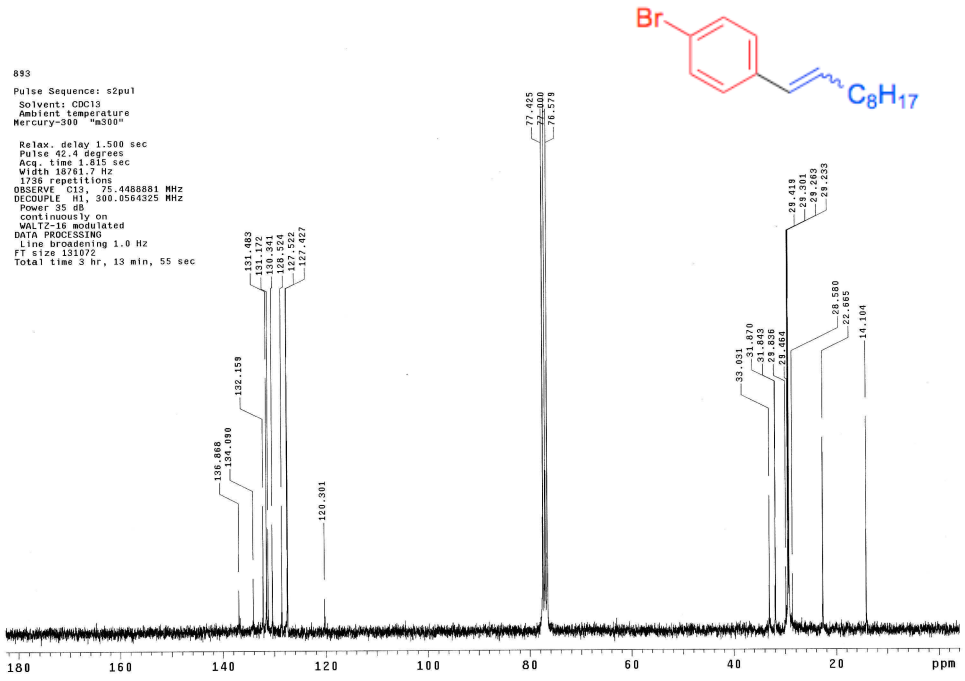
855

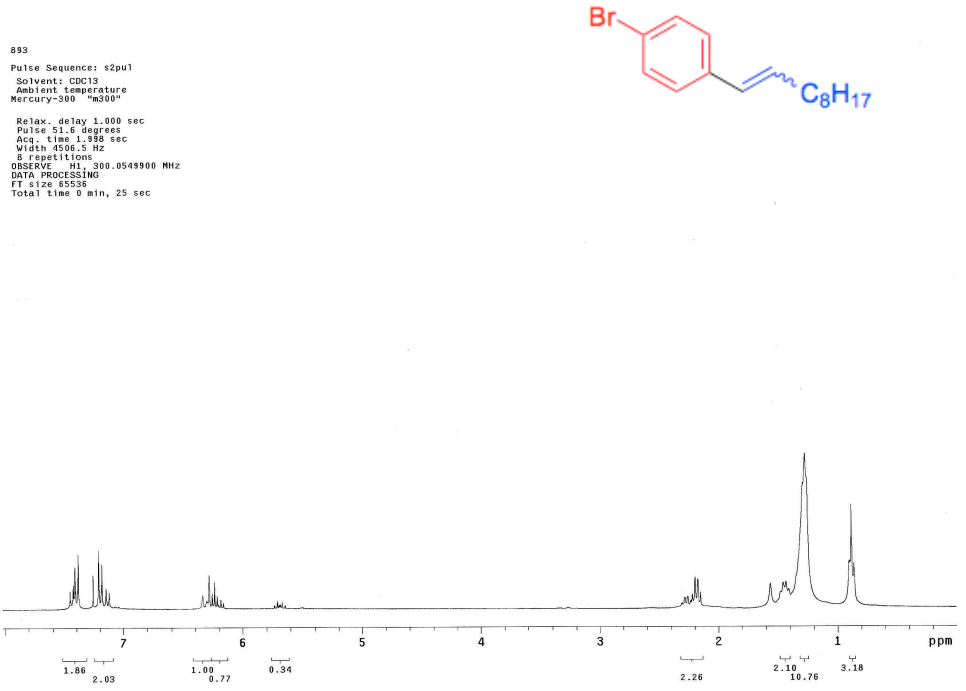

OMe
C_8H_{17}
156.940
156.165
133.145
131.892
129.892
127.708
126.998
126.539
126.312
124.100
123.917
120.590
119.941
110.721
110.280
77.421
77.000
76.575
55.418
55.383
33.494
31.885
31.655
29.946
29.506
29.472
29.384
29.290
28.690
22.676
14.108
180
160
140
120
100
80
60
40
20
ppm

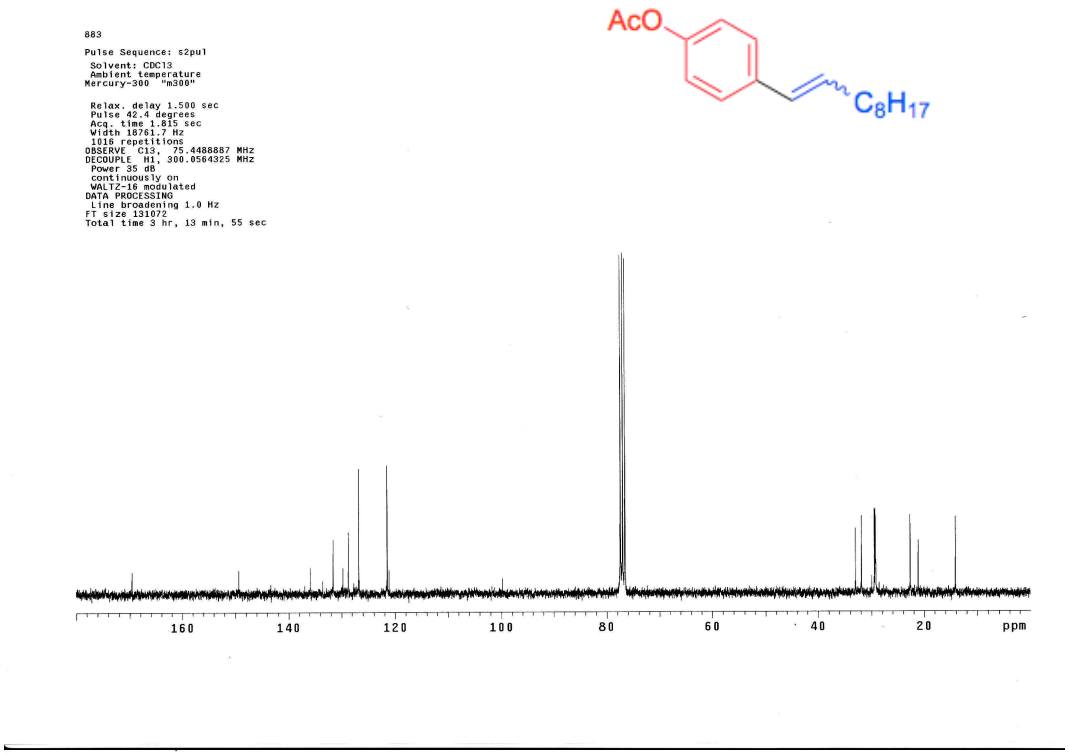

855
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 51.6 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
8 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 0 sec
OMe
C_8H_{17}
7
6
5
4
3
2
1
ppm
0.56
1.15
2.11
0.61
0.39
0.63
0.38
3.00
1.96
2.08
10.20
3.06

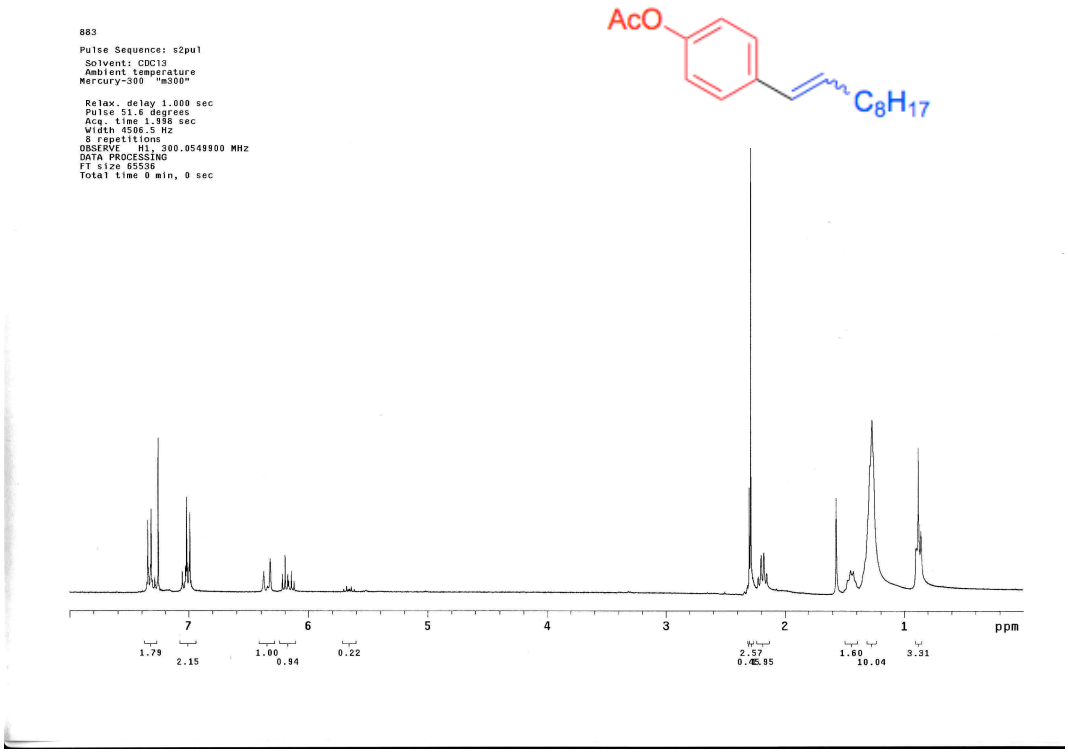

Ph
C8H17
889
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 42.4 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1264 repetitions
OBSERVE C13, 75.4488890 MHz
DECOUPLE H1, 300.0564325 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 3 hr, 13 min, 55 sec
160
140
120
100
80
60
40
20
ppm

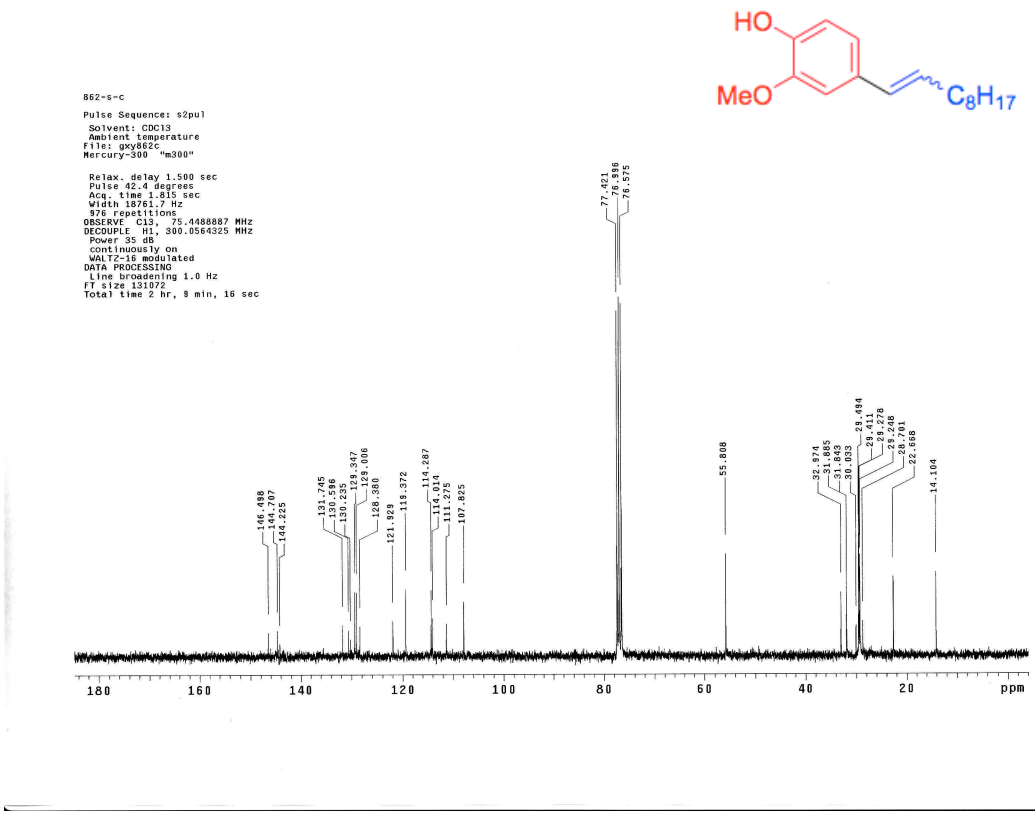

Ph
C8H17
889
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 51.6 degrees
Acq. time 1.898 sec
Width 4506.5 Hz
8 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 0 sec
7
6
5
4
3
2
1
ppm
4.18
5.17
1.00
0.83
0.20
0.49
1.56
2.00
10.22
3.19

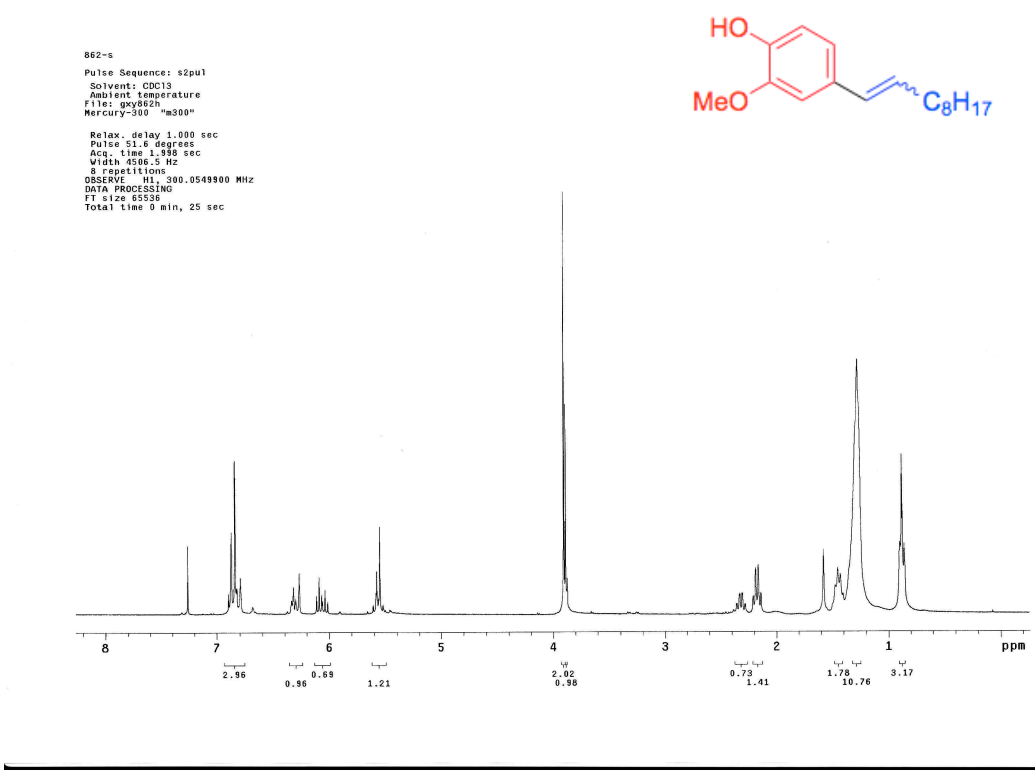

Br
C8H17
893
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 42.4 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1736 repetitions
OBSERVE C13, 75.4488881 MHz
DECOUPLE H1, 300.0564325 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 3 hr, 13 min, 55 sec
131.483
131.172
130.341
128.524
127.522
127.427
77.455
77.000
76.579
29.419
29.301
29.263
29.233
28.580
22.665
14.104
33.031
31.870
31.843
29.836
29.464
136.868
134.090
132.159
120.301
180
160
140
120
100
80
60
40
20
ppm

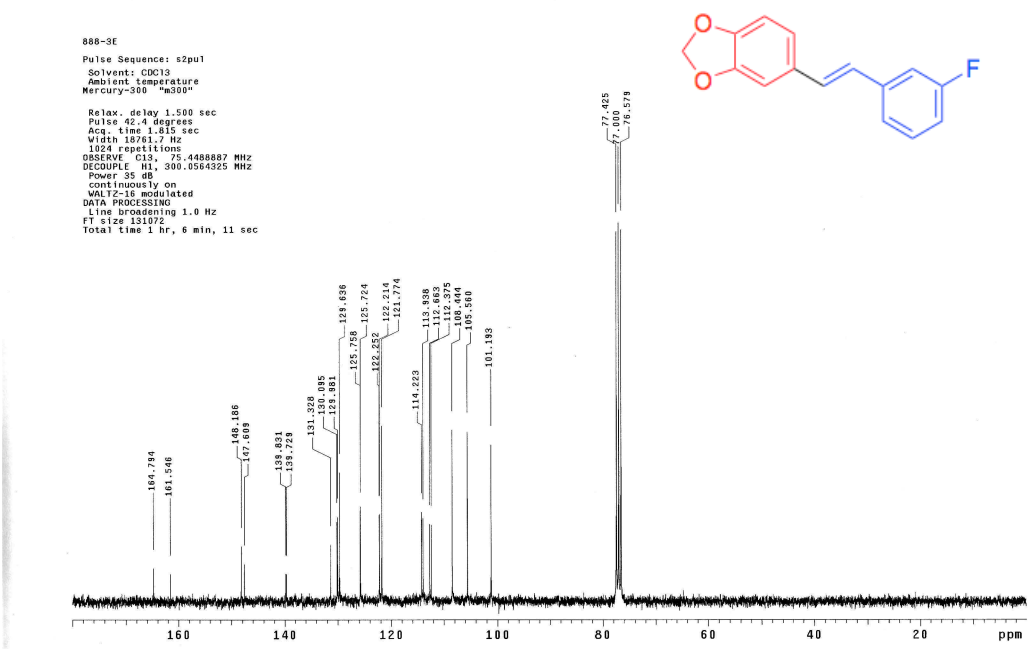

Br
C8H17
893
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 51.6 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
8 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 25 sec
7
6
5
4
3
2
1
ppm
1.86
2.03
1.00
0.77
0.34
2.26
2.10
10.76
3.18

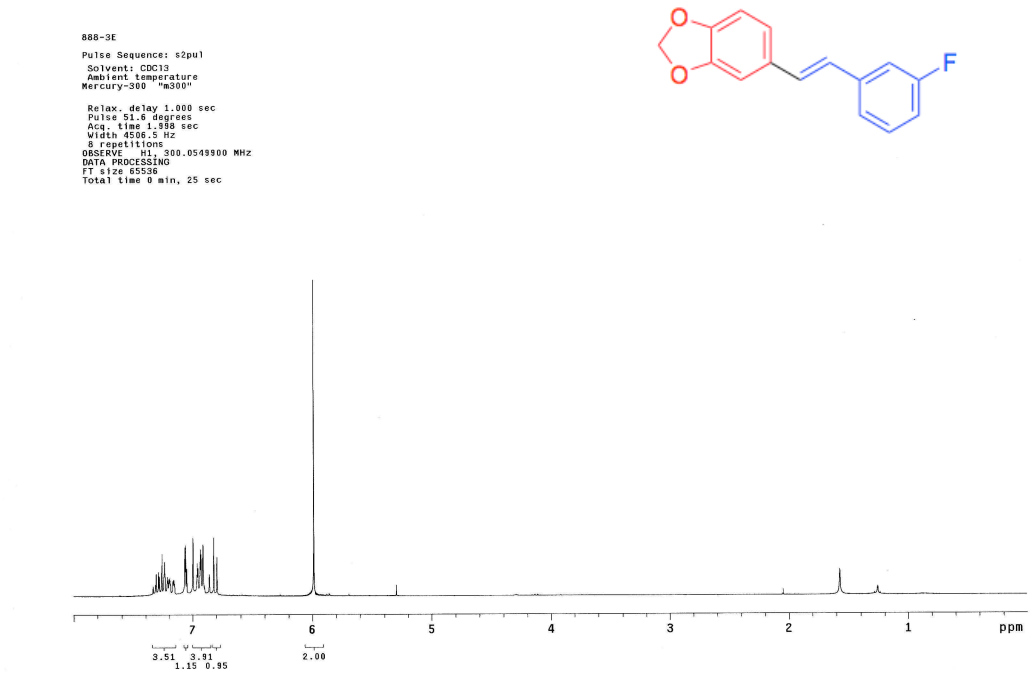

883
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 42.4 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1016 repetitions
OBSERVE C13, 75.4488887 MHz
DECOUPLE H1, 300.0564325 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 3 hr, 13 min, 55 sec
AcO
C8H17
160
140
120
100
80
60
40
20
ppm

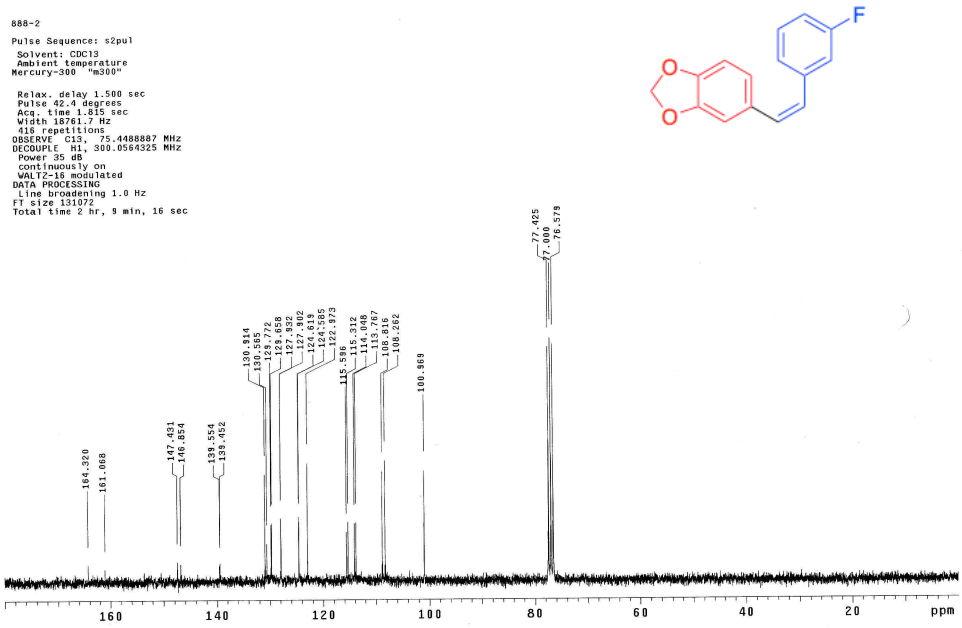

883
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 51.6 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
8 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 0 sec
AcO
C8H17
7
6
5
4
3
2
1
ppm
1.79
2.15
1.00
0.94
0.22
2.57
0.45
5.95
1.60
10.04
3.31

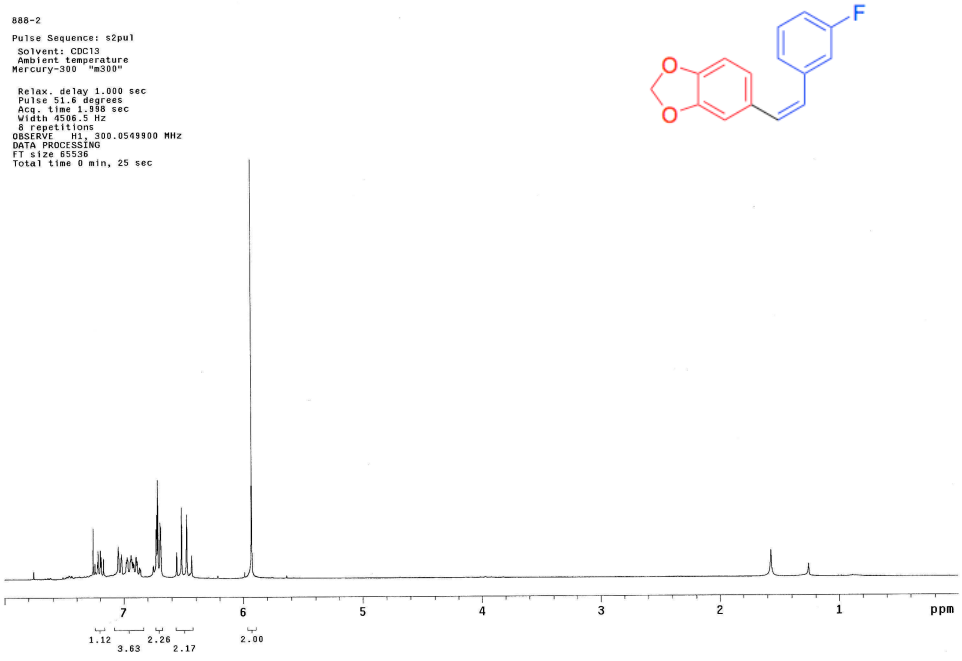

HO
MeO
C8H17
862-s-c
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: gxy862c
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 42.4 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
976 repetitions
OBSERVE C13, 75.4488887 MHz
DECOUPLE H1, 300.0564325 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 2 hr, 9 min, 16 sec
146.488
144.707
144.225
131.745
130.546
130.235
129.347
129.006
128.380
121.929
119.372
114.287
114.014
111.275
107.825
77.421
76.996
76.575
55.608
32.974
31.885
31.163
30.033
29.494
29.411
29.278
29.060
28.701
22.668
14.104
180
160
140
120
100
80
60
40
20
ppm


HO
MeO
C8H17
862-s
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: gxy862h
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 51.6 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
8 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 25 sec
8
7
6
5
4
3
2
1
ppm
2.96
0.96
0.69
1.21
2.02
0.98
0.73
1.41
1.78
10.76
3.17

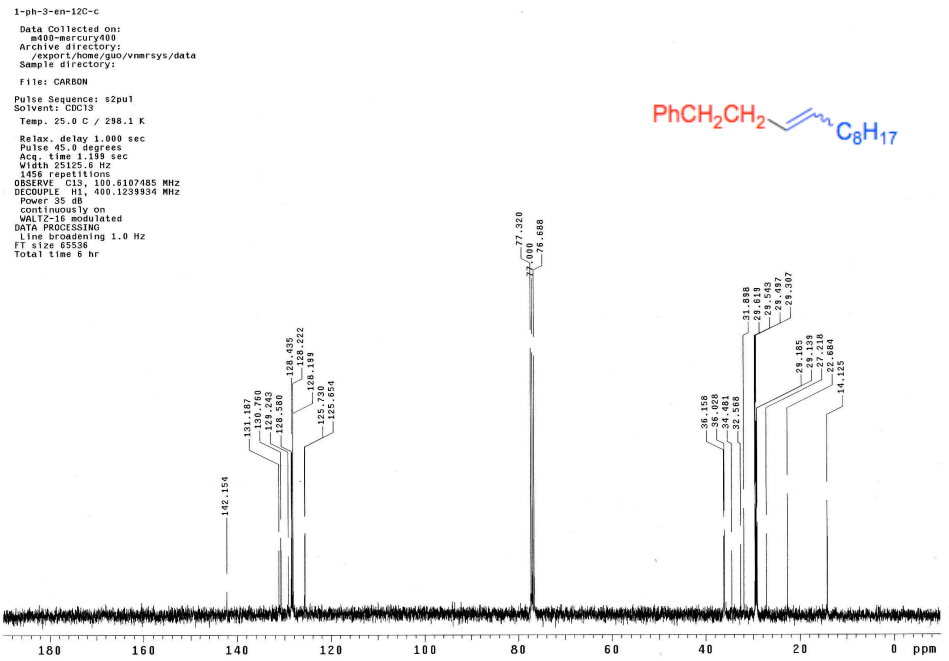

888-3E
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 42.4 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1024 repetitions
OBSERVE C13, 75.4488887 MHz
DECOUPLE H1, 300.0564325 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 6 min, 11 sec
O
O
F
77.425
77.000
76.579
164.734
161.546
148.186
147.688
139.831
139.728
131.328
130.095
129.861
129.636
125.758
125.724
122.252
122.214
121.774
114.223
113.938
112.663
112.375
108.414
105.560
101.193
160
140
120
100
80
60
40
20
ppm

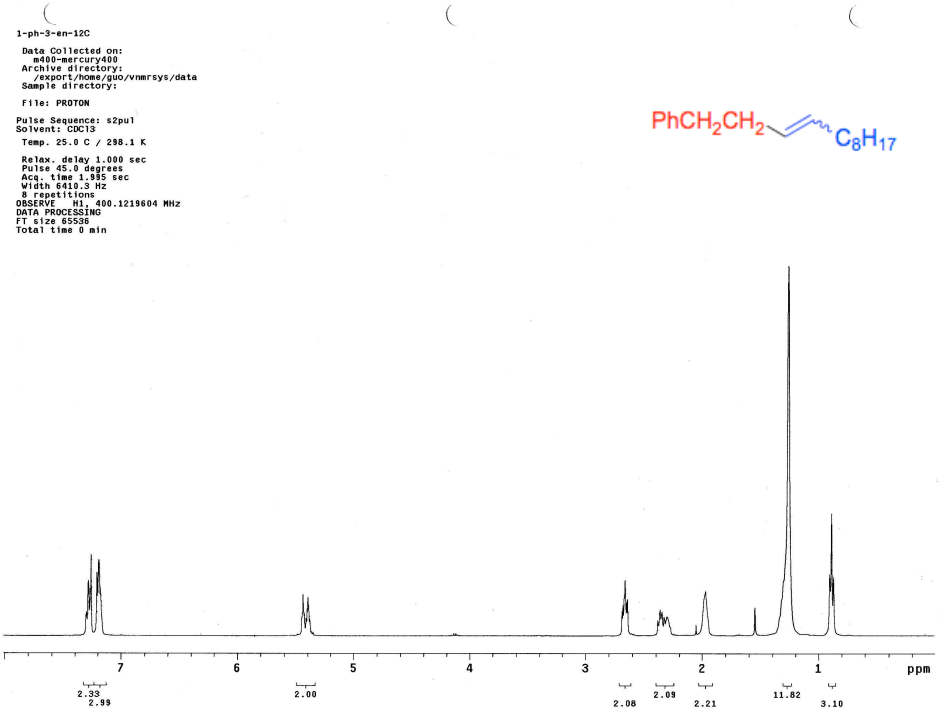

888-3E
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 51.6 degrees
Acq. time 1.898 sec
Width 4506.5 Hz
8 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 25 sec
O
O
F
7
6
5
4
3
2
1
ppm
3.51
3.91
1.15
0.95
2.00

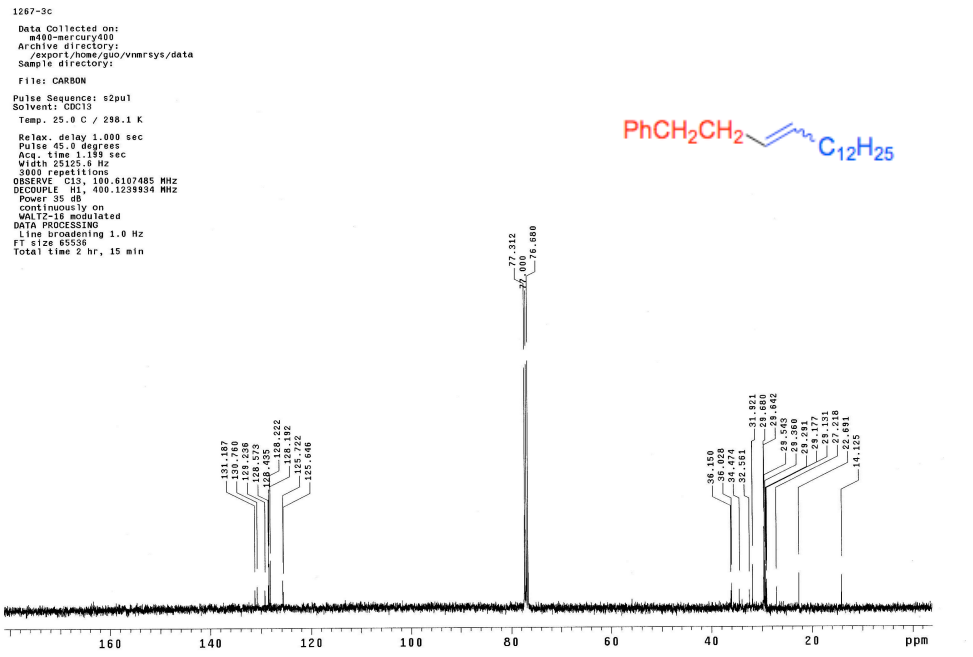

888-2
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.500 sec
Pulse 42.4 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
416 repetitions
OBSERVE C13, 75.4488887 MHz
DECOUPLE H1, 300.0564325 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 2 hr, 9 min, 16 sec
F
O
O
77.425
77.000
76.575
130.814
130.585
129.772
129.658
129.037
127.902
124.819
124.585
122.973
115.556
115.312
114.048
113.787
108.418
108.282
100.969
164.320
161.068
147.431
146.854
139.554
139.452
160
140
120
100
80
60
40
20
ppm

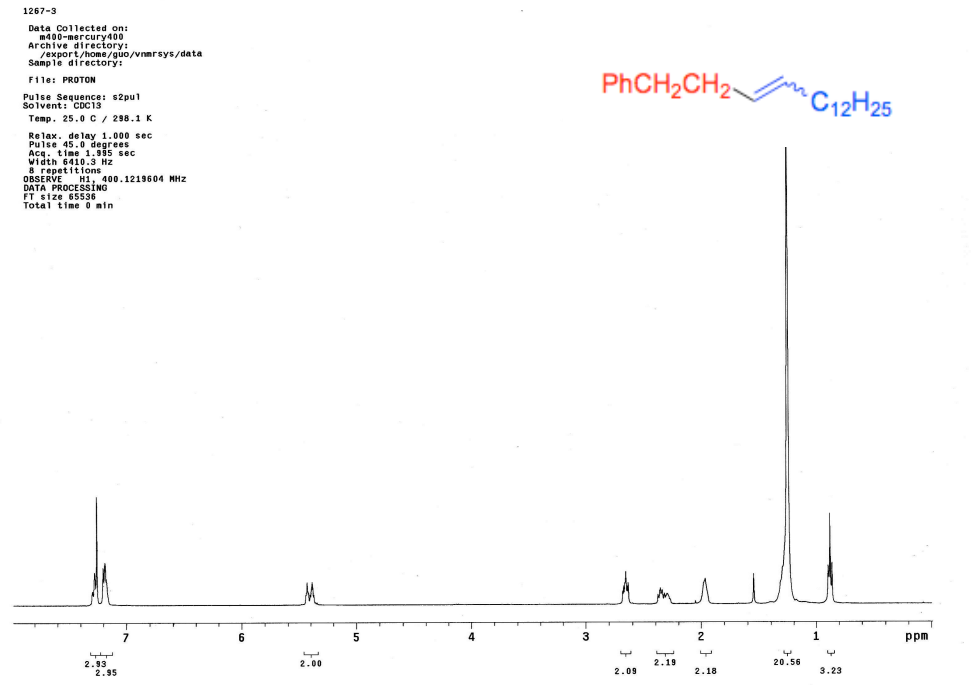

888-2
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 51.6 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
8 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 25 sec
F
O
O
7
6
5
4
3
2
1
ppm
1.12
3.63
2.26
2.17
2.00

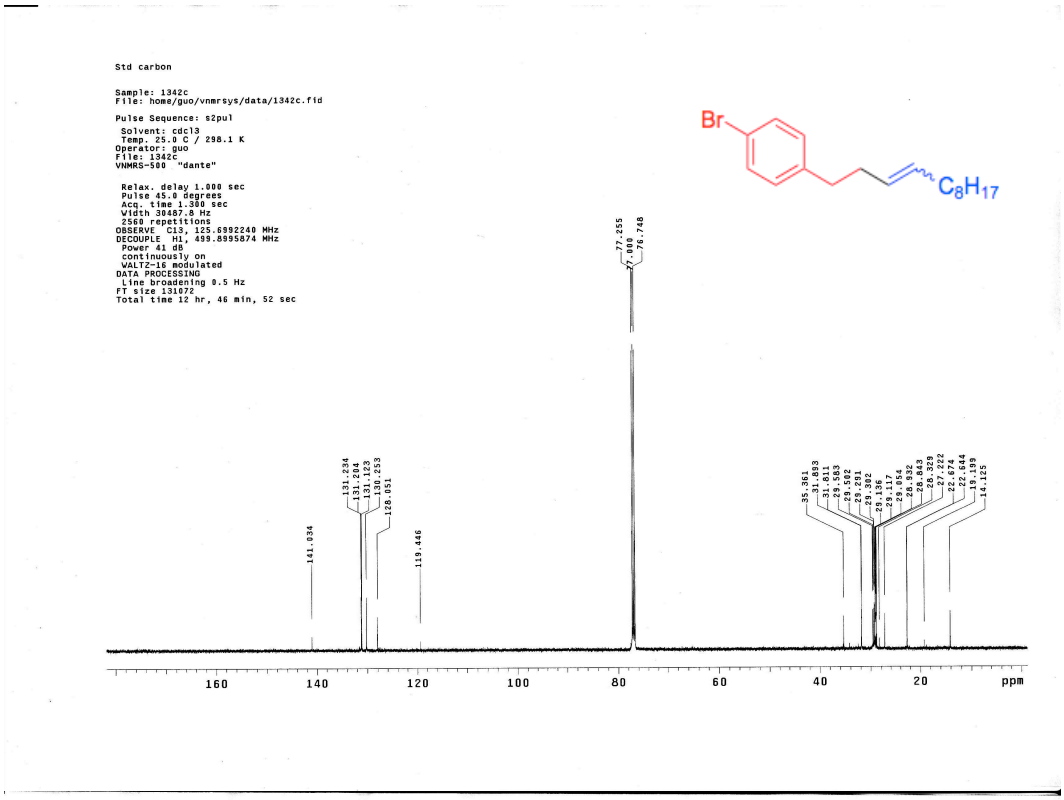
NMR spectrums for chapter 6

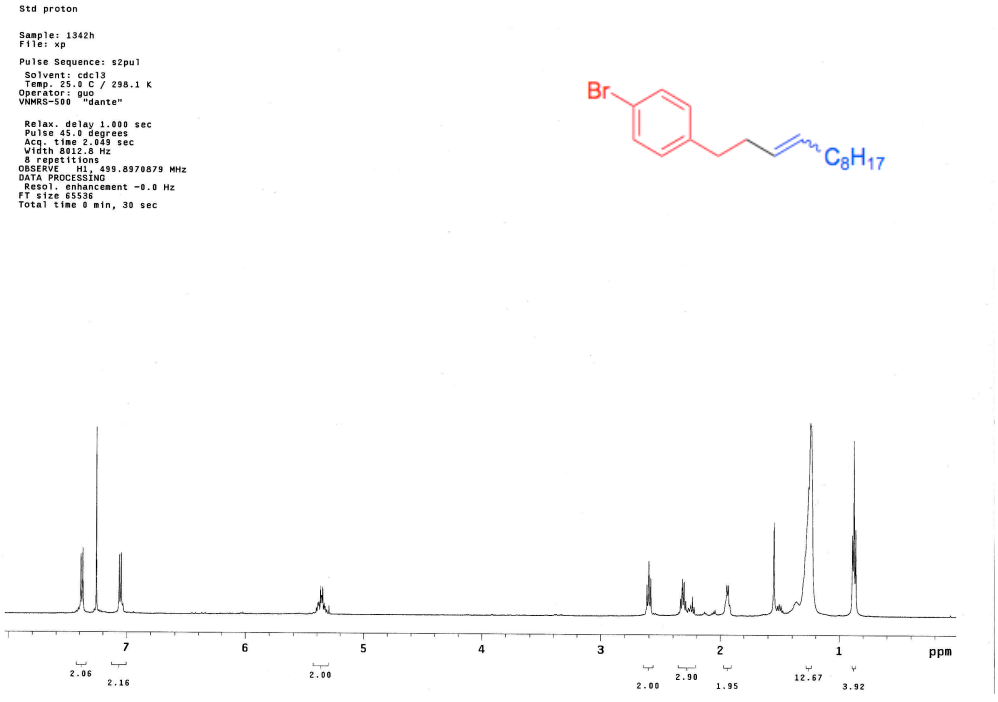


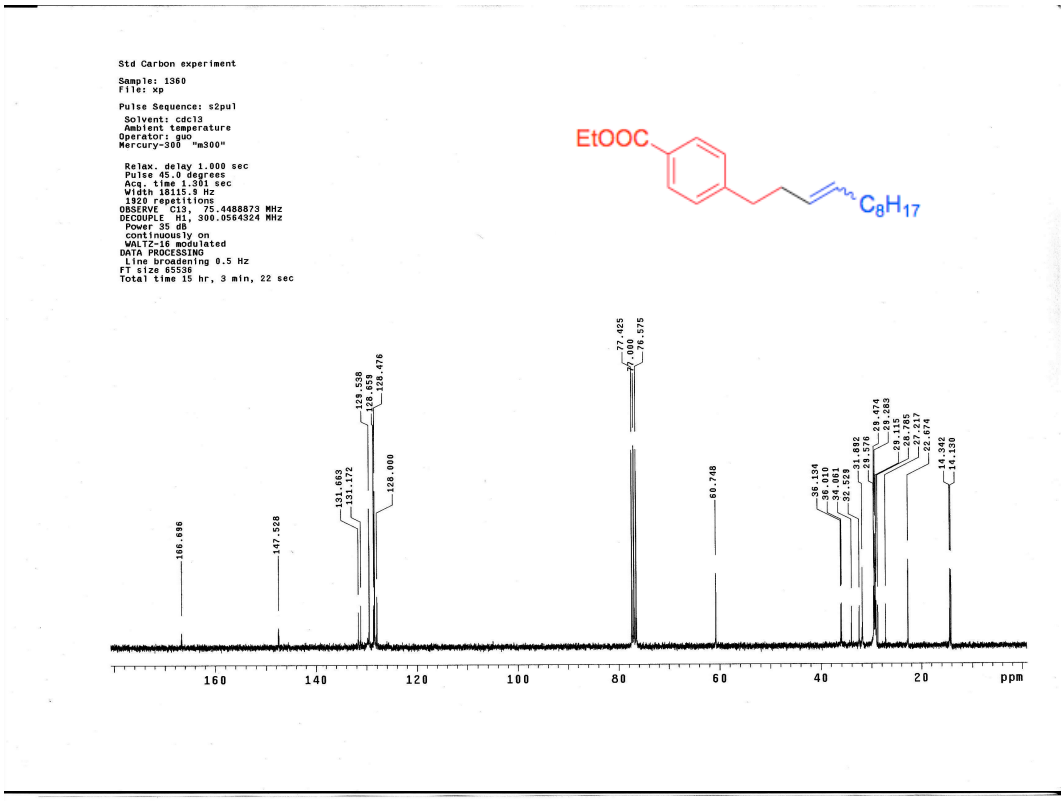


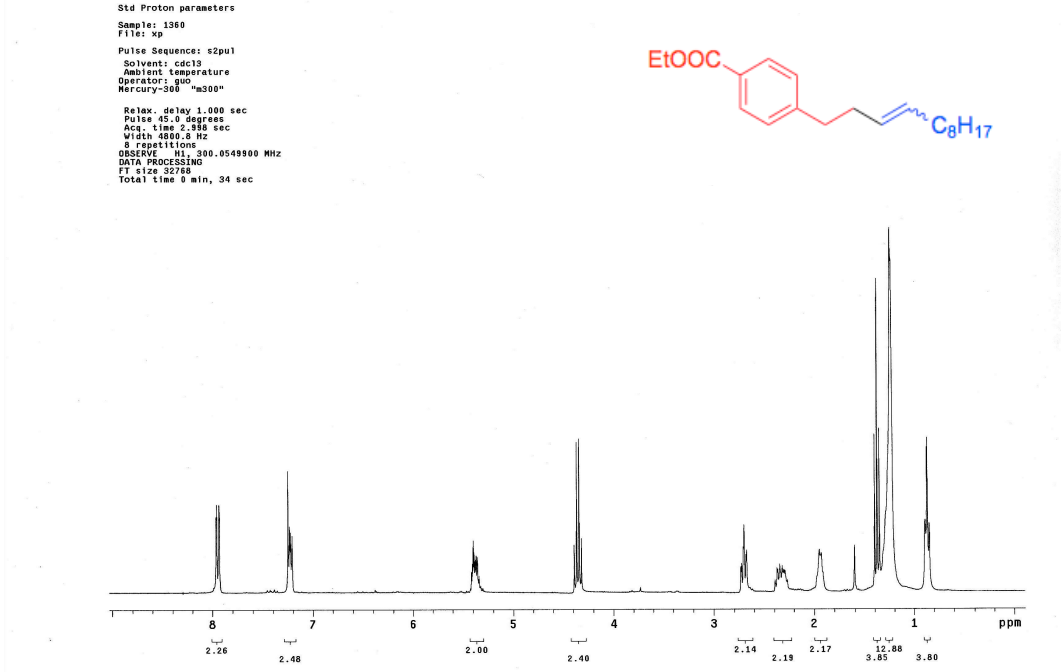

1267-3c
Data Collected on:
m400-mercury400
Archive directory:
/export/home/guo/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
3000 repetitions
OBSERVE C13, 100.6107485 MHz
DECOUPLE H1, 400.1239934 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 2 hr, 15 min
PhCH2CH2
C12H25
77.312
77.100
76.680
131.187
130.760
130.226
128.573
128.435
128.222
128.192
125.922
125.646
36.150
35.908
35.474
32.561
31.821
29.680
29.642
29.543
29.360
29.301
29.177
29.131
27.218
22.691
14.125
160
140
120
100
80
60
40
20
ppm

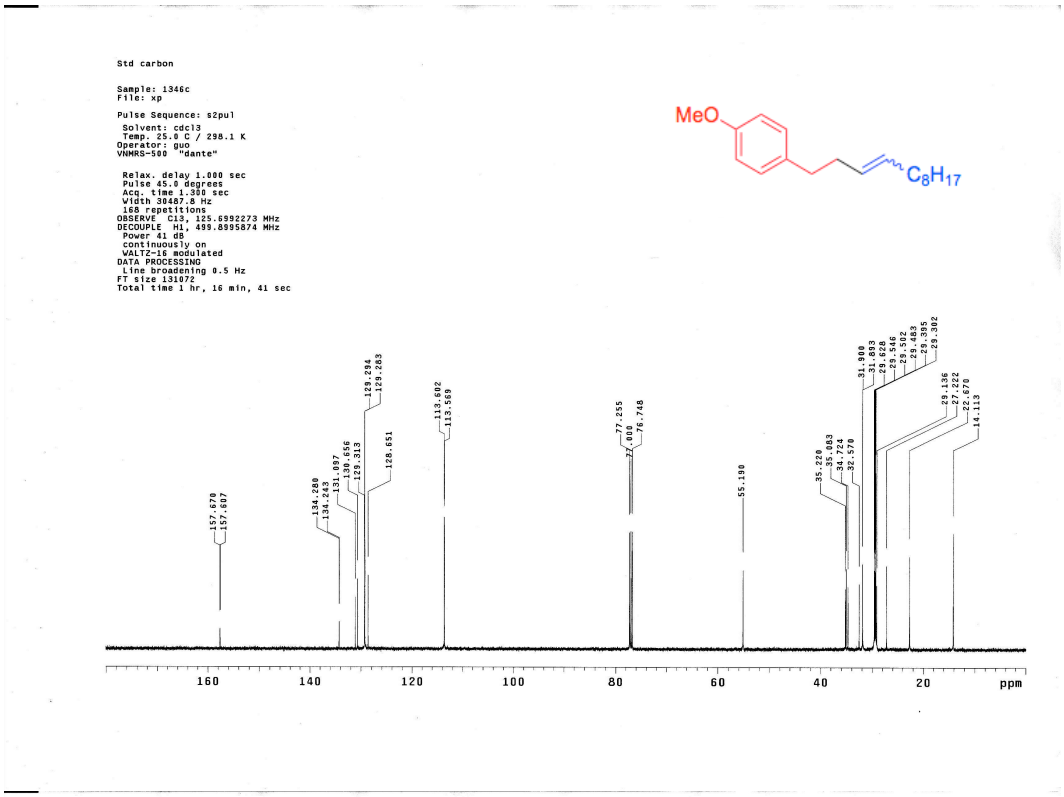

1267-3
Data Collected on:
m400-mercury400
Archive directory:
/export/home/guo/vnmrsys/data
Sample directory:
File: PROTON
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.995 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 400.1219604 MHz
DATA PROCESSING
FT size 65536
Total time 0 min
PhCH2CH2
C12H25
7
6
5
4
3
2
1
ppm
2.93
2.95
2.00
2.09
2.19
2.18
20.56
3.23

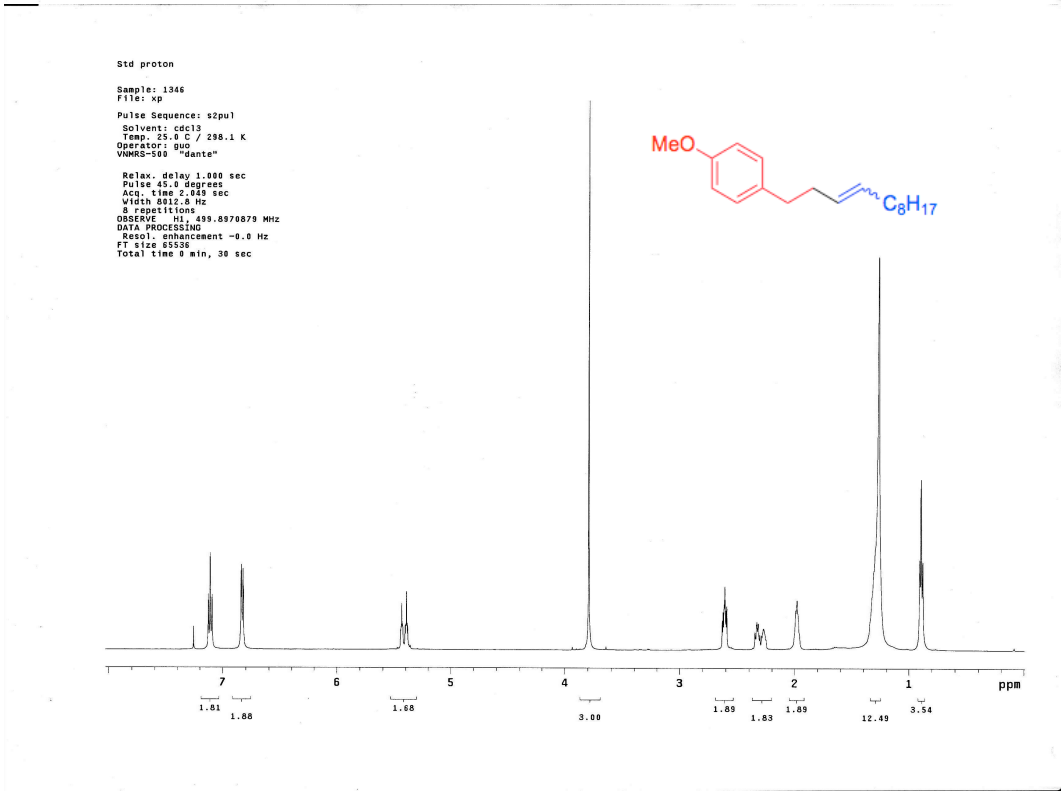

Std carbon
Sample: 1342c
File: home/guo/vnmrsys/data/1342c.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: guo
File: 1342c
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.380 sec
Width 30487.8 Hz
2560 repetitions
OBSERVE C13, 125.6992240 MHz
DECOUPLE H1, 499.8995874 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 12 hr, 46 min, 52 sec
Br
C8H17
77.255
77.000
76.748
141.934
131.234
131.204
131.123
130.253
128.091
119.446
35.361
31.893
31.611
30.553
29.592
29.291
29.302
29.185
29.117
29.054
28.932
28.844
28.328
27.222
22.674
22.664
19.199
14.125
160
140
120
100
80
60
40
20
ppm


Std proton
Sample: 1342h
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.048 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8970879 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
Br
C8H17
7
6
5
4
3
2
1
ppm
2.06
2.16
2.00
2.00
2.90
1.95
12.67
3.92


Std Carbon experiment
Sample: 1360
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: guo
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.301 sec
Width 18115.9 Hz
1920 repetitions
OBSERVE C13, 75.4488873 MHz
DECOUPLE H1, 300.0564324 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 15 hr, 3 min, 22 sec
EtOOC
C8H17
166.696
147.528
131.663
131.172
128.538
128.459
128.476
128.000
77.425
77.000
76.575
60.748
36.134
36.010
34.661
32.529
31.892
29.576
29.474
29.283
29.115
29.036
27.217
22.674
14.342
14.130
160
140
120
100
80
60
40
20
ppm


Std Proton parameters
Sample: 1360
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: guo
Mercury-300 "m300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.898 sec
Width 4800.8 Hz
8 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 34 sec
EtOOC
C8H17
8
7
6
5
4
3
2
1
ppm
2.26
2.48
2.00
2.40
2.14
2.19
2.17
12.88
3.85
3.80


Std carbon
Sample: 1346c
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
168 repetitions
OBSERVE C13, 125.6992273 MHz
DECOUPLE H1, 499.8995874 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 1 hr, 16 min, 41 sec
MeO
C8H17
157.670
157.607
134.280
134.243
131.097
130.656
129.313
129.294
129.263
128.651
113.602
113.569
77.255
77.004
76.748
55.190
35.220
35.083
34.724
32.570
31.900
31.693
29.628
29.566
29.502
29.483
29.395
29.302
29.136
27.222
22.670
14.113
160
140
120
100
80
60
40
20
ppm

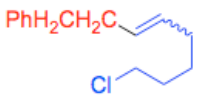

Std proton
Sample: 1346
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: guo
VNMRS-500 "dante"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.8970879 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
MeO
C8H17
7
6
5
4
3
2
1
ppm
1.81
1.88
1.68
3.00
1.89
1.83
1.89
12.49
3.54

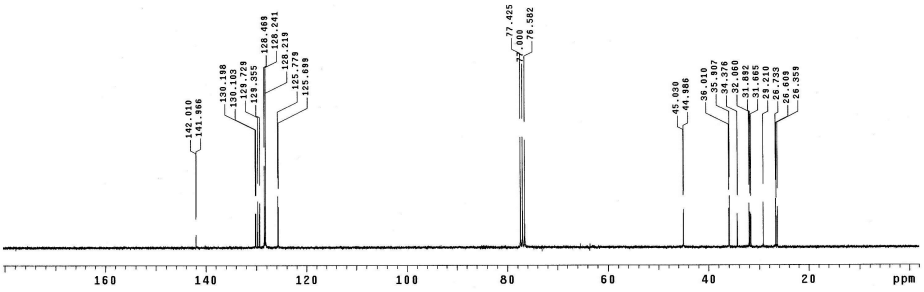
Std Carbon experiment

Sample: 1312
File: xp

Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: guo
Mercury-300 "m300"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.301 sec
Width 18115.9 Hz
1728 repetitions
OBSERVE C13, 75.4488862 MHz
DECOUPLE H1, 300.0564324 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 13 hr, 12 min, 55 sec





Std Proton parameters

Sample: 1312
File: xp

Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: guo
Mercury-300 "m300"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.998 sec
Width 4800.8 Hz
8 repetitions
OBSERVE H1, 300.0549900 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 34 sec