Application of Metallocarbene Decomposed from Diazoesters with Organic Azides and 1,2,3-Triazoles

by

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Abstract

Metallocarbenes, *in situ* generated from catalytic decomposition of diazocarbonyl compounds, contain only 6 electrons at carbon center, therefore are highly electrophilic. Over the years, the metallocarbene intermediates have been continuously explored as a versatile tool toward C-C and C-X bond formations. An overview regarding the reactivities and typical transformations of metallocarbene species is discussed in Chapter 1.

Chapter 2 discusses the use of organic azide as a nucleophile to intercept high-energy metallocarbene species. The α-imino ester was then generated in high yield. This transformation demonstrated a unique advantage over the traditional methods for α-imino ester synthesis since the only by-products are two equivalents of nitrogen gas. The subsequent trapping of α-imino esters with variety of carbon nucleophiles was also attempted to aim for generating α–quaternary amino esters; however, the process was not successful at the current stage.

1,2,3-Triazole compounds are one of the most important heterocycles in organic chemistry. From the past studies, these compounds are rather stable under oxidative, reductive, acidic and basic conditions due to its aromaticity. Chapter 3 illustrates a novel reactivity of stable 1,2,3-triazole compounds toward metallocarbenes, which process constructs a highly functionalized pyrroline-3-one heterocycles. A plausible reaction mechanism of this transformation has been rationalized yet inconclusive at current stage. The optimization and substrate scope of this reaction are detailed in Chapter 3.

For My Family

Acknowledgements

I would like to express my deepest gratitude to my immediate supervisor, Professor F. G. West, of my master degree for his unconditional supports and continuous encouragement. Thank you for encouraging me to freely explore our own ideas and always providing your invaluable feedback to our research projects.

Also, I would like to extend my million thanks to all past and present West's Group members who made my graduate study so unforgettable. Their kindness and friendliness have given me a great deal of positive energy to work in the chemistry lab.

At last, I must thank my husband and all family members for their continuous love and support. It is the inner strength within them that I finally sought after that made me break through my own dilemma. Thank you and I love all of you.

Table of Contents

List of Tables

Chapter 1

Chapter 2

Chapter 3

List of Figures

Chapter 1

Chapter 2

Chapter 3

List of Schemes

Chapter 1

Chapter 2

Chapter 3

List of Symbols and Abbreviations

^{1}H	proton
^{13}C	carbon-13
Å	angstrom
Ac	acetyl
acac	acetylacetonate
app.	apparent (spectral)
aq	aqueous solution
Ar	aryl
atm	atmosphere
BARF	tetrakis(pentafluorophenyl)borate
BHT	butylated hydroxytoluene
Bn	benzyl
br	broad (spectral)
Bu	butyl
^{o}C	degrees Celsius
calcd	calculated
cat.	indicates that the reagent was used in a catalytic amount
cm^{-1}	wave numbers
conc.	concentrated
d	day(s); doublet (spectral)
dd	doublet of doublets (spectral)
ddd	doublet of doublet of doublets (spectral)
DFT	density functional theory
DMAD	dimethyl acetylenedicarboxylate
DMB	2,2-dimethylbutane
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio

dt	doublet of triplets (spectral)
E^+	an unspecified electrophile
EDG	electron-donating group
EI	electron impact (mass spectrometry)
er	enantiomeric ratio
ESI	electrospray ionization (mass spectrometry)
Et	ethyl
EtOAc	ethyl acetate
equiv.	equivalent(s)
EWG	electron-withdrawing group
g	gram(s)
h	hour(s)
Hex	hexyl
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
hv	light
Hz	hertz
i-Pr	isopropyl
IR	infrared
J	coupling constant
kcal	kilocalories
L	liter(s)
LA	Lewis acid
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet (spectral)
M^+	generalized Lewis acid or protic acid; molecular ion
Me	methyl
mg	milligram(s)
MHz	megahertz

min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
Nu	an unspecified nucleophile
pbf	perfluorobutyrate
Ph	phenyl
ppm	parts per million
Pr	propyl
R	generalized alkyl group of substituent
R_f	retention factor (in chromatography)
rt	room temperature
s	singlet (spectral)
RVC	reticulated vitreous carbon
t	triplet (spectral)
T	temperature
t-Bu	*tert*-butyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid
δ	chemical shift

Chapter 1

Reactivity of Metal Carbenoids Derived From Diazocarbonyl Compounds

1.1 Background

Carbenes are neutral species containing a divalent carbon atom with only 6 valence electrons, and as a result are highly electrophilic.[1] Carbenes are classified as either singlet or triplet, depending upon their electronic states (Figure 1). Most carbenes are short lived and high-energy molecule which could undergo a wide variety of transformations such as C-H/X-H (X = O, N, S, B *etc*.) insertions,[2a] cyclopropanation,[2b] ylide generation,[2c] and rearrangements.[2d] Early on, carbenes were generated through photochemical or thermal decomposition of diazo or diazirine compounds, or from the reaction between chloroform and a strong base, however reactions of these types of carbenes were rather random owing to its high reactivity and consequent low selectivity.[3] It is not until the introduction of transition metals to generate free carbenes by Fischer in 1964,[4] the fascinating species have emerged as a powerful synthetic tool and are involved in many reactions of high synthetic interest.

Figure 1. Singlet and triplet carbene

In the early 1960s, free carbenes were found to be stabilized by coordination to transition metals *via* formal metal-to-carbon double bond, and some of them could even be isolated as metal-carbene complexes.[5] The donation of d-orbital electrons on the metal to the electron-deficient carbene carbon makes the carbene more stable and easier to work with. When this d-electron donation is moderate, as in the low oxidation state of middle and late d-series metals, the carbenoids still behave electrophilically, and are known as Fischer carbenes (Figure 1). When the electron donation from the metal to the carbene carbon is extreme, as in the early transition metals, the carbenes become nucleophilic in their reactivity and are known as Schrock carbenes.[6]

These carbene complexes are used as either stoichiometric reagents or catalysts for various transformations, some of which are different from those of free carbenes, such as the alkene metathesis[7a] and carbonyl alkenation[7b] (Wittig type).

Carbenoid is a rather vague term used for describing a molecule in which all carbons are tetravalent but still has properties resembling those of a carbene.[8] (The IUPAC definition of carbenoids is as "complexed carbene-like entities that display the reactivity characteristics of carbenes, either directly or by acting as sources of carbenes"[8b]) Often, the term carbenoid is used to describe organometallic species [$LnMCH_2X$] that contain a good leaving group and a metal-carbon bond at the same site, such as Simmons–Smith reagent (iodomethylzinc iodide) and the diazo compounds species (Figure 2).[9] Carbenoids are structurally related to singlet carbenes and possess similarly reactivity. Moreover, coordination of the carbene with the metal tempers the reactivity of the divalent carbon species and imparts greater selectivity to the reaction.

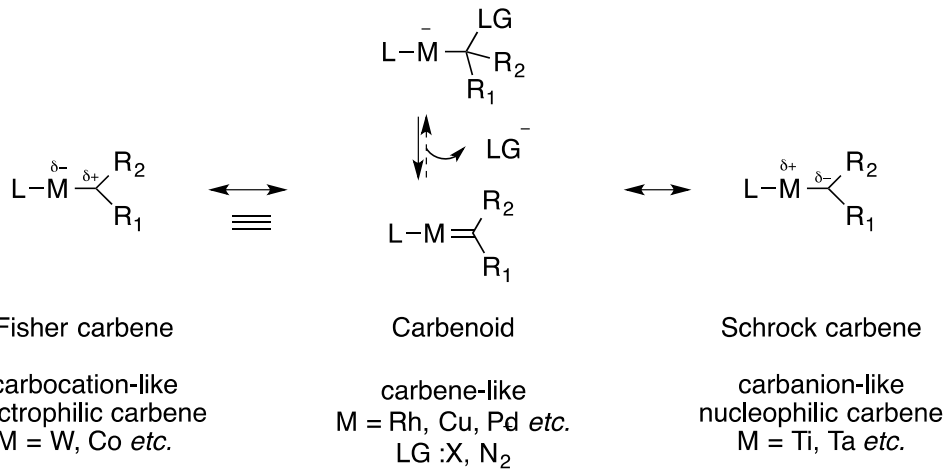


Figure 2. Classification of metal-carbene complexes

One of the most important classes of carbenoid precursors that are synthetically useful for catalytic reactions is diazo compounds.[10] Several of the late transition metals are capable of generating transitory metal carbenoids in this manner. Copper,[11a] iron,[11b] rhodium[11c] and ruthenium[11d] *etc.* are most commonly associated with this type of diazo decomposition. Alternative carbenoid precursors such as iodonium ylides,[12a] sulfonium ylides,[12b] sulfoxonium ylides,[12c] and phosphonium ylides[12d] have been explored, yet these are not discussed in detail in this chapter as their chemistry is usually similar with that of carbenoids derived from diazo

compounds. The *N*-sulfonyl-1,2,3-triazoles,[12e] which have recently been shown to be precursors to iminocarbenoid, will be discussed in Chapter 3.

Although the catalytic decomposition of diazo compounds had been known for almost a century, no mechanism was proposed until in 1952 by Yates.[13] There is now a general agreement that the Lewis acidic transition metal complexes **1** can be attacked by basic diazo compounds **2** to give diazonium ion **3**. The nitrogen extrusion from the electrophilic adduct **3** produces the metal-stabilized carbene complex **4**. Transfer of the electrophilic carbenoid entity to an electron-rich substrate (:B) regenerates the catalytic active MLn and completes the catalytic cycle.

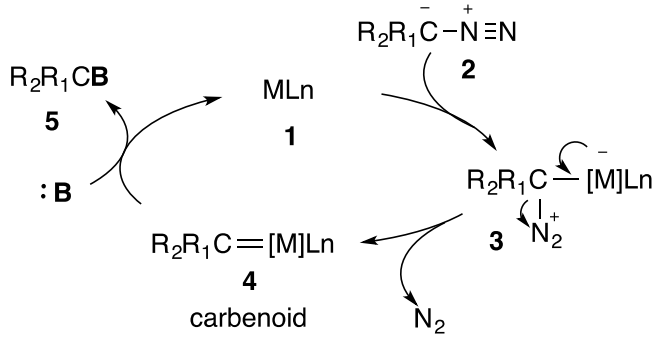
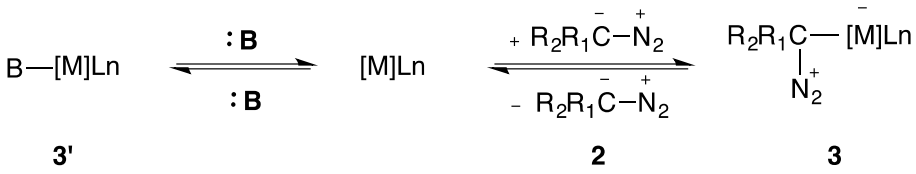


Figure 3. Mechanism of carbenoid formation by decomposition of diazo compounds

Lewis basic moieties (B:) can coordinate to the unsaturated metal catalyst, thereby inhibiting diazo decomposition (Scheme 1). The stability of **6** determines the degree to which association with diazo compounds is restricted. Amines, sulfides, and nitriles are all known to bind to Lewis acidic transition metal, and their presence can impede metallocarbene formation. Alkenes or arenes can also play this role with selected transition metal catalysts.[14] Halogenated hydrocarbons, typically dichloromethane and 1,2-dichloroethane, are not known to coordinate with catalytically active transition metal complexes, and therefore serve as useful solvents for the generation and transfers of carbenoids.[15]



Scheme 1. Inhibition of catalytic decomposition of diazo compound with Lewis base

The reactivity of transitory metal carbenoids is greatly influenced by the nature of the substituents on the carbenoid. Consequently, reviews of metal carbenoids often classify the carbenoids into three distinct groups, the acceptor carbenoids, the acceptor/acceptor carbenoids and the donor/acceptor carbenoids.[16] The terms "acceptor" and "donor" refer, respectively, to the withdrawal and donation of electron density by the functional groups flanking the carbenoid (Figure 4). Generally, an acceptor substituent makes the carbenoid species more electrophilic and more reactive, whereas a donor group makes the carbenoid more stable and thus more selective in the reaction.[17]

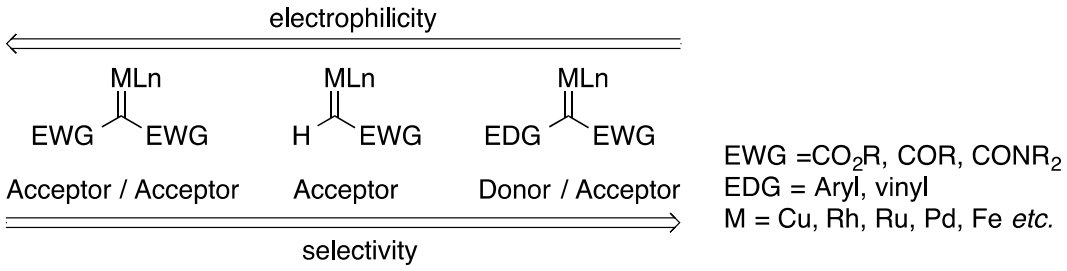


Figure 4. Classification of carbenoid intermediates

It should be noted that the transition metal catalyzed diazo decomposition is dependent not only on the Lewis acidity of the transition metal but also on the basicity of the diazo compounds. Among the diazocarbonyl precursors, those with more withdrawing groups tend to be more stable than those with fewer withdrawing groups since the formal negative charge on diazo carbon can be further delocalized into the additional groups (Figure 5).[18] Thus, a larger amount of energy is required for its decomposition to generate a metal carbene. In general, higher temperatures are required for the decomposition of an acceptor/acceptor diazocarbonyl than for acceptor/donor. Additionally, dichloromethane is the preferred solvent of diazo decomposition as discussed above. However, with the less reactive diazomalonate, and diazoacetoacetate, high temperatures are often required, thus solvents such as 1,2-dichloromethane, benzene and toluene are most often employed.[14,15]

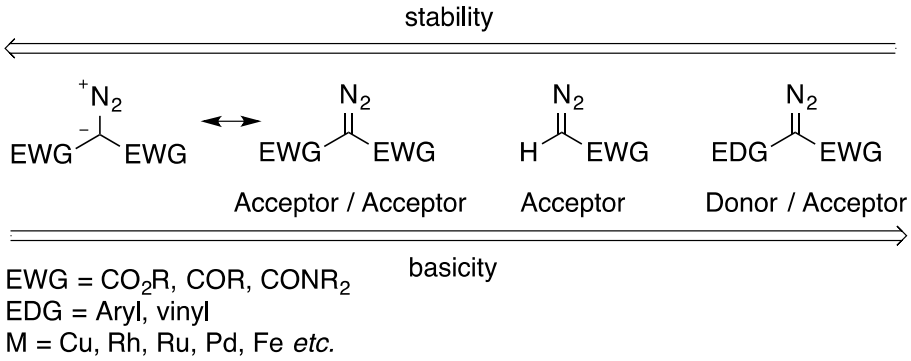


Figure 5. Stability and reactivity of carbenoid precursors in catalytic decomposition

Catalyst design remains a central issue in transition metal catalyzed reactions of diazo compounds. The reactivity profile of these transient metal-stabilized carbenoids is highly dependent on the structure of the carbenoid and the type of the metal. Professor Padwa noted this problem succinctly: 'A survey of the literature dealing with the topic of catalytic diazo decomposition can be both enlightening and frustrating.'[17a] A wide variety of transformations can occur with these transitory carbenoids, such as X-H (X= C, N, O *etc.*) insertions,[17b] cyclopropanation,[19a] ylide generation[19b] and rearrangements[19d] *etc.* and their chemoselectivity was found to be depended on the metal species, ligands and substrates.

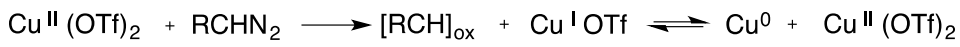
Chapter 1 will focus on introducing the general reactivities of selected transition metal catalysts, mainly of copper and rhodium derived catalysts. Recent advances in metal catalyzed diazocarbonyl decomposition and transformations, including intermolecular cyclopropanation, C-H insertion, oxygen and sulfur ylide generation from carbenoid will be discussed subsequently. More detailed nitrogen ylide generation and subsequent reactions will be discussed in Chapter 2.

1.2 Catalysis

1.2.1 Copper Catalysts

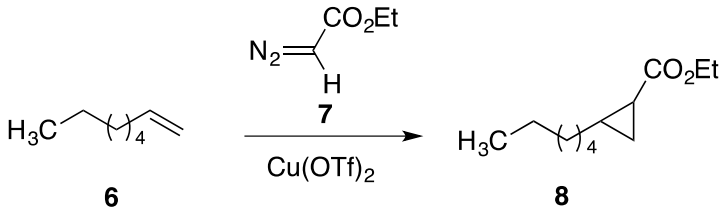
Copper bronze and Cu(II) sulfate ($CuSO_4$) are the oldest of the copper catalysts employed for diazo decomposition.[20] Although these catalysts are still employed today, their use has decreased significantly with the advent of homogeneous copper catalysts such as bis(acety1acetonate)Cu(II) ($Cu(acac)_2$), or trialkyl or triarylphosphite complexes of CuCl.[21] In 1972, Salomon and Kochi published a benchmark article that has greatly influenced the basic

understanding of copper catalysis in diazo decomposition and carbenoid transformation.[22] They found that copper(II) triflate was an active catalyst for the cyclopropanation of olefins with diazo compounds (Scheme 2). However, they observed that the reaction mixture was darkened as the reaction progressed and was almost black when completed. If additional Cu(II) triflate was added at this point the darkened reaction mixture rapidly lightened to a clear pale blue solution, from which Cu(I) triflate was isolated in good to excellent yields. It was found that the dark coloration was attributed to colloidal copper (0). When external Cu(II) was added, the Cu(0) was re-oxidized into Cu(I). This observation shows that diazo compounds are capable of reducing Cu(II) in the process of cyclopropanation (Scheme 2).



Scheme 2. Reducing Cu(II) with diazo compounds

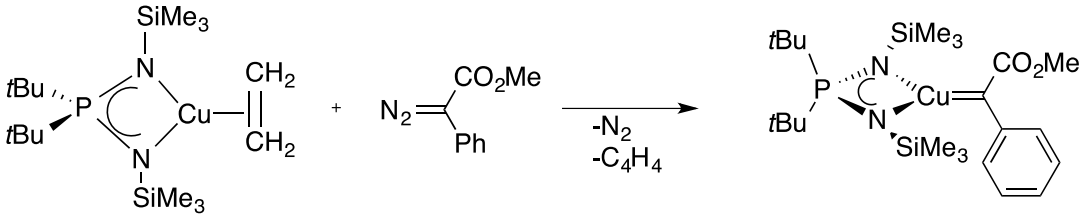
Another experiment was subsequently conducted with incremental addition of ethyl diazoacetate **7** into 1-octene **6** and $Cu(OTf)_2$. They found that the yield of ethyl 2-hexylcyclopropanecarboxylate **8** was negligible initially after addition of one equivalent of ethyl diazoacetate **7** relative to Cu(II) triflate. As the addition of ethyl diazoacetate **7** was continued, the yield of **8** eventually approached quantitative (based on the incremental amounts of ethyl diazoacetate added). Moreover, the addition of more Cu(II) triflate at this point caused a sharp drop in the relative yield of **8**, but with continued addition of ethyl diazoacetate the yield increased again. The reaction mixture remained homogeneous during these manipulations and the Cu(I) triflate was isolated in excellent yields.



Scheme 3. Incremental addition experiment

Based on these observations, they concluded that Cu(II) triflate did not catalyze the cyclopropanation. Instead, Cu(I) triflate, which is produced from Cu(II) triflate via in situ reduction by the diazo compound, was the genuine reactive species in diazo decomposition and cyclopropanation.

Although extension of this interpretation to other copper catalysts remained controversial for years, there is a general agreement that the active form of copper catalyst exists in the Cu(I) oxidation state.[23] In 2001, the structure of a Cu(I) carbenoid complex was for the first time elucidated by Hofmann[24] as shown in Scheme 4. The Cu(I) complex **11** was successfully synthesized from Cu(I) ethylene complex **9** with methyl 2-phenyl-2-diazoacetate **10** and characterized spectroscopically.

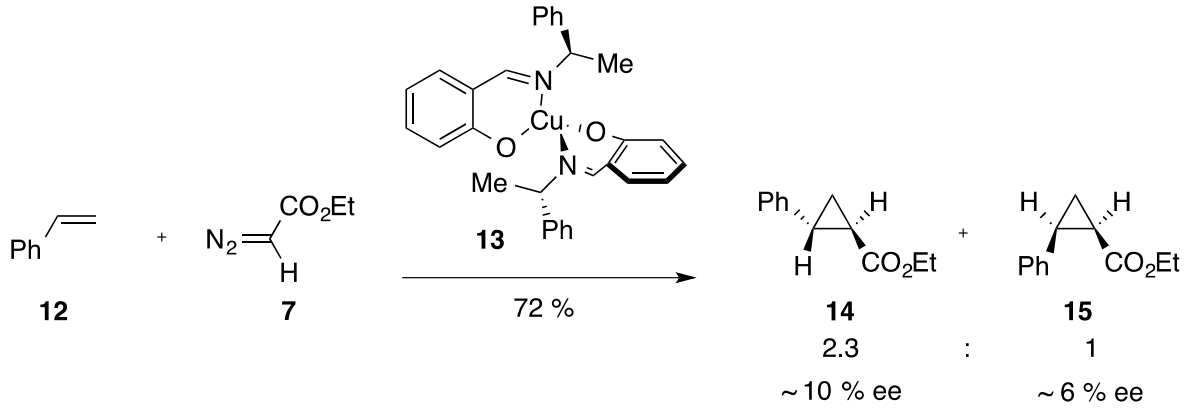


9 **10** **11**

Scheme 4. Cu(I) carbenoid complex

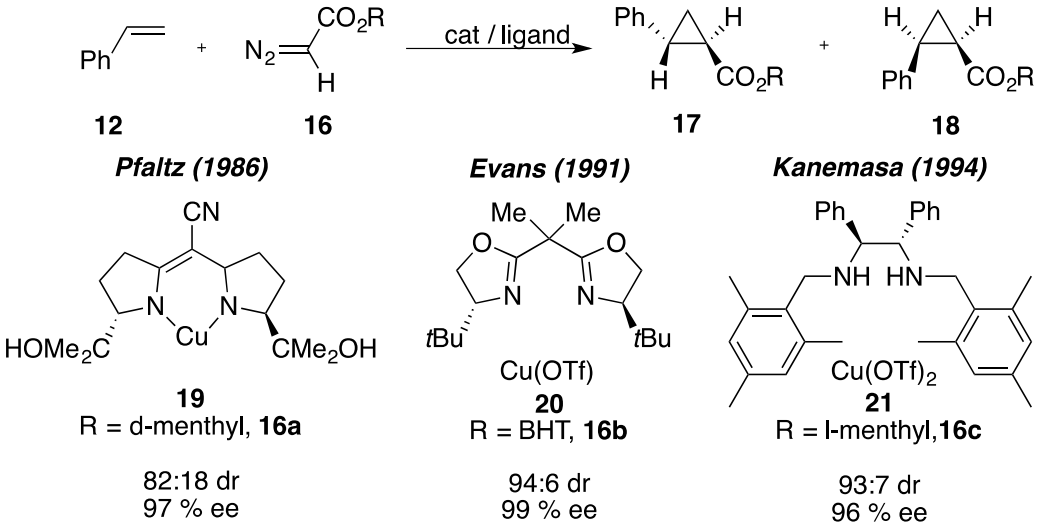
Due to the stabilities and general ease of preparation and handling, and their ready in situ reduction, Cu(II) complexes have been utilized as the pre-catalysts in preference of direct use of air sensitive Cu(I) complexes.[25] It should be noted that two bidentate ligands such as acetylacetonate are bound to Cu(II), but upon reduction by diazo compounds to Cu(I) one of these bidentate ligands is presumed to dissociate from copper.[26]

The first enantioselective transformation of copper carbenoid was reported in 1966,[27] by Nozaki and co-workers. Schiff base 2-phenethylamine copper complex **13** catalyzed the cyclopropanation of styrene **12** with ethyl diazoacetate **7** to give products **14** and **15** in 72% yield with 10% and 6 % ee respectively (Scheme 5).



Scheme 5. First report of enantioselective cyclopropanation with chiral salicylaldimine ligand

Although the enantioselectivity was low, this seminal report led to the great interest in designing chiral ligands for copper complexes. Since then, a wide range of asymmetric copper catalysts were reported including semicorrin derivatives **19**,[28a] bis-oxazoline (BOX) **20**[28b] and 1,2-diamines **21** (Scheme 6).[28c]



Scheme 6. Highlighted copper chiral ligands

Electronic influences of copper ligands were evaluated in a series of substituted Cu(II) acetylacetonates, since these changes would allow electronic modulation of the metal center without changing the overall geometry of the complex. Increased fluorine substitution (**23** and **24**) appears to increase the reactivity of the carbenoid yet decrease selectivity in reactions (Figure 6).[29]

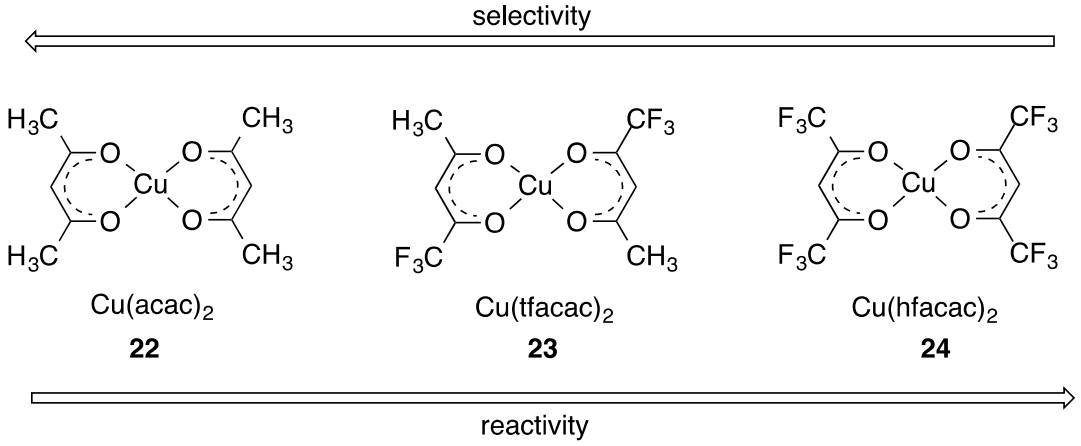
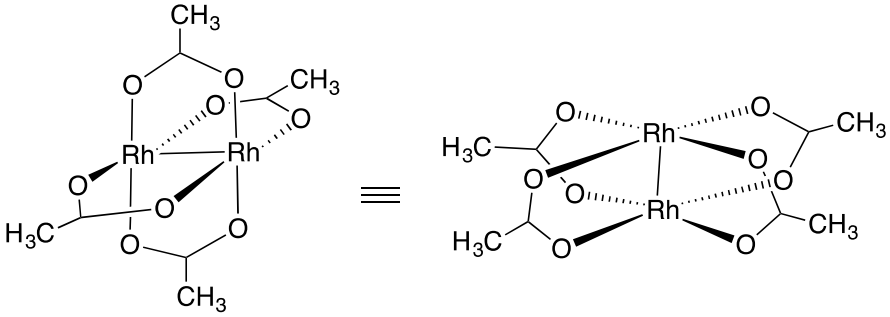


Figure 6. Cu(II) acetylacetonate complexes and its derivatives

1.2.2 Rhodium Catalysts

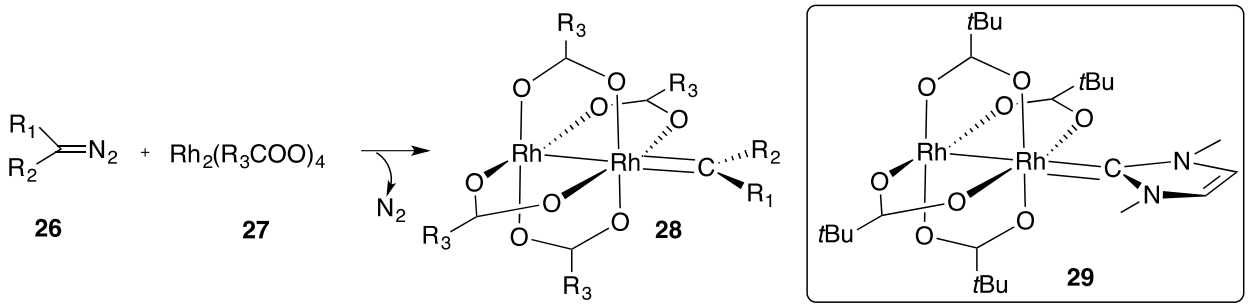
Dirhodium(II) complexes, discovered by Teyssie and co-workers in 1973,[31] are widely recognized as one of the most effective classes of catalysts for diazo decomposition and selective transformations.[16,17,30] These catalysts are usually easily made by direct synthesis from hydrous rhodium trichloride [Rh(III)Cl_3(H_2O)x] with a carboxylic acid such as acetic acid.[18,32] The resulting dimeric Rh(II) complex **25** has the 'lantern' or 'paddlewheel' structure consisting of a Rh-Rh single bound cluster surrounded by four acetate ligands, each of which is bonded to both rhodium atoms (Figure 7).



25

Figure 7. Structure of dirhodium(II) tetraacetate

The reactive Rh(II) carbenoid **28** was generated from coordination of the diazo carbon of **26** onto the electrophilic dirhodium dimer **27** followed by nitrogen extrusion (Scheme 7).[33] The detailed structure of such intermediates was not elucidated until 2001. For the first time a stable dirhodium(II) tetracarboxylate carbenoid **29** was isolated and its structure was determined by X-ray crystallography.[34]



26 **27** **28** **29**

Scheme 7. Decomposition of diazo by rhodium(II) dimer

A growing number of examples has demonstrated that the reactivity of rhodium carbenoids is

greatly affected by the electronic nature of the bridging ligands by participating in π back-bonding on the metal.[35] As a result, reactivity and selectivity of rhodium carbenoids can be tuned by the choice of ligands. The more electron density a ligand removes, the more electrophilic yet less selective the carbenoid becomes. Conversely, the more electron donating the ligand is, the more stable the carbenoid becomes. Dirhodium(II) perfluorobutyrate **31**, ($Rh_2(pfb)_4$) is the most reactive among the dirhodium(II) carboxylate catalysts and, often, the least selective in diazo decomposition reactions.[35,36] In contrast, dirhodium(II) tetraacetamide **30**, ($Rh_2(acam)_4$) in which the ligand coordinates rhodium centers with both oxygen and nitrogen donor atoms, is less reactive than dirhodium(II) carboxylates towards diazo decomposition but, more selective in metal carbene transformations (Figure 8).

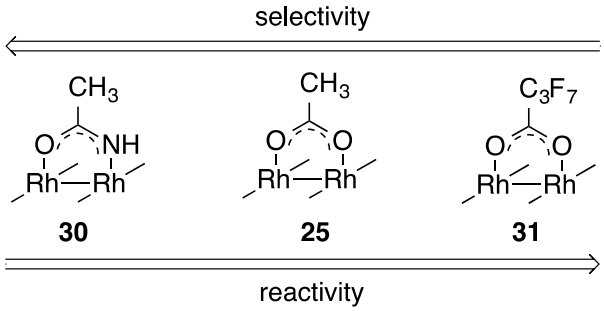
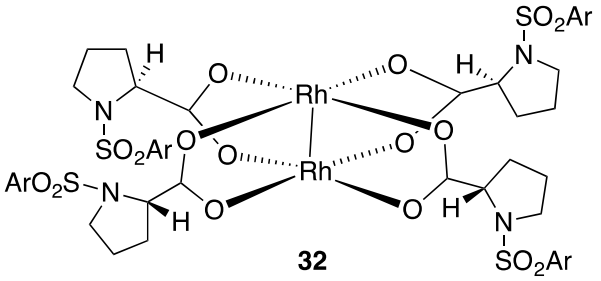


Figure 8. General trend of ligand effect on rhodium carbenoid

The unique structures of dirhodium(II) carboxylates have led to the development of a class of chiral dirhodium(II) complexes.[37] High enantiocontrol in carbenoid reactions has been achieved with the use of these catalysts. For example, proline and phthalimide derived rhodium (II) carboxylates **32** and **33** have shown good selectivity toward cyclopropanation[38,56] and C-H insertion reactions (Scheme 8). [16,17,39]



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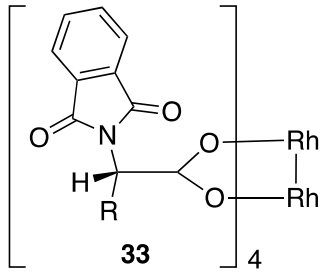
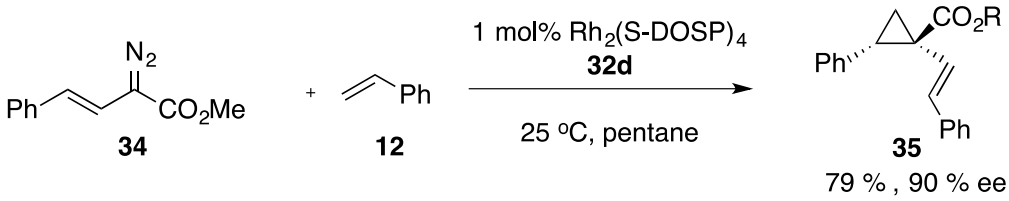
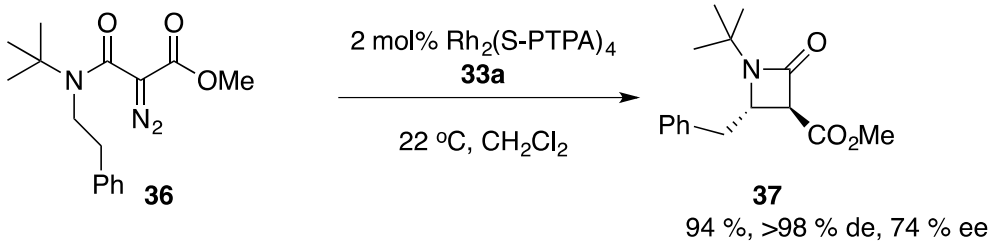


33

Ar = C_6H_5	Rh_2(S-BSP)$_4$	**a**	R = Bn	Rh_2(S-PTPA)$_4$	**a**
4-*t*-BuC_6H_4	Rh_2(S-TBSP)$_4$	**b**	Me	Rh_2(S-PTA)$_4$	**b**
2,4,6-tri-*i*PrC_6H_4	Rh_2(S-TISP)$_4$	**c**	*i*Pr	Rh_2(S-PTV)$_4$	**c**
4-($C_{12}H_{25}$)C_6H_4	Rh_2(S-DOSP)$_4$	**d**	*t*Bu	Rh_2(S-PTTL)$_4$	**d**
			Ph	Rh_2(S-PTPG)$_4$	**e**

Selected examples of enantioselective cyclopropanation and C-H activation:





Scheme 8. Representative prolinate **32** and phthalimide-based **33** Rh(II) carboxylates

Chiral dirhodium(II) carboxamidate catalysts were intensively studied by Doyle and co-workers.[40] The high electron density on the ligand served to tame the reactivity of the dirhodium carbenoid and thus increased the reaction selectivity. The dirhodium(II) carboxamidates catalysts derived from 2-oxopyrrolinine **38**, 2-oxazolidione **39** and *N*-acylimidazolidin-2-ones **40** and 2-acetidinones **41** have shown a good selectivity particularly in intramolecular C-H insertions reaction to form lactones or lactams (Figure 9).[41]

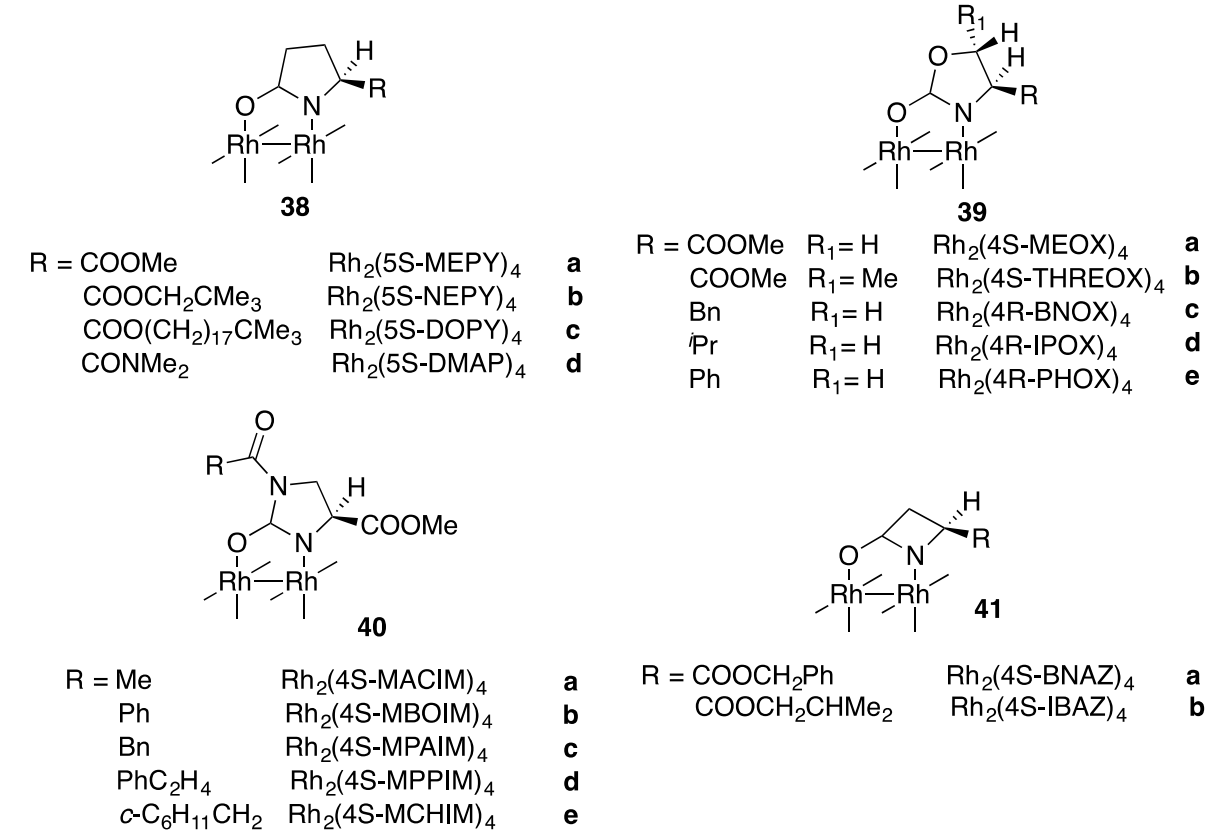
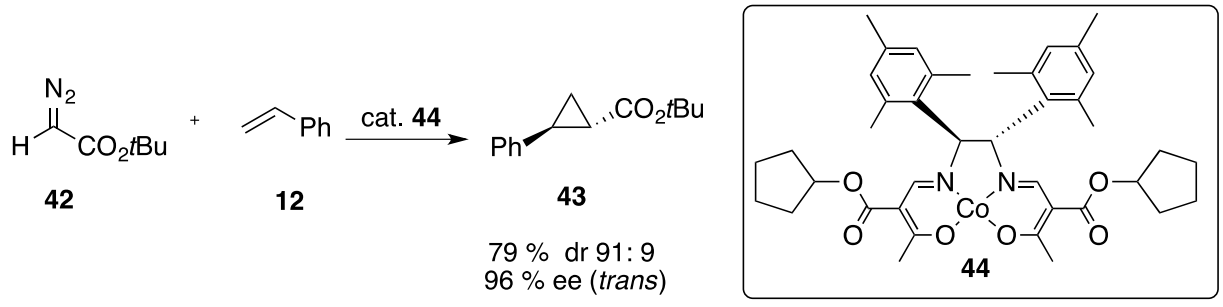


Figure 9. Representative chiral rhodium(II) carboxamidates

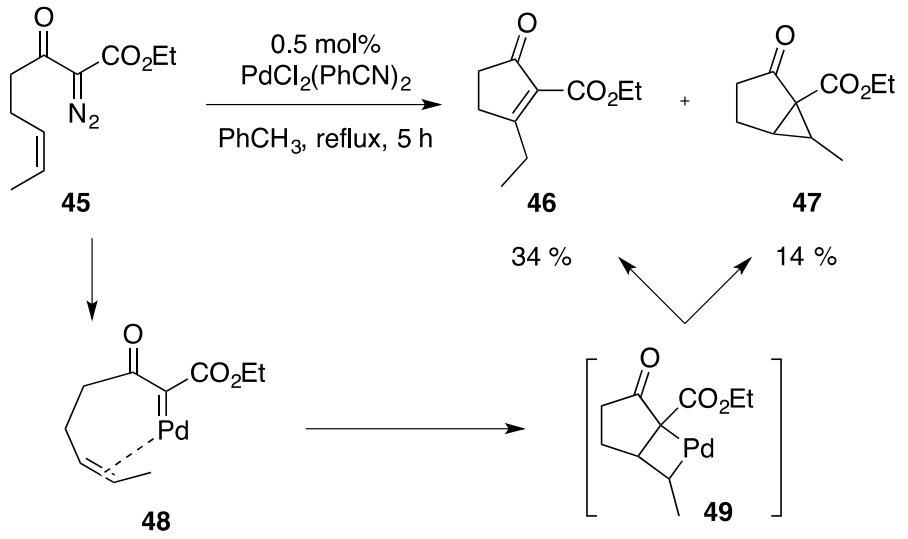
1.2.3 Other Transition Metal Catalysts

A wide array of other transition metals, such as cobalt, palladium, ruthenium, iron and iridium have been reported in catalytic diazo decompositions.[11,41,44] For example, Yamada and co-workers[42] reported the chiral cobalt(II)-salen complexes **44** catalyzed decomposition of **42** with styrene to give cyclopropanation **43** in 79% yield with high diastereo- and enantioselectivity (Scheme 9).



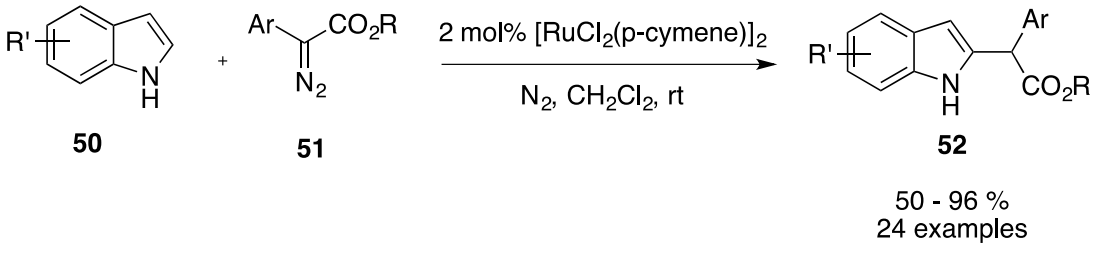
Scheme 9. Yamada's chiral cobalt catalyst

Taber and co-workers are among the pioneers in using palladium complexes as catalysts in α-diazocarbonyl decomposition.[43] Palladium carbene intermediates have shown a different behavior from Cu/Rh metal carbenoids.[44] For example, when $Pd(II)Cl_2(PhCN)_2$ was used as catalyst, β-alkenyl-diazoketones **45** underwent intramolecular cyclopropanation to generate **47** in 14% yield; however, the unexpected cyclopentenone **46** was isolated as major product.[43] Based on this observation, the authors proposed that the reaction proceeded through a palladacyclobutane intermediate **49** that partitions to the enone **46** or the cyclopropanes **47**.



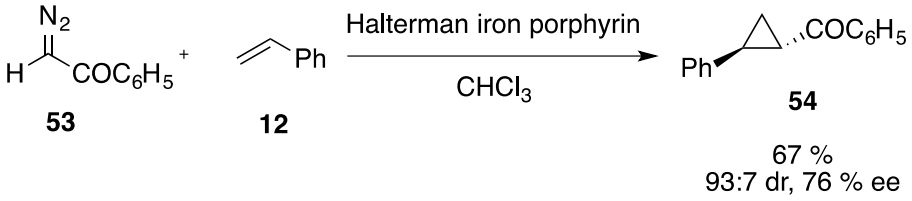
Scheme 10. Palladium catalyzed reactions of β-alkenyl-α-diazoketones

A wide range of ruthenium-based catalysts have shown good reactivity that could compete with their rhodium and copper counterparts.[45] For example, a paper has been published recently by Yu and coworker[45b] that uses dichloro(*p*-cymene)ruthenium(II) dimer $[RuCl_2(p\text{-cymene})]_2$ as catalyst in the decomposition of β-aryldiazoesters **51** with indole **50**. The C-2 alkylated indole **52** was selectively obtained without the need for any additional directing group.



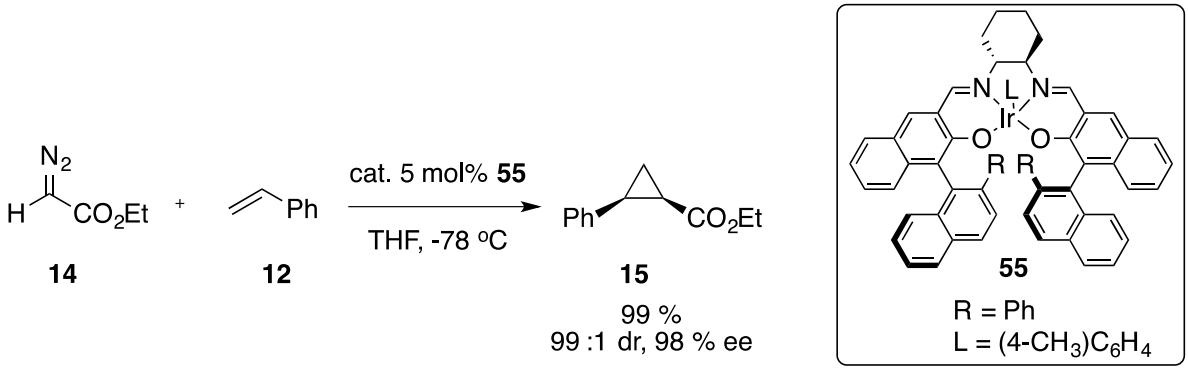
Scheme 11. Regioselective indole alkylation with ruthenium carbenoid

The earth abundant metal, iron, is especially inexpensive compared with other transition metals, and a few complexes have been reported to be catalytically reactive in cyclopropanation.[46] For example, cyclopropanation of diazoacetophenone **53** to styrene **12** was carried out using chiral iron porphyrins as homogeneous chiral catalysts, and the optically active cyclopropylketone was obtained in 76% ee.



Scheme 12. Iron catalyzed cyclopropanation

In recent years, iridium has emerged as one of the newcomers in metal-carbenoid reactions.[47] Katsuki and co-workers reported a highly diastereo- and enantioselective cyclopropantion of styrene **12** with ethyl diazoacetate **14** in the presence of chiral iridium–salen complex **55**. Interstingly, the *cis*-cyclopropane **15** was obtained as major diastereomer (Scheme 13).



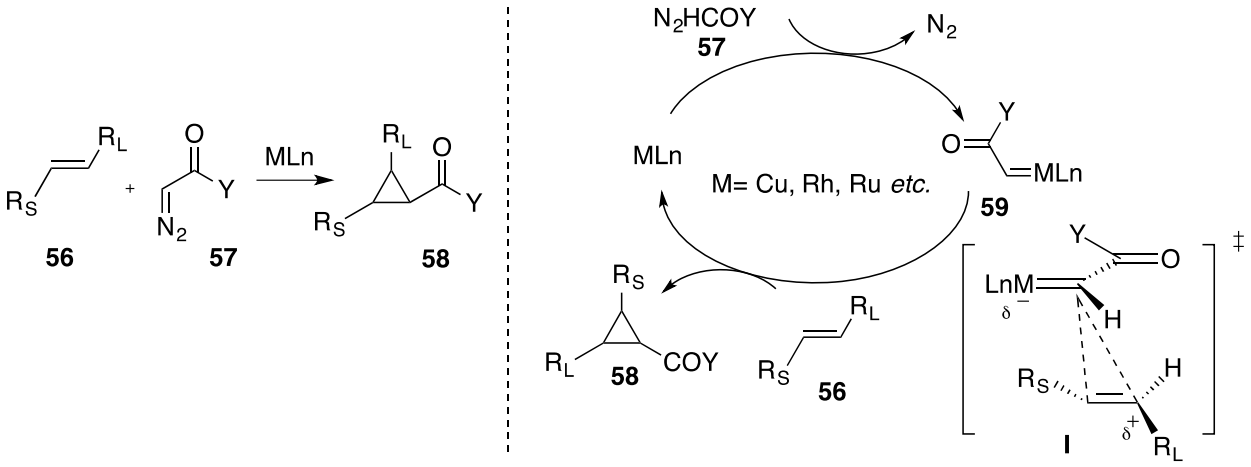
Scheme 13. Iridium-salen catalyzed cyclopropanation

In conclusion, diazocarbonyl compounds can be decomposed with different types of transition metal catalysts, such as Cu, Rh, Co, Pd, Ru, Fe and Ir, to generate the respective metal carbenoids. Copper and rhodium are the most popular catalysts in diazo decomposition and their carbenoid structures have been elucidated. The reactivities of copper and rhodium carbenoids and their reactions will be discussed in the following sections.

1.3 Intermolecular Cyclopropanation

Carbenoids generated from metal-catalyzed decomposition of diazocarbonyl can cyclopropanate

olefins to form cyclopropane derivatives. The reaction stands as one of the most general approaches in constructing those smallest all-carbon ring structures (Scheme 14). A wide range of metal complexes, such as Cu,[28] Rh,[48] Co,[42] Pd,[59] Ru[44] Fe[46] and more recently Ir,[47] have been developed to achieve high stereocontrol and efficiency (see some examples discussed above). The reaction mechanism is shown in Scheme 14. Decomposition of diazocarbonyl **57** in the presence of the metal gave carbenoid **59**. The concerted nonsynchronous addition of alkene **56** to electrophilic carbenoid **59** furnished cyclopropane **58** (transition state **I**, Scheme 14).[49]



Scheme 14. Cyclopropanation of alkene

The orientation of the olefin with respect to the carbenoid controls the relative stereochemistry of cyclopropanation. As illustrated in the transition structure **I**, the diastereoselectivity favoring the *trans* isomer usually improves when the steric demand of the Y group on diazocarbonyl increases. That is because increasing the size of the Y will place the steric demands on the approaching alkene, thus the preferred orientation will be the one with the large group R_L on the alkene orientated trans to the C(=O)Y.[50]

Asymmetric cyclopropanation has been attempted by introducing a chiral auxiliary on the diazo reagent; however, this approach has not been very successful.[51] The reaction of menthol diazoacetate **60**[51a] and oxazolidone diazo derivative **61**[51b] for the cyclopropanation of styrene have shown both low diastereoselectivity and enantioselectivity.

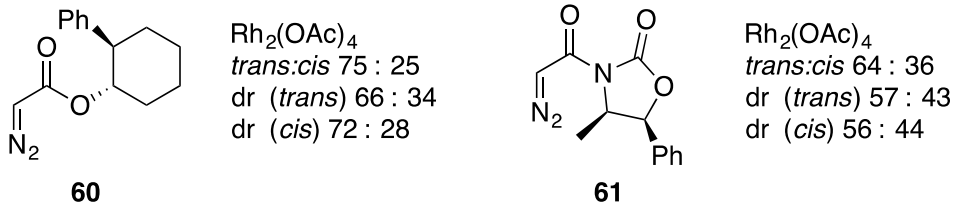
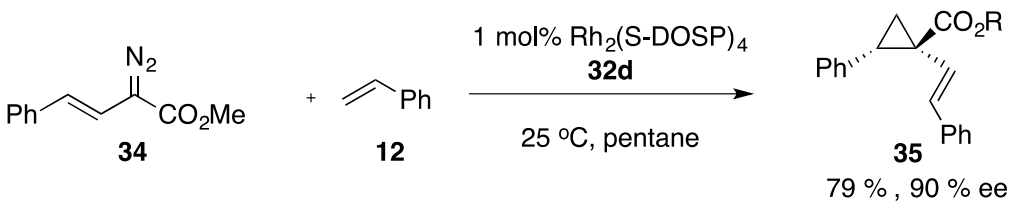


Figure 10. Chiral auxiliary induced enantioselective cyclopropanation

Asymmetric cyclopropanation of alkenes by chiral Cu complexes c has shown to be effective. The bidentate chiral semicorrin derivatives, bis-oxazolines (BOX) and 1,2-diamine ligands are among the most widely used chiral copper ligands (Scheme 6). High enantioselectivity was achieved in the copper catalyzed reaction of diazoacetate **16** and styrene **12** (Scheme 6).

Copper catalyzed cyclopropanation of diazoacetate with alkenes, in regard to diastereoselectivity, generally requires a bulky diazoacetate to maximize the cyclopropanes *trans:cis* ratio.[52,53] As shown in Scheme 6, high diastereoselectivity were frequently observed when a bulky diazoacetate, such as mentyl diazoacetate **16a** and butylated hydroxytoluene diazoacetate **16b** , were applied.

Chiral Rh complexes have also been studied for asymmetric cyclopropanation of diazocarbonyl and alkenes. A large number of chiral rhodium complexes have been synthesized and tested (see Scheme 8 and Figure 9). Generally, cyclopropanation of diazoacetate and alkenes catalyzed by chiral rhodium complexes proceeded with high enantioselectivity; however, achieving high levels of diastereoselectivity can be problematic. The level of diastereocontrol with rhodium catalysts does not match that observed with copper, cobalt and iron (see previous examples in Scheme 6, 9 and 12). Even with sterically hindered diazoacetates, the cyclopropane *tran:cis* ratio was still observed to be low to moderate. This important drawback has minimized the use of rhodium catalysts in asymmetric cyclopropanation with diazoaceates.[54] However, when vinyldiazoester **34** was used, the rhodium(II) carboxylate catalyzed cyclopropanation shows excellent diastereoselectivity.[55] Davies and co-workers[56] have intensively studied and shown that the prolinate-derived dirhodium catalyst **32d** is most effective for vinyldiazoester substrates **34** and complete diastereocontrol is observed in these transformations (Scheme 15).



Scheme 15. Cyclopropanation of vinyldiazomethanes with prolinate-based dirhodium catalyst

A model has been proposed to explain the high diastereoselectivity observed in cyclopropanation of vinyldiazoesters with alkenes (Figure 10).[56,57] The presence of donor/acceptor type diazos (an electron-withdrawing substituent (ester) and an electron-donating substituent (vinyl group)) is crucial for achieving the high diastereoselectivity. As shown in Figure 11, the bulky ligand can be envisioned as a wall in which the metal is embedded, thus alkenes have to be tilted up to avoid steric repulsion (**A**, Figure 11). Alkene preferentially approaches from the same side of the carboxylate group on Rh carbenoid. This is plausible due to the partial positive charge that built on during the transition state can be stabilized by the oxygen lone pairs of the carboxyl group (**B**, Figure 11). Releasing the catalyst in final step gave cyclopropanes as *E*-isomer (**C**, Figure 11).

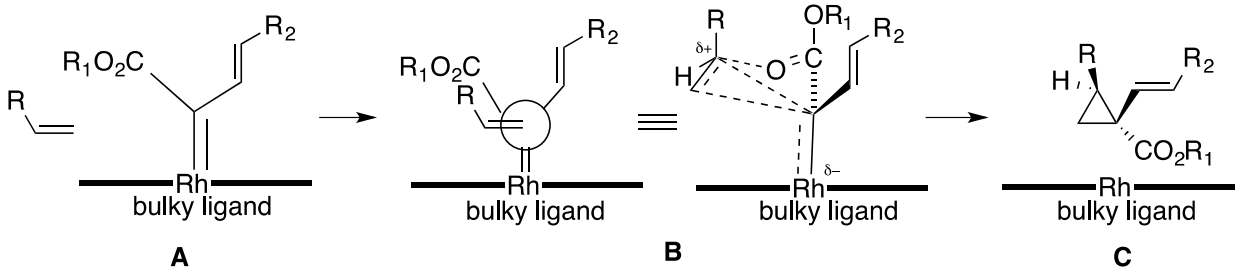


Figure 11. Relative diastereocontrol of cyclopropanation from donor/accepter diazos with alkenes

When chiral prolinate-based ligands were applied, approach of the alkene from the most accessible trajectory led to the corresponding cyclopropanes with a high level of enantioselectivity (Figure 12).

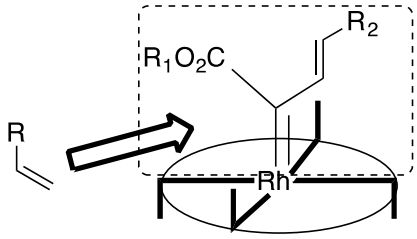
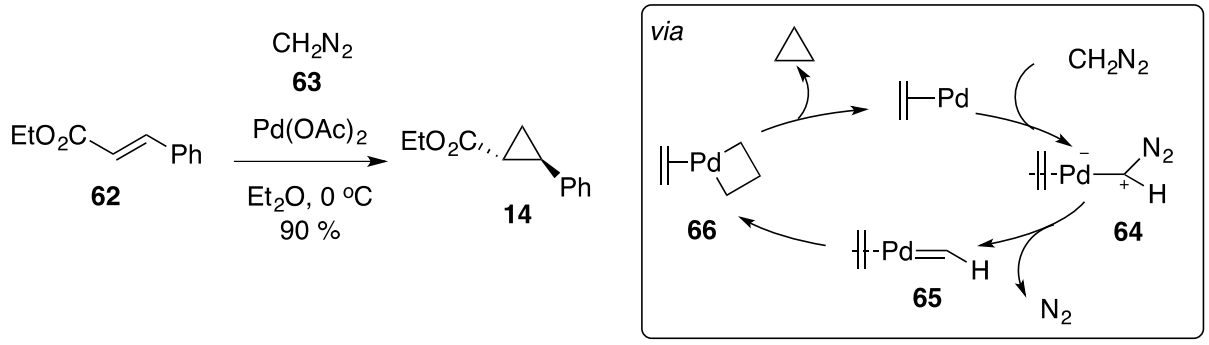


Figure 12. Enantioselectivity induced from prolinate-based dirhodium catalysts

Palladium has shown a very good reactivity towards the cyclopropanation of electron-deficient double bonds, particularly with diazomethane.[43,58,60] This chemoselectivity is attractive since most of the other catalytic systems described above are more efficient with electron-rich alkenes. Studies[59] indicated that olefin coordination to the Pd species played an important role in the cyclopropanation mechanism (Scheme 16). The cyclopropanation was speculated to proceed through a palladacyclobutane **66** as shown in Scheme 16 (right). However, the larger application of palladium in cyclopropanation has been limited, generally due to its incapacity to induce asymmetry reactions upon coordination of chiral ligands.[60]



Scheme 16. Palladium catalyzed diastereoselective cyclopropanation of electron-deficient alkenes with diazomethane

1.4 C-H Insertion

The process of C-H functionalization has aroused great interest in the past 30 years since it allows immediate carbon-carbon bond formation from ubiquitous C-H bonds without pre-functionalization. The insertion of a free carbene directly into a C-H bond had been known for long time;[2a] however the reaction was unselective and rather random. It was not until the development of transition metal-stabilized carbenoids that the C-H insertion reaction became synthetically applicable.[16,17]

The mechanism of carbenoid C-H insertion was intensively studied by Doyle and co-workers.[18] They proposed that the bond formation was initiated by an overlap of the empty p-orbital on the carbenoid carbon with the σ orbital of the reacting C-H bond to give three-centered transition state **II**. The old C-H bond broke while the new C-H and C-C bond formed and the metal was dissociated (Figure 13). The configuration of the C-H carbon center is retained. This proposal was later supported by theoretical DFT (density functional theory) calculations by Nakamura and coworkers.[61]

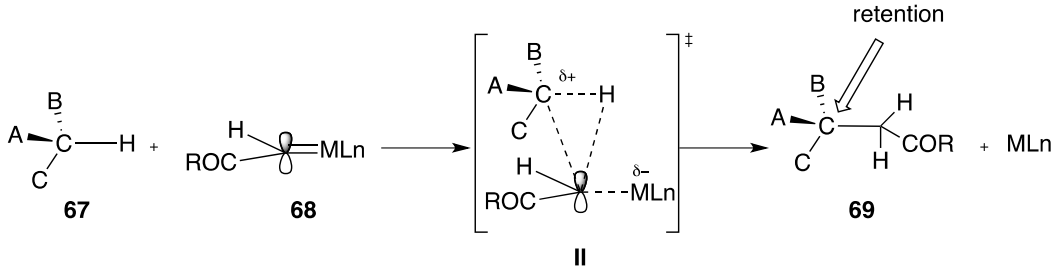


Figure 13. Mechanism of carbenoid C-H insertion

Copper, silver and gold[62] carbenoids are known to be reactive in C-H insertion reactions; however, the reactions are limited and the catalysts are less effective. So far, dirhodium carbenoids are considered as the most utilized and versatile catalysts for C-H intertion.[63] Nakamura and coworkers[61] conducted a DFT calculation of dirhodium(II) carboxylate **III** catalyzed C-H insertion of methane. The calculation had shown that the second rhodium on the rhodium dimer provided additional stabilization for the transition state (Figure 14). In the C-H insertion TS **V**, the Rh^1-Rh^2 bond was shorted comparing with the length in carbenoid **IV** (from 2.482 Å in **IV** to 2.460 Å in **V**) and the Rh^2 atom lost negative charge (from +0.68 in **IV** to +0.74 in **V**). Those changes illustrated that the Rh^2 transferring electrons to stabilize the electron deficient transition state TS **V**. The DFT calculation was also conducted with ligated copper and ruthenium catalyst. It showed that the activation energies of C-H insertion by ligated Cu-carbenoid and Ru-carbenoid were higher than the dirhodium carbenoids.

The transition process was also calculated. The hydride transfer from the methane is calculated to be half completed (the forming C^1-H bond being 1.244 Å, the carbene carbon being partially pyramidalized). The C-C bond formation (C^1-C^2 distance, 2.134 Å) lags behind the hydride transfer. These data together supported Doyle's proposal that the C-H bond activation/C-C bond formation is a 3-centered, nonsynchronous, concerted process.

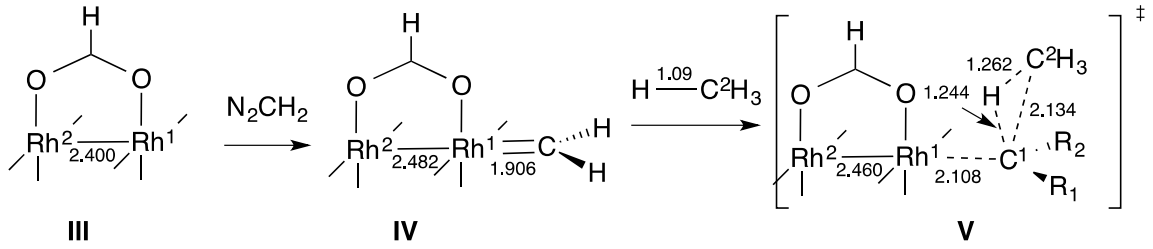
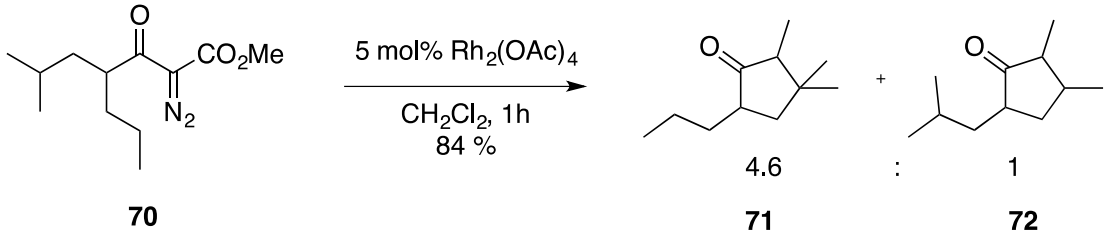


Figure 14. DFT calculation of dirhodium(II) carboxylate catalyzed C-H insertion

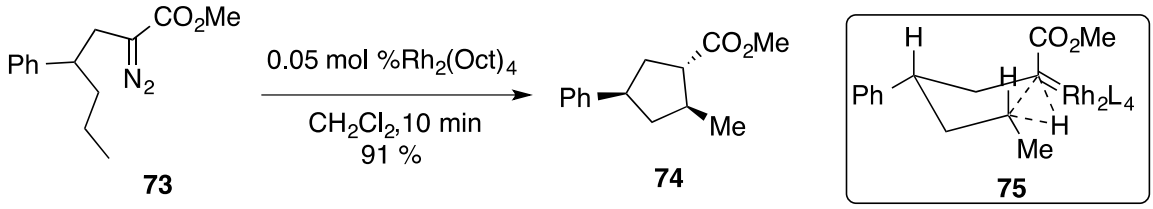
1.4.1 Intramolecular C-H Insertion

Selective insertion to a specific C-H bond is very challenging due to the existence of ubiquitous C-H bonds in a typical substrate.[64] One approach to solve the challenges of achieving selective reactions is to conduct the chemistry in kinetically favored intramolecular fashion.[65] Several synthetically useful intramolecular carbenoid C-H insertion examples were developed and many excellent reviews have been published in this field.[63a, 63b] Generally, the regioselectivity in intramolecular carbenoid C-H insertion reactions favors five membered ring compounds (1,5-C-H insertion).[66] From an electronic perspective, the greater ability to stabilize the build-up of positive charge in transition state **II** or **V** (see Figure 12 & 13), the more reactive for C-H insertion, thus the reactivity is expected to follow the order tertiary C-H > secondary C-H > primary C-H.[61, 67] For example,[68] when diazoketoester **70** was treated with $Rh_2(OAc)_4$ a 4.6:1 mixture of cyclopentanones **71** and **72** was observed (Scheme 17).



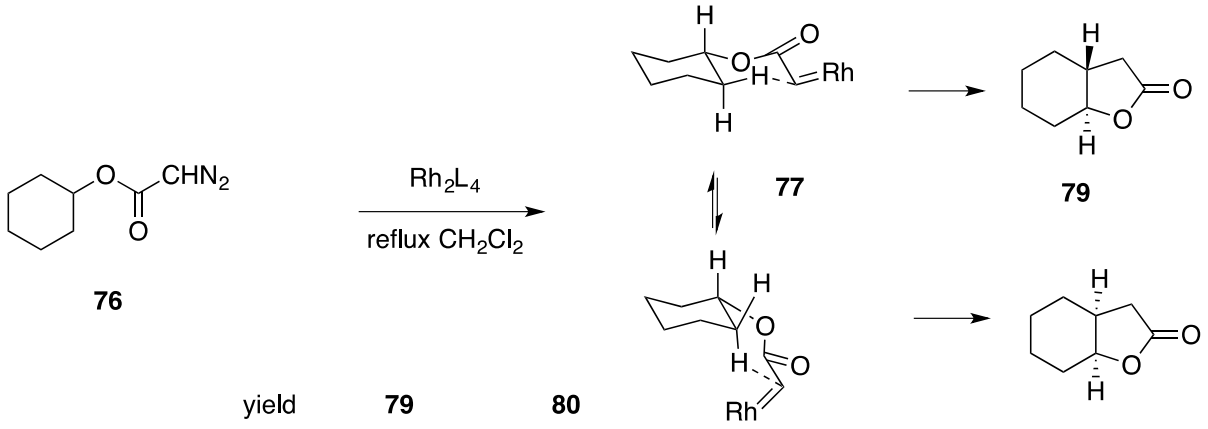
Scheme 17. Regioselectivity of intramolecular C-H insertion

Intramolecular C-H insertions can provide exceptional diastereocontrol in C-C bond formation. Taber and co-workers[65a,69] proposed a useful evaluation of the transition structure in C-H insertion. As exemplified in the reaction of **73**, the diastereoisomer **74** was obtained in high yield through a pseudo cyclohexane chair-like transition conformer **75** in which substituents are preferentially in the pseudo equatorial positions (Scheme 18).[70]



Scheme 18. Diastereoselective intramolecular C-H insertion

The diastereoselectivity of intramolecular C-H insertion is influenced by the ligand on the catalysts.[71] For example, there are two types of C-H bonds accessible for cyclohexyl diazoacetate **76** by 1,5-C-H insertion: insertion into the equatorial C-H bond of **77** gives the *trans*- bicyclic lactone stereoisomer **79**, whereas insertion into the axial C-H bond gives the *cis*-isomer **80**. When $Rh_2(OAc)_2$ was used as catalyst, low diastereocontrol was observed. With bulky chiral carboxamidate rhodium complexes, stereo discrimination was enhanced and selective insertion to equatorial C-H was observed (Scheme 19).



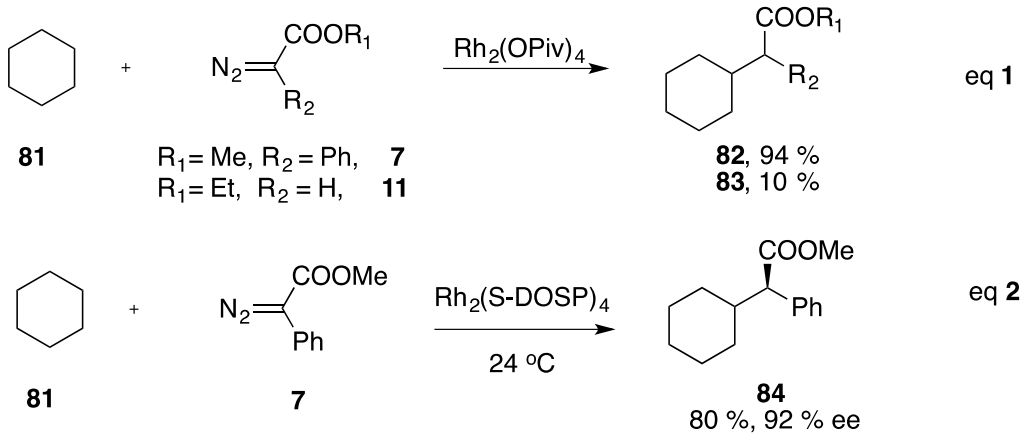
		yield	79	80
$Rh_2(OAc)_4$		46 %	40	60
$Rh_2(4S\text{-}MEOX)_4$	**39a**	50 %	55 (96 % ee)	45 (95 % ee)
$Rh_2(5S\text{-}MEPY)_4$	**38a**	65 %	86 (96 % ee)	14 (93 % ee)
$Rh_2(4S\text{-}MACIM)_4$	**40a**	70 %	99 (96 % ee)	1 (65 % ee)

Scheme 19. Influence of the ligand on diastereoselectivity

1.4.2 Intermolecular C-H Insertion

For a long time, intermolecular C-H insertion was considered to be of little synthetic utility because the process displayed very poor chemo- and regioselectivity. However, in recent years Davies and co-workers[17, 63] have shown that the poor chemoselectivity can be controlled by using donor/accepter type of diazo precursors.[72] The presence of the donor group stabilizing the highly electron-deficient rhodium carbenoid makes the reactions more selective than those

employing carbenoids lacking the donor group. Thus, under identical conditions with dirhodium tetrapivalate $Rh_2(OPiv)_4$ as catalyst, the donor/acceptor diazophenylacetate **7** gave the C-H insertion product **82** in 94% yield while only 10% yield of **83** was obtained from the reaction with acceptor diazoacetate **11** (Scheme 20, eq 1).[72a] Additionally, in combination with chiral prolinate-based Rh_2(S-DOSP)$_4$ catalyst, the intermolecular C-H insertions were achieved in highly enantioselectivity (Scheme 20, eq 2).[72b]



Scheme 20. Donor/acceptor carbenoid induced C-H insertion

Davies and co-workers have systematically studied the factors that influence the selectivity in C-H insertion and the trends of competing reactivities is given in Figure 15.[16,17,73]

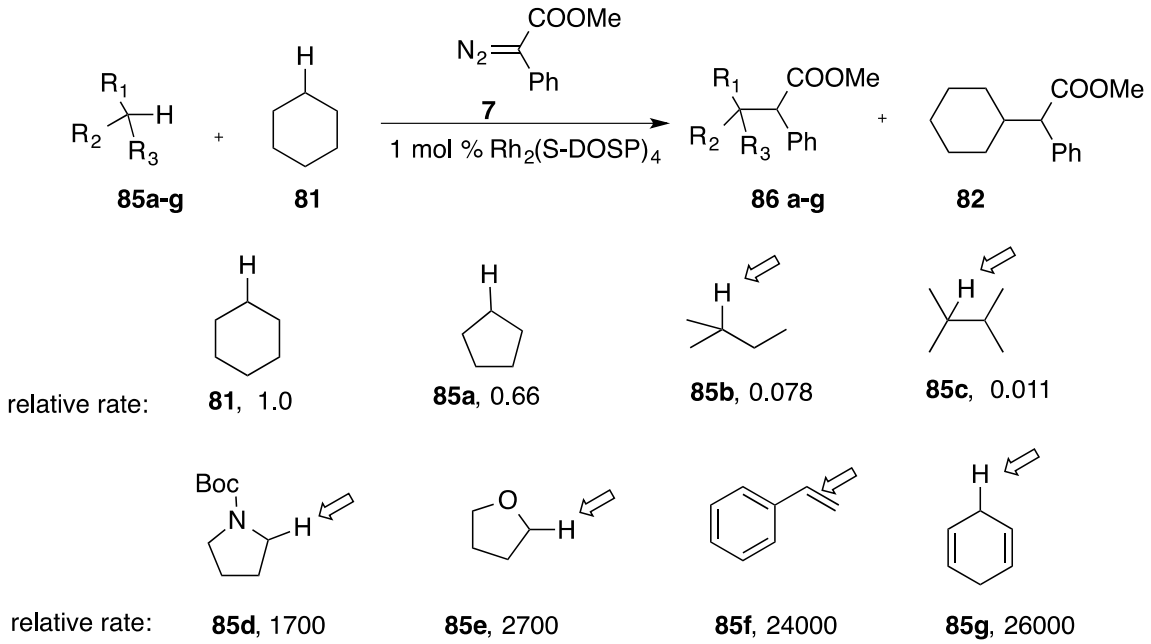
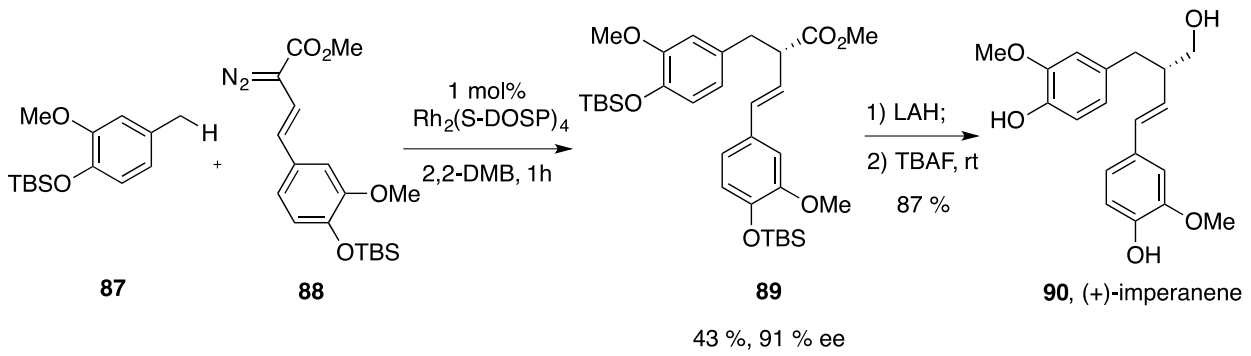


Figure 15. The relative rates for C-H insertion into various hydrocarbons using methyl phenyldiazoacetate

These experiments showed the importance of both electronic and steric factors in selective intermolecular C-H insertion reactions. The C-H sites that could stabilize the partial positive charge built up during the transition state are very susceptible towards C–H insertion. 1,4-Cyclohexadiene **85g** undergoes C–H insertion 26000 times faster than cyclohexane **81**, which is an even faster reaction than styrene cyclopropanation. The C–H sites adjacent to a heteroatom, such as those in tetrahydrofuran **85d** and *N*-Boc-pyrrolidine **85e**, react over 1000 times faster than cyclohexane. However, the insertion into the tertiary C–H bonds of 2-methylbutane **85b** and 2,3-dimethylbutane **85c**, which should be electronically more favorable than secondary C–H bonds, is over 10 times slower than in cyclohexane **81** due to the steric hindrance.

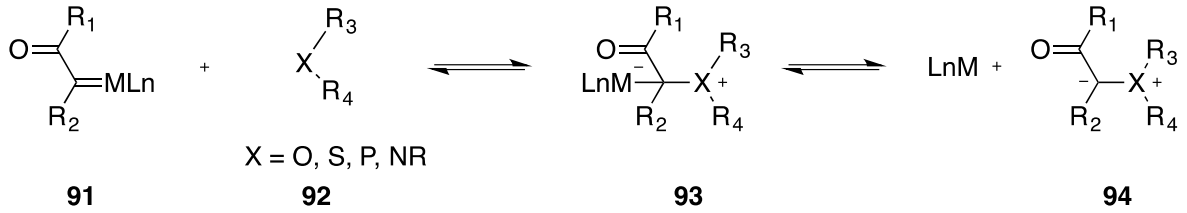
Application of C-H insertion chemistry to total synthesis of biologically relevant compounds has aroused attention and publications are increasing in number.[74] Recently, Davies and co-workers demonstrated an impressive and very concise route to synthesize (+)-imperanene **90** from direct C- H insertion of vinyldiazomethanes derivative **88** into a benzylic C-H of **87** (Scheme 21).[75]



Scheme 21. Synthesis of (+)-imperanene

1.5 Ylide Generation

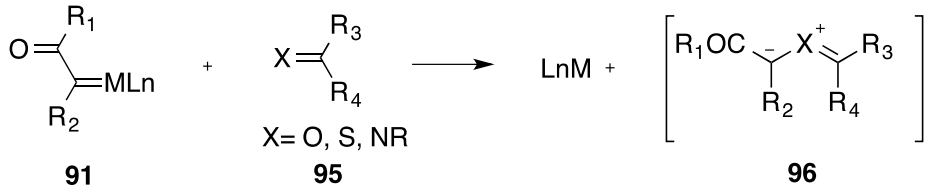
Metal-carbenoid species derived from α-diazocarbonyls are highly electrophilic and therefore can readily react with heteroatom nucleophiles to generate ylides (Scheme 22).[76]



Scheme 22. General ylide formation from carbenoids

The major categories of ylides are oxygen, sulfur, phosphorus, nitrogen and halogen ylides. It is worth noting that sulfur, nitrogen and phosphorus ylides can alternatively be generated from deprotonation next to the positively charged heteroatom.[77] However, in the case of the oxonium ylides, due to their known instability and high reactivity,[78] the ylides are usually generated from catalytic decomposition of a diazo compound in the presence of an ether. Ylides are reactive intermediates which are known to undergo a number of useful transformations such as [2,3]-sigmatropic rearrangement, [1,2]-shift (Stevens rearrangement) and β-hydride elimination.

Other important categories are the carbonyl, thiocarbonyl and azomethine ylides. These ylides are generated through the reaction of the metallocarbenes with the nucleophilic heteroatoms on the polarized C=O, C=S, or C=NR bonds (Scheme 23).[79] They can directly undergo reversible ring closure to give epoxide, episulfides and aziridine respectively. They also can be readily trapped inter- or intramolecularly with π-bonds, such as aldehydes, ketones, alkenes or alkynes, *via* a 1,3-dipolar cycloaddition reaction affording interesting heteroatom containing cyclic or polycyclic systems.

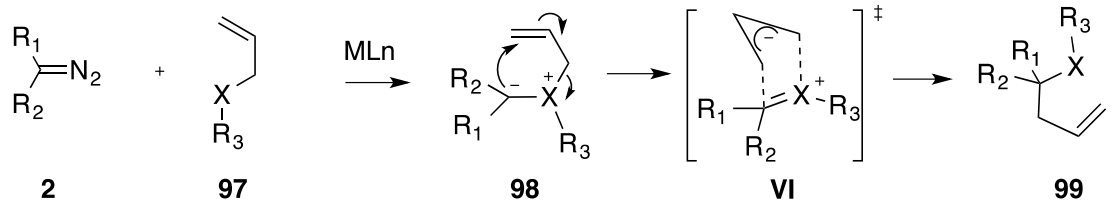


Scheme 23. Generation of carbonyl, thiocarbonyl and azomethine ylides

Ylide formation from metal carbenes and the subsequent reaction can occur in either inter- or intramolecular manner. This cascade process has shown a great versatility in organic synthesis and some examples will be given in the following section concerning the generation and subsequent reactions involving sulfur and oxygen ylides. The generation and subsequent reactions of nitrogen containing ylides will be discussed in Chapter 2.

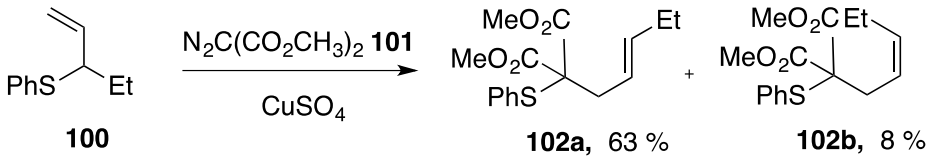
1.5.1 [2, 3]-Sigmatropic Rearrangement

The ylidic [2,3]-sigmatropic rearrangement has been generally accepted as symmetry allowed, concerted, suprafacial reaction which has been observed in the case of allylic or propargylic oxygen, nitrogen or sulfur ylides (Scheme 24). This process is considered to follow a six-electron five-membered transition state **VI** where the forming carbon-carbon bond and the breaking heteroatom-carbon bond are almost in parallel.[80]



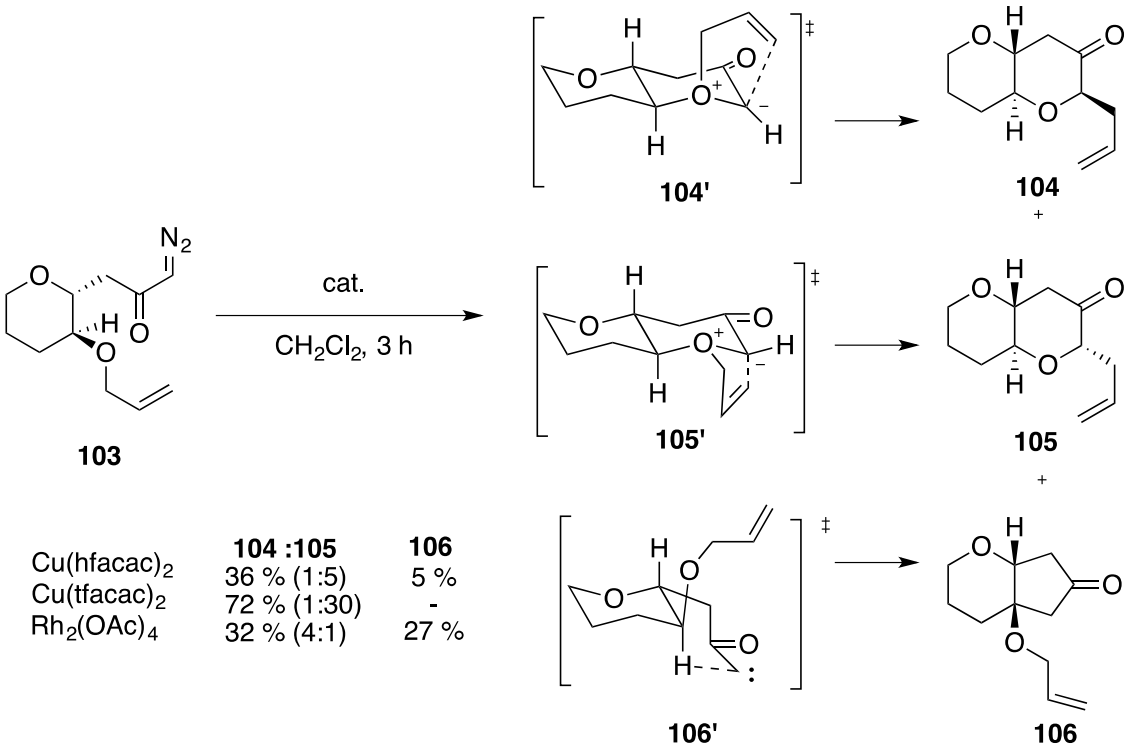
Scheme 24. General scheme of [2, 3]-rearrangement

Copper catalysts have long been known for their role in the generation of allylsulfonium ylides. For example, the [2,3]-sigmatropic rearrangement of allylic sulfur ylides derived from copper carbenoids has been used in the synthesis of substituted olefins (Scheme 25). A high level of stereoselectivity was obtained with a 9:1 ratio preferring the *E* alkene **102a** over the *Z* alkene **102b**.[81]



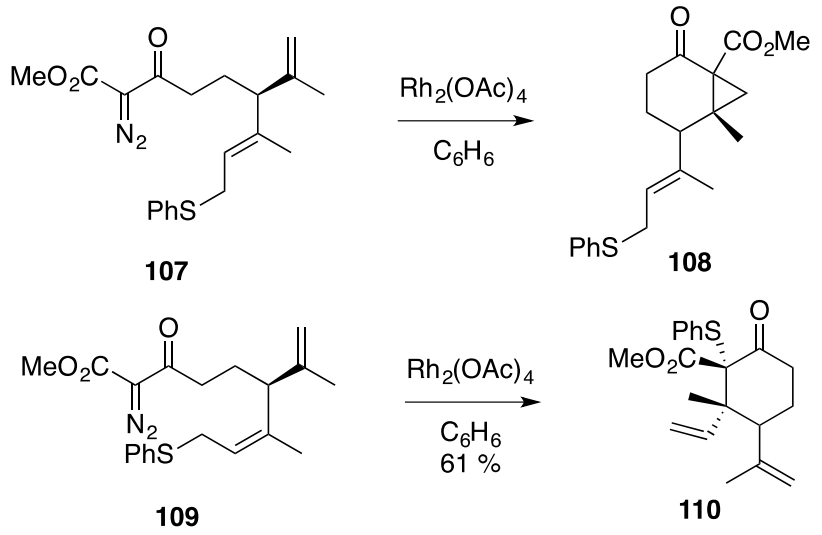
Scheme 25. Copper catalyzed [2, 3]-rearrangement of allylic sulfur ylide

In early cases, copper catalysts were not particular successfully for the generation and rearrangement of ylides,[82,] possibly due to the reaction often requiring higher temperatures which causes decomposition of the reaction system. Later, Clark[83] and West[84] demonstrated that $Cu(acac)_2$ and its electron-deficient derivatives $Cu(tfacac)_2$, $Cu(hfacac)_2$ catalysts show a better reactivity in ylide generation from diazoketones. These catalytic systems also eliminated the possibility for C-H insertion which was frequently observed as side reactions in the use of rhodium catalysts.[85] For example, West[86] reported a oxonium ylide [2,3]-rearrangement for the synthesis of polycyclic ethers (Scheme 26). The optimal copper catalyst was found to be $Cu(tfacac)_2$, which furnished the desired products **104** and **105** in good yield with excellent diastereoselectivity. However, when $Rh_2(OAc)_4$ was used, the undesired cyclopentanone side product **106** was significantly increased from the C-H insertion, whereas the desired polycyclic ethers were only obtained in 32% yield. Interestingly, the diastereoselectivity was also reversed with the rhodium catalyst.



Scheme 26. Catalyst optimization for the synthesis of polycyclic ethers

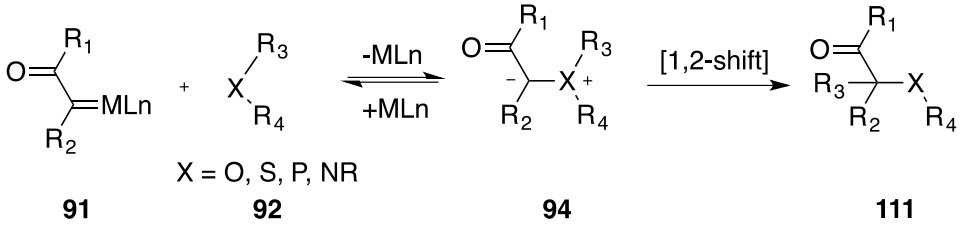
The chemo- and diastereoselectivity of [2,3]-rearrangements were strongly dependent upon the nature of the diazocarbonyl compound, the choice of metal catalysts, and the olefin geometry. Examples are known where intramolecular reactions of metal carbenes with allyl sulfides result in competition between formation of the cyclic sulfonium ylide and cyclopropanation, and in these cases, metal catalyst choice was very important.[87] The olefin geometry also plays an important role. For example,[88] the rhodium acetate catalyzed-decomposition of α-diazo-β-ketoester **107** bearing an *E*-olefin afforded the cyclopropane derivative **108** leaving the allylic sulfide group intact, whereas the corresponding *Z* olefin α-diazo-β-ketoester **109** yielded the cyclohexanone **110** (Scheme 27).



Scheme 27. Allylic geometry effect on chemoselectivity

1.5.2 [1, 2]- Rearrangement

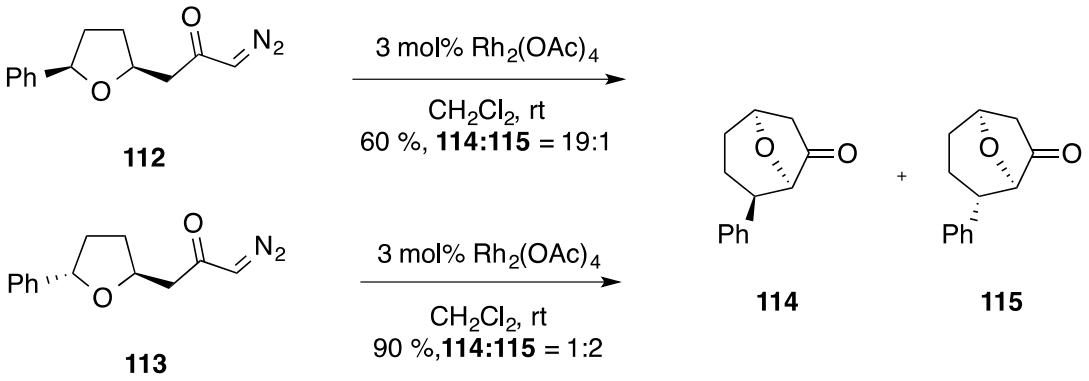
Another major class of ylide rearrangements is the [1,2]-shift or Stevens rearrangement (Scheme 28). According to the Woodward-Hoffmann rules, a concerted [1,2]-shift is a symmetry forbidden process; however, products resulting from a [1,2]-shift are obtained in many cases. Thus, in general, the mechanism of [1,2]-shift was suspected to proceed under either homolysis to give a radical pair, or heterolysis to give an ion pair followed by rapid recombination.[89]



Scheme 28. General scheme of [1, 2]-rearrangement

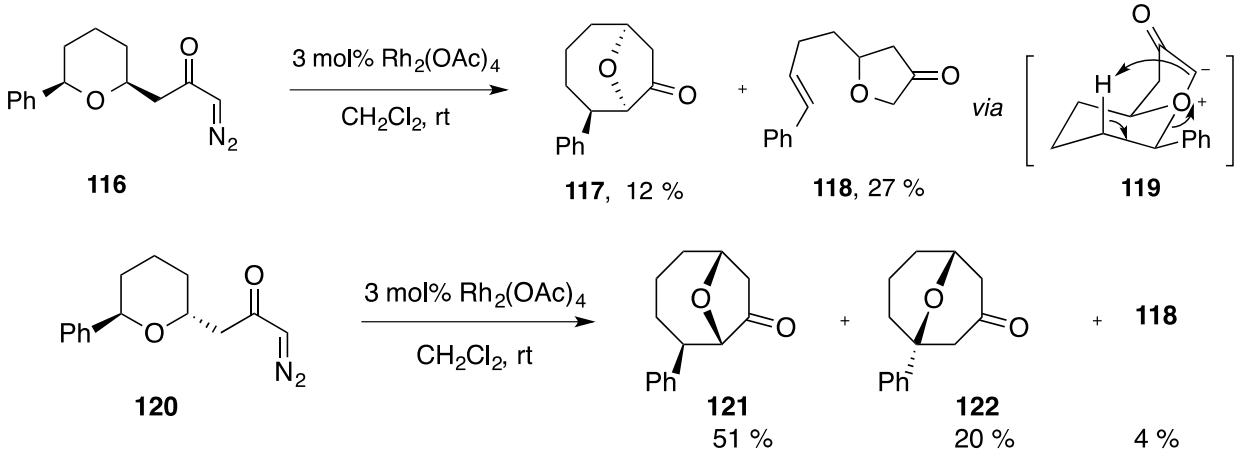
West and co-workers have successfully exploited oxonium ylide [1,2]-shift to construct oxygen-bridged ring systems.[90] Decomposition of the diazoketones **112** and **113** delivered a diastereoisomeric mixture of the cycloheptanones **114** and **115** (Scheme 29). In both cases, the benzylic group selectively and exclusively migrated to form the seven-membered ring. The relative stereochemistry of the diazoketone **112** and **113** had a significant influence on the stereochemical outcome of the reaction. The major diastereoisomer in each case arose from

migration with retention of configuration; the *cis*-tetrahydrofuran **112** gave a higher degree of retention.



Scheme 29. [1,2]-Rearrangement furnishing ether bridged seven-membered ring

However, when changing the heterocycle into six-membered tetrahydropyran **116**, the [1,2]-shift of oxonium ylide afforded cyclooctanone **117** as a single diastereoisomer yet in low yield. The formation of tetrahydrofuranone **118** was observed as side-product presumably resulting from the β-elimination of oxonium ylide intermediate **119**. The *trans*-isomer **120** also underwent the same process to give the cyclooctanones **121** and **122** in good yield. The major diastereoisomer **121** arose from migration with retention of configuration (Scheme 30).

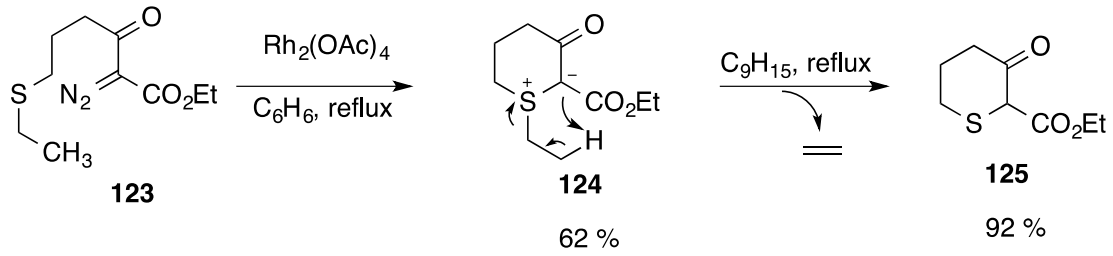


Scheme 30. Synthesis of oxygen-bridged ring systems *via* bicyclic oxonium ylides

1.5.3 β-Elimination

In addition to the [2,3]- and the [1,2]-rearrangements, the other reaction pathway for decomposition of ylides is the β-elimination. Some sulfonium ylides undergo thermal

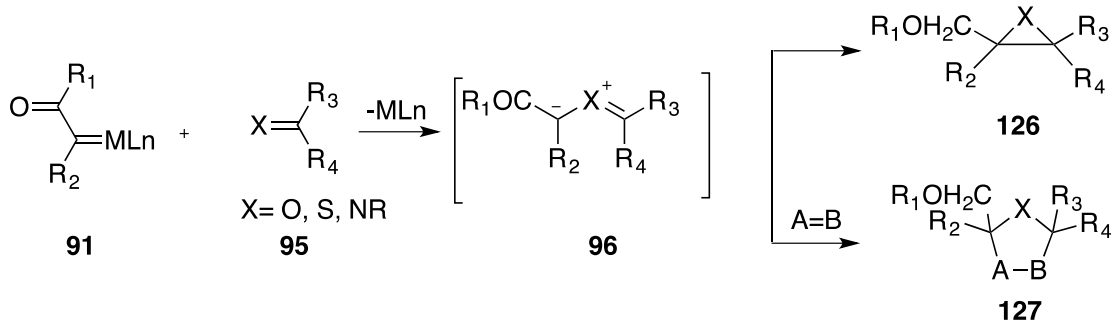
intramolecular eliminations, especially those carrying large alkyl groups on the sulfur atoms.[91] For example, as shown in Scheme 31, decomposition of S-ethyl diazosulfide **123** with $Rh_2(OAc)_4$ in refluxing benzene gave the isolable ylide **124** in 62% yield. Upon further heating in xylene, elimination of ethylene gave the ethyl-3-oxothiane-2-carboxy1ate **125** in good yield.[92]



Scheme 31. Representative examples of intramolecular β-elimination of sulfonium ylides

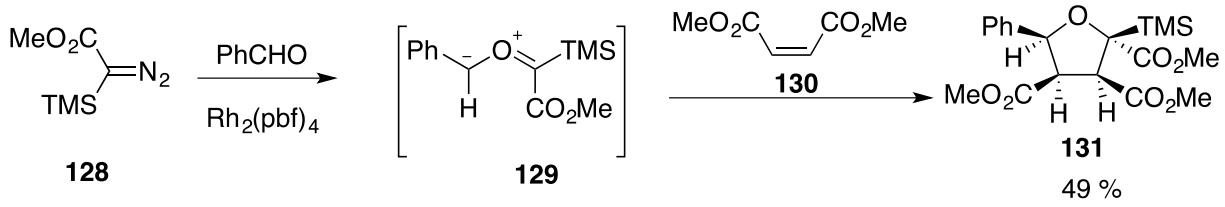
The Dipolar Cycloaddition

The carbonyl, thiocarbonyl or azomethine ylides **93** generated through the reaction of a metallocarbene with a polarized π-bond can undergo reversible ring closure to give an epoxide, episulfides and aziridine respectively **126** or can be readily trapped with a dipolarophile in a 1,3-dipolar cycloaddition reaction leading to oxygen/sulfur/nitrogen-containing heterocycles **127** with the general structure shown in Scheme 32.



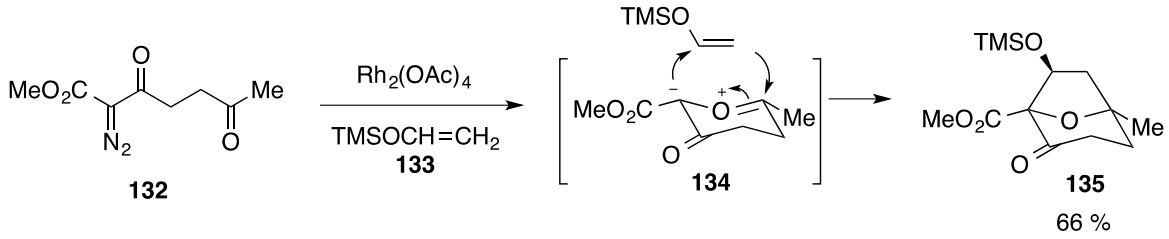
Scheme 32. General reactivity of carbonyl or azomethine ylide

For example, the tandem carbonyl ylide generation and 1,3-dipolar cycloaddition strategy has been used for the formation of tetrahydrofurans (Scheme 33). The rhodium-catalyzed decomposition of the diazoester **128** in the presence of benzaldehyde generated the carbonyl ylide **129**, which was trapped with dimethyl maleate **130** to give tetrahydrofuran **131** in 49% yield.[93]



Scheme 33. Tetrahydrofuran formation

The intramolecular formation of a carbonyl ylide followed by intermolecular trapping with a π-bond was initially described by Ibata[94] and well extended by Padwa.[79] This method has been widely used and permitted the construction of highly functionalized bicyclic compounds. For example, six-membered cyclic carbonyl ylide **134**, derived from $Rh_2(OAc)_4$ catalyzed decomposition of diazoester **132**, undergoes [1,3]-dipolar cycloaddition with enol ether dipolarophile **133** to give the carbocyclic analog of the zaragozic acid core **135** as a single adduct in good yield (Scheme 34).[95]



Scheme 34. Cycloaddition of carbonyl ylide with enol ether

1.6 Conclusion

This overview highlights the reactivity and typical transformations of metal carbenoids, and their application in organic synthesis. Since we are interested in exploring novel processes by harnessing these high-energy reactive carbenoid intermediates, proper substrates have been carefully designed to intercept these reactive species. In Chapter 2, trapping of a metallocarbene using azide as a nucleophile was examined, and the imine was obtained smoothly with very good yield. It should be noted that compared with traditional imine synthesis, the only by-product from azide/metallocarbene coupling methodology is two equivalent of nitrogen gas. The second project, which will be discussed in Chapter 3, has uncovered an unusual reactivity of stable triazoles with metallocarbene species, from which the interesting heterocycle pyrroline-3-ones were obtained. The details of the analysis of the transformation and experimental procedures will be discussed subsequently.

1.7 References

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Chapter 2

Imine Formation from Metallocarbene with Organic Azides

2.1 Introduction: Reaction of Metallocarbene with Nitrogen Containing Compounds

The metallocarbenes, as discussed in Chapter 1, are commonly generated from catalytic decomposition of diazo compounds with late translation metals such as Cu, Rh, Pd, Fe, Co, Ru, etc.[1] One of the typical reactions of the metallocarbene is to interact with the non-bonding lone pair of a Lewis base (B:) to generate a metal complex-associated ylide or a free ylide.[2] The ylide thus generated is usually highly reactive and undergoes subsequent rearrangement reactions.

The reactivity of metallocarbenes towards nitrogen-containing compounds to generate nitrogen ylides is well established in the literature.[3] Amines,[4a] imines[4b] and nitriles[4c] are among the most frequently encountered nitrogen Lewis bases in the nitrogen ylide formation (Figure 1). Generation and subsequent rearrangements of these nitrogen ylides (**I**-**III**) offer an effective route to nitrogen-containing targets.[4]

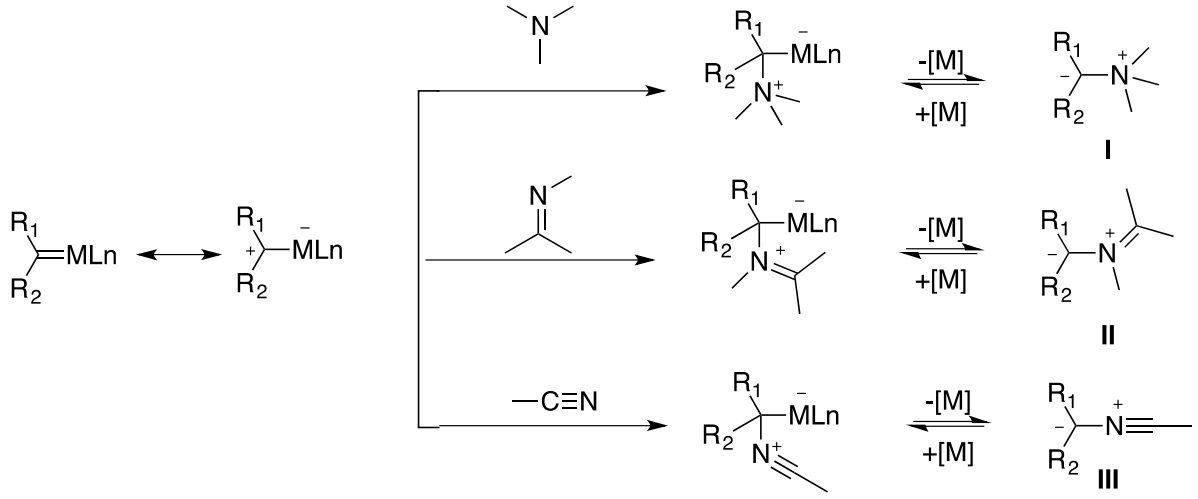


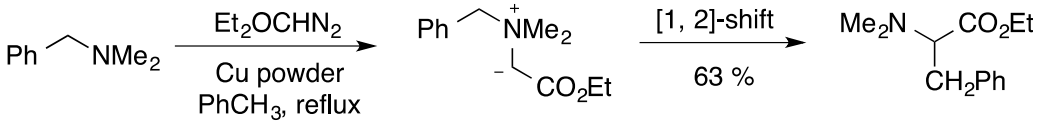
Figure 1. Reactivity of metallocarbenes with nitrogen nucleophiles

However, there are unique challenges in nitrogen ylide formation from metallocarbenes with nitrogen containing compounds. The Lewis basic nitrogen precursor can complex tightly to the transition metal catalyst.[1,3,5] In some cases, this leads to coordinative saturation of a metal center, and resultant loss of catalytic activity.[2,6] Furthermore, the final product typically contains an amine motif offering potential of coordination on the metal. Consequently, metal complex-

catalyzed diazo decomposition in the presence of an amine or imine usually requires relatively higher reaction temperatures in order to permit catalyst turnover.[7]

2.1.1 Reaction of Metallocarbene with Amines

The ammonium ylide formation and subsequent intra- and intermolecular [1,2]-Stevens rearrangements have been intensively explored by West and co-workers to synthesize a wide variety of acyclic and cyclic nitrogen-containing compounds.[8] In 1993, West and co-workers[9] reported a general route to access the racemic amino ester **3** from simple tertiary amines and diazocarbonyl compounds (Scheme 1). In this reaction, copper powder catalyzed decomposition of diazoester compounds resulted in an acyclic ylide, such as **2,** which underwent benzyl ($CH_2C_6H_5$) [1,2]-Stevens shift to form amino ester **3**. However, the dirhodium (II) acetate catalyst was found inefficient in this reaction presumably due to coordinative saturation of the catalyst by the amine.



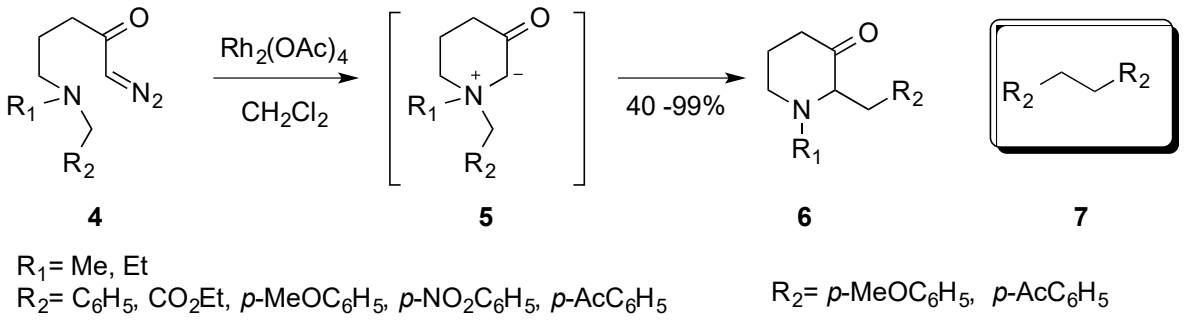
1 **2** **3**

Scheme 1. [1, 2]-Shift of the acyclic ammonium ylide **2** to form α-aminocarbonyl compound **3**

The mechanism for the Stevens [1, 2]-shift has been debated for years.[8,9,10] According to the Woodward-Hoffmann rules, a concerted [1,2]-shift is a symmetry forbidden process; however, products resulting from a [1,2]-shift are often obtained. Thus, in general, the mechanism of [1,2]-rearrangement was suspected to occur by a stepwise process involving either homolysis to give a radical pair, or heterolysis to give an ion pair followed by rapid recombination.

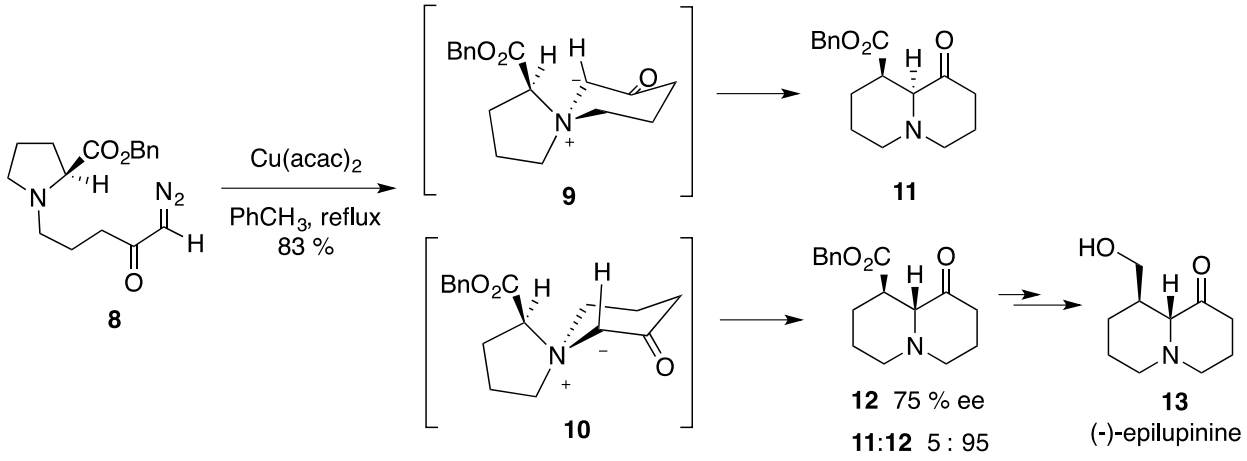
In 1993, West and Naidu reported[11] the first systematic study of [1,2]-Stevens shift of cyclic ammonium ylides **5** (Scheme 2). In this report, the rhodium carbene generated from decomposition of a diazoketone was trapped by the tethered amine to generate cyclic ammonium ylide **5**, followed by [1,2]-shift to give piperidine derivative **6** (Scheme 2). The preferred migrating groups were found to be the benzyl (CH_2Ar) and CH_2CO_2Et groups, where the CH_2 were attached to a radical stabilizing groups. Interestingly, when $CH_2C_6H_4$(4-OMe) and $CH_2C_6H_4$(4-Ac) groups were applied as migrating groups, the homocoupling product **7** was

isolated in 19% or 25% yield respectively. These results together suggest that the [1,2]-shift preferentially proceeds through a radical pair.



Scheme 2. Synthesis of substituted piperidin-3-ones

West and Naidu[12] extended the ammonium ylide [1,2]-shift approach in the synthesis of biologically active (-)-epilupinine. $Cu(acac)_2$ catalyzed decomposition of enantiomerically pure diazoketone **8** in refluxing toluene generated spiro ammonium ylide intermediates **9** and **10**. [1,2]-Shift of the methine carbon bearing the ester substituent gave quinolizidine **11** and **12**, in a total 84% yield in 5 : 95 ratio (Scheme 3). The major diastereomer **12** was obtained in 75% ee.

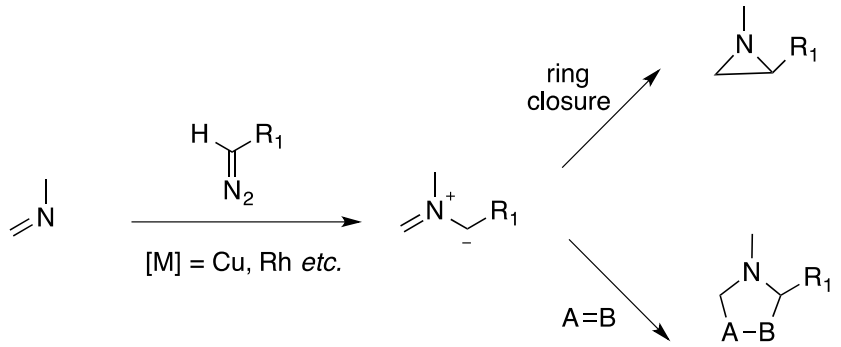


Scheme 3. Piperidine formation via [1,2]-shift of cyclic ammonium ylide

2.1.2 Reaction of Metallocarbene with Imines

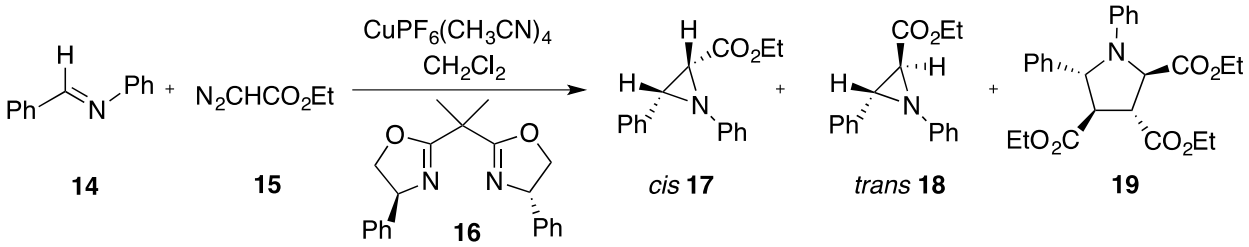
Metallocarbenes react with the nucleophilic nitrogen on polarized C=NR bonds to generate azomethine ylides.[13] The azomethine ylide intermediate could undergo the reversible ring closure to generate aziridine or be trapped with π-bonds, such as aldehydes, ketones, alkenes or alkynes,

via a 1,3-dipolar cycloaddition reaction affording synthetically useful heterocyclic compounds (Scheme 4). [14]



Scheme 4. General reactivity of azomethine ylides from metallocarbene with imine

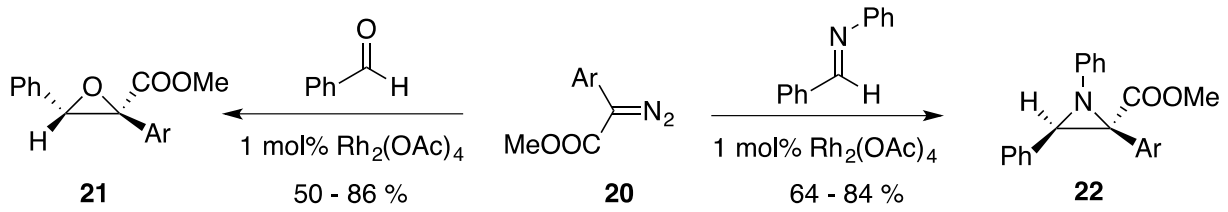
One of the first enantioselective aziridination reactions of imines with a metallocarbene was reported by Jacobsen and co-workers[15] in 1995. Decomposition of diazoester **15** in the presence of $CuPF_6(MeCN)_4$ and chiral bisoxazoline ligand **16** followed by imine **14** trapping to give *cis*-aziridine **17** and *trans*- **18** in a combined 37% yield, together with 10% of pyrrolidine **19**. Moderate enantioselectivity was observed for the *cis*- and *trans*-aziridines with 44% ee and 35% ee, respectively (Scheme 5). This seminal study has firstly demonstrated that catalytic asymmetric induction can be achieved in azomethine ylide formation and its subsequent reactions. The racemic side-product pyrrolidine **19** was presumed to arise from the 1,3-dipolar cycloaddition of azomethine ylide with the side product diethyl fumarate which was generated from homocoupling of ethyl diazoacetate **15**.



Scheme 5. Asymmetric aziridination

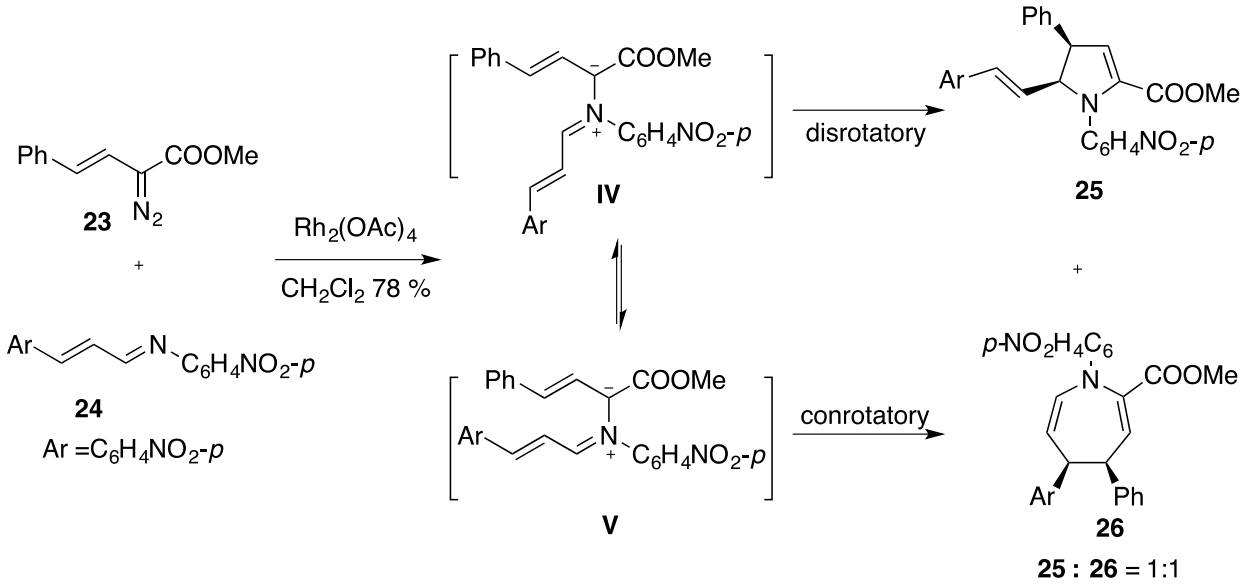
In 2003, Doyle and co-workers reported a dirhodium(II) catalyzed decomposition of aryldiazoacetate with imines or aldehydes to generate aziridine or epoxide with high diastereoselectivity.[16] *Trans*-aziridine **22** was observed as major product in the presence of 5-fold

of arylimine.[17] When the reaction was carried out with 10-fold excess of aldehyde, epoxide **21** was obtained as a single diastereomer (Scheme 6).



Scheme 6 Diastereoselective formation of aziridine and epoxide

When cinnamaldehyde derived imine **24** and vinyldiazoacetate **23** were used in the presence of $Rh_2(OAc)_4$, dihydropyrrole **25** and dihydroazepine **26** were found to be generated in 78% yield in 1:1 ratio.[18] Each of the products was obtained as a single diastereomer from the sterospecific electrocyclization of the intermediate ylides **IV** and **V** (Scheme 7). There was no aziridine detected in the reaction.

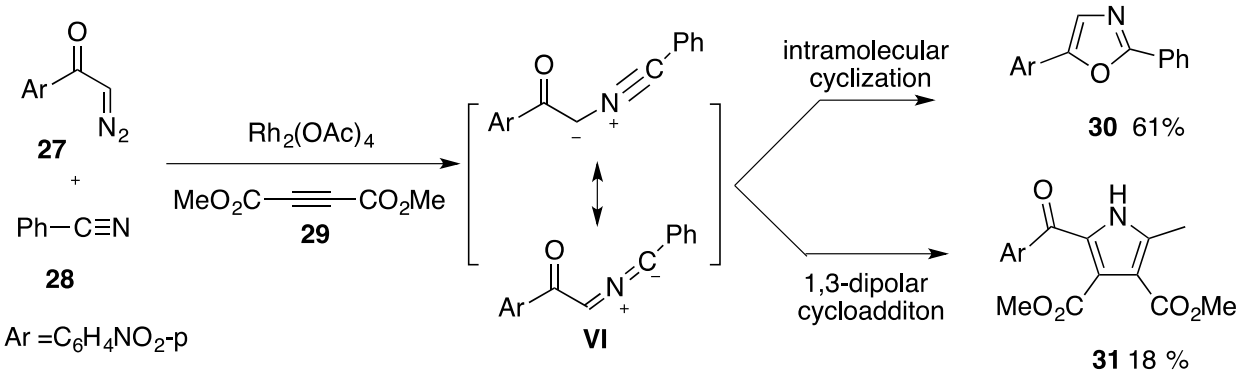


Scheme 7. Formation of dihydropyrrole and dihydroazepine

2.1.3 Reaction of Metallocarbene with Nitriles

The metallocarbenes decomposed from α-diazocarbonyl compounds react with nitriles to generate unstable α-carbonyl nitrile ylide intermediates **VI**, which could undergo intramolecular *5-endo* cyclization to generate oxazoles. When a dipolarophile is presented, nitrile ylide **VI** could undergo 1,3-dipolar cycloaddition to form complex heterocycles.[19] As an example, Ibata and co-

workers have reported[20] a dirhodium(II) catalyzed decomposition of α-diazoacetopheone **27** in benzonitrile **28** with DMAD (dimethyl acetylenedicarboxylate), the 1,3-dipolar cycloadduct pyrrole-3,4-dicarboxylates **31** was isolated in 18% together with phenyloxazole **30** in 61% yield (Scheme 8).



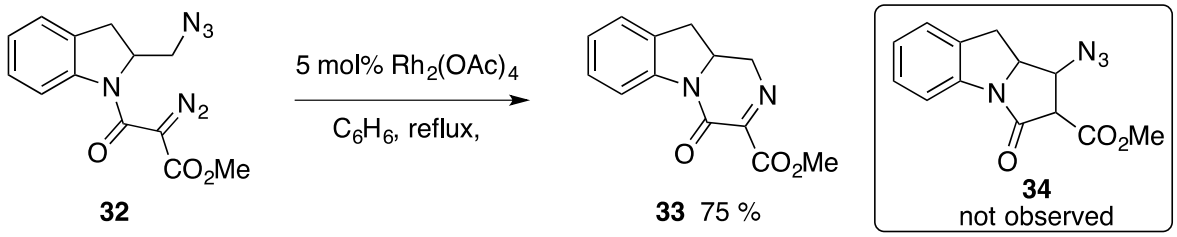
Scheme 8. Intramolecular cyclization and 1,3- dipolar cycloaddition of nitrile ylide

2.1.4 Reaction of Metallocarbene with Azides

2.1.4.1 Intramolecular Reaction

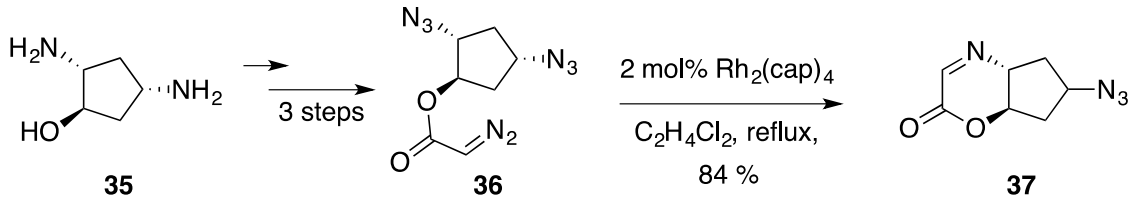
The azide group has been used extensively to facilitate the introduction of nitrogen atoms in synthetic organic chemistry.[21] Organic azides can intercept a variety of electrophilic species in a synthetically useful fashion, such as aziridination of electron-deficient alkenes or Schmidt rearrangement.[22] Among these efforts, interestingly, only a few successful interceptions of organic azide with electrophilic free carbenes or carbenoids have been reported.[23]

In the paper of metal catalyzed reactions of indoline diazoamides, Wee and Slobodian[24] reported for the first time two examples of $Rh_2(OAc)_4$ catalyzed conversion of a diazocarbonyl compound **32** with a tethered azide to generate a tricyclic C-acylimine **33** as an unexpected result (Scheme 9). The expected C-H insertion of product **34**, however, was not observed in the reaction.



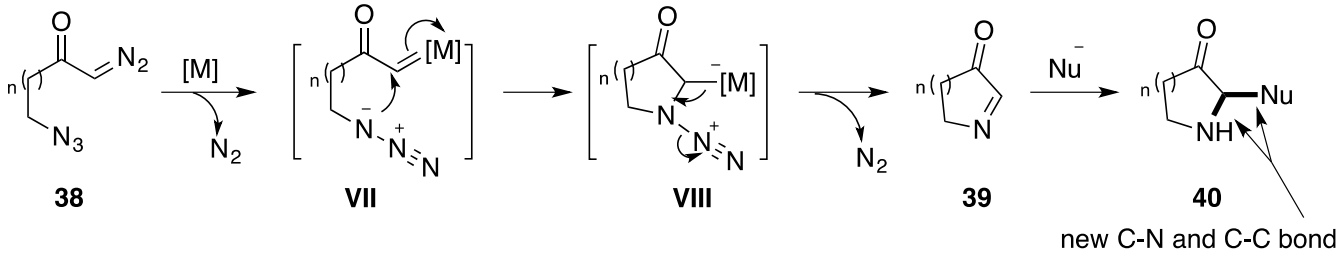
Scheme 9 First example of Rh-catalyzed intramolecular metallocarbene/azide coupling

In 2011, with Wee's report as a precedent, Micouin, Lecourt and co-workers[25] employed the same approach to prepare a surrogate of 2-deoxystreptamine **37** in four steps from diaminocyclopentanol **35** (Scheme 10).



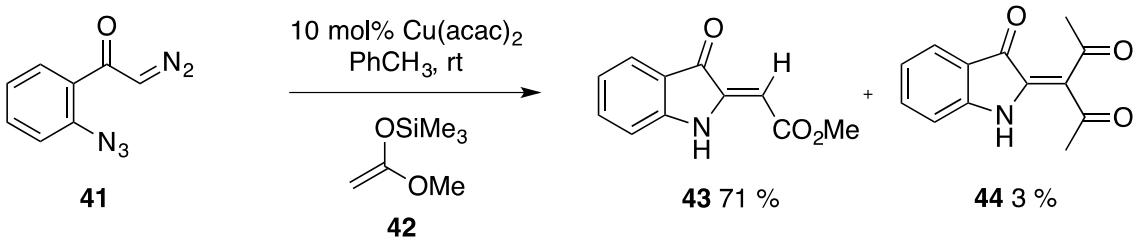
Scheme 10. Formation of 2-deoxystreptamine surrogate via metallocarbene/azide coupling

With the limited number of examples of this potentially useful transformation available, West and co-workers suspected that with a tethered azide and diazocarbonyl functionalities **38**, the internal nitrogen on the azide motif underwent intramolecular cyclization with generated metallocarbene **VII** to give the betaine **VIII** followed by extrusion of dinitrogen to furnish cyclic C- acylimine **39**. If this reaction were carried out in the presence of the suitable nucleophile, **39** would be further trapped by the nucleophiles to provide adduct **40** (Scheme 11).



Scheme 11. Speculated pathway of metallocarbene/azide coupling

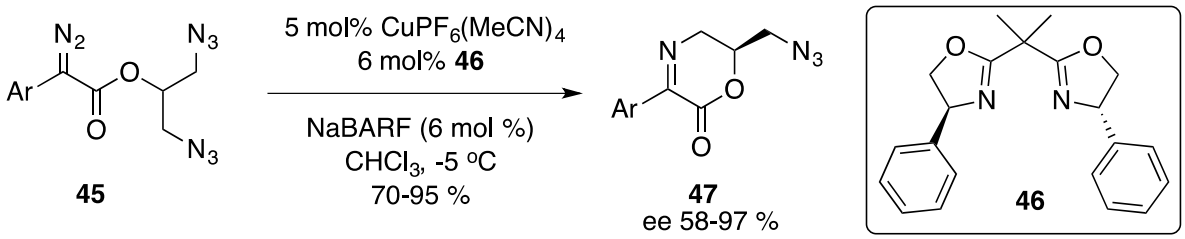
In 2014, West and co-workers successfully tested[26] the feasibility of this hypothetical process with anthranilic acid derived substrates **41** in the presence of 10 mol% $Cu(acac)_2$ with addition of one equivalent of silyl ketene acetal nucleophile **42** (Scheme 12). The reaction led to the rapid formation of multiple highly colored mixtures. Fortunately, the desired alkylideneindolone **43** was obtained and separated in good yield. A small quantity of by-product alkylideneindolone **44** was also observed, which was presumably generated from nucleophilic trapping by acetylacetonate ligand on the copper catalyst followed by autoxidation.



Scheme 12. Formation of indolone derivatives by *in situ* trapping of the C-acylimine with silyl ketene acetal

Other catalysts with non-nucleophilic ligands, such as $Cu(tfacac)_2$, $Cu(hfacac)_2$ and $Rh_2(OAc)_4$ have shown the capability of catalyzing the reaction. $Cu(hfacac)_2$ was found to give optimal results, affording the product in high yield. Domino metallocarbene/azide coupling followed by nucleophilic addition has been achieved with a variety of nucleophiles, including highly substituted silyl ketene acetals, Danishefsky's diene, sodium acetoacetate or *N*-methylindole. This work has been published in 2014.[26]

In the same year, right after West's publication, Peiming Gu and co-workers[27] developed a similar methodology to synthesize an enantioenriched cyclic α-imino ester derivatives **47**. The reaction selectivity was controlled by diastereoselective interception of alkyl azides with the *in situ* generated chiral Cu metallocarbene (Scheme 13).

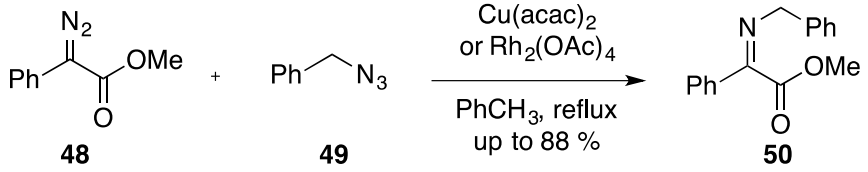


Scheme 13. Asymmetric metallocarbene/alkyl azide coupling

2.1.4.2 Intermolecular Reaction

For reactions proceeding via highly reactive intermediates, intramolecularity is often a powerful tool for improving efficiency.[28] and this is certainly the case for many processes involving metallocarbene intermediates. Although the corresponding intermolecular process would likely be more challenging, it is appealing since it would involve assembly of a useful adduct from two simple building blocks.

A preliminary study of intermolecular metallocarbene/azide coupling was carried out by former West group member Dr. Tina M. Bott. The reaction was surprisingly efficient when treating diazophenylacetate **48** with benzyl azide **49** in the presence of copper or rhodium catalysts to furnish a known α-imino ester **50** in very good yield (Scheme 14).



Scheme 14. Initial trial of intermolecular reaction of metallocarbene with azide

The intermolecular extension of metallocarbene/azide coupling methodology would be very useful for synthesizing a wide range of α-imino esters in a quick and environmentally benign fashion. This transformation demonstrated a unique advantage over the traditional methods for α-imino ester formation[29] since the only by-products are two equivalents of nitrogen gas. Furthermore, we speculated that with Lewis acidic transition metal present in the system, the generated imino ester could be further activated, which would allow *in situ* nucleophilic trapping by proper nucleophiles leading to the construction of important α-quaternary amino acid derivatives.[30] We also speculated the *N*-addition of the α-imino ester might occur by a Michael-type addition in the presence of proper activating catalyst and nucleophiles (Figure 2).[31]

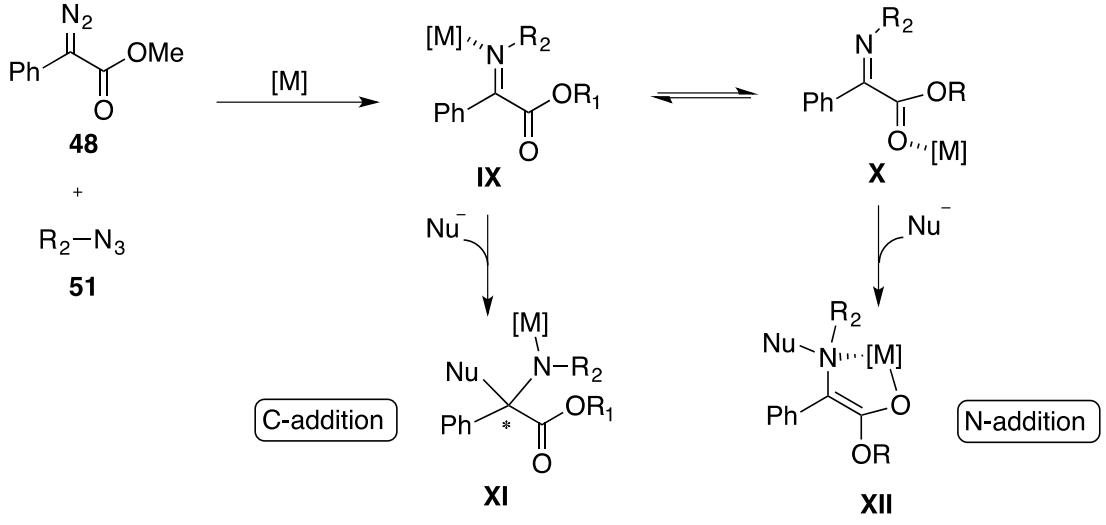
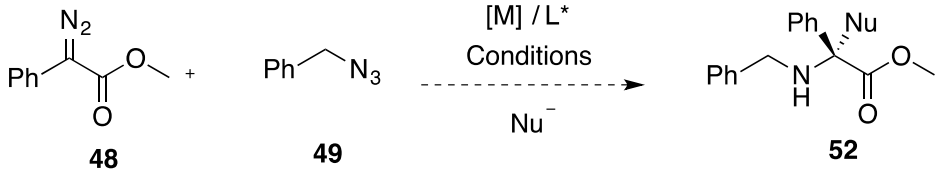


Figure 2. Proposed nucleophilic trapping of iminoester

The goal of my first project in the West group involved further exploring intermolecular

metallocarbene/azide coupling methodology for the synthesis of α-imino ester under mild condition. Our ultimate goal is to examine a range of nucleophiles, which would allow for the one-pot *in situ* trapping to achieve the α-all carbon quaternary amino acid derivatives. Eventually, carrying out the reaction in an asymmetric catalytic fashion would afford optically pure amino acid derivatives (Scheme 15).

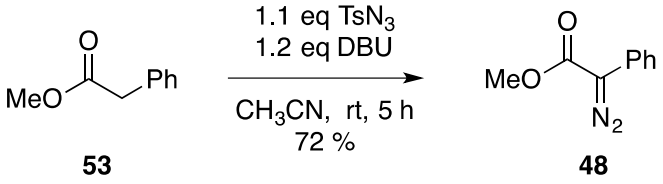


Scheme 15. Project objective to achieve the α–quaternary amino acid derivatives

2.2 Results and Discussion

2.2.1 Synthesis of the Substrates

Preparation of the diazocarbonyl compound **48** was accomplished by using standard Regitz diazo transfer conditions from methyl phenylacetate **53** with TsN_3 (Scheme 16).[32] The benzyl azide substrate **51** can be easily prepared by the S_N2 reaction of commercially available benzyl bromide with sodium azide.[33]



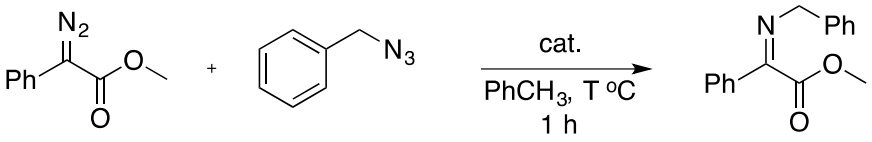
Scheme 16. Synthesis of diazocarbonyl compound

2.2.2 Optimization of Reaction Conditions

Initial efforts for optimization were directed toward the reactions of benzyl azide **49** with 1.2 equivalent of methyl diazophenylacetate **48** in the presence of 1 mol% of $Rh_2(OAc)_4$ (Table 1). Reactions at room temperature were sluggish presumably due to the coordination of the imine product with the Lewis acidic $Rh_2(OAc)_4$ catalyst. When the reaction was performed at 90 °C in toluene for 1 h, the desired α-imino ester **50** was obtained in 90% yield (Table 1, entries 1–2). Alternative usage of $Cu(acac)_2$ and $Cu(OAc)_2$ lowered the yield significantly (entries 4−5). Fortunately, when 5 mol% $Cu(hfacac)_2$ monohydrate was applied in the system, imine **52** was

obtained with 83% yield (entry 3). The reaction was clean and no outstanding impurity was observed. Considering that $Cu(hfacac)_2$ monohydrate is significantly cheaper than rhodium catalysts and the yields of the reactions were comparable, $Cu(hfacac)_2$ was therefore was chosen as the optimal catalyst.

Table 1. Survey of catalyst and temperature of the imine formation [a]



48 **49** **50**

entry	cat. (mol %)		T (°C)	time (h)	yield [b]	*E*/*Z* [c]
1	$Rh_2(OAc)_4$	1	90	1	90	1 : 5
2 [d]	$Rh_2(OAc)_2$	1	r.t.	o.n. [e]	trace	--
3	$Cu(hfacac)_2 \cdot H_2O$	5	90	1	83	1 : 6
4	$Cu(acac)_2$	10	90	1	70	1 : 5
5	$Cu(OAc)_2$	10	90	3	51	1 : 5
6	--	--	90	o.n. [e]	trace	--

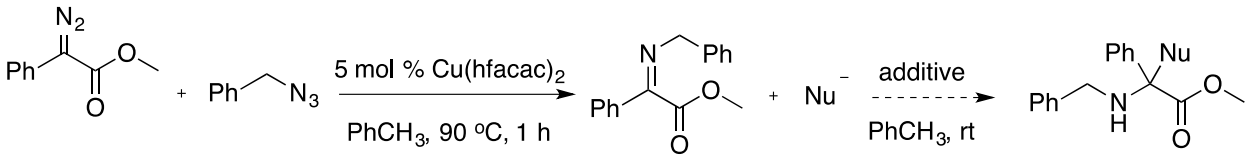
[a] Reaction conditions: benzyl azide **49** (0.25 mmol) and catalyst were stirred in toluene (2.0 mL) at 90 °C under argon. A solution of diazo compound **48** (0.3 mmol) in 1 mL of toluene was slowly added by injection *via* a syringe over 10 min. [b] Isolated yield. [c] E/Z ratios were determined by the benzylic protons (4.78 and 4.74 ppm) in ^{1}H NMR spectra. [d] Prolonged reaction time (20 hours) gave increased yield of **50**. [e] o.n. = overnight.

2.2.3 Intermolecular Trapping of the Ketimine with Nucleophiles

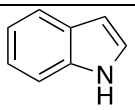
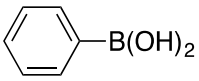
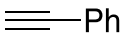
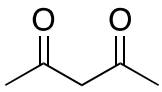
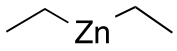
Having identified effective conditions for the formation of α-imino ester **50** formation, and on the basis of the idea that the formed α-imino ester **50** could be further activated by the Lewis acidic transition metal complex present in the reactions mixture. We quickly investigated the possibility of one-pot nucleophilic trapping to the ketimine **50** under a variety of conditions (Table 2). For that purpose, we directly added the nucleophiles after ketimine formation without separating. The reaction of **48** and **49** with catalysts was carried out first, by stirred in toluene at 90 °C for 1 h. To the resulting reaction mixture containing the catalysts and the generated ketimine **50**, two equivalent of nucleophile then was added and the reaction was stirred at room

temperature for 12-16 hours. Different nucleophiles such as indole, phenylboronic acid, phenylacetylene, trimethylsilyl ketene acetal, acetylacetone and diethyl zinc were examined. However, there was no desired trapping product **55** observed, whereas the ketimine **50** was detected as major product in most of the cases (Table 2).

Table 2. Initial survey of one-pot nucleophilic trapping of ketimine[a]



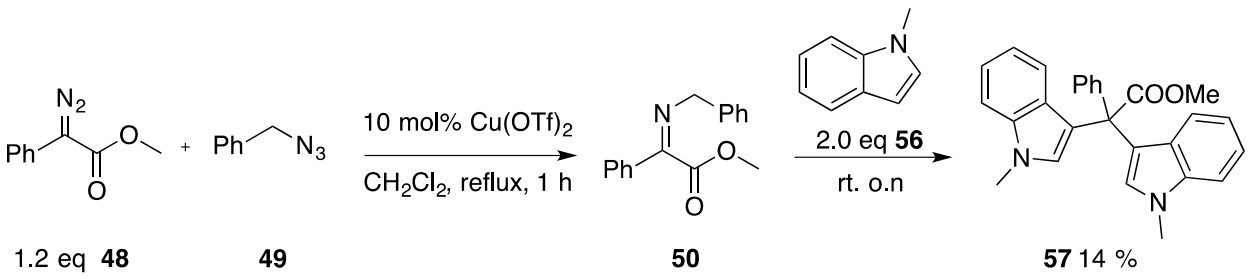
1.2 eq **48** **49** **50** **54** 2.0 eq **55**

entry		nucleophile	additive	result
1	**54a**		--	n.r. [d]
2 [b]	**54b**		--	n.r.
3	**54c**		CuI (10 mol %) Cs_2CO_3 (1.5 eq)	n.d. [e]
4	**54d**		 Cs_2CO_3 (4.0 eq)	n.d.
5 [bc]	**54e**		--	n.d.

[a] Reaction conditions: benzyl azide **49** (0.25 mmol), and $Cu(hfacac)_2$ monohydrate (0.0125 mmol) were stirred in toluene (2.0 mL) at 90 °C under argon. A solution of diazo compound **48** (0.3 mmol) in 1 mL of toluene was slowly added by injection *via* a syringe over 10 min. The reaction mixture was allowed to stir for 1 h at 90 °C. The reaction was allowed to cool to room temperature, then 2.0 equiv of nucleophiles were added (along with any additive) and the reactin was stirred at rt for a further 12-16 h. [b] $MgSO_4$ was added as additive before diazo **48** was charged. [c] Diethyl zinc was added at 0 °C over 1 hour and then the reaction mixture was stirred at room temperature for 16 hours. [d] n.r.= no reaction. [e] n.d.= not detected.

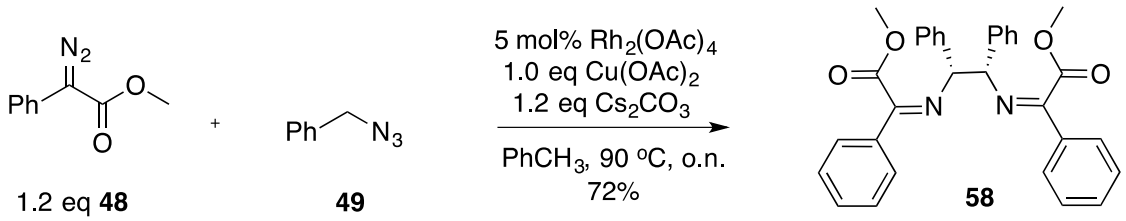
The initial trapping result showed that the nucleophilic addition to C-terminus of *N*-alkyl-α-disubstituted imine **50** was not facilitated. The low reactivity of ketimine is extended by the steric hindrance at the C-terminus of the imine in the C-C bond forming step. Therefore, despite the tremendous amount of work and effort devoted to the development of efficient and versatile reactions, the structure of the imines have been restricted to mono substituted aldimines.[34] The catalytic nucleophilic attack to α-disubstituted ketimines is, to date, very limited.[35]

Interestingly, when we modified the reaction conditions to 10 mol% $Cu(OTf)_2$ in dichloromethane, after applying methyl indole **56** as a trapping reagent, the bis(indole) **57** was obtained in 14% yield (Scheme 2.17). However, the mono methyl indole adduct was not observed.



Scheme 17. Methyl indole trapping result

An interesting result was observed when applying a 1.0 equivalent of $Cu(OAc)_2$ as an internal oxidant and a 1.2 equivalent of Cs_2CO_3 as base in the system; the diimine **58**[36] was obtained in 72% yield (Scheme 18). The mechanism is not clear at this stage. A tentative mechanistic hypothesis is proposed below (Figure 3). The ketimine **50** generated from azide **49** and diazocarbonyl **48** was deprotonated by Cs_2CO_3 giving conjugated enolate **VIII,** followed by SET (single electron transfer) reaction to generate radical **IX**, which resonance into **X**. Diradical dimerization of intermediate **X** furnished the dimer **58**. The structure of **58** was confirmed by X-ray chromatography.



Scheme 18. Dimerization of ketimine **50**

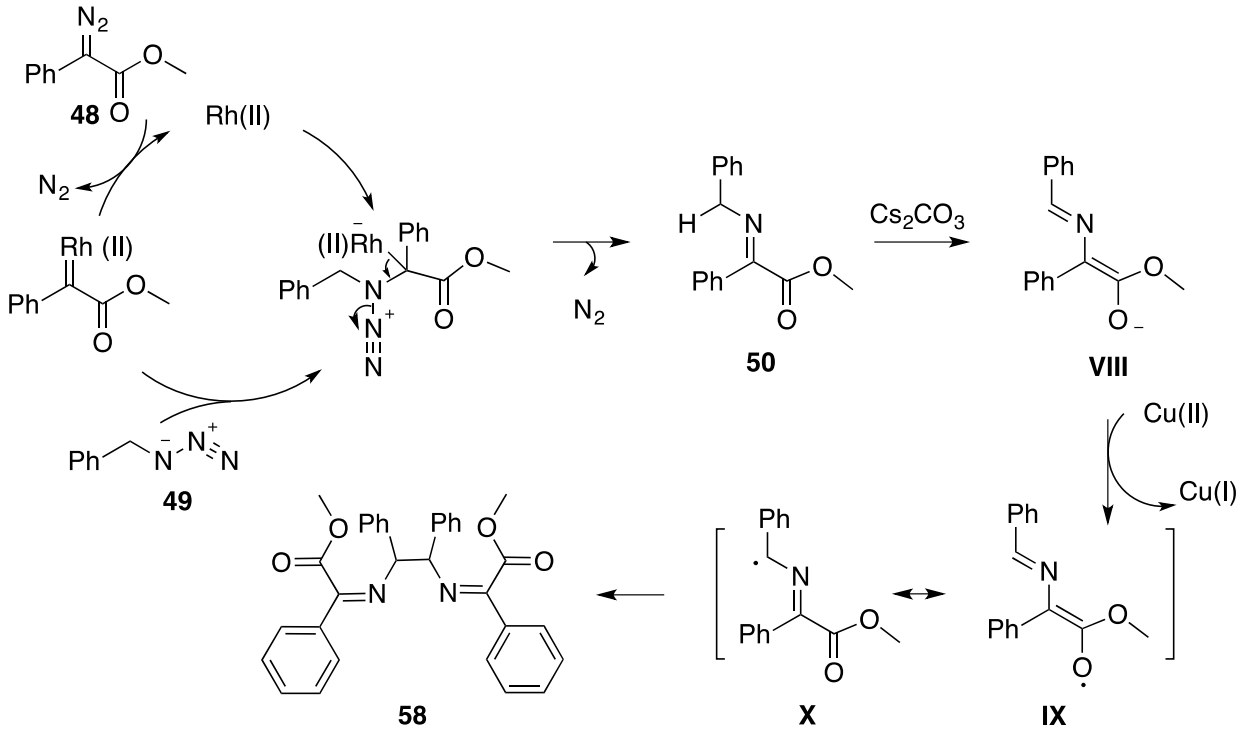
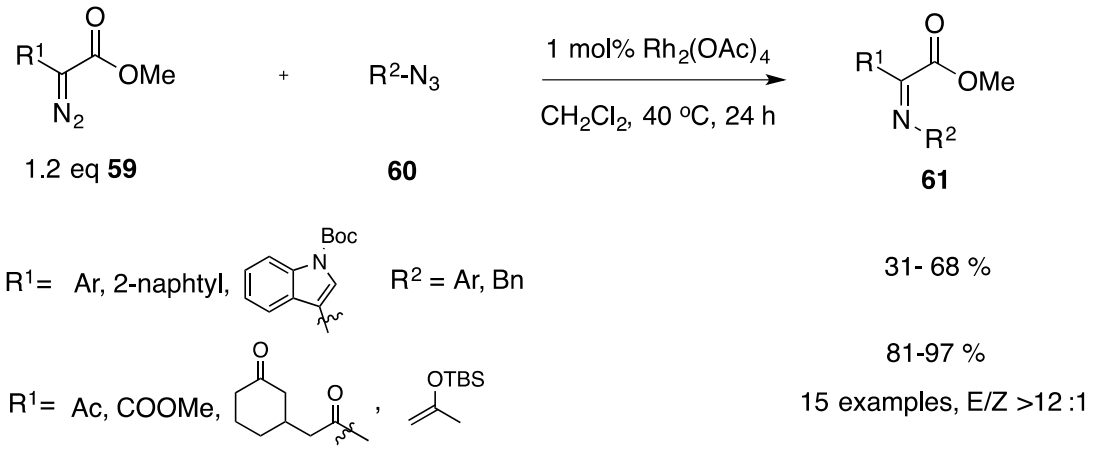


Figure 3. Proposed mechanism of dimerization of ketimine

2.3 Conclusion

This project has successfully demonstrated that alkyl azides can react intermolecularly with metallocarbene decomposed from diazoester to generate ketimine derivatives in high yield. However, the resulting α-imino ester was found to be less reactive; and the *in situ* trapping with a variety of carbon nucleophiles to generate α–quaternary amino esters was not successful. When the methyl indole was applied as nucleophile, bis(indole) adduct was obtained, albeit in low yield. Notably, when an external oxidant and base were applied in the azide/diazo system, the homocoupling of ketimine occurred.

In early 2014, while we were studying the *in situ* nucleophilic trapping of the ketimines, Doyle's group published the same methodology of intermolecular metallocarbene/azide coupling from α-diazoesters and organic azides to generate ketimine (Scheme 19).[37] They used the similar substrates yet milder reaction conditions: 1 mol% $Rh_2(OAc)_4$ as a catalyst in dichloromethane at 40 ^oC for 24 hour. The generality of this process was evaluated under these optimized conditions with a selection of azides and diazo compounds, and the Z-ketimines were obtained as the major diastereomer (*Z/E* ratio >12:1) in a relatively moderate to good yield.



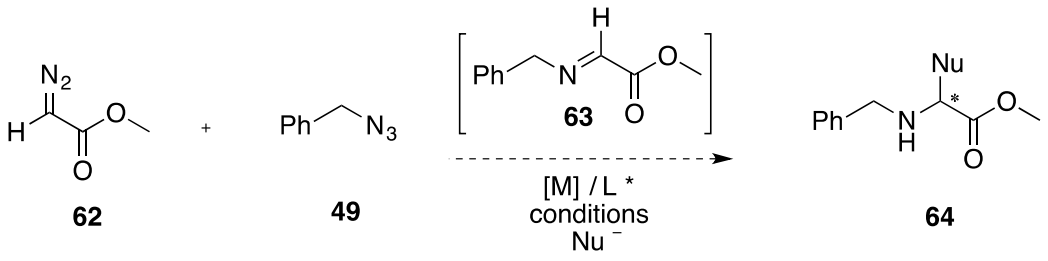
Scheme 19. Intermolecular metallocarbene/azide coupling methodology unveiled by Doyle's group

Regrettably, since the proposed *in situ* nucleophilic trapping to the α-imino ester has not been successful so far and the azide with diazo coupling methodology has been unveiled, the first project has been set aside for now.

2.4 Future Plans

The intermolecular metallocarbene/azide coupling has been successfully explored to generate imine derivatives, which has shown particular advantages over the traditional imine formation process. The potential of trapping the generated ketimine through one-pot or multicomponent reactions is still interesting. It was found that the *N*-alkyl-α-disubstituted imine is less reactive mostly due to its congested carbon center. If we could carry out the reaction with diazocarbacetate **62**, the less-hindered aldimine **63** would be formed correspondingly, which would be more likely to undergo effective trapping to afford nucleophilic adduct **64**. The reaction would still allow the generation of new C-N and C-C bonds in one step. The potential

for achieving this in an asymmetric fashion in the presence of a chiral ligand would achieve valuable chiral amine products (Scheme 20).



Scheme 20. Nucleophilic trapping of aldimine from α-diazoacetate and organic azide

2.5 Unexpected Result and New Discovery Related to Project

Our original proposal of *in situ* nucleophilic trapping was based on the idea that the catalyst used in the reaction would further function as a Lewis acid to activate the ketimine species, which, therefore, facilitates the nucleophile attack. Recently, rhodium has been extensively explored and used in a C-H activation reaction.[38] We have re-envisioned that the generated imine function could be a good directing group. In the presence of the rhodium catalyst, the imine directed *in situ* C-H activation would possibly occur. Thus, we proposed the *in situ* C-H activation pathway to generate the dihydro isoquinoline derivatives as shown in Figure 4. After the generation of ketimine ester **50** from metallocarbene/azide coupling, the rhodium would coordinate on nitrogen to give the complex **XI**.[39] An imine directed aromatic C-H bond, thus, could be activated by the rhodium catalyst to generate the cyclic metal complex **XII** through concerted metallation deprotonation or oxidative addition of rhodium depending on the oxidative state of the catalyst. If the proper coupling partner were used, in the case of phenyl acetylene **65**, migratory insertion of the coupling partner would generate the intermediate **XIII**. Using copper as transmetalating reagent would regenerate the rhodium catalyst and form the copper complex **XIV.** Conjugate addition of copper complex **XIV** followed by work up would furnish dihydro isoquinoline **66**.

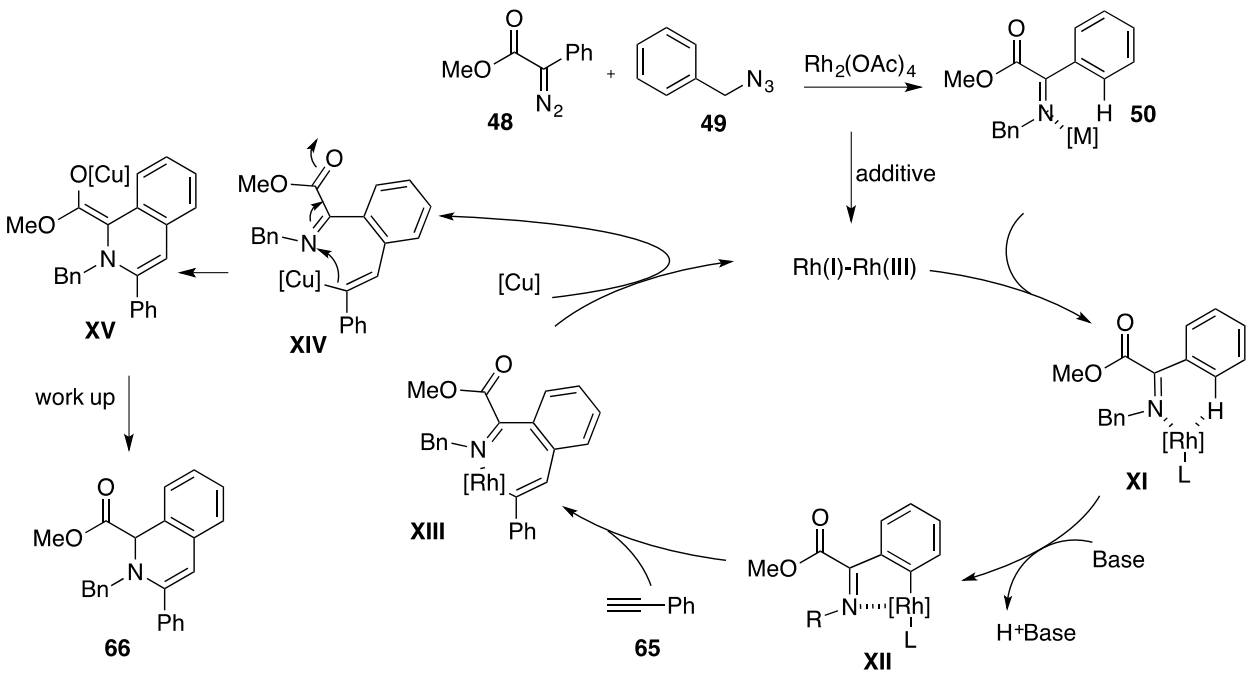
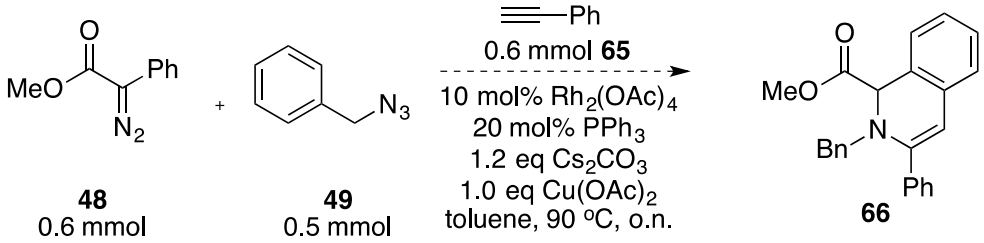


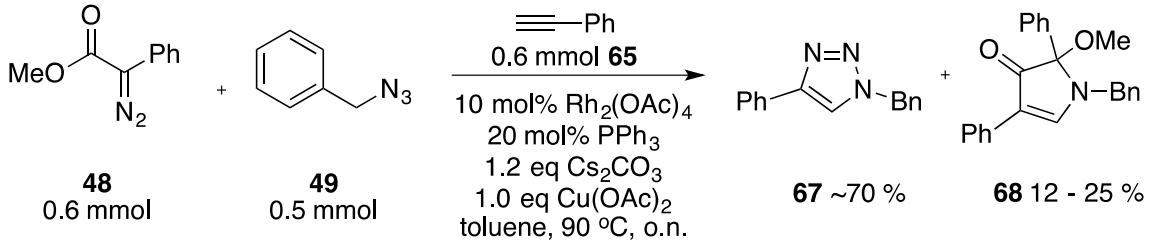
Figure 4. Proposed *in situ* C-H activation pathway to generate dihydro isoquinoline derivatives

With this proposal in mind, a preliminary experiment was conducted with the following reaction conditions (Scheme 21): using 10 mol% $Rh_2(OAc)_2$ as catalyst, 20 mol% PPh_3 as additive, 1.2 equiv Cs_2CO_3 as base, and 1.0 equiv $Cu(OAc)_2$ as transmetalating reagent in toluene at 90 ^oC for overnight.



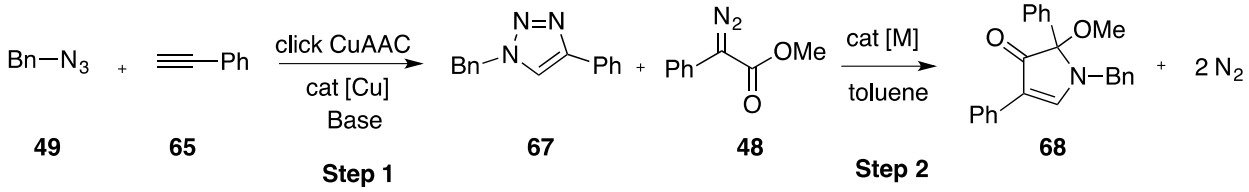
Scheme 21. Proposed *in situ* C-H activation pathway to generate dihydro isoquinoline derivatives

However, the desired product was not observed after work up. Instead, 70% of triazole **67** was isolated with 12–25% of strongly fluorescent compound **68**. The structure of **68** was confirmed by X-ray crystallography as 1-benzyl-2-methoxy-2,4-dihydro-3*H*-pyrrol-3-one, as shown in Scheme 22.



Scheme 22. Unexpected result from the *in situ* C-H activation proposal

The effective components involved in the formation of pyrrolinone **68** were found to be the diazoester **48** and triazole **67** (Scheme 23). Benzyl azide **49** was quickly cyclized with terminal alkyne **65** under CuAAC (copper catalyzed alkyne/azide cycloaddition) to give triazole **67** (Scheme 2.20, Step 1).[40] In the presence of the dirhodium catalyst, diazoester **50** was decomposed and reacted with triazole **67** to generate pyrrolinone **68** (Scheme 23, Step 2).



Scheme 23. Reaction components elucidation to form pyrrolin-3-ones **68**

The unexpected result has quickly attracted our attention. First of all, the reaction generates the relatively uncommon 4-pyrroline-3-one heterocyclic system.[41] The 4-pyrroline-3-one **68** bearing a methoxy group at 2-position give a strong fluorescence (Ex/Em = 385/480 nm) and is potentially useful in material chemistry and pharmaceutical industry.[46] Moreover, to our knowledge, the reaction shows a unprecedented reactivity of stable 1,2,3-triazole with metalocarbenes.[47] The details of this methodology will be discussed in Chapter 3.

2.6 Experimental Procedures and Characterization

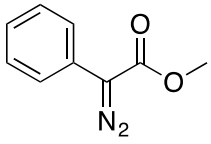
2.6.1 General Information

Reactions were conducted in flame-dried glassware under a positive argon atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: methylene chloride from calcium hydride, tetrahydrofuran, diethyl ether from Na/benzophenone ketyl, toluene from sodium metal. All other solvents and commercially available reagents were either purified by standard

procedures or used without further purification. Thin layer chromatography was performed on glass plates precoated with 0.25 mm silica gel. The developed plate was analyzed under a UV lamp (254 nm and 350 nm) and/or stained with potassium permanganate solution (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10% NaOH in 200 mL H_2O) or 2.5% *p*-anisaldehyde in AcOH-H_2SO_4-EtOH (1:3:85) and further heating until the development of color. Flash chromatography was performed on a 230–400 mesh silica gel with the indicated eluents. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz or 500 MHz on Varian Inova 400 and 500, Mercury 400, or Unity 500 spectrometers, and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane (0 ppm). Coupling constants (*J*) are reported in Hz. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 125 MHz or 100 MHz and are reported (ppm) relative to the center line of a triplet at 77.23 ppm for deuterochloroform. Infrared (IR) spectra were measured with a Nicolet Magna 750 FT-IR infrared spectrophotometer and were recorded and reported in cm^{-1}. Mass spectra were determined on a Kratos Analytical MS-50 (EI) or Applied Biosystems Mariner Biospectrometry Workstation (ESI). Elemental analyses were obtained on a Carlo Erba CHNS-O EA 1108 Elemental Analyzer.

2.6.2 Characterization

Methyl diazo(phenyl)acetate 48[32]



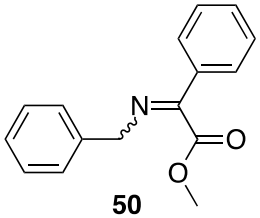
48

To a solution of methyl phenylacetate (2.25 g, 15.0 mmol) and *p*-toluenesulfonyl azide (3.29 g, 16.7 mmol) in CH_3CN (25.0 mL) at 0 ^oC was added 1,8-diazabicyclo [5.4.0]undec-7-ene (2.70 mL, 18.0 mmol) dropwise. The mixture was stirred at room temperature for 5 h. The orange-colored reaction mixture was partitioned between Et_2O (50.0 mL) and water (25.0 mL). The organic layer was washed successively with water (25.0 mL) and brine (25.0 mL), and dried over anhydrous $MgSO_4$. Filtration and evaporation gave crude product, which was purified by column

chromatography (silica gel, hexane/EtOAc = 20:1 as an eluent) to provide **50** (1.90 g, 72%) as an orange oil. Spectral data were consistent with those reported in the literature. [32]

Methyl 2-diazo-2-phenylacetate 48: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 3.86 (s, 3H).

Procedure for the Synthesis of Imine 50

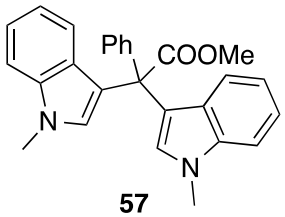


50

To a flame-dried round bottom flask equipped with a magnetic stir bar was added benzyl azide **49** (33.3 mg, 0.250 mmol), $Cu(hfacac)_2$ monohydrate (6.20 mg, 0.0125 mmol), and toluene (2.00 mL). The flask was connected with a condenser which was capped with a rubber septum, and an argon line was attached through a needle into the septum while the mixture was stirred at 90 °C in an oil bath. Then, a solution of diazo compound **48** (52.8 mg, 0.300 mmol) in 1 mL of toluene was slowly added by injection via a syringe over 10 min. The reaction mixture was allowed to stir for 1 h at 90 ^{o}C. After cooling, the solvent was removed by rotary evaporation and the reaction mixture was purified by flash column chromatography (silica gel) using hexanes/EtOAc = 10:1 with 1 % Et_3N as the eluent to provide an inseparable mixture of isomeric imines **50** with ratio 1:5 as a light yellow oil (52.3 mg, 83% yield from benzyl azide **49**). The major imine isomer was assigned to be *(Z)* by analogy to a known compound with stereochemistry was verified by X-ray crystallography in the literature.[42]

Methyl 2-(benzylimino)-2-phenylacetate 50 TLC R_f (Hexane/EtOAc = 1/10 with 1 % Et_3N) = 0.45; IR (film) 3062, 3030, 2952, 2921, 2851, 1734, 1639, 1452, 1206, 1042, 1003, 777, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.80 (m, 2H), 7.52-7.28 (m, 8H), 4.79 (s, 2H), 4.02 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) 166.0, 160.5, 138.8, 134.3, 131.2, 128.6, 128.5, 128.0, 127.4, 127.1, 58.7, 52.0. HRMS (EI, M+) $C_{16}H_{15}NO_2$ calcd 253.1103, found: m/z 253.1107.

Procedure for Preparation of Bis(indole) product 57

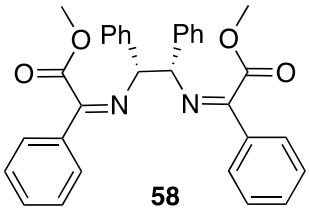


57

To a flame-dried round bottom flask equipped with a magnetic stir bar was added benzyl azide **49** (26.7 mg, 0.200 mmol), $Cu(OTf)_2$ (7.20 mg, 0.0200 mmol), and dichloromethane (2.00 mL). The flask was connected with a condenser which was capped with a rubber septum, and an argon line was attached through a needle into the septum while the mixture was stirred at reflux in an oil bath. Then, a solution of diazo compound **48** (42.3 mg, 0.240 mmol) in 1 mL of dichloromethane was slowly added by injection via a syringe over 10 min. The reaction mixture was allowed to stir for 1 h at reflux. Cooling the reaction to room temperature, methyl indole (52.5 mg, 0.400 mmol) was added in the system under argon. The reaction mixture was stirred at rt for 12 h. The mixture was extracted with dichloromethane (10.0 mL) and washed with water (2 x 10.0 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography to afford the **57** (11.5 mg, 14% yield) as a white solid.

Methyl 2,2-bis(1-methyl-1*H*-indol-3-yl)-2-phenylacetate 57 ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.38 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2 H) 7.29-7.28 (m, 3 H), 7.23-7.19 (m, 4 H), 6.97 (dt, *J* = 8.0, 1.0 Hz, 2 H), 6.70 (s, 2 H), 3.8 (s, 3H), 3.7 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.5, 142.3, 137.5, 129.5, 129.1, 127.7, 127.4, 126.8, 122.0, 121.3, 118.9, 117.4, 109.2, 56.5, 52.4, 32.8.

Procedure for Preparation of 58



58

To a flame-dried round bottom flask equipped with a magnetic stir bar was added benzyl azide **49** (66.6 mg, 0.500 mmol), $Rh_2(OAc)_4$ (11.0 mg, 0.0250 mmol), Cs_2CO_3 (195.5 mg, 0.600 mmol), $Cu(OAc)_2$ (90.8 mg, 0.500 mmol), and toluene (4.00 mL). The flask was connected with a condenser which was capped with a rubber septum, and argon line was attached through a needle into the septum while the mixture was stirred at 90 °C in an oil bath. Then, a solution of diazo compound **48** (122 mg, 0.600 mmol) in 1 mL of toluene was slowly added by injection via a syringe over 10 min. The reaction mixture was allowed to stir at 90 ^oC for 14 h. The reaction mixture was partitioned between Et_2O (50.0 mL) and water (25.0 mL). The organic layer was washed successively with water (25.0 mL) and brine (25.0 mL), and dried over anhydrous $MgSO_4$. Filtration and evaporation gave crude residue, which was purified by column chromatography (silica gel, hexane/EtOAc = 10:1 as an eluent, 1% Et_3N) to provide **58** (90.8 mg, 72 %) as white solid as single diastereomer according to the X-ray structure and proton NMR. The structure was assigned by X-ray crystallography.

(2*Z*, 2'*Z*)-dimethyl 2,2'-1,2-diyl)bis(azan-1-yl-1-ylidene)bis(2-phenylacetate) 58 IR (br) 3085, 3030, 2950, 2897, 1735, 1600, 1208, 1029,817, 761, 698 cm^{-1}; ^1H NMR (400 MHz, d6-DMSO/$CDCl_3$) 7.89 (m, 2 H), 7.63 (dt, J = 7.6, 1.6 Hz, 4 H), 7.34-7.27 (m, 6 H), 7.09-7.05 (m, 8 H), 4.84 (s, 2 H), 3.91 (s, 6 H). ^{13}C NMR (100 MHz, DMSO) 165.3, 159.1, 139.6, 134.4, 131.2, 128.7, 128.3, 128.1, 127.6, 127.5, 75.1, 52.0; HRMS (EI, ½ M+H) for $C_{32}H_{28}N_2O_4$ calcd 505.2121, found: m/z 505.2122. m.p: 171-174 ^oC.

2.7 References

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Chapter 3

Formation of 4-Pyrroline-3-ones from 1,2,3-Triazoles *via* Metallocarbenes

3.1 Chemistry of 1,2,3-Triazoles

1,2,3-Triazoles are among the most important heterocyclic compounds with a broad spectrum of applications in areas ranging from medicinal chemistry to material science (Figure 1).[1] 1,2,3-Triazoles have been investigated extensively in heterocyclic chemistry since their initial preparation in 1888 by von Pechmann.[2] However, it was not until the beginning of the 21st century that 1,2,3-triazoles became commonplace due to the discovery of the CuAAC (copper-catalyzed azide/alkyne cycloaddition) reaction by Sharpless/Fokin and Meldal groups.[3] Since then, great additional interest in 1,2,3-triazole chemistry has led to a surge of publications and new applications.[4,21,24-26]

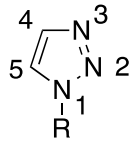
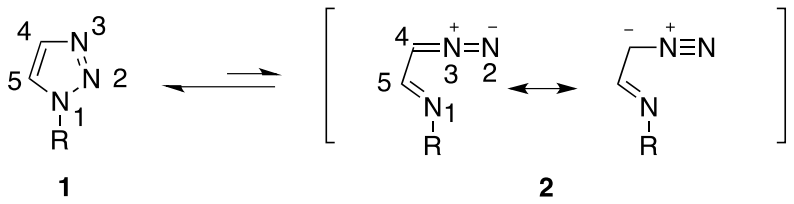


Figure 1. General structure of the *N*-substituted-1,2,3-triazoles

In general, the 1,2,3-triazole ring system is remarkably stable under oxidative, reductive, acidic and basic conditions due to its aromaticity.[5] Despite its high stability, some synthetically useful reactions have been reported with this system.[6] In Chapter 3, we will briefly review the ring transformation reactions of 1,2,3-triazole compounds including ring chain tautomerization and rearrangement, thermolysis and metal catalyzed transannulation reactions. The transannulation reaction of stable 1,2,3-triazoles with metallocarbene have also been discovered in this chapter. Its application to the formation of the relatively uncommon 4-pyrroline-3-one heterocyclic system is included at the end of the chapter.

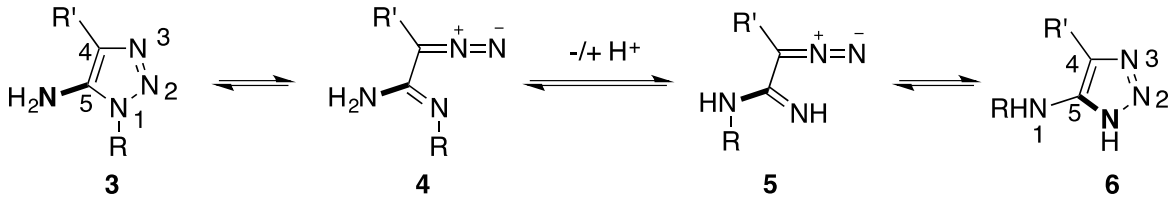
3.1.1 Ring Chain Tautomerization and Rearrangement of 1,2,3-Triazoles

Ring-chain tautomerization is an important phenomenon in the chemistry of 1,2,3-triazoles. Its diazoimine tautomers **2** are essential intermediates in numerous rearrangements and other ring-transformation reactions (Scheme 1).[7]



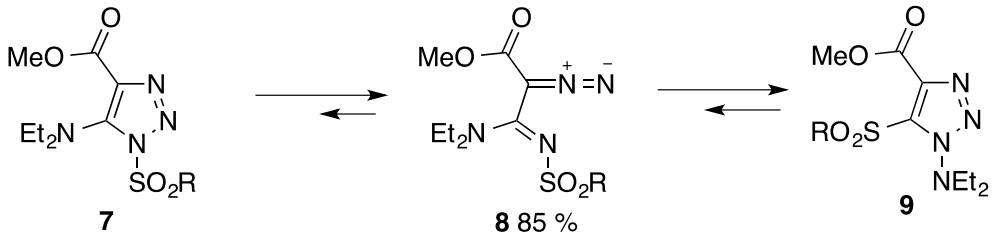
Scheme 1. Tautomerization of 1,2,3-triazoles: diazoimine/1,2,3-triazole equilibrium

Tautomerization of 1,2,3-triazoles was first described by Dimroth in 1904.[8] He found that 1,2,3-triazoles **3** with an amino group at 5-position were isomerized into 5-amino-1,2,3-triazoles **6**, where the endocyclic and exocyclic nitrogen atoms switched places. It was proposed that the reaction proceeded *via* a ring cleavage of **3** into diazoimine **4** followed by proton transfer to generate isomeric diazoimine **5**. The 1,2,3-triazole isomer **6** was subsequently formed *via* ring cyclization of diazoimine **5**. It should be noted that the equilibrium was shifted towards the isomer **6** when additional electron-withdrawing substituents were attached at the 1- and 4-position (Scheme 2).



Scheme 2. Dimroth rearrangement of 1,2,3-triazoles

The mechanism of 1,2,3-triazole tautomerization has aroused great interest since its discovery.[9] Examples have been published confirming the existence of the equilibrium between 1,2,3-triazole **3** and diazoimine **4,** which was believed to be the key intermediate in the transformation. For example, in the isomerization reaction of 5-amino-1-sulfonyltriazoles **7** into tautomers **9**, the diazoimines **8** was isolated from the process in good yield (Scheme 3).[10]



Scheme 3. Isolation of diazoimines from 1-sulfonyltriazoles

The ring closure of diazoimine into triazole was proposed to occur through pseudopericyclization.[11,12] The new N–N bond occurs from the in-plane interaction of the lone pair on the imino group nitrogen (1-position) with the π* orbital on the terminal nitrogen of the diazo group.[13] Density functional theory (DFT) calculation by Oliver Kappe and co-workers[13] has shown a low activation energy (9–12 kcal) for the cyclization from diazoimine **11** into 1,2,3-triazoles **12** (Figure 2), which supported the pseudopericyclization mechanism.

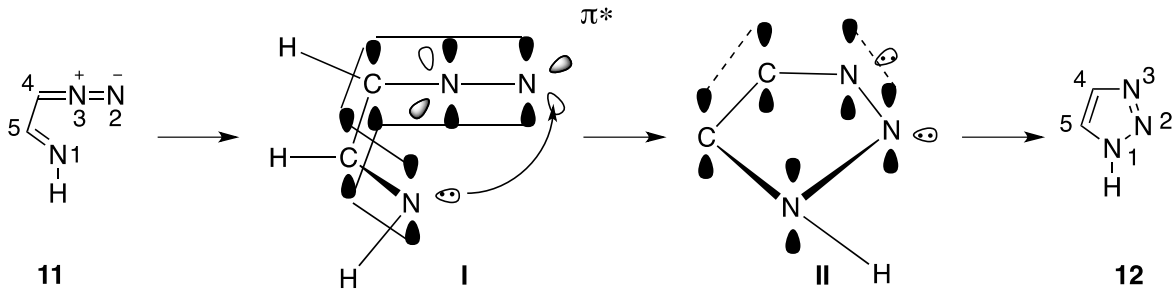
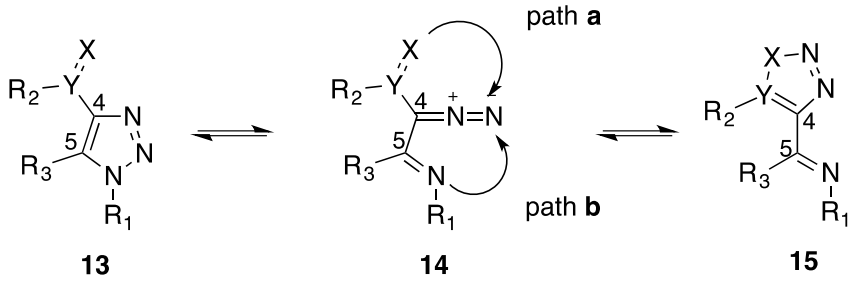


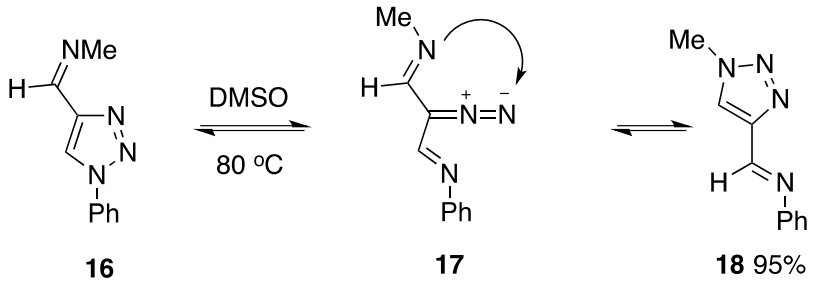
Figure 2. The pseudopericyclic 1,5-electrocyclization of diazoimine **11** to triazole **12**

1,2,3-Triazoles **13** possessing a conjugated X=Y substituent such as C=N, C=S or N=N at the 4-postion can rearrange to imino-substituted heterocycles **15**[14] (Scheme 4). A key feature of this type of rearrangement, as shown in the intermediate **14**, is the competitive cyclization of diazo function either onto the nitrogen of the imino group (path b) to give **13**, or onto the X=Y group (path a) to generate the rearranged product **15**.



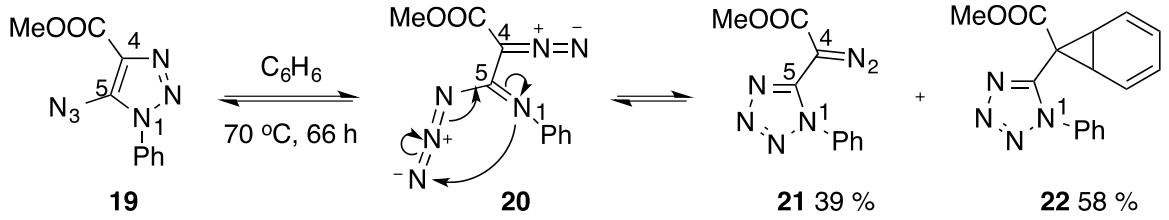
Scheme 4. Rearrangement with participation of two atoms of the side chain

As an example, L'abbé and co-workers[15] reported when heating the iminomethyltriazole **16** in dimethyl sulfoxide at 80 °C, isomeric triazole **18** was obtained in 95% yield *via* cyclization of diazoimine intermediate **17** (Scheme 5).



Scheme 5. Rearrangement of 4-imino-1,2,3-triazoles

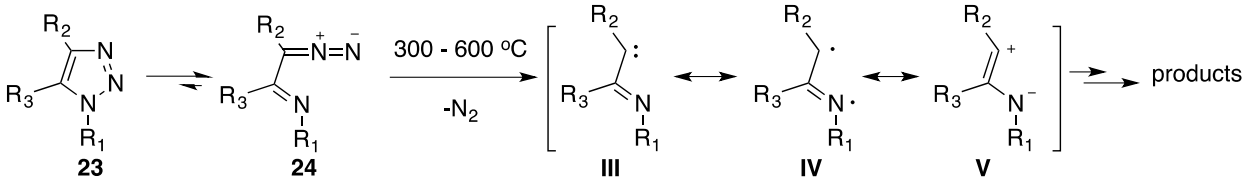
Another type of rearrangement by 1,2,3-triazoles involves competitive 1,5-cyclizations of a single imino group onto two distinct 1,3-dipole moieties. For example, 5-azido-1,2,3-triazoles **19** with electron-withdrawing ester substituents at 4-position would rearrange into 5-diazomethyl-tetrazoles **21** upon heating in benzene at 70 °C (Scheme 6).[16] Compound **22** was observed as side-product *via* cyclopropanation of **21** with benzene solvent.



Scheme 6. Rearrangement of 5-azido-1,2,3-triazoles

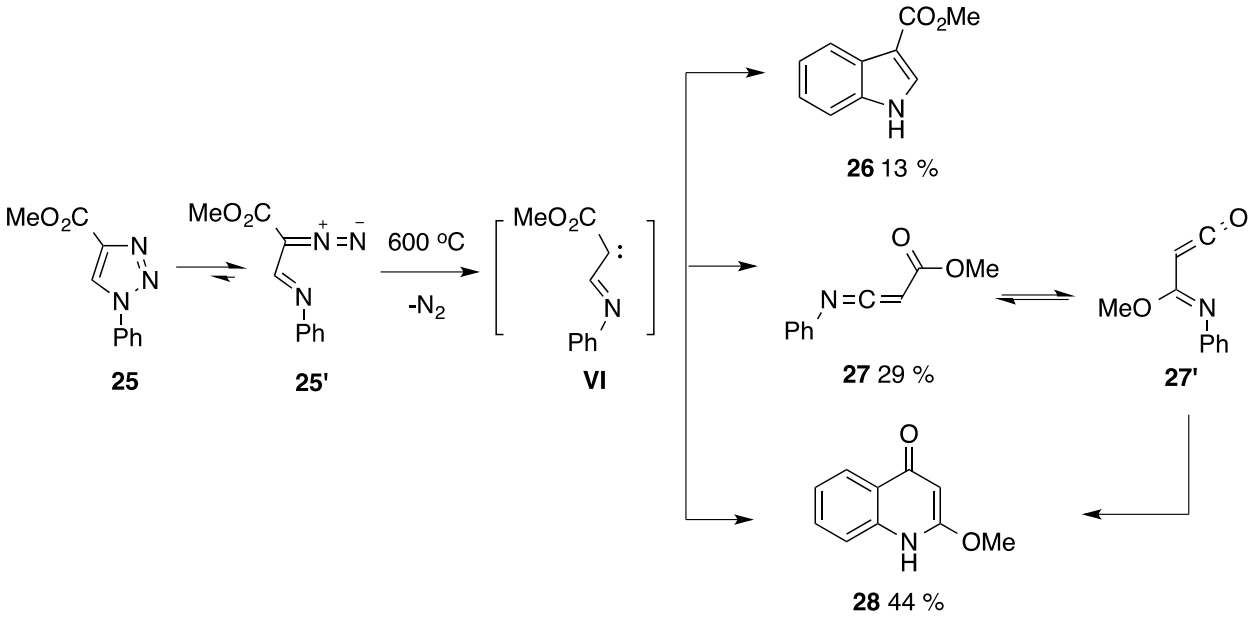
3.1.2 Flash Vacuum Pyrolysis and Thermolysis of 1,2,3-Triazoles

Flash vacuum pyrolysis (FVP) is a gas-phase continuous-flow technique where a substrate is sublimed through a hot quartz tube under high vacuum at high temperatures (400–1100 °C).[17] FVP is a useful technique to identify reactive intermediates and investigate the reaction mechanisms. Since the process only allows a short period of exposure for the substance at a high temperature, the kinetically controlled products could be isolated exclusively without processing to subsequent transformations.[17b] The FVP reactions of 1,2,3-triazoles generally require high temperatures due to their high stability. The reaction pathway was presumed to undergo the elimination of dinitrogen to form free carbene **III**, with may exist as alternative diradical (**IV)**, or zwitterion (**V)** forms. Further transformations of those reactive intermediates generate a variety of products (Scheme 7).[18]



Scheme 7. The carbene **III**, diradical **IV**, or zwitterion **V** resonance from FVP reaction of 1,2,3-triazoles

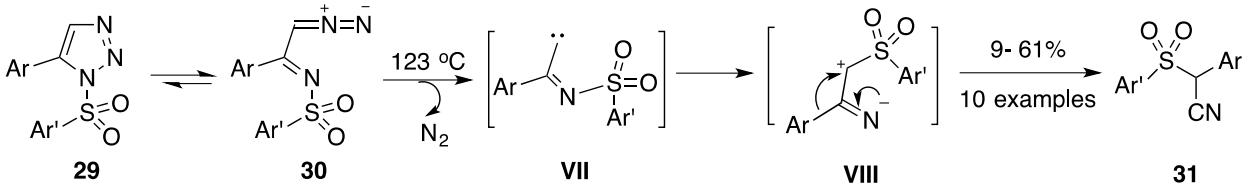
Wentrup and Fulloon[19] reported an FVP reaction of 1-phenyl-1,2,3-triazole-4-carboxylate **25** at 600 °C generating indole **26**, ketenimine **27** and quinolone **28** (Scheme 8). Imidoylcarbene intermediate **VI** was initially generated by extrusion of dinitrogen of triazole **25** at high temperature. Intramolecular cyclization of imidoylcarbene **VI** provided indole **26** in 13% yiled.[19b] Ketenimine **27** was obtained *via* a 1,2-hydride shift of imidoylcarbene **VI**.[19c] Quinolone **28** was presumed to be generated from intramolecular cyclization of ketene **27',** which is isomerized from ketenimine **27**.



Scheme 8. FVP of 1-phenyl-1,2,3-triazole-4-carboxylate **25**

The introduction of electron withdrawing substituents at N-1 position of 1,2,3-triazole significantly lowered the activation energy of ring-chain tautomerization in thermal conditions. Croatt and co-workers[20] reported that 1-sulfonyl-1,2,3-triazoles **29** underwent thermolysis at 123 °C to generate **31** in moderate to low yield (Scheme 9). The author proposed that extrusion of

dinitrogen of **29** generates a carbene **VII** followed by a 1,3-sulfonyl shift to form zwitterion **VII**. [1,2]-Shift of the resulting zwitterion **VIII** provided α-nitrile **31**.

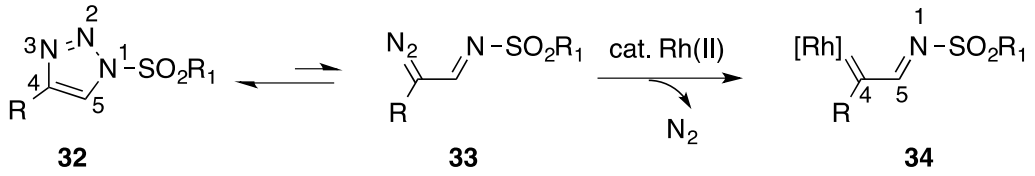


Scheme 9. Thermolysis of 1,5-disubstituted sulfonyl-triazoles **29** to generate α-nitrile **31**

3.1.3 Metal Catalyzed Transformations of 1,2,3-Triazoles

Although ring transformations of 1,2,3-triazoles were known from the middle of the last century, applying metal catalysis to 1,2,3-triazole chemistry has only become popular in recent years. Starting in 2007, with early reports from the Gevorgyan group and followed subsequently by Fokin and Murakami,[2] the metal catalyzed transannulation of *N*-sulfonyl-1,2,3-triazoles have been merged as a powerful synthetic tool to achieve a variety of nitrogen containing heterocycles.

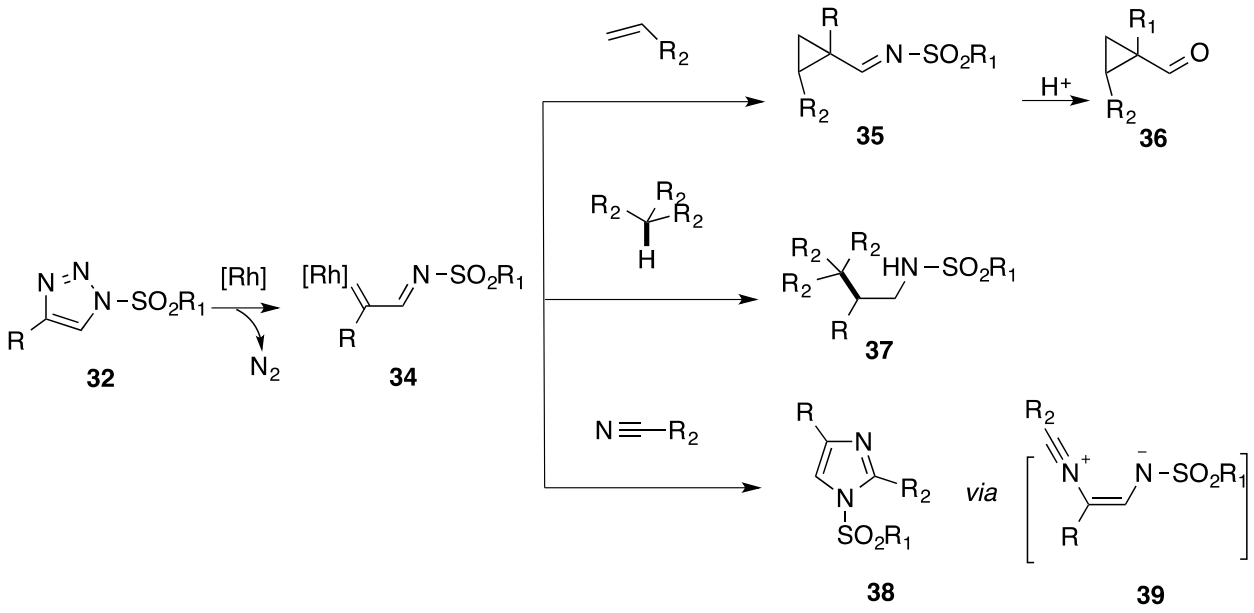
The isomerization of the 1,2,3-triazole ring is strongly affected by the substituents on the heterocycles.[22] Triazoles **32** bearing an electron withdrawing sulfonyl group at N1 atom experience polarization of the triazole aromatic system, facilitating ring-opening equilibrium towards diazoimine tautomer **33**. Gevorgyan and Fokin took advantage of this process by trapping diazoimine **33** with a rhodium catalyst to produce the putative Rh(II)-iminocarbene **34** (Scheme 10).[23]



Scheme 10. Decomposition of *N*-sulfonyl triazoles with Rh(II) to generate Rh(II)-iminocarbenes

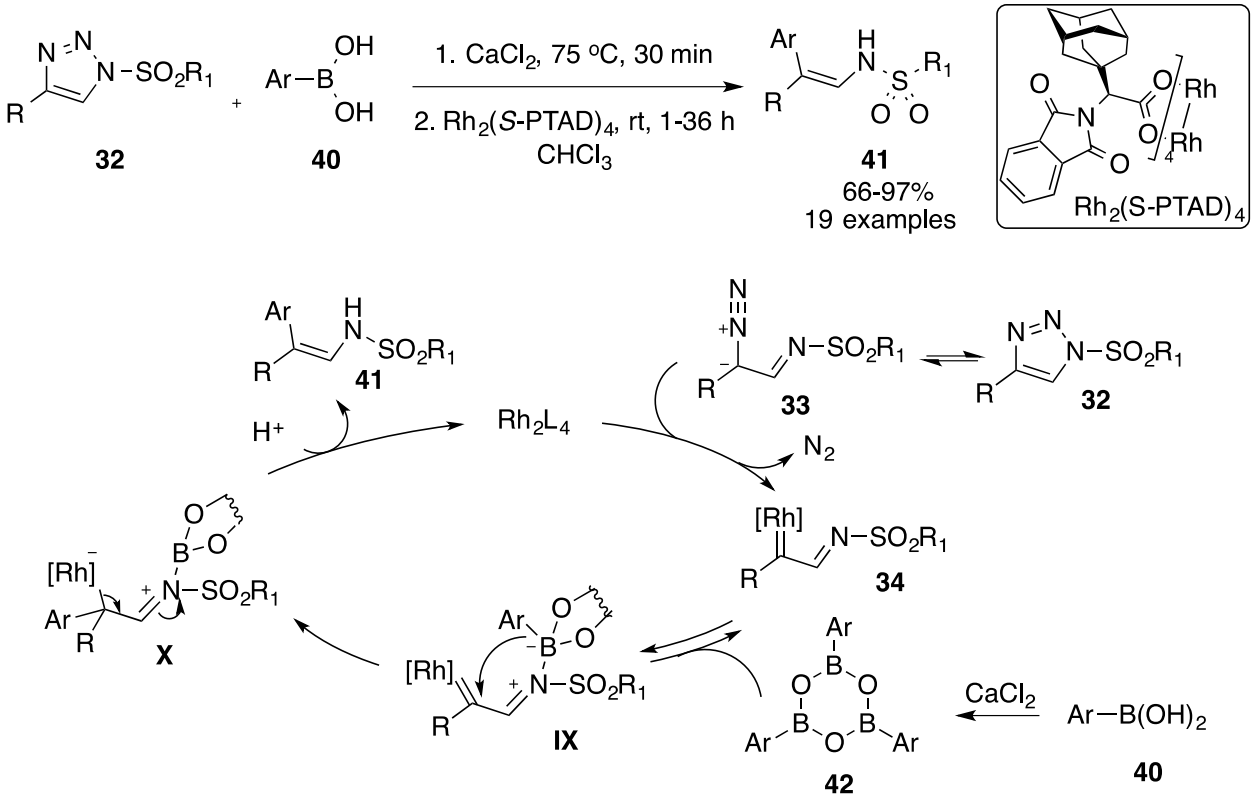
Rh(II)–iminocarbenes **34** possess a reactivity inherent to Rh(II) carbenoids. For example (Scheme 11), Rh(II)–iminocarbene **34** cyclopropanates with alkenes to generate α-imino cyclopropanes **35** followed by hydrolysis to form **36**.[24] Rh(II)–iminocarbenes **34** undergoes C-H insertion into a secondary or tertiary aliphatic C-H bonds to generate amines **36**.[25] When treating

Rh(II)–iminocarbene **34** with nitrile compounds,[26] a nucleophilic attack of nitrile N atom on the Rh(II)–iminocarbene **34** followed by intramolecular cyclization provides imidazole **38** (Scheme 11).



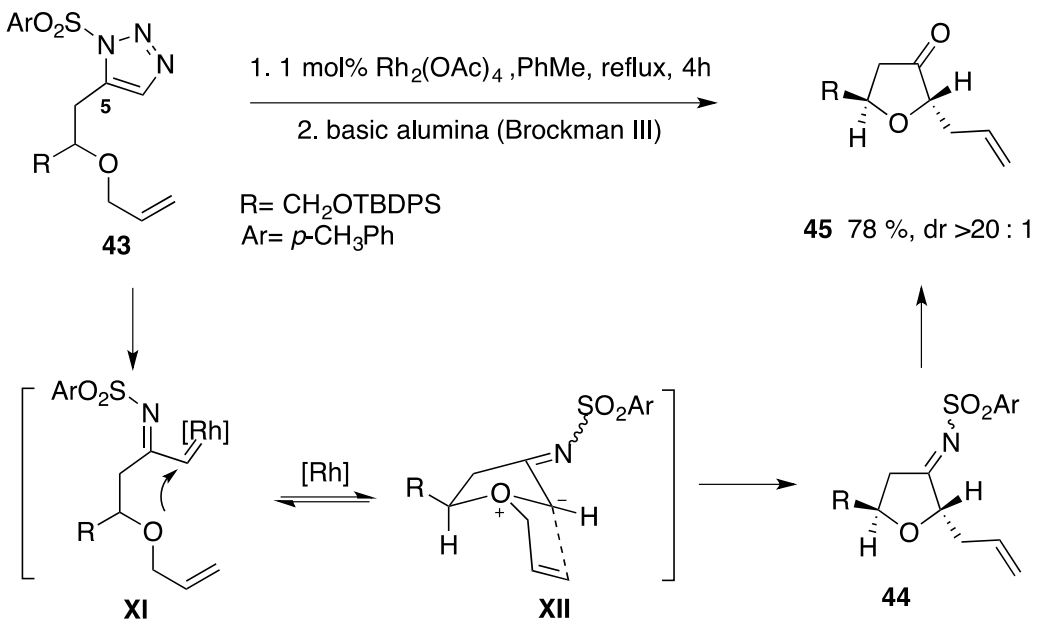
Scheme 11. General reactivity of Rh(II)-iminocarbenes

Fokin and co-workers[27,28] recently discovered a direct arylation of Rh(II)-iminocarbenes with arylboronic acids **40** generated enamines **41** in moderate to good yield with high diastereoselectivity where the Ar group was *cis* to the amine group (Scheme 12). The authors proposed a plausible mechanism as shown in Scheme 12. Ring-chain tautomerization of triazole **32** allowed generation of diazoimine **33**, which was decomposed by the rhodium carboxylate catalyst to form Rh(II)-iminocarbene **34**. The lone pair of the imine nitrogen of **34** reversibly coordinated with the empty $2p_z$ orbital of the boron atom to form intermediate **IX**. The stereochemical outcome was likely dictated by the irreversible facial-selective delivery of the aryl group from complex **IX** to **X**. Finally, dissociation of rhodium afforded the enamine product **41**. It was noted by authors that the active arylation species was believed to be a trimeric arylboroxine **42**, since the product enamines **41** could be obtained directly from commercially available arylboroxines without the use of $CaCl_2$.



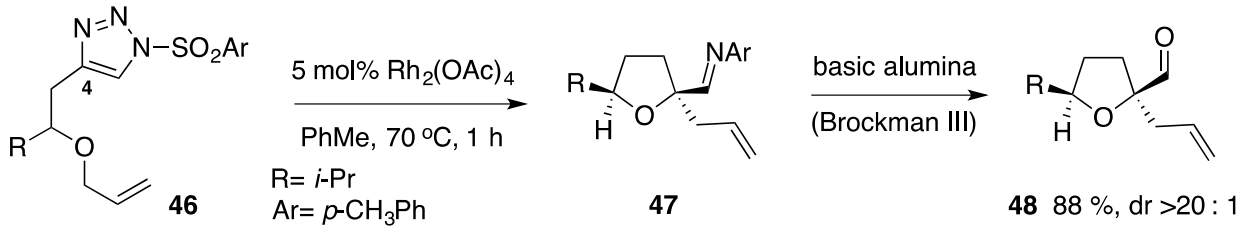
Scheme 12. Direct arylation of Rh(II)-iminocarbene with boronic acids

Recently, Boyer[29] reported the formation of dihydrofuran-3-imines **45** from the Rh(II)-catalyzed rearrangement of triazoles **43** bearing remote allyl ether substituents at the 5-position (Scheme 13). The reaction was proposed to proceed *via* [2,3]-sigmatropic rearrangement of oxonium ylide **XI,** which was generated from the intramolecular nucleophilic attack of an oxygen lone pair on Rh(II)-iminocarbene **XII**. The high diastereoselectivity was presumed to arise from preferred conformer **XII** where the bulky substituent R and allyl group are positioned in a pseudo equatorial position.



Scheme 13. [2,3]-Rearrangement of oxonium ylide from intramolecular interaction of oxygen with Rh(II)-iminocarbene

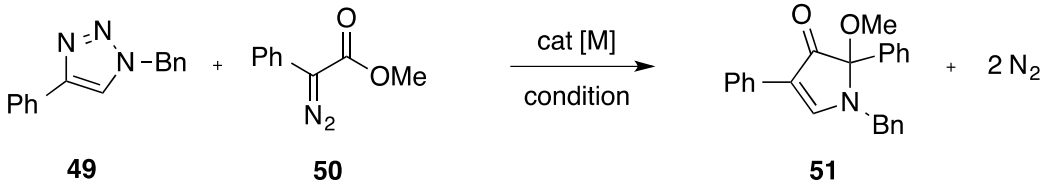
Later, a complementary reaction was published by the same author.[30] When the pendent allyl ether group was installed at 4-position of triazole **46**, in the presence of 5 mol% $Rh_2(OAc)_4$, tetrahydrofuran **48** was obtained in excellent yield with high diastereoselectivity (Scheme 14).



Scheme 14. Synthesis of tetrasubstituted tetrahydrofuran **48** from *N*-sulfonyl-4-subsituted triazole **46**

A brief overview of the ring transformation reactions of 1,2,3-triazoles has been discussed above. However, most 1,2,3-triazole ring transformation reactions require harsh reaction conditions such as high temperature or need to be activated with a strong electron-withdrawing substituent on the saturated tirazole nitrogen atom. The majority of the stable triazoles are unresponsive to all types of reactions in normal conditions. Herein, we report for the first time the transannulation of stable, non-activated 1,2,3-triazole **49** with diazocarbonyl **50** in the presence

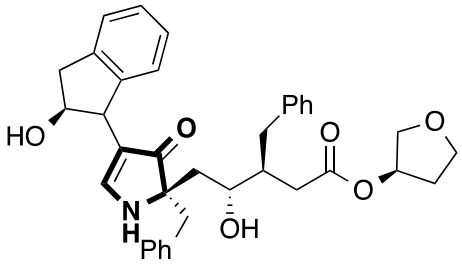
of rhodium catalyst generate the 4-pyrroline-3-one derivatives **51**. The structure of the heterocycle **51** was further confirmed by X-ray crystallography (Scheme 15).



49 **50** **51**

Scheme 15. Formation of 4-pyrrol-3-one from unactivated 1,2,3-triazole with metallocarbene

Moreover, the pyrrolinone scaffold similar to **51** is present in diverse pharmaceutically active compounds and is potentially useful in the development of drugs for treating many infectious diseases.[31] For example, peptide-pyrrolinone hybrid complex molecule **52** has been investigated and shows promising activity as HIV-1 protease inhibitors (Figure 3).[31b]



52 HIV-1 protease inhibitor

Figure 3. HIV-1 protease inhibitor containing a pyrrolinone core

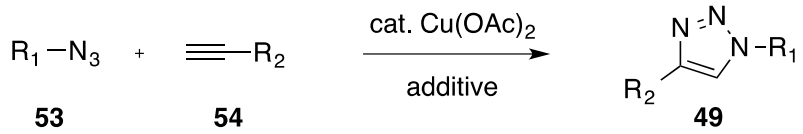
Interestingly, the obtained 4-pyrroline-3-ones **51** bearing a methoxy substituent at the 2-position possess a strong fluorescence (Ex/Em = 385/480 nm), which have potential applications in the filed of fluorescence chemistry.[31g-h] However, straightforward procedures for pyrrolinones were limited in the past, and only a few methods have been known for the preparation of pyrrolinone derivatives; although various processes have been documented for the synthesis of pyrroles.[32] In general, methods can be employed for this purpose including (i) [2 + 3] cycloaddition reaction of cyclopropenones with imines;[32a] (ii) flash-vacuum pyrolysis of aminomethylene Meldrum's acid derivatives;[32b, 32c] (iii) cyclocondensations of α-amino esters with aldehydes;[31b, 32d] reaction of vicinal tricarbonyls with enamines;[32e] (iv) hypervalent iodine reagent-mediated cyclization reaction of enaminones;[32f] (v) intramolecular alkylation reaction of 3-hydroxypyrrole-2-carboxylates;[32g] (vi) NIS-promoted coupling/cyclization of symmetrical diynones;[32h] (vii) Pt[32i] and Au[32j] mediated intramolecular amination of aminoynones; and (viii) the more recently

developed thermal cyclization of acetylenic enamines.[32k] Invariably, some of these methods suffer from serious drawbacks such as multi-step operations, and non-readily available reactants and/or lower product yields. Herein, we described a new synthetic method that constructed 4-pyrroline-3-one rings with simultaneous formation of a tetrasubstituted carbon center at the 2-position.

3.2 Results and Discussion

3.2.1 Synthesis of the Substrates

With the goal of examining the scope and limitation of pyrrolinone formation from transannulation of stable 1,2,3,-triazole with diazocarbonyl compounds, several triazole starting materials were prepared. Preparation of the triazole was accomplished via the known procedure using CuAAC (copper catalyzed azide-alkyne cycloaddition) process employing an organic azide with a terminal alkyne.[33] High regioselectivity was observed in all reactions, where no isomeric 5-substituted 1,2,3-triazoles were detected (Scheme 16). The corresponding diazocarbonyl partners could be prepared by standard Regitz diazo transfer conditions, as discussed in Chapter 2.

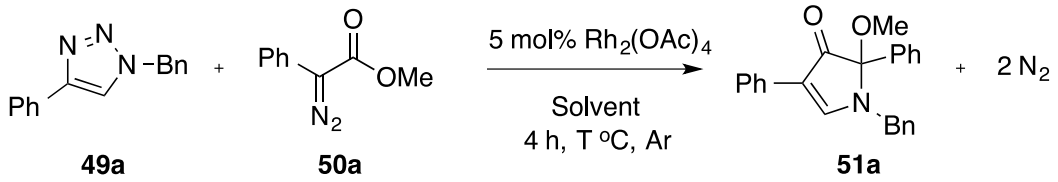


Scheme 16. General scheme for CuAAC reaction to form triazole substrates

3.2.2 Optimization of the Reaction

An initial survey of the reaction solvent with variable temperatures was quickly executed with 1-benzyl-4-phenyl-1,2,3-triazole **49a** and methyl diazophenylacetate **50a** in the presence of 5 mol% of dirhodium tetraacetate. The representative results are summarized in Table 1. Primary solvent screening disclosed that the desired product **51a** could be obtained albeit with a low yield using DCE as solvent at 85 ^{o}C (entry 1). Other solvents such as CH_3CN and DMF were inappropriate and no target product was observed (entries 2 and 4). However, heating the reaction in toluene at reflux furnished product **51a** in 52% yield (entry 3). Either higher-boiling solvents such as xylene, or the lower boiling halocarbon DCM provided lower yields (entries 5 and 6). As a result, toluene was initially selected as the optimal solvent for further investigation.

Table 1. Primary survey of solvent with variable temperatures [a]



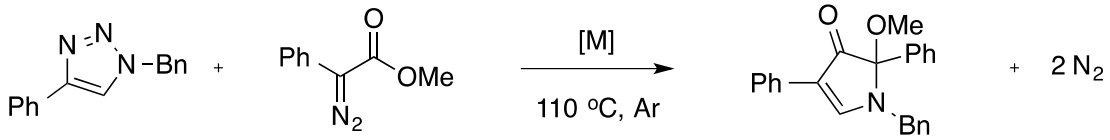
49a **50a** **51a**

Entry	**50a** (equiv)	Solvent	T (°C)	Yield (%) [b]
1	2.5	DCE	85	18
2	2.5	CH_3CN	85	n.d.
3	2.5	toluene	110	52
4	2.5	DMF	110	n.d.
5	2.5	xylene	140	23
6	3.0	DCM	40	(43) [c]

[a] Reaction conditions: triazole **49a** (0.15 mmol) and $Rh_2(OAc)_4$ (0.0075 mmol) were stirred in toluene at reflux (3 mL), and a solution of diazoester **50a** in toluene (1 mL) was added by syringe pump over a 3 h period. The reaction was then allowed to stir for an additional 1 hour at 110 °C under argon. [b] Isolated yield. [c] Calculated yield based on integration of aromatic proton on pyrrolinone (8.1 ppm) resonance in ^1H NMR spectra using 2,4-dinitrochlorobenzene as the internal standard.

Divalent copper catalysts known for decomposition of diazocarbonyls were also examined under similar conditions, including $Cu(hfacac)_2$, $Cu(acac)_2$, $Cu(OAc)_2$ and $Cu(OTf)_2$. Gladly, the targeted product **51a** was obtained when copper complexes were applied as catalyst; however, the yield was significantly lowered compared with the rhodium catalyst (Table 2, entries 1–5). It should be noted that when $Cu(OTf)_2$ was used, full conversion of 1,2,3-triazole **49a** was observed despite the isolation of the desired **51a** in only 48% yield. It is interesting to note that despite the 52% yield from rhodium catalyzed reaction (entry 1), the remaining byproducts consist of mostly starting material.

Table 2. Survey of different catalysts [a]



49a **50a** **51a**

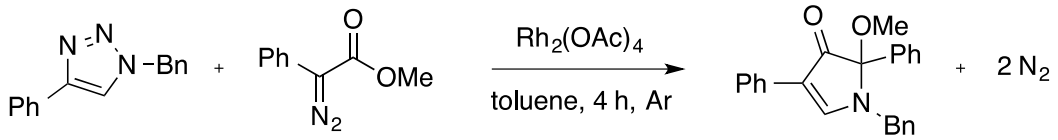
Entry	**50a** (equiv)	Cat. [M] (mol%)		Yield (%) [b]	
				51a	**49a**
1	2.5	$Rh_2(OAc)_4$	5	52	41 [c]
2	2.5	$Cu(hfacac)_2$	10	24	n/a [d]
3	2.5	$Cu(acac)_2$	10	14	n/a
4	2.5	$Cu(OAc)_2$	10	22	n/a
5	3.5	$Cu(OTf)_2$	10	48	n.d.[f]

[a] Reaction conditions: triazole **49a** (0.15 mmol) and $Rh_2(OAc)_4$ (0.0075 mmol) were stirred in toluene at reflux (3 mL), and a solution of diazoester **50a** in toluene (1 mL) was added by syringe pump over a 3 h period. The reaction was then allowed to stir for an additional 1 hour at 110 °C under argon. [b] Isolated yield. [c] 5 mol% of catalyst was used. [d] n/a: not available. [f] n.d. : not detected.

The loading amount of the reagent/catalyst and reaction temperature in a model reaction was examined next (Table 3). It was found that increasing the equivalents of diazo **50a** steadily would increase the conversion of the stable triazole **49a**, hence increased the yield of product **51a** (entries 1–4). When 3.5 equivalent of **50a** were used in toluene at 110 °C, the yield of **51a** was increased to 77% (entry 4). A significant temperature effect was also observed. A higher yield of pyrrolinone **51a** (83%) was obtained when the reaction was stirred at 90 °C (entry 5). Upon lowering the temperature to 70 °C, the reaction was sluggish and only 67% of **51a** was obtained (entry 6). By lowering the reaction temperature further to 50 °C yet prolonging the reaction time to 12 hours, the yield of **51a** was obtained in 74% (entry 7). This is an attractive set of

conditions since it would allow us to perform the reaction at a lower temperature with a comparably good result. Thus, the process would possibly display a better functional group tolerance. The reaction at room temperature was very sluggish, and only 32% of the product could be isolated, even with prolonged reaction time (entry 8). Decreasing the $Rh_2(OAc)_4$ catalyst loading to 2 mol% further enhanced the formation of **51a** with a 80% yield at 110 ^oC (entry 9). However, using 2 mol% catalyst loading resulted in a poor turnover rate at 90 ^oC, and the yield of the product **51a** was decreased to 71% (entry 10).

Table 3. Survey of reagent/catalyst loading, reaction time and temperature [a]



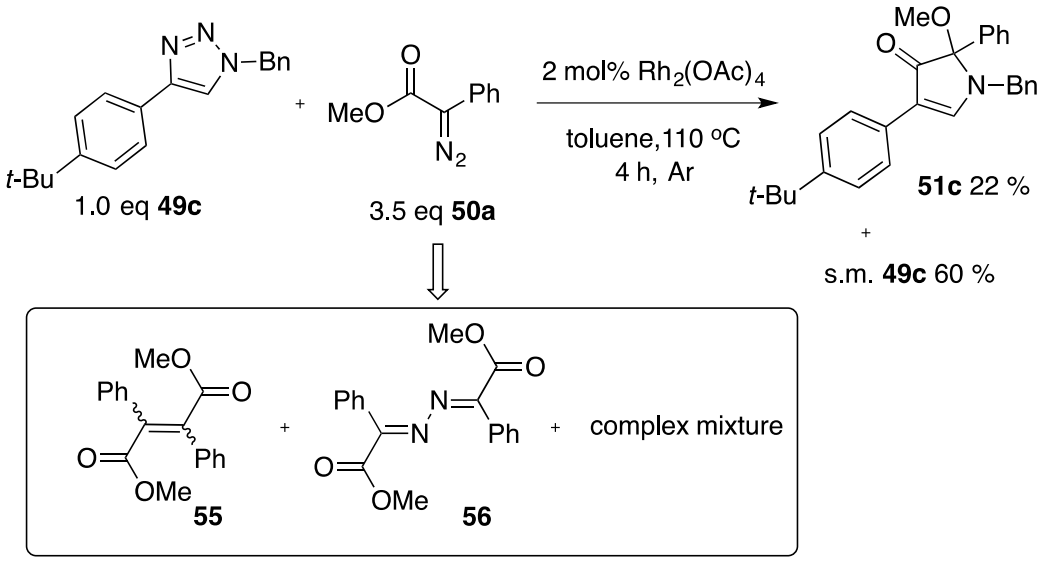
49a **50a** **51a**

Entry	**50a** (equiv)	$Rh_2(OAc)_4$ (mol %)	T (^oC)	Time (h)	Yield (%) [b]	
					51a	**49a**
1	1.4	5	110	4	30	46
2	2.5	5	110	4	52	41
3	3.0	5	110	4	62	16
4	3.5	5	110	4	77	n/a[c]
5	3.5	5	90	4	83	n/a
6	3.5	5	70	4	67	n/a
7[d]	**3.5**	**5**	**50**	**12**	**74**	n/a
8[d]	3.5	5	r.t	48	32	48
9	**3.5**	**2**	**110**	**4**	**80**	n/a
10	3.5	2	90	4	71	n/a

[a] Reaction conditions: triazole **49a** (0.15 mmol) and catalyst were stirred in toluene at reflux (3 mL), and a solution of diazoester **50a** in toluene (1 mL) was added by syringe pump over a 3 h period. The reaction was then allowed to stir at indicated temperature under argon. [b] Isolated yield. [c] n/a: not available. [d] Diazoester **50a** was added by syringe pump over a 1 h period.

Based upon these studies, the conditions from entry 9 (3.50 equiv diazo, 2 mol% $Rh_2(OAc)_4$ in toluene at reflux, 4 h) were selected as optimal reaction condition for substrates scope study.

However, when we attempted to apply these reaction conditions to other substrates, some of the results were poor due to the fact that in the presence of the catalyst at a high temperature, the diazo compound **50a** was quickly self-decomposed[34] before reacting with the triazole substrate. For example, when substrate **49c** was employed, the desired pyrrolinone **51c** was isolated in only 22% yield with 60% of starting material **49c** recovered. The diazo reagent **50a** was fully converted and dimer **55** and azine **56** were obtained as majorly side-products (Scheme 17).



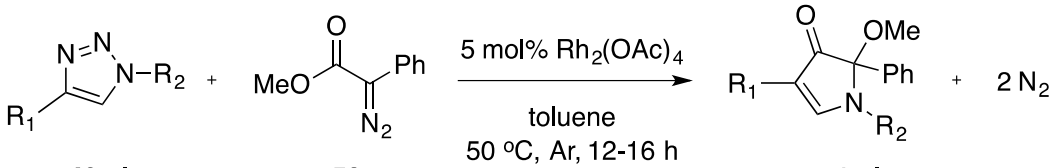
Scheme 17. Side-reaction at high temperature

In light of these problems, we chose to employ the conditions of Table 3, entry 7 instead: 3.5 equiv diazo, 5 mol% $Rh_2(OAc)_4$, toluene at 50 °C, overnight. This was performed with the expectation that higher catalyst loadings and lower temperatures would maximize the likelihood of achieving the desired coupling reaction.

Having found the optimal conditions, evaluation of substrates with various substituents on aromatic cores of 1,2,3-triazoles was conducted (Table 4). 4-Aryl-1,2,3,-triazoles **49** prepared from the corresponding alkyne and azide building blocks in analogy to **49a** were firstly examined (entries 2-5). Different substituents bearing a donating or withdrawing group (*p*-Me, *p*-*t*Bu, *p*-OMe and *p*-Cl) were subjected to the reaction conditions. The reaction proceeded smoothly and the targeted products **51b**-**51e** were formed in moderate yields (entries 2–5). The structure of **51a** and **51b** were both further confirmed by X-ray crystallography. However, when changing the 4-substituent into alkyl group, the reaction was sluggish and only 15% of product **51f** was obtained

(entry 6). When the triazole with the electron-withdrawing group (COOMe) at 4-position was used as the substrates, no desired product was observed; however, most of the triazole starting material was recovered (entry 7). Different *N*-substituted of 1,2,3-triazoles were then examined (entries 8–10). *N*-alkyl substituted triazole **49h** and **49i** gave the product in moderate yield (entries 9 and 10). However, with *N*-tosyl substituted triazole **49j**, no desired product was observed, and 50% of triazole **49j** was decomposed according to crude NMR spectroscopic analysis.

Table 4. Substrate scope of 1,2,3-triazoles [a]



49a-l **50a** **51a-l**

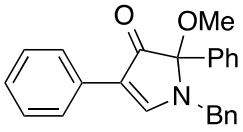
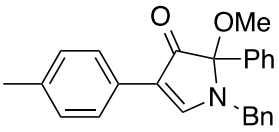
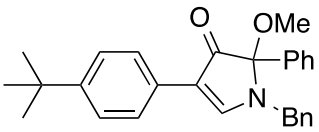
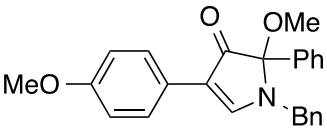
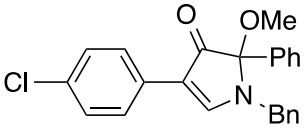
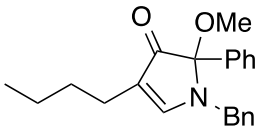
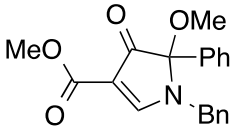
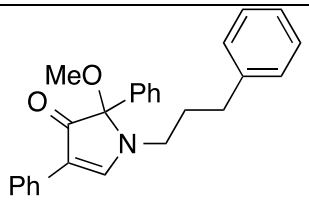
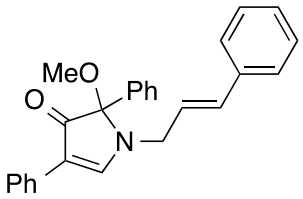
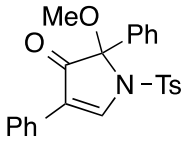
Entry	**49**	R_1	R_2	Product	**51**	Yield [b]
1	**49a**	C_6H_4	Bn		**51a**	74 (80) [c]
2	**49b**	*p*-MeC_6H_4	Bn		**51b**	56
3	**49c**	*p*-*t*BuC_6H_4	Bn		**51c**	51
4	**49d**	*p*-MeO C_6H_4	Bn		**51d**	46
5	**49e**	*p*-ClC_6H_4	Bn		**51e**	57
6	**49f**	C_4H_9	Bn		**51f**	15
7	**49g**	COOMe	Bn		**51g**	n.d.

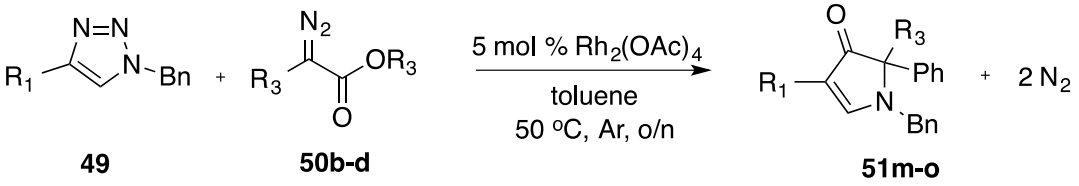
Table 4 Cont'd

8	**49h**	C_6H_4	$(CH_2)_3C_6H_4$		**51h**	36 [c]
9	**49i**	C_6H_4	$CH_2(CH)_2C_6H_4$		**51i**	35 [c]
10	**49j**	C_6H_4	*p*-$CH_3C_6H_4SO_2$ (Ts)		**51j**	n.d.

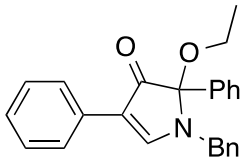
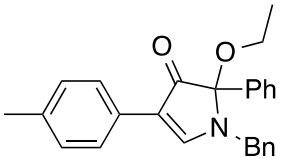
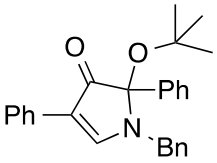
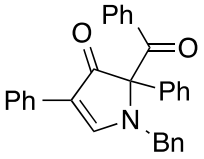
[a] Reaction conditions: triazole **49(a-j)** (0.2 mmol) and $Rh_2(OAc)_4$ (0.01 mmol) were stirred in toluene (4 mL) at 50 °C and a solution of diazoester **50a** in toluene (1 mL) was added by syringe over a 1 h period. The reaction was then allowed to stir at 50 °C under argon for 12-16 hours. [b] Isolated yield. [c] Reaction under 110 °C with 2 mol % of the $Rh_2(OAc)_4$. Slow addition of diazo **50** over 3 hours with syringe pump, reaction for another hour under argon.

Subsequently, we attempted to investigate the scope with various diazocarbonyls **50b-d**, and the results are listed in Table 3.5. Ethyl diazophenylacetate **50b** reacting with triazoles gave an expected pyrrolinone **50k** and **50l** in moderate yield (entries 1-2). When *tert*-butyl diazophenylacetate **50c** was applied, the desired **51m** was obtained in only 22% yield (entry 4), and dihydro-5,5-dimethyl-3-phenyl-2-furanone was observed as a by-product from internal C-H insertion of **50c**. With acceptor/acceptor carbene precursors **50d**, the reaction did not proceed but the starting material triazole was fully recovered from the reaction (entry 4).

Table 5. Substrate scope of diazo compounds [a]



49 **50b-d** **51m-o**

Entry	R_1	R_3	**50**	Product	**51**	Yield [b]
1	C_6H_4	Et	**50b**		**51k**	59 (81) [c]
2	*p*-$CH_3C_6H_4$	Et	**50b**		**51l**	58 [c]
3	C_6H_5	*t*Bu	**50c**		**51m**	22
4	C_6H_4	C_6H_4CO	**50d**		**51n**	n.d.

[a] Reaction conditions: triazole **49(a-b)** (0.2 mmol) and $Rh_2(OAc)_4$ (0.01 mmol) were stirred in toluene (4 mL) at 50 °C and a solution of diazoester **50** in toluene (1 mL) was added by syringe over a 1 h period. The reaction was then allowed to stir at 50 °C under argon for 12-16 hours. [b] Isolated yield. [c] Reaction under 110 °C with 2 mol % of the $Rh_2(OAc)_4$. Slow addition of diazo **50** over 3 hours with syringe pump, reaction for another hour under argon.

3.2.3 Possible Reaction Mechanism

Our initial mechanistic hypothesis involved triazole ring opening to a diazo imine intermediate **49'** (Figure 4). As discussed in the introduction, 1,2,3-triazole is known to undergo ring opening in the presence of rhodium(II) catalyst to form an Rh(II)-iminocarbene complex, although the ease of ring opening varies substantially with the nitrogen substituent. The rhodium iminocarbene **XIII** generated from diazo decomposition could then be attacked by diazoester **50a** followed by loss of dinitrogen to form unstable 1,2-dihydroazete intermediate **XV**.[35] Ring expansion of dihydroazete **XV** would form intermediate **XVI**. Stepwise methoxy migration would then lead to the product pyrrolinone **51a**.

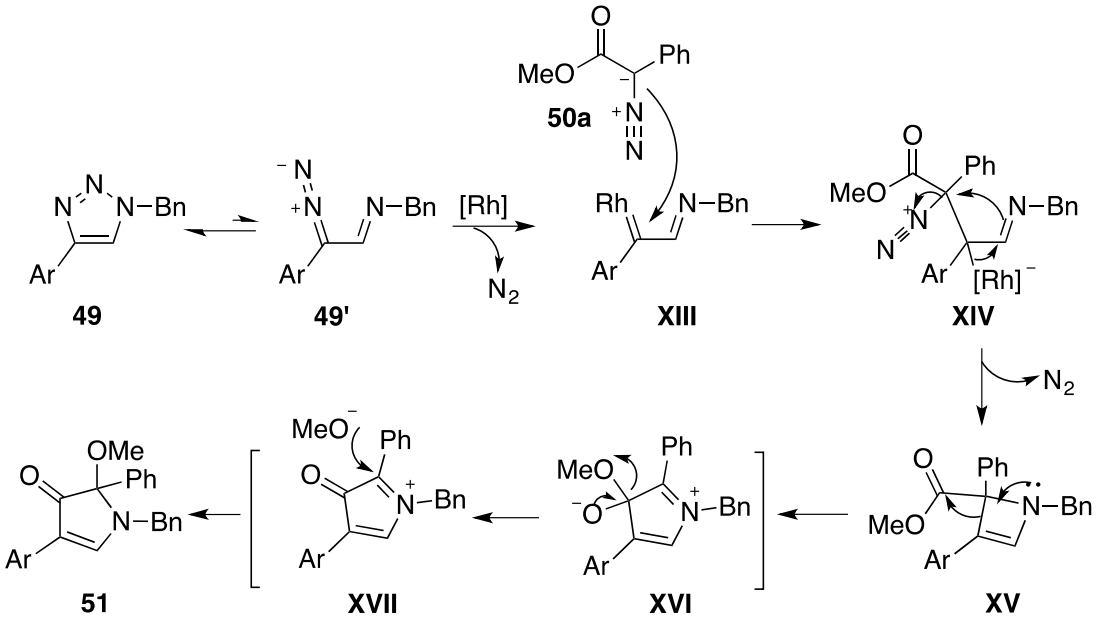
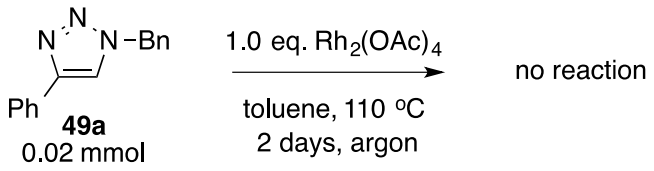


Figure 4. Proposed mechanism I

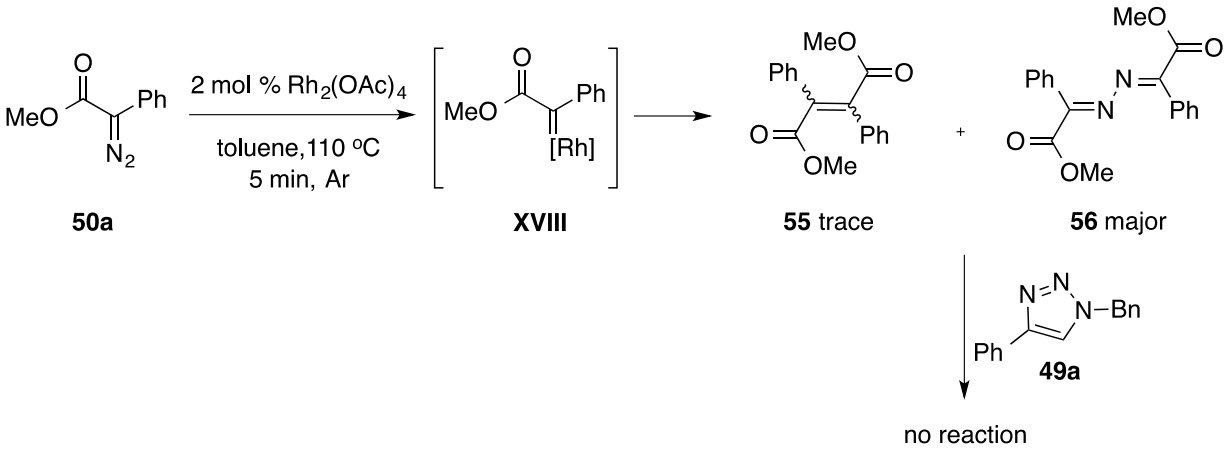
To investigate the reaction mechanism, a blank experiment was performed with triazole **49a** and dirhodium catalyst (Scheme 18). In the presence of 1.0 equivalent of rhodium, stirring triazole **49a** in toluene at reflux for 2 days, no reaction was observed and the starting material was fully recovered. This experiment suggested that 1-benzyl-4-phenyl-1*H*-1,2,3-triazole **49a** was stable in the presence of the rhodium catalyst and did not undergo the ring opening process. In light of this result, the first mechanism could be ruled out.



Scheme 18. Control experiment of triazole **49a** with rhodium catalyst

Interestingly, when the control reaction (Scheme 18) was cooled to room temperature and stirred overnight, the colorless solution changed into dark purple; however, the color disappeared upon heating. The observation suggested that the triazoles might coordinate with the Lewis acidic Rh(II) centers of the catalyst at lower temperature while undergo dissociation at higher temperatures. This association/dissociation process of triazole with dirhodium catalyst may contribute to the sluggish reaction of the pyrrolinone formation at lower temperature shown in Table 2.

Decomposition of diazoester **50a** in the presence of a rhodium catalyst is well known to generate azine **56**, dimer **55** and other byproducts.[34] We wanted to confirm that these side-products are not able to react with triazole **49a**. A blank reaction was performed with diazo **50a** and $Rh_2(OAc)_4$ in toluene at 110 ^oC (Scheme 19). Checking the reaction after 5 min, the diazo **50a** was fully decomposed and the azine **56** was observed as the principal component in the reaction mixture, along with a trace amount of dimer **55**. When triazole **49a** was added and the resulting mixture was stirred overnight at 110 °C, no new products were observed. This result strongly suggested that the key coupling event involved reaction of triazole **49a** with diazo-derived metallocarbene **XVIII** rather than its dimerization products.



Scheme 19. Blank reaction of decomposition of diazo **50a**

Based on these experiments, we proposed an alternative mechanism (Figure 5). Metallocarbene complex **XVIII** would firstly be generated from Rh(II)-catalyzed decomposition of diazo **50a**. The attack of the substituted triazole **49** on **XVIII** would give ylide **XIX**. Dissociation of the rhodium catalyst with concomitant loss of dinitrogen would provide transient dipolar species **XX**. Bond rotation to **XXI** would allow ring closure to intermediate **XXII**, which could then undergo [1,2]-methoxy migration in analogy to that shown in Figure 4 to afford the pyrrolinone product **51**.

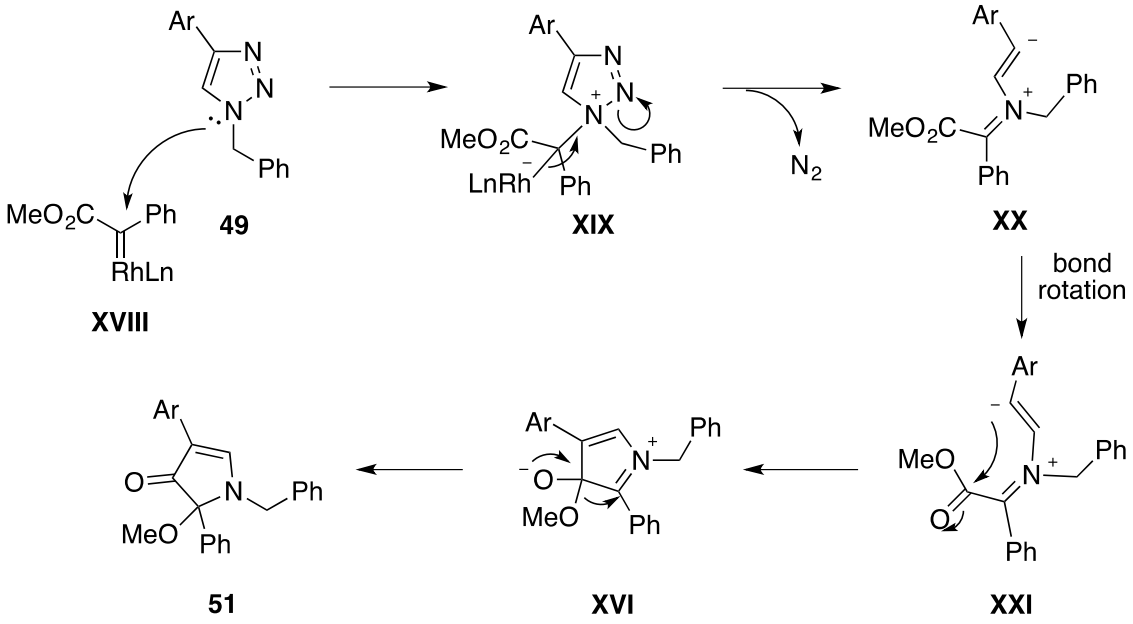


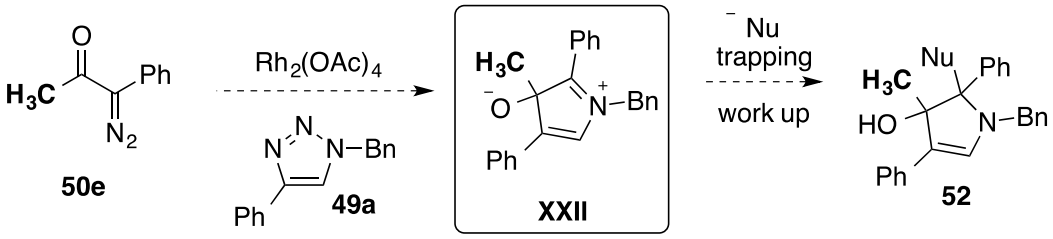
Figure 5. Proposed mechanism II

3.3 Conclusion

In summary, a novel rhodium-catalyzed transannulation of triazole with diazocarbonyl compounds was developed, providing a straightforward method to construct highly functionalized pyrroline-3-one heterocycles under mild conditions. Although 1,2,3-triazole compounds have been intensively studied for the past few years, the reaction described in this chapter represents an unprecedented and unique reaction pattern in the chemistry of 1,2,3-triazole. Possible reaction pathways for the transformation were also discussed; however, the mechanism is still unclear at this stage. Further work on the scope of the protocol and its application should be investigated.

3.4 Future Directions

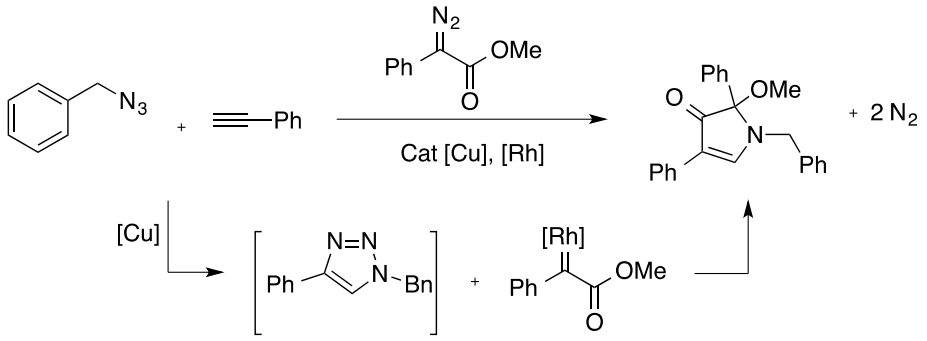
To carry on with future work on this project, additional properly designed experiments are required to better understand the reaction mechanism. We propose to interrupt the potential intermediate **XVII**, which is most likely to exist in the reaction according to the final product. It may be possible to divert the ring-expanded alkoxy intermediate from the methoxy migration pathway by using a methyl ketone **50e** in place of the ester (Scheme 20). In this case, intermediate **XXII** might be subject to trapping by an added nucleophile to afford adducts such as **52**.



Scheme 20. Designed mechanistic study

Further optimization of reaction conditions and a broadening substrate scope of this methodology would also be investigated. Triazoles with more substituents with a combination of diverse diazo compounds should be further explored.

A preliminary study had indicated that the potential one-pot reaction from azide, phenylacetylene and diazocarbonyl produced the desired pyrroline product in low yield (see Chapter 2, Scheme 22). Further examination of this reaction which allows for the formation of highly functionalized pyrroline-3-one heterocycles in a one-pot sequence would be a nice extension.



Scheme 21. One-pot reaction from organic azide, phenylacetylene and diazoester

3.5 Experimental Procedures and Characterization

3.5.1 General Information

Reactions were conducted in flame-dried glassware under a positive argon atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannula. Solvents were distilled before use: methylene chloride from calcium hydride, tetrahydrofuran, diethyl ether from sodium/benzophenone ketyl, toluene from sodium metal. All other solvents and commercially available reagents were either purified by standard procedures or used without further purification. Thin layer chromatography was performed on glass plates precoated with 0.25 mm silica gel. The developed plate was analyzed under a UV lamp (254 nm and 350 nm) and/or stained with potassium permanganate solution (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10% NaOH in 200 mL H_2O) or 2.5% *p*-anisaldehyde in AcOH-H_2SO_4-EtOH (1:3:85) and further heating until the development of color. Flash chromatography was performed on a 230–400 mesh silica gel with the indicated eluents. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz or 500 MHz on Varian Inova 400 and 500, Mercury 400, or Unity 500 spectrometers, and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane (0 ppm). Coupling constants (*J*) are reported in Hz. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 125 MHz or 100 MHz and are reported (ppm) relative to the center line of a triplet at 77.23 ppm for deuterochloroform. Infrared (IR) spectra were measured with a Nicolet Magna 750 FT-IR infrared spectrophotometer and were recorded and reported in cm^{-1}. Mass spectra were determined on a Kratos Analytical MS-50 (EI) or Applied Biosystems Mariner Biospectrometry Workstation (ESI). Elemental analyses were obtained on a Carlo Erba CHNS-O EA 1108 Elemental Analyzer.

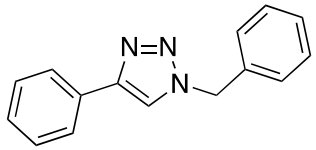
3.5.2 Characterization

Preparation of triazoles 49 by Cu(I)-Catalyzed Reactions.[33]

General: solution of azide **53a** (133 mg, 1.00 mmo)l and alkyne (123 mg, 1.20 mmol) in 4 mL of CH_2Cl_2 was stirred and 3 mL of water was added followed by (25.0 mg, 0.100 mmol) of $CuSO_4 \cdot 5H_2O$. Sodium ascorbate (99.0 mg, 0.500 mmol) was then added in small portions and the mixture was stirred for 12 h at room temperature. The CH_2Cl_2 phase was then separated and

dried over $MgSO_4$. After filtration, the solvent was removed using a rotary evaporator and the crude residue was purified by flash column chromatography (EtOAc/hexane, 1:5) to give the desired product **49a** (223 mg, 95%), as a white solid.

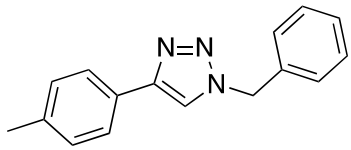
Representative Starting Materials Characterization:



49a

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole 49a was prepared in 95% yield and isolated as white solid. Spectral data were consistent with those reported in the literature.[33c]

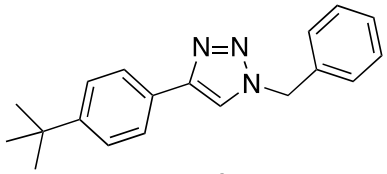
^{1}H NMR (400 MHz, $CDCl_3$) δ7.80 (d, *J* = 7.6 Hz, 2 H), 7.67 (s, 1 H), 7.44-7.38 (m, 5 H), 7.35-7.30 (m, 3 H), 5.60 (s, 2 H); ^{13}C NMR (100 MHz, CDCl3) δ148.2, 134.7, 130.6, 129.17, 128.8, 128.8, 128.2, 128.1, 125.7, 119.5, 54.2.



49b

1-Benzyl-4-tolyl-1*H*-1,2,3-triazole 49b was prepared in 86% yield and isolated as a white solid. Spectral data were consistent with those reported in the literature.[33c]

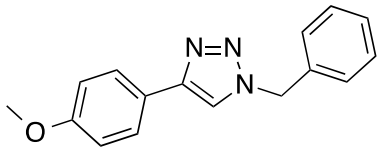
^{1}H NMR (500 MHz, $CDCl_3$) δ7.71 (d, *J* = 8.0 Hz, 2 H), 7.64 (s, 1 H), 7.43-7.38 (m, 3 H), 7.34-7.32 (m, 2 H), 7.20 (dd, *J* = 8.0, 0.5 Hz, 2 H), 5.91 (s, 2 H), 2.38 (s, 3 H).



49c

1-Benzyl-4-(4-*tert*-butylphenyl)-1*H*-1,2,3-triazole 49c was prepared in 92% yield and isolated as a white solid. Spectral data were consistent with those reported in the literature.[33e]

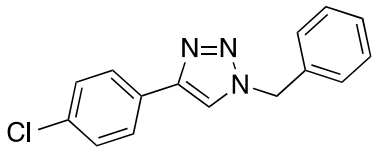
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dt, *J* = 8.8, 2.0 Hz, 2 H), 7.63 (s, 1 H), 7.44-7.34 (m, 5 H), 7.31-7.26 (m 2 H), 5.58 (s, 2 H), 1.33 (s, 9 H).



49d

1-Benzyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole 49d was prepared in quantitative yield and isolated as a white solid. Spectral data were consistent with those reported in the literature.[33c]

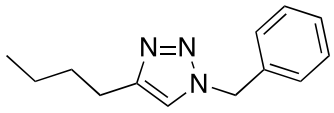
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dt, *J* = 9.2, 2.6 Hz, 2 H), 7.58 (s, 1 H), 7.38-7.32 (m, 3 H), 7.31-7.28 (m 2 H), 6.93 (dt, *J* = 9.2, 2.6 Hz, 2 H), 5.58 (s, 2 H), 3.82 (s, 3 H).



49e

1-Benzyl-4-(4-chlorophenyl)-1*H*-1,2,3-triazole 49e was prepared in 47% yield and isolated as a yellow solid. Spectral data were consistent with those reported in the literature.[33f]

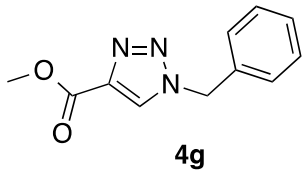
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dt, *J* = 8.4, 1.8 Hz, 2 H), 7.64 (s, 1 H), 7.41-7.36 (m, 5 H), 7.33-7.30 (m 2 H), 5.58 (s, 2 H).



4f

1-Benzyl-4-butyl-1*H*-1,2,3-triazole 49f was prepared in 88% yield and isolated as a white solid. Spectral data were consistent with those reported in the literature.[33d]

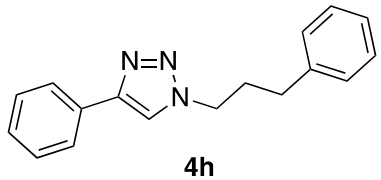
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 3 H), 7.28-7.25 (m, 2 H), 7.19 (s, 1 H), 5.50 (s, 2 H), 2.70 (t, *J* = 7.8 Hz, 2 H), 1.63 (quintet, *J* = 7.4 Hz, 2 H), 1.37 (sextet, *J* = 7.4 Hz, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H).



4g

Methyl 1-benzyl-1*H*-1,2,3-triazole-4-carboxylate 49g was prepared in 88% yield and isolated as a white solid. Spectral data were consistent with those reported in the literature.[33c]

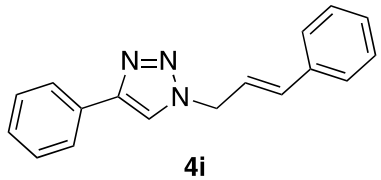
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.33 (m, 3 H), 7.29-7.26 (m, 2 H), 5.58 (s, 2 H), 3.93 (s, 3 H).



4h

4-Phenyl-1-(3-phenylpropyl)-1*H*-1,2,3-triazole 49h as a white solid. Spectral data were consistent with those reported in the literature.[33a]

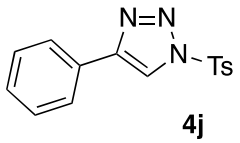
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.84 (m, 2 H), 7.74 (s, 1 H), 7.44-7.42 (m, 2 H), 7.40-7.32 (m, 4 H), 7.26- 7.20 (m, 2 H), 4.41 (t, *J* = 5.6 Hz, 1 H), 2.71 (t, *J* = 5.6 Hz, 2 H), 2.31 (app. quintet, *J* = 6.0, Hz 2 H).



4i

1-Cinnamyl-4-phenyl-1*H*-1,2,3-triazole 49i was prepared in quantitative yield as a white solid. Spectral data were consistent with those reported in the literature.[33g]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.82 (m, 2 H), 7.81 (s, 1 H), 7.44-7.40 (m, 4 H), 7.37-7.30 (m, 4 H), 6.72 (dt, *J* = 15.6, 1.2 Hz, 1 H), 6.40 (dt, *J* = 15.6, 6.8 Hz, 1 H), 5.20 (dd, *J* = 6.8, 1.2 Hz, 2 H).



4j

4-Phenyl-1-tosyl-1*H*-1,2,3-triazole 49f

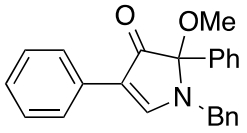
was prepared in 74% yield and isolated as a pale yellow solid. Spectral data were consistent with those reported in the literature.[33d]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1 H), 8.02 (dt, *J* = 8.8, 2.2 Hz, 2 H), 7.84-7.81 (m, 2 H), 7.45-7.37 (m, 5 H), 7.44-7.40 (m, 4 H), 2.45 (s, 3 H).

General Precedure for the synthesis of 4-pyrrol-3one (51a-f, h-i, k-m)

Condition A : To a flame-dried round bottom flask equipped with a magnetic stir bar was added triazole **49** (0.200 mmol), $Rh_2(OAc)_4$ (0.02 equiv, 0.00400 mmol), and toluene (4.00 mL). The flask was connected with a condenser which was capped with a rubber septum, and argon line was attached through a needle into the septum while the mixture was stirred at 110 °C in an oil bath. Then, a solution of diazo compound **50** (3.50 eqiv, 0.700 mmol) in 1 mL of toluene was slowly added by injection via a syringe over 3 hours. The reaction mixture was allowed to stir for 1-3 h at 110 ^oC. After cooling the solvent was removed by rotary evaporation, and the reaction mixture was purified by flash column chromatography (silica gel) using hexanes/EtOAc eluent or recrystallization with DCM : Hexane =1:10 to provide **51** as bright yellow solid or oil.

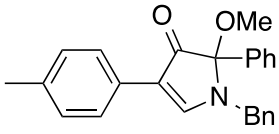
Condition B : To a flame-dried round bottom flask equipped with a magnetic stir bar was added triazole **49** (0.200 mmol), $Rh_2(OAc)_4$ (0.05 equiv, 0.0100 mmol), and toluene (4.00 mL). The flask was connected with a condenser which was capped with a rubber septum, and argon line was attached through a needle into the septum while the mixture was stirred at 50 °C in an oil bath. Then, a solution of diazo compound **50** (3.50 eq, 0.700 mmol) in 1 mL of toluene was slowly added by injection via a syringe over 1 h. The reaction mixture was allowed to stir for 12-16 h at 50 ^oC. After cooling the solvent was removed by rotary evaporation, and the reaction mixture was purified by flash column chromatography (silica gel) eluted with increasing amounts of EtOAc in hexane or recrystallization with DCM : Hexane =1:10 to provide **51** as a light yellow solid or yellow oil.



51a

1-Benzyl-2-methoxy-2,4-diphenyl-1,2-dihydro-3-*H*-pyrrol-3-one 51a The reaction was performed following method B to afford **51a** (52.5 mg, yield 74%) as a bright yellow solid though recrystallization in DCM : Hexane (1:10)

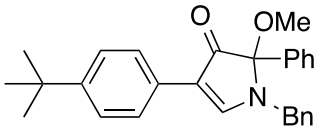
TLC R_f=0.4 (EtOAc: hexane= 1: 5); mp: 224-226 ^oC; IR (film) 3060, 3032, 2933, 2834, 1663, 1569, 1452, 1219, 961, 780, 766, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1 H), 7.63-7.60 (m, 2 H), 7.49-7.45 (m, 2 H), 7.38-7.32 (m, 5 H), 7.27-7.32 (m, 5 H), 7.10 (dt, J = 7.2, 1.2 Hz, 1 H), 4.24 (d, J_{ab} = 14.0 Hz, 1H), 4.20 (d, J_{ab} = 14.0 Hz, 1H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ195.9, 161.7, 134.5, 134.1, 131.1, 128.9, 128.6, 128.4, 128.3, 128.1, 128.0, 125.2, 125.1, 123.4, 108.8, 95.5, 51.9, 48.7; UV/Vis: λ 282, 385 nm; HRMS (EI, M+) for $C_{24}H_{21}NO_2$ calcd 355.1572, found: m/z 355.1548; Fluorescence: Ex/Em= 285/470 nm, Ex/Em=385/470 nm; X-Ray crystallography:See attachment.



51b

1-Benzyl-2-methoxy-2-phenyl-4-(*p*-toyl)-1,2-dihydro-3-*H*-pyrrol-3-one 51b Reaction was performed under the standard procedure B. Flash chromatography with increasing amounts of EtOAc in hexane (from 1:10 to 1: 5) gave **51b** (41.5 mg, yield 56%) as a bright yellow solid.

TLC R_f=0.4 (EtOAc: hexane= 1: 5); mp: 215-217^oC; IR (film) 3030, 2933, 2875, 1667, 1573, 1225, 820, 760, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.52 (m, 1 H), 7.44-7.34 (m, 6 H), 7.30-7.27 (m, 5 H), 7.11 (d, J = 8.0 Hz, 1 H), 4.28 (d, J_{ab} = 14.0 Hz, 1 H), 4.23 (d, J_{ab} = 14.0 Hz, 1 H), 3.37 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ195.9, 161.9, 135.3, 135.2, 134.8, 129.4, 129.2, 129.1, 128.9, 128.8, 128.6, 128.5, 125.8, 123.9, 109.6, 95.9, 52.4, 49.2, 21.1; HRMS (EI, M+) for $C_{25}H_{23}NO_2$ calcd 370.1802, found: m/z 355.1798; X-Ray crystallography:See attachment.

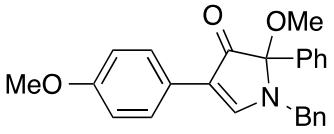


51c

1-Benzyl-4-(4-(*tert*-butyl)phenyl)-2-methoxy-2-phenyl-1,2-dihydro-3-*H*-pyrrol-3-one 51c

Reaction was performed under the standard procedure B. Flash chromatography with increasing amounts of EtOAc in hexane (from 1:10 to 1: 5) gave **51c** (41.5 mg, yield 51%) as a bright yellow solid.

TLC R_f=0.4 (EtOAc: hexane= 1: 5); IR (film) 3060, 2953, 1731, 1574, 1434, 1231, 1004, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1 H), 7.57-7.55 (dt, *J* = 8.8, 1.6 Hz, 2 H), 7.48-7.46 (m, 2 H), 7.37-7.33 (m, 5 H), 7.28 (dt, *J* = 8.4, 2.0 Hz, 2 H), 7.24-7.22 (m, 3 H), 4.23 (d, J_{ab} = 14.0 Hz, 1 H), 4.18 (d, J_{ab} = 14.0 Hz, 1 H), 3.31 (s, 3 H), 1.26 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ196.0, 161.5, 148.2, 134.6, 134.2, 129.2, 128.9, 128.6, 128.3, 128.2, 128.1, 128.0, 125.2, 124.9, 108.9, 95.4, 51.8, 48.7, 33.9, 30.8; UV/Vis: λ 267, 384 nm. HRMS (EI, M+) for $C_{28}H_{29}NO_2$ calcd 411.2198, found: m/z 411.2198;

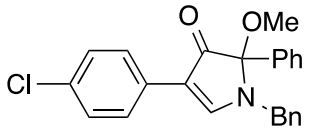


51d

1-Benzyl-2-methoxy-4-(4-methoxyphenyl)-2-phenyl-1,2-dihydro-3-*H*-pyrrol-3-one 51d

Reaction was performed under the standard procedure B. Flash chromatography with increasing amounts of EtOAc in hexane (from 1:10 to 1: 5) gave **51d** (34.5 mg, yield 46%) as a bright yellow solid.

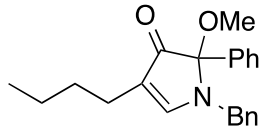
TLC R_f= 0.3 (EtOAc: hexane = 1: 5); IR (film) 3031, 2921, 2851, 1664, 1571, 1512, 1246, 833, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1 H), 7.61 (d, *J* = 9.0 Hz, 2 H), 7.54-7.52 (m, 2 H), 7.42-7.37 (m, 6 H), 7.29 (dd, *J* = 9.0, 1.7 Hz, 2 H), 6. 86 (d, *J* = 7.2 Hz, 2 H), 4.28 (d, J_{ab} = 14.0 Hz, 1 H), 4.23 (d, J_{ab} = 14.0 Hz, 1 H), 3.80 (s, 3 H), 3.37 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ196.6, 161.5, 157.7, 135.2, 134.9, 129.4, 129.1, 128.9, 128.8, 128.5, 125.8, 125.3, 124.2, 114.0, 109.4, 95.8, 51.3, 52.4, 49.2; HRMS (EI, M+) for $C_{25}H_{23}NO_3$ calcd 386.1751, found: m/z 386.1748.



51e

1-Benzyl-4-(4-chlorophenyl)-2-methoxy-2-phenyl-1,2-dihydro-3-*H*-pyrrol-3-one 51e Reaction was performed under the standard procedure B. Flash chromatography with increasing amounts of EtOAc in hexane (from 1:10 to 1: 5) gave **51e** (44.3 mg, yield 57%) as a bright yellow solid.

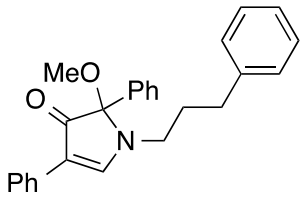
TLC R_f= 0.4 (EtOAc: hexane= 1: 5); mp= 215-217 ^{o}C; IR (film) 3032, 2951, 1741, 1671, 1570, 1450, 1434, 1214, 1015, 835, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1 H), 7.61 (dd, *J* = 9.0, 2.0 Hz, 2 H), 7.51 (dd, *J* = 8.5, 2.0 Hz, 2 H), 7.44-7.39 (m, 5 H), 7.30-7.29 (m, 3 H), 7. 25 (dd, *J* = 9.2, 1.7 Hz, 2 H), 4.29 (d, J_{ab} = 14.0 Hz, 1 H), 4.24 (d, J_{ab} = 14.0 Hz, 1 H), 3.37 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ196.2, 162.0, 134.8, 134.4, 130.9, 130.0, 129.5, 129.2, 129.0, 128.9, 128.8, 128.7, 125.7, 125.1, 108.3, 96.0, 52.4, 49.2; UV/Vis: λ 287, 385 nm; HRMS (EI, M+) for $C_{24}H_{20}{}^{35}ClNO_2$ calcd 389.1183, found: m/z 389.1177.



51f

1-Benzyl-4-butyl-2-methoxy-2-phenyl-1,2-dihydro-3-*H*-pyrrol-3-one 51f Reaction was performed under the standard procedure B. Flash chromatography with increasing amounts of EtOAc in hexane (from 1:10 to 1: 5) gave **51f** (8.0 mg, yield 12%) as a bright yellow oil.

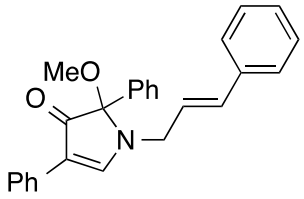
TLC R_f= 0.4 (EtOAc: hexane= 1: 3); IR (film) 3031, 2953, 2922, 2851, 1740, 1680, 1434, 1212, 1016, 777, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1 H), 7.48-7.46 (m, 2 H), 7.41-7.35 (m, 6 H), 7.26-7.24 (m, 2 H), 4.15 (d, J_{ab} = 14.0 Hz, 1 H), 4.11 (d, J_{ab} = 14.0 Hz, 1 H), 3.31 (s, 3 H), 2.16 (dd, *J* = 15.5, 7.5 Hz, 1 H), 2.14 (dd, *J* = 15.5, 8.0 Hz, 1 H), 1.43 (m, 2 H), 1.32 (sex, *J* = 7.0 Hz, 2 H), 0.91 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ199.6, 163.5, 135.7, 135.5, 129.2, 128.9, 128.7, 128.6, 128.2, 125.7, 111.3, 95.0, 52.0, 49.0, 31.4, 22.4, 22.0, 13.9.



51h

2-Methoxy-1-phenethyl-2,4-diphenyl-1,2-dihydro-3*H*-pyrrol-3-one 51h Reaction was performed under the standard procedure A with 0.17 mmol of **49h** (0.17 mmol, 45.2 mg). Flash chromatography with increasing amounts of EtOAc in hexane (from 1:10 to 1: 5) gave **51h** (24.8 mg, yield 36%) as a bright yellow solid.

TLC R_f= 0.4 (EtOAc: hexane= 1: 4);IR (film) 3060, 3029, 2928, 2855, 1665, 1570, 1452, 1231, 1214, 1095, 780, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1 H), 7.70 (m, 2 H), 7.40 (m, 2 H), 7.29 (m, 7 H), 7.19 (tt, *J* = 7.2, 1.6 Hz, 1 H), 7.12 (dt, *J* = 7.6, 1.4 Hz 1 H), 7.09-7.07 (m, 2 H), 3.35 (s, 3 H), 3.23 (ddd, *J* = 14.5, 8.0, 2.2 Hz, 1 H), 3.22 (ddd, *J* = 12.6, 7.6, 2.5 Hz, 1 H), 2.57 (t, *J* = 7.6, Hz, 2 H), 1.98-1.84 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ195.7, 162.6, 140.0, 134.8, 131.1, 128.3, 128.2, 128.1, 128.0, 127.2, 125.8, 125.1, 125.0, 123.3, 108.3, 95.5, 51.8, 44.8, 32.5, 30.1; UV/Vis: λ 282, 387 nm; HRMS (EI, M+) for $C_{26}H_{25}NO_2$ calcd 383.1885, found: m/z 383.1887.

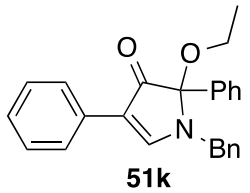


51i

(*E*)-2-Methoxy-2,4-diphenyl-1-cinammyl-1,2-dihydro-3-*H*-pyrrol-3-one 51i Reaction was performed under the standard procedure A with 0.5 mmol of **49i** (0.5 mmol, 130.7 mg). Flash chromatography with increasing amounts of EtOAc in hexane (from 1:10 to 1: 5) gave **51h** (64.7 mg, yield 35%) as a bright yellow solid.

TLC R_f= 0.4 (EtOAc: hexane= 1: 4); IR (film) 3060, 3030, 2951, 2834, 1670, 1568, 1495, 1215, 1014, 780, 749, 696. cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8. 57 (s, 1 H), 7.72-7.68 (ddd, *J* = 8.4, 1.2, 0.4 Hz, 2 H), 7.49-7.45 (m, 2 H), 7.38-7.33 (m, 6 H), 7.32-7.25 (m, 3 H), 7.12 (tt, *J* = 7.2, 0.4 Hz, 2 H), 6.18 (d, *J* = 15.6 Hz, 1 H), 6.13 (dt, *J* = 15.6, 6.8 Hz, 1 H), 3.90 (d, *J* = 6.8 Hz, 2

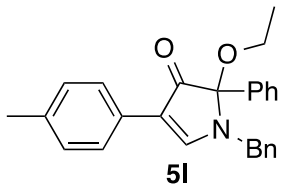
H), 3.40 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ195.9, 161.7, 135.3, 135.2, 134.5, 131.1, 128.4, 128.3, 128.3, 128.0, 127.9, 126.1, 125.2, 125.1, 123.4, 122.3, 108.8, 95.2, 51.8, 46.8; UV/Vis: λ 253, 277, 387 nm; HRMS (EI, (M+H)+) for $C_{25}H_{24}NO_2$ calcd 370.1802, found: m/z 370.1800.



51k

1-Benzyl-2-ethoxy-2,4-diphenyl-1,2-dihydro-3-*H*-pyrrol-3-one 51k Reaction was performed under the standard procedure A. Flash chromatography with increasing amounts of EtOAc in hexane (from 1:10 to 1: 5) gave **51k** (45.1 mg, yield 81%) as a bright yellow solid.

TLC R_f= 0.4 (EtOAc: hexane= 1: 4); IR (film) 3060, 3031, 2925, 2854, 1665, 1569, 1415, 1218, 781, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8. 33 (s, 1 H), 7.67 (dd, *J* = 8.5, 1.5 Hz, 2 H), 7.67 (dd, *J* = 7.0, 1.5 Hz, 2 H), 7.43-7.37 (m, 5 H), 7.31 (m, 2 H), 7.31-7.27 (m, 3 H), 7.14 (tt, *J* = 7.5, 1.0 Hz, 1H), 4.29 (s, 2 H), 3.70 (dt, *J* = 15.5, 7.0 Hz, 1 H), 3.42 (dt, *J* = 15.5, 7.0 Hz, 1 H), 1.25 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl3) δ196.6, 161.9, 135.3, 134.8, 131.7, 129.3, 129.1, 128.8, 128.7, 128.6, 128.5, 125.8, 125.5, 123.9, 109.1, 95.7, 60.3, 49.3, 15.0. HRMS (EI, (M+H)+) for $C_{25}H_{24}NO_2$ calcd 370.1802, found: m/z 370.1800.

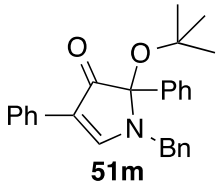


5l

1-Benzyl-2-ethoxy-2-phenyl-4-(*p*-tolyl)-1,2-dihydro-3-*H*-pyrrol-3-one 51l Reaction was performed under the standard procedure A with 0.5 mmol **49a**. Flash chromatography with increasing amounts of EtOAc in hexane (from 1:10 to 1: 5) gave **51l** (105.3 mg, yield 57%) as a bright yellow solid.

TLC R_f= 0.4 (EtOAc: hexane= 1: 4); IR (film) 3030, 2977, 2924, 1667, 1572, 1223, 1214, 1075, 820, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ8. 32 (s, 1 H), 7.58-7.54 (m, 4 H), 7.54-7.36 (m, 6 H), 7.29-7.28 (m, 2 H), 7.12 (d, *J* = 7.5 Hz, 2 H), 4.28 (s, 2 H), 3.69 (dt, *J* = 15.5, 7.5 Hz, 1 H), 3.42 (dt, *J* = 15.5, 7.5 Hz, 1 H), 2.33 (s, 3 H), 1.25 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz,

CDCl3) δ196.7, 161.7, 135.4, 135.2, 135.0, 129.3, 129.2, 129.1, 128.9, 128,8, 128.7, 128.5, 125.8, 123.9, 109.2, 95.7, 60.3, 49.3, 21.6, 15.0; HRMS (EI, M+) for $C_{26}H_{25}NO_2$ calcd 383.1885, found: m/z 383.1892; UV/Vis: λ 229, 282, 387 nm.



51m

1-Benzyl-2-(*tert*-butoxy)-2,4-diphenyl-1,2-dihydro-3-*H*-pyrrol-3-one 51m Reaction was performed under the standard procedure B. Flash chromatography with increasing amounts of EtOAc in hexane (from 1:10 to 1: 5) gave **51m** (18.0 mg, yield 22%) as a bright yellow oil.

TLC R_f= 0.4 (EtOAc: hexane= 1: 5); IR (film) 3032, 2924, 2853, 1728, 1664, 1571, 1448, 1227, 1172, 761, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ8.04 (s, 1 H), 7.63 (dd, *J* = 8.5, 0.8 Hz, 2 H), 7.53 (d, *J* = 8.5 Hz, 2 H), 7.43-7.30 (m, 7 H), 7.27-7.25 (m, 3 H), 7.13 (t, *J* = 7.5 Hz, 1 H), 4.44 (d, *J* = 14.0 Hz, 1 H), 4.15 (d, *J* = 14.0 Hz, 1 H), 1.51 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ197.3, 158.8, 137.7, 134.1, 132.3, 129.8, 129.2, 128.7, 128.6, 128.5, 128.4, 125.6, 125.4, 123.9, 109.3, 95.2, 79.2, 49.0, 30.3; HRMS (EI, (M+H)+) for $C_{27}H_{28}NO_2$ calcd 398.2115, found: m/z 398.2115;

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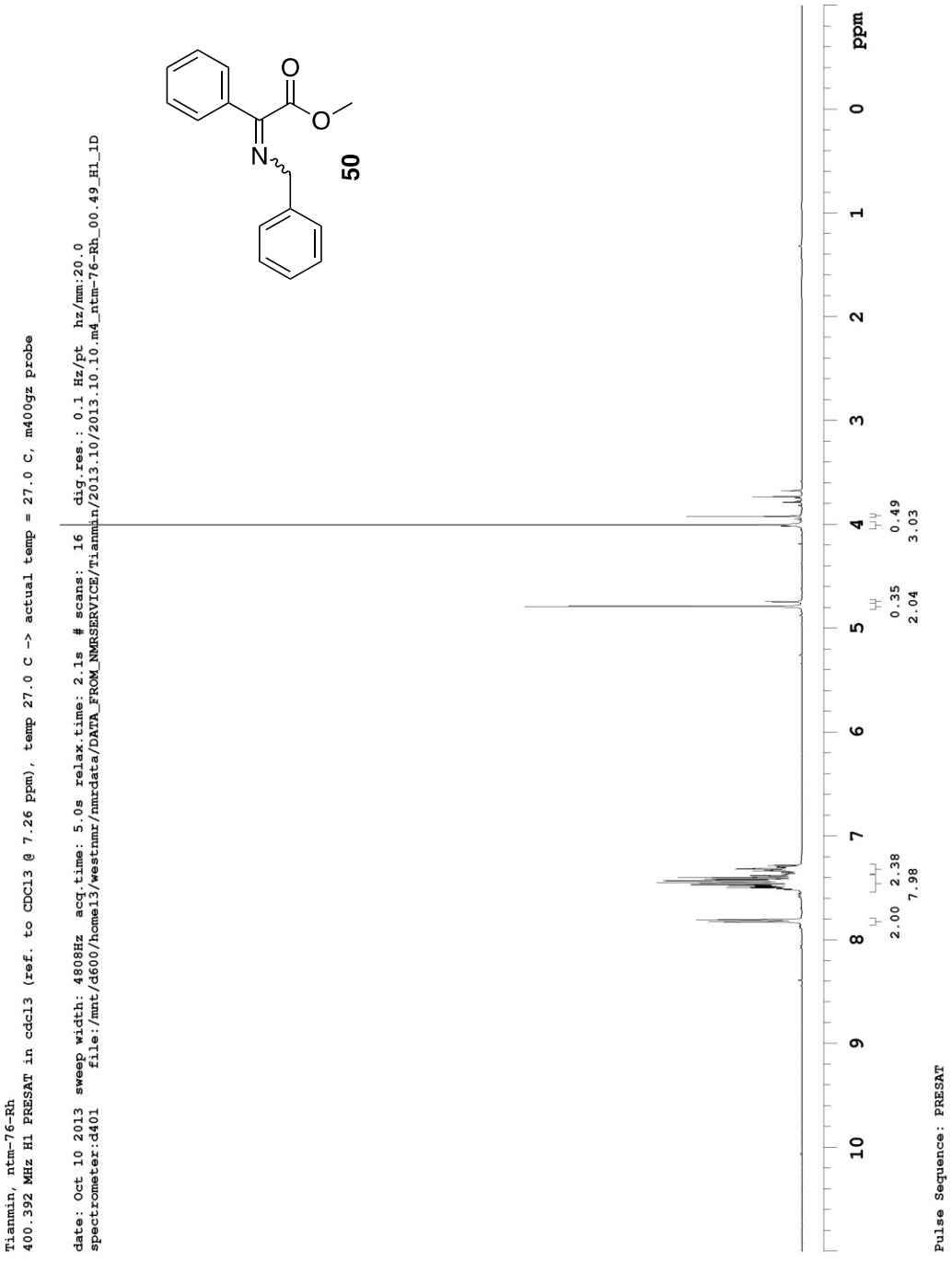
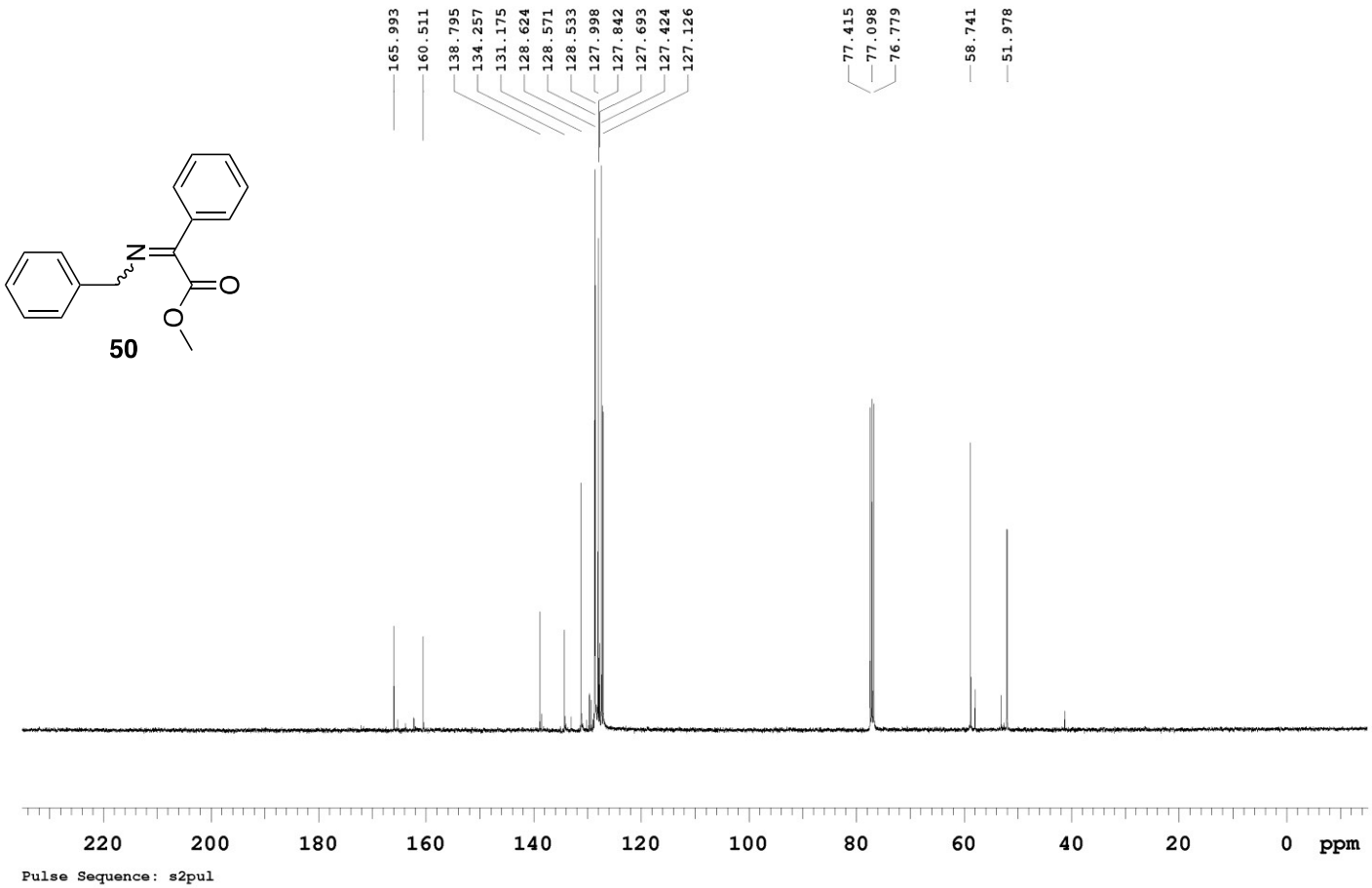
Appendix I: Selected NMR Spectra (Chapter 2)



Tianmin, ntm-76-Rh
100.689 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

date: Oct 10 2013 sweep width: 25189Hz acq.time: 2.5s relax.time: 1.1s # scans: 1300 dig.res.: 0.2 Hz/pt hz/mm:105.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2013.10/2013.10.10.m4_ntm-76-Rh_06.21_C13_1D

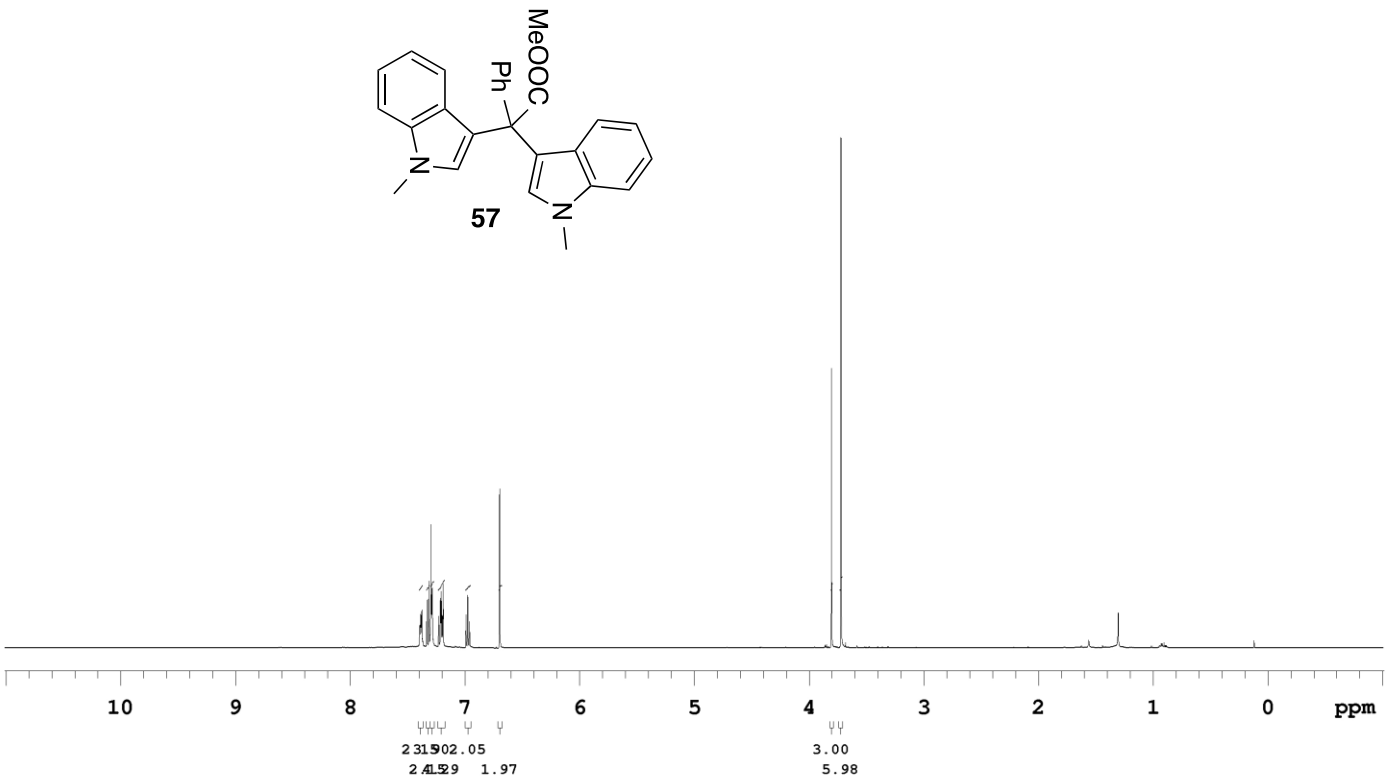


50

Pulse Sequence: s2pul

Tianmin, ntm-133-2
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

date: Feb 14 2014 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:25.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2014.02/2014.02.14.u5_ntm-133-2_05.02_H1_1D

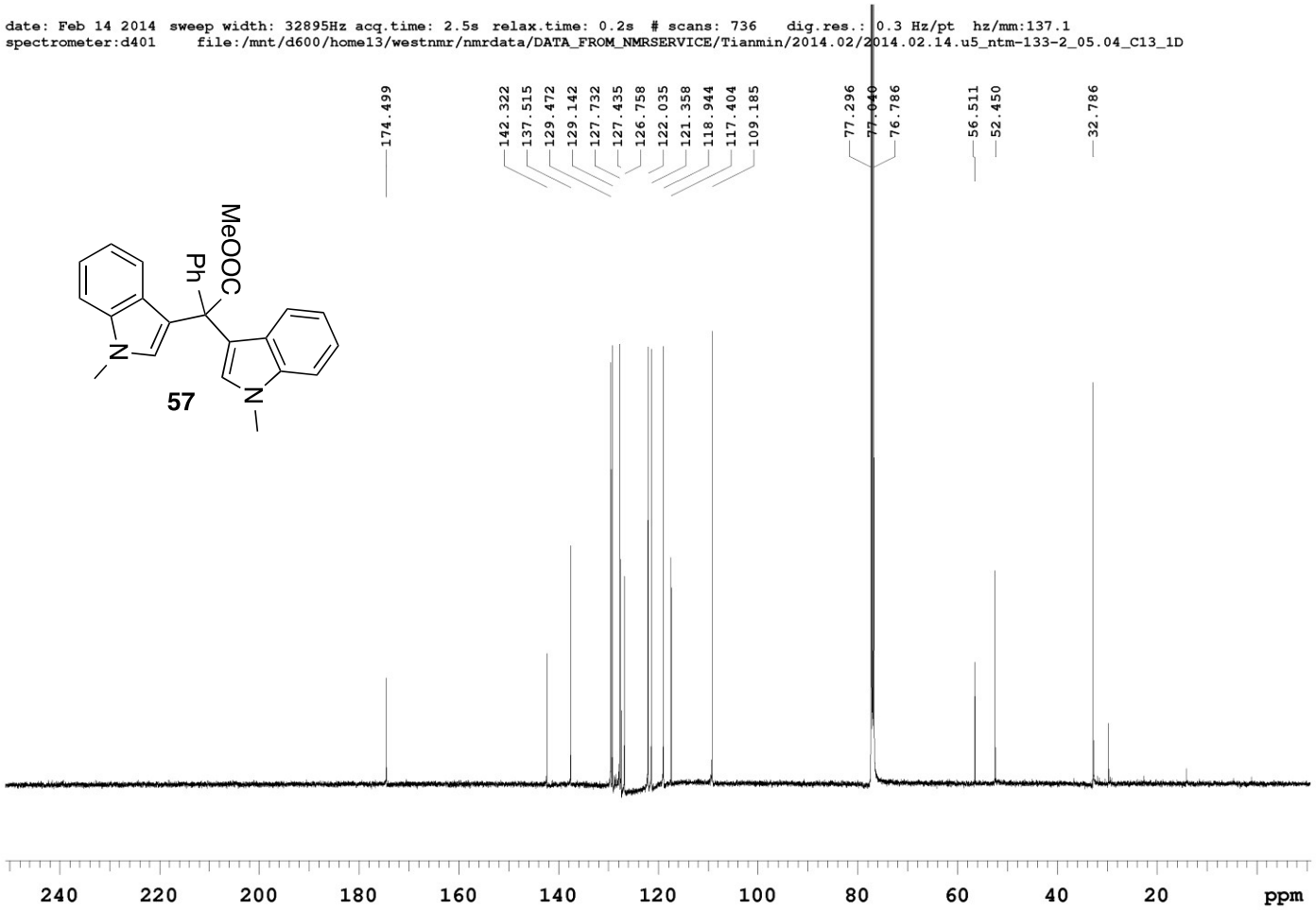


57

Pulse Sequence: PRESAT

Tianmin, ntm-133-2
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

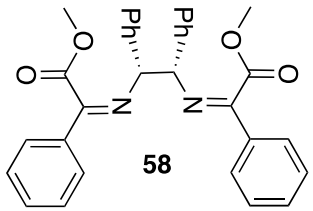
date: Feb 14 2014 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 736 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2014.02/2014.02.14.u5_ntm-133-2_05.04_C13_1D



Pulse Sequence: s2pul

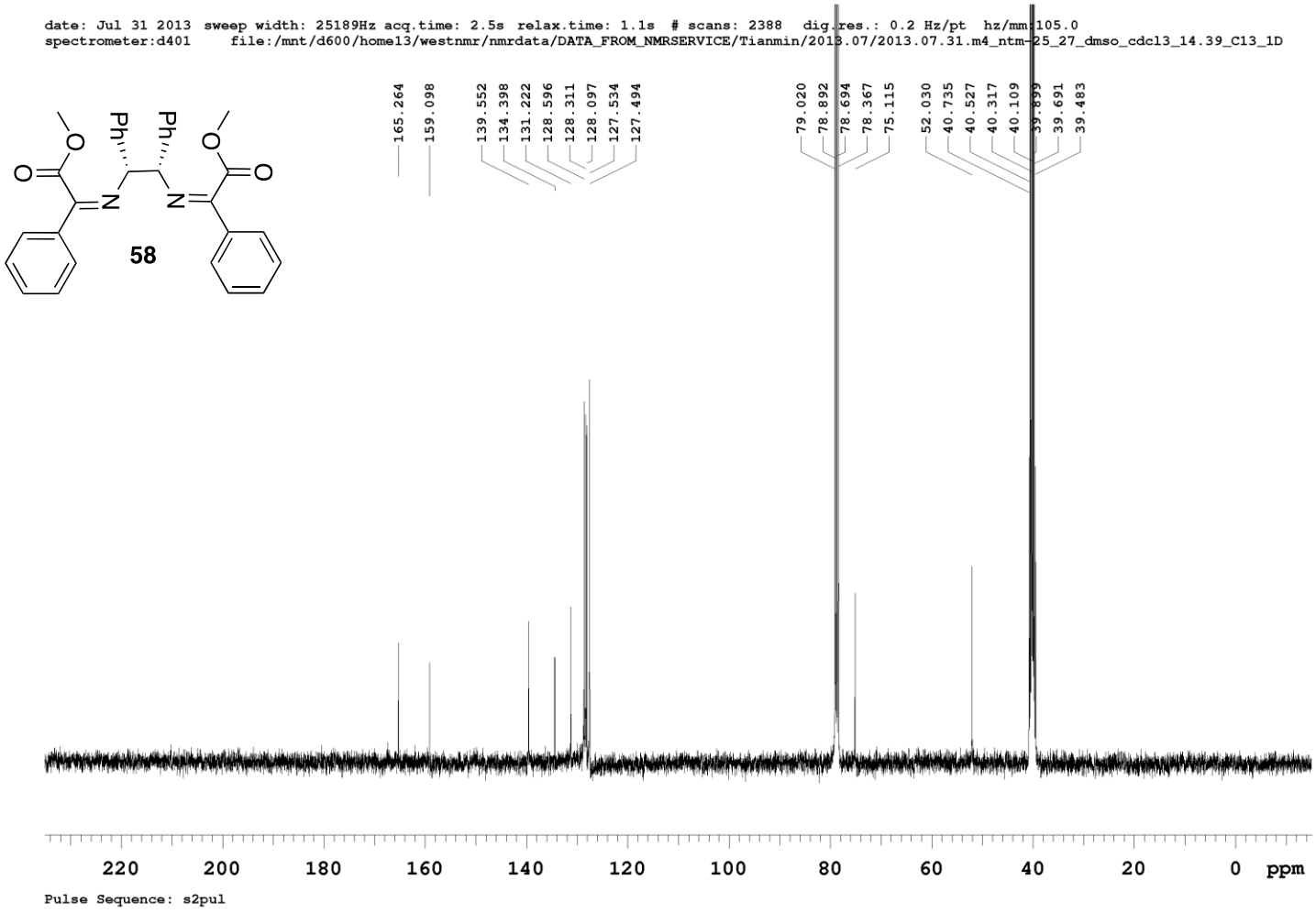
Tianmin, ntm-25_27_dmso_cdcl3
400.394 MHz H1 PRESAT in dmso (ref. to DMSO @ 2.49 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

date: Jul 31 2013 sweep width: 4808Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:20.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2013.07/2013.07.31.m4_ntm-25_27_dmso_cdcl3_14.37_H1_1D

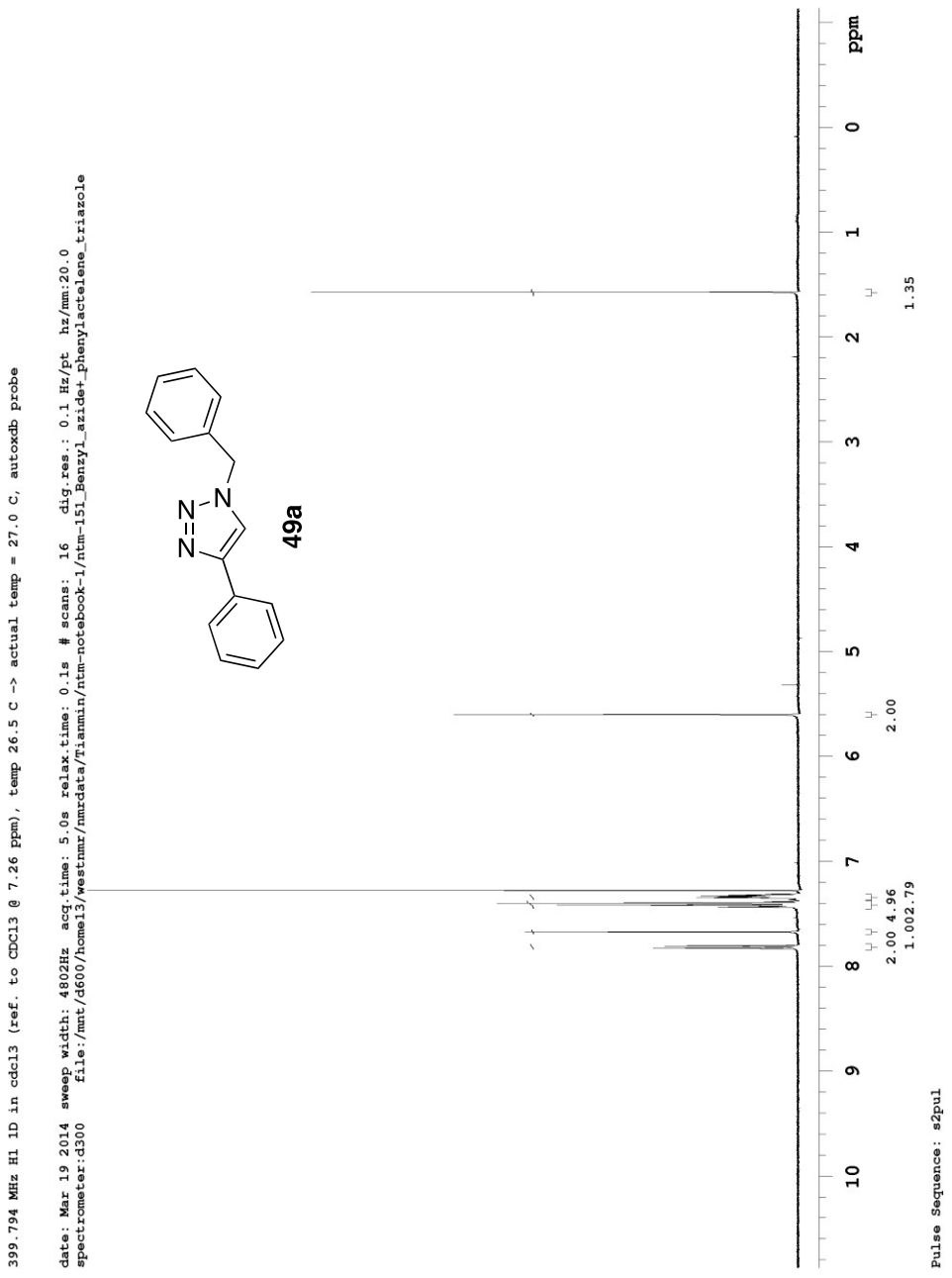


58

Pulse Sequence: PRESAT

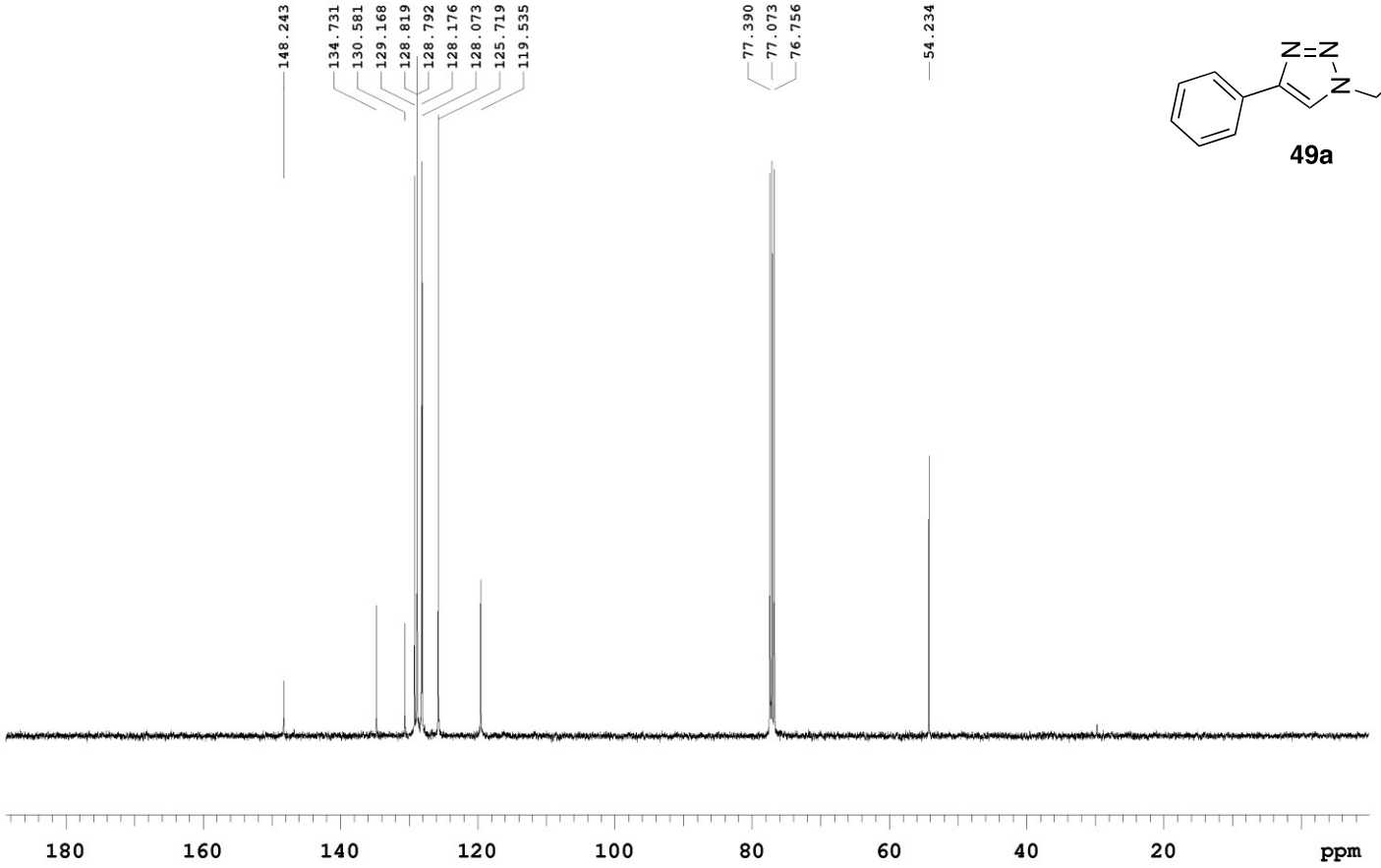

Tianmin, ntm-25_27_dmso_cdcl3
100.690 MHz C13[H1] 1D in dmso (ref. to DMSO @ 39.5 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
date: Jul 31 2013 sweep width: 25189Hz acq.time: 2.5s relax.time: 1.1s # scans: 2388 dig.res.: 0.2 Hz/pt hz/mm: 105.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2013.07/2013.07.31.m4_ntm-25_27_dmso_cdcl3_14.39_C13_1D
58
165.264
159.098
139.552
134.398
131.222
128.596
128.311
128.097
127.534
127.494
79.020
78.892
78.694
78.367
75.115
52.030
40.735
40.527
40.317
40.109
39.899
39.691
39.483
220
200
180
160
140
120
100
80
60
40
20
0
ppm
Pulse Sequence: s2pul

Appendix II: Selected NMR Spectra (Chapter 3)



Tianmin, ntm-13-2
100.689 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

date: Jul 5 2013 sweep width: 25189Hz acq.time: 2.5s relax.time: 1.1s # scans: 1300 dig.res.: 0.2 Hz/pt hz/mm:83.3
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/Tianmin/ntm-notebook-1/2013.07.5.m4_ntm-13-2_20.32_C13_1D

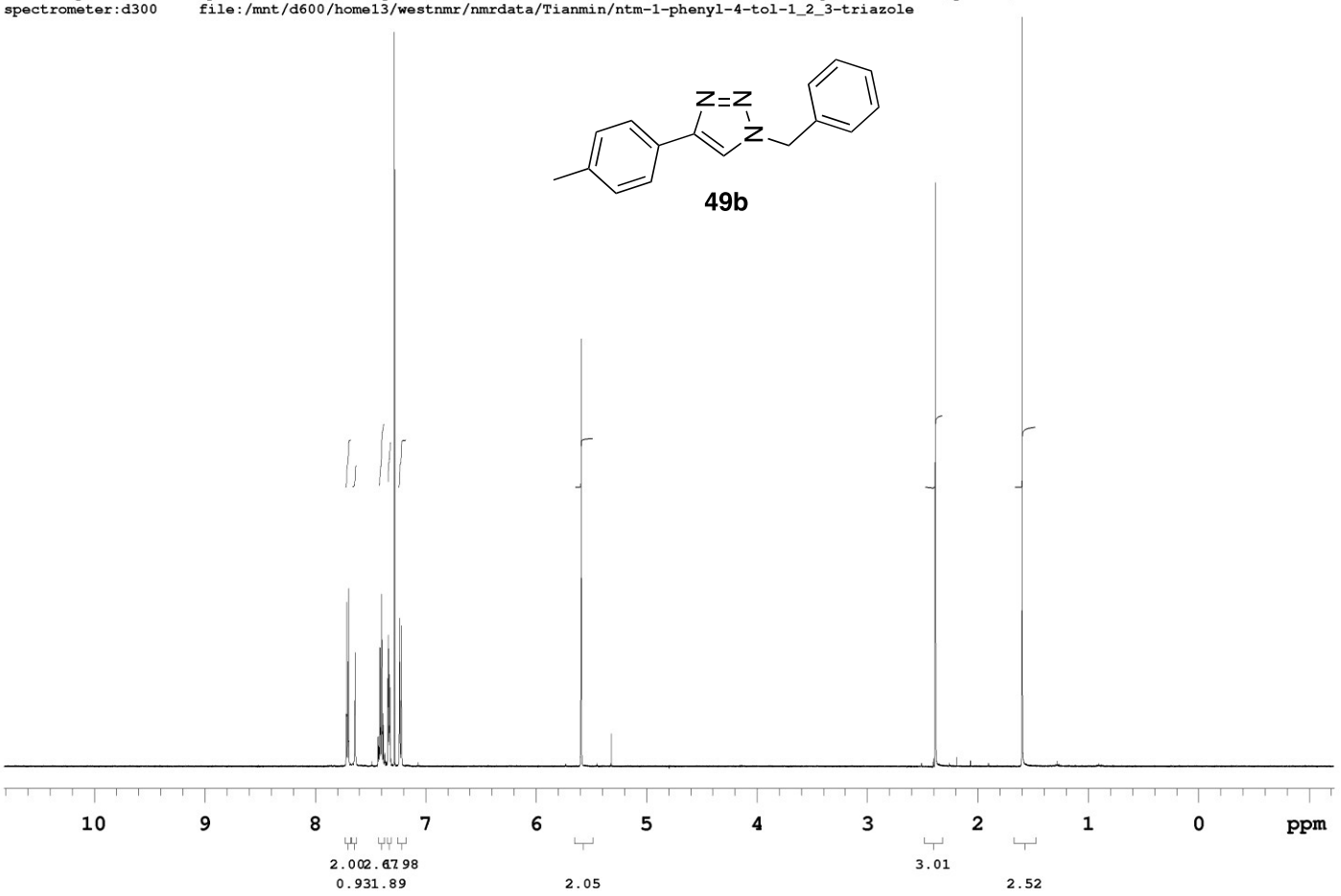


49a

Pulse Sequence: s2pul

498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

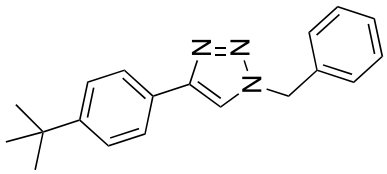
date: Sep 1 2015 sweep width: 6001Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:25.0
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/Tianmin/ntm-1-phenyl-4-tol-1_2_3-triazole



Pulse Sequence: s2pul

399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe

date: Aug 22 2014 sweep width: 4808Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:20.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/Tianmin/ntm-notebook-2/ntm-n2-68-N-benzyl-4-t-butyl-phenyl-triazole

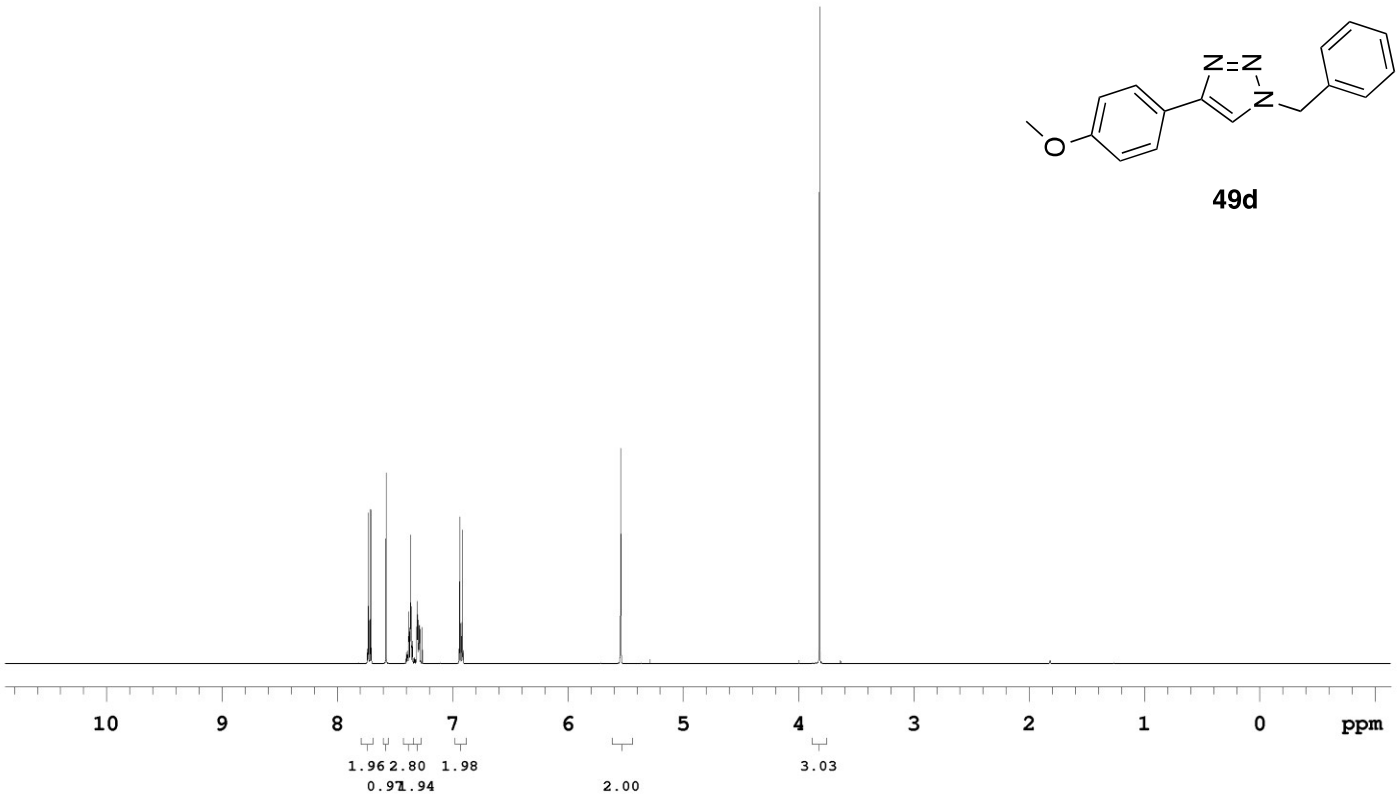


49c

Pulse Sequence: s2pul

399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe

date: Apr 15 2014 sweep width: 4808Hz acq.time: 5.0s relax.time: 0.1s # scans: 8 dig.res.: 0.1 Hz/pt hz/mm:20.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/Tianmin/ntm-notebook-1/ntm-174-N-Benzyl-4-PMP-triazole

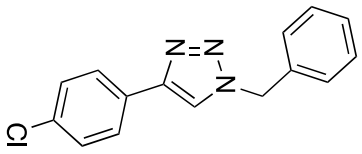


49d

Pulse Sequence: s2pul

399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe

date: Aug 25 2014 sweep width: 4808Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:20.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/Tianmin/ntm-notebook-2/ntm-n2-69-N-benzyl-4-p-Cl-phenyl-triazole

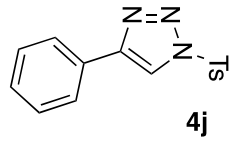


49e

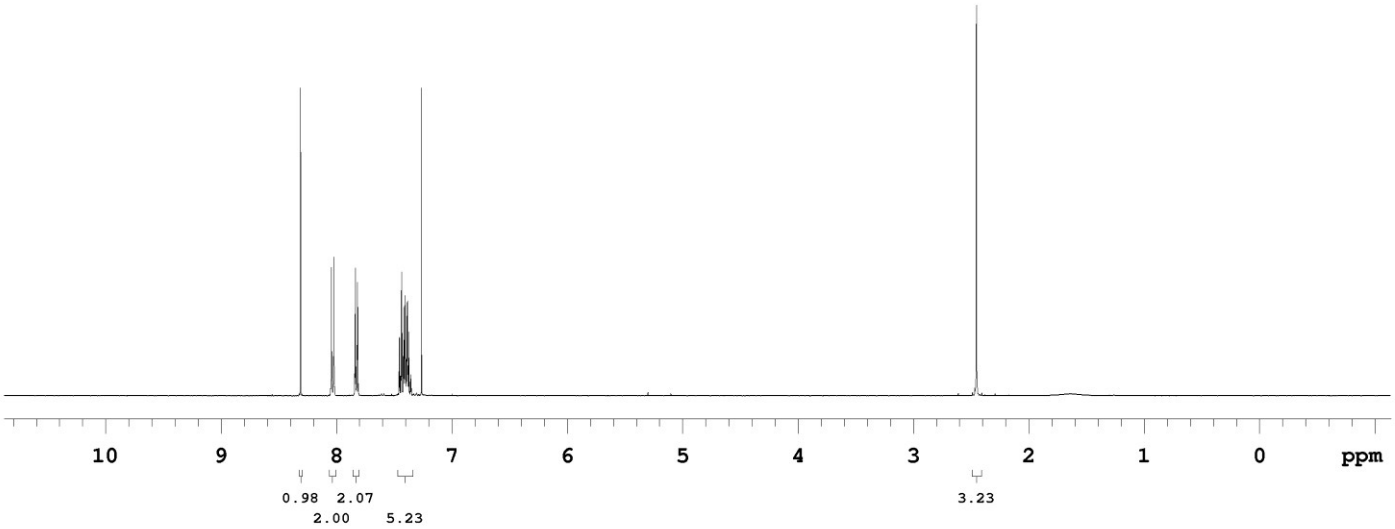
Pulse Sequence: s2pul

399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe

date: Apr 28 2014 sweep width: 4808Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:20.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/Tianmin/ntm-notebook-1/ntm-188-tosylzide_sm



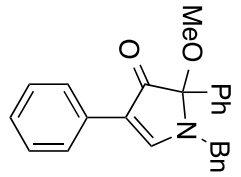
4j



Pulse Sequence: s2pul

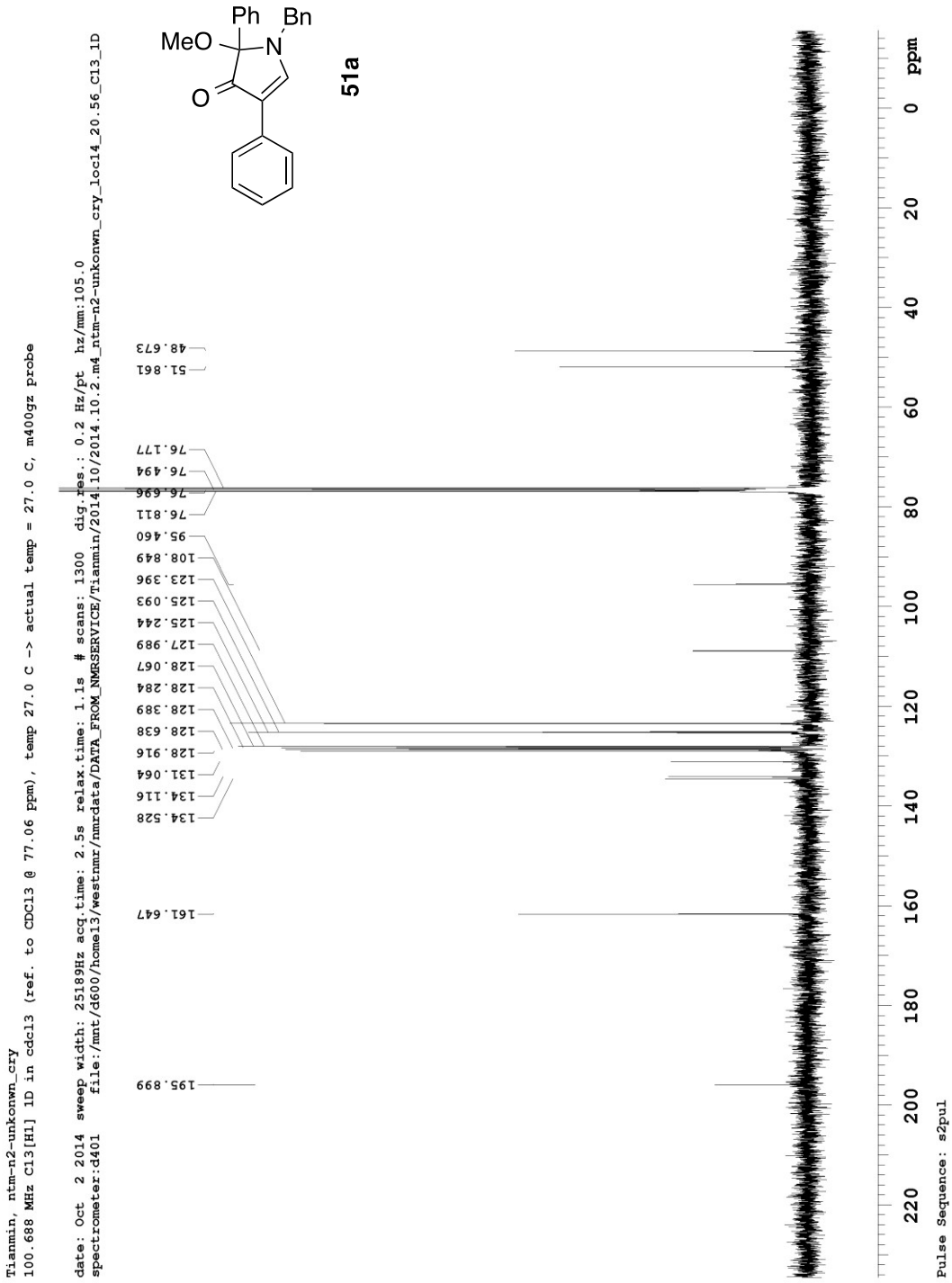
Tianmin, ntm-n2-unkonwn_cry
400.389 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

date: Oct 2 2014 sweep width: 4808Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:20.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2014.10/2014.10.2.m4_ntm-n2-unkonwn_cry_loc14_20.54_H1_1D



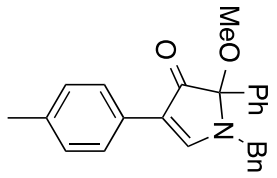
51a

Pulse Sequence: PRESAT

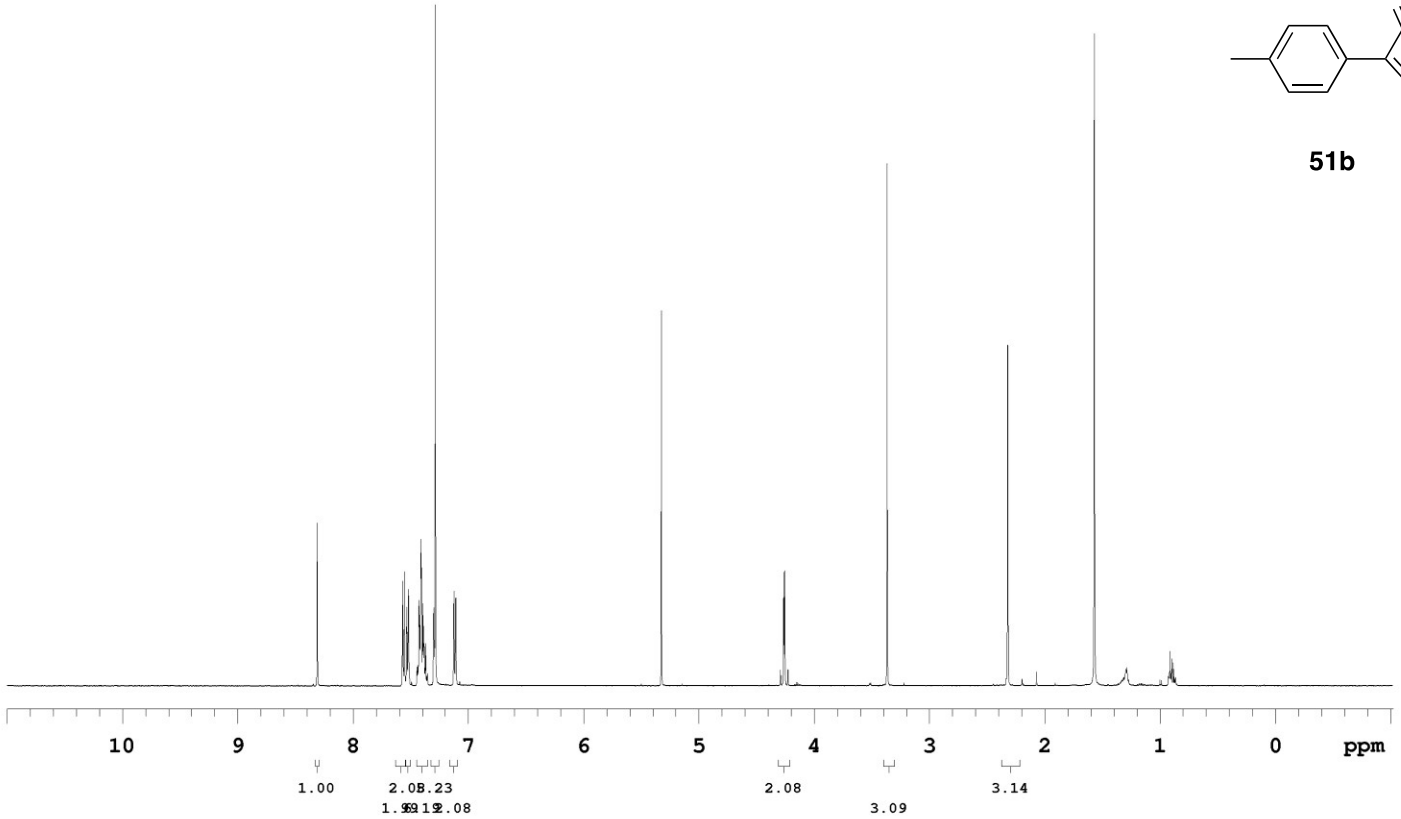

Tianmin, ntm-n2-unkonwn_cry
100.688 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
date: Oct 2 2014 sweep width: 25189Hz acq.time: 2.5s relax.time: 1.1s # scans: 1300 dig.res.: 0.2 Hz/pt hz/mm:105.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2014_10/2014.10.2.m4_ntm-n2-unkonwn_cry_loc14_20.56_C13_1D
Ph
Bn
MeO
N
O
51a
48.673
51.861
76.177
76.494
76.696
76.811
95.460
108.849
123.396
125.093
125.244
127.989
128.067
128.284
128.389
128.638
128.916
131.064
134.116
134.528
161.647
195.899
220
200
180
160
140
120
100
80
60
40
20
0
ppm
Pulse Sequence: s2pul

Tianmin, ntm-n2-178-1
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

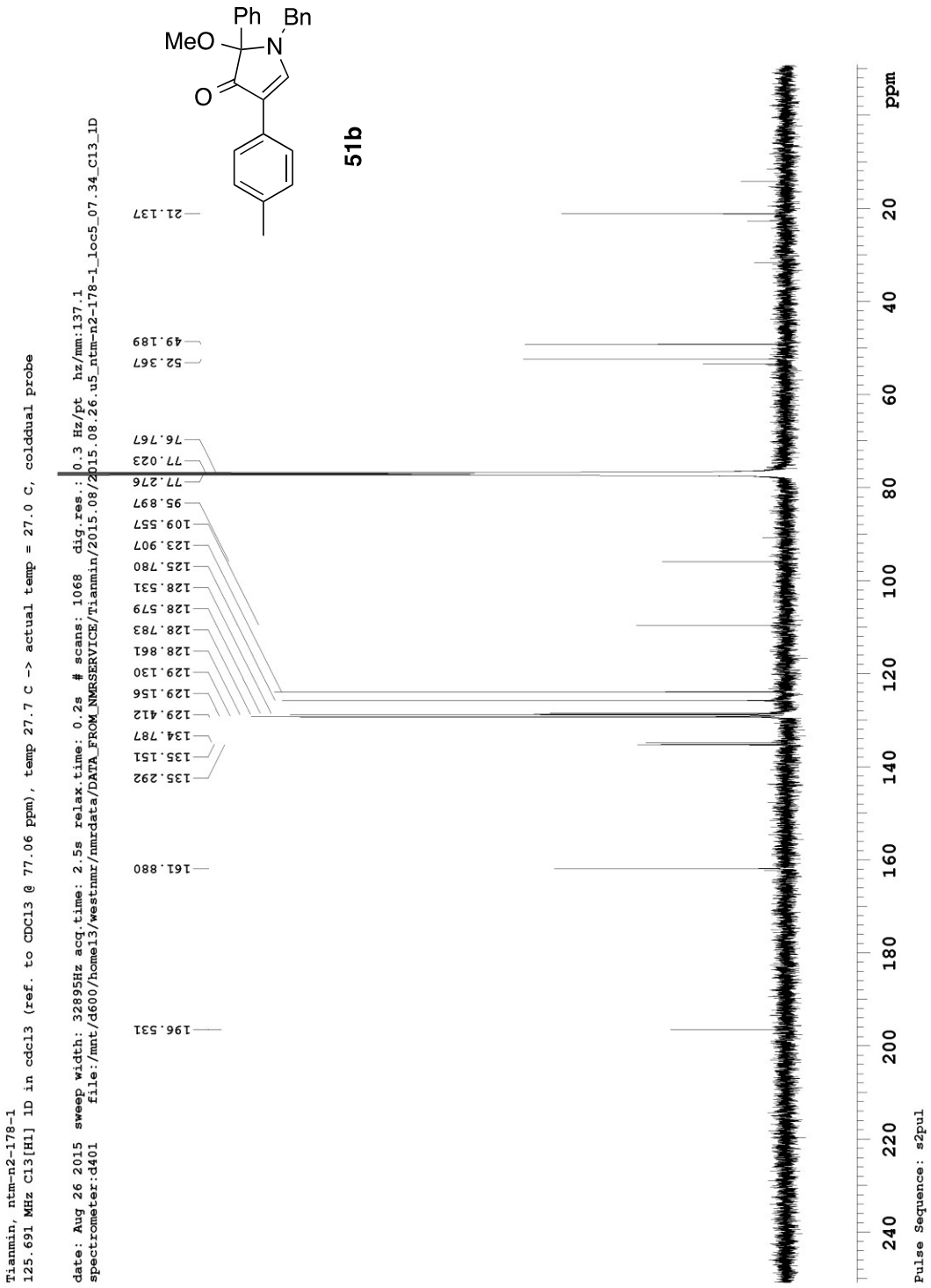
date: Aug 26 2015 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:25.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2015.08/2015.08.26.u5_ntm-n2-178-1_loc5_07.32_H1_1D



51b

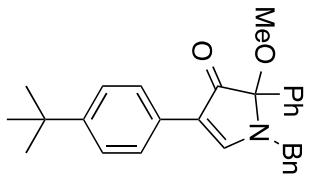


Pulse Sequence: PRESAT


Tianmin, ntm-n2-178-1
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Aug 26 2015 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 1068 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2015.08/2015.08.26.u5_ntm-n2-178-1_loc5_07.34_C13_1D
Ph
Bn
MeO
N
O
51b
21.137
49.189
52.367
76.767
77.023
77.276
95.897
109.557
123.907
125.780
128.531
128.579
128.783
128.861
129.130
129.156
129.412
134.787
135.151
135.292
161.880
196.531
ppm
Pulse Sequence: s2pul

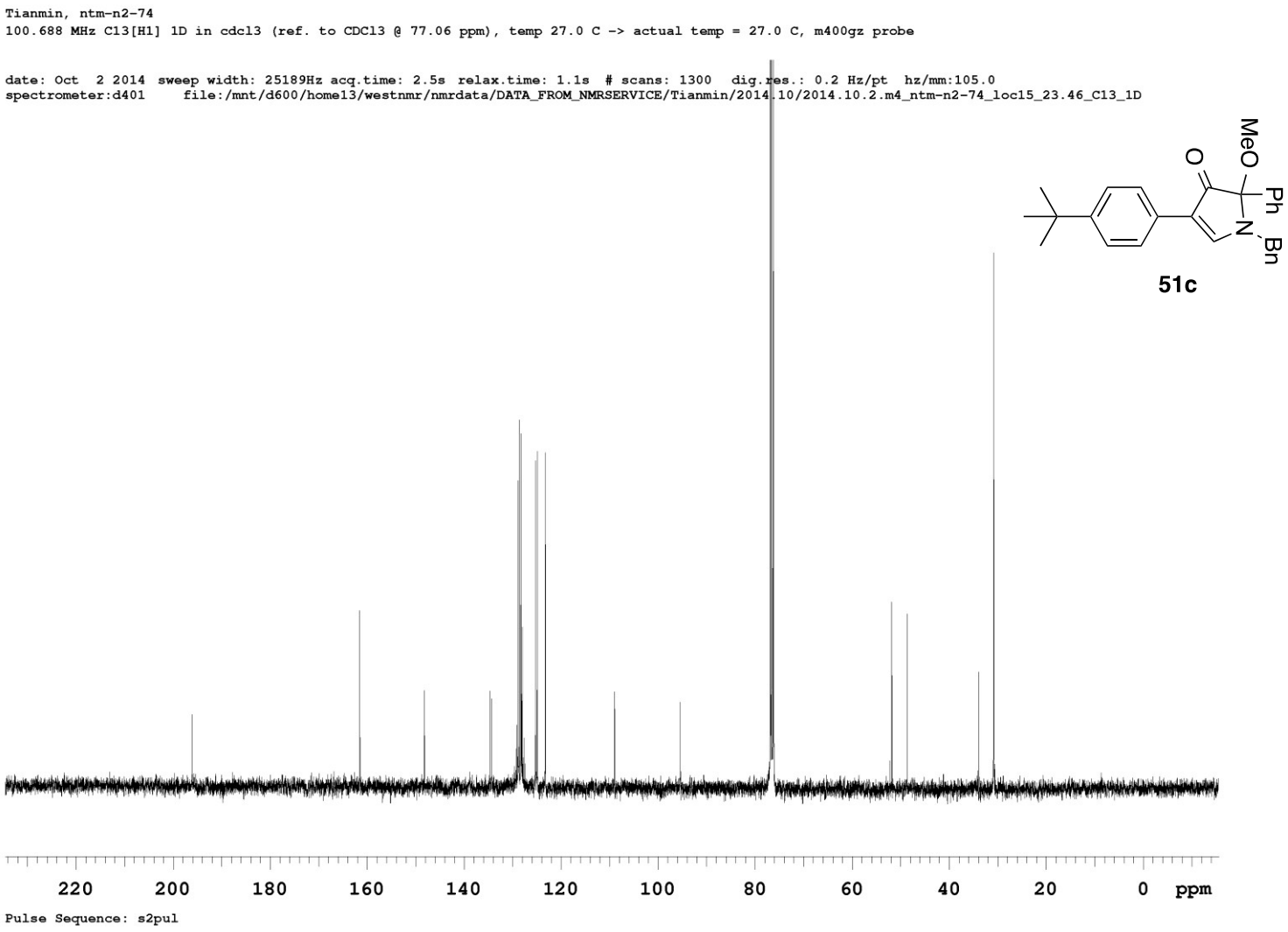
Tianmin, ntm-n2-74
400.389 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

date: Oct 2 2014 sweep width: 4808Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:20.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2014.10/2014.10.2.m4_ntm-n2-74_loc15_23.44_H1_1D



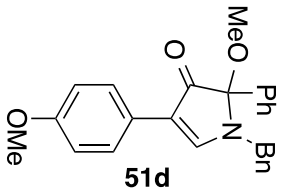
51c

Pulse Sequence: PRESAT

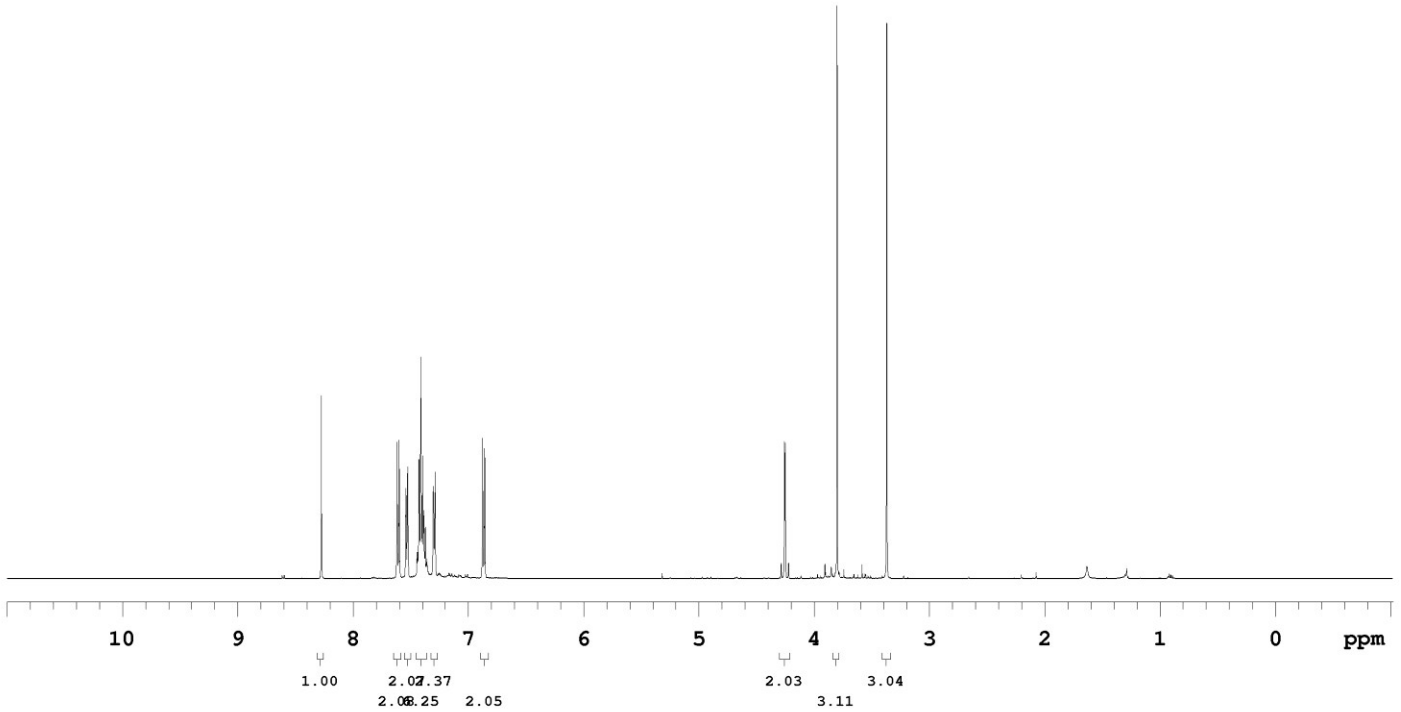

Tianmin, ntm-n2-74
100.688 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
date: Oct 2 2014 sweep width: 25189Hz acq.time: 2.5s relax.time: 1.1s # scans: 1300 dig.res.: 0.2 Hz/pt hz/mm:105.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2014.10/2014.10.2.m4_ntm-n2-74_loc15_23.46_C13_1D
MeO
O
Ph
N
Bn
51c
220
200
180
160
140
120
100
80
60
40
20
0
ppm
Pulse Sequence: s2pul

Tianmin, ntm-n2-119-1
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

date: Aug 26 2015 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:25.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2015.08/2015.08.26.u5_ntm-n2-119-1_loc8_04.16_H1_1D



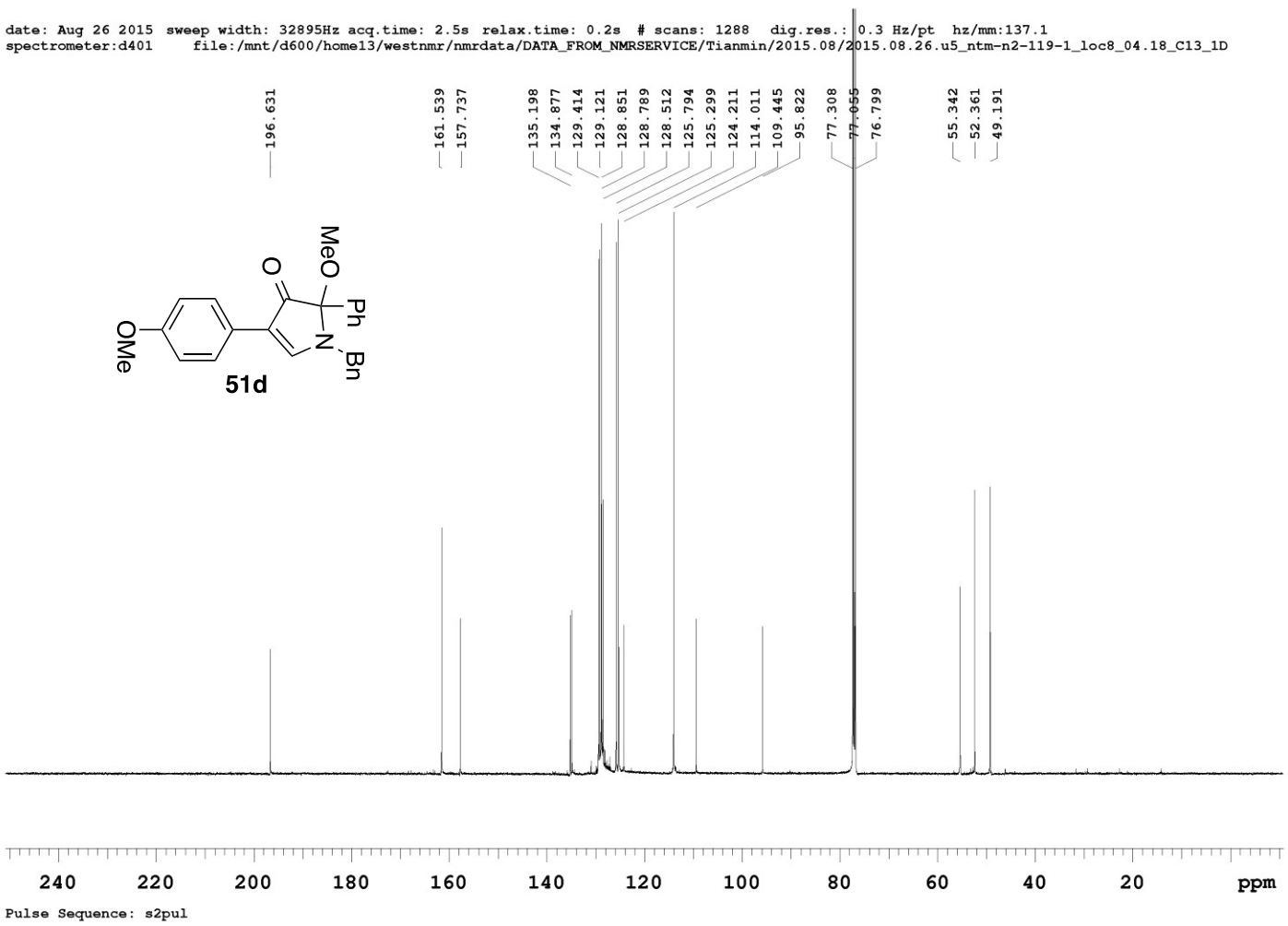
51d



Pulse Sequence: PRESAT

Tianmin, ntm-n2-119-1
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

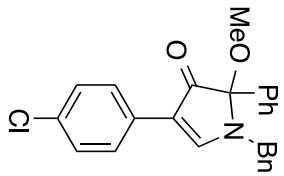
date: Aug 26 2015 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 1288 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2015.08/2015.08.26.u5_ntm-n2-119-1_loc8_04.18_C13_1D



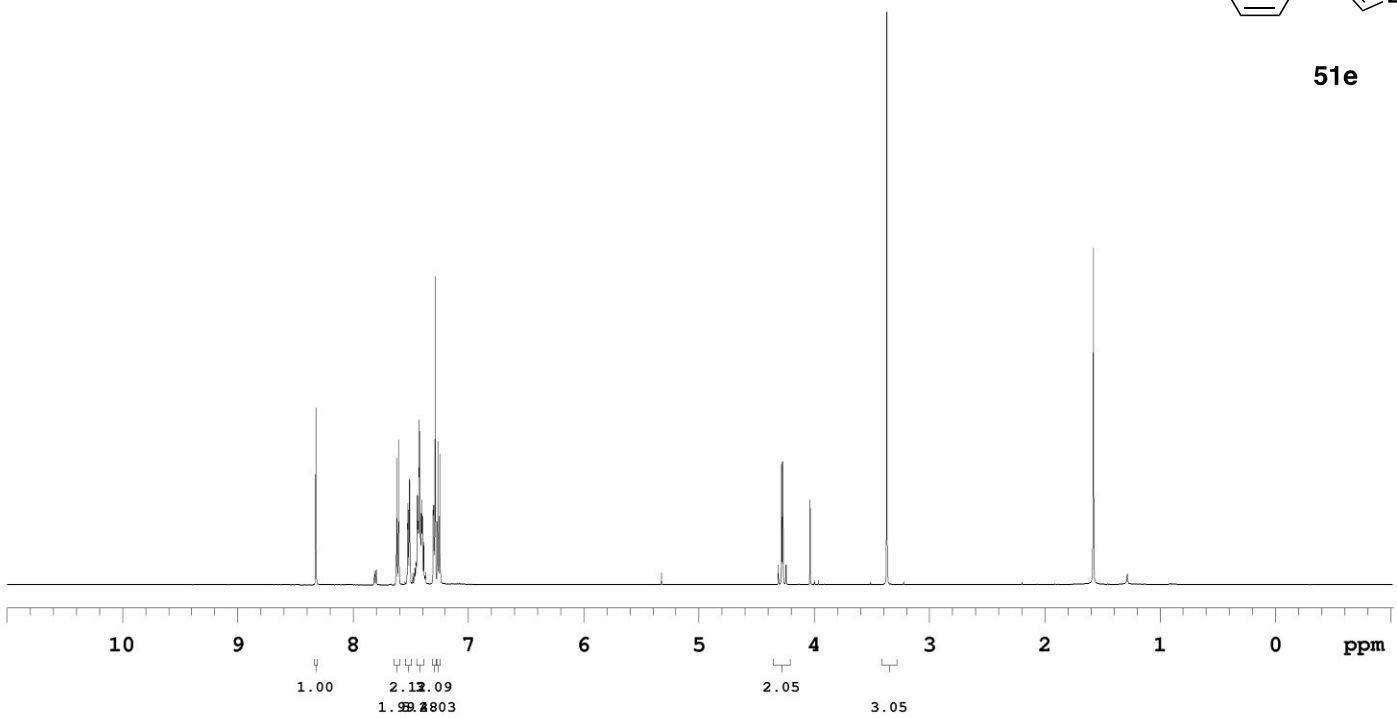
Pulse Sequence: s2pul

Tianmin, ntm-n2-117
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

date: Aug 27 2015 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:25.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2015.08/2015.08.27.u5_ntm-n2-117_loc8_06.33_H1_1D



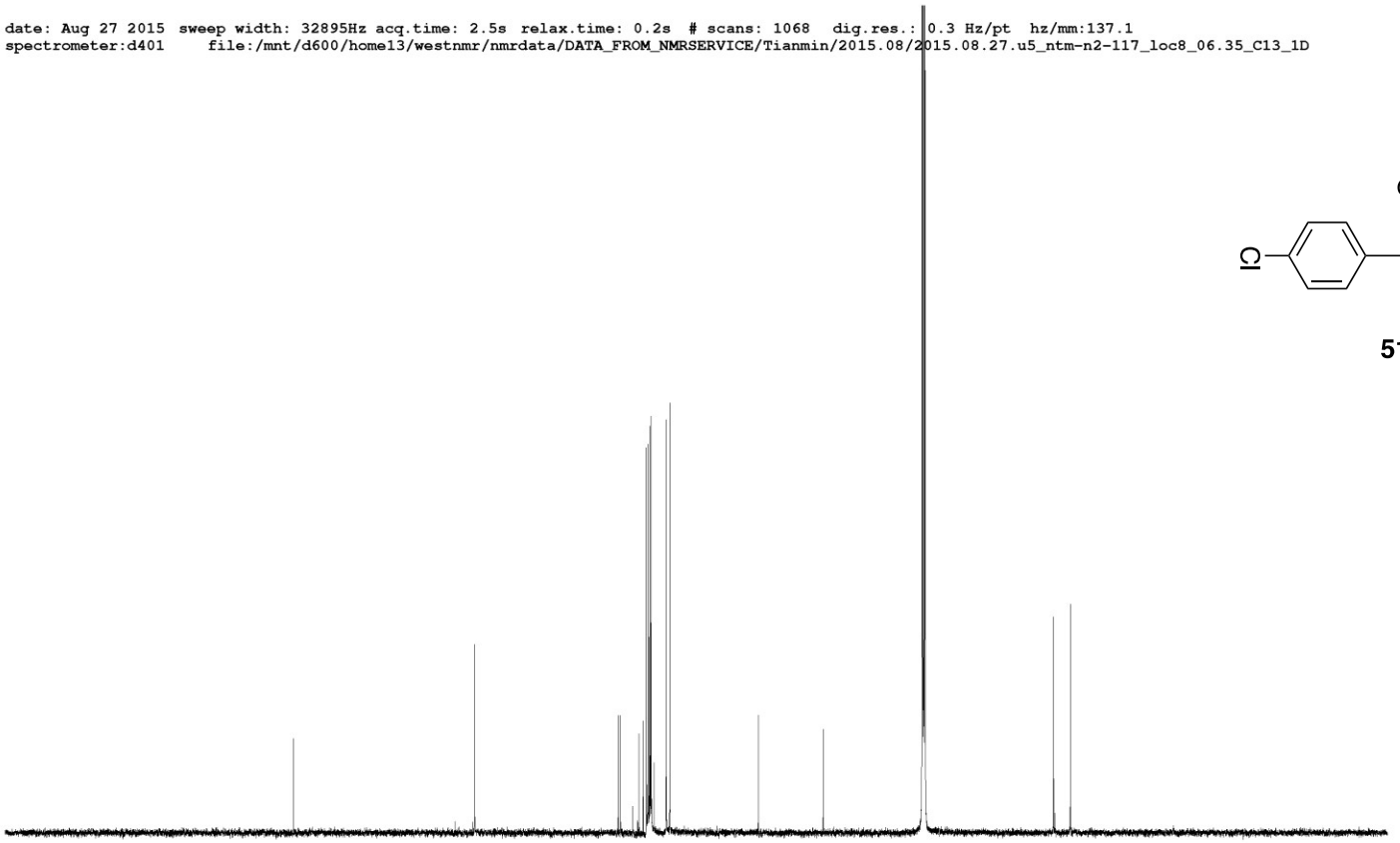
51e



Pulse Sequence: PRESAT

Tianmin, ntm-n2-117
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

date: Aug 27 2015 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 1068 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2015.08/2015.08.27.u5_ntm-n2-117_loc8_06.35_C13_1D

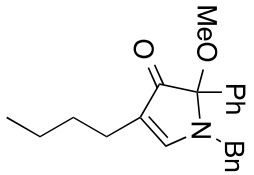


Pulse Sequence: s2pul

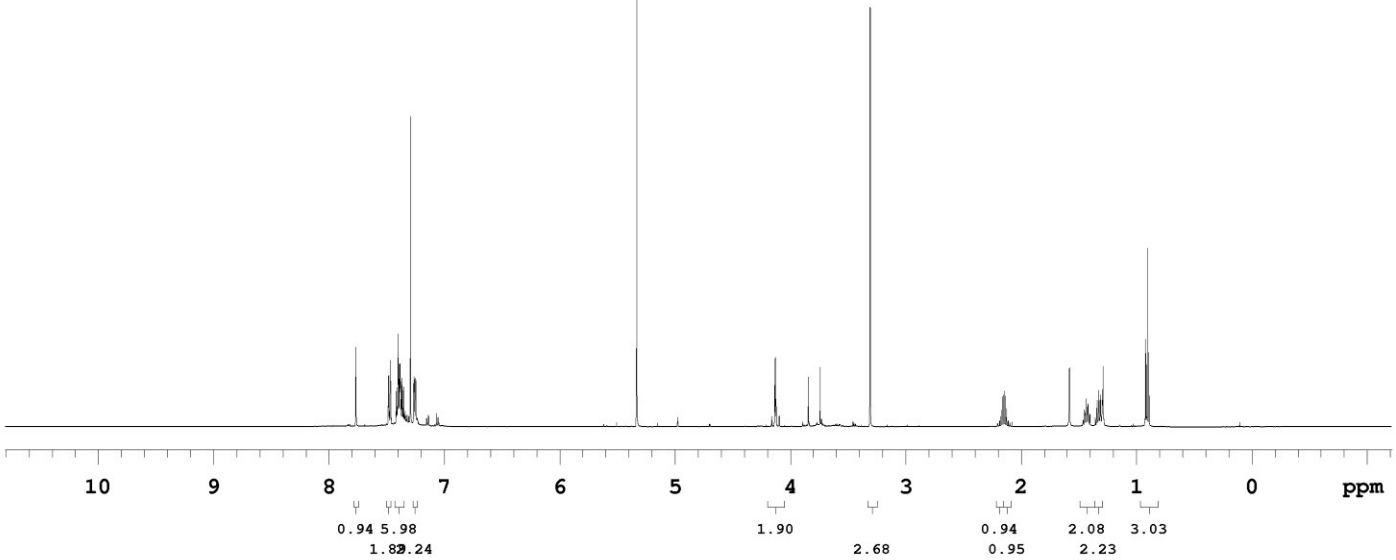
51e

499.806 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

date: Apr 8 2014 sweep width: 6010Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:25.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/Tianmin/ntm-notebook-1/2014.04.08.u5_ntm-170_H1_1D



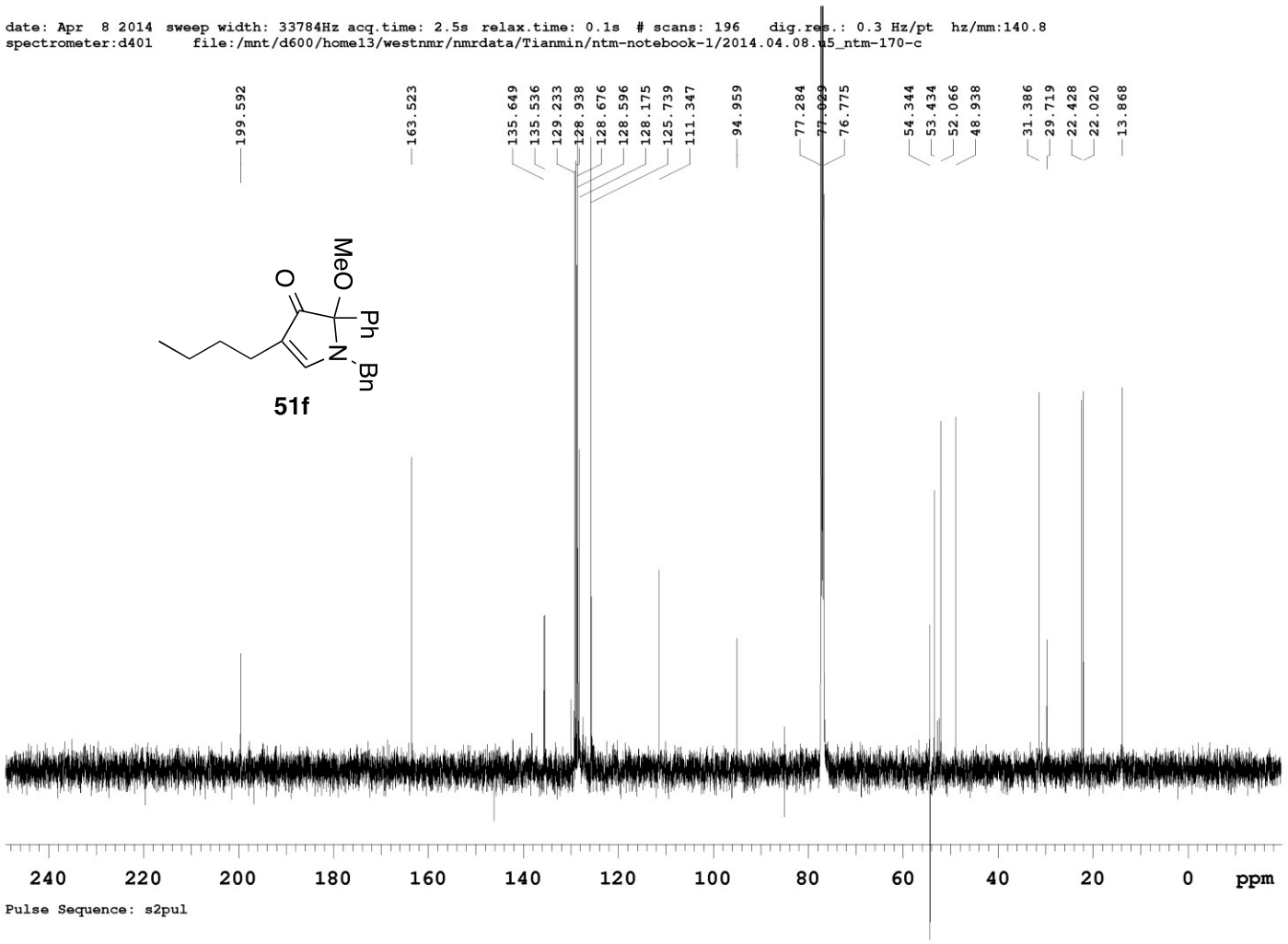
51f



Pulse Sequence: s2pul

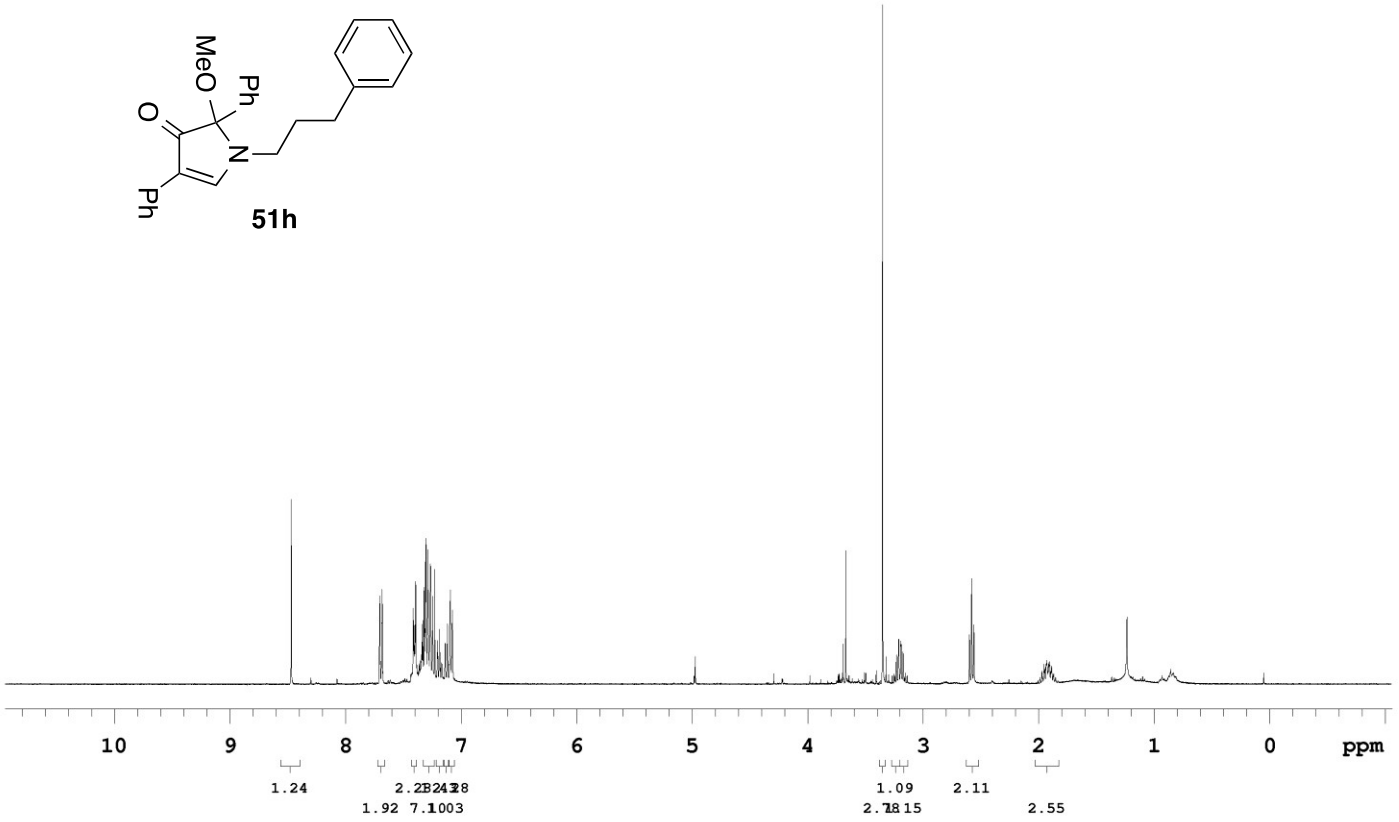
125.690 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

date: Apr 8 2014 sweep width: 33784Hz acq.time: 2.5s relax.time: 0.1s # scans: 196 dig.res.: 0.3 Hz/pt hz/mm:140.8
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/Tianmin/ntm-notebook-1/2014.04.08.u5_ntm-170-c



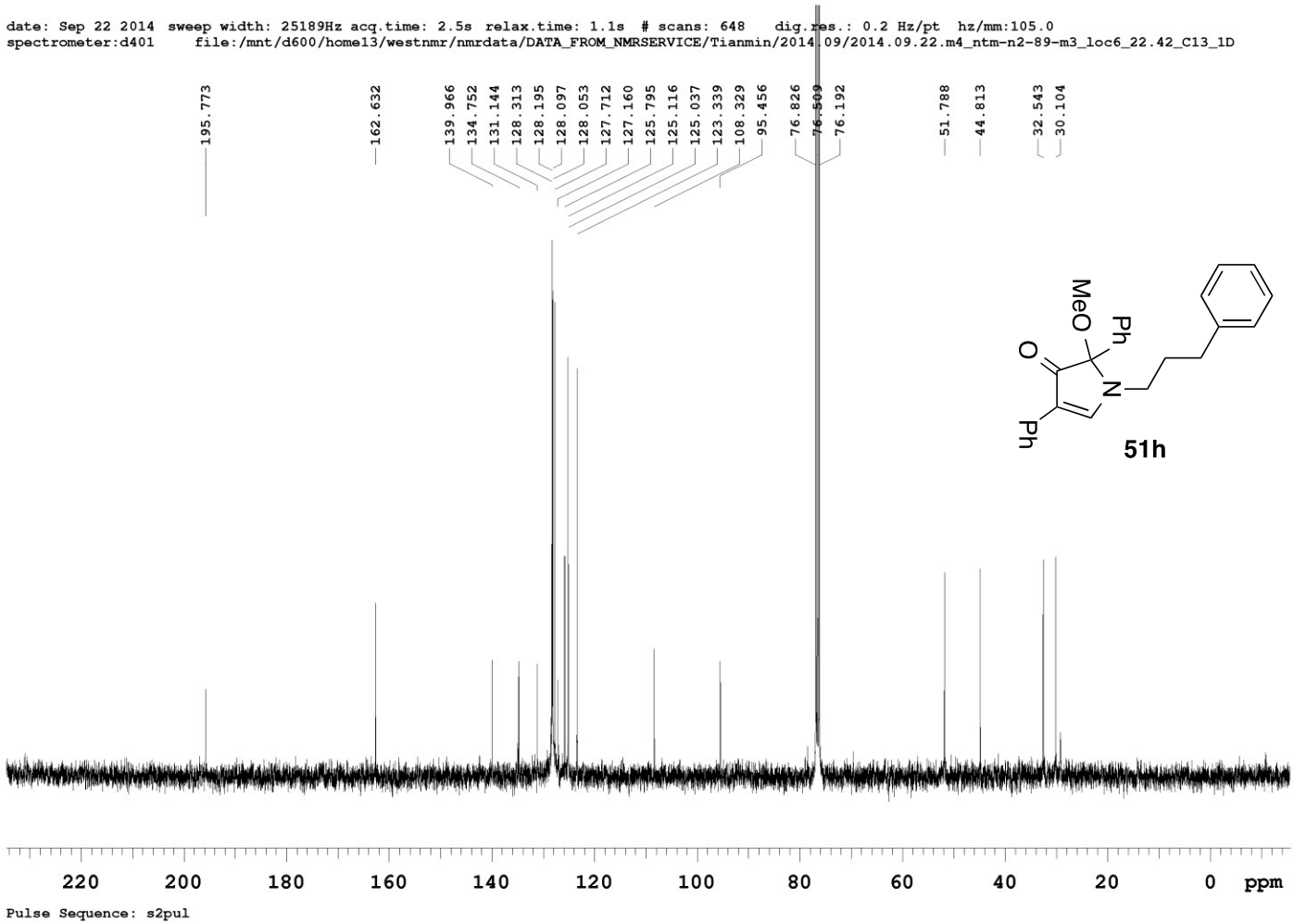
Tianmin, ntm-n2-89-m3
400.389 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe

date: Sep 22 2014 sweep width: 4808Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:20.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2014.09/2014.09.22.m4_ntm-n2-89-m3_loc6_22.41_H1_1D



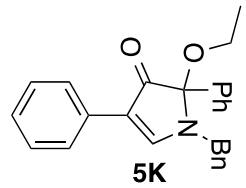
51h

Pulse Sequence: PRESAT

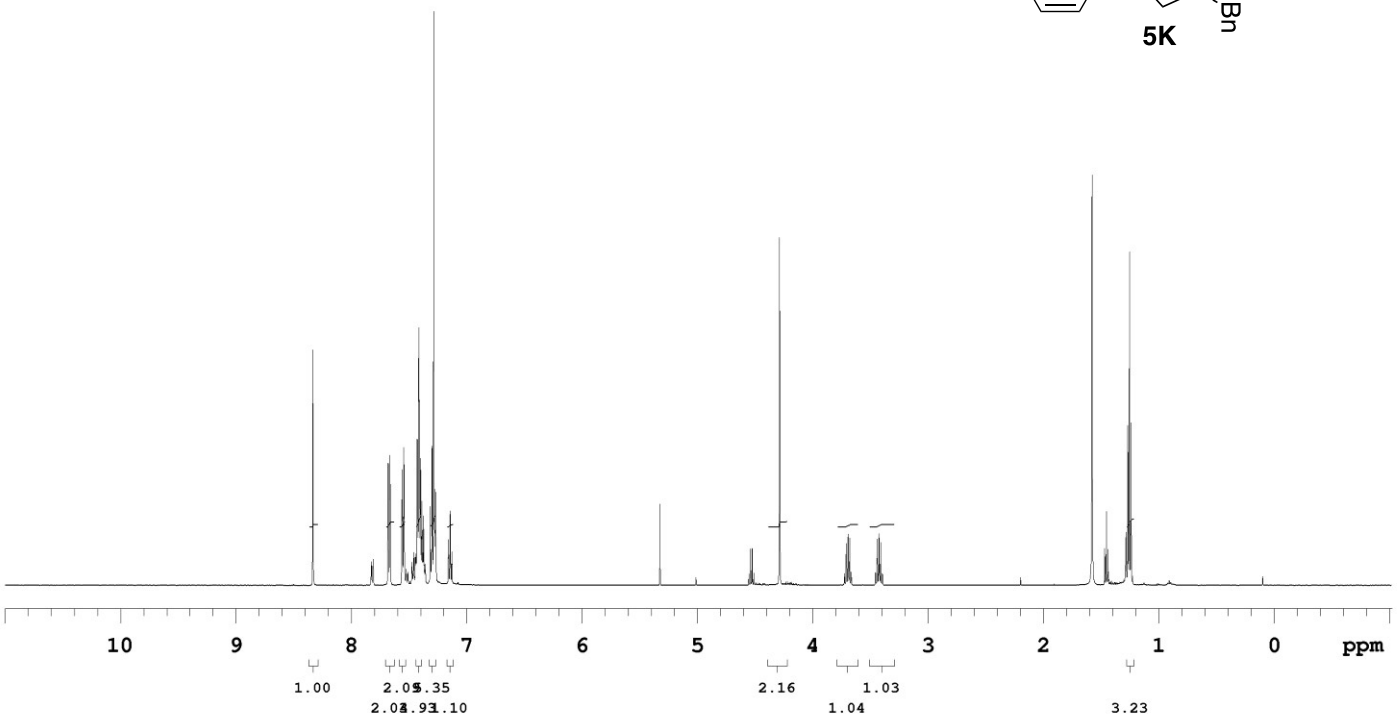

Tianmin, ntm-n2-89-m3
100.688 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
date: Sep 22 2014 sweep width: 25189Hz acq.time: 2.5s relax.time: 1.1s # scans: 648 dig.res.: 0.2 Hz/pt hz/mm:105.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2014_09/2014.09.22.m4_ntm-n2-89-m3_loc6_22.42_C13_1D
195.773
162.632
139.966
134.752
131.144
128.313
128.195
128.097
128.053
127.712
127.160
125.795
125.116
125.037
123.339
108.329
95.456
76.826
76.509
76.192
51.788
44.813
32.543
30.104
MeO
Ph
O
N
Ph
51h
220
200
180
160
140
120
100
80
60
40
20
0
ppm
Pulse Sequence: s2pul

Tianmin, ntm-n2-55
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

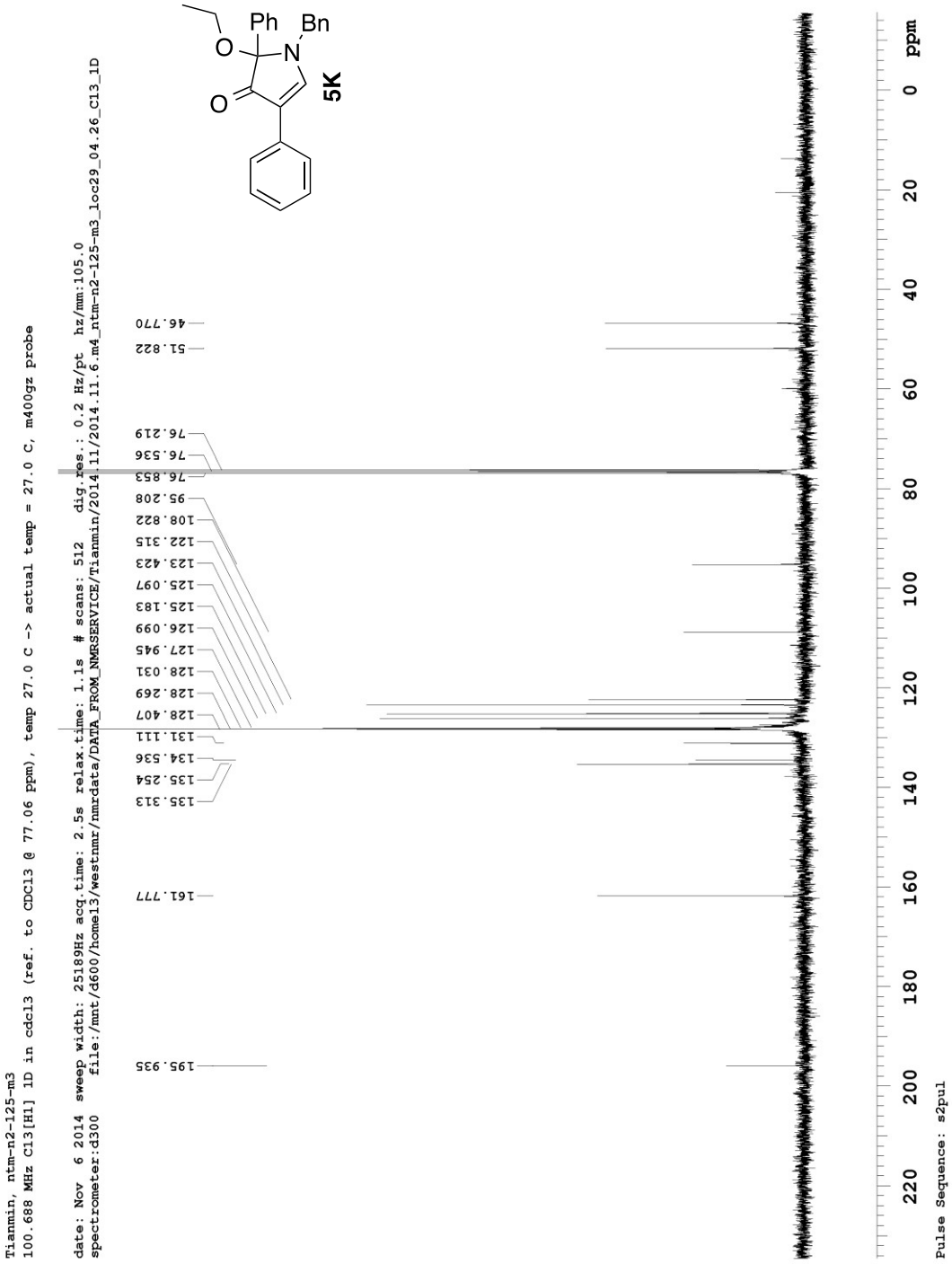
date: Sep 1 2015 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:25.0
spectrometer:d300 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2015.09/2015.09.01.u5_ntm-n2-55_loc12_09.35_H1_1D



5K

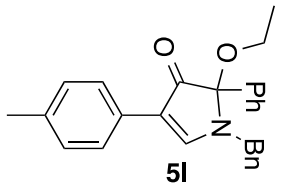


Pulse Sequence: PRESAT


Tianmin, ntm-n2-125-m3
100.688 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
date: Nov 6 2014 sweep width: 25189Hz acq.time: 2.5s relax.time: 1.1s # scans: 512 dig.res.: 0.2 Hz/pt hz/mm:105.0
spectrometer::d300 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2014.11/2014.11.6.m4_ntm-n2-125-m3_loc29_04.26_C13_1D
Ph
Bn
O
N
O
5K
46.770
51.822
76.219
76.536
76.853
95.208
108.822
122.315
123.423
125.097
125.183
126.099
127.945
128.031
128.269
128.407
131.111
134.536
135.254
135.313
161.777
195.935
220
200
180
160
140
120
100
80
60
40
20
0
ppm
Pulse Sequence: s2pul

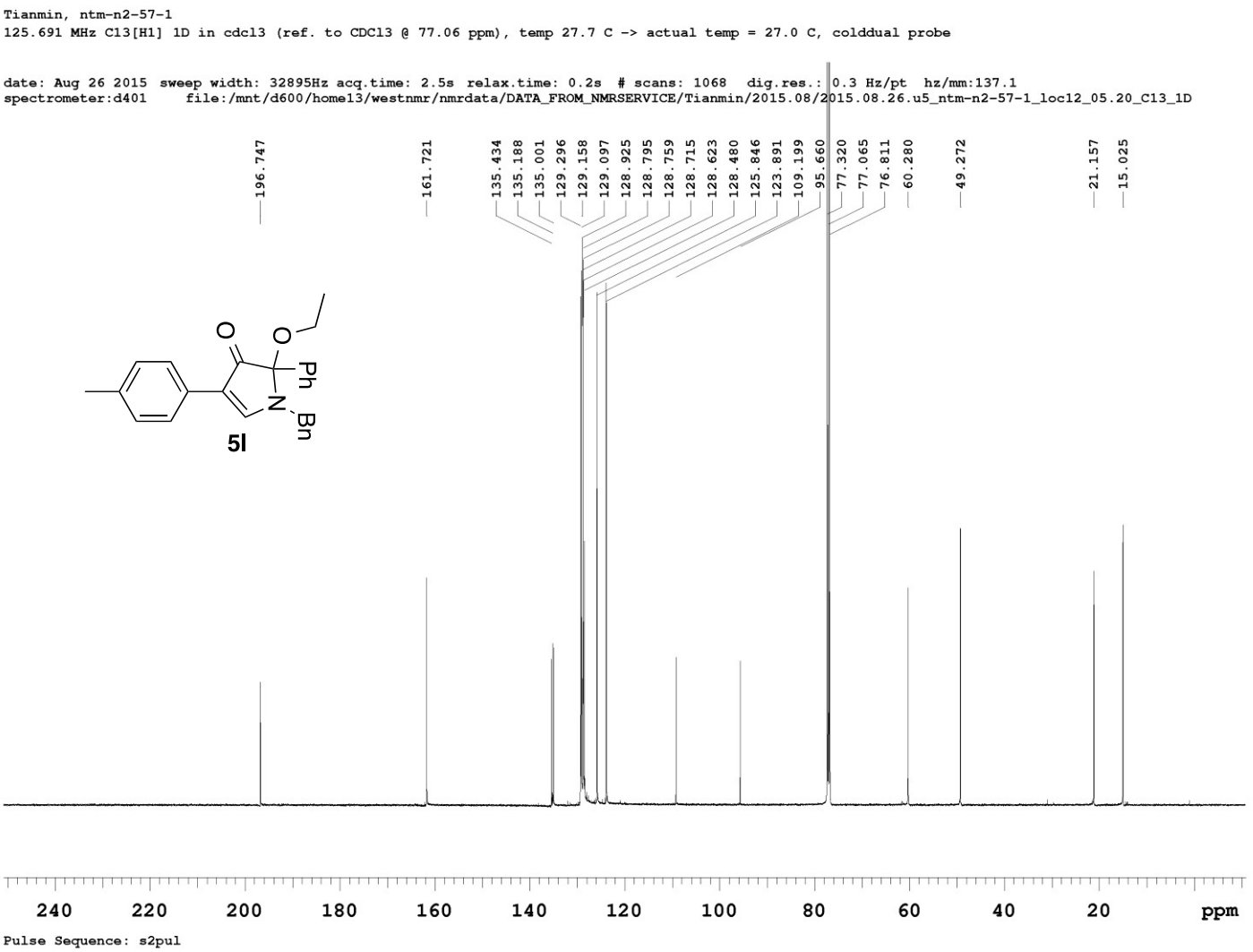
Tianmin, ntm-n2-57-1
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

date: Aug 26 2015 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:25.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2015.08/2015.08.26.u5_ntm-n2-57-1_loc12_05.19_H1_1D



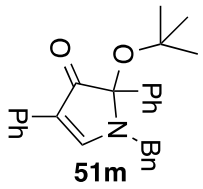
5l

Pulse Sequence: PRESAT


Tianmin, ntm-n2-57-1
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Aug 26 2015 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 1068 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2015.08/2015.08.26.u5_ntm-n2-57-1_loc12_05.20_C13_1D
196.747
161.721
135.434
135.188
135.001
129.296
129.158
129.097
128.925
128.795
128.759
128.715
128.623
128.480
125.846
123.891
109.199
95.660
77.320
77.065
76.811
60.280
49.272
21.157
15.025
O
O
Ph
N
Bn
5l
240
220
200
180
160
140
120
100
80
60
40
20
ppm
Pulse Sequence: s2pul

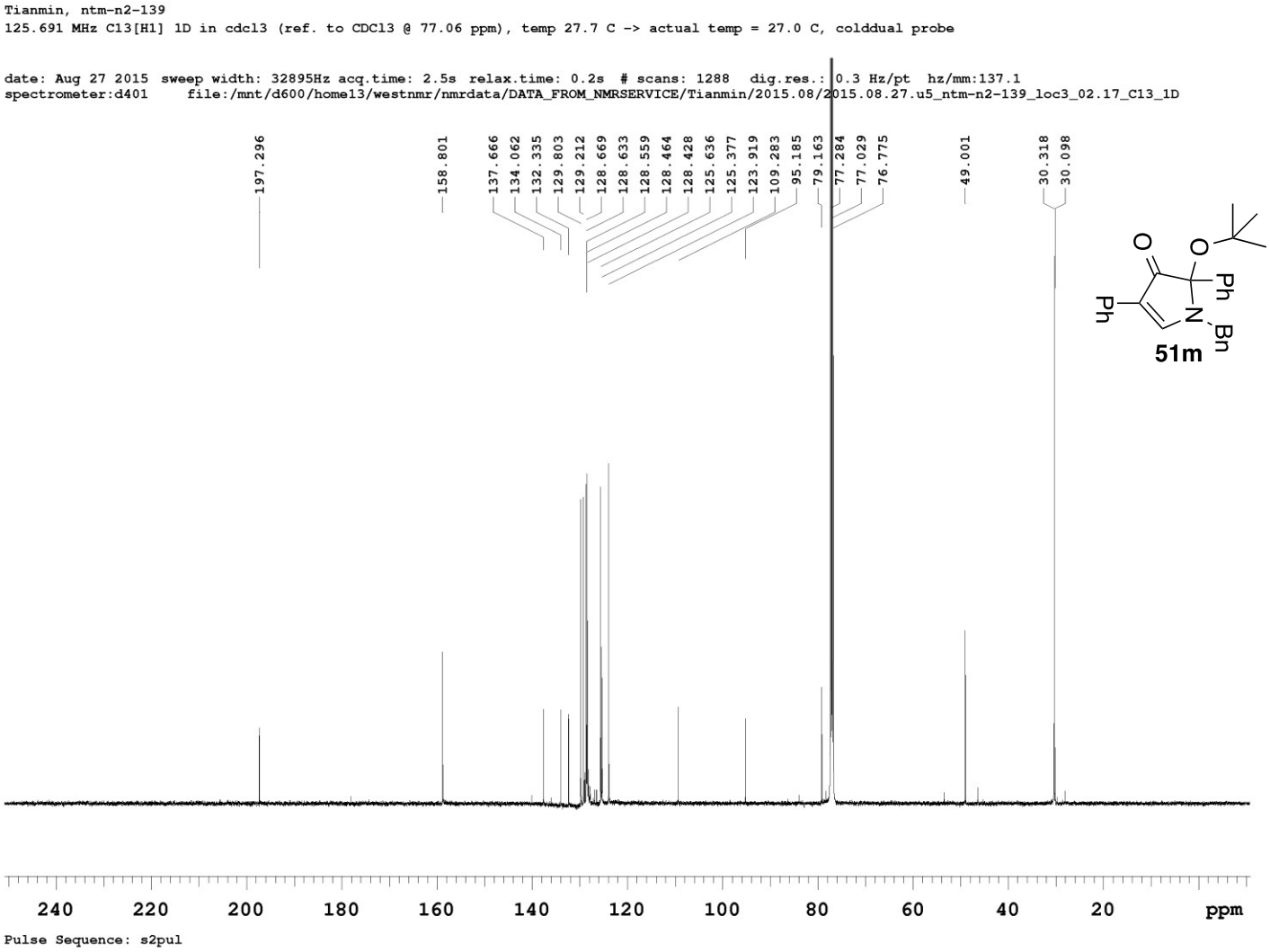
Tianmin, ntm-n2-139
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

date: Aug 27 2015 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:25.0
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2015.08/2015.08.27.u5_ntm-n2-139_loc3_02.15_H1_1D



51m

Pulse Sequence: PRESAT


Tianmin, ntm-n2-139
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Aug 27 2015 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 1288 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d401 file:/mnt/d600/home13/westnmr/nmrdata/DATA_FROM_NMRSERVICE/Tianmin/2015.08/2015.08.27.u5_ntm-n2-139_loc3_02.17_C13_1D
197.296
158.801
137.666
134.062
132.335
129.803
129.212
128.669
128.633
128.559
128.464
128.428
125.636
125.377
123.919
109.283
95.185
79.163
77.284
77.029
76.775
49.001
30.318
30.098
O
O
Ph
Ph
N
Bn
51m
240
220
200
180
160
140
120
100
80
60
40
20
ppm
Pulse Sequence: s2pul

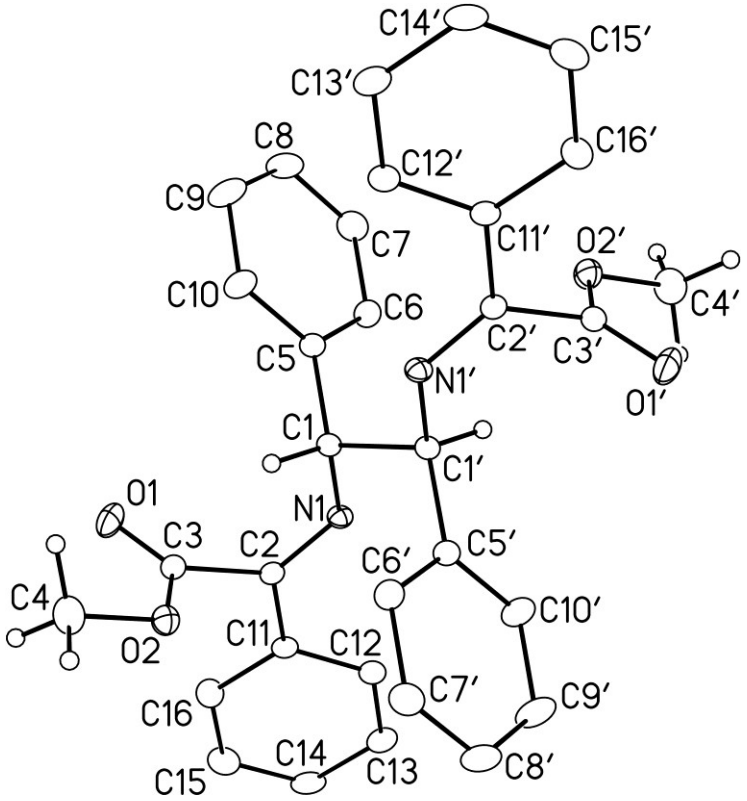
Appendix III: X-ray Crystallographic Data for Compound 58 (Chapter 2)

STRUCTURE REPORT

XCL Code: FGW1313 **Date:** 12 August 2013

Compound: Dimethyl 2,2'-{(1,2-diphenylethane-1,2-diyl)dinitrilo}bis(phenylethanoate)
Formula: $C_{32}H_{28}N_2O_4$

Supervisor: F. G. West **Crystallographer:** R. McDonald



Compound **58**

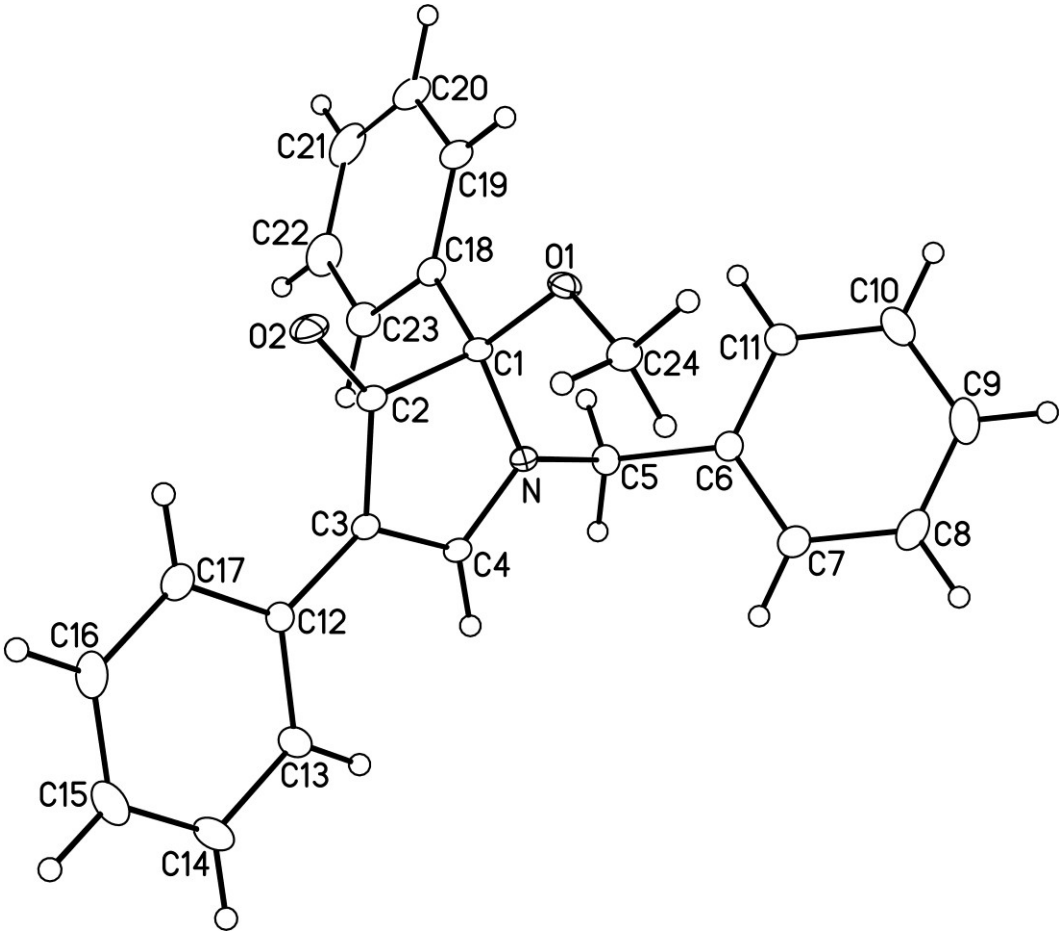
Appendix IV: X-ray Crystallographic Data for Compounds **51a** and **51b** (Chapter 3)

STRUCTURE REPORT

XCL Code: FGW1316 **Date:** 22 August 2013

Compound: 1-benzyl-2-methoxy-2,4-diphenyl-1,2-dihydro-3*H*-pyrrol-3-one
Formula: $C_{24}H_{21}NO_2$

Supervisor: F. G. West **Crystallographer:** M. J. Ferguson



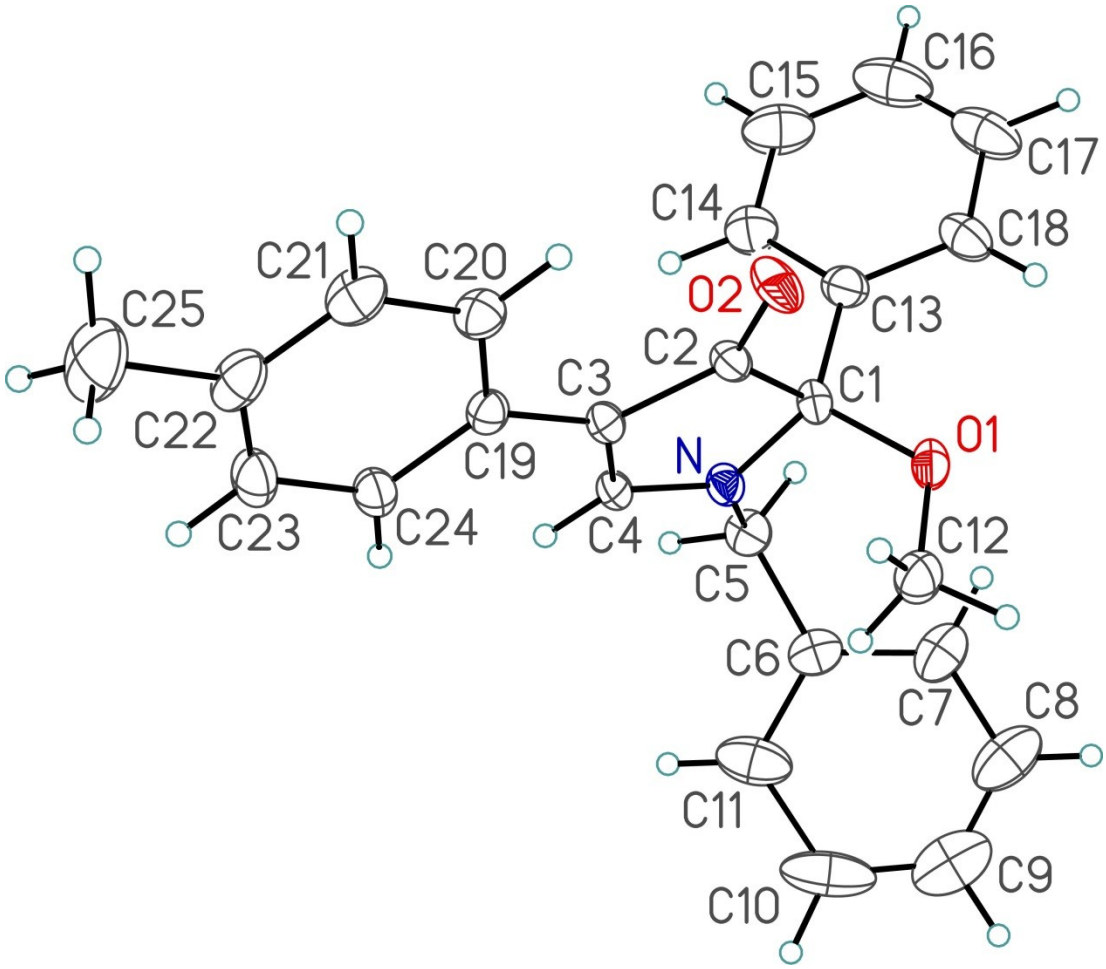
Compound **51a**

STRUCTURE REPORT

XCL Code: FGW1408 **Date:** 3 October 2014

Compound: 1-Benzyl-2-methoxy-4-(4-methylphenyl)-2-phenyl-1,2-dihydro-3*H*-pyrrol-3-one
Formula: $C_{25}H_{23}NO_2$

Supervisor: F. G. West **Crystallographer:** R. McDonald



Compound **51b**