Catalyzed carbon-heteroatom bond formation of alkenes or aromatic rings

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**NANYANG
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**CATALYZED CARBON-HETEROATOM BOND
FORMATION OF ALKENES OR AROMATIC RINGS**

**CHEN YUCHEN
SCHOOL OF PHYSICAL AND MATHEMATICAL
SCIENCES
2015**

**CATALYZED CARBON-HETEROATOM BOND
FORMATION OF ALKENES OR AROMATIC RINGS**

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LIST OF ABBREVIATIONS

δ	chemical shift
$^{\circ}\text{C}$	degree centigrade
atm	atmosphere
Ar	aryl
BQ	1,4-benzoquinone
BINAP	1,1'-Binaphthalene-2,2'-diyl)bis(diphenylphosphine)
calcd	calculated
CH_2Cl_2	dichloromethane
CDCl_3	deuterated chloroform
cm^{-1}	inverse centimeter
Cy	cyclohexanyl
d	doublet
DCM	dichloromethane
DBAD	Di-tert-butyl azodicarboxylate
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
dd	doublet of doublets
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
ee	enantiomeric excess
EPR	Electron paramagnetic resonance
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
Et_3N	triethylamine
EtOAc or EA	ethyl acetate
g	gram

h or hrs	hour(s)
HRMS	high resolution mass spectrometry
Hz	hertz
m	multiplet
m/z	mass per charge ratio
M ⁺	parent ion peak (mass spectrum)
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	mega hertz
min	minute(s)
mL	millilitres
mmol	millimole
mol%	mole percent
MS	mass spectrometry
NMP	N-Methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Pd	palladium
Ph	phenyl
PhCl	chlorobenzene
ppm	parts per million
q	quartet
R _f	retention factor
rt	room temperature
S	singlet
t	triplet
^t Bu	<i>tert</i> -butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

SUMMARY

This thesis consists of four chapters. In chapter 1, a brief overview about the difunctionalization of alkenes was included. Chapter 2 described the difunctionalization reactions of allylic alkenes using metal-free system. Chapter 3 presented palladium-catalyzed C-C cleavage reaction with aminooxygenation products of allylic hydrazones. In chapter 4, an iron-catalyzed aromatic C-H bonds amination using azides as nitrogen source was disclosed.

Chapter 1

A brief summary about the difunctionalization of alkenes, including aminooxygenation, dioxygenation and diamination was demonstrated in this chapter. The mechanism of the difunctionalization was also included.

Chapter 2

A highly diastereoselective methodology to *trans*-diamines initiated by radical was introduced. The methodology gives various functionalized products with a wide substrate scope and provides a new strategy to the diamination applied in organic synthesis. One pot reactions were also applied. Mechanism involving radical process was described in this chapter.

Chapter 3

A C-C bond cleavage was observed in the palladium-catalyzed aminohydroxylation of allylic hydrazones, using atmospheric oxygen as the sole oxidant. This reaction could also proceed in a one-pot manner, starting

from keto-alkene compounds and phenylhydrazine.

Chapter 4

Aminations of aromatic $\text{Csp}^2\text{-H}$ bonds were described using the iron catalysts, by employing organic azides as aminating source. The methodology gives various functionalized products with good yields and selectivities and provides a new route for amination with aromatic rings using cheap metal catalysts.

CHAPTER 1

*Overview of difunctionalization of alkenes:
A brief introduction of direct aminooxygenation,
dioxygenation and diamination*

Introduction

Catalyzed difunctionalisation of alkenes is one of the most fundamental and widely studied topics in synthetic organic chemistry. In this process, two functional groups could be introduced to one double bond within a single transformation. The demands for higher efficiency and atom-economy are increasing for the carbon-heteroatom formation. Therefore, the direct formation of carbon-heteroatom bonds across the alkenes could be the most efficient and

Scheme 1.1 Difunctionalized alkene structures presented in pharmaceuticals and agrochemicals

straightforward route to increase molecular complexity. In most cases, homogeneous catalytic systems based on palladium complexes were used, because they represent the most economical means to carry out the reaction.¹ In

¹ (a) Jensen, K.; Sigman, M. *Org. Biomol. Chem.* **2008**, *6*, 4083. (b) Jacques, B. and Muñiz, K. (2010) Palladium Catalysis for Oxidative 1,2-Difunctionalization of Alkenes, in *Catalyzed Carbon-Heteroatom Bond Formation* (ed A. K. Yudin), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany. (c) Muñiz, K. Addition Reactions with Formation of Carbon-Heteroatom Bonds: Asymmetric Methods of Dihydroxylation, Aminohydroxylation, and Diamination. In *Comprehensive Organic Synthesis II*; Knochel P., Ed.; Elsevier: Amsterdam, 2014, pp 411-430. (d) Knappke, C.; Wangelin, A. *ChemCatChem* **2010**, *2*, 1381. (e) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981.

addition, some metal-free systems for the difunctionalisation have also been reported.² Among various possible difunctionalisations, aminooxygenation, dioxygenation and diamination presented the most attractive strategies, due to their ubiquitous occurrence in a number of biologically active nature products and in ligands or catalysts applied in the asymmetric synthesis (Scheme 1.1).

In this chapter, we will discuss the transformation of double bonds and the reactions would be limited to aminooxygenation, dioxygenation and diamination. The main discussion will be focused on palladium-catalyzed as well as metal-free system.

Palladium-catalyzed 1,2 -Difunctionalization reactions: Dioxygenation

Transition-metal-catalyzed dioxygenation of alkenes have been a very active topic in recent years. Osmium catalysis has been widely reported as efficient system of asymmetric dioxygenation reactions, which is mostly contributed by Sharpless's works.³ However, a more efficient, safe and economical methodology for dioxygenation have been developed. Initially, several works involving palladium catalysis were introduced separately by Le Bras, Muzart and Sigman (Scheme 1.2).

In 2005, Le Bras and coworkers reported a palladium salt catalyzed dioxygenation, giving hydrogen peroxide as the oxidant, and the methodology

² (a) Muñiz, K.; Martínez, C. *J. Org. Chem.* **2013**, 78, 2168. (b) Romero, R. M.; Wöste, T. H.; Muñiz, K. *Chem. Asian J.* **2014**, 9, 972. (c) Cao, M-Y.; Ren, X.; Lu, Z. *Tetrahedron Lett.* **2015**, 56, 3732.

³ (a) Schröder, M. *Chem. Rev.* **1980**, 80, 187. (b) Wai, J.; Marko, I.; Sharpless, K. *J. Am. Chem. Soc.* **1989**, 111, 1123. (c) Sharpless, K.; Amberg, W. *J. Org. Chem.* **1992**, 57, 2768. (d) Johnson, R.; Sharpless, K. B. *Catalytic Asymmetric Dihydroxylation-Discovery and Development* (2nd Ed.), **2000**, 357.

produced a mixture of products consisting of 1,2-diols and its monomethylated derivatives (Scheme 1.2.a).⁴ The plausible mechanism that was proposed, involved a palladium-catalyzed epoxidation, and a benzylic ring opening caused by the solvent nucleophiles.

In the same year, Sigman described a similar dioxygenation with

Scheme 1.2 Palladium-catalyzed dioxygenation reactions

palladium catalysts, yielding the products in moderate to good diastereoselectivities (Scheme 1.2.b).⁵ In this work, a different mechanism was given, suggesting a nucleopalladation of the 2-propenyl phenol *via* methanol to yield an intermediate **B** which collapsed to a quinone methide intermediate **C**,

⁴ Chevrin, C.; Le Bras, J.; Hénin, F.; Muzart, J. *Synthesis* **2005**, 15, 2615.

⁵ Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, 128, 1460.

followed by reduction of palladium, and a subsequent addition with another MeOH from solvent to deliver the dioxygenation product (Scheme 1.3).

An enantioselective version was published in 2007 by the same group, using a chiral quinox ligand (Scheme 1.2.c).⁶ By carefully choosing the ligands,

Scheme 1.3 Proposed mechanism for palladium-catalyzed dioxygenation

moderate to good enantioselectivities and yields were observed for both electron-donating and electron-withdrawing substrates. And the authors suggested that the absolute configuration of the products was determined by the β -nucleopalladation, evidencing that a dimethyl substituted terminal alkene led

Conditions:

1. $[\text{Pd}(\text{dppp})(\text{H}_2\text{O})_2](\text{OTf})_2$, $\text{PhI}(\text{OAc})_2$, $\text{AcOH}/\text{H}_2\text{O}$, rt; 2. Ac_2O , rt.⁸
- $\text{Pd}(\text{OAc})_2$, O_2 , KI , AcOH , 100°C .⁹
- $\text{Pd}(\text{OAc})_2$, AcOOH , Ac_2O , anhydrous AcOH , rt.¹⁰

Scheme 1.4 Palladium-catalyzed dioxygenation reactions of unactivated alkenes

0% *ee*. This proved β -nucleopalladation as the enantio-determining step.

⁶ Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3076.

Following these seminal breakthroughs on dioxygenation of activated alkenes, more reports about the dialkoxylation of unfunctionalized alkenes were presented by Song, Dong⁷, Jiang⁸ and Jung⁹ (Scheme 1.4). These reactions employed acetic acid or acetic anhydride as the oxygen sources, leading to the formation of hydroxyl acetates or diacetates.

The reaction could also proceed with an intramolecular cyclization to form tetrahydrofurans or lactones. For example, 1-phenyl-but-3-en-1-ol furnished a tetrahydrofuran product in good yield as a mixture of diastereoisomers (Scheme 1.5).⁸

Scheme 1.5 Palladium-catalyzed intramolecular dioxygenations of olefins

In 2010, our group also reported an oxime-assisted intramolecular dioxygenation under palladium acetate, using aerobic oxygen as the oxygen source (Scheme 1.6).¹⁰ Given the evidence from isotopic labeling experiments with ¹⁸O₂, molecular oxygen is proposed to be the origin of the hydroxyl group in the products.

Scheme 1.6 Palladium-catalyzed dioxygenation of unactivated alkenes

Transition-metal catalysts are widely used in dioxygenation reactions. However, the expensiveness and/or toxicity associated with many transition metals constitute serious drawbacks for these types of reactions. Therefore, it is

⁷ Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962.

⁸ Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* **2009**, *131*, 3846.

⁹ Park, C. P.; Lee, J. H.; Yoo, K. S.; Jung, K. W. *Org. Lett.* **2010**, *12*, 2450.

¹⁰ Zhu, M.-K.; Zhao, J.-K.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 6284.

desirable to develop a metal-free alternative for common dioxygenation reactions. Various attempts of metal-free dioxygenation were reported in recent years.¹¹ Although a number of methods featuring peroxide derivatives and hypervalent iodines were reported, they always required excess amounts of oxygen sources which resulted in the stoichiometric generation of byproducts. Radical initiated reactions thus offer a promising route in dioxygenation, thanks to the catalytic usage of the radical initiator and the mild reaction conditions that are often associated with these types of transformations.

In 2010, Alexanian reported a metal-free aerobic intramolecular dioxygenation of alkenes (Scheme 1.7).¹² In this work, dilauroyl peroxide was

Scheme 1.7 Alkene dioxygenation using *N*-aryl hydroxamic acids

used as an initiator. Although the radical initiator was not necessary in the reaction, it has been used for increasing the reaction rate.

Recently, another radical involved dioxygenation reaction has been presented by Punniyamurthy (Scheme 1.8).¹³ In this work, *N*-

Scheme 1.8 Copper acetate catalyzed dioxygenation of alkenes

¹¹ Rawling, M. J.; Tomkinson, N. C. O. *Org. Biomol. Chem.* **2013**, *11*, 1434.

¹² (a) Giglio, B. C.; Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 13320. (b) Schmidt, V. A.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4491. (c) Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 11402.

¹³ Bag, R.; Sar, D.; Punniyamurthy T. *Org. let.* **2015**, *17*, 2010.

hydroxyphthalimide and aerobic oxygen were used as oxygen sources, though a copper salt was necessary. The radical pathway was proven by radical trapping experiments, using TEMPO as radical trapper, indicating that *N*-hydroxyphthalimide initially reacted with copper salt to deliver the radical, followed by reaction with alkenes.

Palladium-catalyzed 1,2 -Difunctionalization reactions:

aminooxygenation

In recent years, a number of works about aminooxygenated reactions have been presented by organic chemists. Initially, vicinal amino alcohol was synthesized through the osmium catalyzed pathways.¹⁴ Nitrogen-involved nucleophiles were widely applied in palladium-catalyzed addition of alkenes. Similar to the dioxygenation reactions, aminooxygenation reactions have been studied using palladium catalysis (Scheme 1.9). The mechanism employing aminopalladdation/ β -hydride elimination¹⁵ includes two pathways: 1) reductive replacement of palladium (II) to give a palladium (0) compound, which would be reoxidized to regenerate the palladium (II) complexes; 2) oxidation of palladium (II) to palladium (IV) intermediate, which would then promote bond formation upon reductive elimination of the initial palladium (II) species.

¹⁴ (a) Bruncko, M.; Sharpless, K. *Angew. Chem. Int. Ed.* **1997**, 36, 1483. (b) Muñiz, K. *Chem. Soc. Rev.* **2004**, 33, 166.

¹⁵ Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, 127, 2868.

Scheme 1.9 Reaction pathways for Pd-catalyzed oxidative amination of alkenes

In 2005, Sorensen¹⁶ reported an intramolecular palladium-catalyzed aminoacetoxylation of alkenes (Scheme 1.10). The author proposed a Pd^{II}/Pd^{IV} catalytic cycle, which involved an aminopalladation of alkenes, followed by an oxidation of Pd^{II} complex to Pd^{IV} intermediate and a reductive elimination to yield the aminoacetoxylated product. Hypervalent iodine was used as both oxidizing agent and oxygen source in this reaction.

Scheme 1.10 Palladium acetate catalyzed intramolecular aminoacetoxylation of alkenes

Besides intramolecular aminooxygenated reactions, a highly regioselective Pd-catalyzed intermolecular aminooxygenation of unactivated alkenes was presented by Stahl (Scheme 1.11a).¹⁷ Although the aminooxygenated molecule was obtained as the major product, a small amount of diacetoxylation product and enamide product were also observed under this condition. Only *erythro* product was obtained with *cis*-alkene, while no reaction occurred with the *trans*-alkenes (Scheme 1.11b). Further studies with the same *cis*-alkenes under conditions favoring β -hydride elimination, only the (*Z*)-

¹⁶ Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690.

¹⁷ Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179.

enamide was formed (Scheme 1.11c). The stereochemistry was interpreted by a sequence of *cis*-aminopalladation and S_N2 carbon-oxygen bond formation.

Scheme 1.11 Pd-catalyzed intermolecular aminooxylation with unactivated alkenes

Another palladium-catalyzed intermolecular aminooxygenation reaction was presented by Sanford in 2007, using phthalimide as the nitrogen source (Scheme 1.12).¹⁸ A similar mechanism study as previous work was carried out. It was concluded that a *cis*-aminopalladation of olefin and a C-O bond-forming reductive elimination were involved in this reaction.

Scheme 1.12 Palladium acetate catalyzed formation of 3-aminotetrahydrofuran derivatives using PhI(OAc)₂ as oxidant

However, despite the high efficiency, repulsive cost and/or toxicity of the transition metals tarnish heavy metal catalysis. Metal-free systems are again the solution to these concerns. Cheaper metals like copper and iron salts have

¹⁸ Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, 46, 5737.

been employed as good catalysts to initiate the radical process of aminooxygenation. In these reactions, the radical initiator alone could not give product in an acceptable yield. By adding the metal catalyst, the activity could be promoted, as shown in the case of oxaziridines (Scheme 1.13).¹⁹ The reaction typically gave moderate yield albeit with shorter reaction times.

Scheme 1.13 Examples of copper/iron catalyzed radical mediated aminooxygenation of unactivated alkenes

Besides hypervalent iodine reagents²⁰, radical-involved processes have been commonly applied in direct aminooxygenation of unactivated double

¹⁹ (a) Noack, M.; Goettlich, R. *Chem. Comm.* **2002**, 5, 536. (b) Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P. *J. Am. Chem. Soc.* **2007**, 129, 1866. (c) Williamson, K. S.; Yoon, T. P. *J. Am. Chem. Soc.* **2012**, 134, 12370.

²⁰ (a) Farid, U.; Wirth, T. *Angew. Chem., Int. Ed.* **2012**, 51, 3462. (b) Wardrop, D. J.; Bowen, E. G.; Forslund, R. E.; Sussman, A. D.; Weerasekera, S. L. *J. Am. Chem. Soc.* **2010**, 132, 1188. (c) Bowen, E. G.; Wardrop, D. J. *Org. Lett.* **2010**, 12, 5330. (d) Wardrop, D. J.; Bowen, E. G. *Org. Lett.* **2011**, 13, 2376. (e) Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008**, 10, 5039. (f) Lovick,

bonds. A number of radical initiators, including diisopropyl azodicarboxylate (DIAD), tempo, iminoxyl radical, have been used to mediate the aminooxygenation (Scheme 1.14).²¹

Scheme 1.14 Selective examples of radical-mediated aminooxygenation

Palladium-catalyzed 1,2-Difunctionalization reactions: diamination

The synthesis of vicinal diamines was largely achieved by using indirect methodologies, including aziridination followed by nucleophilic attack and aminooxygenation followed by conversion of oxygen to nitrogen groups.²² However, direct diamination is without doubt, the most straightforward route for the synthesis of vicinal diamines. Like dioxygenation and aminooxygenation, various transition-metal catalysts have been developed in

H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249. (g) Farid, U.; Wirth, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 3462. (h) Ding, H.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2011**, *50*, 676.

²¹ (a) Peng, X.; Deng, Y.; Yang, X.; Zhang, L.; Yu, W.; Han, B. *Org. Lett.* **2014**, *16*, 4650. (b) Duan, X.; Yang, X.; Fang, R.; Peng, X.; Yu, W.; Han, B. *J. Org. Chem.* **2013**, *78*, 10692. (c) Han, B.; Yang, X.; Fang, R.; Yu, W.; Wang, C.; Duan, X.; Liu, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 8816.

²² (a) De Jong, S.; Nosal, D.; Wardrop, D. *Tetrahedron* **2012**, *68*, 4067. (b) de Figueiredo, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1190. (c) Cardona, F.; Goti, A. *Nature* **2009**, *448*, 270.

direct asymmetric diamination, including osmium and ruthenium complexes.²³ Recently, direct diamination using palladium catalysts has drawn considerable attention by organic chemists. Following Backvall's²⁴ first report, plenty of examples were developed in the past decade. In 2005, a palladium-catalyzed direct diamination of dienes has been presented, using urea as nitrogen sources (Scheme 1.15a).²⁵ The author carefully chose urea as nitrogen source, which

Scheme 1.15 palladium-catalyzed intermolecular or intramolecular diamination

aimed to inhibit the β -H elimination, activate the palladium catalyst and control the selectivity. Later, another urea-involving intramolecular diamination using $\text{PhI}(\text{OAc})_2$ as an oxidant has been reported.²⁶ High catalyst loadings (25 mol %) was required while constructing larger rings ($n=2,3$).

Although the above discussed reactions featured the same nitrogen source (urea), they differ significantly with respect to the mechanism. A diverted Wacker type process is proposed to be involved in the intermolecular diamination. The authors concluded that the mechanism in an *anti*-

²³(a) Muñiz, K. *New J. Chem.* **2005**, 29, 1371. (b) Muñiz, K. Oxidation: C–N Bond Formation by Oxidation: Dinitrogen Addition to Double Bond (Diamino). In *Comprehensive Chirality*; Carreira, E. M., Yamamoto, H, Eds.; Elsevier: Amsterdam, 2012, Vol. 5; pp 183–197.

²⁴ Bäckvall, J. E. *Tetrahedron Lett.* **1978**, 19, 163.

²⁵ Bar, G.; Lloyd-Jones, G.; Booker-Milburn, K. *J. Am. Chem. Soc.* **2005**, 127, 7308.

²⁶ Streuff, J.; Hövelmann, C.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, 127, 14586.

Scheme 1.16 Catalytic cycles for the palladium-catalyzed diamination

aminopalladation involving nucleophilic attack by the second nitrogen atom (Scheme 1.16a). The Pd(0) species was reoxidized by benzoquinone. However, Pd(II/IV) cycle is proposed to be responsible for the intramolecular diamination (Scheme 1.16b). A detailed explanation of this transformation was later presented by Muniz in 2008.²⁷ In this case, sodium acetate used in the reaction initiated the reaction. The author proposed that *syn*-aminopalladation is the rate determining step, which is proven by isotopic experiments using deuterated-urea (Scheme 1.17).

²⁷ Muñiz, K.; Hövelmann, C.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763.

Scheme 1.17 Mechanistic study for the palladium-catalyzed intramolecular diamination

Another intramolecular diamination was described by Muniz in 2007 (Scheme 1.18).²⁸ As previously reported, a catalytic cycle involving Pd^{II}/Pd^{IV} was postulated in the mechanism. These two-step reactions also needed one equivalent of sodium acetate to initiate the catalytic cycle. The complete diastereoselectivity was explained by a two-step process: *trans*-aminopalladation and a rapid oxidation process which reserved the stereochemistry of the intermediate, followed by the catalyst reduction to yield the final product.

Scheme 1.18 Palladium acetate catalyzed diamination of internal alkenes

An intermolecular diamination of terminal alkenes using two different nitrogen resources was reported with hypervalent iodines employed as oxidants in 2010 (Scheme 1.19).²⁹ This diamination could tolerate variety of functional groups (ester, amide, azide, halide in the terminal alkenes) on the alkenes, providing reasonable yields of diamination products in all cases.

²⁸ Muñiz, K. *J. Am. Chem. Soc.* **2007**, 129, 14542.

²⁹ Iglesias, Á.; Pérez, E.; Muñiz, K. *Angew. Chem., Int. Ed.* **2010**, 49, 8109.

Scheme 1.19 Palladium-catalyzed intermolecular diamination of terminal alkenes

employing two different nitrogen sources

Besides metal-catalyzed diamination, metal-free systems could also be applied in the diamination reactions. Hypervalent iodines such PhI(OAc)₂ have been developed to facilitate the diamination reaction.³⁰ Besides iodines, radical process is also a rapid practical route for direct diamination of alkenes. As radical-mediated aminooxygenation, diisopropyl azodicarboxylate (DIAD) could serve both a good radical initiator and a nitrogen source.³¹ It is desirable to have more radical-initiated diamination methods to be developed in the future.

³⁰ Duan, X.; Yang, X.; Fang, R.; Peng, X.; Yu, W.; Han, B. *J. Org. Chem.* **2013**, 78, 10692.

³¹ Amaoka, Y.; Kamijo, S.; Hoshikawa, T.; Inoue, M. *J. Org. Chem.* **2012**, 77, 9959.

Conclusion

In conclusion, 1,2-difunctionalization reactions of olefins, though relatively young, have drawn commendable attention from organic chemists. Transition-metals, oxidants and radical processes have been developed towards materializing this reaction. The methodologies incorporating two nucleophiles to carbon-carbon double bonds could be applied in the synthesis of many useful scaffolds.

CHAPTER 2

*Acid-assisted diamination of alkenes with
phenylhydrazine and azodicarboxylates under mild
reaction conditions*

2.1 Introduction

Vicinal diamines are extremely important molecules owing to their ubiquitous presence in asymmetric ligands, pharmaceutical compounds and natural products (Scheme 2.1).³² As shown in Scheme 2.1, Noyori catalyst serves as an important catalyst for asymmetric synthesis; penicillins are a series of well-known antibiotics; tamiflu is an antiviral drug. The development of efficient diamination reactions is a great interest of organic chemists, in which direct diamination is the most straightforward and convenient route. In the common strategy of direct diamination, two nitrogen atoms would be introduced to a carbon-carbon double bond simultaneously.

Scheme 2.1 Structures with 1,2-diamine motif

Metal catalysts have been widely used in diamination reactions.³³

However, the disadvantages of metal catalysis are obvious: toxicity of metals

³² (a) Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (b) Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140. (c) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101. (d) Muñiz, K. *New J. Chem.* **2005**, *29*, 1371.

³³ (a) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. (b) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763. (c) Muñiz, K.; *J. Am. Chem. Soc.* **2007**, *129*, 14542. (d) Hövelmann, C. H.; Streuff, J.; Brelot, L.; Muñiz, K. *Chem. Commun.* **2008**, 2334. (e) Muñiz, K.; Streuff, J.; Chávez, P.; Hövelmann, C. H. *Chem. Asian J.* **2008**, *3*, 1248. (f) Sibbald, P. A.; Michael, F. E. *Org. Lett.* **2009**, *11*, 1147. (g) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945. (h) Martínez, C.; Muñiz, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 7031. nickel catalysis: (i) Muñiz, K.;

and harsh conditions. Metal-free difunctionalization promises a viable alternative and its hot pursuit have offered many such methods in the recent years. Hypervalent iodines and peroxides have been applied in this area³⁴, despite the reaction usually delivering equivalent amount of byproducts and being restricted in substrate scopes. Thus, radical process which is also metal-free and byproduct free adds value to alkene diamination reactions.

Radical chemistry has been developed as a useful tool in organic synthesis in the recent years. Unlike the widely-studied radical-mediated dioxygenation and aminooxygenation, radical-initiated diamination reactions remain a new area and experienced rapid growth recently (Scheme 2.2).³⁵

Scheme 2.2 different alkene difunctionalizations

In our studies of difunctionalization reactions, we recently disclosed a palladium-catalyzed oxime-assisted intramolecular dioxygenation of alkenes

Streuff, J.; Hövelmann, C. H.; Nuñez, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7125. gold catalysis: (j) Iglesias, A.; Muñiz, K. *Chem. Eur. J.* **2009**, *15*, 10563. copper catalysis: (k) Wen, Y.; Zhao, B.; Shi, Y. *Org. Lett.* **2009**, *11*, 2365. (l) Zhao, B.; Du, H.; Shi, Y. *Org. Lett.* **2008**, *10*, 1087. (m) Zhao, B.; Yuan, W.; Du, H.; Shi, Y. *Org. Lett.* **2007**, *9*, 4943.

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with 1 atm air (Scheme 2.3)³⁶. Aerobic oxygen has been used as oxygen source in this reaction. We envisaged that with suitable modification of the substrate and the reagents, diamination could be achieved. Eventually, it was discovered

Scheme 2.3 Proposal of palladium-catalyzed diamination of alkenes

that the anticipated diamination could be rendered in a metal-free, radical mediated fashion.

³⁶ Zhu, M.-K.; Zhao, J.-F.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, 132, 6284.

2.2 Results and discussion

Recently, our group has presented a palladium-catalyzed dioxygenation of unactivated alkenes which has applied aerobic oxygen and oxime motif as oxygen sources.³⁷ In a similar mechanism, we hypothesized that a diamination of alkenes by an intramolecular nucleopalladation and reductive elimination might be realized under palladium (II) acetate. Initially, we have chosen (*E*)-hydrazone (**1a**) containing a designed terminal alkene and azodicarboxylates as the nitrogen sources for model study (Table 2.1).

Upon application of previously developed dioxygenation condition used for dioxygenation reactions, the desired product was afforded in 38% at room temperature (Table 2.1, entry 1). To our surprise, trace amounts of the product was also

Table 2.1. Optimization Studies for diamination.^[a]

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%) ^[b]
1	Pd(OAc) ₂ / HOAc (4 eq.)	PhCl	rt	8	38
2	none	PhCl	rt	8	trace
3	none	PhCl	40	8	55
4	Pd(OAc) ₂	PhCl	rt	8	trace
5	HOAc (4 eq.)	PhCl	rt	8	45
6	HOAc (4 eq.)	PhCl	40	3	75

³⁷ (a) Zhu, M. K.; Zhao, J. F.; Loh, T. P. *J. Am. Chem. Soc.* **2010**, 132, 6284. (b) Zhu, M. K.; Zhao, J. F.; Loh, T. P. *Org. Lett.* **2011**, 13, 6308.

^[a] Unless noted otherwise, the reactions were carried out on a 0.30 mmol scale of **1a** and 2.0 equiv of **2a** (0.6 mmol) in solvent (1.0 mL). ^[b] Isolated yield.

obtained without the palladium catalyst (Table 2.1, entry 2). A series of control experiments revealed that acid significantly increased the yield of diamination products (Table 2.1, entry 3,4). With four equivalent of acidic acid, desired products were delivered in 45% at room temperature. The diamination reaction proceeded more efficiently with a slightly higher temperature at 40 °C, resulting in 75% isolated yield. Therefore, our standard condition proceeds with PhCl as solvent, and four equivalents of acetic acid at 40 °C.

After establishing the optimal conditions, we began to develop the substrate scope of this diamination reaction as shown in Table 2.2. We screened other azodicarboxylates, including diethyl azodicarboxylate (DEAD), dibenzyl azodicarboxylate (DBAD) and di-*tert*-butyl azodicarboxylate (DTAD), and resulted in good to excellent yields 73%, 81% and 90%, respectively (details in supporting information). We chose di-*tert*-butyl azodicarboxylate (DTAD) as our model substrate to explore the substrate scopes. As a result, both electron-withdrawing and electron-donating groups at the *para*-position of aromatic hydrazones transformed to desired products in moderate to excellent yields (Table 2.2, compounds **3c-3g**). However, substrates with electron-withdrawing groups have served as better substrates to deliver the products in near quantitative yields than ones with electron-donating groups (Table 2.2, compounds **3c-3f**). Hydrazones with *meta*-substituted groups also delivered the products in moderate yields (Table 2.2, compounds **3h,3i**). Moreover, hydrazones with 4-methoxyphenyl delivered the desired products in a shorter reaction time than one with phenyl group (Table 2.2, compounds **3j,3k,3n,3o**).

We also applied a series of terminal alkenes in the reaction, and all of them gave the desired products in good yields (Table 2.2, compounds **3n-3r**).

Table 2.2: Diamination of alkenes with the azodicarboxylates. ^{[a], [b]}

^[a] Unless noted otherwise, the reactions were carried out on hydrazone (0.3 mmol), azodicarboxylates (0.36 mmol) with 4.0 equiv. HOAc in PhCl (1.0 mL at 40 °C. ^[b] Isolated yield. ^[c] with 3.0 equiv. of DTAD at 60 °C.

The substrate scope could be expanded to cycloalkene too as shown in Table 2.3. Various substituted cyclopentenyl substrates delivered [3,3,0]-*cis*-fused bicyclic products in excellent yields in 5-*exo* way (Table 2.3, compounds **3s-3u**). In a similar way, cyclohexenes have been served as good substrates to give [4.3.0]-*cis*-fused bicyclic products in excellent yields and diastereoselectivities (Table 2.3, compounds, **3v-3x**). Terminal alkenes with

various α -position substituted groups transformed to desired products in good yields and stereoselectivities (Table 2.3, **3y-3a'**). A *cis*-alkene with 1,2-disubstituted groups underwent the diamination in a 69:31 mixture of two corresponding diastereometric products in 70% (Table 2.3, **3b'**). A substrate

Table 2.3: High selectivity metal-free diamination of alkenes.^{[a], [b], [c]}

^[a] Unless noted otherwise, the reactions were carried out on hydrazone (0.3 mmol), azodicarboxylates (0.36 mmol) with 4.0 equiv HOAc in PhCl (1.0 mL) at 40 °C. ^[b] Isolated yield. ^[c] Diastereomeric ratios determined by crude ¹H NMR spectroscopy. ^[d] at 60 °C. ^[e] using the *E* / *Z* mixture at 50 °C.

with conjugated styrenyl group proceeded smoothly in 60 °C, delivering the product in moderate yield and good stereoselectivity (Table 2.3, compound **3c'**).

Result with a hydrazone of chalcone substrate showed that reactions were not

limited to 5-*endo* trig function. The reaction delivered a single diastereometric product in moderate yield (Table 2.3, compound **3d'**). It is concluded that diamination of cycloalkenes could provide a good alternative route for synthesizing *trans*-diamines.

We also investigated the diamination reactions in a one-pot manner, exploiting the facile formation of hydrazones from hydrazines and ketones as shown in Table 2.4. A number of substrates, including terminal, 1,1-disubstituted, 1,2-disubstituted and trisubstituted alkenes, were applied in the diamination reactions. We found that all of them deliver the desired products in good yields and excellent stereoselectivities. Products like bicyclo-[3,3,1] pyridazine **3h'** and bicyclo-[6,5] pyridazine **3i'** were obtained in good yields and high stereoselectivities, which underwent in 6-*exo* function (Table 2.4, compounds **3h'** & **3i'**). In conclusion, one-pot manner reaction proceeded smoothly with all of substrates with no decrease of yield and stereoselectivity.

The attempted removal of the protecting group was successful with subsequent treatment with trifluoroacetic acid and zinc. This transformation was a good example for further reduction of N-N bonds to deliverer the vicinal diamines in good yield and could be applied in all the compounds given in this work (Scheme 2.4).

To demonstrate the mechanism of the diamination reactions, we used EPR to observe the reaction (details in supporting information). We found out that the reactions were initiated by DTAD. It is proposed that oxygen may oxidize hydrazone to hydrazoneyl radical following a hydrogen atom abstraction process. To further clarify the mechanism, a series of control experiments were conducted. A substrate with an electron-donating substituent group **1j** was

subjected with 1 atm air and 10 equivalents of acetic acid, giving the aminooxygenation product in 45% yield. In a similar way, we applied TEMPO

Table 2.4: One-pot Diamination of alkenes with phenylhydrazine and di-*tert*-butyl azodicarboxylate.^[a]

$ \begin{array}{c} \text{O} \quad \text{R}^4 \\ \parallel \quad \\ \text{R}^1 - \text{C} - \text{C} = \text{C} - \text{R}^5 \\ \quad \quad \\ \text{R}^2 \quad \text{R}^3 \quad \text{n} \\ \text{n}=1,2 \end{array} + \text{PhNHNH}_2 + \text{BocN}=\text{NBoc} \xrightarrow[\text{PhCl, 3-12h}]{\text{HOAc (4 equiv.)}} \begin{array}{c} \text{Ph} \quad \text{R}^4 \quad \text{R}^5 \\ \quad \quad \\ \text{N} - \text{N} - \text{C} - \text{C} - \text{C} \\ \quad \quad \quad \\ \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \quad \text{n} \\ \text{n}=1,2 \end{array} $		
Alkenes	Products	yield ^[b] (dr = <i>anti</i> / <i>syn</i>) ^[c]
R=H, 52% (3e') R=Me, 83% (3y) dr > 20:1 R=Ph, 50% (3z) dr > 20:1
90% (3n) ^[d] (87%) ^[e]
73% (3p) ^[d] (67%) ^[e]
R=H, 70% (3b') dr = 69:31 R= Me, 51% (3f') ^[d] dr = 55:45
41% (3g') ^[d]
53% (3c') dr = 80:20
R= Me, 97% (3s) ^[d] dr > 20:1 R= Allyl, 85% (3t) ^[d] dr > 20:1 R= Bn, 91% (3u) ^[d] dr > 20:1
72% (3h') ^[d] dr > 20:1
35% (3i') ^[d] dr > 20:1
R=H, 75% (3x) dr > 20:1 R=Me, 90% (3v) ^[d] dr > 20:1

^[a] Unless noted otherwise, the reactions were carried out on a 0.3 mmol scale of **2d** (DTAD) with of alkenes (0.45 mmol) and phenylhydrazine (0.45 mmol) in 1.0 ml PhCl at 40 °C. ^[b] Isolated yield. ^[c] Determined by crude ¹H NMR spectroscopy. ^[d] at 50 °C. ^[e] a gram scale 3 mmol hydrazone was used.

and DTAD to the reaction to trap the radical intermediate and obtained the difunctionalization product in good yields and excellent distereoselectivities (Scheme 2.5). In conclusion, DTAD, TEMPO and oxygen could all be good hydrazoneyl radical initiators and carbon radical traps. We also did comparison

Scheme 2.4. Reduction of difunctionalization product

experiments to examine the role of acetic acid in this reactions. It is notable that acetic acid is not a necessity but helps to increase the yields (Scheme 2.5).

Scheme 2.5. Oxygen, TEMPO, DTAD-initiated hydrazoneyl radical cyclization

We proposed a possible mechanism as shown in Scheme 2.6. The diamination is initiated by DTAD to form the hydrazoneyl radical **II**, which is in

resonance with the radical intermediate **III**. The process was followed by reversible cyclizaion to form the carbon-centre radical **IV**, which could be trapped by DTAD. In the next step, a nitrogen-centre radical **V** was formed, which readily delivered the desired product and regenerated the hydrazonyl radical **II**.

Scheme 2.6. Possible mechanism of radical-initiated diamination reactions

Conclusion

In conclusion, we have successfully developed a metal-free radical-initiated diamination reaction under mild reaction conditions. This new method gave highly functionalized products, with wide substrate scopes and could also proceed in a one-pot manner with ketones and hydrazine instead of hydrazones. It also provides an ideal model to furnish a highly stereoselective diamination reaction without transition-metal catalysts or hypervalent iodine compounds.

2.3 Supporting Information

2.3.1 General Methods

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Commercial grade solvents and reagents were used without further purification. Hexane, ethyl acetate were fractionally distilled.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate.

Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. The oil samples were examined under neat conditions.

High Resolution Mass (HRMS) spectra were obtained using Waters Q-ToF Premier Mass Spectrometer.

Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Bruker Avance DPX 300 and Bruker AMX 400 spectrophotometer (CDCl_3 as solvent). Chemical shifts for ^1H NMR spectra are reported as δ in units of

parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of chloroform-d (δ 7.2600, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dddd (doublets of doublets of doublets of doublet); dt (doublets of triplet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (¹³C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of chloroform-d (δ 77.0, triplet).

2.3.2 Representative experimental procedure

General procedure for the synthesis of β , δ -unsaturated ketones:

1) A round bottomed flask charged with a solution of the allyl bromide (1.2 equiv) or its analogue and indium (1.2 equiv) in THF/H₂O (1:1) was kept at room temperature with stirring. The aldehyde (1.0 equiv) was added to the solution and the resulting suspension was stirred for 10-24 h. Saturated ammonium chloride or 1 N hydrochloride solution was added at 0 °C. The THF layer was separated from the aqueous layer, which was extracted with diethyl ether for 3 times. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was directly used in the next step without further purification.¹

2) A solution of the homoallylic alcohol (1.0 equiv) in diethyl ether was stirred

at 0 °C while Jones reagent (2.0-4.0 equiv) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The diethyl ether layer was then separated from the aqueous layer, which was extracted with diethyl ether for 3 times. The combined diethyl ether layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford the *b, d*-unsaturated ketones.²

General procedure for the synthesis of Cycloalkenes:

1) Lithium aluminum hydride (1.5 equiv) was added portion wise over a period of 2 h to a stirred solution of ester^{3,4} in dry ether at rt. The mixture was stirred for 30 min, cooled to 0 °C, treated with 1.0 N NaOH solution until the mixture turned white, and extracted with for 3 times. The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was directly used in the next step without further purification.³

2) A solution of the alcohol (1.0 equiv) in CH₂Cl₂ was stirred at 0 °C while DMP (1.0-1.2 equiv) was added. The resulting mixture was allowed to warm to room temperature and stirred for 1-3 h monitored by TLC. The reaction was diluted and washed with saturated NaHCO₃, which was extracted with CH₂Cl₂ for 3 times. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was directly used in the next step without further purification.

3) A round bottomed flask charged with a solution of the aldehyde in THF

(20 mL) was kept at 0 °C with stirring. To the solution, PhMgBr (1.5 equiv) was slowly added and stirred for 1 h at rt. The saturated NH₄Cl solution (10 mL) was added slowly at 0 °C with stirring and extracted with diethyl ether for 3 times. The combined organic layers were dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford the alcohols.

4) A solution of the alcohol (1.0 equiv) in diethyl ether was stirred at 0 °C while Jones reagent (2.0-4.0 equiv) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The diethyl ether layer was then separated from the aqueous layer, which was extracted with diethyl ether for 3 times. The combined diethyl ether layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford the ketones.

(1-methylcyclohex-2-en-1-yl)(phenyl)methanone: This compound was

prepared by the general procedure described above and was obtained as a colorless oil in 53% yield: $R_f = 0.64$ (hexane : ethyl acetate = 6:1); ¹H NMR (400 MHz, CDCl₃): δ 7.84-7.85 (m, 2H, ArH), 7.44-7.46 (m, 1H, ArH), 7.36-7.40 (m, 2H, ArH), 5.80-5.86 (m, 2H, CH), 2.29-2.36 (m, 1H, CH₂), 2.09-2.12 (m, 2H, CH₂), 1.69-1.74 (m, 2H, CH₂), 1.52-1.56 (m, 1H, CH₂), 1.37 (s, 3H, CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 206.4, 138.3, 132.0, 131.3, 128.7, 128.0, 127.8, 49.1, 33.2, 26.0, 24.8, 19.3 ppm.

General procedure for the synthesis of b,d-unsaturated ketone

1) Into a 25mL round bottom flask equipped with a magnetic stirrer,

aldehyde (5mmol) was added and cooled using a salt/ice freezing mixture. 1.5 equivalents of the yellow-orange phosphonium ylide were added and the solution was stirred from -10°C to room temperature. The reaction was quenched using saturated sodium bicarbonate solution and extracted three times with ethyl acetate. The combined organic extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo*, and the yellowish liquid was purified using flash column chromatography with 20% ethyl acetate/hexanes to give (about 70%-93% purified yield) of the colorless Wittig acetal product. The acetal product was dissolved in 25ml of CH₃COCH₃ / H₂O (1:1) then added PTSA (10%), which was stirred at 60°C for 1h monitored by TLC. The reaction was quenched using saturated sodium bicarbonate solution and extracted three times with ethyl acetate. The combined organic extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo*, and the crude product was directly used in the next step without further purification.

2) A round bottomed flask charged with a solution of the aldehyde in THF (20 mL) was kept at 0 °C with stirring. To the solution, PhMgBr (1.5 equiv) was slowly added and stirred for 1 h at rt. The saturated NH₄Cl solution (10 mL) was added slowly at 0 °C with stirring and extracted with diethyl ether for 3 times. The combined organic layers were dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford the alcohols.

3) A solution of the alcohol (1.0 equiv) in diethyl ether was stirred at 0 °C while Jones reagent (2.0-4.0 equiv) was added dropwise. The resulting mixture

was allowed to warm to room temperature and stirred for 1 h. The diethyl ether layer was then separated from the aqueous layer, which was extracted with diethyl ether for 3 times. The combined diethyl ether layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford the ketones.

(Z)-1,6-diphenylhex-3-en-1-one: This compound was prepared by the general

procedure described above and was obtained as a colorless oil in 43% yield: $R_f = 0.64$ (hexane : ethyl acetate = 6:1); ¹H NMR (400 MHz, CDCl₃): δ 7.90-7.92 (m, 2H, ArH), 7.53-7.57 (m, 1H, ArH), 7.43-7.47 (m, 2H, ArH), 7.25-7.30 (m, 2H, ArH), 7.16-7.21 (m, 3H, ArH), 5.67-5.76 (m, 2H, CH), 3.61-3.63 (m, 2H, CH₂), 2.69-2.72 (m, 2H, CH₂), 2.40-2.46 (m, 2H, CH₂) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 198.1, 141.7, 136.7, 133.1, 132.2, 128.6, 128.5, 128.5, 128.4, 128.3, 126.0, 122.2, 37.3, 35.5, 29.7 ppm.

General procedure for the synthesis of hydrazones:

To a solution of the ketone (1.0 equiv) in ethanol was added arylhydrazine (1.5 equiv) and acetic acid (2.0 equiv). The mixture was stirred at 60 °C or reflux for 2-6 h and monitored by TLC. Then the mixture was directly concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford the hydrazone (the *Z/E* isomer was separated by flash chromatography on silica gel).

Optimization Studies^a

entry	catalyst	solvent	temp (°C)	time (h)	yield (%) ^b
1	Pd(OAc) ₂ / HOAc (4 eq.)	PhCl	rt	8	38
2	none	PhCl	rt	8	trace
3	none	PhCl	40	8	55
4	Pd(OAc) ₂	PhCl	rt	8	trace
5	HOAc (4 eq.)	PhCl	rt	8	45
6	HOAc (4 eq.)	PhCl	40	3	75
7	HOAc (4 eq.)	PhCH ₃	40	4	65
8	HOAc (4 eq.)	THF	40	6	35
9	HOAc (4 eq.)	1,4-dioxane	40	6	55
10	HOAc (4 eq.)	DMSO	40	6	25
11 ^c	HOAc (4 eq.)	PhCl	40	8	58
12 ^d	HOAc (4 eq.)	PhCl	40	8	63
13 ^e	HOAc (4 eq.)	PhCl	40	3	78
14 ^f	HOAc (4 eq.)	PhCl	40	3	75

^a Unless noted otherwise, the reactions were carried out on a 0.3 mmol scale of **1a** with 2.0 equiv of diisopropyl azodicarboxylate (DIAD) in 1.0 ml solvent. ^b the isolated yield. ^c 4Å MS was added. ^d MgSO₄ was added. ^e 1a:2a = 1.0 : 1.2 . ^f 1a:2a = 1.2 : 1.0

Screening the azodicarboxylates:

entry	R	time (h)	yield (%) ^b
1	i-pr	4	78
2	Et	4	73
3	Bn	4	81
4	tBu	4	90

General Procedure for Radical-mediated Diamination of Alkenes with Azodicarboxylates:

A 5 mL round bottomed flask equipped with a magnetic stirring bar was added with *b*, *d*-unsaturated hydrazones (0.30 mmol), azodicarboxylates (1.2 equiv, 0.36 mmol), and 4 equiv of HOAc (1.2 mmol) in chlorobenzene (1 mL) under argon. The flask was stirred at 40 °C for 3-24 h and the reaction progress was monitored by TLC. The solvent was removed under reduced pressure. The residue was purified through column chromatography on silica gel to give the desired products.

General Procedure for the One-pot Alkenes Diamination with phenylhydrazine and Azodicarboxylates:

A 5 mL round bottomed flask equipped with a magnetic stirring bar was added with ketones (0.30 mmol), phenylhydrazine (0.45 mmol, 1.5 equiv) and 4 equiv of HOAc (1.2 mmol) in chlorobenzene (1 mL) under argon. The flask was stirred at 60 °C or reflux for 2-12 h under argon. The mixture was cooled to room temperature and added the di-*tert*-butyl azodicarboxylate (DTAD) with argon. The reaction was stirred for 5-12h at 50°C then the solvent was removed under reduced pressure and the residue was purified through column chromatography on silica gel to give the desired products.

General Procedure for the One-pot Alkenes Diamination with gram scale:

A 25 mL round bottomed flask equipped with a magnetic stirring bar was added with ketones (4.5 mmol), phenylhydrazine (4.5 mmol, 1.5 equiv) and 2 equiv of HOAc (6.0 mmol) in chlorobenzene (10 mL) under argon. The flask was stirred at 60 °C or reflux for 5 h under argon. The mixture was cooled to room temperature and added the di-*tert*-butyl azodicarboxylate (DTAD) (3mmol) with argon. The reaction was stirred for 6h at 50°C then the solvent was removed under reduced pressure and the residue was purified through column chromatography on silica gel to give the desired products.

Mechanism study:

DTAD initiated the N-center radical

Trap the hydrazoneyl radical using 1 atm air, 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO), DTAD in different conditions

These results demonstrate clearly that DTAD, TEMPO and O₂ could serve as an aromatic hydrazonyl radical initiator as well as carbon radical trapping agent in the reaction.

A 5 mL round bottomed flask equipped with a magnetic stirring bar was added with *b, d*-unsaturated hydrazones (0.30 mmol), 2,2,6,6-tetramethylpiperidine-1-oxyl (2.0 equiv, 0.6 mmol), and 4 equiv of HOAc (1.2 mmol) in chlorobenzene (1 mL) under argon. The flask was stirred at room temperature for 4 h and the reaction progress was monitored by TLC. The solvent was removed under reduced pressure. The residue was purified through column chromatography on silica gel to give the desired products.

1-((3-(tert-butyl)-5-methyl-1-phenyl-4,5-dihydro-1H-

pyrazol-5-yl)methoxy)-2,2,6,6-tetra methylpiperidine:

This compound was prepared by the general procedure

described above and was obtained as a yellowish solid in 93% yield: $R_f = 0.58$ (hexane : ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 7.18-7.26 (m, 4H), 6.87-6.90 (m, 1H), 3.96 (d, $J = 8.4$ Hz, 1H, CH_2), 3.92 (d, $J = 8.4$ Hz, 1H, CH_2), 3.17 (d, $J = 17.2$ Hz, 1H, CH_2), 2.69 (d, $J = 16.8$ Hz, 1H, CH_2), 1.4-1.43 (m, 4H), 1.38 (s, 3H), 1.26-1.29 (m, 1H), 1.24 (s, 9H), 1.07-1.18 (m, 13H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 159.7, 145.9, 128.5, 120.9, 118.4, 80.4, 68.3, 60.1, 60.0, 44.6, 39.8, 33.8, 33.2, 33.0, 28.3, 22.5, 20.3, 17.0 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{39}\text{N}_3\text{OH}^+$ 386.3171, found 386.3177.

3a-methyl-1,3-diphenyl-6-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-

1,3a,4,5,6,6a-hexahydrocyclopenta-pyrazole: (dr > 20:1); $R_f = 0.66$ (hexane :

ethyl acetate = 10:1); ^1H NMR (400 MHz, CDCl_3): δ 7.85-

7.87 (m, 2H), 7.46-7.48 (m, 2H), 7.28-7.37 (m, 5H), 6.81-

6.85 (m, 1H), 4.46 (m, 2H), 2.36-2.43 (m, 1H), 2.06-2.15

(m, 2H), 1.71-1.73 (m, 1H), 1.64 (s, 3H), 1.51-1.53 (m, 5H), 1.17-1.28 (m, 13H)

ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 152.2, 144.6, 131.8, 128.9, 128.4, 127.9,

126.3, 118.6, 113.2, 88.8, 77.6, 60.4, 59.8, 58.4, 40.5, 36.8, 35.5, 34.4, 31.5,

27.0, 25.4, 20.5, 17.2 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{28}\text{H}_{37}\text{N}_3\text{OH}^+$

432.3015, found 432.2993.

General Procedure for Reduction of Difunctionalization products

- 1) Into a 25 mL round bottom flask equipped with a magnetic stirrer, diamines **3** (0.3 mmol) and 10 mL DCM was added to dissolve the solid with Ar₂. 1 mL trifluoroacetic acid was added and the solution was stirred at room temperature for 4h. After the reaction was finished 1 mL acetone was added and stirred for 10 min. The reaction was quenched using potassium bicarbonate and the pH was adjusted to 12 with 1N NaOH solution, then extracted three times with ethyl acetate. The combined organic extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo*, and the crude product was directly used in the next step without further purification.
- 2) The product was dissolved in 4 ml of HOAc then added active Zinc power, which was stirred at RT for overnight with Ar₂ monitored by TLC. Then the reaction was filtered over Celite, the Celite was washed with MeOH (20 mL), the pH was adjusted to 1 with 37% HCl, and the solvents were removed under reduced pressure. The residues were suspended in 1 M HCl (20 mL), the suspension was washed with Et₂O (3x15 mL) and the pH was adjusted to 12 with NaOH pellets. The resulting solution was extracted with Et₂O (3x20 mL), saturated in NaCl and extracted again with Et₂O (20 mL). The combined organic layers were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The yellowish liquid was

purified using flash column chromatography (Al_2O_3) with 2% $\text{CH}_3\text{OH}/\text{DCM}$ to give (about 85%-87% purified yield) of the free amines product

3) Into a 10 mL round bottom flask equipped with a magnetic stirrer, free amines were not purified and 5 mL DCM was added to dissolve the solid with Ar_2 . Boc_2O (2.0 equiv) and Et_3N (2.0 equiv) was added and the solution was stirred at room temperature for 1h. The solvent was removed *in vacuo*, and the yellowish liquid was purified using flash column chromatography with 20% ethyl acetate/hexanes to give (about 81% purified yield) of the yellowish product.

Characterization Data for the hydrazones

(E)-1-(2,2-dimethylhex-5-en-3-ylidene)-2-phenylhydrazine (1a): This

compound was prepared by the general procedure described above and was obtained as a yellow oil in 85% yield: $R_f = 0.59$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.31 (s, 1H, NH), 7.21-7.24 (m, 2H, ArH), 7.01-7.03 (m, 2H, ArH), 6.79-6.83 (m, 1H, ArH), 5.81-5.88 (m, 1H, CH), 5.22 (d, 1H, $J = 10.5$ Hz, CH_2), 5.18 (d, 1H, $J = 17.5$ Hz, CH_2), 3.11-3.13 (m, 2H, CH_2), 1.19 (s, 9H, 3 CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 152.1, 146.2, 132.3, 129.1, 119.5, 117.7, 112.9, 38.7, 30.6, 27.9 ppm.

(E)-1-(2,2-dimethylhex-5-en-3-ylidene)-2-(4-fluorophenyl)hydrazine (1b):

This compound was prepared by the general procedure described above and was obtained as a yellow oil in 87% yield: $R_f = 0.62$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.22

(s, 1H, NH), 6.90-6.97 (m, 4H, ArH), 5.79-5.87 (m, 1H, CH), 5.21 (d, 1H, $J = 10.4$ Hz, CH₂), 5.17 (d, 1H, $J = 17.4$ Hz, CH₂), 3.10-3.11 (m, 2H, CH₂), 1.18 (s, 9H, 3CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 157.0 (d, $J = 238.4$ Hz), 152.6, 142.6, 132.3, 117.7, 115.5 (d, $J = 22.4$ Hz), 113.9 (d, $J = 7.6$ Hz), 38.6, 30.7, 27.9 ppm.

(*E*)-1-(4-chlorophenyl)-2-(2,2-dimethylhex-5-en-3-ylidene)hydrazine (1c):

This compound was prepared by the general procedure described

above and was obtained as a yellow oil in 73% yield: $R_f = 0.63$

(hexane : ethyl acetate = 6:1); ¹H NMR (400 MHz, CDCl₃): δ 7.31

(s, 1H, NH), 7.17 (d, 2H, $J = 8.7$ Hz, ArH), 6.95 (d, 2H, $J = 8.7$ Hz,

ArH), 5.79-5.87 (m, 1H, CH), 5.23 (d, 1H, $J = 10.3$ Hz, CH₂), 5.17 (d, 1H, $J =$

17.3 Hz, CH₂), 3.11-3.12 (m, 2H, CH₂), 1.19 (s, 9H, 3CH₃) ppm; ¹³C NMR

(100 MHz, CDCl₃): δ 152.9, 144.8, 132.2, 129.0, 123.9, 117.8, 114.1, 38.7,

30.6, 27.9 ppm.

(*E*)-1-(4-bromophenyl)-2-(2,2-dimethylhex-5-en-3-ylidene)hydrazine (1d):

This compound was prepared by the general procedure described

above and was obtained as a yellow oil in 68% yield: $R_f = 0.59$

(hexane : ethyl acetate = 6:1); ¹H NMR (400 MHz, CDCl₃): δ 7.31

(s, 1H, NH), 7.27 (d, 2H, $J = 8.9$ Hz, ArH), 6.89 (d, 2H, $J = 8.9$ Hz,

ArH), 5.79-5.86 (m, 1H, CH), 5.22 (d, 1H, $J = 10.3$ Hz, CH₂), 5.16 (d, 1H, $J =$

17.3 Hz, CH₂), 3.09-3.12 (m, 2H, CH₂), 1.18 (s, 9H, 3CH₃) ppm; ¹³C NMR

(100 MHz, CDCl₃): δ 153.0, 145.3, 132.1, 131.8, 117.8, 114.6, 111.2, 38.7,

30.6, 27.8 ppm.

(E)-1-(2,2-dimethylhex-5-en-3-ylidene)-2-(4-iodophenyl)hydrazine (1e):

This compound was prepared by the general procedure described above and was obtained as a yellow oil in 65% yield: $R_f = 0.60$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.47 (d, 2H, $J = 8.9$ Hz, ArH), 7.30 (s, 1H, NH), 6.79 (d, 2H, $J = 8.9$ Hz, ArH), 5.77-5.86 (m, 1H, CH), 5.22 (d, 1H, $J = 10.3$ Hz, CH_2), 5.15 (d, 1H, $J = 17.3$ Hz, CH_2), 3.09-3.11 (m, 2H, CH_2), 1.17 (s, 9H, 3 CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 153.0, 145.9, 137.7, 132.1, 117.8, 115.2, 80.6, 38.7, 30.6, 27.8 ppm.

(E)-1-(2,2-dimethylhex-5-en-3-ylidene)-2-(p-tolyl)hydrazine (1f): This

compound was prepared by the general procedure described above and was obtained as a yellow oil in 70% yield: $R_f = 0.62$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.24 (s, 1H, NH), 7.02 (d, 2H, $J = 8.1$ Hz, ArH), 6.92 (d, 2H, $J = 8.5$ Hz, ArH), 5.78-5.86 (m, 1H, CH), 5.19 (d, 1H, $J = 10.3$ Hz, CH_2), 5.15 (d, 1H, $J = 17.3$ Hz, CH_2), 3.09-3.10 (m, 2H, CH_2), 2.26 (s, 3H, CH_3), 1.18 (s, 9H, 3 CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 151.7, 144.1, 132.3, 129.6, 128.7, 117.6, 113.0, 38.6, 30.6, 27.9, 20.6 ppm.

(E)-1-(2,2-dimethylhex-5-en-3-ylidene)-2-(m-tolyl)hydrazine (1g): This

compound was prepared by the general procedure described above and was obtained as a yellow oil in 65% yield: $R_f = 0.62$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.25 (s, 1H, NH), 7.08-7.12 (m, 1H, ArH), 6.81-

6.83 (m, 2H, ArH), 6.61-6.63 (m, 1H, ArH), 5.78-5.87 (m, 1H, CH), 5.20 (d, 1H, $J = 11.8$ Hz, CH_2), 5.16 (d, 1H, $J = 19.0$ Hz, CH_2), 3.09-3.10 (m, 2H, CH_2),

2.30 (s, 3H, CH₃), 1.18 (s, 9H, 3CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 151.9, 146.2, 138.9, 132.3, 129.0, 120.4, 117.6, 113.5, 110.2, 38.7, 30.6, 27.9, 21.7 ppm.

(E)-1-(2,2-dimethylhex-5-en-3-ylidene)-2-(3,5-dimethylphenyl)hydrazine

(1h): This compound was prepared by the general procedure described above and was obtained as a yellow oil in 63% yield: *R_f* = 0.62 (hexane : ethyl acetate = 6:1); ¹H NMR (400 MHz, CDCl₃): δ 7.23 (s, 1H, NH), 6.64 (s, 2H, ArH), 6.46 (s, 1H, ArH), 5.77-5.85 (m, 1H, CH), 5.20 (d, 1H, *J* = 10.3 Hz, CH₂), 5.15 (d, 1H, *J* = 17.3 Hz, CH₂), 3.08-

3.09 (m, 2H, CH₂), 2.26 (s, 6H, 2CH₃), 1.18 (s, 9H, 3CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 151.7, 146.2, 138.8, 132.3, 121.4, 117.6, 110.8, 38.6, 30.5, 27.9, 21.5 ppm; HRMS (ESI, *m/z*): calcd. for C₁₆H₂₄N₂H⁺ 245.2018, found 245.2013.

(E)-1-phenyl-2-(2,2,5-trimethylhex-5-en-3-ylidene)hydrazine (1i): This

compound was prepared by the general procedure described above and was obtained as a yellow oil in 75% yield: *R_f* = 0.69 (hexane : ethyl acetate = 6:1); ¹H NMR (400 MHz, CDCl₃): δ 7.32 (s, 1H,

NH), 7.20-7.25 (m, 2H, ArH), 7.00-7.02 (m, 2H, ArH), 6.80-6.82 (m, 1H, ArH), 4.91 (s, 1H, CH₂), 4.72 (s, 1H, CH₂), 3.01 (s, 2H, CH₂), 1.84 (s, 3H, CH₃), 1.18 (s, 9H, 3CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 152.7, 146.3, 139.7, 129.1, 119.4, 112.9, 112.5, 38.6, 34.8, 28.0, 23.2 ppm; HRMS (ESI, *m/z*): calcd. for C₁₅H₂₂N₂H⁺ 231.1861, found 231.1857.

(E)-1-(4-methoxyphenyl)-2-(2,2,5-trimethylhex-5-en-3-ylidene)hydrazine

(1j) This compound was prepared by the general procedure described above and

was obtained as a yellow oil in 51% yield: $R_f = 0.45$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.13 (s, 1H, NH), 6.95-6.98 (m, 2H, ArH), 6.80-6.84 (m, 2H, ArH), 4.90 (s, 1H, CH_2), 4.71 (s, 1H, CH_2), 3.60 (s, 3H, OCH_3), 3.00 (s, 2H, CH_2), 1.84 (s, 3H, CH_3), 1.17 (s, 9H, 3 CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 153.4, 152.4, 140.7, 139.7, 114.7, 114.1, 112.2, 55.8, 38.5, 34.8, 28.0, 23.2 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{OH}^+$ 261.1967, found 261.1965.

(E)-1-(5-benzyl-2,2-dimethylhex-5-en-3-ylidene)-2-phenylhydrazine (1k):

This compound was prepared by the general procedure described above and was obtained as a yellow oil in 71% yield: $R_f = 0.63$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.34-7.38 (m, 2H, ArH), 7.26-7.29 (m, 3H, ArH), 7.16-7.23 (m, 2H, ArH), 6.87-6.89 (m, 2H, ArH), 6.86 (s, 1H, NH), 6.75-6.79 (m, 1H, ArH), 4.99 (s, 1H, CH_2), 4.73 (s, 1H, CH_2), 3.42 (s, 2H, CH_2), 2.90 (s, 2H, CH_2), 1.13 (s, 9H, 3 CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 152.3, 146.1, 142.0, 139.1, 129.0, 128.8, 126.8, 119.3, 113.2, 44.2, 38.6, 32.0, 28.0 ppm.

(E)-1-(3-methyl-1-(naphthalen-2-yl)but-3-en-1-ylidene)-2-phenylhydrazine (1l):

(1l): This compound was prepared by the general procedure described above and was obtained as a brown solid in 64% yield: $R_f = 0.46$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 8.20 (d, 1H, $J = 8.7$ Hz, ArH), 7.94 (s, 1H, ArH), 7.82-7.84 (m, 3H, ArH), 7.76 (s, 1H, ArH), 7.46-7.48 (m, 2H, ArH), 7.29-7.33 (m, 2H, ArH), 7.20-7.22 (m, 2H, ArH), 6.89-6.93 (m, 1H, ArH), 4.99 (s, 1H, CH_2), 4.93 (s, 1H, CH_2), 3.57 (s, 2H, CH_2), 1.94 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3):

δ 145.2, 142.4, 139.5, 136.5, 133.4, 133.2, 129.3, 128.3, 128.0, 127.7, 126.2, 126.1, 124.5, 123.8, 120.4, 113.4, 113.0, 35.5, 23.0 ppm; HRMS (ESI, m/z): calcd. for $C_{21}H_{20}N_2H^+$ 301.1705, found 301.1702.

(Z)-1-(2,2-dimethyl-1-phenylbut-3-en-1-ylidene)-2-phenylhydrazine (1m):

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 73% yield: R_f = 0.58 (hexane : ethyl acetate = 6:1); 1H NMR (400 MHz, $CDCl_3$): δ 7.42-7.49 (m, 3H, ArH), 7.17-7.21 (m, 2H, ArH), 7.11-7.13 (m, 2H, ArH), 6.93-6.95 (m, 2H, ArH), 6.82 (s, 1H, NH), 6.76-6.80 (m, 1H, ArH), 6.02 (dd, 1H, J = 10.6, 17.4 Hz, CH), 5.03 (d, 1H, J = 10.6 Hz, CH_2), 4.98 (d, 1H, J = 17.5 Hz, CH_2), 1.32 (s, 6H, 2 CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 145.6, 145.4, 133.4, 129.1, 128.9, 128.9, 128.6, 119.4, 112.6, 112.0, 44.2, 25.6 ppm; HRMS (ESI, m/z): calcd. for $C_{18}H_{20}N_2H^+$ 265.1705, found 265.1704.

(Z)-1-(2,2-dimethyl-1-phenylbut-3-en-1-ylidene)-2-(4-

methoxyphenyl)hydrazine (1n): This compound was prepared by the general

procedure described above and was obtained as a yellowish oil in 63% yield: R_f = 0.50 (hexane : ethyl acetate = 6:1); 1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.45 (m, 3H, ArH), 7.09-7.11 (m, 2H, ArH), 6.87 (d, 2H, J = 9.0 Hz, ArH), 6.76 (d, 2H, J = 8.9 Hz, ArH), 6.66 (s, 1H, NH), 6.01 (dd, 1H, J = 10.6, 17.4 Hz, CH), 5.00 (d, 1H, J = 10.8 Hz, CH_2), 4.96 (d, 1H, J = 17.5 Hz, CH_2), 3.71 (s, 3H, OCH_3), 1.30 (s, 6H, 2 CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 151.8, 145.7, 139.8, 133.6, 128.9, 128.5, 114.7, 113.7, 111.9, 55.8, 44.1, 25.7 ppm; HRMS (ESI, m/z): calcd. for $C_{19}H_{22}N_2OH^+$ 295.1810, found 295.1809.

(Z)-1-(2,2-dimethyl-1-(thiophen-2-yl)but-3-en-1-ylidene)-2-

phenylhydrazine (10): This compound was prepared by the general procedure described above and was obtained as a yellow

oil in 53% yield: $R_f = 0.55$ (hexane : ethyl acetate = 6:1); ^1H

NMR (400 MHz, CDCl_3): δ 7.47-7.49 (m, 1H, ArH), 7.37 (s, 1H,

NH), 7.15-7.23 (m, 3H, ArH), 6.95-6.99 (m, 3H, ArH), 6.80-6.83 (m, 1H, ArH),

6.00 (dd, 1H, $J = 10.7, 17.3$ Hz, CH), 5.31 (d, 1H, $J = 17.5$ Hz, CH_2), 5.24 (d,

1H, $J = 10.6$ Hz, CH_2), 1.34 (s, 6H, 2 CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3):

δ 145.3, 145.0, 144.3, 131.5, 129.2, 128.3, 127.3, 127.2, 119.8, 112.8, 44.5,

25.7 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{SH}^+$ 271.1269, found

271.1262.

(Z)-tert-butyl-3-(2,2-dimethyl-1-(2-phenylhydrazono)but-3-en-1-yl)-1H-

indole-1-carboxylate (1p): This compound was prepared by the general

procedure described above and was obtained as a yellowish

solid in 75% yield: $R_f = 0.55$ (hexane : ethyl acetate = 6:1); ^1H

NMR (400 MHz, CDCl_3): δ 8.18 (d, 1H, $J = 8.2$ Hz, ArH),

7.52 (s, 1H, NH), 7.35-7.38 (m, 1H, ArH), 7.25-7.29 (m, 1H,

ArH), 7.15-7.22 (m, 3H, ArH), 7.11 (s, 1H, ArH), 6.91 (d, 2H, $J = 7.8$ Hz,

ArH), 6.76-6.79 (m, 1H, ArH), 6.04 (dd, 1H, $J = 10.4, 17.7$ Hz, CH), 5.06 (d,

1H, $J = 11.4$ Hz, CH_2), 5.06 (d, 1H, $J = 16.7$ Hz, CH_2), 1.70 (s, 9H, 3 CH_3), 1.34

(br, 6H, 2 CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 145.3, 145.3, 144.5,

129.1, 128.4, 125.1, 124.9, 123.3, 120.7, 119.5, 115.4, 112.7, 112.6, 112.4,

84.4, 44.7, 28.2 ppm.

(Z)-1-((1-methylcyclopent-2-en-1-yl)(phenyl)methylene)-2-phenylhydrazine

(1q): This compound was prepared by the general procedure described above and was obtained as a yellowish solid in 81% yield:

$R_f = 0.56$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.42-7.50 (m, 3H, ArH), 7.15-7.21 (m, 4H, ArH), 6.92-6.94 (m, 2H, ArH), 6.82 (s, 1H, NH), 6.76-6.79 (m, 1H, ArH), 5.69-5.73 (m, 2H, CH), 2.32-2.44 (m, 2H, CH_2), 2.15-2.23 (m, 1H, CH_2), 1.69-1.76 (m, 1H, CH_2), 1.38 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 152.7, 145.4, 137.8, 133.9, 130.2, 129.1, 129.0, 128.7, 128.5, 119.3, 112.6, 55.7, 35.9, 31.9, 25.7 ppm.

(Z)-1-((1-allylcyclopent-2-en-1-yl)(phenyl)methylene)-2-phenylhydrazine

(1r): This compound was prepared by the general procedure described above and was obtained as a yellowish solid in 83% yield:

$R_f = 0.56$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.42-7.49 (m, 3H, ArH), 7.15-7.21 (m, 4H, ArH), 6.92-

6.94 (m, 2H, ArH), 6.85 (s, 1H, NH), 6.76-6.79 (m, 1H, ArH), 5.88-5.95 (m, 1H, CH), 5.75-5.77 (m, 1H, CH), 5.68-5.69 (m, 1H, CH), 5.05-5.10 (m, 2H, CH_2), 2.47-2.59 (m, 2H, CH_2), 2.26-2.39 (m, 2H, CH_2), 2.14-2.23 (m, 1H, CH_2), 1.81-1.88 (m, 1H, CH_2) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 151.2, 145.4, 136.0, 135.9, 133.8, 131.3, 129.1, 129.1, 128.7, 128.6, 119.3, 116.9, 112.6, 59.3, 42.7, 33.0, 32.1 ppm.

(Z)-1-((1-benzylcyclopent-2-en-1-yl)(phenyl)methylene)-2-phenylhydrazine

(1s): This compound was prepared by the general procedure described above and was obtained as a yellow solid in 72% yield:

$R_f = 0.54$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.39-7.45 (m, 3H, ArH), 7.19-7.26 (m, 7H, ArH), 6.96-

7.02 (m, 4H, ArH), 6.90 (s, 1H, NH), 6.78-6.82 (m, 1H, ArH), 5.66-5.69 (m, 2H, CH), 3.24 (d, 1H, $J = 13.3$ Hz, CH_2), 3.14 (d, 1H, $J = 13.3$ Hz, CH_2), 2.24-2.31 (m, 1H, CH_2), 1.90-2.11 (m, 3H, CH_2) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ

151.8, 145.4, 139.3, 136.1, 134.0, 131.6, 130.8, 129.2, 129.1, 128.5, 128.4, 127.7, 125.9, 119.4, 112.6, 60.3, 44.4, 33.9, 32.0 ppm.

(Z)-1-((1-methylcyclohex-2-en-1-yl)(phenyl)methylene)-2-phenylhydrazine

(1t): This compound was prepared by the general procedure described above and was obtained as a yellowish solid in 80% yield:

$R_f = 0.57$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.41-7.50 (m, 3H, ArH), 7.14-7.21 (m, 4H, ArH), 6.92-

6.93 (m, 2H, ArH), 6.79 (s, 1H, NH), 6.75-6.79 (m, 1H, ArH), 5.70-5.75 (m, 1H, CH), 5.62-5.64 (m, 1H, CH), 2.15-2.21 (m, 1H, CH_2), 1.96-1.99 (m, 2H, CH_2), 1.68-1.73 (m, 2H, CH_2), 1.46-1.53 (m, 1H, CH_2), 1.28 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 153.1, 145.5, 133.7, 129.1, 129.0, 128.9, 128.5, 126.5, 119.3, 112.6, 42.3, 33.7, 27.5, 25.1, 19.4 ppm.

(E)-1-(2-methyl-1-phenylbut-3-en-1-ylidene)-2-phenylhydrazine (1u): This

compound was prepared by the general procedure described above and was obtained as a yellowish oil in 42% yield: $R_f = 0.58$

(hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.39-

7.45 (m, 3H, ArH), 7.17-7.23 (m, 4H, ArH), 7.16 (s, 1H, NH), 6.94-6.96 (m, 2H, ArH), 6.76-6.80 (m, 1H, ArH), 5.89-5.98 (m, 1H, CH), 5.00-5.04 (m, 2H, CH_2), 3.39-3.42 (m, 1H, CH), 1.30 (d, 3H, $J = 6.9$ Hz, CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 149.4, 145.3, 140.7, 134.0, 129.2, 129.2, 128.8, 128.1, 119.5, 114.6, 112.7, 45.8, 17.9 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{H}^+$ 251.1548, found 251.1546.

Characterization data for the products

Diisopropyl-1-((3-(tert-butyl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-

yl)methyl)hydrazine- 1,2-dicarboxylate (3a): This compound was prepared

by the general procedure described above and was obtained as a yellowish oil in 78% yield: $R_f = 0.45$ (hexane : ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 7.20-7.26 (m,

2H), 7.04-7.06 (m, 2H), 6.75-6.79 (m, 1H), 6.44-6.65 (m, 1H), 4.80-5.05 (m, 2H), 4.32-4.52 (m, 1H), 3.35-3.82 (m, 2H), 2.78-3.14 (m, 2H), 1.09-1.34 (m, 21H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 160.9, 160.3, 156.1, 155.7, 145.6, 129.2, 118.5, 112.8, 71.0, 70.4, 70.1, 69.9, 58.3, 51.0, 36.7, 33.9, 28.2, 22.1, 22.0 ppm; FTIR (KBr, neat): ν 1735, 1741, 1674, 1597, 1494, 1242, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{22}\text{H}_{34}\text{N}_4\text{O}_4\text{H}^+$ 419.2658, found 419.2650.

Diethyl-1-((3-(tert-butyl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-

yl)methyl)hydrazine-1,2-di carboxylate: This compound was prepared by the

general procedure described above and was obtained as a yellowish solid in 73% yield: $R_f = 0.45$ (hexane : ethyl

acetate = 4:1); Mp = 62.6-64.2 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 7.21-7.26 (m, 2H), 7.04-7.06 (m, 2H), 6.76-6.79 (m, 1H), 6.48-6.57 (m, 1H), 4.35-4.47 (m, 1H), 4.19-4.27 (m, 4H), 3.52-3.72 (m, 2H), 2.81-3.10 (m, 2H), 1.15-1.35 (m, 15H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.5, 145.5, 129.2, 128.7, 118.6, 112.8, 62.3, 62.2, 62.1, 58.2, 50.9, 36.4, 33.9, 28.2, 14.5, 14.4 ppm; FTIR (KBr, neat): ν 1736, 1714, 1599, 1502, 1392, 1269, 1253, 1151, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{20}\text{H}_{30}\text{N}_4\text{O}_4\text{H}^+$ 391.2345, found 391.2348.

Dibenzyl-1-((3-(tert-butyl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-

yl)methyl)hydrazine-1,2- dicarboxylate: This compound was prepared by the general procedure described above and

was obtained as a yellowish oil in 81% yield: $R_f = 0.32$ (hexane : ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 7.11-7.30 (m, 12H), 6.94-7.02 (m, 2H),

6.64-6.81 (m, 1H), 4.95-5.22 (m, 4H), 4.35-4.42 (m, 1H), 3.41-3.82 (m, 2H), 2.78-3.14 (m, 2H), 1.01-1.24 (m, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 161.1, 156.4, 155.7, 145.5, 135.5, 129.3, 128.6, 128.5, 128.1, 128.0, 118.7, 112.9, 69.0, 68.3, 67.7, 58.3, 51.2, 36.5, 33.9, 28.2 ppm; FTIR (KBr, neat): ν 1735, 1714, 1674, 1597, 1494, 1303, 1242, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{34}\text{N}_4\text{O}_4\text{H}^+$ 515.2658, found 515.2659.

Di-*tert*-butyl-1-((3-(*tert*-butyl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-

yl)methyl)hydrazine-1,2-dicarboxylate (3b): This compound was prepared

by the general procedure described above and was obtained as a yellowish oil in 90% yield: R_f = 0.47 (hexane : ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 7.20-7.26 (m,

2H), 7.05-7.07 (m, 2H), 6.75-6.78 (m, 1H), 6.16-6.45 (m, 1H), 4.31-4.50 (m, 1H), 3.32-3.82 (m, 2H), 2.78-3.12 (m, 2H), 1.19-1.58 (m, 18H), 1.21 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 160.8, 155.7, 155.3, 154.9, 145.7, 129.1, 118.4, 112.8, 82.2, 81.4, 81.1, 58.4, 51.2, 50.8, 36.5, 33.9, 28.2, 28.1 ppm; FTIR (KBr, neat): ν 1745, 1714, 1599, 1215, 1174 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{38}\text{N}_4\text{O}_4\text{H}^+$ 447.2971, found 447.2974.

Di-*tert*-butyl-1-((3-(*tert*-butyl)-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-

5-yl)methyl)-hydrazine-1,2-dicarboxylate (3c): This compound was prepared by the general procedure described above and was obtained as a yellow solid in 96% yield: R_f = 0.48 (hexane : ethyl acetate = 4:1); M_p = 58.5-60.0 $^\circ\text{C}$; ^1H

NMR (400 MHz, CDCl_3): δ 7.09-7.12 (m, 2H), 6.89-6.99 (m, 2H), 6.21-6.33 (m, 1H), 4.24-4.39 (m, 1H), 3.62-3.79 (m, 1H), 3.31-3.52 (m, 1H), 2.82-3.12 (m, 2H), 1.36-1.52 (m, 18H), 1.20 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ

162.4, 161.1, 160.6, 157.8, 155.6, 155.4, 154.9, 142.5, 138.9, 127.3, 116.1, 115.8, 115.6, 115.4, 114.2, 114.2, 82.3, 81.5, 59.1, 51.3, 50.7, 36.8, 33.8, 30.5, 28.2, 28.1 ppm; FTIR (KBr, neat): ν 1735, 1714, 1597, 1508, 1242, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{37}\text{N}_4\text{O}_4\text{FH}^+$ 465.2877, found 465.2872.

Di-*tert*-butyl-1-((3-(*tert*-butyl)-1-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (3d): This compound was prepared

by the general procedure described above and was obtained as a yellowish solid in 91% yield: R_f = 0.46 (hexane : ethyl acetate = 4:1); M_p = 60.3-62.1 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 7.16 (d, 2H, J = 8.8 Hz), 6.98 (d, 2H, J = 7.8 Hz),

6.23-6.33 (m, 1H), 4.29-4.46 (m, 1H), 3.60-3.72 (m, 1H), 3.25-3.52 (m, 1H), 2.82-3.13 (m, 2H), 1.38-1.51 (m, 18H), 1.20 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 162.6, 161.5, 160.8, 155.7, 155.3, 154.9, 144.2, 130.2, 129.2, 128.9, 126.4, 122.9, 113.9, 82.4, 81.6, 81.3, 58.3, 51.0, 50.4, 36.7, 33.9, 30.5, 28.2, 28.1 ppm; FTIR (KBr, neat): ν 1735, 1714, 1597, 1496, 1242, 1150 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{37}\text{N}_4\text{O}_4\text{ClH}^+$ 481.2582, found 481.2571.

Di-*tert*-butyl-1-((1-(4-bromophenyl)-3-(*tert*-butyl)-4,5-dihydro-1H-pyrazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (3e): This

compound was prepared by the general procedure described above and was obtained as a yellowish oil in 96% yield: R_f = 0.43 (hexane : ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 7.29 (d, 2H, J = 8.8 Hz), 6.93 (d, 2H, J = 7.1 Hz), 6.24-6.48 (m, 1H),

4.28-4.45 (m, 1H), 3.53-3.72 (m, 1H), 3.20-3.52 (m, 1H), 2.80-3.13 (m, 2H), 1.33-1.51 (m, 18H), 1.21 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 162.7, 161.5, 155.7, 155.3, 154.9, 144.5, 132.2, 131.8, 126.7, 114.3, 110.1, 82.4, 81.6,

81.3, 58.2, 51.0, 50.3, 36.7, 33.9, 30.5, 28.2, 28.1 ppm; FTIR (KBr, neat): ν 1716, 1597, 1494, 1392, 1242, 1153 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{37}\text{N}_4\text{O}_4\text{BrH}^+$ 525.2076, found 525.2087.

Di-*tert*-butyl-1-((3-(*tert*-butyl)-1-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (3f): This

compound was prepared by the general procedure described above and was obtained as a yellow oil in 96% yield: R_f = 0.45 (hexane : ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 7.46 (d, 2H, J = 8.5 Hz), 6.83 (d, 2H, J = 7.1 Hz), 6.22-6.52 (m, 1H), 4.29-4.47 (m, 1H), 3.53-3.71 (m, 1H), 3.20-3.52 (m, 1H), 2.80-3.15 (m, 2H), 1.38-1.51 (m, 18H), 1.21 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 162.7, 161.6, 160.9, 155.7, 155.2, 154.9, 145.0, 138.2, 137.7, 126.8, 114.9, 82.4, 81.6, 81.3, 79.3, 58.0, 51.0, 50.3, 36.7, 33.9, 30.5, 28.2, 28.1 ppm; FTIR (KBr, neat): ν 1736, 1714, 1597, 1494, 1242, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{37}\text{N}_4\text{O}_4\text{H}^+$ 573.1938, found 573.1938.

Di-*tert*-butyl-1-((3-(*tert*-butyl)-1-(*p*-tolyl)-4,5-dihydro-1H-pyrazol-5-

yl)methyl)hydrazine-1,2-dicarboxylate (3g): This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 56% yield: R_f = 0.48 (hexane : ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 7.03 (d, 2H, J = 8.2 Hz), 6.97 (d, 2H, J = 8.2 Hz), 6.02-6.45 (m, 1H), 4.23-4.43 (m, 1H), 3.28-3.82 (m, 2H), 2.75-3.13 (m, 2H), 2.26 (s, 3H), 1.39-1.50 (m, 18H), 1.21 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 160.7, 160.0, 155.7, 155.3, 154.9, 143.9, 129.6, 129.1, 129.0, 128.6, 128.0, 113.3, 82.2, 81.4, 81.1, 59.0, 51.6, 50.9, 36.7, 36.5, 33.8, 28.2, 28.1, 20.5 ppm; FTIR (KBr, neat): ν 1735, 1714,

1674, 1597, 1493, 1303, 1242, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{40}\text{N}_4\text{O}_4\text{H}^+$ 461.3128, found 461.3127.

Di-*tert*-butyl-1-((3-(*tert*-butyl)-1-(*m*-tolyl)-4,5-dihydro-1H-pyrazol-5-

yl)methyl)hydrazine-1,2-dicarboxylate (3h): This compound was prepared by

the general procedure described above and was obtained as

a yellowish solid in 65% yield: R_f = 0.48 (hexane : ethyl

acetate = 4:1); M_p = 59.1-60.2 $^{\circ}\text{C}$; ^1H NMR (400 MHz,

CDCl_3): δ 7.08-7.12 (m, 1H), 6.92 (s, 1H), 6.80-6.82 (m, 1H), 6.58-6.60 (m,

1H), 6.12-6.48 (m, 1H), 4.35-4.46 (m, 1H), 3.31-3.78 (m, 2H), 2.95-3.13 (m,

1H), 2.68-2.92 (m, 1H), 2.30 (s, 3H), 1.35-1.50 (m, 18H), 1.21 (s, 9H) ppm; ^{13}C

NMR (100 MHz, CDCl_3): δ 155.3, 154.9, 145.7, 139.3, 138.9, 129.0, 119.5,

113.7, 110.0, 81.4, 81.1, 58.5, 50.9, 36.5, 33.9, 28.2, 28.1, 21.8 ppm; FTIR

(KBr, neat): ν 1735, 1714, 1597, 1494, 1242, 1143 cm^{-1} ; HRMS (ESI, m/z):

calcd. for $\text{C}_{25}\text{H}_{40}\text{N}_4\text{O}_4\text{H}^+$ 461.3128, found 461.3130.

Di-*tert*-butyl-1-((3-(*tert*-butyl)-1-(3,5-dimethylphenyl)-4,5-dihydro-1H-

pyrazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (3i): This compound was

prepared by the general procedure described above and was

obtained as a yellowish solid in 76% yield: R_f = 0.46

(hexane : ethyl acetate = 4:1); M_p = 65.2-66.9 $^{\circ}\text{C}$; ^1H NMR

(400 MHz, CDCl_3): δ 6.97-7.01 (m, 1H), 6.68 (s, 1H), 6.43 (s, 1H), 6.11-6.39

(m, 1H), 4.31-4.45 (m, 1H), 3.31-3.72 (m, 2H), 2.94-3.12 (m, 1H), 2.78-2.91 (m,

1H), 2.26 (s, 6H), 1.38-1.52 (m, 18H), 1.21 (s, 9H) ppm; ^{13}C NMR (100 MHz,

CDCl_3): δ 161.9, 160.7, 155.7, 154.9, 145.8, 138.9, 138.7, 129.7, 123.1, 120.5,

110.8, 81.4, 58.5, 50.9, 36.4, 30.6, 28.2, 28.1, 21.7 ppm; FTIR (KBr, neat): ν

1741, 1716, 1597, 1253, 1153 cm^{-1} ; HRMS (ESI, m/z): calcd. for

$C_{26}H_{42}N_4O_4H^+$ 475.3284, found 475.3282.

Di-tert-butyl-1-((3-(tert-butyl)-5-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (3j): This compound was prepared

by the general procedure described above and was obtained as a yellowish oil in 67% yield: R_f = 0.42 (hexane : ethyl acetate = 4:1); 1H NMR (400 MHz, $CDCl_3$): δ 7.17-7.23 (m,

4H), 6.75-6.92 (m, 1H), 6.05-6.51 (m, 1H), 3.91-4.22 (m, 1H), 3.42-3.69 (m, 1H), 3.02-3.28 (m, 1H), 2.59-2.76 (m, 1H), 1.31-1.47 (m, 21H), 1.20 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 156.4, 154.1, 145.6, 128.8, 121.0, 120.2, 119.6, 117.9, 117.3, 116.6, 81.3, 80.6, 68.6, 54.0, 44.7, 33.8, 28.1, 22.9 ppm; FTIR (KBr, neat): ν 1736, 1714, 1597, 1494, 1242, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $C_{25}H_{40}N_4O_4H^+$ 461.3128, found 461.3127.

Di-tert-butyl-1-((3-(tert-butyl)-1-(4-methoxyphenyl)-5-methyl-4,5-dihydro-1H-pyrazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (3k): This compound

was prepared by the general procedure described above and was obtained as a yellow oil in 67% yield: R_f = 0.40 (hexane : ethyl acetate = 4:1); 1H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, 2H, J = 8.8 Hz), 6.78 (d, 2H, J = 8.7 Hz), 6.05-

6.63 (m, 1H), 3.87-4.15 (m, 1H), 3.76 (s, 3H), 3.25-3.63 (m, 1H), 3.02-3.15 (m, 1H), 2.55-2.72 (m, 1H), 1.50 (s, 3H), 1.38-1.47 (m, 18H), 1.18 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 156.2, 155.1, 154.4, 154.2, 139.4, 122.0, 120.7, 119.4, 113.9, 83.7, 82.0, 81.6, 81.3, 80.8, 69.7, 55.7, 55.5, 54.6, 43.6, 33.8, 28.2, 28.1 ppm; FTIR (KBr, neat): ν 1735, 1714, 1494, 1303, 1242, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $C_{26}H_{42}N_4O_5H^+$ 491.3233, found 491.3262.

Di-tert-butyl-1-((5-benzyl-3-(tert-butyl)-1-phenyl-4,5-dihydro-1H-pyrazol-

5-yl)methyl)hydrazine-1,2-dicarboxylate (3l): This compound was prepared

by the general procedure described above and was

obtained as a yellowish oil in 50% yield: $R_f = 0.43$ (hexane : ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 7.18-7.31 (m, 8H), 7.01-7.12 (m, 1H), 6.78-6.93 (m, 1H), 5.98-6.52 (m, 1H), 4.51-4.97 (m, 1H), 4.18-4.45 (m, 1H), 3.70-4.05 (m, 1H), 3.10-3.41 (m, 1H), 2.95-3.08 (m, 1H), 2.59-2.82 (m, 1H), 1.31-1.45 (m, 18H), 1.01 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 159.4, 159.1, 156.5, 155.2, 154.8, 154.1, 145.5, 136.2, 130.6, 129.0, 128.5, 128.3, 127.5, 126.6, 119.3, 116.7, 115.5, 82.0, 81.3, 80.6, 71.8, 53.9, 53.5, 40.5, 39.8, 33.6, 28.2, 28.1, 27.9 ppm; FTIR (KBr, neat): ν 1741, 1714, 1597, 1496, 1242, 1153, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{44}\text{N}_4\text{O}_4\text{H}^+$ 537.3441, found 537.3440.

Di-tert-butyl-1-((5-methyl-3-(naphthalen-2-yl)-1-phenyl-4,5-dihydro-1H-

pyrazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (3m): This compound was

prepared by the general procedure described above and

was obtained as a yellowish solid in 50% yield: $R_f =$

0.45 (hexane : ethyl acetate = 4:1); $\text{Mp} = 79.2\text{-}80.6\text{ }^\circ\text{C}$;

^1H NMR (400 MHz, CDCl_3): δ 8.09-8.11 (m, 1H), 7.81-7.86 (m, 4H), 7.44-7.49 (m, 2H), 7.35-7.37 (m, 2H), 7.28-7.30 (m, 2H), 6.95-6.96 (m, 1H), 6.05-6.51 (m, 1H), 3.98-4.38 (m, 1H), 3.50-3.80 (m, 2H), 3.17-3.22 (m, 1H), 1.31-1.47 (m, 21H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 154.3, 148.2, 144.7, 133.4, 133.4, 130.5, 128.9, 128.4, 128.1, 127.8, 126.5, 126.3, 125.2, 123.3, 121.3, 121.0, 117.7, 117.2, 81.6, 80.8, 69.6, 55.7, 54.5, 45.1, 28.1, 28.0, 23.3 ppm; FTIR (KBr, neat): ν 1735, 1714, 1597, 1494,

1143 cm⁻¹; HRMS (ESI, m/z): calcd. for C₃₁H₃₈N₄O₄H⁺ 531.2971, found 531.2975.

Di-tert-butyl-1-((4,4-dimethyl-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-

yl)methyl)hydrazine-1,2-dicarboxylate (3n): This

compound was prepared by the general procedure described above and was obtained as a yellowish solid in 84% yield: *R*_f = 0.43 (hexane : ethyl acetate = 4:1); *Mp* = 65.8-67.2 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.71-7.73 (m, 2H), 7.33-7.39 (m, 3H), 7.18-7.27 (m, 4H), 6.81-6.85 (m, 1H), 5.86-6.32 (m, 1H), 4.15-4.40 (m, 1H), 3.85-4.08 (m, 1H), 3.11-3.62 (m, 1H), 1.37-1.45 (m, 24H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 156.2, 155.2, 144.9, 132.4, 129.2, 128.4, 128.4, 126.9, 119.2, 113.9, 81.5, 81.4, 81.3, 68.2, 49.9, 48.0, 28.2, 27.3, 18.7 ppm; FTIR (KBr, neat): ν 1735, 1714, 1597, 1494, 1143 cm⁻¹; HRMS (ESI, m/z): calcd. for C₂₈H₃₈N₄O₄H⁺ 495.2971, found 495.2970.

Di-tert-butyl-1-((1-(4-methoxyphenyl)-4,4-dimethyl-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (3o): This compound

was prepared by the general procedure described above and was obtained as a yellow solid in 84% yield: *R*_f = 0.41

(hexane : ethyl acetate = 4:1); *Mp* = 73.3-74.8 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.70-7.72 (m, 2H), 7.34-7.36 (m, 3H), 7.16 (d, 2H, *J* = 7.6 Hz), 6.85 (d, 2H, *J* = 8.8 Hz), 5.56-6.18 (m, 1H), 3.85-4.35 (m, 2H), 3.78 (s, 3H), 3.35-3.68 (m, 1H), 1.37-1.47 (m, 24H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 155.9, 155.2, 154.9, 154.1, 139.8, 132.5, 128.4, 128.3, 126.8, 117.8, 117.3, 114.6, 81.7, 81.3, 69.7, 55.7, 49.9, 48.1, 28.2, 26.7, 18.8 ppm; FTIR (KBr, neat): ν 1735, 1714, 1597, 1494, 1242, 1143 cm⁻¹; HRMS (ESI, m/z): calcd. for C₂₉H₄₀N₄O₅H⁺ 525.3077, found 525.3076.

Di-tert-butyl-1-((4,4-dimethyl-3-phenethyl-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)methyl)hydrazine-1,2-dicarboxylate (3p): This compound was

prepared by the general procedure described above and

was obtained as a yellowish solid in 73% yield: $R_f = 0.51$

(hexane : ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 7.20-7.29 (m, 7H), 7.06-7.08 (m, 2H), 6.70-6.89 (m, 1H), 5.91-6.35 (b, 1H), 3.71-4.19 (b, 2H), 3.15-3.60 (b, 1H), 3.01-3.06 (m, 2H), 2.51-2.55 (m, 2H), 1.44-1.49 (m, 18H), 1.19 (s, 3H), 1.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 160.1, 159.3, 155.3, 155.0, 146.1, 145.8, 141.9, 129.1, 128.5, 128.5, 126.1, 119.2, 118.8, 113.7, 81.7, 66.8, 50.2, 48.1, 32.7, 28.2, 26.3, 17.8 ppm; FTIR (KBr, neat): ν 1735, 1714, 1597, 1494, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{42}\text{N}_4\text{O}_4\text{H}^+$ 523.3284, found 523.3288.

Di-tert-butyl-1-((4,4-dimethyl-1-phenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl) methyl)hydrazine-1,2-dicarboxylate (3q): This compound was

prepared by the general procedure described above

and was obtained as a yellowish solid in 87% yield:

$R_f = 0.46$ (hexane : ethyl acetate = 4:1); $\text{Mp} = 78.4$ -

$80.1\text{ }^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 7.23-7.30

(m, 4H), 7.15-7.17 (m, 2H), 7.02-7.04 (m, 1H), 6.82-6.85 (m, 1H), 5.62-6.32 (m, 1H), 4.11-4.40 (m, 1H), 3.72-4.08 (m, 1H), 3.02-3.62 (m, 1H), 1.55 (s, 3H), 1.37-1.46 (m, 21H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 155.2, 144.4, 135.5, 129.1, 127.4, 126.0, 124.8, 119.4, 114.0, 81.5, 81.4, 68.0, 50.0, 48.4, 28.2, 27.2, 18.9 ppm; FTIR (KBr, neat): ν 1735, 1714, 1597, 1494, 1242, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{36}\text{N}_4\text{O}_4\text{SH}^+$ 501.2536, found 501.2538.

Di-*tert*-butyl-1-((3-(1-(*tert*-butoxycarbonyl)-1H-indol-3-yl)-4,4-dimethyl-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)methyl)hydrazine-1,2-dicarboxylate

(3r): This compound was prepared by the general procedure described above and was obtained as a yellowish solid in 81% yield: R_f = 0.41 (hexane : ethyl acetate = 4:1); M_p =

96.0-97.8 °C; 1H NMR (400 MHz, $CDCl_3$): δ 8.49-8.51 (m, 1H), 8.12 (s, 1H), 7.89 (s, 1H), 7.35-7.41 (m, 2H), 7.24-7.32 (m, 4H), 6.83-6.87 (m, 1H), 5.65-6.38 (m, 1H), 4.10-4.38 (m, 1H), 3.75-4.08 (m, 1H), 3.02-3.62 (m, 1H), 1.71 (s, 9H), 1.61 (s, 3H), 1.35-1.45 (m, 21H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 151.6, 149.7, 144.9, 135.2, 129.2, 129.1, 125.2, 123.5, 123.3, 119.4, 119.1, 114.8, 113.8, 112.9, 84.4, 81.4, 66.8, 50.4, 47.9, 28.2, 27.9, 27.3, 19.2 ppm; FTIR (KBr, neat): ν 1735, 1597, 1155, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $C_{35}H_{47}N_5O_6H^+$ 634.3605, found 634.3599.

Di-*tert*-butyl-1-(3a-methyl-1,3-diphenyl-1,3a,4,5,6,6a-

hexahydrocyclopenta[c]pyrazol-6-yl)hydrazine-1,2-dicarboxylate (3s): This

compound was prepared by the general procedure described above and was obtained as a white solid in 99% yield (anti/syn > 20:1): R_f = 0.43 (hexane :

ethyl acetate = 4:1); M_p = 167.7-169.0 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.82-7.84 (m, 2H), 7.34-7.38 (m, 2H), 7.25-7.31 (m, 5H), 6.81-6.84 (m, 1H), 6.03-6.42 (m, 1H), 4.06-4.75 (m, 2H), 2.30-2.44 (m, 1H), 2.15-2.22 (m, 1H), 1.93-2.08 (m, 1H), 1.79-1.92 (m, 1H), 1.58 (s, 3H), 1.51 (s, 9H), 1.41 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 154.1, 152.2, 144.1, 131.7, 129.1, 128.5, 128.0, 126.3, 119.1, 113.3, 81.9, 81.6, 65.7, 58.8, 37.0, 30.8, 28.2, 28.2, 24.6

ppm; FTIR (KBr, neat): ν 1735, 1676, 1597, 1494, 1242, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{38}\text{N}_4\text{O}_4\text{H}^+$ 507.2971, found 507.2993.

Di-*tert*-butyl-1-(3a-allyl-1,3-diphenyl-1,3a,4,5,6,6a-

hexahydrocyclopenta[c]pyrazol-6-yl)hydrazine-1,2-dicarboxylate (3t): This

compound was prepared by the general procedure described above and was obtained as a white solid in 99% yield (anti/syn > 20:1); R_f = 0.43 (hexane : ethyl acetate = 4:1); M_p = 106.4-107.3 $^{\circ}\text{C}$; ^1H NMR (400

MHz, CDCl_3): δ 7.82-7.83 (m, 2H), 7.33-7.37 (m, 2H), 7.25-7.30 (m, 5H), 6.81-6.84 (m, 1H), 6.40 (br, 1H), 5.46-5.56 (m, 1H), 4.92-5.04 (m, 2H), 4.26-4.75 (m, 2H), 2.75-3.08 (m, 1H), 2.25-2.64 (m, 2H), 2.12-2.25 (m, 1H), 1.75-2.03 (m, 2H), 1.25-1.55 (m, 18H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.3, 154.1, 150.0, 143.8, 133.8, 132.0, 129.1, 128.5, 128.0, 126.2, 119.0, 118.5, 113.4, 81.9, 81.6, 73.0, 65.8, 63.0, 41.3, 35.8, 30.4, 28.3, 28.2 ppm; FTIR (KBr, neat): ν 1739, 1678, 1597, 1365, 1350, 1155 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{40}\text{N}_4\text{O}_4\text{H}^+$ 533.3128, found 533.3123.

Di-*tert*-butyl-1-(3a-benzyl-1,3-diphenyl-1,3a,4,5,6,6a-

hexahydrocyclopenta[c]pyrazol-6-yl)hydrazine-1,2-dicarboxylate (3u): This

compound was prepared by the general procedure described above and was obtained as a white solid in 99% yield (anti/syn > 20:1); R_f = 0.42 (hexane : ethyl

acetate = 4:1); M_p = 170.1-171.7 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 7.90-7.92 (m, 2H), 7.40-7.44 (m, 2H), 7.32-7.35 (m, 1H), 6.89-7.21 (m, 9H), 6.74-6.78 (m, 1H), 6.21 (br, 1H), 4.60-5.26 (m, 1H), 4.32-4.57 (m, 1H), 3.21-3.75 (m, 1H), 2.78-3.08 (m, 1H), 2.23-2.64 (m, 2H), 1.75-2.03 (m, 2H), 1.55 (s, 9H), 1.39 (s,

9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.3, 154.1, 149.8, 143.7, 137.1, 132.3, 129.6, 128.9, 128.6, 128.1, 128.0, 126.6, 126.3, 118.9, 113.3, 81.8, 81.7, 72.7, 66.0, 63.9, 42.6, 35.9, 29.9, 29.8, 28.3, 28.1 ppm; FTIR (KBr, neat): ν 1735, 1674, 1597, 1494, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{35}\text{H}_{42}\text{N}_4\text{O}_4\text{H}^+$ 583.3284, found 583.3282.

Di-tert-butyl-1-(3a-methyl-1,3-diphenyl-3a,4,5,6,7,7a-hexahydro-1H-

indazol-7-yl)hydrazine-1,2-dicarboxylate (3v): This compound was prepared

by the general procedure described above and was

obtained as a white solid in 98% yield (anti/syn > 20:1):

R_f = 0.41 (hexane : ethyl acetate = 4:1); Mp = 90.2-

91.6 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 7.68-7.69 (m,

2H), 7.36-7.38 (m, 3H), 7.21-7.26 (m, 4H), 6.75-6.86 (m, 1H), 4.71-5.79 (m,

1H), 3.61-4.39 (m, 1H), 2.38-2.42 (m, 1H), 1.75-2.02 (m, 1H), 1.53-1.68 (m,

1H), 1.02-1.52 (m, 24H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 155.5, 153.7,

145.7, 132.7, 129.2, 128.4, 126.6, 119.6, 115.0, 81.1, 69.3, 52.4, 31.2, 28.2,

28.1, 25.9, 22.1 ppm; FTIR (KBr, neat): ν 1735, 1674, 1597, 1494, 1143 cm^{-1} ;

HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{40}\text{N}_4\text{O}_4\text{H}^+$ 521.3128, found 521.3127.

Di-tert-butyl-1-(3a-benzyl-1,3-diphenyl-3a,4,5,6,7,7a-hexahydro-1H-

indazol-7-yl)hydrazine-1,2-dicarboxylate (3w): This compound was prepared

by the general procedure described above and was

obtained as a white solid in 99% yield (anti/syn >

20:1): R_f = 0.41 (hexane : ethyl acetate = 4:1); Mp =

90.7-92.7 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 7.51-

7.72 (m, 2H), 7.05-7.42 (m, 12H), 6.81-6.85 (m, 1H), 4.80-5.65 (m, 1H), 4.02-

4.55 (m, 1H), 2.93-3.08 (m, 1H), 2.83-2.93 (m, 1H), 2.37-2.48 (m, 1H), 1.52-

1.80 (m, 2H), 1.12-1.45 (m, 21H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 155.8, 154.1, 153.6, 145.3, 136.7, 133.0, 130.7, 129.3, 128.3, 126.8, 119.8, 119.6, 114.6, 113.9, 81.1, 80.8, 66.3, 65.6, 57.3, 55.6, 44.2, 28.1, 28.0, 27.2, 21.8 ppm; FTIR (KBr, neat): ν 1735, 1674, 1597, 1494, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{36}\text{H}_{44}\text{N}_4\text{O}_4\text{H}^+$ 597.3441, found 597.3436.

Di-tert-butyl-1-(1,3-diphenyl-3a,4,5,6,7,7a-hexahydro-1H-indazol-7-

yl)hydrazine-1,2-dicarboxylate (3x): This compound was prepared by the

general procedure described above and was obtained as a white solid in 75% yield (anti/syn > 20:1); R_f = 0.42 (hexane : ethyl acetate = 4:1); Mp = 82.4-84.4 $^{\circ}\text{C}$; ^1H

NMR (400 MHz, CDCl_3): δ 7.62-7.64 (m, 2H), 7.33-7.40 (m, 3H), 7.26-7.31 (m, 4H), 6.82-6.93 (m, 1H), 5.45-6.21 (m, 1H), 4.15-4.79 (m, 1H), 3.61-3.82 (m, 1H), 1.71-1.95 (m, 3H), 1.22-1.63 (m, 22H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.0, 153.8, 153.6, 145.8, 132.6, 129.3, 129.0, 128.5, 128.5, 127.6, 127.0, 126.6, 120.8, 116.5, 81.8, 81.3, 62.8, 54.4, 45.7, 29.7, 28.2, 27.9, 27.1, 23.8 ppm; FTIR (KBr, neat): ν 1735, 1714, 1674, 1597, 1494, 1242, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{38}\text{N}_4\text{O}_4\text{H}^+$ 507.2971, found 507.2969.

Di-tert-butyl-1-((4-methyl-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-

yl)methyl)hydrazine-1,2-dicarboxylate (3y): This compound was prepared by

the general procedure described above and was obtained as a yellowish solid in 85% yield (anti/syn > 20:1); R_f = 0.45 (hexane : ethyl acetate = 4:1); Mp

=78.1-79.5 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 7.76-7.78 (m, 2H), 7.35-7.40 (m, 2H), 7.24-7.32 (m, 3H), 7.20 (m, 2H), 6.79-6.83 (m, 1H), 6.28-6.46 (m, 1H), 4.32 (m, 1H), 3.55-3.63 (m, 3H), 1.42-1.48 (m, 18H), 1.27-1.26 (m, 3H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 155.5, 154.9, 153.1, 144.1, 132.0, 129.3, 129.0, 128.6, 128.5, 126.4, 126.1, 119.0, 113.0, 82.3, 81.5, 65.7, 49.5, 49.3, 43.4, 28.2, 18.1 ppm; FTIR (KBr, neat): ν 1735, 1674, 1597, 1494, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{27}\text{H}_{36}\text{N}_4\text{O}_4\text{H}^+$ 481.2815, found 481.2814.

Di-*tert*-butyl-1-((1,3,4-triphenyl-4,5-dihydro-1H-pyrazol-5-

yl)methyl)hydrazine-1,2-dicarboxylate (3z): This compound was prepared by

^1H NMR (400 MHz, CDCl_3): δ 7.67-7.69 (m, 2H), 7.40-7.49 (m, 12H), 6.78-6.92 (m, 1H), 6.08-6.62 (m, 1H), 4.60-4.81 (m, 1H), 4.42-4.57 (m, 1H), 3.83-4.05 (m, 1H), 3.41-3.75 (m, 1H), 1.42 (s, 18H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 155.5, 154.7, 150.5, 149.8, 144.0, 140.2, 132.1, 129.4, 129.2, 128.5, 127.4, 126.3, 119.3, 113.2, 82.7, 81.7, 81.3, 67.7, 55.1, 50.8, 28.1 ppm; FTIR (KBr, neat): ν 1735, 1674, 1597, 1494, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{32}\text{H}_{38}\text{N}_4\text{O}_4\text{H}^+$ 543.2971, found 543.2971.

Di-*tert*-butyl-1-((3-cyclohexyl-4-methyl-1-phenyl-4,5-dihydro-1H-pyrazol-

5-yl)methyl)hydrazine-1,2-dicarboxylate (3a'): This compound was

7.19-7.23 (m, 2H), 7.02-7.09 (m, 2H), 6.73-6.77 (m, 1H), 6.01-6.45 (m, 1H), 3.83-4.05 (m, 1H), 3.21-3.75 (m, 2H), 2.95-3.15 (m, 1H), 2.31-2.36 (m, 1H), 1.58-1.98 (m, 6H), 1.23-1.49 (m, 22H), 1.15 (d, 3H, J = 7.1 Hz) ppm; ^{13}C NMR

(100 MHz, CDCl₃): δ 161.9, 161.0, 155.5, 154.7, 145.6, 129.1, 129.0, 118.2, 112.7, 82.2, 81.4, 81.1, 65.4, 50.0, 45.0, 37.5, 31.9, 30.2, 28.1, 26.3, 26.1, 26.0, 17.7 ppm; FTIR (KBr, neat): ν 1735, 1674, 1597, 1494, 1242, 1143 cm⁻¹; HRMS (ESI, m/z): calcd. for C₂₇H₄₂N₄O₄H⁺ 487.3284, found 487.3280.

Di-tert-butyl-1-(1-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-3-

phenylpropyl)hydrazine -1,2-dicarboxylate (3b'): This compound was

prepared by the general procedure described above and was obtained as a yellowish solid in 70% yield (*syn* / *anti* = 31:69); R_f = 0.46 (hexane : ethyl acetate = 4:1); Mp = 71.2-72.8 °C; ¹H NMR (400 MHz, CDCl₃): (syn) δ 7.73-7.74 (m, 2H), 7.05-7.40 (m, 12H), 6.78-6.85 (m, 1H), 5.63-6.15 (m, 1H), 4.05-4.85 (m, 2H), 3.15-3.53 (m, 2H), 2.31-3.03 (m, 2H), 2.01-2.19 (m, 1H), 1.61-1.95 (m, 1H), 1.05-1.50 (m, 18H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 156.3, 155.7, 155.1, 141.5, 132.5, 129.2, 129.1, 128.9, 128.6, 128.5, 126.0, 125.8, 119.0, 113.6, 113.2, 112.9, 81.9, 81.4, 61.9, 33.2, 32.8, 30.6, 28.3, 28.1, 27.8 ppm; ¹H NMR (400 MHz, CDCl₃): (anti) δ 7.59-7.73 (m, 2H), 6.95-7.43 (m, 12H), 6.79-6.89 (m, 1H), 5.55-6.15 (m, 1H), 4.45-4.95 (m, 2H), 3.05-3.55 (m, 2H), 2.31-2.69 (m, 2H), 1.73-1.95 (m, 1H), 1.61-1.75 (m, 1H), 1.43-1.53 (m, 18H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 156.3, 155.7, 155.0, 154.9, 148.5, 148.0, 144.4, 141.5, 141.2, 140.4, 132.9, 132.7, 129.3, 129.1, 128.5, 128.4, 128.2, 125.9, 125.7, 119.2, 113.5, 113.2, 82.6, 81.8, 81.5, 62.1, 61.8, 54.8, 33.3, 32.3, 28.4, 28.2, 25.1 ppm; FTIR (KBr, neat): ν 1735, 1674, 1597, 1494, 1143 cm⁻¹; HRMS (ESI, m/z): calcd. for C₃₄H₄₂N₄O₄H⁺ 571.3284, found 571.3282.

Di-tert-butyl-1-((1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-

yl)(phenyl)methyl)hydrazine-1, 2-dicarboxylate (3c'): This compound was

prepared by the general procedure described above

and was obtained as a yellowish solid in 53% yield

(dr = 4:1): R_f = 0.43 (hexane : ethyl acetate = 4:1);

^1H NMR (400 MHz, CDCl_3): (major) δ 7.65-7.83 (m, 2H), 7.42-7.63 (m, 2H), 6.95-7.41 (m, 10H), 6.75-6.88 (m, 1H), 6.17 (br, 1H), 5.31-5.72 (m, 1H), 4.93-5.13 (m, 1H), 3.11-3.85 (m, 2H), 1.15-1.41 (m, 18H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 155.0, 145.6, 138.0, 132.6, 129.0, 128.9, 128.8, 128.4, 128.4, 127.7, 126.2, 125.9, 119.7, 114.1, 82.0, 81.0, 63.3, 62.0, 36.8, 28.2, 28.0 ppm; FTIR (KBr, neat): ν 1735, 1714, 1674, 1597, 1494, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{32}\text{H}_{38}\text{N}_4\text{O}_4\text{H}^+$ 543.2971, found 543.2974.

Di-tert-butyl-1-(1,3,5-triphenyl-4,5-dihydro-1H-pyrazol-4-yl)hydrazine-1,2-

dicarboxylate (3d'): This compound was prepared by the

general procedure described above and was obtained as a

yellow solid in 51% yield (dr > 20:1): R_f = 0.58 (hexane : ethyl

acetate = 4:1); Mp = 152.5-153.2 $^\circ\text{C}$; ^1H NMR (400 MHz,

CDCl_3): δ 7.68-7.76 (m, 2H), 7.28-7.43 (m, 8H), 7.13-7.21 (m, 2H), 7.05-7.11 (m, 2H), 6.73-6.85 (m, 1H), 6.02-6.20 (m, 1H), 5.51-5.87 (m, 2H), 1.46-1.51 (m, 9H), 1.16-1.38 (m, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 155.4, 154.2, 143.6, 142.4, 138.9, 131.6, 129.2, 129.1, 129.0, 128.9, 128.8, 128.6, 128.5, 128.5, 127.7, 127.6, 126.1, 126.0, 125.6, 125.4, 119.4, 113.3, 113.2, 82.2, 81.5, 70.0, 68.2, 67.9, 28.3, 28.1, 27.8, 27.7 ppm; FTIR (KBr, neat): ν 1735, 1674, 1597, 1504, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{31}\text{H}_{36}\text{N}_4\text{O}_4\text{H}^+$ 529.2815, found 529.2820.

Di-tert-butyl-1-((1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-

yl)methyl)hydrazine-1,2-dicarboxylate (3e'): This compound was prepared

by the general procedure described above and was

obtained as a yellowish solid in 52% yield: $R_f = 0.45$

(hexane : ethyl acetate = 4:1); $M_p = 72.9-74.2\text{ }^\circ\text{C}$; ^1H

NMR (400 MHz, CDCl_3): δ 7.71-7.73 (m, 2H), 7.15-7.43 (m, 7H), 6.78-6.86 (m, 1H), 6.12-6.55 (m, 1H), 4.59-4.78 (m, 1H), 3.72-3.83 (m, 1H), 3.12-3.65 (m, 3H), 1.39-1.49 (m, 18H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 155.6, 155.3, 148.6, 148.1, 144.4, 132.8, 129.3, 128.7, 128.5, 125.8, 119.1, 113.1, 82.5, 81.6, 81.3, 58.3, 51.0, 37.1, 28.2, 28.0 ppm; FTIR (KBr, neat): ν 1735, 1714, 1674, 1597, 1494, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{34}\text{N}_4\text{O}_4\text{H}^+$ 467.2658, found 467.2657.

Di-tert-butyl-1-(1-(5-methyl-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-3-

phenylpropyl) hydrazine-1,2-dicarboxylate (3f'): This compound was

prepared by the general procedure described above and

was obtained as a yellow oil in 51% yield (dr = 45:55):

$R_f = 0.45$ (hexane : ethyl acetate = 4:1); ^1H NMR (400

MHz, CDCl_3): δ 7.64-7.72 (m, 2H), 6.90-7.64 (m, 13H), 5.63-6.35 (m, 1H), 4.65-5.12 (m, 1H), 3.45-3.73 (m, 1H), 2.46-3.15 (m, 3H), 1.85-2.19 (m, 2H), 1.41-1.62 (m, 21H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.1, 155.6, 155.5, 147.8, 147.7, 147.3, 144.4, 144.2, 141.0, 140.4, 133.3, 133.1, 132.8, 129.3, 129.0, 128.7, 128.7, 128.5, 128.5, 128.5, 128.3, 128.3, 126.3, 126.2, 125.7, 125.5, 125.4, 122.0, 121.1, 119.2, 117.9, 117.9, 113.9, 82.4, 81.4, 72.3, 72.1, 72.0, 59.6, 59.1, 53.5, 42.9, 41.3, 33.2, 32.4, 28.5, 28.3, 28.2, 28.1, 26.9, 26.5 ppm; FTIR (KBr, neat): ν 1735, 1674, 1597, 1494, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{35}\text{H}_{44}\text{N}_4\text{O}_4\text{H}^+$ 585.3441, found 585.3445.

Di-*tert*-butyl-1-((1,3-diphenyl-3a,4,5,6,7,7a-hexahydro-1H-indazol-7a-

yl)methyl)hydrazine-1,2-dicarboxylate (3g'): This compound was prepared

by the general procedure described above and was obtained as a yellow oil in 41% yield: $R_f = 0.45$ (hexane : ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 7.68-7.75 (m, 2H), 7.21-7.43 (m, 7H), 6.85-6.98 (m, 1H), 5.90-6.35

(m, 1H), 3.22-4.31 (m, 3H), 2.15-2.38 (m, 1H), 1.75-1.95 (m, 2H), 1.20-1.51 (m, 23H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.1, 155.4, 154.1, 153.2, 144.8, 132.1, 129.3, 128.9, 128.5, 128.4, 126.2, 125.6, 118.6, 116.4, 115.1, 82.3, 81.2, 80.6, 71.9, 71.3, 53.5, 47.9, 47.2, 29.7, 28.2, 28.2, 27.8, 27.6, 23.7, 20.7, 19.8, 19.1 ppm; FTIR (KBr, neat): ν 1735, 1741, 1674, 1597, 1494, 1303, 1242, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{40}\text{N}_4\text{O}_4\text{H}^+$ 521.3128, found 521.3125.

Di-*tert*-butyl-1-(2,4-diphenyl-2,3-diazabicyclo[3.3.1]non-3-en-8-

yl)hydrazine-1,2-dicarboxylate (3h'): This compound was prepared by the

general procedure described above and was obtained as a yellowish solid in 72% yield (dr > 20:1): $R_f = 0.43$ (hexane : ethyl acetate = 4:1); $\text{Mp} = 106.8\text{-}108.0$

$^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 7.85-7.93 (m, 2H), 7.68-7.83 (m, 2H), 7.35-7.43 (m, 4H), 7.28-7.33 (m, 1H), 6.91-6.94 (m, 1H), 6.30-6.55 (m, 1H), 4.22-4.81 (m, 2H), 3.18 (br, 1H), 1.95-2.25 (m, 2H), 1.79-1.89 (m, 1H), 1.65-1.75 (m, 2H), 1.51-1.62 (m, 19H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.3, 156.2, 155.5, 155.2, 146.6, 141.6, 137.5, 129.0, 128.3, 127.3, 127.2, 124.4, 119.6, 113.8, 113.7, 81.8, 81.3, 55.4, 55.1, 54.6, 50.9, 28.2, 28.2, 28.1, 27.8, 27.2, 26.4, 21.3, 21.2 ppm; FTIR (KBr, neat): ν 1735, 1674, 1597, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{38}\text{N}_4\text{O}_4\text{H}^+$ 507.2971, found 507.2970.

Di-tert-butyl-1-(1,3-diphenyl-4,4a,5,6,7,7a-hexahydro-1H-

cyclopenta[c]pyridazin-7-yl)hydrazine-1,2-dicarboxylate (3i'): This

compound was prepared by the general procedure described above and was obtained as a yellow oil in 35% yield (dr > 20:1): $R_f = 0.41$ (hexane : ethyl acetate =

4:1); ^1H NMR (400 MHz, CDCl_3): δ 7.75-7.85 (m, 2H), 7.26-7.43 (m, 7H), 6.85-6.94 (m, 1H), 5.20-6.05 (m, 1H), 4.21-4.81 (m, 2H), 2.62-2.80 (m, 1H), 2.35-2.55 (m, 1H), 2.01-2.35 (m, 3H), 1.51-1.62 (m, 2H), 1.15-1.50 (m, 18H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.3, 153.9, 148.1, 141.2, 138.7, 129.1, 128.3, 127.7, 124.7, 120.3, 114.6, 81.6, 81.2, 81.0, 57.2, 30.4, 28.1, 28.1, 24.8, 24.0, 22.7 ppm; FTIR (KBr, neat): ν 1735, 1714, 1674, 1597, 1494, 1303, 1242, 1143 cm^{-1} ; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{38}\text{N}_4\text{O}_4\text{H}^+$ 507.2971, found 507.2968.

(3-tert-butyl-1-(4-methoxyphenyl)-5-methyl-4,5-dihydro-1H-pyrazol-5-

yl)methanol (5): This compound was prepared by the general procedure A described above and was obtained as a yellow oil in 45% yield: $R_f = 0.32$ (hexane : ethyl acetate = 3:1); ^1H NMR

(400 MHz, CDCl_3): δ 7.08 (d, 2H, $J = 8.9$ Hz, ArH), 6.83 (d, 2H, $J = 8.9$ Hz, ArH), 3.78 (s, 3H, OCH_3), 3.67 (d, 1H, $J = 11.4$

Hz, CH_2), 3.49-3.54 (m, 1H, CH_2), 3.18 (d, 1H, $J = 16.5$ Hz, CH_2), 2.59 (d, 1H, $J = 16.5$ Hz, CH_2), 2.47-2.49 (m, 1H, OH), 1.22 (s, 9H, 3CH_3), 0.80 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 162.0, 156.4, 138.6, 123.0, 114.0, 71.2, 66.4, 55.5, 42.6, 33.9, 28.2, 19.5 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2\text{H}^+$ 277.1916, found 277.1919.

(4,4-dimethyl-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)methanamine (4):

This compound was prepared by the procedure described above and was obtained as a colourless oil in 85% yield;

$R_f = 0.30$ (methanol : dichloromethane = 1:20); ^1H NMR (400 MHz, CDCl_3): δ 7.26-7.40 (m, 2H, ArH), 7.22-7.36 (m, 7H, ArH), 6.84-6.85 (m, 1H, ArH), 3.85-3.95 (m, 1H), 3.16-3.19 (m, 1H), 2.91-2.94 (m, 1H), 1.52 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.05 (br, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.0, 144.9, 132.5, 129.2, 128.4, 128.4, 126.9, 119.3, 114.1, 73.7, 49.2, 39.7, 28.4, 19.1 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{H}^+$ 280.1814, found 280.1814.

3a-methyl-1,3-diphenyl-1,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrazol-6-

amine: This compound was prepared by the procedure described above and

was obtained as a colourless oil in 87% yield; $R_f = 0.31$

(methanol : dichloromethane = 1:20); ^1H NMR (400 MHz, CDCl_3): δ 7.85-7.87 (m, 2H, ArH), 7.20-7.38 (m, 7H, ArH), 6.82-6.85 (m, 1H, ArH), 3.89-3.97 (m, 1H), 3.50-3.60 (m, 1H), 2.46-2.48 (m, 1H), 2.19-2.26 (m, 1H), 1.85-1.95 (m, 1H), 1.74-1.83 (m, 1H), 1.67 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 152.4, 144.3, 131.7, 129.2, 128.5, 128.1, 126.3, 118.8, 112.8, 81.7, 59.0, 58.4, 36.3, 34.4, 26.7 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{H}^+$ 292.1814, found 292.1823.

1,3-diphenyl-5-(3-phenyl-1-(2-(propan-2-ylidene)hydrazinyl)propyl)-4,5-

dihydro-1H-pyr azole: This compound was prepared by the procedure

described above and was obtained as a colourless oil in

80% yield; $R_f = 0.41$ (hexane : ethyl acetate = 4:1); ^1H

NMR (400 MHz, CDCl_3): δ 7.65-7.82 (m, 2H, ArH),

7.06-7.39 (m, 12H, ArH), 6.81-6.85 (m, 1H, ArH), 4.82-

4.87 (m, 1H), 4.42 (br, 1H), 3.73-3.76 (m, 1H), 3.25-3.28 (m, 2H), 2.64-2.68 (m, 2H), 1.85 (s, 3H, CH₃), 1.75-1.83 (m, 1H), 1.60-1.70 (m, 1H), 1.54 (s, 3H, CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 148.5, 145.8, 145.1, 141.8, 132.8, 129.2, 128.5, 128.4, 128.4, 125.9, 125.8, 118.9, 113.5, 62.2, 59.7, 33.9, 33.3, 29.3, 25.3, 15.3 ppm; HRMS (ESI, m/z): calcd. for C₂₇H₃₀N₄H⁺ 411.2549, found 411.2511.

4-methyl-1,3-diphenyl-5-((2-(propan-2-ylidene)hydrazinyl)methyl)-4,5-

dihydro-1H-pyrazole: This compound was prepared by the procedure

described above and was obtained as a colourless oil in

88% yield; R_f = 0.43 (hexane : ethyl acetate = 4:1); ¹H

NMR (400 MHz, CDCl₃): δ 7.74-7.75 (m, 2H, ArH),

7.34-7.38 (m, 2H, ArH), 7.25-7.30 (m, 3H, ArH), 7.19-7.23 (m, 2H, ArH),

6.80-6.83 (m, 1H, ArH), 4.21-4.23 (m, 1H), 3.61-3.66 (m, 1H), 3.40-3.41 (m,

2H), 1.64 (s, 3H, CH₃), 1.47 (s, 3H, CH₃), 1.25 (d, *J* = 7.2 Hz, 3H, CH₃) ppm;

¹³C NMR (100 MHz, CDCl₃): δ 153.1, 146.1, 144.5, 132.0, 129.3, 128.6, 128.4,

126.0, 118.9, 113.2, 67.9, 51.3, 43.6, 24.9, 18.7, 15.4 ppm; HRMS (ESI, m/z):

calcd. for C₂₀H₂₄N₄H⁺ 321.2079, found 321.2084.

tert-butyl

((4-methyl-1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-

yl)methyl)carbamate: This compound was prepared by the procedure

described above and was obtained as a colourless oil in 81% yield; R_f = 0.53

(hexane : ethyl acetate = 4:1); ¹H NMR (400 MHz,

CDCl₃): δ 7.73-7.75 (m, 2H, ArH), 7.34-7.38 (m, 2H,

ArH), 7.27-7.31 (m, 3H, ArH), 7.21-7.23 (m, 2H, ArH),

6.81-6.85 (m, 1H, ArH), 4.70-4.79 (m, 1H), 4.10-4.20 (m, 1H), 3.49-3.59 (m,

2H), 3.09-3.13 (m, 1H), 1.36 (s, 9H, 3CH₃), 1.25 (d, *J* = 7.2 Hz, 3H, CH₃) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 156.4, 152.7, 144.4, 131.9, 129.4, 128.6, 128.5, 126.1, 119.1, 113.1, 79.6, 67.2, 43.4, 41.0, 28.3, 18.8 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_2\text{H}^+$ 366.2182, found 366.2196.

Reference:

1. Wang, R.-B.; Lim, C.-H.; Tan, C.-H.; Lim, B.-K.; Sim, K.-Y.; Loh, T.-P. *Tetrahedron: Asymmetry* **1995**, 6, 1825.
2. Jiang, D. H.; Peng, J. S.; Chen, Y. W. *Org. Lett.* **2008**, 10, 1695.
3. Pichlmair, S.; de Lera Ruiz, M.; Basu, K.; and Paquette, L. A. *Tetrahedron*. **2006**, 62 5178–5194
4. Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, 133, 11402.
5. Li, H.; Loh, T.-P. *J. Am. Chem. Soc.*, **2008**, 130, 7194–7195
6. Fernández-Mateos, A.; Teijón, P. H.; Burón, L. M.; Clemente, R. R.; González, R. R. *J. Org. Chem.* **2007**, 72, 9973.

CHAPTER 3

*Palladium-catalyzed carbon-carbon bond cleavage
reactions, using aerobic oxygen as mild oxidant:
Formation of 1H-pyrazole.*

3.1 Introduction

The exploration to activate carbon-carbon single bonds has become a great interest to organic chemists.³⁸ Recently, transition metal catalysis has provided various catalytic methods toward C-C bond cleavage. In this context, three basic reactions would be focused as follow: 1) decarboxylation; 2) decarbonylation; 3) β -carbon elimination. (Scheme 3.1)

1) Decarboxylation

2) Decarbonylation

3) β -carbon elimination

Scheme 3.1 Three types of carbon-carbon bond cleavage reactions

Decarboxylation:

³⁸ (a) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (b) Jun, C. *Chem. Soc. Rev.* **2004**, *33*, 610. (c) Satoh, T.; Miura, M. *Synthesis* **2010**, *20*, 3395. (d) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740. (e) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (f) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. (g) Rodríguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. (h) Cornella, J.; Larrosa, I. *Synthesis* **2012**, *44*, 653. (i) Ruhland, K. *Eur. J. Org. Chem.* **2012**, 2683. (j) Gooßen, L. J.; Gooßen, K. *Top Organomet. Chem.* **2013**, *44*, 121. (k) Nishimura, T.; Uemura, S. *Synlett* **2004**, *2*, 0201.

In early reports³⁹, decarboxylations of some carboxylic acids under copper, silver or mercury catalysis had very narrow substrate scopes and usually required harsh conditions and/or high catalyst loadings (Scheme 3.2). However, a seminal report of decarboxylation of benzoic acids employed

Scheme 3.2 Copper(I) oxide catalyzed decarboxylation of aromatic carboxylic acids

copper(I) oxide as catalysts in a solvent mixture constituting NMP and quinoline has been presented in 2007.⁴⁰ Various functional groups, including oxo, formyl, nitro, cyano and hydroxyl groups in the *ortho*-, *meta*-, or *para*-positions of benzoic acids, were tolerated. Subsequent mechanism studies suggested that the reaction did not proceed *via* a radical process.

Silver salts were proven to be more efficient in decarboxylation reactions, especially for *ortho*-substituted benzoic acids. In 2010, Jafarpour has

Scheme 3.3 Silver carbonate catalyzed decarboxylation of coumarin 3-carboxylic acid

³⁹ (a) Shepard, A. F.; Winslow, N. R.; Johnson, J. R. *J. Am. Chem. Soc.* **1930**, 52, 2083. (b) Chodowska-Palicka J.; Nilsson, M. *Acta Chem. Scand.* **1970**, 44, 3353. (c) Cairncross, A.; Roland, J. R.; Henderson, R. M.; Sheppard, W. F. *J. Am. Chem. Soc.* 1970, 92, 3187. (d) Cohen, T.; Schambach, R. A. *J. Am. Chem. Soc.* 1970, 92, 3189. (e) Gilman H.; Wright, G. F. *J. Am. Chem. Soc.* **1933**, 55, 3302.

⁴⁰ Goossen, L. J.; Thiel, W. R.; Rodríguez, N.; Linder C.; Melzer, B. *Adv. Synth. Catal.* **2007**, 349, 2241.

presented a silver carbonate-catalyzed decarboxylation of coumarin-3-carboxylic acids, delivering the products in good to excellent yields (Scheme 3.3).⁴¹

In 2007, a palladium salt catalyzed aromatic decarboxylation has been developed by Kozlowski in the presence of excess amounts of trifluoroacetic acid (Scheme 3.4).⁴² A plausible mechanism of this reaction that was proposed, involved the formation of a four-member transition state (**C**), a subsequent insertion with palladium species onto aryl rings, resulted in a loss of carbon dioxide, and a protonation to deliver the

Proposed mechanism:

Scheme 3.4 Palladium-catalyzed decarboxylation of aryl rings and proposed mechanism

⁴¹ Jafarpour, F.; Jalalimanesh, N.; Olia, M. B. A.; Kashani, A. O. *Tetrahedron* **2010**, 66, 9508.

⁴² Dickstein, J. S.; Mulrooney, C. A.; O'Brien, E. M.; Morgan, B. J.; Kozlowski, M. C. *Org. Lett.* **2007**, 9, 2441.

desired products, regenerating the palladium (II) complexes. Rather than a necessity in catalytic cycle, trifluoroacetic acid was proven to increase the reaction efficiency.

Additional decarboxylation reactions were also presented with other heavy metals (rhodium⁴³ and gold⁴⁴). These reactions always occurred under mild conditions, but usually with limited substrate scopes.

Decarbonylation:

Transition-metal catalyzed decarbonylation reactions have been widely studied recently, and have proven to be useful for the reduction of a variety of aromatic rings. However, carbon monoxide was always extruded as the byproduct together with the desired products, which is a significant drawback of these reactions.

In 2011, Li and coworkers described a rhodium-catalyzed oxidative decarbonylation with aromatic aldehydes, employing excess TBP as the oxidants.⁴⁵ By choosing different types of phosphine ligands, either biaryls or diarylketones were afforded respectively in moderate to good yields (Scheme 3).

(1) 1.25 mol % [(CO)₂RhCl]₂, 6 mol % PPh₃, 2.5 equiv TBP, benzene, 150 °C;

(2) 1.25 mol % [(CO)₂RhCl]₂, 3 mol % dppe, 2.5 equiv TBP, benzene, 160 °C;

Scheme 3.5 Rhodium-catalyzed oxidative decarbonylation of aromatic aldehydes to generate biaryls and diarylketones selectively

⁴³ Sun, Z. M.; Zhang, J.; Zhao, P. J. *Org. Lett.* **2010**, *12*, 992.

⁴⁴ Dupuy, S.; Lazreg, F.; Slawin, A. M. Z.; Cazin, C. S. J.; Nolan, S. P. *Chem. Comm.* **2011**, *47*, 5455.

⁴⁵ Yang, L.; Zeng, T.; Shuai, Q.; Guo, X.; Li, C. *Chem. Commun.* **2011**, *47*, 2161.

Another rhodium-catalyzed decarbonylation was presented by Shi's group in 2012 (Scheme 3.6).⁴⁶ The reaction could tolerate various functional

Scheme 3.6 Rhodium catalyzed decarbonylation of arenes

groups (halides, methoxy, hydroxyl and methyl, *etc*), delivering the desired products in moderate to good yields. In this case, one drawback was the requirement of a nitrogen-containing directing group, which limited the substrate scopes.

Alternatively, palladium salts were also explored in decarbonylation reactions. A ligand-free palladium catalyzed aromatic decarbonylation was reported with a wide substrate scope by Maiti's group in 2012 (Scheme 3.7).⁴⁷ The reaction proceeded best with palladium acetate and molecular sieves, giving decarbonylated products in moderate to good yields.

Scheme 3.7 Palladium acetate catalyzed decarbonylation of aromatic aldehydes

β-Carbon elimination:

In recent years, a series of β-carbon elimination reactions have been reported, which all appeared to follow the same mechanism.⁴⁸ These reactions have been developed significantly and applied not only in the ring opening

⁴⁶ Lei, Z.; Li, H.; Li, Y.; Zhang, X.; Chen, K.; Wang, X.; Sun, J.; Shi, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 2690.

⁴⁷ Modak, A.; Deb, A.; Patra, T.; Rana, S.; Maity, S.; Maiti, D. *Chem. Commun.*, 2012, 48, 4253.

⁴⁸ Nishimura, T.; Uemura, S. *Synlett* **2004**, 2, 201.

reaction, but also in acyclic systems. In this context, we only would be discussing only the β -carbon elimination associated with acyclic systems.

Owing to their inherent reactivity to form stable intermediates, tertiary alcohols have been widely utilized in β -carbon elimination reactions. In 1998, the initial example of a ruthenium-catalyzed β -carbon elimination employing tertiary homoallyl alcohols has been presented by Kondo and Mitsudo (Scheme 3.8).⁴⁹ The authors suggested a β -allyl elimination mechanism through a π -allylruthenium intermediate (**A**).

Scheme 3.8 Ruthenium-catalyzed C-C cleavage reactions with tertiary homoallyl alcohols

Additional reports following β -carbon elimination mechanism have been developed by utilizing other transition-metal catalysts. In 2001, Miura reported a palladium-catalyzed C-C bond cleavage reaction with α,α -disubstituted arylmethanol (Scheme 3.9).⁵⁰ The authors also proposed an enantioselective example. In presence of chiral ligands (*R*)-BINAP and palladium acetate, an enantioselective product was obtained in 83% yield, 63% ee. Later, a variety of phosphine ligands (PCy_3 , P(o-tolyl)_3 , P(1-Nap)_3 , $\text{P}(t$ -

⁴⁹ Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587.

⁵⁰ Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407.

Bu)₃⁵¹) have been applied in similar β -carbon elimination reactions employing palladium acetate as catalyst.

Scheme 3.9 Palladium acetate catalyzed C-C bond cleavage reaction with tertiary alcohols in the presence of phosphine ligands

In a similar mechanism, secondary or primary alcohols could also be applied in β -carbon elimination reactions. In 2011, Shi and coworkers have described a rhodium-catalyzed C-C bond cleavage reaction with secondary alcohols in the presence of moderate to excess amounts of silver carbonate as the oxidant (Scheme 3.10).⁵² Albeit the requirement of a directing group in the substrates, the reactions could yield the desired products in moderate to good yields with tolerance of different functional groups (halide, hydroxyl and alkyl groups). The mechanism of this reaction was proposed to be shown as following. Coordination of rhodium complexes with substrate was followed by subsequent β -carbon elimination, which was resulted in the release of benzaldehyde. An alkene insertion and β -H elimination then took place to afford the desired product.

⁵¹ (a) Terao, Y.; Wakui, H.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, 68, 5236. (b) Yokooji, A.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2004**, 60, 6757. (c) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, 219, 211.

⁵² Li, H.; Li, Y.; Zhang, X.; Chen, K.; Wang, X.; Shi, Z. *J. Am. Chem. Soc.* **2011**, 133, 15244.

Scheme 3.10 Rhodium catalyzed C-C bond cleavage reactions with secondary alcohols and proposed mechanism

Conclusion

In conclusion, transition-metal-catalyzed C-C bond cleavage represents an attractive approach to C-C single bonds activation with its potential applications in organic synthesis. Three common methodologies, including decarboxylation, decarbonylation and β -carbon elimination, have been studied over the past several decades. There is certainly room for further improvement in many of those methods, particularly regarding their generality and overall synthetic efficiency.

3.2 Our Strategy

In chapter 2, we have successfully developed a radical-initiated diamination of homoallylic hydrazones in the presence of acetic acid. In view of easy formation of C-X (X=N,O), we intended to explore the aminooxygenation of homoallylic hydrazones, owing to their importance as critical organic building blocks. After initial studies with palladium acetate, we have observed an aminooxygenation reaction and a subsequent C-C cleavage reaction, which led to the formation of 1*H*-pyrazole (Scheme 3.11).

Classical methods for synthesizing pyrazole scaffolds include: 1,3-dipolar cycloaddition of diazo structures with alkynes; and condensation of 1,3-dicarbonyls with hydrazines.⁵³ In spite of these existing methods, the development of novel methodologies for polysubstituted pyrazoles is still an attractive area for organic chemists.⁵⁴

Herein, we presented an easy access to 1*H*-pyrazole, using palladium acetate as catalyst and 1 atm air as the sole oxidant. The reaction was proposed to undergo a β -carbon elimination mechanism, which delivered the products in moderate to good yields.

⁵³ (a) Makino, K.; Kim, H. S.; Kurasawa, Y. *J. Heterocycl. Chem.* **1999**, *36*, 321. (b) Yet, L. in *Comprehensive Heterocyclic Chemistry III, Vol. 4* (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Oxford, **2008**, p. 1. (c) Fustero, S.; Simón-Fuentes, A.; Sanz-Cervera, J. F. *Org. Prep. Proced. Int.* **2009**, *41*, 253. (d) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (e) Dadiboyena, S., Nefzi, A. *Eur. J. Med. Chem.* **2011**, *46*, 5258.

⁵⁴ (a) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles, 2nd ed.*, Wiley & Sons: New York, **2004**, p. 179. (b) Mowbray, C. E.; Burt, C.; Corbau, R.; Gayton, S.; Hawes, M.; Perros, M.; Tran, I.; Price, D. A.; Quinton, F. J.; Selby, M. D.; Stupple, P. A.; Webster, R.; Wood, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5857. (c) Lahm, G. P.; Cordova, D.; Barry, J. D. *Bioorg. Med. Chem.* **2009**, *17*, 4127. (d) Mukherjee, R. *Coord. Chem. Rev.* **2000**, *203*, 151. (e) Kong, Y.; Tang, M.; Wang, Y. *Org. Lett.* **2014**, *16*, 576. (f) Hao, L.; Hong, J.; Zhu, J.; Zhan, Z. *Chem. Eur. J.* **2013**, *19*, 5715. (g) Zhang, J.; Shao, Y.; Wang, H.; Luo, Q.; Chen, J.; Xu, D.; Wan, X. *Org. Lett.* **2014**, *16*, 3312. (h) Yang, W.; Yu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 2501.

Scheme 3.11 Pd-catalyzed C-C cleavage reactions

3.3 Palladium-Catalyzed C-C Bond Cleavage Reaction of Allylic Hydrazones Using Aerobic Oxygen as the Sole Oxidant

3.3.1 Results and Discussion: Optimization of Reaction Conditions

In our initial experiment, (*E*)-1-phenyl-2-(2,2,5-trimethylhex-5-en-3-ylidene) hydrazine (**1a**) was tested with 5.0 mol% palladium acetate, 7.5 mol%

Table 3.1 Optimization of reaction conditions^a

entry	oxidant	time (h)	total yield(yield of 2a) (%) ^b	ratio (2a : 3a : 4a) (%) ^c
1	air	4	81(38)	47:37:16
2	O ₂	4	82(39)	48:40:12
3	Cu(OAc) ₂	24	<10	-
4	PhI(OAc) ₂	24	<10	-
5	K ₂ S ₂ O ₈	24	<10	-
6	^t BuOO ^t Bu	24	<10	-
7	BQ	24	<10	-
8 ^d	air	5	89(69)	78:15:7
9 ^e	air	2	87(52)	60:35:5
10	O ₂	5	93(73)	79:17:4
11 ^f	air	2	94(75)	80:15:5
12 ^g	air	2	94(72)	77:19:4
13 ^h	air	8	79(62)	78:18:4
14 ⁱ	air	24	<10	-

^aUnless noted otherwise, the reactions were carried out on a 0.15 mmol scale of **1a** with 5 equiv of HOAc, 7.5 mol% of 1,10-phenanthroline and 5 mol% of Pd(OAc)₂ in 1,2-dichloroethane (1.0 mL) at rt under 1 atm air. ^bThe yield of **2a**. ^cThe ratio of **2a/3a/4a** was determined by crude ¹H NMR. ^dPhCl/MeOH = 0.5 mL/0.5 mL. ^e15 equiv HOAc. ^fThe reaction at 40 °C. ^g10mol % of Pd(OAc)₂. ^h3mol % of Pd(OAc)₂. ⁱwithout Pd(OAc)₂.

1,10-phenanthroline and five equivalents of acetic acid under atmospheric oxygen (Table 3.1, entry 1). Among three products obtained in the reaction, **2a** was the major product in an acceptable yield. After screening a series of oxidants, atmospheric oxygen was chosen as the oxidants due to the efficiency, rapid availability and low cost (Table 3.1, entry 1-7). A mixture of

chlorobenzene and methanol was used as solvent to increase the yield (Table 3.1, entry 8). However, higher loading of Pd(OAc)₂ provided a slightly higher yield of the desired product **2a** (Table 3.1, entry 12, 13). We chose a medium loading of 5 mol% palladium catalyst as the model condition. The best result was given with 5 mol% palladium acetate and 7.5 mol% ligands, under 1 atm air at 40 °C in 2 h, using PhCl and MeOH as mixed solvent.

Screening of differently substituted hydrazones

Under the optimized conditions, the effect of the nitrogen protecting groups was investigated, including acetyl, benzoyl, benzyl and aromatic groups (Table 3.2). It was found out that only hydrazones with aromatic protecting groups were able to deliver desired products smoothly under the standard

Table 3.2 Screening of nitrogen protecting groups^{a, b}

entry	R ⁴	yield (%) ^c
1	C ₆ H ₅ (1a)	75 (2a)
2	4-OMe-C ₆ H ₄ (1b)	61 (2b)
3	4-Me-C ₆ H ₄ (1c)	73 (2c)
4	4-F-C ₆ H ₄ (1d)	75 (2d)
5	4-Cl-C ₆ H ₄ (1e)	60 (2e)
6	3-Me-C ₆ H ₄ (1f)	65 (2f)
7	3,4-OMe-C ₆ H ₃ (1g)	63 (2g)
8	3-Cl, 4-F-C ₆ H ₃ (1h)	72 (2h)
9	4-CN-C ₆ H ₄ (1i)	-
10	2-Me-C ₆ H ₄ (1j)	-

^aUnless noted otherwise, the reactions were carried out on a 0.15 mmol of **1** with HOAc (5.0 equiv), 1,10-phenanthroline (7.5 mol%) and Pd(OAc)₂ (5.0mol %) in PhCl:MeOH = 1:1 (0.25 mL:0.25 mL) at 40 °C under 1 atm air. ^bIn all cases, **3** and **4** were obtained in less than 20% yield. ^cIsolated yield of **2**.

conditions. Substrates with electron-withdrawing groups or electron-donating groups could both deliver the desired product in moderate yields (Table 3.2,

entry 2-6). Hydrazone with 4-OMe substituted phenyl also yielded the desired product in 61%, whose protecting group could be easily removed Table 3.2, entry 2). Moderate to good yields were also afforded by hydrazones with bulky protecting groups (Table 3.2, entry 7,8). However, no desired product was obtained with 4-CN substituted aromatic protecting hydrazone

Table 3.3 Palladium-catalyzed one-pot C-C bond cleavage reaction ^{a, b}

^aUnless noted otherwise, the reactions were carried out on a 0.15 mmol scale of **6**, and 0.225 mmol scale of PhNHNH₂ (1.5 equiv) with HOAc (5.0 equiv), 1,10-phenanthroline (7.5 mol %) and Pd(OAc)₂ (5.0 mol %) in PhCl:MeOH = 1:1 (0.25 mL:0.25 mL) at 40 °C under 1 atm air. ^bIn all cases, **3** and **4** were obtained in less than 20% yield. ^cHydrazones were used directly at rt. ^dThe reaction at 60 °C.

(Table 3.2, entry 9). Substrate with ortho-methyl substituted aromatic group was unable to deliver desired product, due to the steric factor of the methyl group (Table 3.2, entry 10).

The scope of one-pot palladium-catalyzed C-C bond cleavage reaction

The required hydrazones could easily be prepared from phenylhydrazine and the corresponding ketones. We proposed that the C-C cleavage reaction might be conducted in a one-pot manner under acidic conditions. Therefore, a series of keto-alkenes were subjected in the model conditions with phenylhydrazine, as shown in Table 3.3. It was found out that both electron-withdrawing groups and electron-donating groups could be tolerated and delivered the desired product in comparable yields (Table 3.3, **2o-2t**). Substrates with various alkyl groups afforded the desired products in moderate to good yields (Table 3.3, **2a-2m**). Alkenes with α -substitution gave the desired products in moderate yields (Table 3.3, **2x-2aa**).

Based on previous studies, the reaction pathway as shown in Scheme 3.12 was proposed. Since alcohol **3** was detected as byproduct in the reaction, a β -carbon elimination mechanism was proposed as path 1. The final product might be delivered after β -carbon elimination of aminohydroxyl product **3** followed by subsequent β -hydrogen elimination. Decarbonylation or decarboxylation mechanisms were also possible and proposed as path 2 and path 3, respectively.

Scheme 3.12 Possible pathways for palladium-catalyzed C-C cleavage reaction

To clarify the mechanism, a series of control experiments were conducted under the model reaction conditions as shown in Scheme 3.13.

Scheme 3.13 Transformation from **3o**, **5o** or **6o** to **2o**

Aminohydroxyl product **3o** afforded the final product in 68 % yield under the standard conditions. Only traces of the expected product was obtained with aldehyde **5o**, which made path 2 the most unlikely to occur. Moreover, carboxylic acid **6o** was able to deliver the final product in 60 % yield. However, when carboxylic acid **6o** was just exposed to ethyl acetate, complete transformation from **6o** to the final product was observed. After analyzing the results, we proposed: 1) conversion from **3o** to **5o** could not take place under

the reaction conditions, which made the further oxidation from **5o** to **6o** impossible; 2) although **6o** easily yielded the final product, no plausible route for the formation of **6o** in the standard reaction conditions. Therefore, path 3 is also excluded. Path 1 was proposed as the plausible mechanism in this palladium C-C cleavage reaction. Formaldehyde should be released as byproduct through β -carbon elimination step, but it is difficult to detect it. A secondary alcohol **7** was synthesized and subjected to the standard conditions as shown in Scheme 3.14. The results from crude NMR spectra showed that

Scheme 3.14 Transformation from **7** to **2o**

hexanal peak was observed in addition to the pyrazole product, which confirmed that the reaction might proceed through a β -carbon elimination process. Aminohydroxyl product **3** was proposed to be the key intermediate to

Scheme 3.15 Proposed mechanism

further undergo β -carbon elimination process to release the aldehyde, thereby yielding the final product through subsequent β -hydrogen elimination. We summarized the mechanism as shown in Scheme 3.15.

Conclusion

In summary, we have developed a Pd-based reaction system for the easy access to 1*H*-pyrazole with 1 atm air as oxygen source in the presence of acetic acid. The aminooxygenation products can act as the substrates, which underwent further C-C bond cleavage reactions, forming various substituted 1*H*-pyrazoles. A plausible mechanism involving β -carbon elimination is also proposed. This methodology provided a rare example of C-C bond cleavage reactions employing primary alcohols as substrates, which proceeded through a β -carbon elimination mechanism.

3.4 Supporting Information

3.4.1 General Methods

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Commercial grade solvents and reagents were used without further purification. Hexane, ethyl acetate were fractionally distilled.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate.

Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

High Resolution Mass (HRMS) spectra were obtained using Waters Q-ToF Premier Mass Spectrometer.

Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Bruker Avance DPX 300 and Bruker AMX 400 spectrophotometer (CDCl_3 as solvent). Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 7.2600, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dddd (doublets of doublets of doublets of doublet); dt (doublets of triplet); or m (multiplets). The number of protons (n) for a given

resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 77.0, triplet).

General procedure for the synthesis of hydrazones: ^[1]

To a solution of the ketone (1.0 equiv) in ethanol was added phenylhydrazine (1.5 equiv) and acetic acid (2.0 equiv). The mixture was stirred at rt or heated to 60 oC for 3-6 h and monitored by TLC. Then the mixture was directly concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (hexane:EA = 20:1) to afford the hydrazone (the Z/E isomer was separated by flash chromatography on silica gel).

General Procedure for Carbon-Carbon Cleavage Reaction:

Into a 4 ml vial equipped with a magnetic bar, palladium acetate (5 mol%, 0.0075 mmol) and 1,10-phenanthroline (7.5 mol%, 0.01125 mmol) was added in the air condition. Filled with mixed solvent PhCl/MeOH (0.25 ml/0.25 ml), the solution was allowed to stir in room temperature. After 15 min, the hydrazone (0.15 mmol) and acetic acid (5 equiv, 0.75 mmol) were added to the solution. After that, the solution was heated to 40 oC and stirred for 12h in open air. The solvent was removed under reduced pressure. The residue was purified through column chromatography (hexane:EA = 15:1) on silica gel to give the desired products.

General Procedure for one-pot maner of Carbon-Carbon Cleavage

Reaction:

Into a 4 ml vial equipped with a magnetic bar, ketone (0.15 mmol), phenylhydrazine (1.5 equiv) and HOAc (5 equiv) was added under Nitrogen. Filled with mixed solvent PhCl/MeOH (0.25 ml/0.25 ml), the solution was allowed to stir in 50 oC for 3 h. Then palladium acetate (5 mol%, 0.0075 mmol) and 1,10-phenanthroline (7.5 mol%, 0.01125 mmol) was added in the air condition. The solution was heated to 40 oC and stirred for 12h in open air. The solvent was removed under reduced pressure. The residue was purified through column chromatography (hexane:EA = 15:1) on silica gel to give the desired products.

General Procedure for Carbon-Carbon Cleavage Reaction (Scheme 3):

Into a 4ml vial equipped with a magnetic bar, palladium acetate (5 mol%, 0.0075 mmol) and 1,10-phenanthroline (7.5 mol%, 0.01125 mmol) was added in the air condition. Filled with mixed solvent PhCl/MeOH (0.25 ml/0.25 ml), the solution was allowed to stir in room temperature. After 15 min, the 3o, 5o or 6o (0.15 mmol) and acetic acid (5 equiv., 0.75 mmol) were added to the solution. After that, the solution was heated to 40 oC and stirred for 12h in open air. The solvent was removed under reduced pressure. The residue was purified through column chromatography (hexane:EA = 15:1) on silica gel to give the desired products.

Preparation of secondary alcohol (7): ^[2]

In a 50 ml 2 neck-RBF, (8.5 ml, 1.5 equiv) Magnesium bromide (2M in

EE) was added under Nitrogen at 0 °C. Aldehyde (11.4 mmol, 3 g) in 10 ml THF was added dropwise to the solution. The solution was stirred in rt for 6 h. NH₄Cl sat. was added to quench the reaction. After dried with MgSO₄, the product was purified through column chromatography (hexane:EA = 10:1).

General Procedure for Carbon-Carbon Cleavage Reaction of secondary alcohol (7):

Into a NMR tube equipped with a magnetic stirrer bar, palladium acetate (30 mol%, 0.0225 mmol) and 1,10-phenanthroline (40 mol%, 0.03 mmol) was added in the air condition. Filled with mixed solvent d₄-DCE/MeOH (0.25 ml/0.25 ml), the solution was allowed to stir in room temperature. After 15 min, the hydrazones (0.075 mmol) and acetic acid (5 equiv, 0.375 mmol) was added to solution. The solution was stirred under oxygen in room temperature. The reaction was checked by crude NMR from time to time. After starting material was finished, the solvent was removed under reduced pressure. The residue was purified through column chromatography (hexane:EA = 15:1) on silica gel to give the desired products.

Crude NMR detected:

Reference:

- 1, M. K. Zhu, Y. C. Chen, T. P. Loh, *Chem. Eur. J.* **2013**, *19*, 5250.
- 2, M. P. Sibi, L. M. Stanley, C. P. Jasperse, *J. Am. Chem. Soc.* **2005**, *127*, 8276.

Characterization data for the hydrazones

1-(4-methoxyphenyl)-2-(2,2,5-trimethylhex-5-en-3-ylidene)hydrazine (1b)

This compound was prepared by the general procedure described above and was obtained as a yellow oil in 0.49g, 63% yield: $R_f =$

0.45 (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3):

δ 7.13 (s, NH, 1H), 6.98 – 6.95 (m, 2H), 6.84-6.80 (m, 2H), 4.90-4.89 (m, 1H), 4.71 (m, 1H), 3.76 (s, 3H), 3.0 (s, 2H), 1.84 (s, 3H), 1.17 (s, 9H)

ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 153.41, 152.43, 140.69, 139.71, 114.65,

114.14, 112.22, 55.78, 38.50, 34.80, 28.03, 23.21 ppm.

1-(*p*-tolyl)-2-(2,2,5-trimethylhex-5-en-3-ylidene)hydrazine (1c)

This compound was prepared by the general procedure described above and was obtained as a yellow oil in 0.44g, 60% yield: $R_f = 0.62$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.24 (s, NH, 1H), 7.03 – 7.01 (d, $J = 8.4\text{Hz}$, 2H), 6.93-6.91 (m, $J = 8.4\text{Hz}$, 2H), 4.89 (s, 1H), 4.70 (s, 1H), 3.0 (s, 2H), 2.25 (s, 3H), 1.83 (s, 3H), 1.17 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 152.26, 144.17, 139.71, 129.55, 128.60, 113.04, 112.34, 38.54, 34.76, 28.04, 23.21, 20.56 ppm.

1-(4-fluorophenyl)-2-(2,2,5-trimethylhex-5-en-3-ylidene)hydrazine (1d)

This compound was prepared by the general procedure described above and was obtained as a yellow oil in 0.49g, 66% yield: $R_f = 0.61$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.23 (s, NH, 1H), 6.97- 6.89 (m, 4H), 4.90 (m, 1H), 4.70 (s, 1H), 3.0 (s, 2H), 1.83 (s, 3H), 1.17 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 158.16, 155.80, 153.17, 142.74, 139.71, 115.61, 115.39, 113.89, 113.81, 112.38, 38.56, 34.87, 27.99, 23.20 ppm.

1-(4-chlorophenyl)-2-(2,2,5-trimethylhex-5-en-3-ylidene)hydrazine (1e)

This compound was prepared by the general procedure described above and was obtained as a yellow oil in 0.55g, 70% yield: $R_f = 0.63$ (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3): δ 7.32 (s, NH, 1H), 7.17 (d, $J = 8.4\text{Hz}$, 2H), 6.95 (d, $J = 8.4\text{Hz}$, 2H), 4.92 (s, 1H), 4.71 (s, 1H), 3.01 (s, 2H), 1.84 (s, 3H), 1.18 (s, 9H) ppm; ^{13}C

NMR (100 MHz, CDCl₃): δ 153.48, 144.90, 139.68, 128.93, 123.87, 114.06, 112.55, 38.63, 34.86, 27.97, 23.19 ppm.

1-(*m*-tolyl)-2-(2,2,5-trimethylhex-5-en-3-ylidene)hydrazine (1f)

This compound was prepared by the general procedure described above and was obtained as a yellow oil in 0.43g, 60% yield: R_f = 0.60 (hexane : ethyl acetate = 6:1);: ¹H NMR (400 MHz, CDCl₃): δ 7.27 (s, NH, 1H), 7.11-7.08 (m, 1H), 6.83-6.81 (m, 2H), 6.63- 6.61 (m, 1H), 4.90 (s, 1H), 4.71 (s, 1H), 3.00 (s, 2H), 2.30 (s, 3H), 1.83 (s, 3H), 1.18 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 152.44, 146.29, 139.73, 138.89, 128.95, 120.30, 113.51, 112.46, 110.16, 38.58, 34.77, 28.21, 28.05, 23.20, 21.64 ppm.

1-(3,4-dimethoxyphenyl)-2-(2,2,5-trimethylhex-5-en-3-ylidene)hydrazine (1g)

This compound was prepared by the general procedure described above and was obtained as a yellow oil in 0.43g, 50% yield: R_f = 0.40 (hexane : ethyl acetate = 6:1);: ¹H NMR (400 MHz, CDCl₃): δ 7.17 (s, NH, 1H), 6.98-6.96 (m, 1H), 6.82 (s, 1H), 6.79- 6.77 (m, 1H), 4.90 (s, 1H), 4.70 (s, 1H), 3.00 (s, 2H), 2.22(s, 3H), 2.18(s, 3H), 1.84 (s, 3H), 1.18 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 152.07, 144.51, 139.69, 137.13, 130.10, 127.34, 114.47, 112.31, 110.50, 38.52, 34.73, 28.05, 23.21, 20.03, 18.87 ppm.

4-(2-(2,2,5-trimethylhex-5-en-3-

ylidene)hydrazinyl)benzonitrile (1i)

This compound was prepared by the general procedure described above and was obtained as a yellow oil in 0.46g, 60% yield: $R_f =$

0.60 (hexane : ethyl acetate = 6:1); ^1H NMR (400 MHz, CDCl_3):

δ 7.69 (s, NH, 1H), 7.48 (d, $J=8.8\text{Hz}$, 2H), 7.01 (d, $J=8.8\text{Hz}$, 2H), 4.95 (s, 1H), 4.72 (s, 1H), 3.03 (s, 2H), 1.84 (s, 3H), 1.18 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 155.63, 149.07, 139.66, 133.56, 120.26, 113.05, 112.66, 101.13, 38.86, 34.94, 27.87, 23.12 ppm.

Characterization data for intermediate 7:

This compound was obtained as a redish solid in 2.90g, 73%

yield: ^1H NMR (400 MHz, CDCl_3): δ 7.71-7.73 (m, 2H), 7.33-

7.42 (m, 6H), 7.11-7.13 (m, 2H), 4.08-4.10 (m, 1H), 3.57(d, 1H),

2.99 (d, 1H), 2.02 (s, 1H), 1.52 (s, 3H), 1.20-1.52 (m, 10H),

0.84 (t, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 147.73, 143.50, 132.61, 131.63, 128.67, 128.51, 125.63, 118.11, 112.60, 75.77, 71.99, 42.98, 31.65, 30.85, 28.98, 26.15, 23.28, 22.52, 13.98 ppm.

Characterization data for the products

3-(*tert*-butyl)-5-methyl-1-phenyl-1*H*-pyrazole (2a)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in

24.2 mg, 75% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.40-7.46 (m, 4H), 7.28-7.32 (m, 1H), 6.06 (s, 1H), 2.30 (s, 3H), 1.34 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 162.05, 140.17, 138.70, 128.89, 126.95, 124.76, 103.59, 32.00, 30.49, 12.49 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{H}^+$ 215.1548, found 215.1548.

3-(*tert*-butyl)-1-(4-methoxyphenyl)-5-methyl-1*H*-pyrazole (2b)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 22.4 mg, 61% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.33 (d, $J = 8.8$ Hz, 2H, *ArH*), 6.96 (d, $J = 8.8$ Hz, 2H, *ArH*), 6.03 (s, 1H), 3.83 (s, 3H), 2.25 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 161.75, 158.70, 138.84, 133.44, 126.48, 114.13, 102.95, 55.55, 32.03, 30.59, 12.31 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{OH}^+$ 245.1654, found 245.1655.

3-(*tert*-butyl)-5-methyl-1-(*p*-tolyl)-1*H*-pyrazole (2c)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 25.0 mg, 73% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.32 (d, $J = 8.4$ Hz, 2H, *ArH*), 6.96 (d, $J = 8.4$ Hz, 2H, *ArH*), 6.04 (s, 1H), 2.38 (s, 3H), 2.27 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 161.88, 138.70, 137.81, 136.90, 129.50, 124.81, 103.29, 32.05, 30.58, 21.06, 12.46 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{H}^+$ 229.1705, found 229.1703.

3-(*tert*-butyl)-1-(4-fluorophenyl)-5-methyl-1*H*-pyrazole (2d)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 26.0 mg, 75% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.40 - 7.43 (m, 2H, *ArH*), 7.10-7.14 (m, 2H, *ArH*), 6.06 (s, 1H), 2.27 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 162.78, 162.24, 160.32, 138.88, 136.40, 126.72, 126.63, 115.92, 115.69, 103.63, 32.06, 30.52, 12.40 ppm; HRMS (ESI, *m/z*): calcd. for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{FH}^+$ 233.1454, found 233.1455.

3-(*tert*-butyl)-1-(4-chlorophenyl)-5-methyl-1*H*-pyrazole (2e)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 22.5 mg, 60% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.40 (m, 4H, *ArH*), 6.07 (s, 1H), 2.30 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 162.51, 138.85, 138.79, 132.64, 129.10, 125.86, 104.14, 32.09, 30.48, 12.59 ppm; HRMS (ESI, *m/z*): calcd. for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{ClH}^+$ 249.1159, found 249.1159.

3-(*tert*-butyl)-5-methyl-1-(*m*-tolyl)-1*H*-pyrazole (2f)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 22.3 mg, 65% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.28 - 7.32 (m, 2H, *ArH*), 7.20- 7.21 (m, 1H, *ArH*), 7.11- 7.13 (m,

1H, ArH), 6.05 (s, 1H), 2.39 (s, 3H), 2.29 (s, 3H), 1.34 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 161.99, 140.15, 139.05, 138.75, 128.65, 127.88, 125.75, 121.88, 103.46, 32.06, 30.59, 21.39, 12.53 ppm; HRMS (ESI, m/z): calcd. for C₁₅H₂₀N₂H⁺ 229.1705, found 229.1702.

3-(*tert*-butyl)-1-(3,4-dimethoxyphenyl)-5-methyl-1*H*-pyrazole (2g)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 28.0 mg, 63% yield: ¹H NMR (400 MHz, CDCl₃): δ 7.22 (m, 1H, ArH), 7.11- 7.17 (m, 2H, ArH), 6.03 (s, 1H), 2.27- 2.29 (m, 9H), 1.33 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 161.75, 138.67, 137.99, 137.42, 135.65, 129.84, 126.31, 122.24, 103.10, 32.04, 30.60, 19.84, 19.38, 12.44 ppm; HRMS (ESI, m/z): calcd. for C₁₆H₂₂N₂O₂Na⁺ 297.1579, found 297.1580.

3-(*tert*-butyl)-1-(3-chloro-4-fluorophenyl)-5-methyl-1*H*-pyrazole (2h)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 28.7 mg, 72% yield: ¹H NMR (400 MHz, CDCl₃): δ 7.56- 7.54 (m, 1H, ArH), 7.34- 7.30 (m, 1H, ArH), 7.22- 7.18 (m, 1H, ArH), 6.07 (s, 1H), 2.30 (m, 3H), 1.32 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 162.71, 158.21, 155.73, 139.01, 136.86, 136.83, 127.16, 124.35, 124.28, 121.52, 121.33, 116.74, 116.52, 104.25, 32.09, 30.44, 12.50 ppm; HRMS (ESI, m/z): calcd. for C₁₄H₁₆N₂ClFH⁺ 267.1064, found

267.1067.

5-benzyl-3-(*tert*-butyl)-1-phenyl-1*H*-pyrazole (2i)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 30.9 mg, 71% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.39- 7.38 (m, 4H, *ArH*), 7.36- 7.21 (m, 4H, *ArH*), 7.13- 7.11 (m, 2H, *ArH*), 5.97 (s, 1H), 3.96 (s, 2H), 1.33 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 162.22, 142.05, 140.11, 138.43, 129.00, 128.64, 128.54, 127.46, 126.50, 125.49, 103.84, 32.68, 32.15, 30.59 ppm; HRMS (ESI, *m/z*): calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{H}^+$ 291.1861, found 291.1862.

3-(*tert*-butyl)-5-butyl-1-phenyl-1*H*-pyrazole (2j)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 26.8 mg, 70% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.45- 7.42 (m, 4H, *ArH*), 7.35- 7.31 (m, 1H, *ArH*), 6.07 (s, 1H), 2.60 (t, $J=8.4\text{Hz}$, 2H), 1.60- 1.56 (m, 2H), 1.35 (m, 11H), 0.90-0.86 (m, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 162.06, 143.98, 140.36, 128.96, 127.24, 125.43, 101.88, 32.10, 31.00, 30.61, 26.18, 22.45, 13.82 ppm; HRMS (ESI, *m/z*): calcd. for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{H}^+$ 257.3874, found 257.3878.

3-cyclohexyl-5-methyl-1-phenyl-1*H*-pyrazole (2k)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 20.2 mg, 56% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.44- 7.41 (m, 4H, *ArH*), 7.34- 7.31 (m, 1H, *ArH*), 6.01 (s, 1H), 2.71- 2.64 (m, 1H), 2.31 (s,

3H), 2.03- 2.00(m, 2H), 1.83- 1.80(m, 2H), 1.74- 1.70(m, 1H), 1.51- 1.40(m, 4H), 1.34- 1.25(m, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 158.68, 140.10, 138.90, 128.95, 127.09, 124.79, 104.07, 37.68, 33.37, 26.46, 26.19, 12.57 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{H}^+$ 241.1705, found 241.1706.

5-methyl-3-(1-methylcyclohexyl)-1-phenyl-1H-pyrazole (2l)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 19.0mg, 50% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.46- 7.41 (m, 4H, ArH), 7.33- 7.29 (m, 1H, ArH), 6.05 (s, 1H), 2.32 (s, 3H), 2.06- 2.03(m, 2H), 1.57- 1.50(m, 6H), 1.50- 1.41(m, 2H), 1.25(m, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 161.31, 140.37, 138.67, 128.93, 126.89, 124.76, 104.15, 37.82, 35.60, 26.31, 22.76, 12.65 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{H}^+$ 255.1861, found 255.1863.

5-methyl-3-(pentan-3-yl)-1-phenyl-1H-pyrazole (2m)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 14.7 mg, 43% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.44- 7.43 (m, 4H, ArH), 7.33- 7.31 (m, 1H, ArH), 5.96 (s, 1H), 2.57- 2.50 (m, 1H), 2.31 (s, 3H), 1.69- 1.63(m, 4H), 0.90- 0.87 (t, J = 7.2Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 157.19, 138.98, 128.93, 126.99, 124.78, 104.38, 42.48, 28.17, 12.64, 12.08 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{H}^+$ 229.1705, found 229.1704.

3-(bicyclo[2.2.1]hept-5-en-2-yl)-5-methyl-1-phenyl-1*H*-pyrazole (2n)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 14.2 mg, 38% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.45- 7.41 (m, 4H, *ArH*), 7.34- 7.31 (m, 1H, *ArH*), 6.27- 6.24 (m, 1H), 5.97- 5.95 (m, 1H), 5.84 (s, 1H), 3.44- 3.97 (m, 1H), 3.16 (s, 1H), 2.94 (s, 1H), 2.27 (s, 3H), 2.25- 2.19 (m, 1H), 1.50- 1.39 (m, 3H), 1.28- 1.26 (m, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.95, 140.03, 138.73, 137.12, 133.43, 128.93, 127.06, 124.72, 105.45, 50.04, 47.68, 42.99, 37.24, 33.34, 12.56 ppm; HRMS (ESI, *m/z*): calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{H}^+$ 251.1548, found 251.1550.

5-methyl-1,3-diphenyl-1*H*-pyrazole (2o)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 19.7 mg, 56% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.88- 7.86 (m, 2H, *ArH*), 7.55- 7.47 (m, 4H, *ArH*), 7.43- 7.39 (m, 3H, *ArH*), 7.33- 7.31 (m, 1H, *ArH*), 6.54 (s, 1H), 2.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 151.52, 140.17, 139.96, 133.36, 129.11, 128.58, 127.76, 127.62, 125.73, 125.01, 104.38, 12.61 ppm; HRMS (ESI, *m/z*): calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{H}^+$ 235.1235, found 235.1234.

3-(2-methoxyphenyl)-5-methyl-1-phenyl-1*H*-pyrazole (2p)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 20.2 mg, 51% yield: ^1H NMR (400 MHz, CDCl_3): δ 8.01- 7.99 (m, 1H, *ArH*), 7.54- 7.51 (m, 2H, *ArH*), 7.49- 7.45 (m, 2H,

ArH), 7.38- 7.37 (m, 1H, *ArH*), 7.32- 7.27 (m, 1H, *ArH*), 7.03- 6.97 (m, 2H, *ArH*), 6.75 (s, 1H), 3.93 (s, 3H), 2.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.89, 148.53, 140.09, 139.11, 129.04, 128.92, 128.85, 127.44, 125.01, 122.34, 120.87, 111.17, 108.41, 55.51, 12.63 ppm; HRMS (ESI, *m/z*): calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{OH}^+$ 265.1341, found 265.1342.

3-(4-chlorophenyl)-5-methyl-1-phenyl-1H-pyrazole (2q)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 16.8 mg, 42% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.80- 7.78 (m, 2H, *ArH*), 7.51- 7.49 (m, 4H, *ArH*), 7.37- 7.35 (m, 3H, *ArH*), 6.50 (s, 1H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.41, 140.41, 139.82, 133.45, 131.90, 129.15, 128.74, 127.78, 126.95, 125.01, 104.29, 12.55 ppm; HRMS (ESI, *m/z*): calcd. for $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{H}^+$ 269.0846, found 269.0850.

3-(4-bromophenyl)-5-methyl-1-phenyl-1H-pyrazole (2r)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 18.7 mg, 40% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.74- 7.71 (m, 2H, *ArH*), 7.53- 7.47 (m, 6H, *ArH*), 7.42- 7.38 (m, 1H, *ArH*), 6.50 (s, 1H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.41, 140.42, 139.80, 132.35, 131.67, 129.14, 127.79, 127.26, 125.00, 121.62, 104.27, 12.55 ppm; HRMS (ESI, *m/z*): calcd. for $\text{C}_{16}\text{H}_{13}\text{BrN}_2\text{H}^+$ 313.0340, found 313.0362.

3-(4-fluorophenyl)-5-methyl-1-phenyl-1H-pyrazole (2s)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 15.5 mg, 41% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.84- 7.80 (m, 2H, *ArH*), 7.53- 7.49 (m, 4H, *ArH*), 7.41- 7.39 (m, 1H, *ArH*), 7.26- 7.06 (m, 2H, *ArH*), 6.48 (s, 1H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 163.84, 161.40, 150.64, 140.31(d, $J = 44.0$ Hz), 129.62(d, $J = 3.0$ Hz), 129.12, 127.69, 127.40(d, $J = 8.0$ Hz), 124.98, 115.55(d, $J = 21.0$ Hz), 104.16, 12.55 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{13}\text{FN}_2\text{H}^+$ 253.1141, found 253.1136.

5-methyl-1-phenyl-3-(4-(trifluoromethyl)phenyl)-1H-pyrazole (2t)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil 18.1 mg, in 40% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.97- 7.95 (m, 2H, *ArH*), 7.66- 7.64 (m, 2H, *ArH*), 7.52- 7.50 (m, 4H, *ArH*), 7.43- 7.42 (m, 1H, *ArH*), 6.57 (s, 1H), 2.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): 150.05, 140.62, 139.70, 136.80, 129.68(d, $J = 33.0$ Hz), 129.19, 127.96, 125.79, 125.59(q, $J = 7.0$ Hz), 125.04, 122.98, 104.66, 12.53 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}_2\text{H}^+$ 303.1107, found 303.1109.

5-butyl-1,3-diphenyl-1H-pyrazole (2u)

This compound was prepared by the general

procedure described above and was obtained as a yellowish oil in 21.0 mg, 51% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.89- 7.87 (m, 2H, *ArH*), 7.50- 7.49 (m, 4H, *ArH*), 7.40- 7.38 (m, 3H, *ArH*), 7.33- 7.31 (m, 1H, *ArH*), 6.55 (s, 1H), 2.68 (t, J = 8.0Hz, 2H), 1.65- 1.62 (m, 2H), 1.40- 1.34 (m, 2H), 0.92-0.88 (m, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 151.49, 145.37, 140.07, 133.45, 129.11, 128.55, 127.85, 127.70, 125.72, 125.59, 102.79, 30.99, 26.08, 22.32, 13.79 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{H}^+$ 277.1705, found 277.1707.

5-methyl-3-(naphthalen-2-yl)-1-phenyl-1H-pyrazole (2v)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 22.2 mg, 52% yield: ^1H NMR (400 MHz, CDCl_3): δ 8.33 (s, 1H, *ArH*), 8.07- 8.04 (m, 1H, *ArH*), 7.91- 7.88 (m, 2H, *ArH*), 7.86- 7.84 (m, 1H, *ArH*), 7.59- 7.58 (m, 2H, *ArH*), 7.54- 7.46 (m, 4H, *ArH*), 7.44- 7.41 (m, 1H, *ArH*), 6.68 (s, 1H), 2.42 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 151.48, 140.37, 139.97, 133.66, 133.16, 130.81, 129.17, 128.23, 127.75, 127.72, 126.14, 125.78, 125.08, 124.24, 124.19, 104.66, 12.64 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{H}^+$ 285.1392, found 285.1394.

tert-butyl 3-(5-methyl-1-phenyl-1H-pyrazol-3-yl)-1H-indole-1-carboxylate (2w)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 37.5 mg, 67% yield: ^1H NMR (400 MHz, CDCl_3): δ 8.27- 8.26 (m, 1H, *ArH*), 8.21- 8.20 (m, 1H, *ArH*), 7.94 (s, 1H,

ArH), 7.58- 7.56 (m, 2H, ArH), 7.51- 7.47 (m, 2H, ArH), 7.40- 7.24 (m, 3H, ArH), 6.54 (s, 1H), 2.41 (s, 3H), 1.68 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 149.78, 146.16, 140.05, 139.56, 135.83, 129.09, 128.64, 127.45, 124.81, 124.59, 123.04, 121.77, 115.10, 114.74, 105.41, 83.77, 28.26, 12.64 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_2\text{H}^+$ 374.1869, found 374.1872.

3-cyclohexyl-4,5-dimethyl-1-phenyl-1H-pyrazole (2x)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 15.6 mg, 41% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.42- 7.41 (m, 4H, ArH), 7.32- 7.28 (m, 1H, ArH), 2.68- 2.62 (m, 1H), 2.21 (s, 3H), 2.02 (s, 3H), 1.93- 1.91(m, 2H), 1.85- 1.82 (m, 2H), 1.73- 1.58 (m, 2H), 1.43- 1.29 (m, 4H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.38, 140.43, 135.92, 128.92, 126.78, 124.81, 111.87, 36.96, 32.18, 26.85, 26.20, 10.88, 8.43 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{H}^+$ 255.1861, found 255.1865.

4,5-dimethyl-3-(naphthalen-2-yl)-1-phenyl-1H-pyrazole (2y)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 22.8 mg, 51% yield: ^1H NMR (400 MHz, CDCl_3): δ 8.20 (s, 1H, ArH), 7.97- 7.86 (m, 4H, ArH), 7.56- 7.55 (m, 2H, ArH), 7.52- 7.46 (m, 4H, ArH), 7.38- 7.37 (m, 1H, ArH), 2.34 (s, 3H), 2.33 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.60, 140.19, 137.40, 133.51, 132.78, 131.71, 129.11, 128.26, 127.97, 127.70, 127.49, 126.48, 126.17, 126.02, 125.82, 125.12, 112.97, 11.07, 10.00 ppm; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{H}^+$ 299.1548,

found 299.1552.

1,3-diphenyl-4,5,6,7-tetrahydro-1*H*-indazole (2z)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 29.2 mg, 71% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.85- 7.83 (m, 2H, *ArH*), 7.59- 7.57 (m, 2H, *ArH*), 7.49- 7.41 (m, 4H, *ArH*), 7.35- 7.31 (m, 2H, *ArH*), 2.83 (s, 2H), 2.78 (s, 2H), 1.86- 1.85 (m, 4H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 149.10, 140.09, 139.72, 134.16, 129.07, 128.45, 127.36, 126.97, 126.74, 123.44, 115.56, 23.98, 23.14, 22.79, 22.60 ppm; HRMS (ESI, *m/z*): calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{H}^+$ 275.1548, found 275.1550.

3-isopropyl-1-phenyl-4,5,6,7-tetrahydro-1*H*-indazole (2aa)

This compound was prepared by the general procedure described above and was obtained as a yellowish oil in 18.0 mg, 50% yield: ^1H NMR (400 MHz, CDCl_3): δ 7.49- 7.48 (m, 2H, *ArH*), 7.42- 7.38 (m, 2H, *ArH*), 7.27- 7.23 (m, 1H, *ArH*), 3.06-2.99 (m, 1H), 2.73 (s, 2H), 2.60 (s, 2H), 1.83- 1.81 (m, 4H), 1.37- 1.35 (d, $J=7.2\text{Hz}$, 6H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.14, 140.26, 138.74, 128.94, 126.06, 123.02, 114.73, 27.56, 23.88, 23.05, 22.91, 21.76, 21.01 ppm; HRMS (ESI, *m/z*): calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{H}^+$ 241.1705, found 241.1704.

CHAPTER 4

*Iron-catalyzed carbon-nitrogen bond formation of
aromatic rings using azide as nitrogen source*

4.1 Introduction

The formation of C-N bonds is an important transformation in organic synthesis, as the amine functionality is found in various natural products, biologically active reagents and asymmetric catalysts.⁵⁵ Several catalytic methodologies to produce C-N bonds have been developed, such as C-N cross-

a) C-N cross-coupling reactions
Ullmann & Goldberg Coupling:

Buchwald & Hartwig Coupling:

b) C-H direct amination

Scheme 4.1 Metal-catalyzed C-N bond Forming Reactions

coupling reactions and C-H amination (Scheme 4.1).⁵⁶ In C-N bonds coupling reactions, a prefunctionalized substrate is usually required to react with other nitrogen sources. Recently, the direct and selective introduction of a nitrogen

⁵⁵ (a) Comprehensive Natural Products Chemistry, ed. D. H. R. Barton, K. Nakanishi and O. Meth-Cohn, Elsevier, Oxford, **1999**, vol. 4. 2. (b) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *6*, 284. (c) Feher M.; Schmidt, J. M. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218. (d) Henkel, T.; Brunne, R. M.; Müller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643.

⁵⁶ (a) Collet, F.; Dodd, R.; Dauban, P. *Chem. Commun.* **2009**, 5061. (b) Raoufmoghaddam, S. *Org. Biomol. Chem.* **2014**, *12*, 7179. (c) Zatolochay, O.; Gevorgyan, V. *Nature Chem.* **2014**, *6*, 661. (d) Cho, S.; Kim, J.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068.

atom into C-H bond has appeared as attractive alternative methodology, which is both step- and atom- efficient. In this context, two general nitrogen sources have been largely studied: 1) amines and amides, 2) pre-activating nitrogen sources, including *N*-carboxylates, *N*-tosylates, *N*-halides (Scheme 4.2).^{57,58}

Scheme 4.2 Examples of preactivating nitrogen sources

Amines and amides are the most straightforward reagents of direct amination, but in obvious drawbacks of their low activities and requirement of external oxidants. Another option is pre-activating nitrogen sources. Although reagents with N-X (X=halide, O) moiety could serve as internal oxidants in the reaction, external oxidants were usually required and stoichiometric byproducts were generated in most cases.

Most recently, organic azides have been regarded as the environmentally benign nitrogen sources in direct amination/amidation of C-H

⁵⁷ (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (d) Bariwal, J.; Van der Eycken, E. *Chem. Soc. Rev.* **2013**, *42*, 9283.

⁵⁸ (a) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862. (b) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (c) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860. (d) Liu, X.-Y.; Gao, P.; Shen, Y.-W.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 4196. (e) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2012**, *77*, 617. (f) Shuai, Q.; Deng, G.; Chua, Z.; Bohle, D. S.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 632. (g) Yu, S.; Wan, B.; Li, X. *Org. Lett.* **2013**, *15*, 3706. (h) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (i) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694. (j) Ng, K.-H.; Ng, F.-N.; Yu, W.-Y. *Chem. Commun.* **2012**, *48*, 11680. (k) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656. (l) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2013**, *15*, 3014.

bonds.⁵⁹ Since the seminal organic azides were introduced by Griess in 1864⁶⁰, these aminating reagents have drawn a lot of attention in spite of the explosive hazardous especially in large scales. However, the advantages of organic azide

Scheme 4.3 Rhodium-catalyzed direct amination of aromatic C-H bonds through organo azides

are obvious: the ready availability, no requirement of internal or external oxidants and generation of the only by-product, nitrogen gas. Azides have shown great activities towards various classes of molecules, including sp^3 C-H bonds and sp^2 C-H bonds. As known to all, azides could cause serious safety incidents, when not handle properly. In our lab, we have done experiments with azides only in small amounts and under inspection by other lab mates. Herein, we would only discuss intermolecular aromatic sp^2 C-H bonds activation by

⁵⁹ (a) Intrieri, D.; Zardi, P; Caseli, A.; Gallo, E. *Chem. Commun.* **2014**, 50, 11440. (b) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, 48, 1040.

⁶⁰ Griess, P. *Proc. R. Soc. London* **1864**, 13, 375.

using azides as aminating reagents.

The amination of aromatic sp^2 C-H bonds through organic azides have been largely reported in recent years. Chang and co-workers successfully demonstrated and extended the application of organic azides through chelation-assisted C-H activation. In 2012, Chang's group disclosed a first rhodium catalyzed direct amination of aromatic sp^2 C-H bonds using sulfonyl azides as aminating reagents (Scheme 4.3.a).⁶¹ Since then, this RhCp* catalyst was well established by the same group by employing different types of organic azides or aromatic rings with different directing groups (Scheme 4.3.b-4.3.c).^{62, 63} Mechanism about this direct amination process, which involving a stepwise nitrenoid pathway, was proposed by authors as shown in Scheme 4.4. Besides

Scheme 4.4 Proposed mechanism of rhodium-catalyzed direct amination of aromatic C-H bonds through aryl azides

rhodium-catalysis, the same group has also presented Ir-catalyzed⁶⁴ and Ru-catalyzed⁶⁵ direct aminations of aromatic C-H bonds with sulfonyl azides. The reactions catalyzed by IrCp* occurred under a particularly mild conditions and

⁶¹ Kim, J.; Park, S.; Ryu, J.; Cho, S.; Kim, S.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110.

⁶² Ryu, J.; Shin, K.; Park, S.; Kim, J.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 9904.

⁶³ Shin, K.; Baek, Y.; Chang, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8031.

⁶⁴ Kim, J.; Chang, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 2203.

⁶⁵ Kim, J.; Kim, J.; Chang, S. *Chem. Eur. J.* **2013**, *19*, 7328.

delivered the desired products in excellent yields.

In 2013, Glorius and coworkers has described another RhCp* involved synthesis of 1*H*-indazoles from arylimidates and organic azides (Scheme 4.5).⁶⁶

Scheme 4.5 Rh/Cu co-catalyzed synthesis of indazoles with sulfonyl azides

In this case, the authors have developed a co-catalyzed Rh/Cu system, which included an amination of aromatic C-H bonds and subsequently intramolecular N-N bonds formation. Radical process was proposed to be involved in the N-N bond formation steps, proven by a series of control experiments in which radical traps significantly inhibited the reactions.

In the same year, another C-H bond amination through sodium azide and subsequently N-N bonds formations under palladium catalysts have been presented by Jiao's group (Scheme 4.6).⁶⁷ A Pd^{II}/Pd^{IV} catalytic cycle has been

Scheme 4.6 Pd catalyzed C-H azidation and N-N formation

proposed by the author, in which a strong oxidant Ce(SO₄)₂ was required in the

⁶⁶ Yu, D.; Suri, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 8802.

⁶⁷ Zheng, Q.; Feng, P.; Liang, Y.; Jiao, N. *Org. Lett.* **2013**, *15*, 4262.

reactions.

In 2014, Zhu and co-workers have reported a copper catalyzed C-H amidation of aromatic C-H bonds, followed by N-N bonds formations (Scheme 4.7).⁶⁸ It has been found out that with stronger acid HFIP, a

Scheme 4.7 Cu catalyzed C-H amidation with azides

subsequently N-N bonds formation would occur after amidation. A Cu(III) intermediate rather than a copper nitrenoid was proposed by the author, which was formed by a further oxidation through TsN_3 in the presence of a strong acid.

Several works using Ruthenium catalytic system have been also reported recently by Ackermann,⁶⁹ Sahoo,^{70,71} Jiao⁷² and others. In these works, strong coordinating groups like amines were employed in most cases, but weak coordinating groups like ketones and amides were also employed as directing groups.

Most recently, Kanai's group has reported $CoCp^*$ catalyzed Csp^2 C-H

⁶⁸ Peng, J.; Xie, Z.; Chen, M.; Wang, J.; Zhu, Q. *Org. Lett.* **2014**, *16*, 4702.

⁶⁹ Thirunavukkarasu, V.; Raghuvanshi, K.; Ackermann, L. *Org. Lett.* **2013**, *15*, 3286.

⁷⁰ Bhanuchandra, M.; Yadav, M.; Rit, R.; Kuram, M.; Sahoo, A. *Chem. Commun.* **2013**, *49*, 5225.

⁷¹ Yadav, M.; Rit, R.; Sahoo, A. *Org. Lett.* **2013**, *15*, 1638.

⁷² Zheng, Q.; Liang, Y.; Qin, C.; Jiao, N. *Chem. Commun.* **2013**, *49*, 5654.

amidation of indoles.^{73,74} Besides sulfonyl azides, phosphorous azides have been employed to the reaction and shown high reactivity to deliver the phosphoramidation products in good yields.

A novel work recently presented by König *et al* employed visible light to accomplish the Ru-catalyzed amidation of heterocycles with benzoyl azides under very mild and practical conditions (Scheme 4.8).⁷⁵ Mechanism about this

Scheme 4.8 Ru-catalyzed C-H amidation with benzoyl azides under visible light photocatalysis was proposed by the author, which suggested readily formed nitrenium ion intermediates to react with heteroarenes. Blue light irradiated ruthenium catalysts in the reaction was proposed to act as a triplet sensitizer for benzoyl azides.

In conclusion, organic azides serve as efficient reagents for intermolecular amination/amidation of C-H bonds. In most cases, directing groups and heavy metal catalysts are essential in the reactions.

⁷³ Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Adv. Synth. Catal.* **2014**, 356, 1491.

⁷⁴ Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Chem. Commun.* **2015**, 51, 4659.

⁷⁵ Brachet, E.; Ghosh, T.; Ghosh, I.; König, B. *Chem. Sci.* **2015**, 6, 987.

4.2 Our Strategy

Organic azides have been largely utilized in the amination/amidation of aromatic Csp^2 -H bonds. In most cases, directing groups at ortho position of arenes and expensive transition metal catalysts are required for achieving sp^2 C-H bond amination/amidation (Scheme 4.9). Therefore, it is very desirable to explore a cheaper and more efficient catalytic system for direct C-H bond amidation of aromatic rings with organic azides as the aminating sources especially in the absence of directing groups. Our interest lies in two aspects: (i) the achievement of regioselective C-H bond amidation of simple arenes and complex organic molecules containing aromatic rings using the environmentally benign nitrogen sources through electronic effect and steric control; (ii) the development of inexpensive, simple iron salt catalytic systems for direct C-H bond amidation of aromatic rings.⁷⁶ We herein reported a method for iron-catalyzed amination of aromatic sp^2 C-H bonds employing organic azides as the aminating agents.

Previous work:

This work:

Scheme 4.9 C-N bond formation with azides

⁷⁶ (a) Hennessy, E.; Liu, R.; Iovan, D.; Duncan, R.; Betley, T. *Chem. Sci.* **2014**, *5*, 1526. (b) Liu, Y.; Che, C. *Chem. Eur. J.* **2010**, *16*, 10494. (c) Hennessy, E.; Betley, T. *Science* **2013**, *340*, 591.

4.3 Results and discussion

Initially, we began the study by reacting *m*-Xylene **1a** with 4-nitrobenzenesulfonazide (NsN₃) in presence of several iron salts (Table 4.1, entries 2-6). It was found out that the desired product was delivered in all cases.

Table 4.1 Condition Screening of Iron-catalyzed amination.^a

Entry	Catalyst (equiv.)	Solvent	T (°C)	t (h)	Yield (%) ^b	Ratio (b:c:d) ^c
1	—	DCE	100	72	0	—
2	FeCl ₂ (0.2)	DCE	100	72	70	29:71:0
3	Fe(OAc) ₂ (0.2)	DCE	100	72	18	25:75:0
4	Fe(OTf) ₂ (0.2)	DCE	100	72	12	23:77:0
5	Fe(acac) ₃ (0.2)	DCE	100	72	7	27:73:0
6	FeBr ₂ (0.2)	DCE	100	48	75	25:75:0
7	FeBr ₂ (0.2)	DCE	80	48	49	25:75:0
8 ^d	FeBr ₂ (0.2)	DCE	100	72	66	28:72:0
9 ^e	FeBr ₂ (0.2)	DCE	100	72	33	26:74:0
10	FeBr ₂ (0.1)	DCE	100	48	48	27:73:0
11	FeBr ₂ (0.2)	MeCN	100	72	0	—
12	FeBr ₂ (0.2)	1,4-Dioxane	100	72	trace	—

^a Reaction conditions: **1a** (1.00 mmol), **2a** (0.25 mmol), Fe salts (20 mol %), DCE (1ml), N₂, seal tube, 100 °C. ^b Isolated yields. ^c Ratio is determined by NMR. ^d Arene:azide (3:1); ^e Arene:azide (1:1.5).

And the best result was obtained in 75% yield and good selectivity by using FeBr₂ (20 mol%) as catalysts at 100 °C in 48 h (Table 4.1, Entry 6). The results showed that metal catalysts were essential in this reaction, no product was given without any iron catalyst (Table 4.1, Entry 1) When subjected in a lower temperature, the reaction gave a lower yield (Table 4.1, Entry 7). To find out

the best amount of aromatic substrates used in the reaction, a series of control experiments were carried out. The results suggested that four equivalents of aromatic substrates showed the best efficiency in this reaction (Table 4.1, Entry 6,8,9). And it turned out that less amount of catalysts significantly reduced reaction efficiency (Table 4.1, Entry 10). Then, a number of solvents were also screened, and no better results were obtained than DCE (Table 4.1, Entry 11,12). The best result was obtained with 20 mol% of FeBr₂ and 4 equiv of arenes, using dichloroethane as solvent at 100 °C in 48 h (Table 4.1, entry 6).

Next, we extended the C-N bond formation of *m*-xylene with various sulfonyl azides (Table 4.2). It is notable that the substituents on the aromatic ring of azides have a great impact on the amination process. Both electron

Table 4.2. Reactions with different azides with *m*-xylene.^{a,b,c}

^a Reaction conditions: **1a** (1.00 mmol), **2a** (0.25 mmol), Fe salts (20 mol%), DCE (1ml), N₂, seal tube, 100 °C. ^b Isolated yields. ^c Ratio of the products is determined by NMR.

withdrawing and electron donating substituent could deliver desired product in

good to moderate yields (Table 4.2, **3aa,3ad,3af**). The azide bearing a non-bulky naphthyl group also gave the desired product efficiently (Table 4.2, **3ai**). Due to steric factor, other bulky substituents could not give desired product in acceptable yields (Table 4.2, **3ab,3ag**). Considered about the efficiency and selectivity of the reaction, NsN_3 was chosen to be our model substrate for further investigation.

The substrate scope of the amidation of xylene under optimized conditions is summarized in Table 3. A series of simple arenes were subjected with azides under the standard conditions. The reaction with *p*-xylene gave the desired product in moderate yield (Table 3, compound **3bb**). When mesitylene was subjected to the reaction, the desired product was obtained in 89% yield (Table 4.3, compound **3bc**). Another hindered C-H bonds in 1,2,4,5-tetramethylbenzene showed less reactivity, giving **3bd** in 48%. When with common functional groups, including both electron donating groups and electron withdrawing groups, the reaction could also give the desired product in moderate to good yields. A multiple substituted substrate with methyl and bromide groups gave the desired products in good yield (Table 4.3, compound **3be**). Several para-substituted substrates were also applied into the reaction conditions, the desired products were given in good selectivities and moderate yields (Table 4.3, compounds **3bf-3bh**). When oxydibenzene was subjected with reaction condition, the desired product was delivered in 46% (Table 4.3, compound **3bi**). When 1-bromo-3,5-dimethoxybenzene was subjected to the reaction, good yield and moderate selectivity were obtained (Table 4.3, compound **3bj**). Two meta-substituted substrates gave the desired products in a mixture of three isomers in moderate yields (Table 4.3, compounds **3bk** and **3bl**).

under the standard conditions. When 1-bromo-3,5-dimethylbenzene was subjected to the reaction, two isomers were given as product in a similar ratio and in a total yield of 69% (Table 4.3, compound **3bm**). Naphthalene was also applied into our reaction conditions, the desired products were given in two isomers as a ratio of 75:25 and in a total yield of 71% (Table 4.3, compound **3bn**).

Table 4.3. Substrate scopes of C-H amination with Azides.^{a,b,c}

$ \begin{array}{c} \text{R} \\ \\ \text{C}_6\text{H}_5 \\ \text{1, 4.0 equiv} \end{array} + \text{NsN}_3 \xrightarrow[\text{DCE, 100 } ^\circ\text{C}]{\text{FeBr}_2 \text{ (0.2 equiv.)}} \begin{array}{c} \text{R} \\ \\ \text{C}_6\text{H}_4\text{NHNs} \\ \text{3} \end{array} $				
 3aa , 75% ^c (b:c:d 25:75:0)	 3bb , 50%	 3bc , 89%	 3bd , 48%	 3be , 77%
 3bf , 56% (b:c>94:6)	 3bg , 52% (b:c>94:6)	 3bh , 44% (b:c>94:6)	 3bi , 46%	 3bj , 75% (b:d 68:32)
 3bk , 49% (b:d:f 45:34:21)	 3bl , 47% (b:d 14:86)	 3bm , 69% (b:d 45:55)	 3bn , 71% ^c (a:b 75:25)	

^a Reaction conditions: **1a** (1.00 mmol), **2a** (0.25 mmol), Fe salts (20 mol %), DCE (1ml), N₂, seal tube, 100 °C. ^b Isolated yields. ^c ratio of the products is determined by NMR.

Addition of TEMPO significantly inhibited the reaction, which indicated that radicals might be involved in the C-N bond formation. On the

basis of mechanistic studies and literature reports⁷⁷, a possible reaction mechanism was proposed in Scheme 4.10. A three stepwise mechanism was proposed (path a): 1) iron salts were oxidized by azides to form the Fe^{III} radical imido; 2) the Fe-imido intermediate abstracted an H-atom from the arene substrate to form an aromatic radical; 3) radical recombination with form the amination products. Alternatively, direct C-H insertion by the Fe^{III} radical imido was also possible (path b).

Scheme 4.10. Mechanism proposed for the amination reactions

⁷⁷ (a) Hennessy, E.; Betley, T. *Science* **2013**, 340, 591. (b) King, E.; Hennessy, E.; Betley, T. *J. Am. Chem. Soc.* **2011**, 133, 4917. (c) Hennessy, E.; Liu, R.; Iovan, D.; Duncan, R.; Betley, T. *Chem. Sci.* **2014**, 5, 1526.

In summary, we have developed a Fe-catalyzed reaction system for the conversion of aromatic C-H to C-N bonds with sulfonyl azides as aminating sources in the absence of directing group of arenes. The amination gave the desired products in good yields and regional selectivities, which provided a new protocol for the synthesis of aminated arenes. A plausible reaction mechanism has been proposed, which involved a radical process. The exploration of related transformation and detailed mechanism studies are currently underway in our laboratories.

4.4 Supporting Information

General Methods

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Commercial grade solvents and reagents were used without further purification. Hexane, ethyl acetate were fractionally distilled.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate.

Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

High Resolution Mass (HRMS) spectra were obtained using Waters Q-ToF Premier Mass Spectrometer.

Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Bruker Avance DPX 300 and Bruker AMX 400 spectrophotometer (CDCl_3 as solvent). Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.2600, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dddd (doublets of doublets of doublets of doublet); dt

(doublets of triplet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (¹³C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.0, triplet).

General procedure for the synthesis of organic azides:¹

A solution of the sulfonyl chloride (1.0 equiv) in 10 ml acetone was cooled in ice-bath under N₂ for a while. NaN₃ (2.0 equiv) in 6 ml H₂O was added dropwise to the previous solution in a period of 2h in 0°C. The mixture was then stirred at rt for 6 h. After the reaction finished, the acetone was directly removed in *vacuo*. And the resulting solution was washed with ethyl acetate, water and sat. Na₂CO₃. After dried with MgSO₄, the azide was used directly after concentration.

General Procedure for Iron-catalyzed Amination Reaction of Aromatic Rings:

Into a 10 ml seal tube equipped with a magnetic bar, iron bromide (20 mol % ,

0.05 mmol, 11 mg) and organic azides (0.25 mmol) was added under nitrogen. Filled with anhydrous DCE (1 ml) and aromatic substrate (4 equiv. 1 mmol), the solution was allowed to be heated to 100 °C and stirred for 60 h under nitrogen. The solvent was removed under reduced pressure. The residue was purified through column chromatography (Hexane:EA = 10:1 to 5:1) on silica gel to give the desired products.

Reference:

1, C. Olivier, P. Renaud, *J. Am. Chem. Soc.* **2001**, *123*, 4717.

Characterization data for the amination products:

N-(2,4-dimethylphenyl)-4-nitrobenzenesulfonamide or N-(2,6-dimethylphenyl)-4-nitrobenzenesulfonamide (3aa)

This compound was prepared by the general procedure described above and was obtained as mixture (b:c:e=25:75:0), beige solid, Mp: 117.7-118.3 °C in 57 mg, 75 % yield: R_f = 0.45 (hexane : ethyl acetate = 5:1): ^1H NMR (400 MHz, CDCl_3): δ 8.32-8.26 (m, ArH, 2.67H), 7.94-7.87 (m, ArH, 2.63H), 7.13-7.11 (m, ArH, 1.37H), 7.10-7.03 (m, ArH, 0.64H), 6.96-6.94 (m, ArH, 2.08H), 6.56 (s, NH, 1H), 6.35 (s, NH, 0.31H), 2.27 (s, 3H), 2.04 (s, 1.88H), 1.97 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.17, 146.29, 145.42, 137.71, 137.52, 132.75, 131.87, 131.64, 130.53, 129.09, 128.52, 128.48, 127.82, 125.77, 124.29, 124.21,

20.91, 18.82, 17.62 ppm. HRMS (ESI, m/z): calcd. for $C_{14}H_{14}N_2O_4SH^+$ 307.0753, found 307.0749.

N-(2,6-dimethylphenyl)-2-methyl-5-nitrobenzenesulfonamide or N-(2,4-dimethylphenyl)-2-methyl-5-nitrobenzenesulfonamide (3ac)

3ac

This compound was prepared by the general procedure described above and was obtained as a yellow solid, in 23 mg, 29 % yield: $R_f = 0.40$ (hexane : ethyl acetate = 3:1): 1H NMR (400 MHz, $CDCl_3$): δ 8.76-8.73 (m, ArH, 1.16H), 8.32-8.27 (m, ArH, 1.26H), 7.50-7.48 (m, ArH, 1.30H), 7.15-7.11 (m, ArH, 0.37H), 7.05-7.03 (m, ArH, 0.64H), 6.97 (s, 1.05H), 6.88 (s, 2.02H), 6.35 (s, NH, 1H), 6.15 (s, NH, 0.28H), 2.68 (s, 2.93H), 2.25 (s, 3.00H), 2.14 (s, 2.90H), 2.05 (s, 1.46H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.83, 140.08, 137.85, 137.33, 133.72, 132.74, 132.67, 131.93, 130.66, 129.03, 128.68, 127.75, 127.11, 127.02, 125.10, 124.99, 20.90, 20.87, 18.79, 17.77 ppm.

N-(2,6-dimethylphenyl)-3,5-bis(trifluoromethyl)benzenesulfonamide or N-(2,4-dimethylphenyl)-3,5-bis(trifluoromethyl)benzenesulfonamide (3ad)

3ad

This compound was prepared by the general procedure described above and was obtained as a yellow solid, in 66.5 mg, 67 % yield: $R_f = 0.40$ (hexane : ethyl acetate = 3:1): 1H NMR (400 MHz, $CDCl_3$): δ 8.16-8.05 (m, ArH, 4.89H),

7.17-7.13 (m, ArH, 0.60H), 7.06-7.02 (m, ArH, 2.20H), 6.97-6.96 (m, ArH, 2.15H), 6.62 (s, NH, 1H), 6.44 (s, NH, 0.52H), 2.28 (s, 3.24H), 2.03 (s, 3.31H), 1.98 (s, 3.20H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 143.14, 142.28, 138.01, 137.54, 133.22, 133.03, 132.90, 132.69, 132.56, 132.21, 131.95, 131.41, 130.21, 129.16, 128.70, 127.81, 127.53(d, $J=3.1$), 126.26(m), 126.06, 123.70, 120.99, 118.27, 20.82, 18.61, 17.47 ppm.

N-(2,6-dimethylphenyl)-4-nitro-3-(trifluoromethyl)benzenesulfonamide or N-(2,4-dimethylphenyl)-4-nitro-3-(trifluoromethyl)benzenesulfonamide (3ae)

3ae

This compound was prepared by the general procedure described above and was obtained as a yellow solid, in 32 mg, 34 % yield: R_f = 0.42 (hexane : ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3): δ 7.98-7.97 (m, ArH, 1.48H), 7.88-7.83 (m, ArH, 1.51H), 7.35-7.29 (m, ArH, 1.55H), 7.13-7.03 (m, ArH, 2.68H), 6.96-6.95 (m, ArH, 2.01H), 6.39 (s, NH, 1H), 6.19 (s, NH, 0.50H), 2.28 (s, 3.03H), 2.07 (s, 2.80H), 1.99 (s, 2.88H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 143.21, 137.57, 137.32, 136.79, 135.84, 132.57, 131.96 (m), 131.79, 130.79, 129.04, 128.39, 127.73, 127.01 (m), 125.55, 119.93(m), 20.87, 18.78, 17.60 ppm.

4-(tert-butyl)-N-(2,6-dimethylphenyl)benzenesulfonamide or 4-(tert-butyl)-N-(2,4-dimethylphenyl)benzenesulfonamide (3af)

3af

This compound was prepared by the general procedure described above and was obtained as a yellow solid, in 46 mg, 58 % yield: $R_f = 0.45$ (hexane : ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3): δ 7.67-7.64 (m, ArH, 2.95H), 7.47-7.42 (m, ArH, 3.14H), 7.16-7.14 (m, ArH, 1.10H), 7.09-7.06 (m, ArH, 0.51H), 7.02-6.99 (m, ArH, 0.99H), 6.94-6.91 (m, ArH, 2.18H), 6.51 (s, NH, 1H), 6.25 (s, NH, 0.32H), 2.26 (s, 2.85H), 2.03 (s, 2.16H), 1.96 (s, 2.83H), 1.24 (s, 3.50H), 1.32 (s, 9.21H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 56.84, 156.69, 137.82, 137.65, 136.87, 136.65, 136.87, 136.20, 132.65, 132.07, 131.81, 131.46, 128.76, 127.77, 127.47, 127.05, 127.01, 125.93, 125.93, 125.12, 35.15, 31.12, 31.08, 20.88, 18.62, 17.47 ppm.

N-(2,6-dimethylphenyl)-2-methylbenzenesulfonamide or N-(2,4-dimethylphenyl)-2-methylbenzenesulfonamide (3ag)

3ag

This compound was prepared by the general procedure described above and was obtained as a yellow solid, in 21 mg, 31 % yield: $R_f = 0.50$ (hexane : ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3): δ 7.89-7.85 (m, ArH, 1.24H), 7.46-7.42 (m, ArH, 1.42H), 7.30-7.24 (m, ArH, 2.90H), 7.10-7.06 (m, ArH, 0.30H), 7.01-6.99 (m, ArH, 0.47H), 6.93-6.92 (m, ArH, 2.12H), 6.90-6.84 (m, ArH,

1.07H), 6.34 (s, *NH*, 1H), 6.09 (s, *NH*, 0.20H), 2.60 (s, 3.12H), 2.57 (s, 0.75H), 2.23 (s, 3.12H), 2.10 (s, 3.29H), 2.04 (s, 1.19H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 139.57, 138.17, 138.02, 137.45, 137.26, 136.19, 132.97, 132.89, 132.71, 132.58, 132.53, 131.99, 131.65, 131.58, 129.86, 129.22, 128.73, 128.04, 127.42, 126.43, 126.30, 124.47, 20.82, 20.75, 20.59, 18.61, 17.62 ppm.

N-(2,6-dimethylphenyl)naphthalene-1-sulfonamide or N-(2,4-dimethylphenyl)naphthalene-1-sulfonamide (3ah)

3ah

This compound was prepared by the general procedure described above and was obtained as a yellow solid, in 22 mg, 28 % yield: R_f = 0.35 (hexane : ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3): δ 8.70-8.68 (m, *ArH*, 1.08H), 8.59-8.56 (m, *ArH*, 0.34H), 8.16-8.12 (m, *ArH*, 1.35H), 8.08-8.03 (m, *ArH*, 1.48H), 7.95-7.92 (m, *ArH*, 1.47H), 7.66-7.56 (m, *ArH*, 2.88H), 7.51-7.43 (m, *ArH*, 1.52H), 7.07-7.03 (m, *ArH*, 0.50H), 6.94-6.78 (m, *ArH*, 3.89H), 6.39 (s, *NH*, 1H), 6.15 (s, *NH*, 0.33H), 2.19 (s, 3.14H), 1.91 (s, 3.09H), 1.88 (s, 1.87H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 138.05, 136.29, 134.72, 134.47, 134.35, 134.20, 132.73, 132.22, 131.62, 131.46, 130.28, 129.14, 128.93, 128.62, 128.35, 128.18, 128.00, 127.30, 126.87, 124.75, 124.62, 124.40, 124.16, 20.78, 18.61, 17.53 ppm.

N-(2,6-dimethylphenyl)naphthalene-2-sulfonamide or N-(2,4-dimethylphenyl)naphthalene-2-sulfonamide (3ai)

3ai

This compound was prepared by the general procedure described above and was obtained as a yellow solid, in 41 mg, 53 % yield: $R_f = 0.35$ (hexane : ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3): δ 8.33-8.31 (m, *ArH*, 1.30H), 7.95-7.88 (m, *ArH*, 4.32H), 7.80-7.75 (m, *ArH*, 1.42H), 7.67-7.53 (m, *ArH*, 3.04H), 7.18-7.11(m, *ArH*, 1.45H), 7.10-6.90 (m, *ArH*, 2.09H), 6.57 (s, *NH*, 1H), 6.33 (s, *NH*, 0.33H), 2.26 (s, 3.06H), 2.05 (s, 2.14H), 2.00 (s, 3.03H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 137.84, 137.76, 136.75, 136.47, 134.85, 134.82, 132.55, 132.20, 132.13, 132.04, 131.57, 131.54, 129.32, 129.28, 128.84, 128.80, 128.63, 128.28, 127.93, 127.89, 127.52, 127.48, 125.24, 122.65, 122.41, 20.84, 18.81, 17.63 ppm.

N-(2,5-dimethylphenyl)-4-nitrobenzenesulfonamide

3bb

This compound was prepared by the general procedure described above and was obtained as a white solid, Mp: 165.7-167.5 °C in 38 mg, 50 % yield: $R_f = 0.40$ (hexane : ethyl acetate = 5:1): ^1H NMR (400 MHz, CDCl_3): δ 8.29-8.27 (m, *ArH*, 2H), 7.91-7.88 (m, *ArH*, 2H), 7.14 (s, *ArH*, 1H), 7.00-6.96 (m, *ArH*, 2H), 6.51 (s, *NH*, 1H), 2.29 (s, 3H), 1.91 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.18, 145.40, 137.21, 133.07, 130.87, 128.64, 128.39, 128.06, 125.69, 124.20, 20.97, 17.13 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4\text{SNa}^+$

329.0572, found 329.0575.

N-mesityl-4-nitrobenzenesulfonamide

This compound was prepared by the general procedure described above and was obtained as a white solid Mp: 143.4-146.5 °C in 71 mg, 89 % yield: R_f = 0.45 (hexane : ethyl acetate = 5:1): ^1H NMR (400 MHz, CDCl_3): δ 8.31-8.28 (m, ArH, 2H), 7.93-7.91 (m, ArH, 2H), 6.84 (s, ArH, 2H), 6.34 (s, NH, 1H), 2.25 (s, 3H), 1.98 (s, 6H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.07, 146.42, 138.42, 137.41, 129.78, 128.96, 128.51, 124.24, 20.90, 18.69 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4\text{SNa}^+$ 343.0728, found 343.0711.

4-nitro-N-(2,3,5,6-tetramethylphenyl)benzenesulfonamide

This compound was prepared by the general procedure described above and was obtained as a white solid Mp: 171.3-173.2 °C in 39 mg, 48 % yield: R_f = 0.45 (hexane : ethyl acetate = 5:1): ^1H NMR (400 MHz, CDCl_3): δ 8.30-8.27 (m, ArH, 2H), 7.90-7.87 (m, ArH, 2H), 6.96 (s, ArH, 1H), 6.36 (s, NH, 1H), 2.16 (s, 6H), 1.89 (s, 6H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.04, 146.28, 135.10, 133.57, 131.81, 131.23, 128.60, 124.12, 20.18, 15.43 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_4\text{SH}^+$ 335.1066, found 335.1069.

N-(3-bromo-2,4,6-trimethylphenyl)-4-nitrobenzenesulfonamide

This compound was prepared by the general procedure described above and was obtained as a yellow solid Mp: 190.0-191.2 °C in 77 mg, 77 % yield: R_f = 0.40 (hexane : ethyl acetate = 2:1);: ^1H NMR (400 MHz, CDCl_3): δ 8.34-8.31 (m, ArH, 2H), 7.93-7.90 (m, ArH, 2H), 6.97 (s, ArH, 1H), 6.30 (s, NH, 1H), 2.37 (s, 3H), 2.13 (s, 3H), 1.97 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.19, 146.10, 139.15, 138.19, 136.39, 130.41, 129.92, 128.56, 125.92, 124.34, 23.92, 20.47, 18.61 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_4\text{SBrH}^+$ 400.9994, found 400.9990.

N-(5-methyl-2-methoxyphenyl)-4-nitrobenzenesulfonamide

This compound was prepared by the general procedure described above and was obtained as a brown solid, Mp: 152.3-155.1 °C in 45 mg, 56 % yield: R_f = 0.38 (hexane : ethyl acetate = 2:1);: ^1H NMR (400 MHz, CDCl_3): δ 8.25-8.22 (m, ArH, 2H), 7.91-7.90 (m, ArH, 2H), 7.37 (s, ArH, 1H), 6.97 (s, NH, 1H), 6.90 (d, ArH, 1H), 6.63 (d, ArH, 1H), 3.57 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.10, 147.85, 144.94, 130.96, 128.49, 126.96, 124.27, 123.87, 123.04, 110.57, 55.63, 20.72 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_5\text{SNa}^+$ 345.0521, found 345.0522.

N-(5-bromo-2-methoxyphenyl)-4-nitrobenzenesulfonamide

This compound was prepared by the general procedure described above and was obtained as a yellow solid Mp: 180.1-182.2 °C in 50 mg, 52 % yield: R_f = 0.40 (hexane : ethyl acetate = 2:1); ^1H NMR (400 MHz, CDCl_3): δ 8.31-8.29 (m, ArH, 2H), 7.99-7.97 (m, ArH, 2H), 7.72 (d, ArH, 1H), 7.24 (dd, ArH, 1H), 7.21 (s, NH, 1H), 6.67 (d, ArH, 1H), 3.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.30, 148.71, 144.61, 128.97, 128.51, 126.08, 124.31, 124.15, 113.35, 112.18, 55.95 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_5\text{SBrH}^+$ 386.9650, found 386.9641.

N-(5-fluoro-2-methoxyphenyl)-4-nitrobenzenesulfonamide

This compound was prepared by the general procedure described above and was obtained as a brown solid Mp: 154.6-155.7 °C in 36 mg, 44 % yield: R_f = 0.40 (hexane : ethyl acetate = 2:1); ^1H NMR (400 MHz, CDCl_3): δ 8.29-8.25 (m, ArH, 2H), 7.99-7.96 (m, ArH, 2H), 7.35 (dd, ArH, 1H), 7.18 (s, NH, 1H), 6.80 (m, ArH, 1H), 6.70 (m, ArH, 1H), 3.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 158.02, 155.64, 150.31, 145.62 (d, $J=2.4$), 144.61, 128.59 (d, $J=8.1$), 125.70 (d, $J=10.8$), 124.1609, 112.01-111.30(m), 108.92 (d, $J=27.8$), 56.17 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_5\text{SFH}^+$ 327.0451, found 327.0445.

4-nitro-N-(4-phenoxyphenyl)benzenesulfonamide

This compound was prepared by the general procedure described above and was obtained as a dark brown solid, Mp: 163.0-165.1 °C in 43 mg, 46 % yield: $R_f = 0.50$ (hexane : ethyl acetate = 5:1);: ^1H NMR (400 MHz, CDCl_3): δ 8.31-8.29 (m, ArH, 2H), 7.92-7.90 (m, ArH, 2H), 7.36 (m, ArH, 2H), 7.15 (m, ArH, 1H), 7.03-6.96 (m, ArH, 4H), 6.92-6.89 (m, ArH, 2H), 6.58 (s, NH, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 156.46, 156.37, 150.33, 144.67, 129.94, 129.74, 128.57, 125.49, 124.28, 123.99, 119.31, 119.27 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_5\text{SH}^+$ 371.0702, found 371.0706.

N-(2-bromo-4,6-dimethoxyphenyl)-4-nitrobenzenesulfonamide

This compound was prepared by the general procedure described above and was obtained as a brown solid Mp: 202.5-204.0 °C in 53 mg, 51 % yield: $R_f = 0.30$ (hexane : ethyl acetate = 2:1);: ^1H NMR (400 MHz, CDCl_3): δ 8.33-8.30 (m, ArH, 2H), 8.00-7.98 (m, ArH, 2H), 6.73 (d, ArH, 1H), 6.73 (d, ArH, 1H), 6.24 (s, NH, 1H), 3.79 (s, 3H), 3.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 160.42, 157.05, 149.95, 146.74, 128.82, 125.46, 123.69, 116.14, 109.35, 98.69, 55.80, 55.47, 31.58, 22.65, 14.11 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_6\text{SBrH}^+$ 418.9735, found 418.9742.

N-(4-bromo-2,6-dimethoxyphenyl)-4-nitrobenzenesulfonamide

3bj-2

This compound was prepared by the general procedure described above and was obtained as a yellow solid Mp: 184.5-186.0 °C in 25 mg, 24 % yield: R_f = 0.35 (hexane : ethyl acetate = 2:1); ^1H NMR (400 MHz, CDCl_3): δ 8.35-8.33 (m, ArH, 2H), 8.06-8.04 (m, ArH, 2H), 6.67 (s, ArH, 1H), 6.29 (s, NH, 1H), 3.60 (s, 6H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 155.24, 149.96, 147.08, 128.51, 123.56, 121.45, 112.59, 108.32, 55.96 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_6\text{SBrH}^+$ 416.9756, found 416.9747.

N-(2-bromo-6-methoxyphenyl)-4-nitrobenzenesulfonamide

3bk-1

This compound was prepared by the general procedure described above and was obtained as a yellow solid, Mp: 129.7-131.3 °C in 21 mg, 22 % yield: R_f = 0.50 (hexane : ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3): δ 8.27-8.25 (m, ArH, 2H), 7.85-7.83 (m, ArH, 2H), 7.64 (d, ArH, 1H, $J=8.8$), 6.95-6.89 (m, ArH, 2H), 6.68 (s, NH, 1H), 3.78 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 158.70, 150.36, 144.50, 128.70, 127.23, 126.15, 124.14, 119.01, 117.78, 114.68, 55.75 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_5\text{SBrNa}^+$ 408.9470, found 408.9464.

N-(4-bromo-2-methoxyphenyl)-4-nitrobenzenesulfonamide

3bk-2

This compound was prepared by the general procedure described above and was obtained as a yellow solid, Mp: 131.8-133.8 °C in 16 mg, 17 % yield: R_f = 0.45 (hexane : ethyl acetate = 3:1): ^1H NMR (400 MHz, CDCl_3): δ 8.28-8.25 (m, *ArH*, 2H), 7.93-7.91 (m, *ArH*, 2H), 7.45 (d, *ArH*, 1H, $J=8.8$), 7.09-7.07 (m, *ArH*, 1H), 6.89 (s, *NH*, 1H), 6.88(s, *ArH*, 1H), 3.64 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.39, 150.27, 144.66, 128.50, 124.38, 124.08, 123.93, 123.20, 119.32, 114.50, 56.01 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_5\text{SBrH}^+$ 388.9630, found 388.9635.

N-(2-bromo-4-methoxyphenyl)-4-nitrobenzenesulfonamide

3bk-3

This compound was prepared by the general procedure described above and was obtained as a yellow solid, Mp: 186.7-188.1 °C in 10 mg, 10 % yield: R_f = 0.40 (hexane : ethyl acetate = 3:1);: ^1H NMR (400 MHz, CDCl_3): δ 8.34-8.32 (m, *ArH*, 2H), 8.04-8.02 (m, *ArH*, 2H), 7.24 (dd, *ArH*, 1H, $J=8.4$), 7.13 (m, *ArH*, 1H), 6.79 (dd, *ArH*, 1H, $J=8.4$), 6.41 (s, *NH*, 1H), 3.45 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 155.91, 150.05, 146.78, 129.64, 128.70, 125.41, 123.76, 123.72, 123.45, 110.70, 55.53 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_4\text{SBrNa}^+$ 410.9449, found 410.9451.

N-(2,6-dimethoxyphenyl)-4-nitrobenzenesulfonamide or **N-(2,4-dimethoxyphenyl)-4-nitrobenzenesulfonamide**

This compound was prepared by the general procedure described above and was obtained as mixture(**3bl-1**:**3bl-2**=1:6) yellow solid, Mp: 152.2-158.2 °C in 40 mg, 47 % yield: R_f = 0.45 (hexane : ethyl acetate = 3:1);: ^1H NMR (400 MHz, CDCl_3): δ 8.23-8.20 (m, *ArH*, 2H), 7.85-7.83 (m, *ArH*, 2H), 7.46 (d, *ArH*, 1H, $J=8.8$), 6.72 (s, *NH*, 1H), 6.48-6.45 (m, *ArH*, 1H), 6.26 (d, *ArH*, 1H, $J=2.8$), 3.76 (s, 3H), 3.46 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 159.22, 152.16, 150.02, 144.94, 128.61, 125.69, 123.69, 117.19, 104.64, 98.76, 55.53, 55.40 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_6\text{SNa}^+$ 361.0470, found 361.0471.

N-(2-bromo-4,6-dimethylphenyl)-4-nitrobenzenesulfonamide

This compound was prepared by the general procedure described above and was obtained as a yellow solid, Mp: 127.3-130.8 °C in 29 mg, 31 % yield: R_f = 0.40 (hexane : ethyl acetate = 5:1);: ^1H NMR (400 MHz, CDCl_3): δ 8.30-8.26 (m, *ArH*, 2H), 7.88-7.84 (m, *ArH*, 2H), 7.09 (d, *ArH*, 1H, $J=6$), 6.34 (s, *NH*, 1H), 2.53 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.32, 145.36, 140.66, 139.88, 132.11, 131.04, 129.07, 124.10, 123.05, 20.71, 20.24 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_4\text{SNa}^+$ 406.9677, found 406.9675.

N-(4-bromo-2,6-dimethylphenyl)-4-nitrobenzenesulfonamide

3bm-2

This compound was prepared by the general procedure described above and was obtained as a yellow solid, Mp: 177.1-179.1 °C in 37 mg, 38 % yield: R_f = 0.35 (hexane : ethyl acetate = 5:1); ^1H NMR (400 MHz, CDCl_3): δ 8.34-8.32 (m, ArH, 2H), 7.95-7.92 (m, ArH, 2H), 7.20 (s, ArH, 1H), 6.23 (s, NH, 1H), 2.01 (s, 6H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.24, 146.11, 139.85, 131.88, 130.82, 128.49, 124.41, 122.34, 18.68 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_4\text{SBrNa}^+$ 406.9677, found 406.9671.

N-(naphthalen-1-yl)-4-nitrobenzenesulfonamide or N-(naphthalen-2-yl)-4-nitrobenzenesulfonamide

3bn-1

3bn-2

This compound was prepared by the general procedure described above and was obtained as mixture 3n-1:3n-2=3:1 (white solid) in 58 mg, 71 % yield: R_f = 0.4 (hexane : ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 8.25-8.17 (m, ArH, 3.1H), 7.95-7.71 (m, ArH, 7.3H), 7.59-7.56 (m, ArH, 0.9H), 7.50-7.39 (m, ArH, 4.9H), 7.21-7.12 (m, ArH, 1.5H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 150.14, 145.01, 134.32, 130.20, 130.13, 129.85, 129.52, 129.04, 128.69, 128.57, 128.51, 128.34, 128.16, 128.08, 127.87, 127.74, 127.58, 127.08, 126.64, 126.21, 125.48, 124.48, 124.29, 124.16, 124.06, 121.68, 121.24, 120.98 ppm. HRMS (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_4\text{SH}^+$ 329.0596, found 329.0589.

LIST OF PUBLICATION

1. Ming-Kui Zhu, **Yu-Chen Chen**, and Teck-Peng Loh, “*Radical-Mediated Diamination of Alkenes with Phenylhydrazine and Azodicarboxylates: Highly Diastereoselective Synthesis of trans-Diamines from Cyclo-alkenes*”, *Chem. Eur. J.* **2013**, *19*, 5250.
2. **Yu-Chen Chen**, Ming-Kui Zhu, and Teck-Peng Loh, “*Csp³-Csp³ Bond Cleavage in the Palladium-Catalyzed Aminohydroxylation of Allylic Hydrazones Using Atmospheric Oxygen as the Sole Oxidant*”, *Org. Let.* **2015**, *17*, 2712.
3. **Yu-Chen Chen**, Jie-Sheng Tian, and Teck-Peng Loh, “*Iron-catalyzed regioselective intermolecular sp² C-H bond amination of aromatic molecules*”, manuscript in preparation.