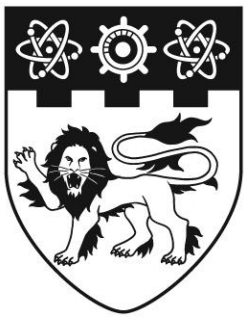

NANYANG TECHNOLOGICAL UNIVERSITY

EXPEDIENT SYNTHESIS OF HETEROCYCLES AND METHYL SULFONYL COMPOUNDS *VIA* C-X BONDS (X = O, N, S) CONSTRUCTION

JIANG YAOJIA

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2014

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School of Physical and Mathematical Sciences

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TABLE OF CONTENTS

SUMMARY

In this thesis, we have described new strategies for the synthesis of heterocycles including furans, 2*H*-azirines, pyrroles, and pyridines through construction of C–O and C–N bonds, respectively as well as novel approaches to synthesis of methyl sulfonyl compounds including *β*-keto methyl sulfones and (*E*)-vinyl methyl sulfones through C–S bond construction.

Chapter 1

In chapter 1, we have described diverse transformations of *α*-diazo-*β*-keto compounds into oxygen or nitrogen containing heterocycles in the presence of transition metal catalysts. For intermolecular reaction, a dual method has been presented to prepare 2-aminofurans and 2-unsubstituted furans based on copper-catalyzed [3 + 2] cycloaddition of *α*-diazo-*β*-keto compounds with enamine derivatives. For intramolecular reaction, a novel cascade rearrangement of *α*-diazo-*β*-keto oxime ethers has been studied to access 2*H*-azirine-2-carboxylic esters with quaternary centers in excellent yields.

Chapter 2

In chapter 2, we have described two methodologies for the synthesis of multi-substituted pyrroles from common substrates, *α*-diazo-*β*-keto oxime ethers, involving 2-vinyl-2*H*-azirines as key intermediates. For the terminal vinyl site with mono-substitution, the nitrene complex was derived from the ring-opening of 2*H*-azirines, which cyclized with the C–C double bond directly to afford highly

substituted pyrroles in the presence of Rh(II) catalyst. On the other hand, for the terminal vinyl site with disubstitutions, 2*H*-pyrroles were initially obtained following the tandem rearrangement pathway and subsequently migrated to form fully substituted pyrroles with Ni(II) catalyst.

Chapter 3

In chapter 3, we have described two methodologies to synthesize multi-substituted pyridines from rhodium-catalyzed nitrene reaction and DBU-mediated ring opening of 2-allyl-2*H*-azirines. *α*-Diazo-*β*-keto oxime ethers underwent cascade rearrangement to yield 2-vinyl-2*H*-azirines as key intermediates, which further underwent ring-opening in the presence of Rh(II) catalyst to achieve amination of sp^3 C–H bond of allylic carbon. This reaction tolerated a variety of functional groups and provided a new access to multi-substituted pyridines. On the other hand, we prepared the 2-allyl-2*H*-azirines according to the known Nebel reaction, and found that in the absence of metal catalysts, only commercially available base DBU could successfully promote the opening of the small ring and the resulting 1-azatrienes formed pyridines in good yields *via* 6π-electrocyclization.

Chapter 4

In chapter 4, we have described a radical strategy promoted by copper, oxygen and $HPO(OEt)_2$ for the difunctionalization of alkenes to synthesize *β*-keto methyl sulfones; meanwhile, we have also demonstrated that alkynes could be directly underwent methyl sulfonylation to afford (*E*)-vinyl methyl sulfones through

modification of the reaction condition. We developed a new catalytic system that involves copper, oxygen and $HPO(OEt)_2$ to generate the hydroxyl radical *in situ* which initiates a cascade radical reactions. DMSO was activated in the reaction system to afford methyl sulfonyl radical that can functionalize both the aryl alkenes and alkynes. Isotopic labeling and $^{18}O_2$ experiments were performed to investigate the reaction mechanism.

List of Abbreviations

Ac	acetyl
Acac	acetylacetonate
Aq	aqueous
Ar	aryl (substituted aromatic ring)
Bn	benzyl
Bu	butyl
calcd	calculated
cat.	catalytic
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N*,*N*-dimethylformamide
eq/equiv	equivalent
ESI	Electrospray Ionization
Esp	*α*,*α*,*α*',*α*'-tetramethyl-1,3-benzenedipropionate
Et	ethyl
EWG	electron-withdrawing group
Hex	hexanoate

hfacac	hexafluoroacetylacetonate
HMDS	hexamethyldisilazane
L	ligand(s)
LDA	lithium diisopropylamide
LG	leaving group
M	concentration (mol/L)
M^+	parent ion peak (mass spectrum)
Me	methyl
Min	minute(s)
mol%	mole percent
mp	melting point
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Enhancement Spectroscopy
Nu	nucleophile
Oct	octanoate
Pfb	perfluorobutyrate
Ph	phenyl
Piv	pivalate
Ppm	parts per million
Pr	propyl
Rt	room temperature
TBAB	tetrabutyl ammonium bromide

Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
tfacam	trifluoroacetamide
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl
Tr	triphenylmethyl
Ts	para-toluenesulfonyl

CHAPTER 1

Synthesis of Furans and 2H-Azirines from α-Diazo-β-Keto Compounds via Carbenoid-Mediated Transformations

CHAPTER 1 SYNTHESIS OF FURANS AND 2*H*-AZIRINES FROM *α*-DIAZO-*β*-KETO COMPOUNDS *VIA* CARBENOID-MEDIATED TRANSFORMATIONS

1.1 OVERVIEW

Furans and their derivatives take an important role in the class of oxygenated heterocycles due to their prevalence in many pharmaceuticals, natural products, and functional materials.[1] 2-Aminofurans serve as important organic intermediates that could undergo facile transformations to various synthetic targets including pyrroles,[2] cyclohexenones,[3] aniline derivatives,[4] and maleic anhydrides.[5] Despite the valuable utility of 2-aminofurans, promising synthetic methods for them are rather limited because of their instability. Our strategy involves the installment of an electron-deficient substituent at the 3-position to enhance the stability of the otherwise unstable 2-aminofurans.[6] In this chapter, we described a dual method to synthesize 2-aminofurans and 2-unsubstituted furans based on a copper-catalyzed [3+2] cycloaddition of *α*-carbonyl diazo compounds with enamine derivatives.

2*H*-Azirine is the smallest nitrogen unsaturated heterocyclic system and has

[1] a) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076; b) Brown, R. C. D. *Angew. Chem., Int. Ed.*, **2005**, *44*, 850; c) Hou, X.-L.; Yang, Z.; Yeung, K.-S.; Wong, H. N. C. in Progress in Heterocyclic Chemistry, ed. Gordon W. G.; John, A. J. Elsevier, **2009**, vol. 21, pp. 179–223; d) Dennis L, W. in Progress in Heterocyclic Chemistry, ed. Gordon, W. G.; John, A. J. Elsevier, **2005**, vol. 17, pp. 1–32.

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[3] a) Boonsompat, J.; Padwa, A. *J. Org. Chem*. **2011**, *76*, 2753; b) Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2006**, *9*, 279.

[4] a) Petronijevic, F. R.; Wipf, P. *J. Am. Chem. Soc.* **2011**, *133*, 7704; b) Trost, B. M.; McDougall, P. J. *Org. Lett.* **2009**, *11*, 3782; c) Medimagh, R.; Marque, S.; Prim, D.; Chatti, S.; Zarrouk, H. *J. Org. Chem.* **2008**, *73*, 2191.

[5] Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Fong, K. C.; Choi, H. S. *J. Am. Chem. Soc.* **2002**, *124*, 2190.

[6] a) Mossetti, R.; Caprioglio, D.; Colombano, G.; Tron, G. C.; Pirali, T. *Org. Biomol. Chem.* **20**11, *9*, 1627; b) Liu, P.; Lei, M.; Ma, L.; Hu, L. *Synlett* **2011**, 1133; c) Medimagh, R.; Marque, S.; Prim, D.; Chatti, S.; Zarrouk, H. *J. Org. Chem.* **2008**, *73*, 2191; d) Nair, V.; Vinod, A. U. *Chem. Commun*. **2000**, 1019.

been extensively studied as useful synthetic intermediates.[7] The azirine moiety is also widespread in natural products such as azirinomycin, (*S*)-(1)-dysidazirine and (*S*)-(1)-antazirine.[8] In view of the synthetic values of this small ring, great efforts have been devoted to develop simpler, milder, and more efficient method to access diversely functionalized 2*H*-azirine derivatives. The existing methods are reliable though suffer from base dependency and substrates limitation. In this chapter, we described a novel cascade rearrangement of *α*-diazo-*β*-keto oxime ether under catalytic and neutral conditions leading to the formation of 2*H*-azirine-2-carboxylic esters.

1.2 SYNTHESIS OF FURANS *VIA* CARBENOID-MEDIATED [3 + 2] CYCLOADDITION

1.2.1 INTRODUCTION

Furans and their derivatives have attracted great interest in last several decades because of its pervasiveness in many medicine chemistry, natural moleculars, and conjugated polymers.[9] Some naturally occurring furans possess exciting biological activities, which allow advancement in the treatment of cancer, diabetes, and allergic activities.[10] Substituted furans are useful building blocks in organic synthesis as well,

[7] a) Khlebnikov, A. F.; Novikov, M. S. *Tetrahedron* **2013**, *69*, 3363; b) Padwa, A. Comprehensive Heterocyclic Chemistry III; Elsevier, Ltd.: Amsterdam, **2008**; pp 1-104; c) Skepper, C. K.; Molinski, T. F. *J. Org. Chem.* **2008**, *73*, 2592; d) Melo, T. M. V. D. P. E.; Gonsalves, A. M. R. *Curr. Org. Synth.* **2004**, *1*, 275; e) Palacios, F.; Retana, A. M. O.; Marigorta, E. M.; Santos, J. M. *Org. Prep. Proced. Int.* **2002**, *34*, 219; f) Gilchrist, T. L. *Aldrichimica Acta* **2001**, 51; g) Padwa, A.; Woolhouse, A. D. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R.; Rees, C. W.; Eds.; Pergamon Press: Oxford; **1984**; Vol. 7, pp 47−93.

[8] a) Skepper, C. K.; Molinski, T. F. *J. Org. Chem.* **2008**, *73*, 2592; b) Salomon, C. E.; Williams, D. H.; Faulkner, D. J. *J. Nat. Prod.* **1995**, *58*, 1463; c) Molinski, T. F.; Ireland, C. M. *J. Org. Chem.* **1988**, *53*, 2103.

[9] a) Gandini, A.; Belgacem, M. N. *Prog. Polym. Sci.* **1997**, *22*, 1203; b) Wu, C. C.; Hung, W. Y.; Liu, T. L.; Zhang, L. Z.; Luh, T. Y. *J. Appl. Phys.* **2003**, *93*, 5465; c) Cui, X.; Xu, X.; Wojtas, L.; Kim, M. M.; Zhang, X. P. *J. Am. Chem. Soc.* **2012**, *134*, 19981; d) Ripaud, E.; Demeter, D.; Rousseau, T.; Boucard-Cetol, E.; Allain, M.; Po, R.; Leriche, P.; Roncali, J. *Dyes Pigm.* **2012**, *95*, 126.

[10] a) Rahmathullah, S. M.; Hall, J. E.; Bender, B. C.; McCrudy, D. R.; Tidwell, R. R.; Boykin, D. W. *J. Med. Chem.* **1999**, *42*, 3994; b) Rodr ǵuez, A. D.; Shi, J.; Huang, S. D. *J. Nat. Prod.* **1999**, *62*, 1228; c)

such as Diels-Alder cycloaddition.[11] Considering the importance of the furan skeleton, diverse methods have been developed in last several decades (Scheme 1.1).

Traditionally, substituted furans **1** can be prepared through the condensation of 1,4-dicarbonyl compounds **2** under acidic condition, more commonly known as Paal-Knorr furan synthesis (Scheme 1.1, route a).[12] Recently, a variety of significant and elegant metal-catalyzed methods have been developed for the synthesis of furan derivatives. Sydnes reported that a novel access to 4-amino-substituted furfurals **1** from γ-hydroxy-α, β-unsaturated acetylenic ketones **3** through reaction with secondary amines, followed by treatment with acid in a mixture of THF and water (Scheme 1.1, route b).[13] Enynedione compounds **4** were successfully applied to construct trisubstituted furans **1** (Scheme 1.1, route c) through intramolecular cyclization.[14]

In 2004, Larock and co-workers discovered the utilization of 2-(1-alkynyl)-2-alkene-1-ones **5** as common substrates to prepare substituted furans *via* gold-catalyzed cyclization (Scheme 1.1, route d).[15] Thereafter, several other groups have employed enynones to synthesize diversely functionalized furans in the presence of various metal catalysts.[16]

Georgiou, T.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2006**, *8*, 1945; d) Chakraborty, T. K.; Arora, A.; Roy, S.; Kumar, N.; Maiti, S. *J. Med. Chem.* **2007**, *50*, 5539; e) Palmer, L. I.; Read de Alaniz, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7167.

[11] a) Dean, F. M. *Adv. Heterocycl. Chem.* **1981**, *30*, 168; b) Sargent, M. V.; Dean, F. M. *Furans and their Benzo Derivatives*. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W.; Cheesman, G. W. H., Eds.; Pergamon Press: London, **1984**; Vol. 4, pp 599-656.

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[13] Erdenebileg, U.; Høstmark, I.; Polden, K.; Sydnes, L. K. *J. Org. Chem.* **2014**, *79*, 1213

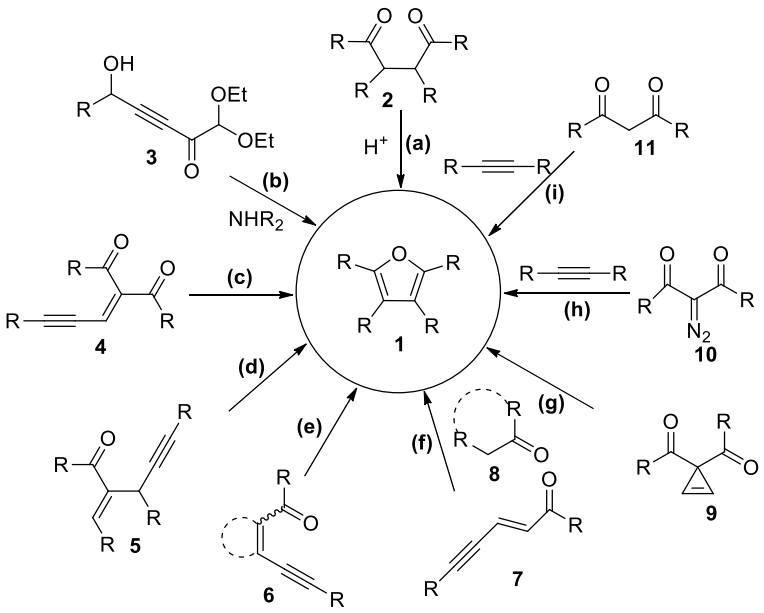
[14] a) Vicente, R.; Gonzalez, J.; Riesgo, L.; Gonzalez, J.; Lopez, L. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8063; b) Gonzalez, J.; Gonzalez, J.; Perez-Calleja, C.; Lopez, L. A.; Vicente, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 1; c) Clark, J. S.; Boyer, A.; Aimon, A.; Garcia, P. E.; Lindsay, D. M.; Symington, A. D. F.; Danoy, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 12128; d) Cao, H.; Zhan, H.; Cen, J.; Lin, J.; Lin, Y.; Zhu, Q.; Fu, M.; Jiang, H. *Org. Lett.* **2013**, *15*, 1080; e) Zhan, H.; Lin, X.; Qiu, Y.; Du, Z.; Li, P.; Li, Y.; Cao, H. *Eur. J. Org. Chem.* **2013**, 2284.

[15] a) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164; b) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679.

[16] a) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531; b) Liu, Y.; Zhou, S. *Org. Lett.* **2005**, *7*, 4609; c) Oh, C. H.; Reddy, V. R.; Kim, A.; Rhim, C. Y. *Tetrahedron Lett.* **2006**, *47*, 5307; d) Xiao, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1903; e) Liu, F.; Yu, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5505; f) Xiao, Y.; Zhang, J. *Chem. Commun.* **2009**, *45*, 3594; g) Liu, F.; Qian, D.; Li,

In addition, 2-alken-4-yn-1-ones **6** (mostly in *Z*-form) were also suitable starting materials to prepare substituted furans (Scheme 1.1, route e).[17]Reddy recently reported a novel and efficient method for the synthesis of polysubstituted furans **1** *via* DBU-promoted tandem Michael addition/5-exo-dig cyclo-isomerization of enynes **7** and keto-methylenes **8** (Scheme 1.1, route f).[18] Cyclopropenes are the highly strained and readily accessible carbocyclic molecules, which have been shown to possess useful reactivity in organic synthesis. Ma group has described the transition metal-catalyzed reaction of functionalized cyclopropenes **9** to generate highly-substituted furans (Scheme 1.1, route g).[19]

Zhang group demonstrated a Co(III)-catalyzed reaction of *α*-diazocarbonyls **10**



Scheme 1.1 Reported methods for the synthesis of furan derivatives

L.; Zhao, X.; Zhang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 6669; h) Li, W.; Zhang, J. *Chem. Commun.* **2010**, *46*, 8839.

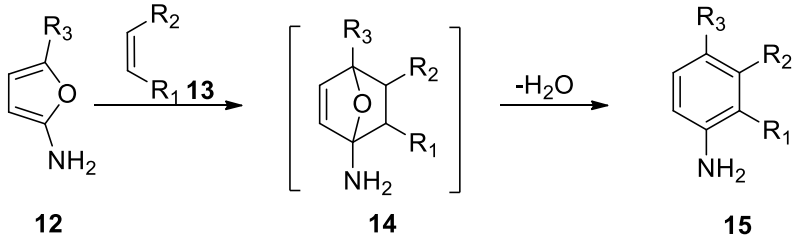
[17] a) Nakatani, K.; Tanabe, K.; Saito, I. *Tetrahedron Lett.* **1997**, *38*, 1207; b) Nakatani, K.; Adachi, K.; Tanabe, K.; Saito, I. *J. Am. Chem. Soc.* **1999**, *121*, 8221; c) Miki, K.; Nishino, F.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 5260; d) Miki, K.; Yokoi, T.; Nishino, F.; Kato, Y.; Washitake, Y.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 1557; e) Kuroda, H.; Hanaki, E.; Kawakami, M. *Tetrahedron Lett.* **1999**, *40*, 3753; f) Kuroda, H.; Hanaki, E.; Izawa, H.; Kano, M.; Itahashi, H. *Tetrahedron* **2004**, *60*, 1913; g) Herndon, J. W.; Wang, H. *J. Org. Chem.* **1998**, *63*, 4564; h) Casey, C. P.; Strotman, N. A. *J. Org. Chem.* **2005**, *70*, 2576; i) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432.

[18] Reddy, C. R.; Reddy, M. D. *J. Org. Chem.* **2014**, *79*, 106.

[19] a) Ma, S.; Zhang, J. *J. Am. Chem. Soc.* **2003**, *125*, 12386; b) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645.

with a wide range of terminal alkynes with varied steric and electronic properties, affording polyfunctionalized furans with excellent regioselectivity (Scheme 1.1, route h).[20] The direct annulation of alkynoates and 1,3-dicarbonyl compounds **11** under oxidative condition to construct polysubstituted furans **1** has also been studied recently.[21] Although these achievements, the existing methods still suffer from harsh reaction conditions, long steps for preparing substrates and functional groups limitions. It is high desireable to develop more atom-economicl and promising methodologies.

2-Aminofurans are important organic intermediates that have been applied to synthesis of pyrroles, cyclohexenones, aniline derivatives, and maleic anhydrides.[2-5] For instance, Padwa reported that a Diels–Alder reaction of 2-aminofuran derivatives **12** with activated dienophiles **13** as the key step in the synthesis of substituted anilines **15** (Scheme 1.2).[22]

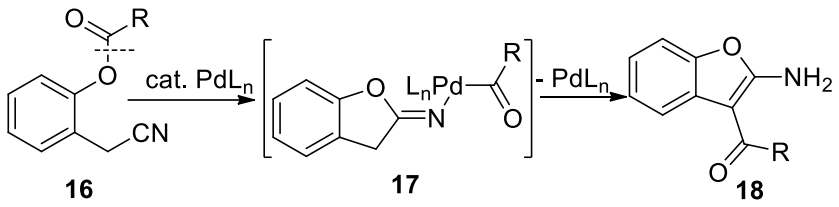


Scheme 1.2 Synthesis of substituted anilines from 2-aminofuran

Despite the enormous value of 2-aminofurans, the reliable synthetic method for their preparation is rather limited because of their instability. [23] It has been known that the presence of electron-deficient substituent at the 3-position remarkably increases

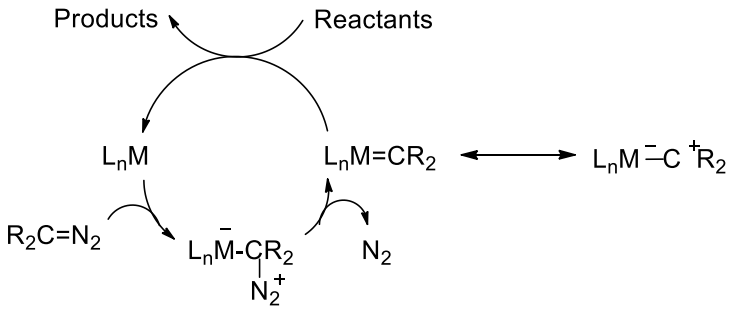
[20] Cui, X.; Xu, X; Wojtas, L.; Kim, M. M.; Zhang, X. P. *J. Am. Chem. Soc.* **2012**, *134*, 19981.
[21] a) Liu, W.-B.; Chen, C.; Zhang, Q. *Synth. Commun.* **2013**, *43*, 951; b) He, C.; Guo, S.; Ke, J.; Hao, J.; Xu, H.; Chen, H.; Lei, A. *J. Am. Chem. Soc.* **2012**, *134*, 5766; c) Sivan, A.; Deepthi, A.; Nandialath, V. *Synthesis* **2011**, *15*, 2466; d) Liu, W.; Jiang, H.; Zhang, M.; Qi, C. *J. Org. Chem.* **2010**, *75*, 966.
[22] a) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. H. *J. Org. Chem.* **1997**, *62*, 4088; b) Li, G.; Padwa, A. *Org. Lett.* **2011**, *13*, 3767.
[23] a) Quai, M.; Frattini, S.; Vendrame, U.; Mondoni, M.; Dossena, S.; Cereda, E. *Tetrahedron Lett.* **2004**, *45*, 1413; b) Bobsikova, M.; Clegg, W.; Coles, S. J.; Dandarova, M.; Hursthouse, M. B.; Kiss, T.; Krutosikova, A.; Liptaj, T.; Pronayova, N.; Ramsden, C. A.; *J. Chem. Soc. Perkin Trans. 1*, **2001**, 680; c) Vargha, L.; Ramonczai, J.; Bite, P. *J. Am. Chem. Soc.* **1948**, *70*, 371.

the stability of the otherwise unstable 2-aminofurans.[24] Existing methods mainly depend on the reduction of 2-nitrofurans[25] and cyclization of nitriles.[26] Ohe and co-workers developed a unique palladium-catalyzed intramolecular cycloisomerisation of 2-(cyanomethyl) phenyl esters **16** to afford 3-acyl-2-aminobenzofurans **18**, substituted heterocycles which were otherwise difficult to access (Scheme 1-3).[27] Other preparation methods include the nucleophilic displacement of activated furans with amines.[28]



Scheme 1.3 Palladium catalyzed synthesis of 2-aminobenzofurans

Playing a significant role in organic chemistry, diazocarbonyl compounds have been well studied in last several decades.[29] They are readily available from simple carbonyl compounds and have been applied in the construction of unique C-C, C-O,



Scheme 1.4 Transition-metal catalyzed reactions of diazocarbonyl compounds

[24] a) Mossetti, R.; Caprioglio, D.; Colombano, G.; Tron, G. C.; Pirali, T. *Org. Biomol. Chem.* **2011**, *9*, 1627; b) Liu, P.; Lei, M.; Ma, L.; Hu, L. *Synlett* **2011**, 1133; c) Medimagh, R.; Marque, S.; Prim, D.; Chatti, S.; Zarrouk, H. *J. Org. Chem.* **2008**, *73*, 2191; d) Nair, V.; Vinod, A. U. *Chem. Commun*. **2000**, 1019.

[25] Rahaim, R. J.; Maleczka, R. E. *Org. Lett.* **2005**, *7*, 5087.

[26] Liu, P.; Lei, M.; Ma, L.; Hu, L. *Synlett* **2011**, 1133.

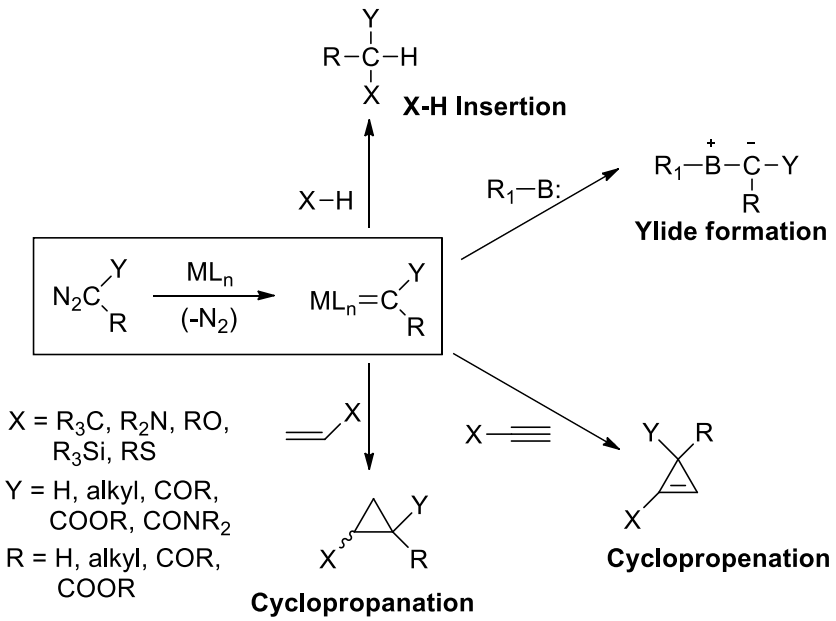
[27] Murai, M.; Miki, K.; Ohe, K. *Chem. Commun.* **2009**, 3466.

[28] Medimagh, R.; Marque, S.; Prim, D.; Chatti, S. *Org. Biomol. Chem.* **2011**, *9*, 6055.

[29] Ferreira, V. F. *Curr. Org. Chem.* **2007**, *11*, 177.

and C-N bonds under very mild conditions.[30] Under thermal or photochemical condition, they liberate free carbenes facilitated through the extrusion of thermodynamically stable dinitrogen.[31] In the presence of transition metals, diazocarbonyl compounds formed the metal-stabilized carbenes (also known as carbenoid) upon release of nitrogen gas. Transfer of the metal carbenes to the reactants complete the catalytic cycle (Scheme 1.4).[32] It should be noted that the central carbon of the carbenoid is electrophilic compared to the nucluphilic property of free carbene.

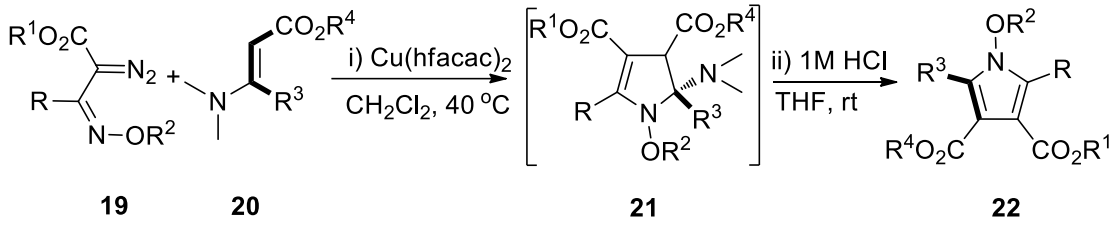
These metal carbene complexes, generated from transition metals and Lewis acids catalyzed decomposition of diazocarbonyl compounds, could promote a wide range of carbenoid transformations (Scheme 1.5), such as cyclopropanation, cyclopropenation, ylide formation, insertion reaction, and Wolff rearrangement.[33, 34]



Scheme 1.5 Diverse transformations of carbenoids

[30] Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.
[31] Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: Orlando, 1986.
[32] Doyle, M. P. *Chem. Rev*. **1980**, *66*, 919.
[33] Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998.
[34] Selected reviews: a) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. b) Padwa, A.; Weingarten, M. D. *Chem. Rev*. **1996**, *96*, 223. c) Doyle, M. P.; Forbes, D. C. *Chem. Rev*. **1998**, *98*, 911. d) Davies, H. M. L.; Beckwith, R. E. *Chem. Rev*. **2003**, *103*, 2861. e) Wee, A. G. H. *Curr. Org. Synth*. **2006**, *3*, 499.

A variety of metal catalysts have been prepared and applied in the reactions of diazocarbonyl compounds. Two of the most conventionally employed catalysts are copper(II) and rhodium(II) complexes, others include cobalt,[35] iron,[36] ruthenium[37,38] and chromium[39] complexes. Park group recently reported on the synthesis of pyrrole derivatives **22** *via* the [3 + 2] cycloaddition of *α*-diazo oxime ethers **19** with substituted enamines **20** (Scheme 1.6).[40]



19 **20** **21** **22**

Scheme 1.6 Synthesis of pyrrole derivatives *via* [3+2] cycloaddition

Inspired by interest in diazo chemistry, we proposed a straightforward dual pathway to 2-aminofurans **27** and 2-unsubstituted furans **28** through the reaction of *α*-diazo-*β*-keto compounds with readily accessed enamine derivatives (Scheme 1.7).

---

[35] For the selected examples of cobalt complex-catalyzed reaction of *α*-diazocarbonyl compounds, see: a) Ikeno, T.; Iwakura, I.; Yabushita, S.; Yamada, T. *Org. Lett*. **2002**, *4*, 517. b) Huang, L.; Chen, Y.; Gao, G.-Y.; Zhang, X. P. *J. Org. Chem*. **2003**, *68*, 8179. c) Chen, Y.; Zhang, X. P. *J. Org. Chem*. **2004**, *69*, 2431. d) Chen, Y.; Fields, K. B.; Zhang, X. P. *J. Am. Chem. Soc*. **2004**, *126*, 14718.

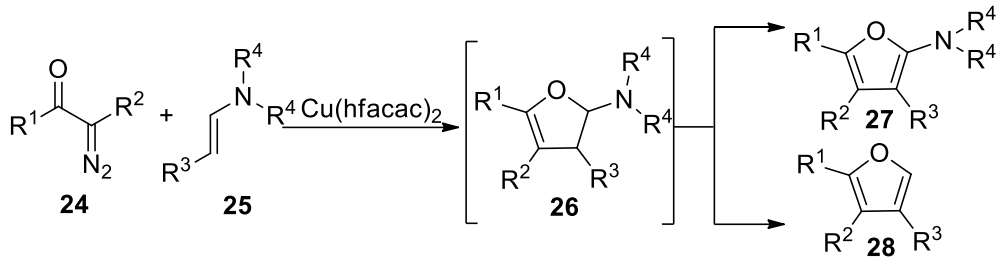
[36] For the selected example of iron complex-catalyzed reaction of *α*-diazocarbonyl compounds, see: a) Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc*. **2002**, *124*, 13185. b) Du, G.; Andrioletti, B.; Rose, E.; Woo, L. K. *Organometallics* **2002**, *21*, 4490. c) Edulji, S. K.; Nguyen, S. T. *Organometallics* **2003**, *22*, 3374. d) Aviv, I.; Gross, Z. *Chem. Commun*. **2006**, 4477.

[37] For a recent review on ruthenium-catalyzed carbenoids cyclopropanation with diazo compounds, see: Maas, G. *Chem. Soc. Rev*. **2004**, *33*, 183.

[38] For the selected examples of ruthenium complex-catalyzed reaction of *α*-diazo carbonyl compounds, see: a) Li, G.-Y.; Chen, J.; Yu, W.-Y.; Hong, W.; Che, C.-M. *Org. Lett*. **2003**, *5*, 2153. b) Zhou, C.-Y.; Yu, W.-Y.; Chan, P. W. H.; Che, C.-M. *J. Org. Chem*. **2004**, *69*, 7072. c) Maux, P. L.; Abrunhosa, I.; Berchel, M.; Simonneaux, G.; Gulea, M.; Masson, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2569. d) Ferrand, Y.; Maux, P. L.; Simonneaux, G. *Org. Lett*. **2004**, *6*, 3211. e) Xu, H.-W.; Li, G.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett*. **2005**, *7*, 5349. f) Cornejo, A.; Fraile, J. M.; Garc á, J. I.; Gil, M. J.; Mart ínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *Organometallics* **2005**, *24*, 3448. g) Bonaccorsi, C.; Mezzetti, A. *Organometallics* **2005**, *24*, 4953. h) Wang, M.-Z.; Xu, H.-W.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Adv. Synth. Catal*. **2006**, *348*, 2391. i) Bonaccorsi, C.; Santoro, F.; Gischig, S.; Mezzetti, A. *Organometallics* **2006**, *25*, 2002. j) Xiao, Q.; Wang, J. *Acta Chim. Sinica*. **2007**, *65*, 1733.

[39] For the selected example of chromium complex-catalyzed reaction of α-diazocarbonyl compounds, see: Hahn, N. D.; Nieger, M.; Dötz, K. H. *Eur. J. Org. Chem*. **2004**, *2004*, 1049.

[40] Lourdusamy, E.; Yao, L.; Park, C.-M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7963.

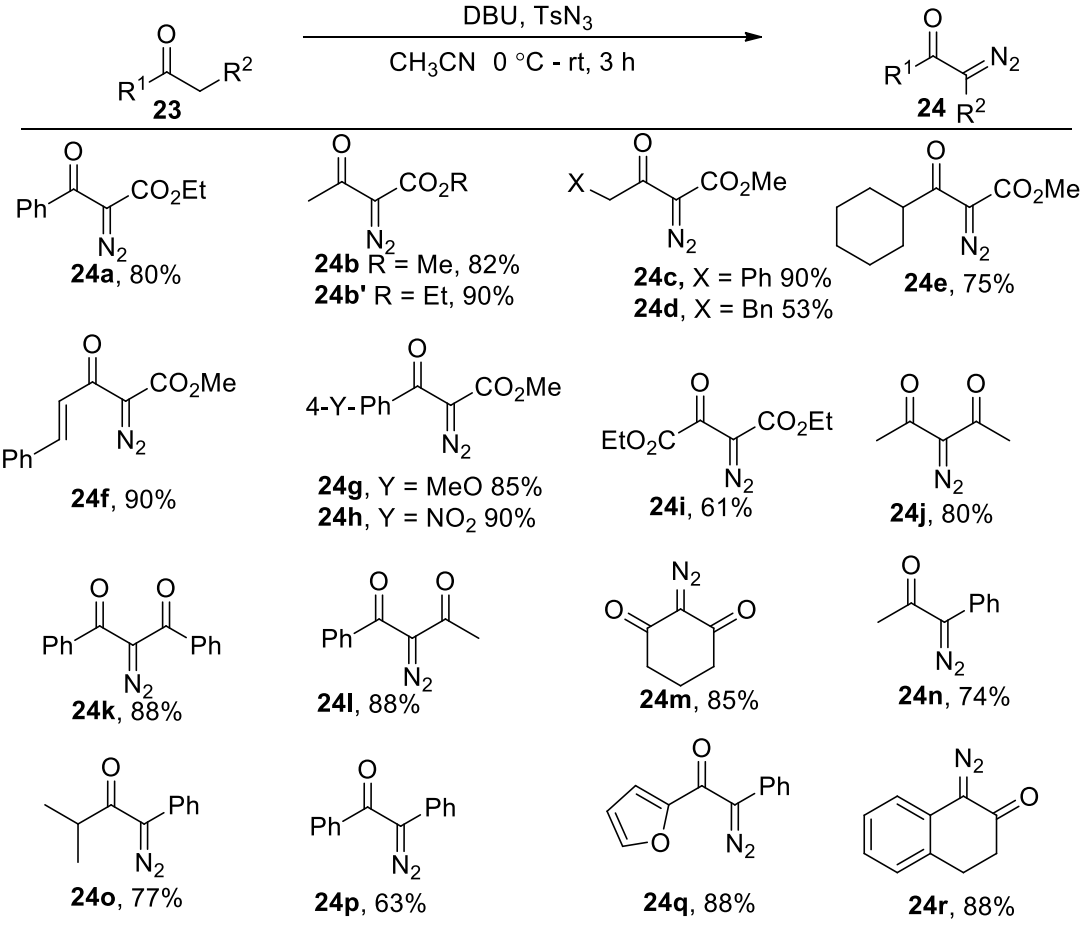


Scheme 1.7 Synthesis of furan derivatives in a dual pathway

1.2.2 RESULT AND DISCUSSION

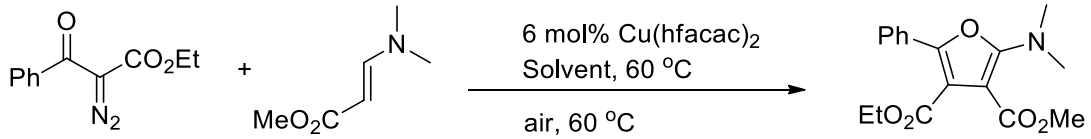
The reported methods allowed a variety of *α*-diazo-*β*-keto compounds **24** to be readily accessed according to reported methods from carbonyl derivatives **23** by diazo transfer reactions under mild conditions (Table 1-1).

Table 1-1 Preparation of *α*-diazo-*β*-keto compounds



Initially, different metal salts were investigated for the cycloaddition of **24a** with **25a** (Table 1-2). The desired furan products were obtained under ambient air atmosphere for oxidation of cycloadducts intermediates **26aa**. Such condition was also identified as the optimal oxidative condition after a comparison with other oxidants tested (Table 1-3). $Rh_2(OAc)_4$ failed to give the corresponding product and the starting materials were recovered (Table 1-2, entry 1). In contrast, copper salts showed better catalytic activities afforded more positive results. For example, both Cu(I) and Cu(II) were found to give the desired product **27aa** albeit in low yields (Table 1-2, entries 2-3). Among them, $Cu(hfacac)_2$ was identified to be the most efficient catalyst, giving the cycloadducts **27aa** in 72% yield (Table 1-2, entry 6). Further screening of the reaction temperature and solvents revealed that the reaction proceeded most efficiently in dichloroethane at 60 °C (Table 1-2, entries 7-10).

Table 1-2 Optimization of cycloaddition



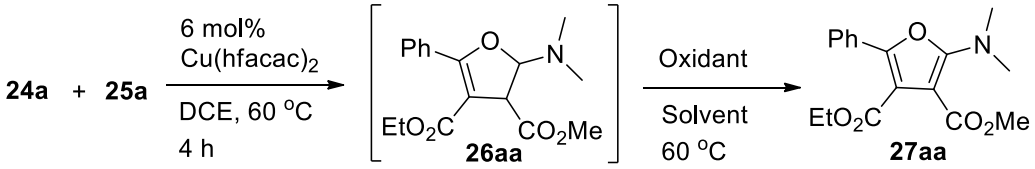
24a **25a** **27aa**

Entry	Catalyst[a]	Solvent[b]	Yield[c] (%)
1	$Rh_2(OAc)_4$	DCE	0
2	$(Cu(OTf))_2$.Benzene	DCE	31
3	$Cu(OTf)_2$	DCE	33
4	$Cu(acac)_2$	DCE	19
5	$Cu(OAc)_2$	DCE	20
6	**$Cu(hfacac)_2$**	**DCE**	**72**
7	$Cu(hfacac)_2$	DCE	48[d]
8	$Cu(hfacac)_2$	PhH	36
9	$Cu(hfacac)_2$	$PhCF_3$	45
10	$Cu(hfacac)_2$	1,4-Dioxane	trace

[a]acac = acetylacetonate, hfacac = hexafluoroacetylacetonate. [b]DCE = dichloroethane. [c]Determined by NMR *vs.* standard. [d]Reaction performed at 80 °C.

As we envisaged that 2-amino-2,3-dihydrofurans **26aa** is the key intermediate of the reaction, our attention then turned to screen the oxidation conditions leading to 2-aminofurans (Table 1-3). The result revealed that the treatment of cycloadduct **26aa** with different organic and metal oxidants could afford 2-aminofuran **27aa** albeit in low to moderate yields (Table 1-3, entries 1-6). Reaction which performed under ambient air condition proceeded well to give **27aa** in 72% yield (Table 1-3, entry 8). However, the substrate decomposed completely when subjected under a pure oxygen atmosphere (Table 1-3, entry 7). 2-Aminofurans are speculated to be extremely sensitive to oxidative condition and tolerated only mild oxidative conditions.

Table 1-3 Optimization of oxidation of 2-amino-2,3-dihydrofuran

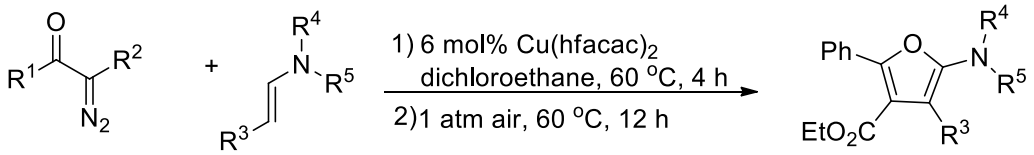


Entry	Oxidant[a]	Solvent[b]	Yield[c] (%)
1	mCPBA	DCM	34
2	DDQ	Toluene	52
3	Ag_2O	Benzene	36
4	$Cu(OAc)_2$	DCE	42
5	$Mn(OAc)_3$	AcOH	45
6	CAN	CH_3CN	49
7	1 atm O_2	DCE	-
8	**1 atm air**	**DCE**	**72**

[a]MCPBA = meta-chloroperbenzoic acid, DDQ = 2,3-dichloro-5,6-dicyano-1,4 benzo-quinone, CAN = cerium ammonium nitrate. [b]DCE = dichloroethane. [c]Determined by NMR *vs.* standard.

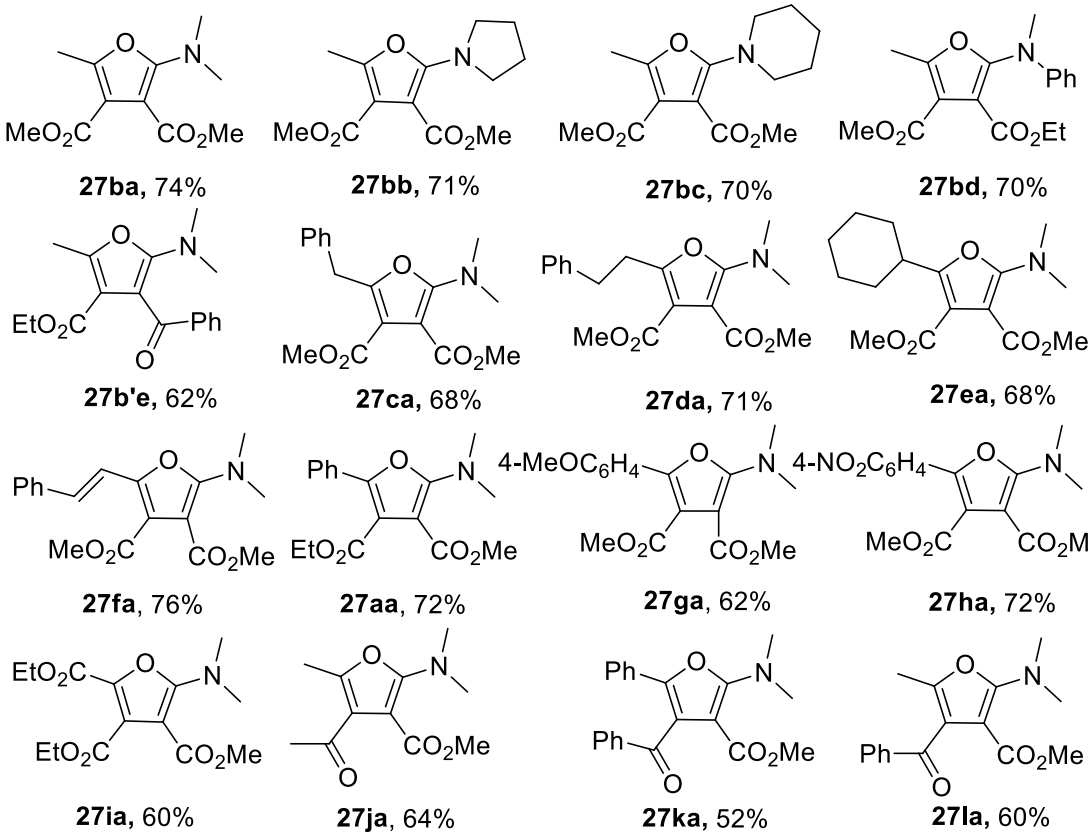
With the optimal reaction conditions in hand, we studied the substrate scope for the synthesis of 2-aminofurans (Table 1-4). Generally, the reaction of various *α*-diazo-*β*-keto compounds with enamines proceeded smoothly to deliver correspondi-

Table 1-4 Substrate scope for 2-aminofurans[a]



24 **25** **27**

25a R^3 = CO_2Me R^4, R^5 = Me, Me
25b R^3 = CO_2Me R^4, R^5 = $(CH_2)_4$
25c R^3 = CO_2Me R^4, R^5 = $(CH_2)_5$
25d R^3 = CO_2Et R^4, R^5 = Me, Ph
25e R^3 = PhC(O) R^4, R^5 = Me, Me



27ba, 74% **27bb,** 71% **27bc,** 70% **27bd,** 70%

27b'e, 62% **27ca,** 68% **27da,** 71% **27ea,** 68%

27fa, 76% **27aa**, 72% **27ga**, 62% **27ha,** 72%

27ia, 60% **27ja**, 64% **27ka,** 52% **27la,** 60%

[a]Yield of isolated products.

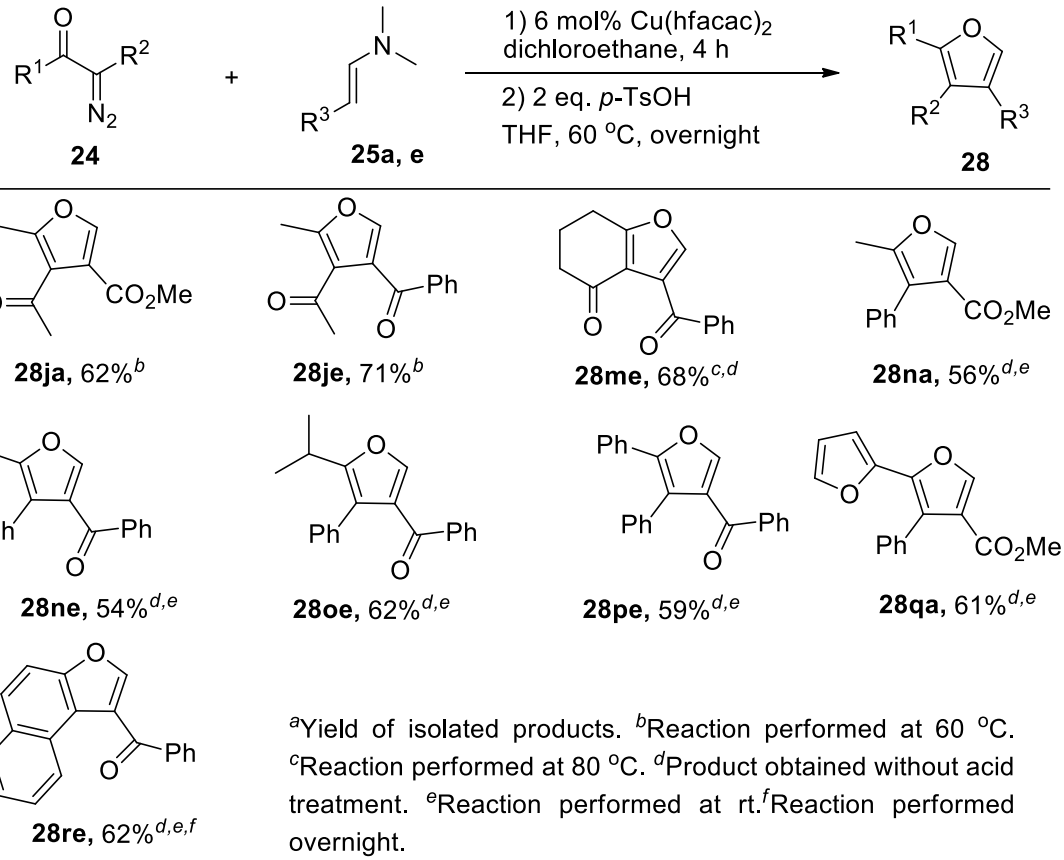
-ng products in good yields. Initially, we examined the *β*-amino acrylates bearing different amino substituents including acyclic, cyclic as well as aromatic amines, and the results showed that the reactions proceeded smoothly to give the corresponding 2-aminofurans in good yields (Table 1-4, **27ba-bd**). Additionally, when 3-amino-2-alkenones was used instead, the reactions could afford the

ketone-substituted 2-aminofurans (Table 1-4, **27b'e**). On the other hand, we also examined the generality of *α*-diazo-*β*-keto esters by varying the substituents on them. Diazo with alkyl substituted compounds reacted efficiently to give the corresponding 2-aminofurans in good yields (Table 1-4, **27ca**-**ea**). Furthermore, the reaction could tolerate the reactive carbon-carbon double bond such as the vinyl substituted diazo compound **24f** to afford the desired 2-aminofuran **27fa** in good yield. Electronic effect was then studied by employing diazo compounds with electron-rich and deficient functional groups. The result demonstrated that electronic effect had minor influence on this reaction, and all substrates gave the corresponding products in good yields regardless of their electronic properties (Table 1-4, **27ga**, **27ha**, and **27ia**). *α*-Diazo-*β*-diketones also reacted well to give the ketone-substituted 2-aminofurans (Table 1-4, **27ja** and **27ka**). Interestingly, reaction of unsymmetrical *α*-diazo-*β*-diketone **24l** with **25a** led to the regioselective formation of **27la**, arising from the less hindered ketone participating in the cycloaddition.

Next, we investigated the synthesis of 2-unsubstituted furans from the cycloaddition intermediates 2-amino-2,3-dihydrofuran through elimination of amines. We subjected *α*-diazo-*β*-diketone **24j** and *β*-amino acrylate **25a** under the same reaction conditions (6 mol % of $Cu(hfacac)_2$, dichloroethane, 60 ℃, 4 h) to generate 2-amino-2,3-dihydrofuran which was then treated with *p*-toluenesulfonic acid to provide furan **28ja**. With the primary result in hand, we explored the generality of the reaction (Table 1-5). We found that the diazo compounds with mono ketones tend to eliminate spontaneously without any acid treatment (Table 1-5, see the footnotes). The enamine derivatives could also be extended to 3-amino-2-alkenone **25e** instead of *β*-amino acrylate to afford **28je** in good yield. Fused bicyclic furan could be obtained in 68% yield when cyclic *α*-diazo-*β*-diketone **24m** was applied. Additionally, diazo

compounds with mono ketones like α-diazo-α-aryl ketone **24n** also proceeded smoothly to give aryl substituted furan **28na**. Further alteration of α-diazo-α-aryl ketones with alkyl and aryl moieties led to the construction of the corresponding furans (Table 1-5, **28oe** and **28pe**). Additionally, heterocyclic of diazo compound **24q** also reacted with **25a** smoothly to afford methyl 3-phenyl-[2,2'-bifuran]-4-carboxylate in 61% yield (Table 1-5, **28qa**). Reaction of β-tetralone-derived diazo compound **24r** with **25e** proceeded efficiently within spontaneous oxidation to afford the tricyclic furan **28re** in good yield.

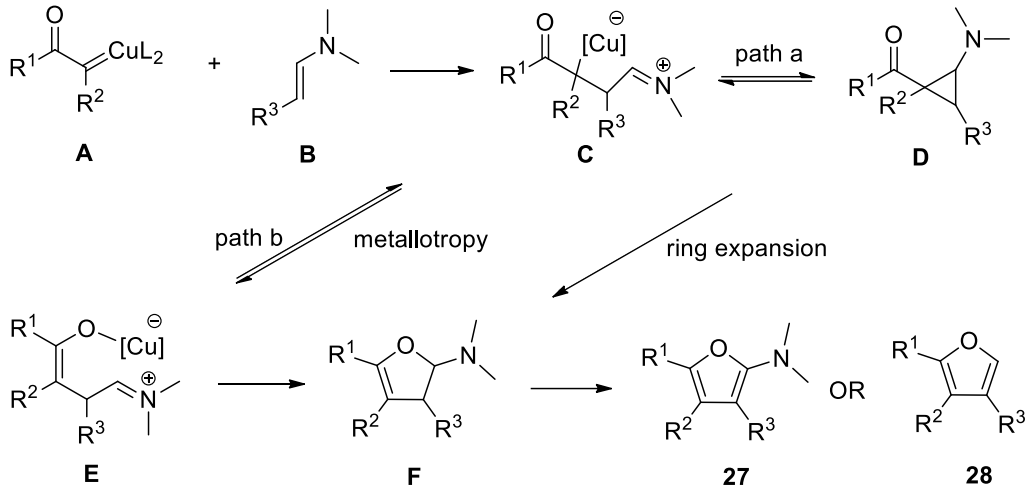
Table 1-5 Substrate scope for 2-unsubstituted furans[a]



[a]Yield of isolated products. [b]Reaction performed at 60 °C. [c]Reaction performed at 80 °C. [d]Product obtained without acid treatment. [e]Reaction performed at rt.[f]Reaction performed overnight.

We proposed the possible pathways for the reaction mechanism (Scheme 1.8). Carbenoid **A**, produced from diazo compound, underwent nucleophilic attack by enamine **B** to generate **C**. **D** could then be formed by cyclopropanation of **C** which

then underwent ring expansion to afford intermediate **F**. On the other hand, it could also undergo direct cyclization from **E** *via* metallotropy to give **F**. The intermediate **F** finally transformed to corresponding products according to the reaction conditions.



Scheme 1.8 Proposed mechanism for synthesis of furan derivatives

1.2.3 SUMMARY

In summary, we demonstrated a dual straightforward methodology for the synthesis of both 2-aminofurans and 2-unsubstituted furans. It was accomplished by reaction of carbenoids with enamines to provide 2-amino-2,3-dihydrofurans, which formed either 2-aminofurans or 2-unsubstituted furans in good yields upon the different subsequent conditions.

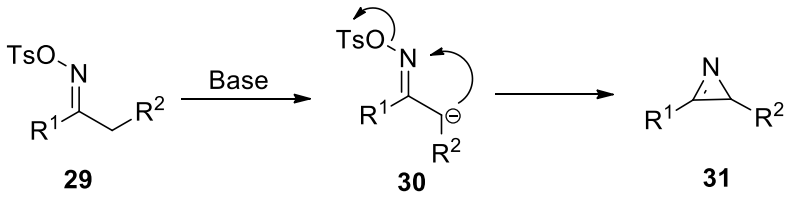
1.3 SYNTHESIS OF 2*H*-AZIRINES *VIA* TANDEM REARRANGEMENT OF *α*-DIAZO-*β*-KETO OXIME ETHERS

1.3.1 INTRODUCTION

2*H*-Azirines are a class of important azaheterocycles widely found in natural

products and also act as valuable synthetic intermediates.[41] Owing to the instability of small ring site, they tend to undergo ring opening to form unique nitrenes, dienophiles and electrophiles[42] in the presence of suitable conditions to construct various aza-compounds including isoxazoles, pyrroles, indoles, piperidines and pyridines.[43]

There are a lot of promising methods to synthesize these useful small rings as reported and summarized in several reviews.[44] For instance, a classical method is the Neber reaction which involved treatment of oxime derivatives **29** with suitable bases to induce the intramolecular cycloaddition (Scheme 1.9).[45]



Scheme 1.9 Neber reaction to 2*H*-azirines

Thermal/photochemical rearrangement of vinyl azides **32** can also afford

[41] a) Skepper, C. K.; Molinski, T. F. *J. Org. Chem.* **2008**, *73*, 2592; b) Salomon, C. E.; Williams, D. H.; Faulkner, D. J. *J. Nat. Prod.* **1995**, *58*, 1463; c) Molinski, T. F.; Ireland, C. M. *J. Org. Chem.* **1988**, *53*, 2103.

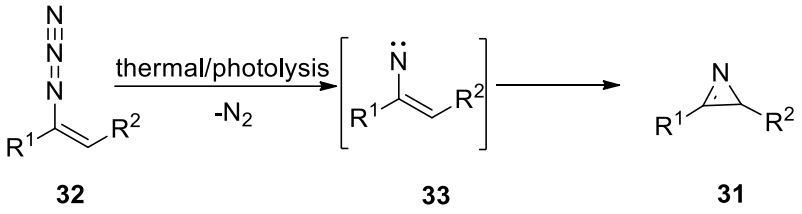
[42] a) Padwa, A. In Advances in Heterocyclic Chemistry; Katritzky, A. R., Ed.; Academic Press: Orlando, FL, 2010; Vol. 99, p 1; b) Gilchrist, T. L.; Alves, M. J. In Organic Azides; John Wiley & Sons Ltd.: Chichester, U.K., **2010**; p 167; c) Singh, G. S.; D'Hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080.

[43] a) Jana, S.; Clements, M. D.; Sharp, B. K.; Zheng, N. *Org. Lett.* **2010**, *12*, 3736; b) Candito, D. A.; Lautens, M. *Org. Lett.* **2010**, *12*, 3312; c) Padwa, A.; Stengel, T. *Tetrahedron Lett.* **2004**, *45*, 5991; d) Johns, B. A.; Gudmundsson, K. S.; Turner, E. M.; Allen, S. H.; Jung, D. K.; Sexton, C. J.; Boyd, F. L. Jr.; Peel, M. R. *Tetrahedron* **2003**, *59*, 9001; e) Stevens, K. L.; Jung, D. K.; Alberti, M. J.; Badiang, J. G.; Peckham, G. E.; Veal, J. M.; Cheung, M.; Harris, P. A.; Chamberlain, S. D.; Peel, M. R. *Org. Lett.* **2005**, *7*, 4753; f) Brahma, S.; Ray, J. K. *J. Heterocycl. Chem.* **2008**, *45*, 311; g) Alves, M. J.; Gil Fortes, A.; Lemos, A.; Martins, C. *Synthesis* **2005**, *2005*, 555; h) Timen, A. S.; Fischer, A.; Somfai, P. *Chem. Commun.* **2003**, 1150; i) Taber, D. F.; Tian, W. *J. Am. Chem. Soc.* **2006**, *128*, 1058.

[44] For reviews, see: a) Khlebnikov, A. F.; Novikov, M. S. *Tetrahedron* **2013**, *69*, 3363; b) Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; Manuel de los Santos, J. *Org. Prep. Proc. Int.* **2002**, *34*, 219; c) Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; Manuel de los Santos, J. *Eur. J. Org. Chem.* **2001**, *13*, 2401; d) Pinho e Melo, T. M. V. D.; Rocha Gonsalves, A. M. d'A. *Curr. Org. Chem.* **2004**, *1*, 275.

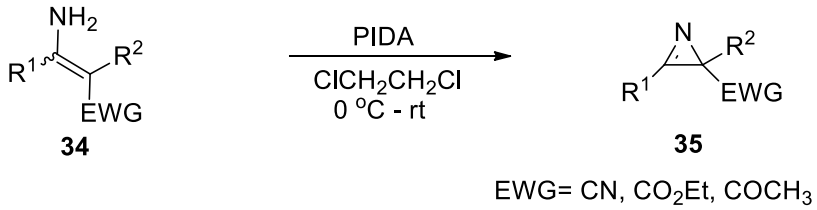
[45] a) Neber, P. W.; Burgard, A. *Liebigs Ann.* **1932**, *493*, 281; b) Neber, P. W.; Huh, G. *Liebigs Ann.* **1935**, *515*, 283.

2*H*-azirine derivatives **31** through nitrene intermediate **33** (Scheme 1.10).[46]



Scheme 1.10 Synthesis of 2*H*-azirines from vinyl azides

In 2009, Zhao Kang group developed a new synthetic methodology through the oxidation of various enamine compounds **34** by phenyliodine(III) diacetate (PIDA) into an assortment of 2-functionalize 2*H*-azirine derivatives **35** in the absence of any transition metal (Scheme 1.11).[47]



Scheme 1.11 Transion-metal-free method to synthesis of 2*H*-azirine derivatives

There are also other approaches such as oxidation of aziridines,[48] ring contraction of isoxazoles[49] and addition of carbenes/nitrenes across nitriles/alkynes[50] albeit in moderate success. In other words, these methodsis normally limited to special functional groups. Park group is interested in developing new methodology to the

[46] a) Ciabattoni, J.; Cabell, M. Jr. *J. Am. Chem. Soc*. **1971**, *93*, 1482; b) Padwa, A.; Blacklock, T. J.; Carlsen, P. H. J.; Pulwer, M. *J. Org. Chem*. **1979**, *44*, 3281; c) Banert, K. In Organic Azides; John Wiley & Sons, Ltd: Chichester, U.K., **2010**; p 113; d) Sjöholm Timén, Å.; Risberg, E.; Somfai, P. *Tetrahedron Lett.* **2003**, *44*, 5339.

[47] Li, X.; Du, Y.; Liang, Z.; Li, X.; Pan, Yan.; Zhao, K. *Org. Lett.* **2009**, *11*, 2643.

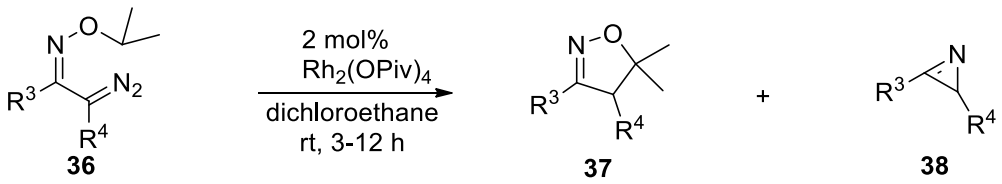
[48] a) Gentilucci, L.; Grijzen, Y.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, *36*, 4665; b) Hodgson, D. M.; Humphreys, P. G.; Miles, S. M.; Brierley, C. A. J.; Ward, J. G. *J. Org. Chem.* **2007**, *72*, 10009.

[49] Ceulemans, E.; Voets, M.; Emmers, S.; Uytterhoeven, K.; Van Meervelt, L.; Dehaen, W. *Tetrahedron* **2002**, *58*, 531.

[50] Knoll, W.; Mieusset, J.-L.; Arion, V. B.; Brecker, L.; Brinker, U. H. *Org. Lett.* **2010**, *12*, 2366.

synthesis of 2*H*-azirine derivatives on the basis of *α*-oximino carbenoids chemistry.[51] We designed diazo substrates **36** with an isopropyl group installed at oximino position as a good leaving group. Although the reaction proceeded as expected to afford the desired 2*H*-azirines **38** in moderate to good yields, it is challenging to inhibit the direct C-H insertion products (2-isoxazolines **37**) at optimized conditions.

Table 1-6 Synthesis of 2*H*-azirines



36 **37** **38**

Entry	**36**	R^3	R^4	Yield[a] (%)	
				37	**38**
1	**36a**	CH_3	CO_2Bn	20	60
2	**36b**	Bn	CO_2Me	16	63
3	**36c**	Bn	CO_2t-Bu	16	56
4	**36d**	4-$MeOC_6H_4CH_2$	CO_2Me	23	61
5	**36e**	4-$ClC_6H_4CH_2$	CO_2Me	20	53
6	**36f**	3-$ClC_6H_4CH_2$	CO_2Me	21	51
7	**36g**	$PhCH_2CH_2$	CO_2Me	23	62

[a]Yields of isolated products.

Wolff rearrangement as a useful transformation of diazo compounds was widely applied in organic synthesis.[52] In the presence of metal catalysts or under thermal/photolytic conditions, *α*-carbonyl diazo compounds preferentially formed ketenes which have been found as versatile intermediates in various transformations including cycloaddition, homologation, nucleophilic addition, and ring contraction.

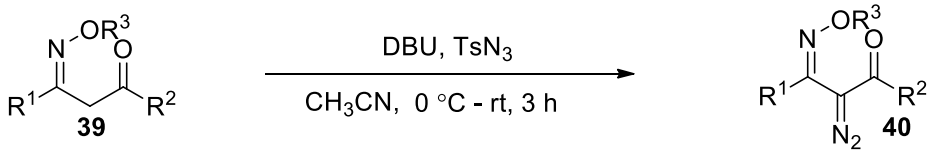
[51] Qi, X.-X.; Jiang, Y.-J.; Park, C.-M. *Chem. Commun.* **2011**, 7848.
[52] a) Kirmse, W. *Eur. J. Org. Chem.* **2002**, *2002*, 2193. (b) Tidwell, T. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5778.

As our continuous interests in the synthesis of 2*H*-azirines based on the *α*-diazo oxime ethers chemistry, we envisaged that *α*-diazo-*β*-keto oxime ethers could potentially formed 2*H*-azirine-2-carboxylic esters under metal-catalyzed condition *via* Wolff rearrangement.

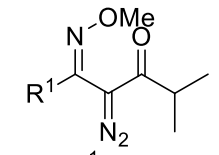
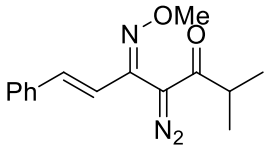
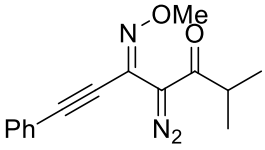
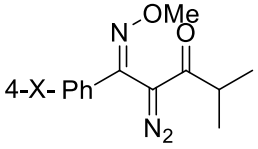
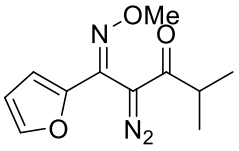
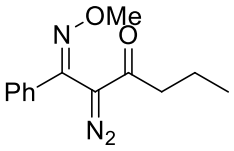
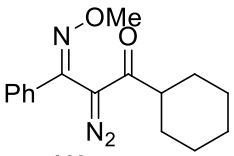
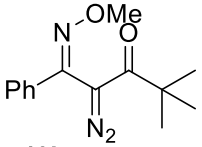
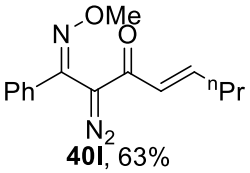
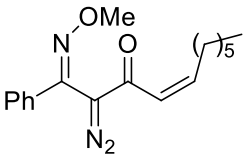
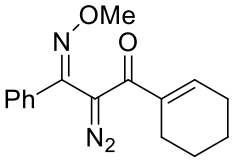
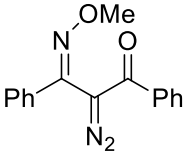
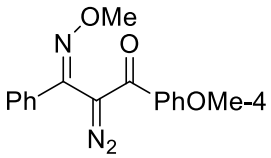
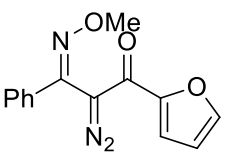
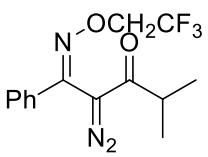
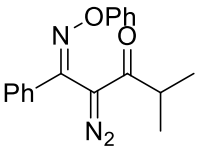
1.3.2 RESULT AND DISCUSSION

A variety of *α*-diazo-*β*-keto oxime ethers **40** can be readily accessed from carbonyl derivatives **39** by diazo transfer reactions under mild conditions (Table 1-7).

Table 1-7 Preparation of *α*-diazo-*β*-keto oxime ethers

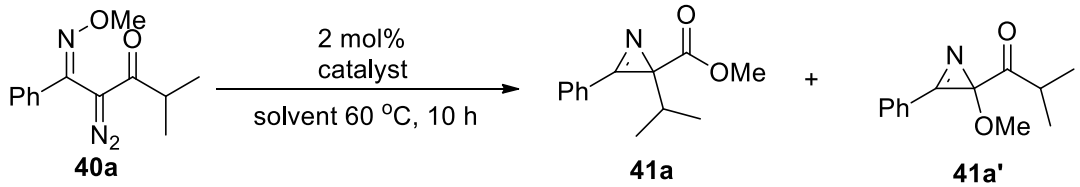


39 → **40**

 **40a,** R^1 = Ph**,** 71% **40b,** R^1 = ^{i}Bu, 56% **40c,** R^1 = ^{t}Bu, 66%	 **40d**, 83%	 **40e**, 76%	 **40f,** X= MeO, 77% **40g**, X = NO_2, 65%
 **40h**, 82%	 **40i**, 80%	 **40j**, 82%	 **40k**, 58%
 **40l**, 63%	 **40m**, 71%	 **40n**, 81%	 **40o**, 88%
 **40p**, 94%	 **40q**, 82%	 **40r**, 75%	 **40s**, 69%

To test our hypothesis, we screened the reaction of *α*-diazo-*β*-keto oxime ether **40a** in different conditions. Treatment of **40a** with different copper catalysts in DCE at 60 ℃ resulted in the formation of two products with low yield and poor selectivity. The two compounds were identified as **41a** and **41a′** (Table 1-8, entries 1-3). Compound **41a** was likely to be generated from the designed cascade rearrangement, while **41a′** resulted from the directly N−O insertion. As silver catalysts are commonly used in the Wolff rearrangement, we then tested various silver catalysts in our reactions. The results revealed that the yield could be improved significantly while the

Table 1-8 Screening of catalysts and solvents



Entry	Catalyst[a]	Solvent[b]	Yield[c] (%)	
			41a	**41a'**
1	$(Cu(OTf))_2$.benzene	DCE	16	13
2	$Cu(OTf)_2$	DCE	12	19
3	$Cu(hfacac)_2$	DCE	19	18
4	$AgNO_3$	DCE	28	28
5	Ag_2CO_3	DCE	44	55
6	AgOBz	DCE	46	54
7	AgOTf	DCE	71	20
8	$AgBF_4$	DCE	69	-
9	$Rh_2(OAc)_4$	DCE	99	-
10	$Rh_2(OAc)_4$	Benzene	95	-
11	$Rh_2(OAc)_4$	Toluene	94	-
12	$Rh_2(OAc)_4$	1,4-Dioxane	96	-

[a]OTf = trifluoromethanesulfonate, hfacac = hexafluoroacetylacetonate, OBz = benzoate. [b]DCE = dichloroethane. [c]Yields determined by NMR *vs*. standard.

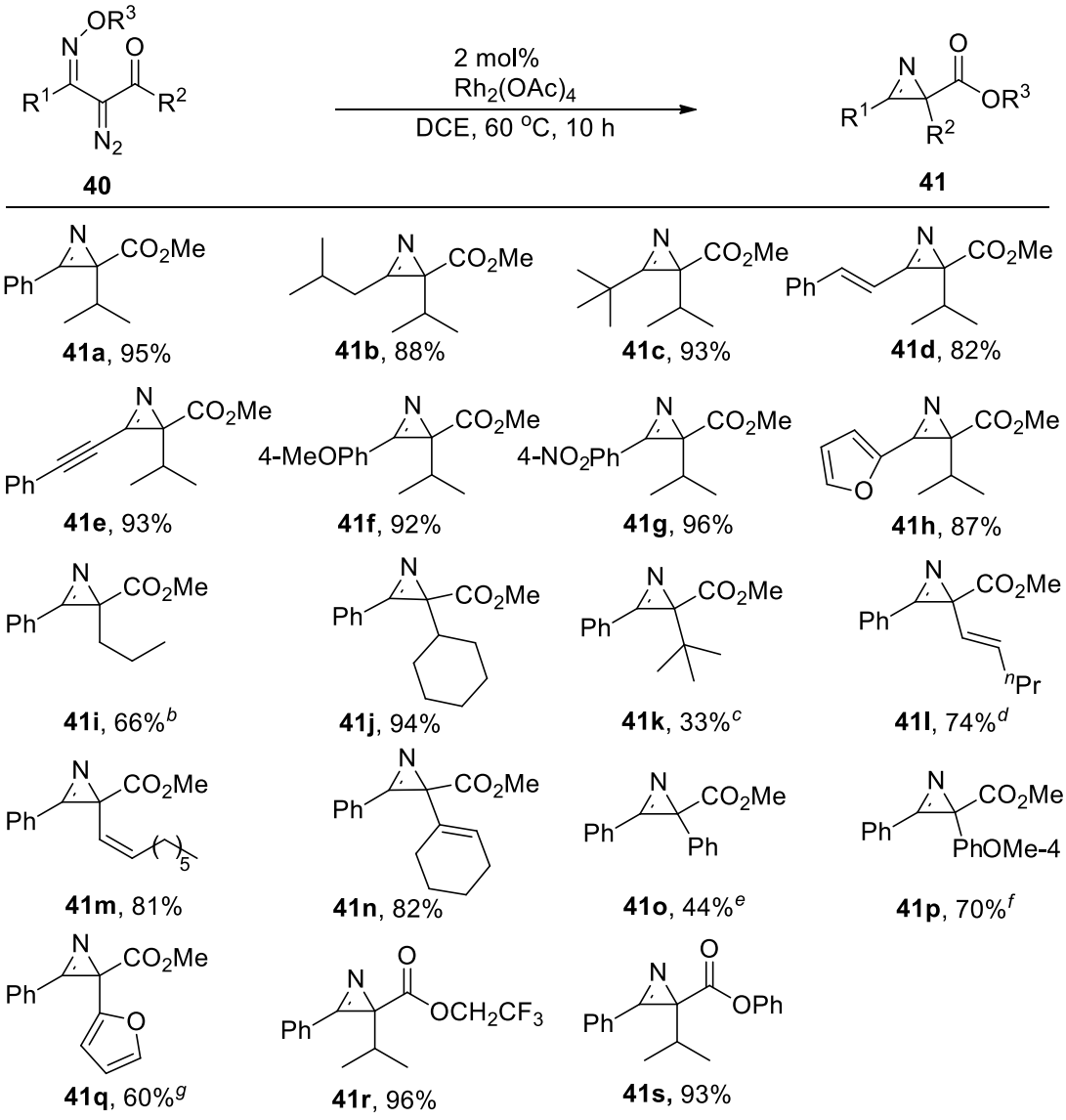
selectivity between the Wolff rearrangement and N−O insertion remained poor (Table 1-8, entries 4-8). Gratefully, reaction of **40a** with 2 mol% of $Rh_2(OAc)_4$ led to exclusive formation of **41a** in nearly quantitative yield (Table 1-8, entry 9). Further study showed that solvents exerted minor influence on the rearrangement reactions (Table 1-8, entries 10-12).

Under the optimal reaction conditions, we next screened the substrate scope of 2*H*-azirine formation (Table 1-9). Generally, the reaction could tolerate different functional groups and led to a plethora of 2*H*-azirine-2-carboxylic esters **41** in good to excellent yields. In order to gain better understanding of the cascade rearrangement, different substituents for each of the three sites (R^1, R^2, and R^3) were investigated. Initially, we changed different R^1 groups adjacent to the oxime ethers (Table 1-9, **41a**-**41h**). The results revealed that reactions with alkyl groups worked efficiently to give the desired products (**41b** and **41c**). Also, alkenyl, alkynyl and aryl substituents tolerate the reaction well to afford the corresponding 2*H*-azirine-2-carboxylic esters in excellent yields (**41d-g**). The electronic effect of R^1 had minor impact on the reaction as observed from varying the substituents on phenyl groups to give 4-methoxyphenyl (**41f**) and 4-nitrophenyl (**41g**) compounds in 92% and 96% yields, respectively. Furthermore, a substrate with heterocyclic group could also participate well in the reaction to afford **41h** in 87% yield.

Next, we examined the influence of R^2 which is adjacent to carbonyl moiety in the migration process (Table 1-9, **41i-q**). Investigation of various R^2 substituents showed that the efficiency of the reaction decreased in the order of secondary, vinyl ≈ primary followed by tertiary alkyl groups: **41j**, 94%; **41l**, 74%; **41i**, 66%; **41k**, 33%. These substrates which gave low yielding are prone to undergo N−O insertion reactions (Table 1-9, footnote). When R^2 is a tertiary alkyl group, we observed an

additional byproduct **41k″** in 18 % yield arose from 1,5-hydride shift of the methyl ether. Both cyclic and acyclic carbon carbon double bond could be well tolerated under the reaction conditions (Table 1-9, **41l**-**41n**). Furthermore, to examine the proba-

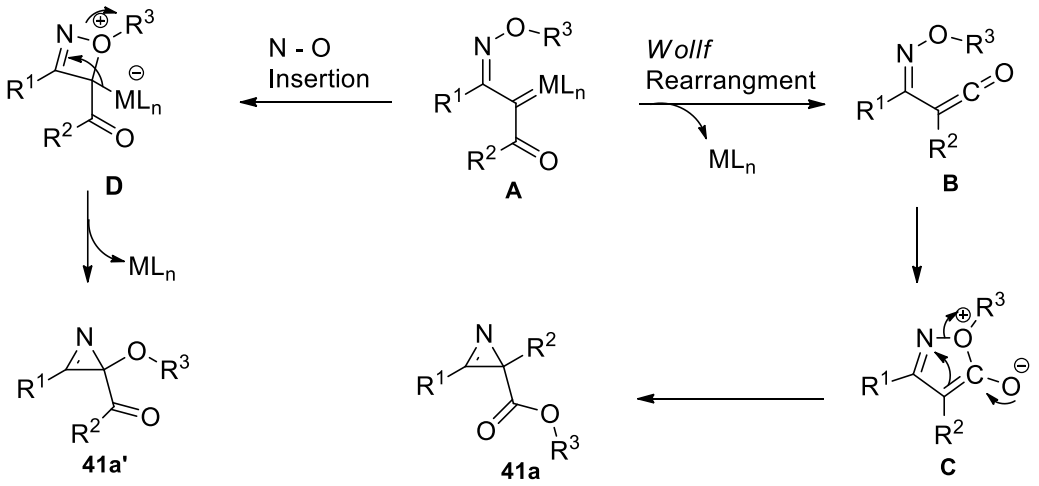
Table 1-9 Substrate scope for 2*H*-azirines[a]



[a]The reported yields in parentheses are of the isolated products. [b]Byproduct: 1-(2-methoxy-3-phenyl-2*H*-azirin-2-yl)butan-1-one **41i'** (29%). [c]Byproducts: 1-(2-methoxy-3-phenyl-2*H*-azirin -2-yl)-2,2-dimethylpropan-1-one **41k'** (46%); 2,2-dimethyl-1-(3-phenyl-2*H*-azirin-2-yl)propan -1-one **41k''** (18%). [d]Byproduct: (*E*)-1-(2-methoxy-3-phenyl-2*H*-azirin-2-yl)hex-2-en-1-one **41l'** (18%). [e]Byproduct: (2-methoxy-3-phenyl-2*H*-azirin-2-yl)(phenyl)methanone **41o'** (44%) obtained as an inseparable mixture with **41o** (yields were determined by NMR). [f]Byproduct: (4-methoxyphenyl)-(3-phenyl-2*H*-azirin-2-yl)methanone **41p'** (21%). [g]Byproduct: furan-2-yl (2-methoxy-3-phenyl-2*H*-azirin-2-yl)-methanone **41q'** (31%).

-bility of isomerization of (*E*)- and (*Z*)-alkenes during migration, **40l** and **40m** were subjected under the typical reaction conditions. Gratifyingly, both substrates afforded the corresponding products with completely retention of geometry (Table 1-9, **41l** and **41m**). We also studied the influence of migrating groups when R^2 = aryl/heteroaryl groups. While the substrates with phenyl (**40o**) and 2-furyl (**40q**) groups gave the desired products **41o** and **41q** (44% and 60%, respectively) along with N−O insertion byproducts **41o′** and **41q′** (44% and 31%, respectively), **40p,** bearing a more electron-rich 4-methoxyphenyl group, gave **41p** in higher yield (70%) along with byproduct **41p'** (21%) formed *via* 1,5-hydride shift (Table 1-9, footnote). Finally, our examination of the alkoxy group (OR^3) of oxime ethers revealed that both electron deficient (**40r**) and phenyl (**40s**) groups proceeded smoothly to afford the corresponding esters in excellent yields.

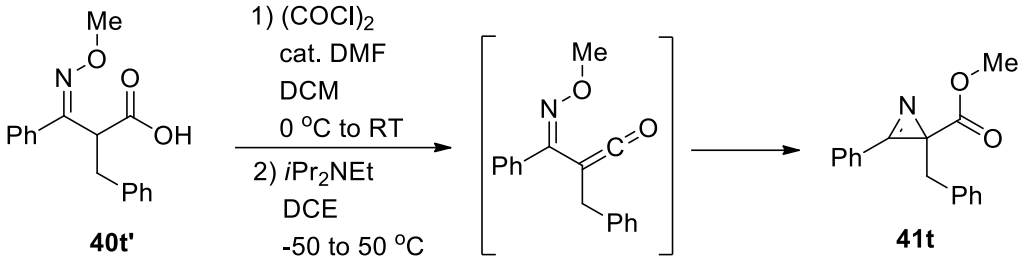
Mechanistically, we proposed that the reaction proceeded *via* a cascade rearrangement from carbenoid **A** (Scheme 1.12). Rhodium promotes migration of the R^2 substitutent to the carbenoid center, resulting in the formation of ketene **B** which is attacked by the oxygen atom of the oxime ether moiety to form of ylides **C.** It further undergoes intramolecular cycloaddion to give 2*H*-azirine-2-carboxylic ester **41a**. On



Scheme 1.12 Proposed mechanism for synthesis of 2-carboxyl-2*H*-azirines

the other hand, the electron from oxygen may attack carbenoid to generate four-member ring metal-complex **D**. **41a'** is obtained through intramolecular cyclization.

To investigate the existence of ketene intermediates in the reaction pathway as shown in Scheme 1.13, we prepared the ketene intermediate independently from carboxylic acid **40t'** which rearranged spontaneously to give **41t** in 85% (Scheme 1.13).



Scheme 1.13 Mechanism study

1.3.3 SUMMARY

In summary, we have described the development of a highly efficient synthesis of 2*H*-azirine-2-carboxylic esters with quaternary centers. Novel rearrangement of *α*-oximino ketenes generated from *α*-diazo-*β*-keto oxime ethers *via* the Wolff rearrangement results in the formation of 2*H*-azirine-2-carboxylic esters in excellent yields.

1.4 CONCLUSION

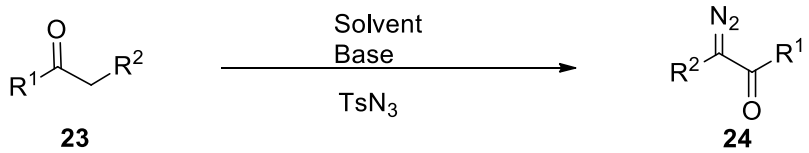
In this chapter, we have described diverse transformations of *α*-diazo-*β*-keto compounds to the synthesis of oxygen or nitrogen containing heterocycles in the presence of transition metal catalysts. For intermolecular reaction, a dual method has

been presented to prepare 2-aminofurans and 2-unsubstituted furans based on copper-catalyzed [3 + 2] cycloaddition of *α*-diazo-*β*-keto compounds with enamine derivatives. For intramolecular reaction, a novel cascade rearrangement of *α*-diazo-*β*-keto oxime ethers has been studied to access 2*H*-azirine-2-carboxylic esters with quaternary centers in excellent yields.

1.5 EXPERMENTAL SECTION

1.5.1 Synthesis of furans *via* carbenoid-mediated [3 + 2] cycloaddition

General procedure for the synthesis of *α*-diazo-*β*-ketoester or -*β*-diketones compounds (24a-24r):



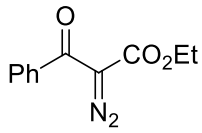
23 **24**

Method A: Under nitrogen, DBU (1.2 eq.) was added dropwise to a solution of *α*-diazo-*β*-ketoesters or *α*-diazo-*β*-ketones **23** (1.0 eq.) and 4-methylbenzenesulfonyl azide (1.2 eq.) in CH_3CN at 0 ^oC. The resulting orange colour solution was stirred for 3 hours at 0 ^oC and then slowly brought to room temperature. After completion of the reaction as indicated by thin layer chromatography (TLC), it was quenched with water, extracted with ethyl acetate and dried with anhydrous Na_2SO_4. The reaction mixture was then concentrated under reduced pressure to give crude yellow viscous liquid, and purified by column chromatography (hexane : ethyl acetate = 9 : 1).

Method B: Under nitrogen, triethylamine (1.2 eq.) was added dropwise to a solution of *β*-diketones **23** (1.0 eq.) and 4-methylbenzenesulfonyl azide (1.2 eq.) in ethanol at room temperature. The reaction mixture was stirred for three hours at the

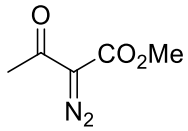
same temperature. After completion of the reaction as indicated by thin layer chromatography (TLC), it was quenched with water, extracted with ethyl acetate and dried with anhydrous Na_2SO_4. The reaction mixture was then concentrated under reduced pressure to give crude yellow viscous liquid, and purified by column chromatography (hexane : ethyl acetate = 9 : 1).

Ethyl 2-diazo-3-oxo-3-phenylpropanoate (24a):



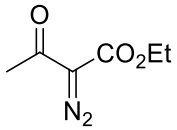
The title compound was prepared according to Method A. The product was obtained as yellow oil. Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 - 7.61 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.53 - 7.41 (m, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0, 161.0, 137.1, 132.3, 128.3, 127.9, 61.6, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{11}N_2O_3$: 219.0770. Found: 219.0765.

Methyl 2-diazo-3-oxobutanoate (24b):



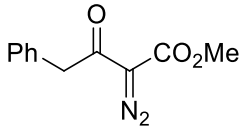
The title compound was prepared according to Method A. The product was obtained as yellow oil. Yield: 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 161.8, 52.1, 28.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_5H_7N_2O_3$: 143.0457. Found: 143.0462.

Ethyl 2-diazo-3-oxobutanoate (24b'):



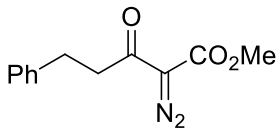
The title compound was prepared according to Method A. The product was obtained as yellow oil. Yield 90%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (q, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2, 161.4, 61.4, 28.2, 14.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_6H_9N_2O_3$: 157.0613. Found: 157.0609.

Methyl 2-diazo-3-oxo-4-phenylbutanoate (24c):



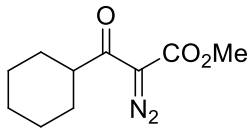
The title compound was prepared according to Method A. The product was obtained as yellow oil. Yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.25 (m, 5H), 4.19 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 161.6, 134.0, 129.7, 128.5, 127.1, 52.3, 45.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{11}N_2O_3$: 219.0770. Found: 219.0765.

Methyl 2-diazo-3-oxo-5-phenylpentanoate (24d):



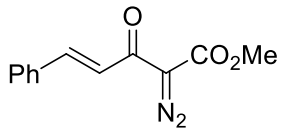
The title compound was prepared according to Method A. The product was obtained as yellow oil. Yield 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 - 7.20 (m, 5H), 3.85 (s, 3H), 3.21 (t, *J* = 7.6 Hz, 2H), 2.99 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 161.7, 140.8, 128.5, 128.5, 126.1, 52.2, 41.8, 30.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{13}N_2O_3$: 233.0926. Found: 233.0931.

Methyl 3-cyclohexyl-2-diazo-3-oxopropanoate (24e):



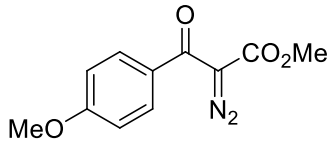
The title compound was prepared according to Method A. The product was obtained as yellow oil. Yield 75%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.35 - 3.28 (m, 1H), 1.81 - 1.67 (m, 5H), 1.47 - 1.19 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 161.7, 52.1, 46.8, 28.7, 25.8, 25.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{15}N_2O_3$: 211.1083. Found: 211.1090.

(*E*)-methyl 2-diazo-3-oxo-5-phenylpent-4-enoate (24f):



The title compound was prepared according to Method A. The product was obtained as yellow oil. Yield 90%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 20.8 Hz, 1H), 7.77 (d, *J* = 21.2 Hz, 1H), 7.64 - 7.61 (m, 2H), 7.40 - 7.38 (m, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 161.9, 143.0, 134.6, 130.6, 128.9, 128.7, 121.7, 52.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{11}N_2O_3$: 231.0770. Found: 231.0767.

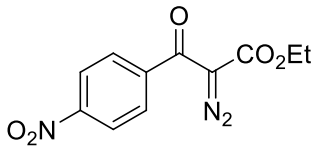
Methyl 2-diazo-3-(4-methoxyphenyl)-3-oxopropanoate (24g):



The title compound was prepared according to Method A. The product was obtained as yellow oil. Yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 12.0 Hz, 2H), 6.92 (d, *J* = 11.6 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.2,

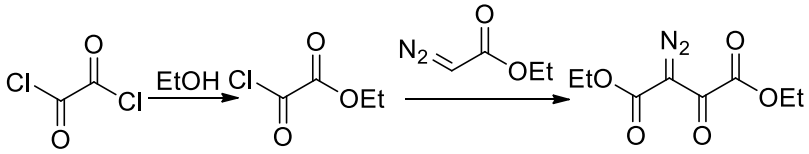
163.2, 161.8, 131.0, 129.3, 113.2, 55.4, 52.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{11}N_2O_4$: 235.0719. Found: 235.0716.

Ethyl 2-diazo-3-(4-nitrophenyl)-3-oxopropanoate (24h):



The title compound was prepared according to Method A. The product was obtained as red oil. Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 - 8.26 (m, 2H), 7.77 - 7.74 (m, 2H), 4.25 (q, J = 6.8 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.6, 160.3, 149.6, 142.5, 129.3, 123.1, 62.0, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{10}N_3O_5$: 264.0620. Found: 264.0622.

Diethyl 2-diazo-3-oxosuccinate (24i):

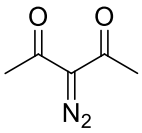


The title compound was prepared according to the follow procedure: Ethyl 2-chloro-2-oxoacetate: Ethanol (10 mmol, 0.58 mL) was added dropwise to the oxalyl chloride (20 mmol, 1.72 mL) by using syringe pump for one hour at 0 ℃. After completion of addition, the mixture was warmed to room temperature for 2 hours. After the completion of the reaction, the solvent was removed under reduced pressure and the product was collected at 40 ℃ under vacuum (1.02g, 75%);

Diethyl 2-diazo-3-oxosuccinate: A solution of EDA (1.5 mmol, 158 μL) in 3 mL anhydrous THF was added to ehthyl 2-chloro-2-oxoacetate (0.5 mmol, 55 μL) in 5

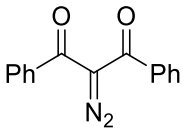
mL anhydrous THF at 0 ℃ and stirred for further 3 hours at the same temperature. After completion of the reaction as indicated by thin layer chromatography (TLC), it was quenched with water, extracted with ethyl acetate and dried with anhydrous Na_2SO_4. The reaction mixture was then concentrated under reduced pressure to give crude yellow viscous liquid, and purified by column chromatography (hexane : ethyl acetate = 9 : 1). The product was obtained as yellow oil. Yield 61%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (m, 4H), 1.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 159.9, 62.8, 62.3, 14.2, 13.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_8H_{11}N_2O_5$: 215.0668. Found: 215.0665.

3-Diazopentane-2,4-dione (24j):



The title compound was prepared according to Method B. The product was obtained as yellow oil. Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2, 28.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_5H_7N_2O_2$: 127.0512. Found: 127.0508.

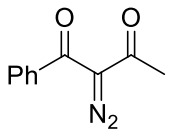
2-Diazo-1,3-diphenylpropane-1,3-dione (24k):



The title compound was prepared according to Method B. The product was obtained as yellow solid, mp: 105 - 107 °C. Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.58 (m, 4H), 7.47 - 7.44 (m, 2H), 7.36 - 7.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 137.0, 132.6, 128.4, 128.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{11}N_2O_2$:

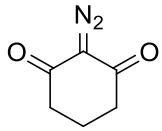
251.0821. Found: 251.0812.

2-Diazo-1-phenylbutane-1,3-dione (24l):



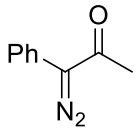
The title compound was prepared according to Method B. The product was obtained as white solid, mp: 55 - 56 °C. Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.63 (m, 2H), 7.59 - 7.50 (m, 1H), 7.48 - 7.47 (m, 2H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 185.1, 137.3, 132.7, 128.9, 127.4, 29.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_9N_2O_2$: 189.0664. Found: 189.0660.

2-Diazocyclohexane-1,3-dione (24m):



The title compound was prepared according to Method B. The product was obtained as yellow solid, mp: 46 - 48 °C. Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (t, J = 6.4 Hz, 4H), 2.09 - 2.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 36.8, 18.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_6H_7N_2O_2$: 139.0508. Found: 139.0509.

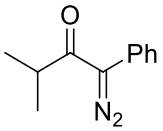
1-Diazo-1-phenylpropan-2-one (24n):



The title compound was prepared according to Method A. The product was obtained as orange solid, mp: 57 - 58 °C. Yield 74%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 - 7.43 (m, 2H), 7.41 - 7.38 (m, 2H), 7.26 - 7.25 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)

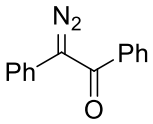
δ 162.5, 129.0, 126.9, 125.8, 125.5, 26.9; HRMS (ESI) m/z $[M+Na]^+$: Calcd for $C_9H_8N_2ONa$: 183.0534. Found: 183.0528.

2-Diazo-3-methyl-1-phenylbutan-1-one (24o):



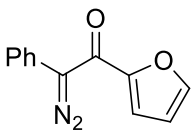
The title compound was prepared according to Method A. The product was obtained as red oil. Yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.54 - 7.52 (m, 2H), 7.43 - 7.39 (m, 2H), 7.27 - 7.24 (m, 1H), 3.02 - 2.95 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 197.2, 130.3, 129.0, 126.9, 126.0, 36.5, 18.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{13}N_2O$: 189.1028. Found: 189.1023.

2-Diazo-1,2-diphenylethanone (24p):



The title compound was prepared according to Method A. The product was obtained as red solid, mp: 78 - 79 °C. Yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 - 7.60 (m, 2H), 7.52 - 7.43 (m, 3H), 7.42 - 7.38 (m, 4H), 7.28 - 7.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 138.0, 131.7, 129.1, 128.5, 127.8, 127.0, 126.1, 126.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{11}N_2O$: 223.0871. Found: 223.0878.

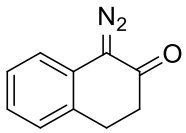
2-Diazo-1-(furan-2-yl)-2-phenylethanone (24q):



The title compound was prepared according to Method A. The product was obtained as

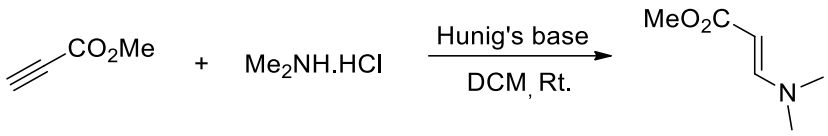
yellow solid, mp: 109 - 110 °C. Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 - 7.60 (m, 2H), 7.58 (d, *J* = 0.8 Hz, 1H), 7.52 - 7.52 (m, 2H), 7.46 - 7.42 (m, 1H), 6.49 (d, *J* = 1.6 Hz, 1H), 6.41 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 152.4, 144.4, 129.0, 127.2, 126.2, 125.9, 116.7, 112.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_9N_2O_2$: 213.0664. Found: 213.0665.

1-Diazo-3,4-dihydronaphthalen-2(1*H*)-one (24r):



The title compound was prepared according to Method A. The product was obtained as red oil. Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.28 (m, 1H), 7.23 - 7.21 (m, 1H), 7.12 - 7.08 (m, 1H), 6.98 - 6.96 (m, 1H), 3.02 (t, *J* = 6.8 Hz, 2H), 2.68 - 2.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 131.3, 128.4, 127.5, 125.4, 124.5, 120.4, 36.9, 27.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_9N_2O$: 173.0715. Found: 173.0713.

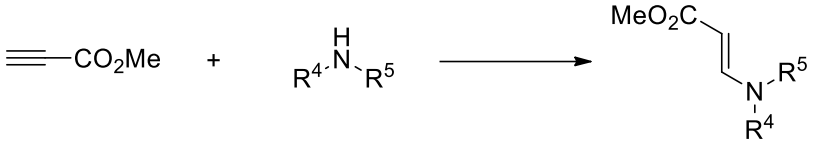
Methyl (*E*)-3-(dimethylamino) prop-2-enoate (25a):



To a solution of methyl propiolate (5.0 mmol, 1.0 eq.) in dry CH_2Cl_2 (50 mL) at room temperature was added dimethyl ammonium chloride (7.5 mmol, 1.5 eq.), which was followed by the addition of Hunig's base dropwise (7.5 mmol, 1.5 eq.). After completion of the reaction (monitored by TLC), it was quenched with water, extracted with CH_2Cl_2 and dried with anhydrous Na_2SO_4, concentrated under reduced pressure, then purified by column chromatography (hexane : ethyl acetate = 3 : 2). The

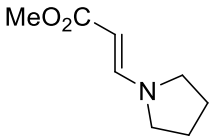
product was obtained as yellow solid. mp: 50 - 51 °C. Yield 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 12.9 Hz, 1H), 4.52 (d, *J* = 12.9 Hz, 1H), 3.66 (s, 3H), 2.88 (s, br, 6H).

General procedure for the synthesis of 3-aminoalkenoate (25b-d):



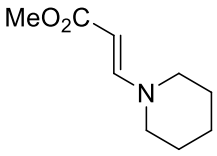
To a solution of methyl propiolate (5.0 mmol, 1.0 eq.) in THF (25 mL) was added amine (6.0 mmol, 1.2 eq.) at room temperature and stirred for overnight. The solvent was then removed under reduced pressure and crude compound was purified by column chromatography (hexane : ethyl acetate = 3 : 2).

Methyl (*E*)-3-pyrrolidin-1-ylprop-2-enoate (25b):



The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 72 - 73 °C. Yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 12.8 Hz, 1H), 4.47 (d, *J* = 12.8 Hz, 1H), 3.65 (s, 3H), 3.23 - 3.18 (m, 4H), 1.92 (s, 4H).

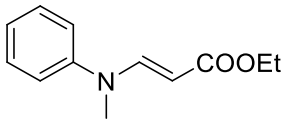
(*E*)-Methyl 3-(piperidin-1-yl)acrylate (25c):



The title compound was prepared according to the general procedure. The product was

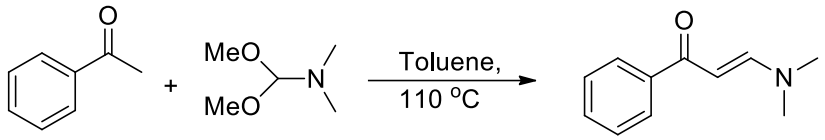
obtained as yellow solid, mp: 40 - 41 °C. Yield 92%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 12.9 Hz, 1H), 4.61 (d, *J* = 13.2 Hz, 1H), 3.64 (s, 3H), 3.17 (m, 4H), 1.59 (m, 6H).

(*E*)-Ethyl 3-(methyl(phenyl)amino)acrylate (25d):



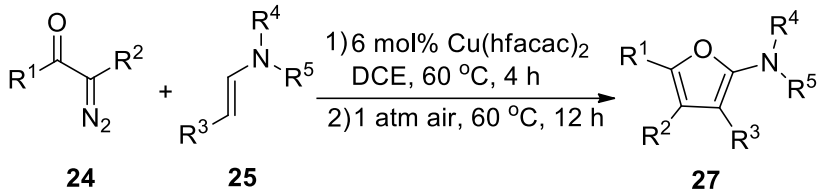
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield 86%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 13.2 Hz, 1H), 7.37 - 7.33 (m, 2H), 7.14 - 7.10 (m, 3H), 4.94 (d, *J* = 13.2 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.24 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H).

(*E*)-3-(Dimethylamino)-1-phenylprop-2-en-1-one (25e):



To a stirred solution of acetophenone (5.0 mmol, 1.0 eq.) in 5.0 mL of toluene, 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (7.0 mmol, 1.4 eq.) was added and stirred at 110 °C. After completion of the reaction (monitored by TLC), it was quenched with water, extracted with ethyl acetate and dried with anhydrous Na_2SO_4. Then the reaction mixture is concentrated under reduced pressure and purified by column chromatography (hexane : ethyl acetate = 1 : 1). The product was obtained as yellow solid, mp: 90 - 91 °C. Yield 57 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 - 7.38 (m, 2H), 7.80 (d, *J* = 12.4 Hz, 1H), 7.45 - 7.39 (m, 3H), 5.71 (d, *J* = 12.4 Hz, 1H), 3.14 (s, 3H), 2.93 (s, 3H).

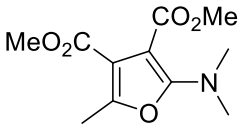
General procedure for the synthesis of 2-aminofurans (27aa - 27la, 27bb - 27be):



24 **25** **27**

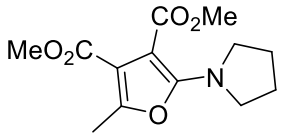
$Cu(hfacac)_2 \cdot H_2O$ (0.012 mmol, 6 mol%) was dried under vacuum at room temperature until it turned gray white. A solution of α-diazo compound **24** (0.24 mmol, 1.2 eq.) in dichloroethane (1.0 mL) was added dropwise to a stirred solution of enamine **25** (0.20 mmol, 1.0 eq.) in dichloroethane (1.0 mL) at room temperature in 10 min. The reaction mixture was reacted at 60 °C under N_2 protection until the diazo compound **24** is fully consumed (about 4 h). Then the mixture was stirred for further several hours (about 12 h) with exposure to air until the intermediate was consumed completely (monitored by TLC). The reaction mixture was then evaporated under reduced pressure to give the crude compound and subsequently purified by column chromatography using hexane : ethyl acetate = 9 : 1 to yield aminofuran.

Dimethyl 2-(dimethylamino)-5-methyl-furan-3,4-dicarboxylate (27ba):



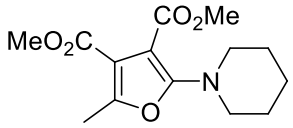
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.71 (s, 3H), 2.99 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 164.1, 159.8, 146.6, 114.5, 90.7, 51.7, 51.3, 40.7, 12.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{16}NO_5$: 242.1028. Found: 242.1033.

Dimethyl 2-methyl-5-pyrrolidin-1-yl-furan-3,4-dicarboxylate (27bb):



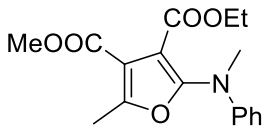
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.73 (s, 3H), 3.53 - 3.50 (m, 4H), 2.30 (s, 3H), 1.94 - 1.91 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 164.2, 157.7, 145.7, 114.6, 87.5, 51.7, 51.1, 49.4, 25.5, 12.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{18}NO_5$: 268.1185. Found: 268.1184.

Dimethyl 2-methyl-5-(piperidin-1-yl)furan-3,4-dicarboxylate (27bc):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.75 (s, 3H), 3.38 - 3.35 (m, 4H), 2.33 (s, 3H), 1.67 - 1.60 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 163.9, 159.9, 147.2, 114.3, 92.6, 51.7, 51.4, 50.1, 25.6, 24.1, 12.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{20}NO_5$: 282.1341. Found: 282.1344.

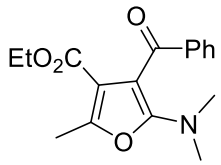
3-Ethyl 4-methyl 5-methyl-2-(methyl(phenyl)amino)furan-3,4-dicarboxylate (27bd):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 - 7.21 (m, 2H), 6.91 - 6.88 (m, 1H), 6.80 - 6.77 (m, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H),

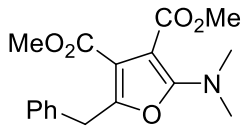
3.33 (s, 3H), 2.46 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 162.4, 153.8, 152.9, 146.5, 129.0, 120.5, 115.4, 113.6, 107.1, 60.7, 51.7, 39.0, 14.0, 13.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{20}NO_5$: 318.1341. Found: 318.1338.

Ethyl 4-benzoyl-5-(dimethylamino)-2-methylfuran-3-carboxylate (27b'e):



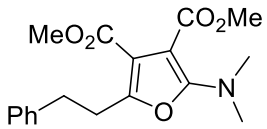
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 - 7.80 (m, 2H), 7.49 - 7.41 (m, 1H), 7.39 - 7.37 (m, 2H), 3.71 (q, *J* = 7.2 Hz, 2H), 2.91 (s, 3H), 2.45 (s, 3H), 0.78 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 163.9, 157.9, 148.5, 140.7, 131.9, 128.8, 128.2, 115.2, 97.9, 60.1, 40.3, 13.4, 12.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{20}NO_4$: 302.1392. Found: 302.1396.

Dimethyl 2-benzyl-5-(dimethylamino)furan-3,4-dicarboxylate (27ca):



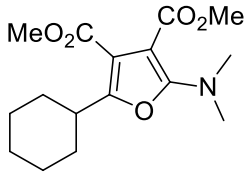
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 - 7.22 (m, 5H), 4.01 (s, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 2.99 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 164.1, 160.1, 147.4, 137.2, 128.6, 128.5, 126.6, 115.3, 90.2, 51.9, 51.4, 40.5, 32.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{20}NO_5$: 318.1341. Found: 318.1345.

Dimethyl 2-(dimethylamino)-5-phenethylfuran-3, 4-dicarboxylate (27da):



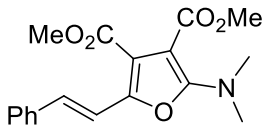
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 - 7.25 (m, 2H), 7.21 - 7.15 (m, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.02 - 2.99 (m, 2H), 2.98 (s, 6H), 2.92 - 2.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 164.1, 159.8, 149.1, 140.7, 128.4, 128.4, 126.1, 114.8, 90.5, 51.7, 51.3, 40.6, 34.4, 28.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{22}NO_5$: 332.1498. Found: 332.1493.

Dimethyl 2-cyclohexyl-5-(dimethylamino)furan-3,4-dicarboxylate (27ea):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.72 (s, 3H), 3.02 (s, 6H), 2.90 - 2.82 (m, 1H), 1.82 - 1.64 (m, 5H), 1.52 - 1.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 164.1, 159.6, 153.0, 112.8, 90.3, 51.8, 51.3, 40.6, 36.3, 31.0, 26.1, 25.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{24}NO_5$: 310.1654. Found: 310.1657.

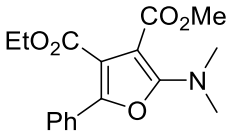
(*E*)-Dimethyl 2-(dimethylamino)-5-styrylfuran-3,4-dicarboxylate (27fa):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.26 - 7.23 (m, 1H), 7.13 (d, *J* = 16.0 Hz, 1H), 6.94 (d, *J*

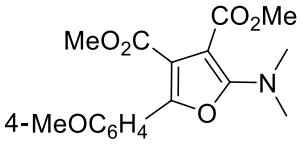
= 16.0 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 164.1, 159.5, 145.1, 136.7, 128.7, 128.4, 127.9, 126.6, 116.5, 114.1, 91.3, 52.0, 51.5, 40.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{20}NO_5$: 330.1341. Found: 330.1343.

4-Ethyl 3-methyl 2-(dimethylamino)-5-phenylfuran-3,4-dicarboxylate (27aa):



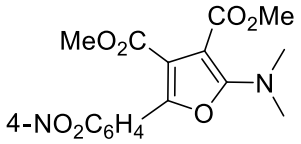
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 8.8 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.75 (s, 3H), 3.17 (s, 6H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 163.1, 160.8, 140.9, 129.2, 128.6, 127.8, 124.9, 116.0, 91.8, 61.6, 51.2, 40.7, 14.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{20}NO_5$: 318.1341. Found: 318.1342.

Dimethyl 2-(dimethylamino)-5-(4-methoxyphenyl)furan-3,4-dicarboxylate (27ga):



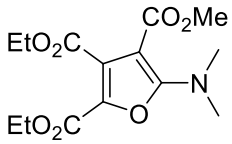
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 - 7.50 (m, 2H), 6.91 - 6.89 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 3.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 163.2, 160.5, 159.4, 141.9, 126.8, 121.9, 114.1, 114.0, 91.7, 55.3, 52.4, 51.3, 40.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{20}NO_6$: 334.1291. Found: 334.1291.

4-Ethyl 3-methyl 2-(dimethylamino)-5-(4-nitrophenyl)furan-3,4-dicarboxylate (27ha):



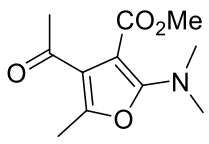
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 - 8.19 (m, 2H), 7.66 - 7.64 (m, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 3.22 (s, 6H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 162.6, 161.1, 146.1, 137.8, 134.9, 124.3, 124.2, 120.5, 92.4, 62.1, 51.4, 40.6, 14.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{19}N_2O_7$: 363.1192. Found: 363.1189.

2,3-Diethyl 4-methyl 5-(dimethylamino)furan-2,3,4-tricarboxylate (27ia):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (q, *J* = 9.6 Hz, 2H), 4.28 (q, *J* = 9.2 Hz, 2H), 3.73 (s, 3H), 3.20 (s, 6H), 1.39 (t, *J* = 9.2 Hz, 3H), 1.31 (t, *J* = 9.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 162.1, 161.8, 157.5, 129.9, 129.5, 91.5, 61.8, 60.9, 51.4, 40.5, 14.2, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{20}NO_7$: 314.1240. Found: 314.1239.

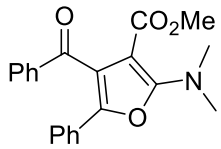
Methyl 4-acetyl-2-(dimethylamino)-5-methylfuran-3-carboxylate (27ja):



The title compound was prepared according to the general procedure. The product was

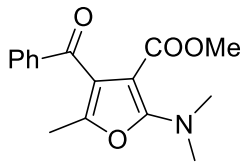
obtained as colorless oil. Yield 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.08 (s, 6H), 2.36 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 163.6, 161.4, 144.0, 124.2, 89.7, 50.9, 41.1, 30.8, 12.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{16}NO_4$: 226.1079. Found: 226.1076.

Methyl 4-benzoyl-2-(dimethylamino)-5-phenylfuran-3-carboxylate (27ka):



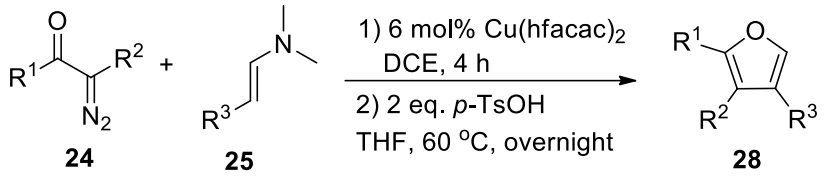
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 - 7.93 (m, 2H), 7.55 - 7.51 (m, 1H), 7.45 - 7.41 (m, 4H), 7.26 - 7.23 (m, 2H), 7.19 - 7.17 (m, 1H), 3.32 (s, 3H), 3.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 163.0, 160.9, 140.2, 137.8, 133.2, 129.2, 129.0, 128.6, 127.4, 124.5, 121.7, 93.0, 50.5, 40.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{20}NO_4$: 350.1392. Found: 350.1401.

3-Ethyl 4-methyl 5-methyl-2-(methyl(phenyl)amino)furan-3,4-dicarboxylate (27la):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.85 - 7.83 (m, 2H), 7.53 - 7.49 (m, 1H), 7.44 - 7.40 (m, 2H), 3.19 (s, 3H), 3.13 (s, 6H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 163.3, 160.7, 143.6, 138.9, 132.5, 128.7, 128.3, 121.7, 91.1, 50.3, 40.7, 12.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{18}NO_4$: 288.1236. Found: 288.1235.

General procedures for the synthesis of 2-unsubstituted furans:



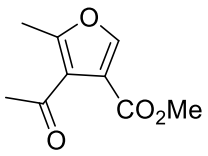
24 **25** **28**

$Cu(hfacac)_2 \cdot H_2O$ (0.012 mmol, 6 mol%) was dried under vacuum at room temperature until it turned gray white. A solution of *α*-diazo compound **24** (0.24 mmol, 1.2 eq.) in dichloroethane (1.0 mL) was added dropwise to a stirred solution of enamine **25** (0.20 mmol, 1.0 eq.) in dichloroethane (1.0 mL) at room temperature in 10 min.

Method A: The reaction mixture was further reacted at room temperature for 4 h under N_2 protection (**28re** for overnight) until the diazo compound is fully consumed. Then the reaction mixture was evaporated under reduced pressure to give the crude compound which was purified by column chromatography using hexane: ethyl acetate = 19:1 to give desired product.

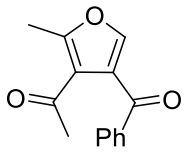
Method B: The reaction mixture was heated at 60 °C under N_2 protection until the diazo compound is fully consumed. After removing dichloroethane under reduced pressure, the crude mixture was dissolved in dry tetrahydrofuran (2.5 mL) and treated with *p*-toluenesulfonic acid (0.40 mmol, 2.0 eq.) at 60 °C under N_2 protection overnight. Then the reaction mixture was evaporated under reduced pressure to give the crude compound which was purified by column chromatography using hexane : ethyl acetate = 19 : 1 to give desired product.

Methyl 4-acetyl-5-methyl-furan-3-carboxylate (28ja):



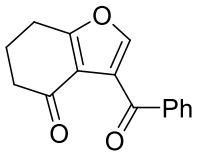
The title compound was prepared according to Method B. The product was obtained as colorless oil. Yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 3.84 (s, 3H), 2.53 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 163.0, 158.1, 146.4, 121.6, 117.8, 51.9, 31.2, 13.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{11}O_4$: 183.0657. Found: 183.0661.

1-(4-Benzoyl-2-methylfuran-3-yl)ethanone (28je):



The title compound was prepared according to Method B. The product was obtained as colorless oil. Yield 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 - 7.90 (m, 2H), 7.64 - 7.60 (m, 1H), 7.52 (s, 1H), 7.50 - 7.44 (m, 2H), 2.55 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 189.5, 158.8, 145.3, 138.2, 133.3, 129.4, 128.7, 125.9, 122.3, 30.7, 13.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{13}O_3$: 217.0865. Found: 217.0860.

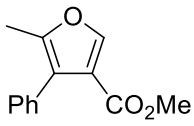
3-Benzoyl-6,7-dihydrobenzofuran-4(5*H*)-one (28me):



The title compound was obtained without acid treatment at 80 ºC. The product was obtained as yellow oil. Yield 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 - 7.88 (m, 2H), 7.66 (s, 1H), 7.60 - 7.58 (m, 1H), 7.49 - 7.45 (m, 2H), 2.98 (t, *J* = 6.4 Hz, 2H), 2.57 -

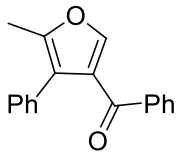
2.54 (m, 2H), 2.25 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 189.0, 167.9, 145.3, 137.8, 133.3, 129.6, 128.4, 123.8, 120.0, 38.2, 23.5, 22.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{13}O_3$: 241.0865. Found: 241.0862.

Methyl 5-methyl-4-phenylfuran-3-carboxylate (28na):



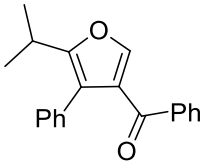
The title compound was prepared according to Method A. The product was obtained as colorless oil. Yield 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.41 - 7.37 (m, 2H), 7.35 - 7.30 (s, 3H), 3.72 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 150.8, 146.7, 131.9, 130.0, 127.8, 127.2, 120.9, 118.4, 51.2, 12.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{12}O_3$: 217.0865. Found: 217.0860.

(5-Methyl-4-phenylfuran-3-yl)(phenyl)methanone (28ne):



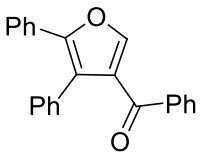
The title compound was prepared according to Method A. The product was obtained as colorless oil. Yield 54%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 - 7.82 (m, 2H), 7.72 (s, 1H), 7.52 - 7.51 (m, 1H), 7.42 - 7.39 (m, 2H), 7.35 - 7.32 (m, 2H), 7.28 - 7.26 (m, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 150.8, 146.9, 138.8, 132.5, 132.1, 129.6, 129.4, 128.3, 128.1, 127.0, 125.9, 121.5, 12.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{15}O_2$: 263.1072. Found: 263.1076.

(5-Isopropyl-4-phenylfuran-3-yl)(phenyl)methanone (28oe):



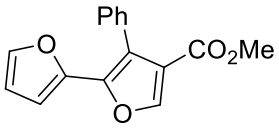
The title compound was prepared according to Method A. The product was obtained as colorless oil. Yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 - 7.82 (m, 2H), 7.73 (s, 1H), 7.54 - 7.50 (m, 1H), 7.42 - 7.38 (m, 2H), 7.35 - 7.32 (m, 2H), 7.31 - 7.24 (m, 3H), 3.13 - 3.06 (m, 1H), 1.28 (d, *J* =6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 158.9, 147.0, 138.9, 132.5, 132.2, 129.8, 129.3, 128.3, 128.1, 127.0, 125.8, 119.7, 26.0, 21.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{19}O_2$: 291.1385. Found: 291.1391.

(4, 5-Diphenylfuran-3-yl)(phenyl)methanone (28pe):



The title compound was prepared according to Method A. The product was obtained as colorless oil. Yield 59%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.85 - 7.84 (m, 2H), 7.53 - 7.25 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 150.8, 147.1, 138.7, 132.7, 132.3, 130.1, 130.0, 129.4, 128.5, 128.4, 128.4, 128.1, 127.6, 127.5, 126.2, 122.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{23}H_{17}O_2$: 325.1229. Found: 325.1225.

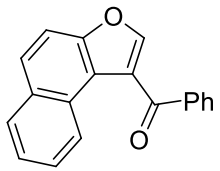
Methyl 3-phenyl-2,2'-bifuran-4-carboxylate (28qa):



The title compound was prepared according to Method A. The product was obtained as colorless oil. Yield 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.42 - 7.37 (m, 5H), 7.36 - 7.36 (m, 1H), 6.33 (dd, J_1 = 3.2 Hz, J_2 = 1.6 Hz, 1H), 6.20 (dd, J_1 = 3.6 Hz,

J_2 = 1.6 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 147.3, 144.8, 143.9, 142.4, 131.0, 130.2, 128.0, 127.9, 121.1, 119.9, 111.2, 107.8, 51.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{13}O_4$: 269.0814. Found: 269.0813.

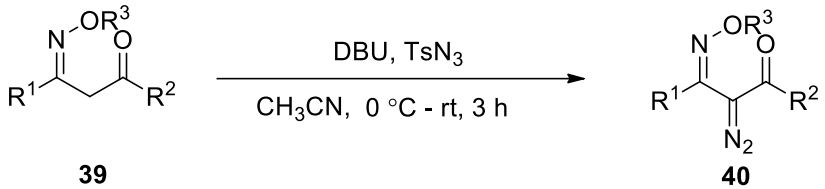
Naphtho[2,1-b]furan-1-yl(phenyl)methanone (28re):



The title compound was prepared according to Method A. The product was obtained as yellow oil. Yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 - 8.88 (m, 1H), 8.04 - 7.95 (m, 4H), 7.88 - 7.86 (m, 1H), 7.72 - 7.51 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 154.0, 151.4, 139.3, 133.0, 131.3, 129.8, 128.7, 128.6, 128.1, 127.9, 126.8, 126.2, 125.3, 123.9, 119.9, 112.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{13}O_2$: 273.0916. Found: 273.0915.

1.5.2 Synthesis of 2*H*-azirines *via* tandem rearrangement of *α*-diazo-*β*-keto oxime ethers

General procedure for *α*-diazo-*β*-keto oxime ethers

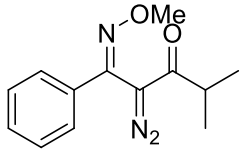


39 **40**

To a solution of *β*-oximino ketones **39** (0.5 mmol, 1.0 eq.) and 4-methylbenzenesulfonyl azide (0.55 mmol, 1.1 eq.) in CH_3CN (5 mL) was added DBU (0.55 mmol, 1.1 eq.) dropwise at 0 ℃. The resulting orange color solution was

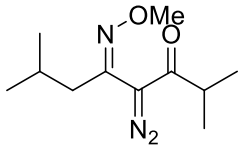
stirred at 0 ℃ for 3 h and slowly brought to room temperature. Upon completion as indicated by TLC, the solvent was removed under reduced pressure, and the crude material was purified by flash chromatography using hexane - ethyl acetate = 19:1.

(*Z*)-2-Diazo-1-(methoxyimino)-4-methyl-1-phenylpentan-3-one (40a):



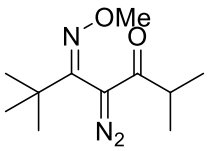
The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 55 - 57 ℃. Yield 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.59 (m, 2H), 7.44 - 7.38 (m, 3H), 4.08 (s, 3H), 2.47 - 2.41 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 144.1, 133.9, 130.2, 128.9, 127.4, 67.3, 62.8, 36.8, 18.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{16}N_3O_2$: 246.1243. Found: 246.1244.

(*Z*)-4-Diazo-5-(methoxyimino)-2,7-dimethyloctan-3-one (40b):



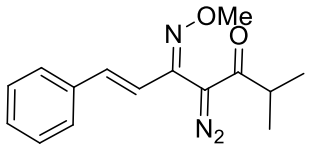
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 2.89 - 2.74 (m, 1H), 2.45 (d, *J* = 7.2 Hz, 2H), 1.85 - 1.70 (m, 1H), 1.14 (d, *J* = 7.2 Hz, 6H), 0.91 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 144.8, 61.9, 40.8, 35.9, 26.9, 22.2, 18.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{20}N_3O_2$: 226.1556. Found: 226.1565.

(*Z*)-4-Diazo-5-(methoxyimino)-2,6,6-trimethylheptan-3-one (40c):



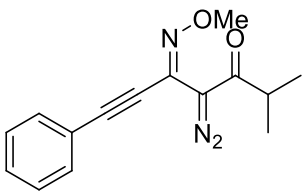
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 2.64 - 2.58 (m, 1H), 1.21 (s, 9H), 1.10 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 150.2, 61.9, 39.4, 36.0, 28.5, 19.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{19}N_3O_2Na$: 248.1375. Found: 248.1372.

(5*Z*, 6*E*)-4-Diazo-5-(methoxyimino)-2-methyl-7-phenylhept-6-en-3-one (40d):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.47 - 7.45 (m, 2H), 7.38 - 7.29 (m, 3H), 6.90 (s, 2H), 4.04 (s, 3H), 2.79 - 2.73 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 197.7, 144.0, 136.1, 135.6, 129.0, 128.9, 127.1, 122.9, 62.8, 36.7, 19.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{18}N_3O_2$: 272.1399. Found: 272.1403.

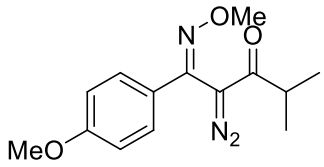
(*Z*)-4-Diazo-5-(methoxyimino)-2-methyl-7-phenylhept-6-yn-3-one (40e):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 76%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.53 - 7.51 (m, 2H),

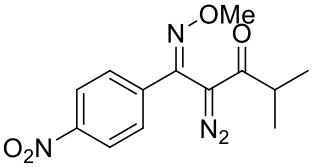
7.40 - 7.34 (m, 3H), 4.07 (s, 3H), 3.34 - 3.31 (m, 1H), 1.18 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 132.0, 129.6, 129.5, 128.5, 121.2, 91.8, 82.6, 63.4, 36.8, 19.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{16}N_3O_2$: 270.1243. Found: 270.1247.

(*Z*)-2-Diazo-1-(methoxyimino)-1-(4-methoxyphenyl)-4-methylpentan-3-one (40f):



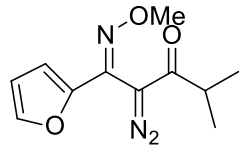
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 - 7.52 (m, 2H), 6.94 - 6.90 (m, 2H), 4.05 (s, 3H), 3.84 (s, 3H), 2.50 - 2.44 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 161.3, 143.7, 128.9, 126.2, 114.3, 62.6, 55.4, 36.8, 18.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{18}N_3O_3$: 276.1348. Found: 276.1355.

(*Z*)-2-Diazo-1-(methoxyimino)-4-methyl-1-(4-nitrophenyl)pentan-3-one (40g):



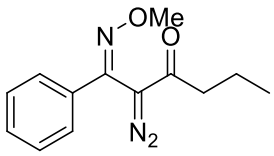
The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 93 - 94 ℃. Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 - 8.23 (m, 2H), 7.74 - 7.71 (m, 2H), 4.13 (m, 3H), 2.63 - 2.59 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 148.5, 142.6, 140.0, 128.1, 123.9, 63.4, 36.5, 18.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{15}N_4O_4$: 291.1093. Found: 291.1094.

(*E*)-2-Diazo-1-(furan-2-yl)-1-(methoxyimino)-4-methylpentan-3-one (40h):



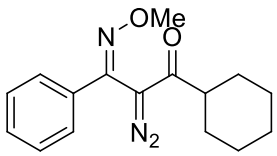
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 1H), 6.68 - 6.67 (m, 1H), 6.50 - 6.48 (m, 1H), 4.08 (s, 3H), 2.58 - 2.51 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 147.4, 144.5, 135.7, 112.1, 111.9, 63.1, 36.7, 18.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{14}N_3O_3$: 236.1035. Found: 236.1044.

(*Z*)-2-Diazo-1-(methoxyimino)-1-phenylhexan-3-one (40i):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.58 (m, 2H), 7.44 - 7.39 (m, 3H), 4.08 (s, 3H), 2.08 (t, *J* = 7.2 Hz, 2H), 1.56 - 1.50 (m, 2H), 0.78 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 144.2, 133.9, 130.2, 128.9, 127.6, 62.8, 41.4, 18.2, 13.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{16}N_3O_2$: 246.1243. Found: 246.1249.

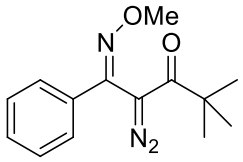
(*Z*)-1-Cyclohexyl-2-diazo-3-(methoxyimino)-3-phenylpropan-1-one (40j):



The title compound was prepared according to the general procedure. The product was

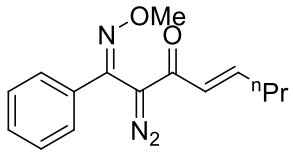
obtained as yellow oil. Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.57 (m, 2H), 7.44 - 7.38 (m, 3H), 4.07 (s, 3H), 2.14 - 2.04 (m, 1H), 1.69 - 1.52 (m, 5H), 1.42 - 1.32 (m, 2H), 1.14 - 1.07 (m, 1H), 0.97 - 0.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 144.3, 134.0, 130.1, 128.8, 127.5, 62.8, 47.2, 28.9, 25.6, 25.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{20}N_3O_2$: 286.1556. Found: 286.1563.

(*Z*)-2-Diazo-1-(methoxyimino)-4,4-dimethyl-1-phenylpentan-3-one (40k):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.55 (m, 2H), 7.39 - 7.35 (m, 3H), 4.07 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 145.1, 134.0, 129.8, 128.6, 127.1, 62.8, 44.5, 26.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{18}N_3O_2$: 260.1399. Found: 260.1398.

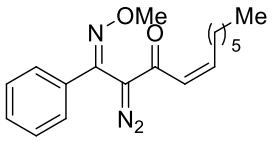
(1*Z*, 4*E*)-2-Diazo-1-(methoxyimino)-1-phenyloct-4-en-3-one (40l):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.58 (m, 2H), 7.42 - 7.36 (m, 3H), 6.82 (dt, J_1 = 8.4 Hz, J_2 = 6.8 Hz, 1H), 5.30 (d, J = 15.2 Hz, 1H), 4.08 (s, 3H), 1.97 - 1.91 (m, 2H), 1.30 - 1.22 (m, 2H), 0.76 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 146.1, 144.1, 134.1, 130.2, 128.8, 127.8, 125.7, 62.8, 34.1, 21.0, 13.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{18}N_3O_2$: 272.1399.

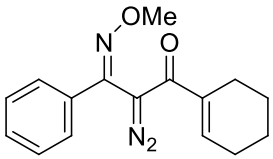
Found: 272.1404.

(1*Z*, 4*Z*)-2-Diazo-1-(methoxyimino)-1-phenylundec-4-en-3-one (40m):



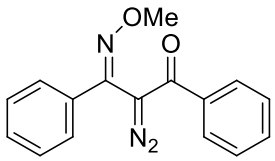
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 - 7.58 (m, 2H), 7.42 - 7.35 (m, 3H), 5.81 (dt, J_1 = 11.6 Hz, J_2 = 7.2 Hz, 1H), 5.65 (d, J = 11.6 Hz, 1H), 4.07 (s, 3H), 2.59 - 2.55 (m, 2H), 1.58 - 1.26 (m, 8H), 0.87 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.0, 148.1, 144.1, 134.0, 130.1, 128.7, 127.7, 123.9, 62.8, 31.6, 29.6, 29.1, 29.0, 22.6, 14.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{24}N_3O_2$: 314.1869. Found: 314.1868.

(*Z*)-1-Cyclohexenyl-2-diazo-3-(methoxyimino)-3-phenylpropan-1-one (40n):



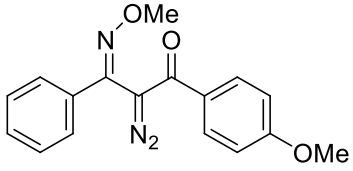
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 - 7.44 (m, 2H), 7.37 - 7.33 (m, 3H), 6.05 - 6.03 (m, 1H), 4.08 (s, 3H), 2.00 - 1.96 (m, 2H), 1.85 - 1.74 (m, 2H), 1.29 - 1.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 145.8, 138.0, 136.7, 135.0, 129.6, 128.7, 127.4, 62.7, 25.2, 24.1, 21.6, 21.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{18}N_3O_2$: 284.1399. Found: 284.1393.

(*Z*)-2-Diazo-3-(methoxyimino)-1,3-diphenylpropan-1-one (40o):



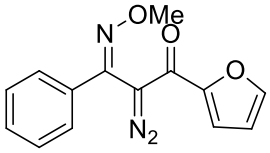
The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 87 - 88 ℃. Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 - 7.47 (m, 4H), 7.34 - 7.29 (m, 1H), 7.26- 7.20 (m, 5H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8, 144.9, 137.6, 133.4, 131.9, 129.9, 128.5, 128.1, 127.6, 127.5, 62.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{14}N_3O_2$: 280.1086. Found: 280.1078.

(*Z*)-2-Diazo-3-(methoxyimino)-1-(4-methoxyphenyl)-3-phenylpropan-1-one (40p):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53- 7.48 (m, 4H), 7.25 - 7.23 (m, 3H), 6.72 - 6.70 (m, 2H), 4.00 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 162.6, 145.2, 133.5, 130.2, 129.9, 128.6, 127.6, 113.3, 62.7, 55.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{16}N_3O_3$: 310.1192. Found: 310.1194.

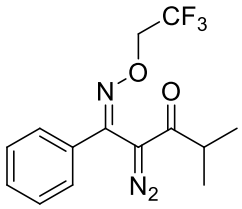
(*Z*)-2-Diazo-1-(furan-2-yl)-3-(methoxyimino)-3-phenylpropan-1-one (40q):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 - 7.60 (m, 2H),

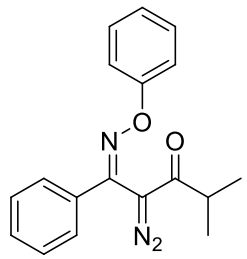
7.35 - 7.32 (m, 4H), 7.01 (d, *J* = 3.6 Hz, 1H), 6.40 - 6.38 (m, 1H), 4.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 151.2, 145.0, 144.1, 133.7, 129.8, 128.6, 127.2, 116.8, 112.1, 62.9; HRMS (ESI) m/z [M+H]+: Calcd for C14H12N3O2: 254.0930. Found: 254.0920.

(*Z*)-2-Diazo-4-methyl-1-phenyl-1-(2,2,2-trifluoroethoxyimino)pentan-3-one (40r):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 - 7.51 (m, 2H), 7.42 - 7.33 (m, 3H), 4.56 (q, *J* = 16.8 Hz, 2H), 2.37 - 2.30 (m, 1H), 0.91 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 147.5, 133.0, 130.9, 129.0, 127.8, 123.3 (q, *J* = 278.2 Hz), 71.6 (q, *J* = 34.2 Hz), 67.5, 37.0, 18.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{15}N_3O_2F_3$: 314.1116. Found: 314.1111.

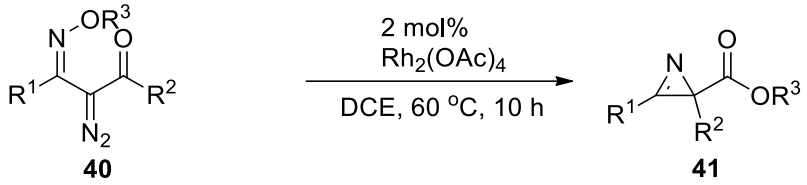
(*Z*)-2-Diazo-4-methyl-1-(phenoxyimino)-1-phenylpentan-3-one (40s):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 - 7.62 (m, 2H), 7.41 - 7.35 (m, 3H), 7.29 - 7.24 (m, 4H), 7.20 - 6.97 (m, 1H), 2.46 - 2.38 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 158.7, 147.6, 133.4, 130.9,

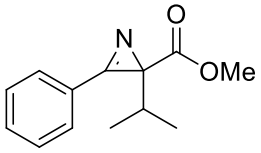
129.5, 128.0, 123.1, 114.7, 68.0, 37.1, 18.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{18}N_3O_2$: 308.1399. Found: 308.1402.

General procedure for 2*H*-azirine-2-carboxylic esters:



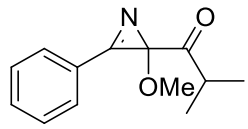
A solution of *α*-diazo-*β*-keto oxime ethers **40** (0.2 mmol) and $Rh_2(OAc)_4$ (0.004 mmol, 2 mol%) in dichloroethane (2.0 mL) was stirred at 60 ℃ until the starting material was fully consumed. The reaction mixture was concentrated under reduced pressure to give the crude material which was purified by flash chromatography using hexane-ethyl acetate = 9:1 to give desired product.

Methyl 2-isopropyl-3-phenyl-2*H*-azirine-2-carboxylate (41a):



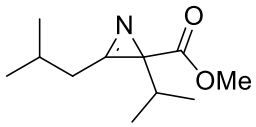
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 - 7.86 (m, 2H), 7.64 - 7.54 (m, 3H), 3.66 (s, 3H), 2.94 - 2.87 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 162.2, 133.5, 130.1, 129.3, 123.4, 52.3, 44.7, 27.3, 20.4, 18.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{16}NO_2$: 218.1181. Found: 218.1184.

1-(2-Methoxy-3-phenyl-2*H*-azirin-2-yl)-2-methylpropan-1-one (41a'):



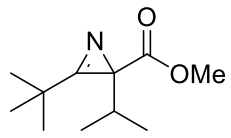
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.39 (m, 2H), 7.34 - 7.29 (m, 3H), 3.73 (s, 3H), 2.78 - 2.71 (m, 1H), 1.16 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.2, 169.3, 138.5, 129.7, 128.2, 124.0, 73.7, 51.6, 25.9, 22.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{16}NO_2$: 218.1181. Found: 218.1178.

Methyl 3-isobutyl-2-isopropyl-2*H*-azirine-2-carboxylate (41b):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.75 - 2.70 (m, 1H), 2.69 - 2.60 (m, 2H), 2.23 - 2.16 (m, 1H), 1.09 (dd, J_1 = 4.0 Hz, J_2 = 4.0 Hz, 6H), 0.90 (d, J = 6.8 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 165.2, 52.0, 42.6, 36.3, 27.2, 25.5, 22.6, 22.5, 19.8, 18.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{20}NO_2$: 198.1494. Found: 198.1494.

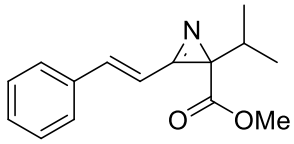
Methyl 3-*tert*-butyl-2-isopropyl-2*H*-azirine-2-carboxylate (41c):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 2.63 - 2.52 (m, 1H), 1.31 (s, 9H), 0.90 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.0, 51.9, 45.5, 33.4, 27.8, 26.8, 20.6, 19.1;

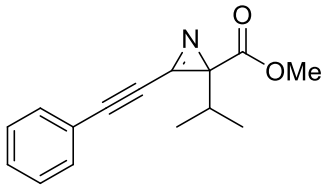
HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{20}NO_2$: 198.1494. Found: 198.1493.

(*E*)-Methyl 2-isopropyl-3-styryl-2*H*-azirine-2-carboxylate (41d):



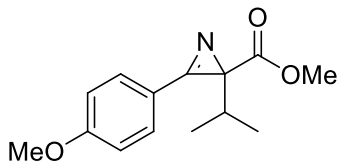
The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 70 - 72 ºC. Yield: 82%. 1H NMR (400 MHz, CDCl3) δ 7.59 - 7.57 (m, 2H), 7.45 - 7.43 (m, 3H), 7.26 (d, *J* = 16.0 Hz, 1H), 7.17 (d, *J* = 16.0 Hz, 1H), 3.68 (s, 3H), 2.91 - 2.84 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) *δ* 172.9, 161.1, 148.2, 134.2, 131.0, 129.1, 128.3, 110.7, 52.3, 43.8, 27.3, 20.3, 18.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{18}N_3O_2$: 272.1399. Found: 272.1393.

Methyl 2-isopropyl-3-(phenylethynyl)-2*H*-azirine-2-carboxylate (41e):



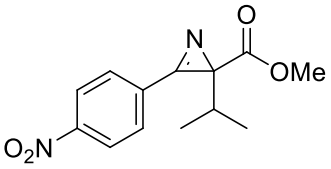
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.63 - 7.61 (m, 2H), 7.50 - 7.48 (m, 1H), 7.45 - 7.41 (m, 2H), 3.72 (s, 3H), 2.89 - 2.79 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.5, 153.2, 132.6, 131.2, 128.8, 120.0, 113.6, 73.3, 52.5, 46.7, 27.1, 19.6, 18.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{16}NO_2$: 242.1181. Found: 242.1180.

Methyl 2-isopropyl-3-(4-methoxyphenyl)-2*H*-azirine-2-carboxylate (41f):



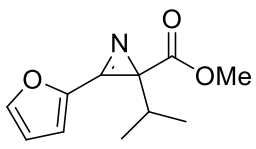
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 - 7.80 (m, 2H), 7.07 - 7.05 (m, 2H), 3.90 (s, 3H), 3.65 (s, 3H), 2.92 - 2.85 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 163.7, 161.1, 132.1, 115.7, 114.8, 55.6, 52.2, 44.2, 27.4, 20.4, 18.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{18}NO_3$: 248.1287. Found: 248.1287.

Methyl 2-isopropyl-3-(4-nitrophenyl)-2*H*-azirine-2-carboxylate (41g):



The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 119 - 121 ℃. Yield: 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 - 8.42 (m, 2H), 8.08 - 8.05 (m, 2H), 3.69 (s, 3H), 2.97 - 2.91 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 162.7, 150.5, 130.8, 129.1, 124.5, 52.5, 46.0, 27.2, 20.5, 18.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{15}N_2O_4$: 263.1032. Found: 263.1039.

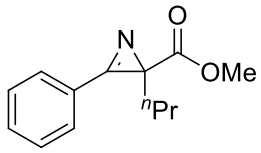
Methyl 3-(furan-2-yl)-2-isopropyl-2*H*-azirine-2-carboxylate (41h):



The title compound was prepared according to the general procedure. The product was

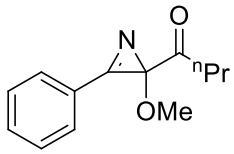
obtained as colorless oil. Yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 - 7.79 (m, 1H), 7.21 - 7.19 (m, 1H), 6.67 - 6.66 (m, 1H), 3.66 (s, 3H), 2.90 - 2.79 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 152.4, 148.5, 140.3, 120.6, 112.8, 52.4, 44.2, 27.2, 20.1, 18.5; HRMS (ESI) m/z [M+H]+: Calcd for C11H14NO3: 208.0974. Found: 208.0975.

Methyl 3-phenyl-2-propyl-2*H*-azirine-2-carboxylate (41i):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 - 7.84 (m, 2H), 7.65 - 7.60 (m, 1H), 7.58 - 7.54 (m, 2H), 3.67 (s, 3H), 2.13 - 1.98 (m, 2H), 1.33 - 1.24 (m, 2H), 0.90 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 163.0, 133.6, 130.1, 129.3, 123.1, 52.4, 39.7, 32.7, 19.6, 14.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{16}NO_2$: 218.1181. Found: 218.1176.

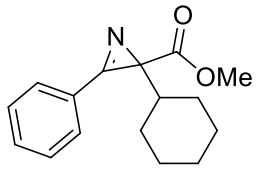
1-(2-methoxy-3-phenyl-2*H*-azirin-2-yl)butan-1-one (41i'):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 29%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 - 7.84 (m, 2H), 7.65 - 7.54 (m, 3H), 3.67 (s, 3H), 2.11 - 1.98 (m, 2H), 1.32 - 1.26 (m, 2H), 0.90 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 170.0, 138.4, 129.6, 128.2, 124.2, 65.8, 51.8, 27.1, 22.1, 13.7; HRMS (ESI) m/z [M+H]+: Calcd for C13H16NO2:

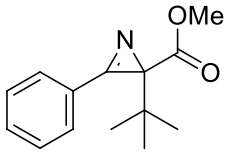
218.1181. Found: 218.1189.

Methyl 2-cyclohexyl-3-phenyl-2*H*-azirine-2-carboxylate (41j):



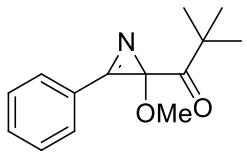
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 - 7.85 (m, 2H), 7.64 - 7.54 (m, 3H), 3.65 (s, 3H), 2.61 - 2.55 (m, 1H), 1.81 - 1.72 (m, 2H), 1.67 - 1.60 (m, 3H), 1.35 - 1.27 (m, 2H), 0.99 - 0.89 (m, 2H), 0.76 - 0.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 162.5, 133.4, 130.1, 129.3, 123.6, 52.3, 44.1, 36.7, 30.9, 29.0, 26.1, 26.0, 25.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for C16H20NO2: 258.1494. Found: 258.1501.

Methyl 2-*tert*-butyl-3-phenyl-2*H*-azirine-2-carboxylate (41k):



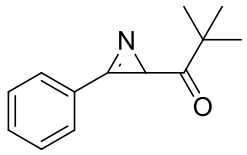
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 33%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 - 7.79 (m, 2H), 7.55 - 7.48 (m, 3H), 3.54 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 164.4, 133.4, 130.0, 129.3, 123.8, 51.9, 46.6, 33.4, 28.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{18}NO_2$: 232.1338. Found: 232.1339.

1-(2-Methoxy-3-phenyl-2*H*-azirin-2-yl)-2,2-dimethylpropan-1-one (41k'):



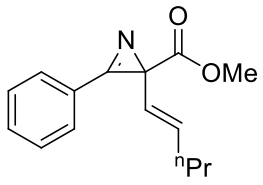
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 - 7.88 (m, 2H), 7.66 - 7.62 (m, 1H), 7.59 - 7.50 (m, 2H), 3.22 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 166.9, 133.8, 129.9, 129.4, 123.3, 74.9, 53.5, 44.0, 26.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{18}NO2$: 232.1338. Found: 232.1335.

2,2-Dimethyl-1-(3-phenyl-2*H*-azirin-2-yl)propan-1-one (41k"):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 18%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 - 7.80 (m, 2H), 7.62 - 7.60 (m, 1H), 7.67 - 7.53 (m, 2H), 3.37 (s, 1H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.2, 156.2, 133.6, 130.4, 129.3, 122.4, 43.9, 32.2, 26.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{16}NO$: 202.1232. Found: 202.1226.

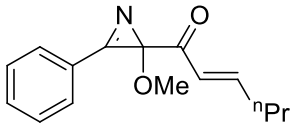
(*E*)-Methyl 2-(pent-1-enyl)-3-phenyl-2*H*-azirine-2-carboxylate (41l):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 - 7.85 (m, 2H), 7.63 - 7.55 (m, 3H), 6.50 (dt, J_1 = 15.6 Hz, J_2 = 1.2 Hz, 1H), 5.30 (dt, J_1 = 15.6

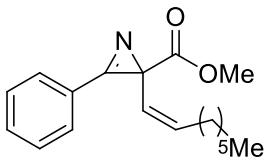
Hz, J_2 = 7.2 Hz, 1H), 3.72 (s, 3H), 2.04 - 1.98 (m, 2H), 1.36 - 1.30 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 172.1, 157.1, 133.7, 133.5, 130.4, 129.4, 125.5, 121.6, 52.6, 38.8, 34.3, 22.1, 13.6; HRMS (ESI) m/z [M+H]+: Calcd for C15H18NO2: 244.1338. Found: 244.1341.

(*E*)-1-(2-Methoxy-3-phenyl-2H-azirin-2-yl)hex-2-en-1-one (41l'):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 18%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 - 7.90 (m, 2H), 7.66 - 7.60 (m, 1H), 7.58 - 7.56 (m, 1H), 7.10 (dt, J_1 = 15.6 Hz, J_2 = 6.8 Hz, 1H), 6.41 (d, *J* = 15.6 Hz, 1H), 3.42 (s, 3H), 2.22 - 2.16 (m, 2H), 1.51 - 1.46 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 166.2, 150.1, 134.1, 130.3, 129.5, 124.4, 122.6, 74.1, 54.3, 34.7, 21.3, 13.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{18}NO_2$: 244.1338. Found: 244.1340.

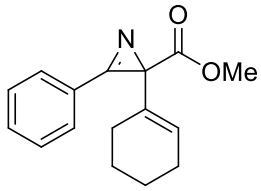
(*Z*)-Methyl 2-(oct-1-enyl)-3-phenyl-2*H*-azirine-2-carboxylate (41m):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 - 7.86 (m, 2H), 7.64 - 7.56 (m, 3H), 6.02 (dt, J_1 = 11.2 Hz, J_2 = 1.6 Hz, 1H), 5.63 (dt, J_1 = 11.2 Hz, J_2 = 7.6 Hz, 1H), 3.72 (s, 3H), 2.00 - 1.94 (m, 2H), 1.23 - 1.12 (m, 4H), 1.11 - 1.08 (m, 4H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 161.0, 136.8,

133.7, 130.2, 129.4, 123.1, 122.8, 52.7, 37.9, 31.6, 29.5, 28.9, 28.5, 22.5, 14.0; HRMS (ESI) m/z [M+H]+: Calcd for C18H24NO2: 286.1807. Found: 286.1802.

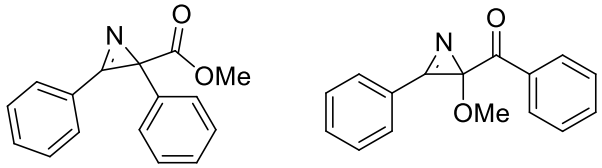
Methyl 2-cyclohexenyl-3-phenyl-2*H*-azirine-2-carboxylate (41n):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 - 7.89 (m, 2H), 7.65 - 7.55 (m, 3H), 5.87 - 5.85 (m, 1H), 3.69 (s, 3H), 2.23 - 2.19 (m, 2H), 2.03 - 1.99 (m, 2H), 1.68 - 1.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 161.9, 134.3, 133.6, 130.3, 129.4, 128.0, 122.9, 52.4, 42.8, 26.4, 25.1, 22.5, 21.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{18}NO_2$: 256.1338. Found: 256.1337.

Methyl 2,3-diphenyl-2*H*-azirine-2-carboxylate (41o) and

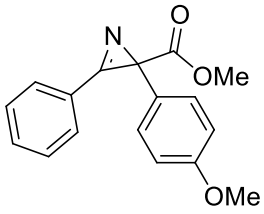
(2-methoxy-3-phenyl-2*H*-azirin-2-yl)(phenyl)methanone (41o'):



The title compound was prepared according to the general procedure. The products were obtained as an inseparable mixture in a ratio of 1:1 as colorless oil. Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 - 8.19 (m, 2H), 7.97 - 7.92 (m, 4H), 7.66 - 7.61 (m, 2H), 7.60 - 7.56 (m, 5H), 7.52 - 7.49 (m, 4H), 7.35 - 7.28 (m, 3H), 3.75 (s, 3H), 3.37(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 171.7, 166.3, 160.7, 136.2, 135.9, 134.0, 133.9, 130.5, 130.2, 129.6, 129.5, 129.4, 128.5, 128.3, 128.2, 127.8, 122.8, 122.0, 74.6,

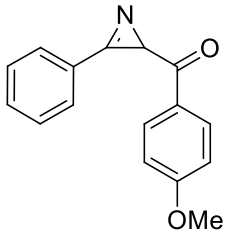
54.5, 52.7, 41.1; HRMS (ESI) m/z [M+H]+: Calcd for C16H14NO2: 252.1025. Found: 252.1020.

Methyl 2-(4-methoxyphenyl)-3-phenyl-2*H*-azirine-2-carboxylate (41p):



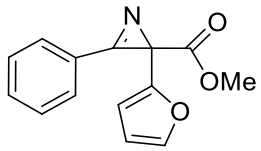
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 - 7.92 (m, 2H), 7.66 - 7.56 (m, 3H), 7.43 - 7.39 (m, 2H), 6.87 - 6.84 (m, 2H), 3.78 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 160.8, 159.2, 133.9, 130.4, 129.6, 129.5, 128.4, 122.2, 113.8, 55.3, 52.7, 40.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{16}NO_3$: 282.1130. Found: 282.1134.

(4-Methoxyphenyl)(3-phenyl-2*H*-azirin-2-yl)methanone (41p'):



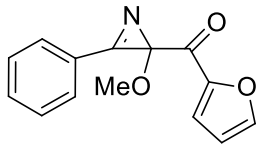
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 21%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 - 8.13 (m, 2H), 7.89 - 7.87 (m, 2H), 7.62 - 7.60 (m, 1H), 7.57 - 7.53 (m, 2H), 7.03 - 7.01 (m, 2H), 3.91 (s, 3H), 3.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 163.8, 157.3, 133.7, 130.7, 130.5, 130.3, 129.3, 122.6, 114.0, 55.6, 33.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{14}NO_2$: 252.1025. Found: 252.1028.

Methyl 2-(furan-2-yl)-3-phenyl-2*H*-azirine-2-carboxylate (41q):



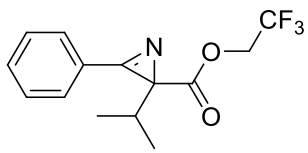
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 - 7.93 (m, 2H), 7.69 - 7.65 (m, 1H), 7.62 - 7.58 (m, 2H), 7.27 - 7.26 (m, 1H), 6.83 - 6.82 (m, 1H), 6.40 - 6.38 (m, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 157.2, 149.6, 142.0, 134.0, 130.6, 129.4, 121.7, 111.0, 111.0, 52.8, 36.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{12}NO_3$: 242.0817. Found: 242.0814.

Furan-2-yl(2-methoxy-3-phenyl-2*H*-azirin-2-yl)methanone (41q'):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 31%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 - 7.93 (m, 2H), 7.68 - 7.57 (m, 4H), 7.44 (d, J = 3.6 Hz, 1H), 6.54 (dd, J_1 = 1.6 Hz, J_2 = 3.6 Hz, 1H), 3.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 165.8, 150.9, 147.4, 134.2, 130.4, 129.5, 122.2, 121.6, 112.3, 73.5, 54.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{12}NO_3$: 242.0817. Found: 242.0818.

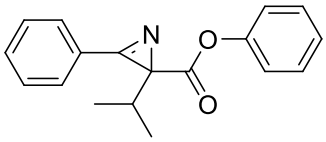
2,2,2-Trifluoroethyl 2-isopropyl-3-phenyl-2*H*-azirine-2-carboxylate (41r):



The title compound was prepared according to the general procedure. The product was

obtained as colorless oil. Yield: 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 - 7.77 (m, 2H), 7.57 - 7.52 (m, 1H), 7.51 - 7.49 (m, 2H), 4.56 - 4.46 (m, 1H), 4.35 - 4.26 (m, 1H), 2.83 - 2.80 (m, 1H), 0.89 (d, J = 6.8 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 162.0, 133.7, 130.1, 129.4, 126.9, 122.8 (q, J = 144.6 Hz), 60.7 (q, J = 36.3 Hz), 44.3, 27.4, 20.2, 18.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{15}NO_2F_3$: 286.1055. Found: 286.1048.

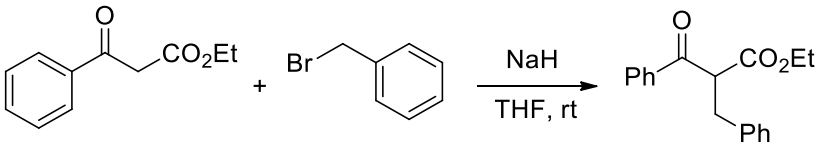
Phenyl 2-isopropyl-3-phenyl-2*H*-azirine-2-carboxylate (41s):



The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 106 - 108 ℃. Yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 - 7.85 (m, 2H), 7.59 - 7.50 (m, 3H), 7.26 - 7.22 (m, 2H), 7.12 - 7.08 (m, 1H), 6.95 - 6.92 (m, 2H), 2.93 - 2.90 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 162.5, 150.8, 133.7, 130.2, 129.4, 129.3, 125.8, 123.2, 121.5, 44.8, 27.5, 20.4, 18.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{18}NO_2$: 280.1338. Found: 280.1342.

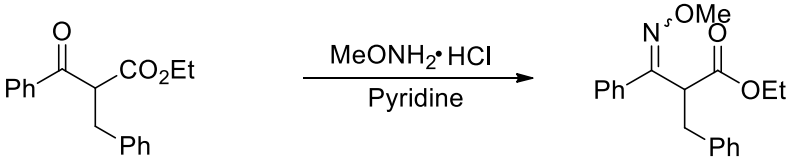
General procedure for 41t

Ethyl 2-benzyl-3-oxo-3-phenylpropanoate:



The title compound was prepared according to literature. [53] The product was obtained as colorless oil. Yield: 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 - 7.95 (m, 2H), 7.58 - 7.54 (m, 1H), 7.47 - 7.43 (m, 2H), 7.28 - 7.17 (m, 5H), 4.62 (t, J = 7.2 Hz, 1H), 4.13 - 4.07 (m, 2H), 3.33 (q, J = 6.8 Hz, 2H), 1.11 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 169.3, 138.4, 136.2, 133.5, 128.9, 128.7, 128.5, 126.6, 61.5, 56.2, 34.8, 13.9.

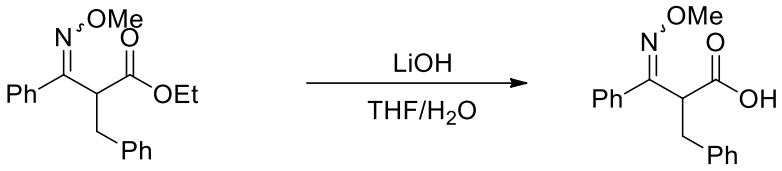
Ethyl 2-benzyl-3-(methoxyimino)-3-phenylpropanoate:



To a solution of β-keto ester (2.0 mmol, 1.0 eq.) in pyridine (2 mL) at room temperature was added *O*-methylhydroxylamine hydrochloride (2.2 mmol, 1.1 eq.) in one portion and the reaction mixture was stirred at room temperature for 3 h. Upon completion as indicated by TLC, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, brine, and dried over Na_2SO_4. The crude material was purified by flash chromatography using hexane : ethyl acetate = 9 : 1. The product was obtained as colorless oil. Yield: 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.15 (m, 10H), 4.22 - 4.17 & 4.09 - 4.06 (m, 2H), 4.05 - 4.04 & 3.85 - 3.88 (m, 1H), 3.95 & 3.86 (s, 3H), 3.49 - 3.44 & 3.26 - 3.21 (m, 1H), 3.18 - 3.07 (m, 1H), 1.14 & 1.11 (t, J = 7.2 Hz & J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 171.1, 156.0, 154.3, 139.1, 138.9, 135.5, 133.2, 129.2, 129.1, 129.0, 128.9, 128.4, 128.3, 128.1, 127.8, 126.8, 126.4, 126.4, 62.2, 62.1, 61.0, 53.5, 47.7, 35.6, 34.4, 14.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{22}NO_3$: 312.1600. Found: 312.1597.

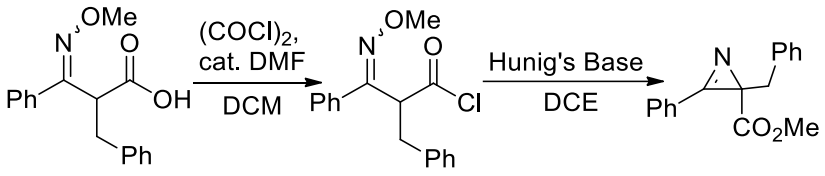
[53] Gonzalez, D. F.; Brand, J. P.; Waser, J. *Chem.-Eur. J.* **2010**, *16*, 9457

Methyl 2-benzyl-3-phenyl-2*H*-azirine-2-carboxylate (40t'):



To a solution of ethyl 2-benzyl-3-(methoxyimino)-3-phenylpropanoate (311 mg, 1.0 mmol) in THF (5 mL) was added LiOH (126 mg, 3.0 mmol) in water (5 mL) and stirred at 45 ℃ for 4 h. The mixture was washed with ethyl acetate. The aqueous layer was acidified to pH = 3 with 1 N HCl and extractd with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by flash chromatography using hexane : ethyl acetate = 1 : 1. The product was obtained as colorless oil. Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.12 (m, 10H), 4.26 - 4.11 & 3.97 - 3.95 (m, 1H), 3.98 & 3.87 (s, 3H), 3.46 - 3.41 & 3.21 - 3.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 157.9, 155.5, 141.5, 141.2, 138.7, 138.2, 135.7, 135.1, 133.8, 129.2, 129.1, 129.1, 128.8, 128.5, 128.4, 128.3, 128.2, 127.8, 126.8, 126.6, 126.5, 126.3, 126.1, 126.0, 62.2, 37.3, 34.1, 33.1, 32.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{18}NO_3$: 284.1287. Found: 284.1289.

Methyl 2-benzyl-3-phenyl-2*H*-azirine-2-carboxylate (41t):



To a stirred solution of methyl 2-benzyl-3-(methoxyimino)-3-phenylpropanoic acid (0.5 mmol, 142 mg) in DCM (2 mL) at 0 ℃ was added a drop of DMF followed by dropwise addition of oxalyl chloride (0.6 mmol, 51 μL). The reaction mixture was

stirred at 0 ℃ for 15 min, brought to room temperature, and stirred for 2 h. After concentration, the crude material was dried by azeotropic distillation with toluene, dissolved in dichloroethane (2 mL), and cooled to -50 ℃. To this solution was dropwisely added a solution of Hunig's base (1.0 mmol, 174 μL) in dichloroethane (1 mL). The resulting solution was warmed to 50 ℃ and stirred for another 10 h. Upon completion as indicated by TLC, the solvent was removed in vacuo, and the crude material was purified by column chromatography using hexane : ethyl acetate = 19 : 1. The product was obtained as colorless oil. Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 - 7.54 (m, 3H), 7.47 - 7.43 (m, 2H), 7.20 - 7.14 (m, 5H), 3.68 (s, 3H), 3.67 (d, J = 14.8 Hz, 1H), 3.13 (d, J = 14.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 162.4, 137.6, 133.5, 130.1, 129.8, 129.1, 128.3, 126.5, 122.6, 52.5, 40.5, 37.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{16}NO_2$: 266.1181. Found: 266.1184.

CHAPTER 2

Synthesis of Highly Substituted Pyrroles via Tandem Rearrangement of α-Diazo-β-Keto Oxime Ethers

CHAPTER 2 SYNTHESIS OF HIGHLY SUBSTITUTED PYRROLES *VIA* TANDEM REARRANGEMENT OF *α*-DIAZO-*β*-KETO OXIME ETHERS

2.1 OVERIEW

Pyrroles[54] are one of the most important aza-heterocycles that are frequently found in pharmaceuticals,[55] natural products,[56] and functional materials.[57] Organic committees have constantly endeavored to construct these small heteroaryl rings.[58] The use of nitrene species to assemble the pyrrole skeletons is one of the most promising strategies. The study by Padwa demonstrated that 2-vinyl-2*H*-azirines undergo rearrangement to furnish pyrroles *via* nitrenes.[59] In continuation of interests in heterocycles synthesis, we envisaged that vinyl substituted 2*H*-azirines arising from Wolff rearrangement of *α*-diazo-*β*-keto oxime ethers, could lead to the formation of substituted pyrroles in an one-pot pathway. In this chapter, we described Rh(II)-catalyzed cascade rearrangement of *α*-diazo-*β*-keto oxime ethers to afford highly substituted pyrroles including 2-vinyl-2*H*-azirines intermediates. Furthermore, we found that 2-vinyl-2*H*-azirines could be activated in the presence of Ni(II) catalyst to construct fully-substituted pyrroles from migration of disubstituted-2*H*-pyrroles.

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2.2 RHODIUM(II)-CATALYZED SYNTHESIS OF HIGHLY SUBSTITUTED PYRROLES

2.2.1 INTRODUCTION

As one of the most important *N*-heterocycles, pyrroles have been well studied by organic chemists in the last several decades.[60] Functionalized pyrroles are normally regarded as versatile building blocks in the synthesis of various heterocycles, including indoles, indolizidine alkaloids and indolizines.[61] Pyrrole skeletons are also widely found in many natural products. Noteworthily, the highly substituted pyrroles often exhibit unique biological and therapeutic activities. For instance, marinopyrroles possess antibiotic activity against methicillin-resistant *Staphylococcus aureus* (Figure 2.1, **a**).[62] Nakamuric acid contains two pyrrole moieties (Figure 2.1, **b**).[63] Furthermore, some drugs contain pyrrole substructures and the representative examples include cholesterol-lowering drug atorvastatin (Figure 2.1, **c**), non-steroidal antiinflamatory compound tolmetin (Figure 2.1, **d**) and antipsychotic drugs (Figure 2.1, **e**).[64, 65] BODIPY dyes (Figure 2.1, **f**)[66] have been widely applied in material science, which also contain the pyrrole moiety.

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[60] a) Wijngaarden, I.; Kruse, C. G.; Heyden, van der J. A. M.; Tulp, M. T. M. *J. Med. Chem.* **1988**, *31*, 1934; b) Aleško vić, M.; Basarić, N.; Halasz, I.; Liang, X.; Qin, W.; Mlinarić-Majerski, K. *Tetrahedron* **2013**, *69*, 1725; c) Sobenina, L. N.; Vasil'tsov, A. M.; Petrova, O. V.; Petrushenko, K. B.; Ushakov, I. A.; Clavier, G.; Meallet-Renault, R.; Mikhaleva, A. I.; Trofimov, B. A. *Org. Lett.* **2011**, *13*, 2524; d) Harman, W. H.; Chang, C. J. *J. Am. Chem. Soc.* **2007**, *129*, 15128.

[61] a) Kim, M.; Vedejs, E.; *J. Org. Chem.* **2004**, *69*, 6945; b) Amos, R. I. J.; Gourlay, B. S.; Molesworth, P. P.; Smith, J. A.; Sprod, O. R. *Tetrahedron*, **2005**, *61*, 8226; c) Virieux, D.; Guillouzic, A.-F.; Cristau, H.-J. *Tetrahedron* **2006**, *62*, 3710; d) Zhu, H.; Stöckigt, J.; Yu, Y.; Zou, H. *Org. Lett.* **2011**, *13*, 2792.

[62] Hughes, C. C.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2008**, *10*, 629.

[63] For a summary of the structures of these alkaloids, see: O'Malley, D. P.; Li, K.; Maue, M.; Zografos, A. L.; Baran, P. S. *J. Am. Chem. Soc*. **2007**, *129*, 4762.

[64] Biava, M.; Porretta, G. C.; Deidda, D.; Pompei, R.; Tafic, A.; Manettic, F. *Bioorg. Med. Chem*. **2004**, *12*, 1453.

[65] Protopopova, M.; Bogatcheva, E.; Nikonenko, B.; Hundert, S.; Einck, L.; Nacy, C. A. *Med. Chem*. **2007**, *3*, 301.

[66] For a review, see: Loudet, A.; Burgess, K. *Chem. Rev*. **2007**, *107*, 4891.

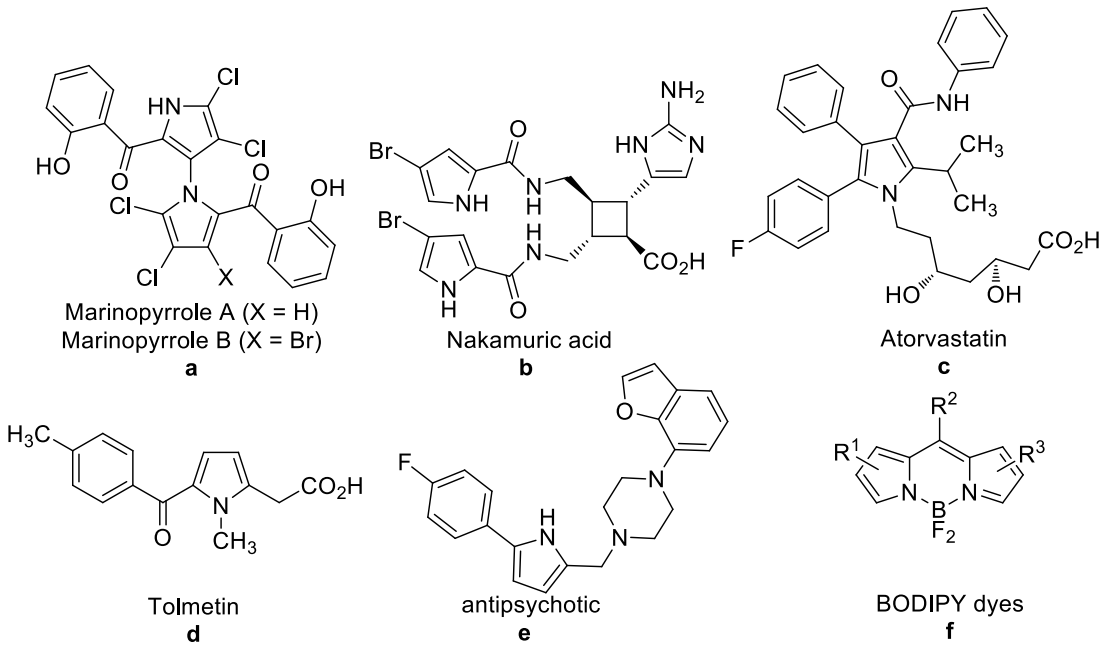
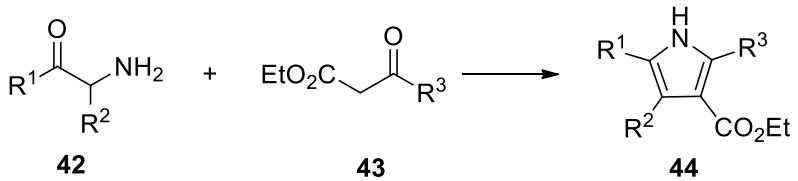


Figure 2.1 Drugs containing multi-substituted pyrroles

Due to the important utilities shown by the pyrrole moiety, many methods have been developed to synthesize substituted pyrroles with various substituents at different positions.[67] A few of classical methods and also recently developed strategies were summarized as below.

Knorr pyrrole synthesis is a widely used method to synthesize substituted pyrrole derivatives **44** through the condensation of α-amino ketones **42** with carbonyl compounds containing active β-methylene groups **43** (Scheme 2.1).[68]

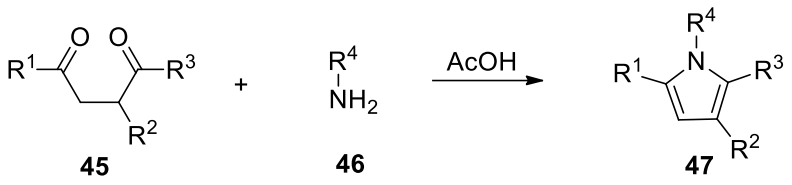


Scheme 2.1 Knorr pyrrole synthesis

[67] a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084; b) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402.

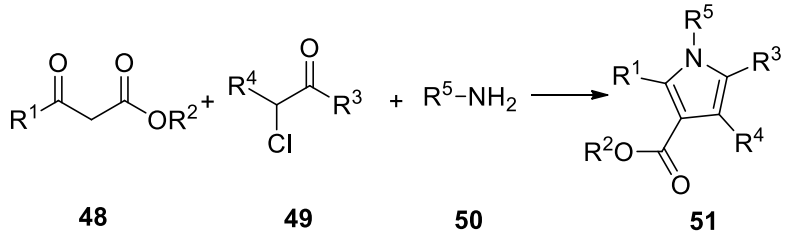
[68] a) Kros, A.; Hövel, van S. W. F. M.; Nolte, R. J. M.; Sommerdijk, N. A. J. M.; *Sens. Actuators, B* **2001**, *80*, 229; b) Lazerges, M.; Chane-Ching, K. I.; Aeiyach, S.; Chelli, S.; Peppin-Donnat, B.; Billon, M.; Lombard, C.; Maurel, F.; Jouini, M.; *J. Solid State Electrochem.* **2009**, *13*, 231; c) Lrich, G.; Ziessel, R.; Harriman, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1184; d) Loudet, A.; Burgess, K. *Chem. Rev.* **2007**, *107*, 4891.

The Paal-Knorr pyrrole synthesis is one of the most efficient methods to assemble multi-substituted pyrroles **47** through the condensation of 1,4-dicarbonyl compounds **45** with an excess of primary amine or ammonia **46** in weakly acidic condition**.** This reaction provides a general approaches to access pyrrole derivatives from a variety of 1,4-dicarbonyl compounds and the primary amines (Scheme 2.2).[69]



Scheme 2.2 Paal-Knorr pyrrole synthesis

Hantzsch pyrrole synthesis or Hantzsch synthesis refers to the synthesis of highly substituted pyrrole derivatives **51** through the condensation of *β*-ketoesters **48**, *α*-halo-ketones **49**, and ammonia or amines **50** (Scheme 2.3).[70]



Scheme 2.3 Hantzsch pyrrole synthesis

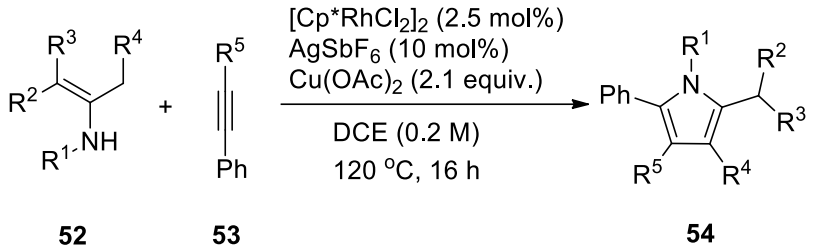
The recent development of transition-metal-catalyzed oxidative annulations of the C−H/N−H bond with alkynes has also been introduced into the field of pyrrole synthesis.[71] In 2010, a pioneering report by Glorius demonstrated pyrrole synthesis

[69] a) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, *5277*; b) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213.

[70] a) Kaupp, G.; Schmeyers, J.; Kuse, A.; Atfeh, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2896; b) Trautwein, A. W.; Sussmuth, R. D.; Jung, G.; *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381; c) Moss, T. A.; Nowak, T. *Tetrahedron Lett.* **2012**, *53*, 3056.

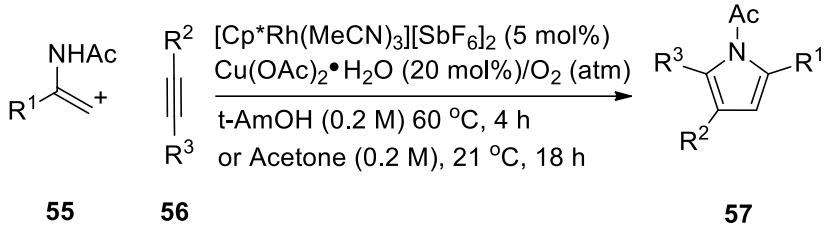
[71] a) Tchabanenko, K.; Sloan, C.; Bunetel, Y.-M.; Mullen, P. *Org. Biomol. Chem.* **2012**, *10*, 4215; b)

pathway *via* allylic sp^3 C-H activation of enamines **52** followed by intermolecular coupling with unactivated alkynes **53** in the presence of rhodium(III) catalyst (Scheme 2.4).[72]



Scheme 2.4 Rhodium catalyzed oxidative pyrrole synthesis

In 2010, Stuart and Fagnou reported the reaction of enamides **55** and alkynes **56** which enabled direct access to a variety of pyrrole substitution patterns by Rh(III) catalyst (Scheme 2.5).[73]



Scheme 2.5 Rhodium catalyzed oxidative pyrrole synthesis

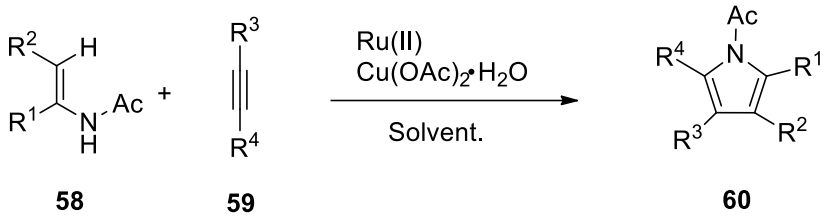
In 2013, Ru-catalyzed pyrroles synthesis by annulation of enamides **58** with alkynes **59** has also been developed independently by the groups of Wang and Ackermann (Scheme 2.6).[74]

Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430; c) Nakanishi, M.; Minard, C.; Ratailleau, P.; Cariou, K.; Dodd, R. H. *Org. Lett.* **2011**, *13*, 5792; d) Cheng, L.; Kuang, Y.; Qin, B.; Zhou, X.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2010**, *12*, 2214.

[72] Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585.

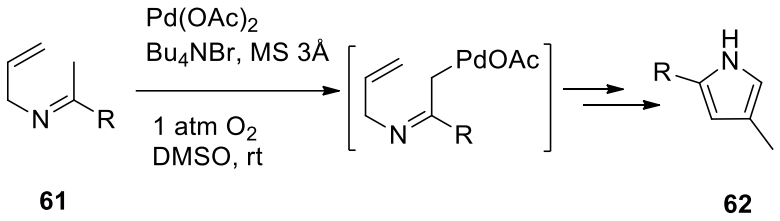
[73] a) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338; b) Stuart, D. R.; Alsabeh, P.; Kuchn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326.

[74] a) Li, B.; Wang, N.; Liang, Y.; Xu, S.; Wang, B. *Org. Lett.* **2013**, *15*, 136; b) Wang, L.; Ackermann, L. *Org. Lett.* **2013**, *15*, 176; c) Murugan, K.; Liu, S. T. *Tetrahedron Lett.* **2013**, *54*, 2608.



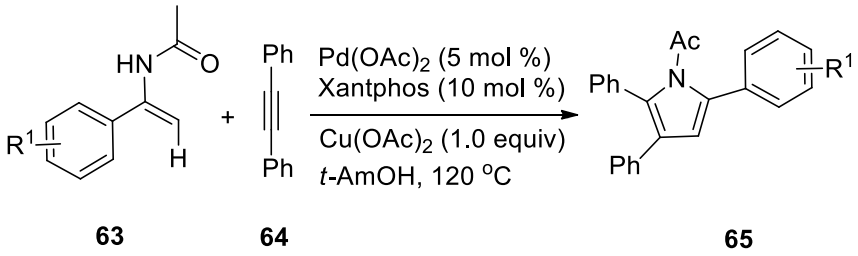
Scheme 2.6 Ruthenium catalyzed oxidative pyrrole synthesis

In 2013, Yoshikai reported a palladium(II)-catalyzed oxidative cyclization reaction of *N*-allylimines **61** derived from methyl ketones, typically acetophenones, affording pyrrole derivatives **62** at room temperature under oxygen atmosphere (Scheme 2.7).[75]



Scheme 2.7 Palladium catalyzed oxidative pyrrole synthesis

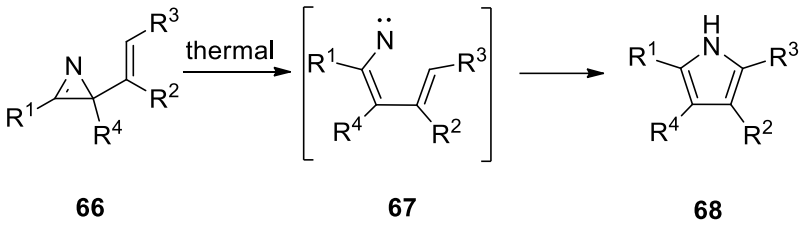
After then, Guan group demonstrated that Pd(II) could also catalyze pyrrole synthesis from enamides **63** and alkynes derivatives **64** in the presence of one equivalent of $Cu(OAc)_2$ as oxidant (Scheme 2.8).[76]



Scheme 2.8 Palladium catalyzed oxidative pyrrole synthesis

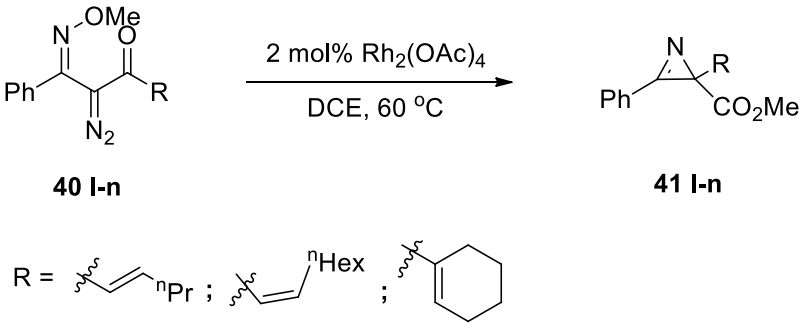
[75] Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. *Org. Lett.* **2013**, *15*, 1966.
[76] Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2014**, *16*, 608.

On the other hand, a study by Padwa and co-workers showed that 2-vinyl-2*H*-azirines **66** could undergo rearrangement to furnish pyrroles **68** *via* nitrene intermediates **67** (Scheme 2.9).[77] They performed the reaction at thermal condition, thus normally it need harsh reaction condition (reflux in benzene). Furthermore, the multi-steps for preparing substrates **66** also limited this method for applications.



Scheme 2.9 Synthesis of pyrroles from ring-expansion of 2*H*-azirines

In chapter one, we have already described a versatile method to synthesize 2*H*-azirine derivatives **41** by rhodium-catalyzed cascade reaction. Among them, it was found that 2-vinyl-2*H*-azirine-2-carboxylic esters (**41 l-n**) could be obtained at mild reaction condition (Scheme 2.10).



Scheme 2.10 Synthesis of 2-vinyl-2*H*-azirine-2-carboxylic esters

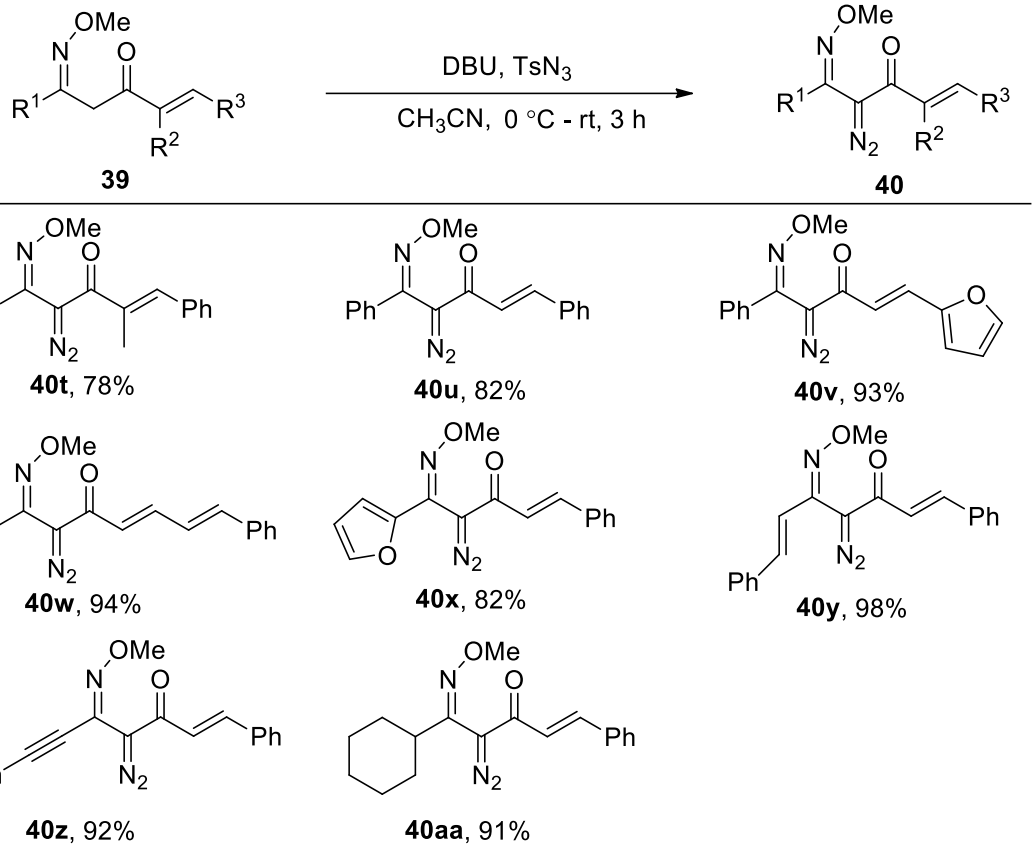
As a continuation of our previous work, we envisioned that 2-vinyl-2*H*-azirines, produced from the rhodium-catalyzed cascade reactions, could be further explored for the synthesis of pyrroles in a tandem fashion.

[77] Padwa, A.; Smolanoff, J.; Tremper, A. *J. Am. Chem. Soc.* **1975**, *97*, 4682.

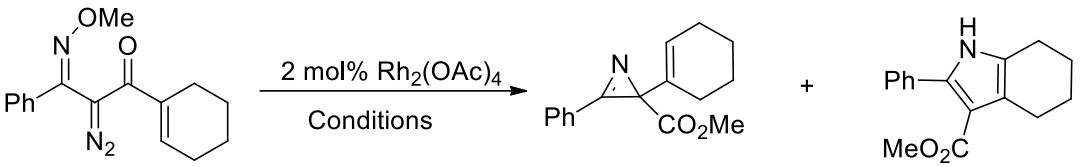
2.2.2 RESULT AND DISCUSSION

A diverse substitution of α-diazo-β-keto oxime ethers **40** can be readily accessed in good to excellent yields from carbonyl derivatives **39** by diazo transfer reactions under mild reaction conditions (Table 2-1).

Table 2-1 Preparation of α-diazo oxime ethers



As discussed in chapter1, reaction of diazo **40n** proceeded smoothly to generate the 2*H*-azirine **41n** in DCE at 60 °C (Scheme 2.11, condition A). With the aim of inducing ring opening, we increased the eaction temperature to 120 °C and employed toluene as solvent (Scheme 2.11, condition B). Indeed, the result showed that the desired product **69n** was successfully achieved in excellent yield.

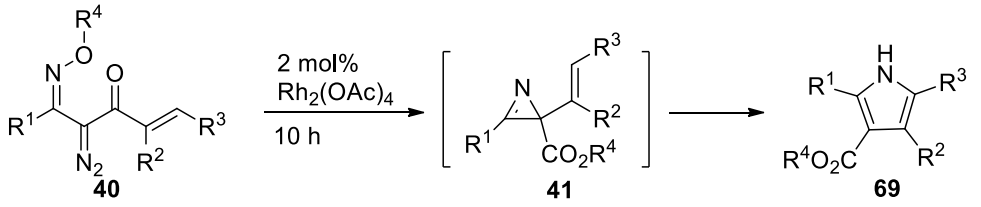


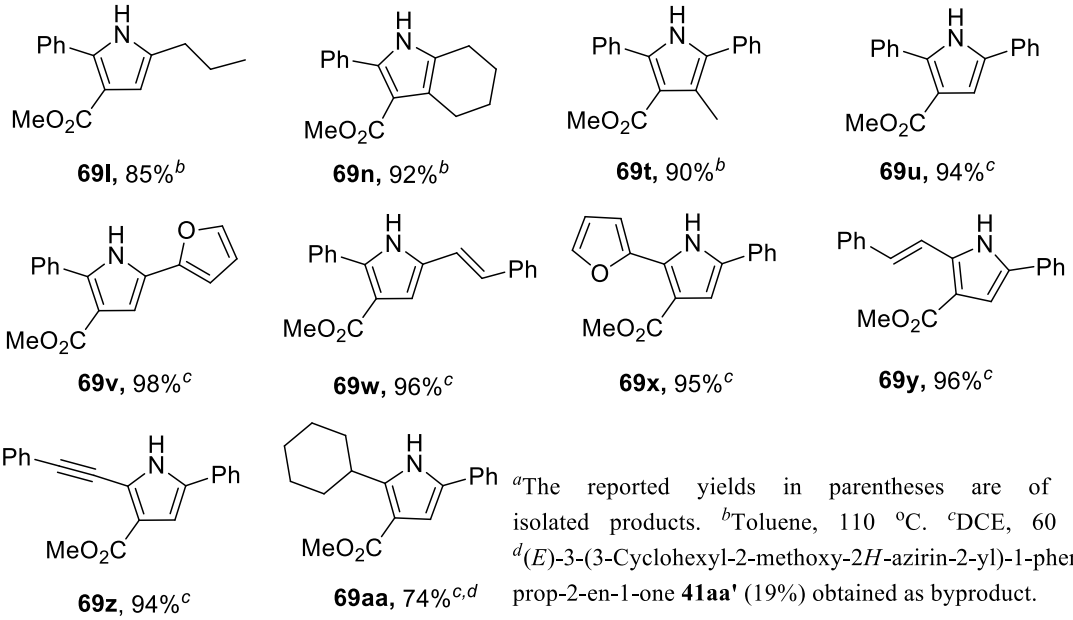
40n	41n	69n
Condition A: DCE, 60 °C	82%	-
Condition B: Tol., 110 °C	-	92%

Scheme 2.11 Temperature controlled synthesis of 2*H*-azirine and pyrrole

Encouraged by the results in hand, we explored the substrate scope of the reaction (Table 2-2). Generally, while substrates with R^3 installing alkyl groups required refluxing in toluene (Table 2-2, **69t**, **69n**, and **69l**), those with aryl groups for R^3 gave the corresponding pyrroles at 60 ℃ in excellent yields (Table 2-2, **69u-aa**). Different R^1 groups including heteroaryl, vinyl, and alkynyl all gave the corresponding

Table 2-2 Substrate scope for highly-substituted pyrroles[a]

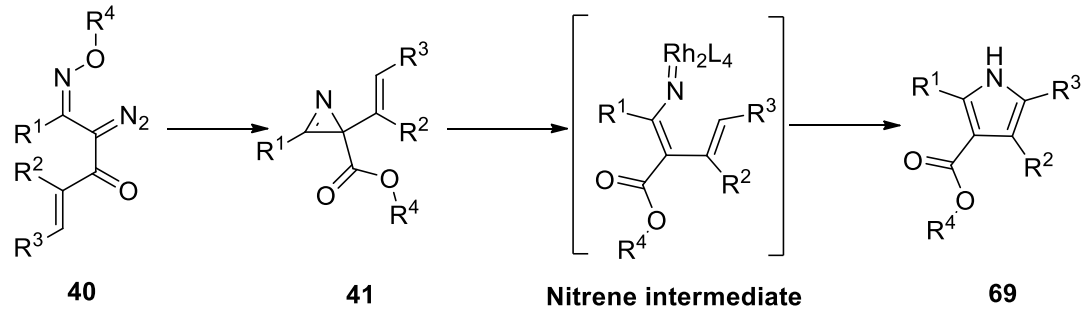




[a]The reported yields in parentheses are of the isolated products. [b]Toluene, 110 °C. [c]DCE, 60 °C. [d](*E*)-3-(3-Cyclohexyl-2-methoxy-2*H*-azirin-2-yl)-1-phenyl-prop-2-en-1-one **41aa'** (19%) obtained as byproduct.

products in excellent yields (Table 2-2, **69x, 69y, and 69z**). When R^1 was substituted with the cyclohexyl group, the N−O insertion product was also detected in 19% besides the desired pyrrole (Table 2-2, **69aa** and footnote).

Mechanistically, we proposed that the rearrangement proceeded through nitrene intermediate. Rhodium-catalyzed the formation of 2-vinyl-2*H*-azirine **41** which further undergoes ring-opening to generate the nitrene intermediate to afford pyrrole **69** *via* C−H insertion (Scheme 2.12).



Scheme 2.12 Proposed pathway for pyrrole synthesis.

2.2.3 SUMMARY

In summary, we have described a highly efficient synthesis of multi-substituted pyrroles in excellent yields *via* ring-opening of 2-vinyl-2*H*-azirine derived from cascade rearrangement of *α*-diazo-*β*-keto oxime ethers. The reaction proceeded in mild and neutral condition as well as tolerated a variety of functional groups including double bond, triple bond and heterocycles.

2.3 NICKEL(II)-CATALYZED SYNTHESIS OF FULLY SUBSTITUTED PYRROLES

2.3.1 INTRODUCTION

Metal nitrenes are very useful synthetic species that have drawn great interest and attention due to their diverse reactivity.[78] Metal nitrenes induced catalytic C–H amination has recently been acknowledged as a promising method that allows the installment of nitrogen functionality onto diverse C–H bonds and an efficient approach to a variety of synthetically important amino derivatives.[79] At the same time, aryl and vinyl azides have been studied to generate metal nitrenes in the presence of metal catalysts that undergo further amination to indoles and other fused *N*-heterocycles,[80] which are widely found in natural products, pharmaceuticals, and functional materials.[81] Recently, Driver et al. demonstrated the synthesis of indoles and pyrroles by the metal-catalyzed rearrangement of aryl azides and 1,3-dienyl azides, respectively.[82]

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[78] a) Dequirez, G.; Pons, V.; Dauban, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 7384; b) Berry, J. F. *Dalton Trans.* **2012**, *41*, 700; c) Wentrup, C. *Acc. Chem. Res.* **2011**, *44*, 393; d) Karila, D.; Dodd, R. H. *Curr. Org. Chem.* **2011**, *15*, 1507; e) Gritsan, N.; Platz, M. *Photochemistry of azides: the azide/nitrene interface*, John Wiley & Sons Ltd, **2010**.

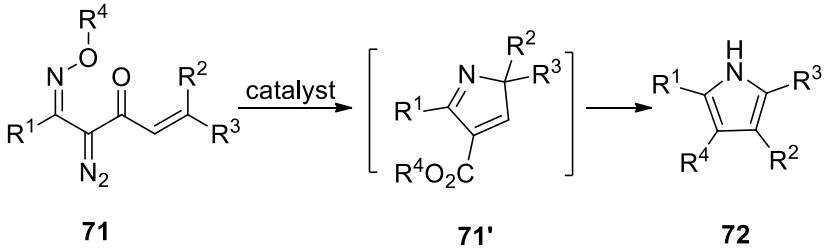
[79] a) Roizen, J. L.; Harvey, M. E.; Du, B. J. *Acc. Chem. Res.* **2012**, *45*, 911; b) Ramirez, T. A.; Zhao, B.; Shi, Y. *Chem. Soc. Rev.* **2012**, *41*, 931; b) Gephart, R. T.; Warren, T. H.; *Organometallics* **2012**, *31*, 7728; c) Lu, H.; Zhang, X. P.; *Chem. Soc. Rev.* **2011**, *40*, 1899; d) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926; e) Che, C.-M.; Lo, V. K.-Y.; Zhou, C.-Y.; Huang, J.-S. *Chem. Soc. Rev.* **2011**, *40*, 1950; f) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061; g) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917.

[80] a) Okamoto, K.; Oda, T.; Kohigashi, S.; Ohe, K. *Angew. Chem.,Int. Ed.* **2011**, *50*, 11470; b) Cano, I.; Álvarez, E.; Nicasio, M. C.; Ṕerez, P. J. *J. Am. Chem. Soc.* **2011**, *133*, 191; c) Driver, T. G. *Org. Biomol. Chem.* **2010**, *8*, 3831; d) Li, X.; Du, Y.; Liang, Z.; Li, X.; Pan, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2643; e) Hajos, G.; Riedl, Z. *Curr. Org. Chem.* **2009**, *13*, 791; f) Alvarez-Corral, M.; Munoz-Dorado, M.; Rodriguez-Garcia, I. *Chem. Rev.* **2008**, *108*, 3174.

[81] a) Pozharskii, A. F.; Soldatenkov, A.; Katritzky, A. R. *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, Wiley, **2011**; b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627; c) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.

[82] Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191.

Cascade reactions offer great advantages to organic synthesis with respect to waste reduction, step efficiency, and alleviation of time and efforts in handling reaction intermediates. [83] As formerly discussed, we have shown a novel method to synthesize highly substituted pyrroles from common substrates, *α*-diazo-*β*-keto oxime ethers, *via* the ring-opening of 2-vinyl-2*H*-azirine intermediates. Inspired by these results, we became interested in the reactivity of 1,3-dienyl nitrenes as a platform for *N*-heterocycle synthesis, which could be readily accessed from *α*-diazo-*β*-keto oxime ethers *via in situ* formation of 2*H*-azirines. However, there are only limited examples to prepare the fully substituted pyrroles due to the substrates limitation (two examples, **69t** and **69n**). In view of our continuous interests in pyrrole synthesis, we turned our attention to develop readily available approach to obtain fully substituted pyrroles based on the cascade rearrangement of *α*-diazo-*β*-keto oxime ethers (Scheme 2.13).



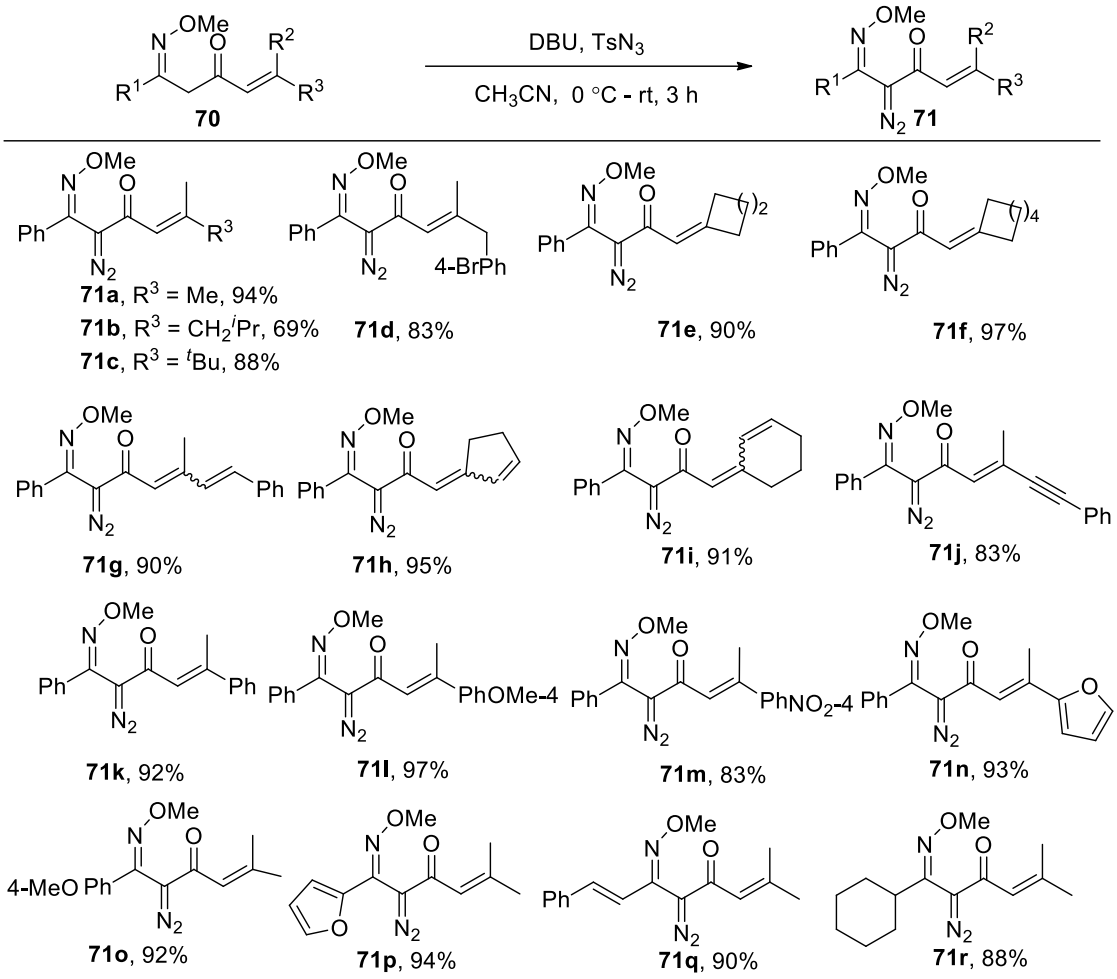
Scheme 2.13 Proposed reaction for fully substituted pyrrole synthesis

2.3.2 RESULT AND DISCUSSION

Initially, we prepared a variety of *α*-diazo-*β*-keto oxime ethers from the corresponding carbonyl derivatives by diazo transfer reactions under mild conditions (Table 2-3).

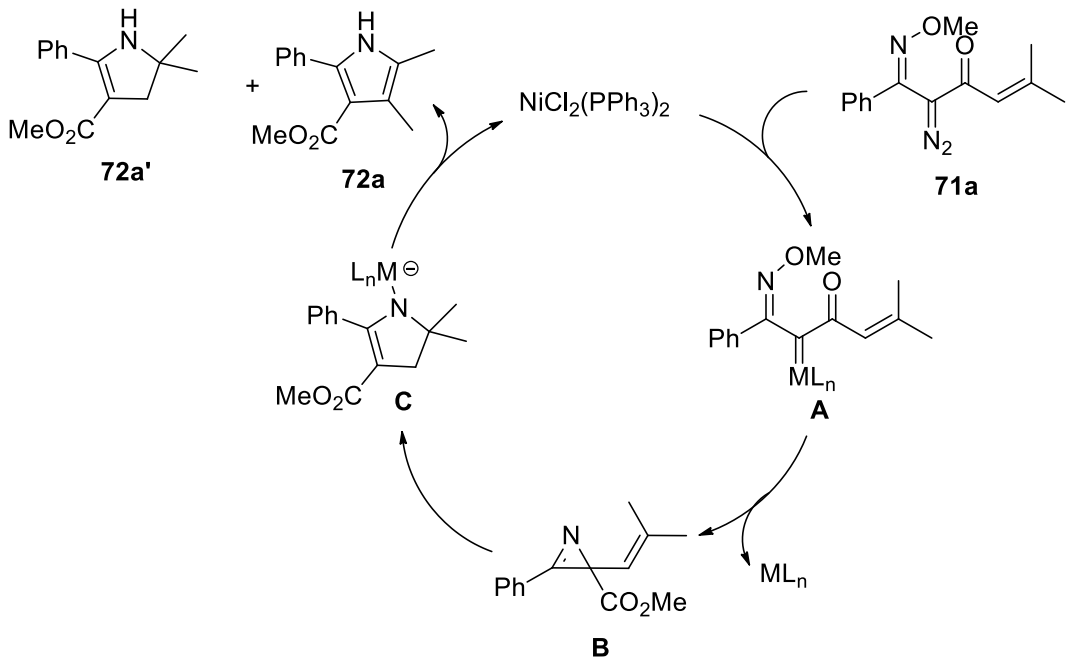
[83] a) Xu, P. F.; Wang, W. *Catalytic Cascade Reactions*, Wiley, **2013**; b) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278; c) Müller, T. J. J. *Metal Catalyzed Cascade Reactions*, Springer, **2010**; d) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167; e) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

Table 2-3 Preparation of *α*-diazo-*β*-keto oxime ethers



With the substrates in hand, we explored the feasibility of the synthesis of pyrroles from the (*Z*)-2-diazo-1-(methoxyimino)-5-methyl-1-phenylhex-4-en-3-one **71a** as model substrate. Therefore, a suitable catalyst would lead to multiple sequential rearrangements initiated by generation of carbenoid **A**, which undergoes Wolff rearrangement to give 2-vinyl-2*H*-azirine **B**. Then, the ring-opening of **B** follows a nitrene pathway to afford intermediate **C**. Subsequent isomerization and substituent shift leads to the formation of pyrrole **72a** (Scheme 2.14). In view of the competitive formation of 2*H*-pyrrole **72a'**, the ability of a catalyst to promote migration of the *gem*-substituents on intermediate **C** is crucial. Thus, we began to search for optimal

the reaction conditions and found that nickel catalysts were efficient for this reaction



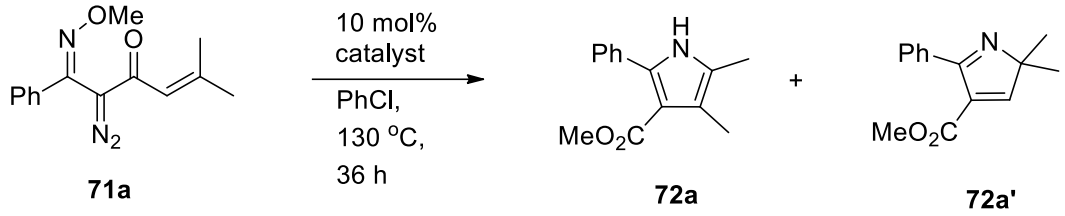
Scheme 2.14 Proposed reaction pathway to fully substituted pyrroles

(Table 2-4). While the reaction was sluggish with Ni(0) leading to the 2*H*-azirine intermediate as the major product (Table 2-4, entry 1), encouraging result was obtained by the use of Ni(II) catalysts along with concomitant formation of **72a'** (Table 2-4, entry 2). While several other ligands tested did not significantly improve the yield (Table 2-4, entries 3-7), the use of $NiCl_2$ with PPh_3 as ligand gave **72a** in 82% yield (Table 2-4, entry 8).

With the optimized condition in hand, we turned our attention to screen the substrate scope of the synthesis of pyrroles (Table 2-5). Overall, the pyrrole formation could tolerate a variety of substituents with good to excellent yields. Firstly, we studied the migratory aptitude of the geminal substituents of the intermediate 2*H*-pyrroles. While substrates bearing similar primary alkyl substituents resulted in the formation of a mixture (**72b** and **72bb**), selective migration was observed with more

disparate substituents such as *t*-Bu and benzylic groups (**72c** and **72d**). When employing cyclic substrates, the reaction also uprogresses smoothly to give the bicycl-

Table 2-4 Optimization of pyrrole synthesis



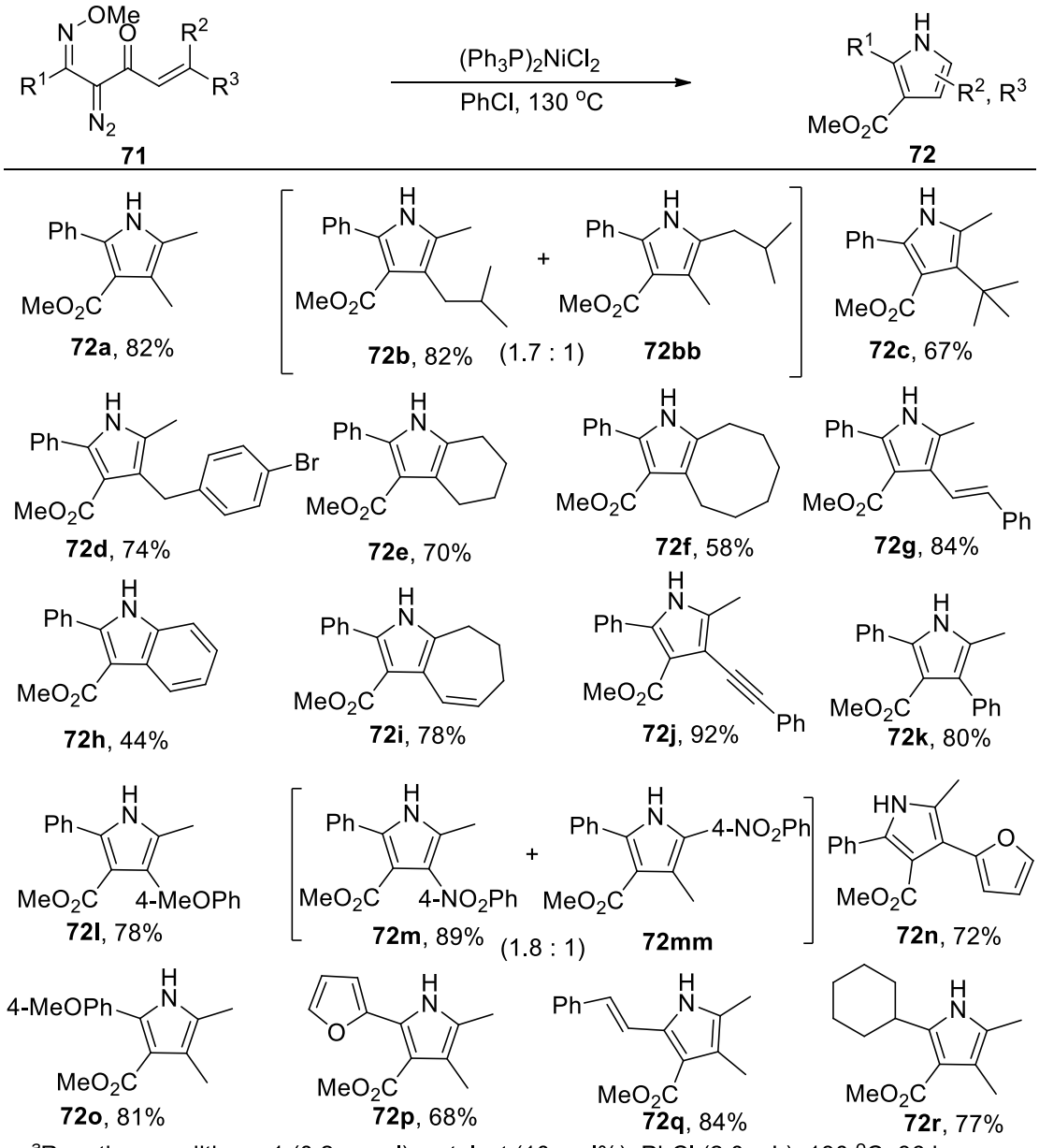
Entry[a]	Catalyst	Yield (%)[b]	
		72a	**72a'**
1[c,d]	$Ni(cod)_2/PPh_3$	10	11
2	$Ni(acac)_2$	62	13
3[e]	$Ni(acac)_2$/dppf	60	23
4[d]	$Ni(acac)_2$/dppe	60	6
5[e]	$NiCl_2$/dppp	66	-
6[d]	$Ni(acac)_2/PPh_3$	78	-
7[d]	$Ni(acac)_2/P(^oTol)_3$	67	6
8	$NiCl_2(PPh_3)_2$	82	6

[a]Reaction conditions: **1a** (0.1 mmol), catalyst (10 mol%), PhCl (1.0 mL), 130 ℃, 36 h. [b]NMR yields. [c]methyl 2-(2-methylprop-1-en-1-yl)-3-phenyl-2*H*-azirine-2-carboxylate (72%). [d]20 mol% ligand. [e]10 mol% ligand. cod = cyclooctadiene, acac = acetylacetonate, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenyl-phosphino)propane, dppf = 1,1'-bis(diphenylphosphanyl)ferrocene, ^{o}Tol = tri(o-tolyl)phosphine.

-ic pyrroles (**72e**, **72f**, **72h** and **72i**). Compared with alkyl groups, both acyclic and *endo*-cyclic vinyl groups undergo a more selective migration (**72g**-**72i**). It is worth noting that indole **72h** was obtained through spontaneous oxidation. Similarly, alkyne group migrates selectively compared to alkyl group (**72j**). Further studying of electronic influence on the migratory aptitude showed that migration of electron deficient substituents is disfavored (**72k**, **72l** *vs.* **72m**). Also, the reaction with heterocyclic substrate proceeds selectively to provide the corresponding pyrrole in

good yield (**72n**). The reaction also tolerated various types of substituents for R^1 such as aryl, heteroaryl and alkyl groups (**72o**-**r**).

Table 2-5 Substrate scope for highly-substituted pyrroles[a]



[a]Reaction conditions: 1 (0.2 mmol), catalyst (10 mol%), PhCl (2.0 mL), 130 °C, 36 h.

2.3.3 SUMMARY

In summary, we have developed a novel method to the synthesis of fully substituted pyrroles from common substrates, *α*-diazo oxime ethers. The reaction

scope of these transformations demonstrates that diverse structures of these important *N*-heterocycles are readily accessible from α-diazo oxime ethers with high efficiency.

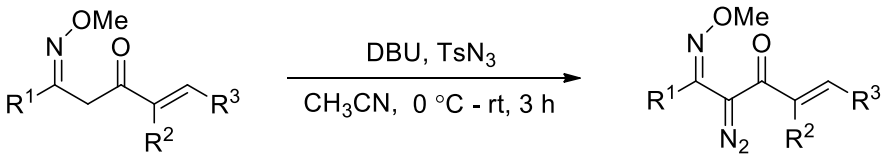
2.4 CONCLUSION

In this chapter, we have described useful methodology for the synthesis of multi-substituted pyrroles from a common substrate, *α*-diazo-*β*-keto oxime ethers, involving 2-vinyl-2*H*-azirines as key intermediates. For the terminal vinyl site with mono-substitution, the nitrene complex was derived from the ring-opening of 2*H*-azirines, which cyclized with the C–C double bond directly to afford highly substituted pyrroles in the presence of Rh(II) catalyst. On the other hand, for the terminal vinyl site with disubstitutions, 2*H*-pyrroles were initially obtained following the tandem rearrangement pathway and subsequently migrated to form fully substituted pyrroles with Ni(II) catalyst.

2.5 EXPERMENTAL SECTION

2.5.1 Rhodium(II)-Catalyzed Synthesis of Highly Substituted Pyrroles

General procedure for *α*-diazo-*β*-keto oxime ethers

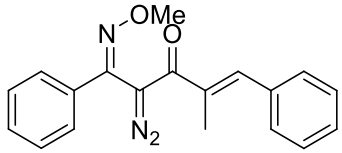


39 **40**

To a solution of *β*-oximino ketones **39** (0.5 mmol, 1.0 eq.) and 4-methylbenzenesulfonyl azide (0.55 mmol, 1.1 eq.) in CH_3CN (5 mL) was added DBU (0.55 mmol, 1.1 eq.) dropwise at 0 ℃. The resulting orange color solution was

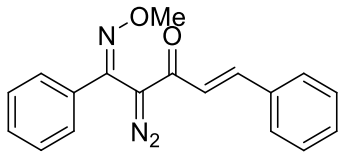
stirred at 0 °C for 3 h and slowly brought to room temperature. Upon completion as indicated by TLC, the solvent was removed under reduced pressure, and the crude material was purified by flash chromatography using hexane: ethyl acetate = 19:1.

(1*E*,5*Z*)-4-Diazo-5-(methoxyimino)-2-methyl-1,5-diphenylpent-1-en-3-one (40t):



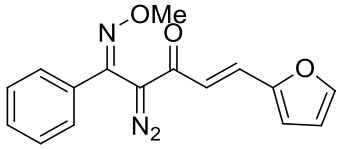
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 - 7.48 (m, 2H), 7.36 - 7.32 (m, 3H), 7.31 - 7.22 (m, 3H), 6.95 - 6.93 (m, 2H), 6.74 (s, 1H), 4.09 (s, 3H), 1.79 (d, *J* = 2.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 145.5, 136.7, 135.8, 135.4, 134.7, 129.8, 129.0, 128.8, 128.2, 128.0, 127.6, 62.8, 14.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{18}N_3O_2$: 320.1399. Found: 320.1406.

(1*E*,5*E*)-5-(Methoxyimino)-1,5-diphenylpent-1-en-3-one (40u):



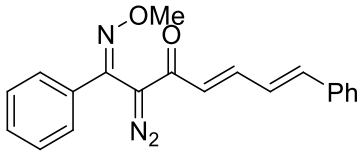
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.65 (m, 2H), 7.56 (d, *J* = 15.6 Hz, 1H), 7.43 - 7.32 (m, 3H), 7.30 - 7.23 (m, 3H), 7.17 - 7.15 (m, 2H), 6.30 (d, *J* = 15.6 Hz, 1H), 4.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 144.0, 140.9, 134.5, 134.2, 130.4, 130.2, 129.0, 128.8, 128.2, 127.9, 122.5, 62.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{16}N_3O_2$: 306.1243. Found: 306.1235.

(1*E*,5*Z*)-4-Diazo-1-(furan-2-yl)-5-(methoxyimino)-5-phenylpent-1-en-3-one (40v):



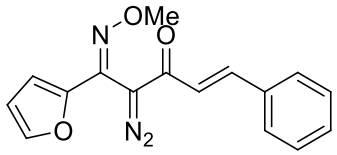
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 - 7.63 (m, 2H), 7.42 - 7.40 (m, 3H), 7.39 - 7.33 (m, 2H), 6.51 (d, J = 3.6 Hz, 1H), 6.39 (dd, J_1 = 3.6 Hz, J_2 = 1.6 Hz, 1H), 6.26 (d, J = 15.2 Hz, 1H), 4.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 151.2, 144.7, 143.9, 133.9, 130.3, 128.9, 127.8, 127.5, 119.8, 115.6, 112.4, 62.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{14}N_3O_3$: 296.1035. Found: 296.1033.

(1*Z*,4*E*,6*E*)-2-Diazo-1-(methoxyimino)-1,7-diphenylhepta-4,6-dien-3-one (40w):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 - 7.63 (m, 2H), 7.44 - 7.25 (m, 9H), 6.87 (d, J = 15.6 Hz, 1H), 6.55 (dd, J_1 = 15.6 Hz, J_2 = 4.4 Hz), 5.89 (d, J = 14.8 Hz, 1H), 4.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 143.9, 141.6, 141.4, 136.0, 134.0, 130.4, 129.1, 128.9, 128.8, 127.8, 127.2, 126.3, 125.5, 62.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{18}N_3O_2$: 332.1399. Found: 332.1404.

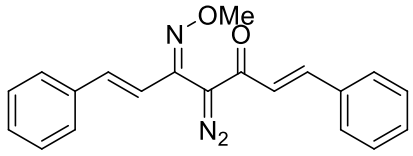
(1*E*,5*E*)-4-Diazo-5-(furan-2-yl)-5-(methoxyimino)-1-phenylpent-1-en-3-one (40x):



The title compound was prepared according to the general procedure. The product was

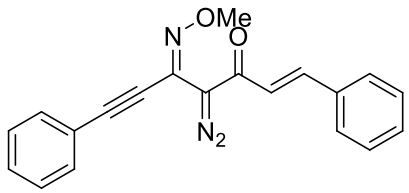
obtained as yellow oil. Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 15.6 Hz, 1H), 7.54 - 7.53 (m, 1H), 7.38 - 7.32 (m, 5H), 6.76 (d, J_1 = 3.2 Hz, 1H), 6.63 (d, J = 16.4 Hz, 1H), 6.50 (dd, J_1 = 3.6 Hz, J_2 = 2.0 Hz, 1H), 6.45 (d, J_1 = 15.6 Hz, 1H), 4.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 147.3, 144.8, 141.4, 135.5, 134.5, 130.3, 128.9, 128.3, 121.7, 112.8, 112.0, 63.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{14}N_3O_3$: 296.1035. Found: 296.1024.

(1*E*,5*Z*,6*E*)-4-Diazo-5-(methoxyimino)-1,7-diphenylhepta-1,6-dien-3-one (40y):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 15.6 Hz, 1H), 7.46 - 7.44 (m, 4H), 7.36 - 7.29 (m, 6H), 6.97 (s, 2H), 6.72 (d, J = 15.6 Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 143.6, 141.6, 137.0, 135.7, 134.5, 130.3, 129.1, 128.9, 128.3, 127.2, 123.0, 121.9, 63.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{18}N_3O_2$: 332.1399. Found: 332.1396.

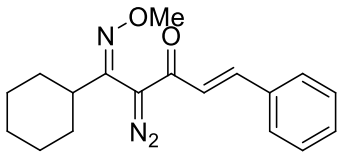
(1*E*,5*Z*)-4-Diazo-5-(methoxyimino)-1,7-diphenylhept-1-en-6-yn-3-one (40z):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 15.6 Hz, 1H), 7.52 - 7.50 (m, 2H), 7.42 - 7.38 (s, 3H), 7.35 - 7.22 (m, 6H), 4.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6, 141.8, 134.6, 131.9, 130.4, 129.7, 129.4, 128.9,

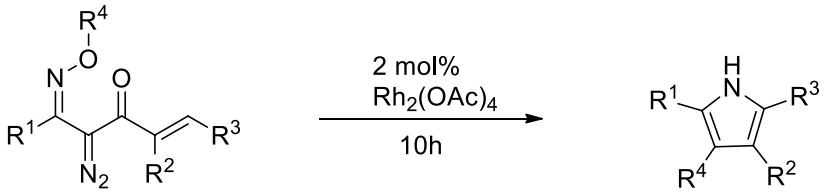
128.4, 122.2, 121.0, 93.2, 83.1, 63.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{16}N_3O_2$: 330.1243. Found: 330.1242.

(1*E*,5*Z*)-5-Cyclohexyl-4-diazo-5-(methoxyimino)-1-phenylpent-1-en-3-one (40aa):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 15.6 Hz, 1H), 7.54 - 7.52 (m, 2H), 7.39 - 7.38 (m, 3H), 6.77 (d, *J* = 15.6 Hz, 1H), 3.91 (s, 3H), 2.68 - 2.61 (m, 1H), 1.99 - 1.96 (m, 2H), 1.82 - 1.76 (m, 2H), 1.70 - 1.67 (m, 1H), 1.47 - 1.19 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 148.1, 142.0, 134.5, 130.4, 129.0, 128.3, 120.7, 68.5, 62.1, 42.1, 31.3, 26.3, 26.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{22}N_3O_2$: 312.1712. Found: 312.1717.

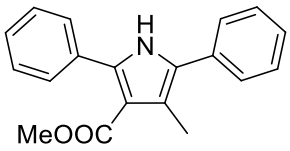
General procedure for highly substituted pyrroles:



40 **69**

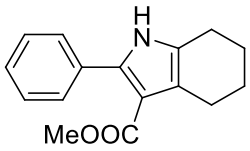
A solution of diazo compound **40** (0.2 mmol) and $Rh_2(OAc)_4$ (0.004 mmol, 2 mol%) in dichloroethane (or toluene) (2.0 mL) was stirred at 60 ℃ (or 110 ℃) until the starting material was fully consumed. The reaction mixture was concentrated under reduced pressure to give the crude material which was purified by column chromatography using hexane: ethyl acetate = 9:1 to give the corresponding product.

Methyl 4-methyl-2,5-diphenyl-1*H*-pyrrole-3-carboxylate (69t):



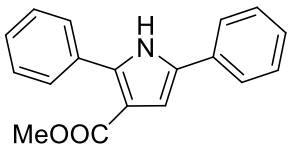
The title compound was prepared according to the general procedure (reaction at 110 °C). The product was obtained as colorless oil. Yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.54 - 7.51 (m, 2H), 7.44 - 7.31 (m, 8H), 3.72 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 136.9, 132.8, 132.5, 129.6, 128.9, 128.8, 128.2, 128.1, 127.5, 127.1, 119.0, 112.9, 50.7, 11.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{18}NO_2$: 292.1338. Found: 292.1336.

Methyl 5-phenyl-2-(phenylethynyl)-1*H*-pyrrole-3-carboxylate (69n):



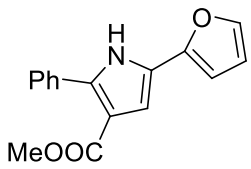
The title compound was prepared according to the general procedure (reaction at 110 °C). The product was obtained as white solid, mp: 126 - 127 ℃. Yield 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.52 - 7.50 (m, 2H), 7.40 - 7.36 (m, 2H), 7.34 - 7.31 (m, 1H), 3.70 (s, 3H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.58 (t, *J* = 6.0 Hz, 2H), 1.84 - 1.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 135.8, 133.0, 128.9, 128.1, 127.8, 127.8, 120.2, 109.9, 50.5, 23.4, 23.4, 22.9, 22.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{18}NO_2$: 292.1338. Found: 292.1343.

Methyl 2,5-diphenyl-1*H*-pyrrole-3-carboxylate (69u):



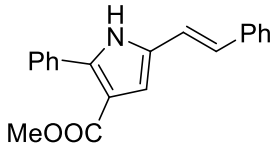
The title compound was prepared according to the general procedure (reaction at 60 °C). The product was obtained as white solid, mp: 172 - 173 ℃. Yield 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.63 - 7.60 (m, 2H), 7.52 - 7.50 (m, 2H), 7.43 - 7.34 (m, 5H), 7.28 - 7.24 (m, 1H), 6.99 (d, *J* = 3.2 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 137.9, 131.8, 131.5, 129.0, 128.9, 128.5, 128.3, 127.1, 124.0, 113.3, 109.1, 51.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{16}NO_2$: 278.1181. Found: 278.1177.

Methyl 5-(furan-2-yl)-2-phenyl-1*H*-pyrrole-3-carboxylate (69v):



The title compound was prepared according to Method A. The product was obtained as yellow solid, mp: 134 - 135 ℃. Yield 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.64 - 7.62 (m, 2H), 7.45 - 7.36 (m, 4H), 6.92 (d, 16.8 Hz, 1H), 6.90 (d, 1H), 6.90 (d, *J* = 2.8 Hz, 1H), 6.46 (d, *J* = 1.2 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 146.8, 141.0, 137.2, 131.6, 128.9, 128.5, 128.3, 123.7, 113.1, 111.7, 108.3, 103.8, 51.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{14}NO_3$: 268.0974. Found: 268.0976.

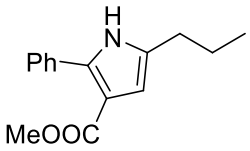
(*E*)-Methyl 2-phenyl-5-styryl-1*H*-pyrrole-3-carboxylate (69w):



The title compound was prepared according to Method A. The product was obtained as yellow solid, mp: 125 - 126 ℃. Yield 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H),

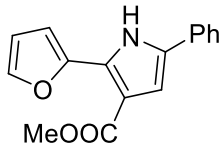
7.64 - 7.62 (m, 2H), 7.44 - 7.22 (m, 9H), 6.92 (d, *J* = 16.8 Hz, 1H), 6.82 - 6.72 (m, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 138.1, 136.9, 131.7, 130.5, 128.9, 128.8, 128.5, 128.2, 127.5, 126.1, 125.4, 117.8, 113.1, 112.1, 51.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{18}NO_2$: 304.1338. Found: 304.1334.

Methyl 2-phenyl-5-propyl-1*H*-pyrrole-3-carboxylate (69l):



The title compound was prepared according to Method A. The product was obtained as red oil. Yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.59 - 7.56 (m, 2H), 7.41 - 7.37 (m, 2H), 7.35 - 7.31 (m, 1H), 6.41 (d, 3.2 Hz, 1H), 3.72 (s, 3H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.70 - 1.59 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 135.9, 132.7, 132.3, 128.7, 128.2, 128.0, 111.6, 108.7, 50.9, 29.4, 22.5, 13.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{18}NO_2$: 244.1338. Found: 244.1334.

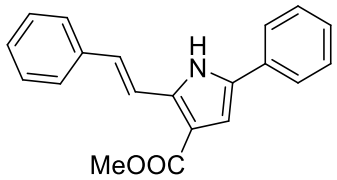
Methyl 2-(furan-2-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate (69x):



The title compound was prepared according to Method A. The product was obtained as yellow solid, mp: 134 - 135 ℃. Yield 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.55 - 7.53 (m, 3H), 7.45 - 7.39 (m, 3H), 7.29 - 7.26 (m, 1H), 6.96 (d, *J* = 2.8 Hz, 2H), 6.54 (dd, J_1 = 3.2 Hz, J_2 = 1.6 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 145.8, 141.4, 131.5, 131.2, 129.1, 128.2, 127.2, 124.1, 112.5, 112.1, 110.9,

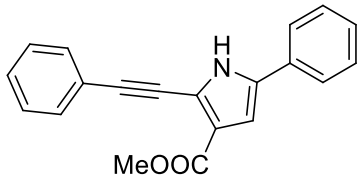
109.1, 51.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{14}NO_3$: 268.0974. Found: 268.0980.

(*E*)-methyl 5-phenyl-2-styryl-1*H*-pyrrole-3-carboxylate (69y):



The title compound was prepared according to the general procedure (reaction at 60 °C). The product was obtained as yellow oil. Yield 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.86 (d, *J* = 16.8 Hz, 1H), 7.56 - 7.54 (m, 4H), 7.51 - 7.23 (m, 6H), 6.93 (d, *J* = 2.8 Hz, 1H), 6.89 (d, *J* = 16.8 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 136.8, 135.5, 132.6, 131.3, 129.1, 128.8, 127.9, 127.6, 127.3, 126.6, 124.2, 117.6, 115.2, 109.0, 51.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{18}NO_2$: 304.1338. Found: 304.1336.

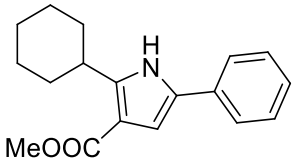
Methyl 5-phenyl-2-(phenylethynyl)-1*H*-pyrrole-3-carboxylate (69z):



The title compound was prepared according to the general procedure (reaction at 60 °C). The product was obtained as yellow solid, mp: 175 - 176 ℃. Yield 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.58 - 7.56 (m, 2H), 7.53 - 7.51 (m, 2H), 7.44 - 7.35 (m, 5H), 7.32 - 7.30 (m, 1H), 6.95 (d, *J* = 2.8 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 133.1, 131.5, 130.8, 129.1, 128.7, 128.4, 127.6, 124.3, 122.6. 120.7, 117.7, 108.2, 95.2, 80.5, 51.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{16}NO_2$:

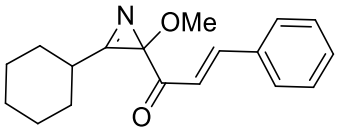
302.1181. Found: 302.1171.

Methyl 2-cyclohexyl-5-phenyl-1*H*-pyrrole-3-carboxylate (69aa):



The title compound was prepared according to the general procedure (reaction at 60 °C). The product was obtained as white solid, mp: 132 - 133 ℃. Yield 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.46 - 7.44 (m, 2H), 7.38 - 7.34 (m, 2H), 7.24 - 7.20 (m, 1H), 6.82 (d, *J* = 3.2 Hz, 1H), 3.82 (s, 3H), 3.54 - 3.48 (s, 1H), 2.06 - 2.03 (m, 2H), 1.87 - 1.84 (m, 3H), 1.50 - 1.37 (m, 4H), 1.27 - 1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 145.8, 131.9, 129.8, 129.0, 126.6, 123.8, 111.6, 107.4, 50.8, 36.0, 32.6, 26.5, 26.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{22}NO_2$: 284.1651. Found: 284.1653.

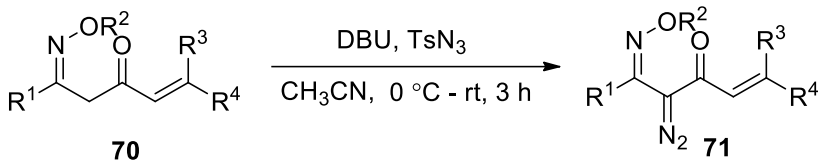
(*E*)-1-(3-Cyclohexyl-2-methoxy-2H-azirin-2-yl)-3-phenylprop-2-en-1-one (41aa'):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 19%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 16.0 Hz, 1H), 7.60 - 7.58 (m, 2H), 7.41 - 7.38 (m, 3H), 7.08 (d, *J* = 16.0 Hz, 1H), 3.42 (s, 3H), 2.98 - 2.93 (m, 1H), 2.05 - 1.97 (m, 2H), 1.81 - 1.75 (m, 2H), 1.67 - 1.54 (m, 3H), 1.46 - 1.34 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 171.6, 144.3, 134.6, 130.8, 129.0, 128.7, 120.6, 74.2, 54.0, 36.3, 28.3, 28.2, 25.6, 24.8, 24.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{22}NO_2$: 284.1651. Found: 284.1648.

2.5.2 Nickel(II)-Catalyzed Synthesis of Fully Substituted Pyrroles

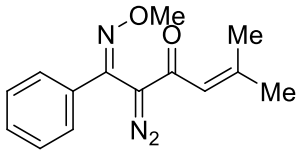
General procedure for *α*-diazo-*β*-keto oximes



70 **71**

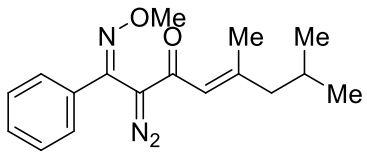
To a solution of *β*-oximino ketones **70** (0.5 mmol, 1.0 eq.) and 4-methylbenzenesulfonyl azide (0.55 mmol, 1.1 eq.) in CH_3CN (5 mL) was added DBU (0.55 mmol, 1.1 eq.) dropwise at 0 ℃. The resulting orange color solution was stirred at 0 ℃ for 3 h and slowly brought to room temperature. Upon completion as indicated by TLC, the solvent was removed under reduced pressure, and the crude material was purified by flash chromatography using hexane: ethyl acetate = 19:1.

(*Z*)-2-Diazo-1-(methoxyimino)-5-methyl-1-phenylhex-4-en-3-one (71a):



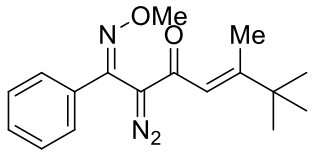
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 - 7.57 (m, 2H), 7.41 - 7.36 (m, 3H), 5.58 (s, 1H), 4.07 (s, 3H), 2.08 (d, J = 0.8 Hz, 3H), 1.62 (d, J = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 154.2, 144.5, 134.1, 130.0, 128.7, 127.7, 121.3, 62.7, 27.4, 20.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{16}N_3O_2$: 258.1243. Found: 258.1245.

(1*Z*,4*E*)-2-Diazo-1-(methoxyimino)-5, 7-dimethyl-1-phenyloct-4-en-3-one (71b):



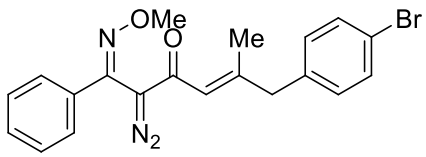
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 - 7.57 (m, 2H), 7.39 - 7.37 (m, 3H), 5.56 (s, 1H), 4.07 (s, 3H), 2.48 (d, J = 6.8 Hz, 2H), 1.86 - 1.80 (m, 1H), 1.57 (s, 3H), 0.87 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 157.5, 144.5, 134.2, 130.0, 128.7, 127.8, 122.5, 62.7, 42.1, 27.4, 25.4, 22.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{22}N_3O_2$: 300.1712. Found: 300.1706.

(1*Z*,4*E*)-2-Diazo-1-(methoxyimino)-5,6,6-trimethyl-1-phenylhept-4-en-3-one(71c):



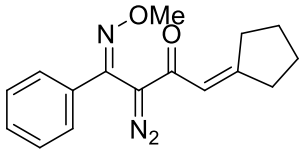
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 - 7.55 (m, 2H), 7.40 - 7.34 (m, 3H), 5.50 (s, 1H), 4.08 (s, 3H), 2.02 (d, J = 1.2 Hz, 3H), 0.72 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.0, 163.8, 144.7, 134.6, 130.0, 128.7, 128.0, 119.1, 62.7, 37.6, 28.1, 15.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{22}N_3O_2$: 300.1712. Found: 300.1706.

(1*Z*,4*E*)-6-(4-Bromophenyl)-2-diazo-1-(methoxyimino)-5-methyl-1-phenylhex-4-en-3-one (71d):



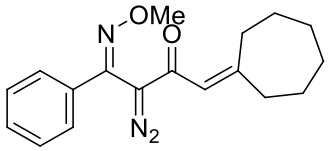
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 - 7.52 (m, 2H), 7.45 - 7.39 (m, 3H), 7.29 - 7.27 (m, 2H), 6.58 (d, J = 8.4 Hz, 1H), 5.41 (s, 1H), 4.07 (s, 3H), 3.06 (s, 2H), 2.04 (d, J = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.9, 155.0, 144.1, 136.2, 134.2, 131.5, 130.8, 130.0, 128.8, 127.7, 122.6, 120.5, 62.8, 46.2, 19.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{19}N_3O_2Br$: 412.0661. Found: 412.0662.

(*Z*)-1-Cyclopentylidene-3-diazo-4-(methoxyimino)-4-phenylbutan-2-one (71e):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.59 (m, 2H), 7.40 - 7.38 (m, 3H), 5.76 (s, 1H), 4.07 (s, 3H), 2.78 - 2.75 (m, 2H), 2.17 - 2.14 (m, 2H), 1.70 - 1.67 (m, 2H), 1.61 - 1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 167.9, 144.5, 134.1, 130.0, 128.8, 127.7, 116.4, 62.7, 36.2, 33.4, 26.5, 25.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{18}N_3O_2$: 284.1399. Found: 284.1398.

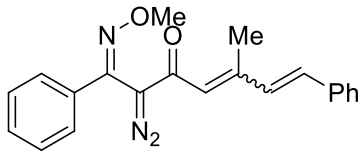
(*Z*)-1-Cycloheptylidene-3-diazo-4-(methoxyimino)-4-phenylbutan-2-one (71f):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 - 7.58 (m, 2H), 7.40 - 7.35 (m, 3H), 5.53 (s, 1H), 4.07 (s, 3H), 2.82 - 2.78 (m, 2H), 2.02 - 2.00 (m, 2H),

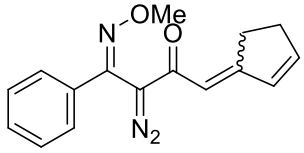
1.68 - 1.59 (m, 2H), 1.43 - 1.33 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5, 164.8, 144.7, 134.3, 129.9, 128.7, 127.8, 121.2, 62.7, 38.8, 32.7, 29.5, 29.1, 28.0, 26.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{22}N_3O_2$: 312.1712. Found: 312.1712.

(1*Z*)-2-Diazo-1-(methoxyimino)-5-methyl-1,7-diphenylhepta-4,6-dien-3-one (71g):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil in *cis* : *trans* ratio of 31 : 69. Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 & 6.80 (d & d, J = 16.4 Hz & 16.0 Hz, 1H), 7.81 - 7.59 (m, 2H), 7.53 - 7.27 (m, 8H), 6.86 & 6.38 (d & d, J = 16.4 Hz & 16.0 Hz, 1H), 5.77 & 5.57 (s, 1H), 4.08 (s, 3H), 2.34 & 1.81 (d & d , J = 1.2 Hz & 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 183.4, 149.9, 148.1, 144.4, 144.3, 136.7, 136.3, 136.3, 134.8, 134.1, 134.1, 131.9, 130.2, 130.1, 129.8, 128.8, 128.7, 127.9, 127.8, 127.5, 127.0, 126.7, 124.5, 123.0, 66.8, 62.8, 62.8, 21.6, 20.7, 14.7, 14.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{20}N_3O_2$: 346.1556. Found: 346.1561.

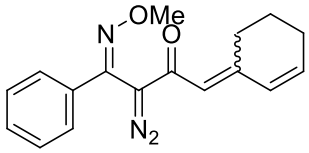
(4*Z*)-1-(Cyclopent-2-enylidene)-3-diazo-4-(methoxyimino)-4-phenylbutan-2-one (71h):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil in a *cis* : *trans* ratio of 39 : 61. Yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 - 7.60 (m, 2H), 7.48 - 7.39 & 6.07 - 5.99 (m & m, 1H), 7.38 - 7.36 (m,

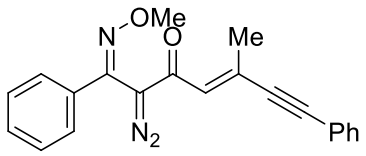
3H), 6.69 - 6.67 & 6.63 - 6.60 (m & m, 1H), 5.72 & 5.54 (s & s, 1H), 4.07 (s, 3H), 3.06 - 3.03 & 2.44 - 2.42 (m & m, 2H), 2.59 - 2.57 & 2.38 - 2.37 (m & m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 182.4, 166.6, 164.3, 151.0, 149.7, 144.6, 135.0, 134.2, 134.1, 132.8, 130.0, 130.0, 129.0, 128.8, 128.7, 128.6, 127.8, 127.7, 113.6, 112.4, 62.7, 33.7, 31.3, 31.0, 30.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{16}N_3O_2$: 282.1243. Found: 282.1238.

(4*Z*)-1-(Cyclohex-2-enylidene)-3-diazo-4-(methoxyimino)-4-phenylbutan-2-one (71i):



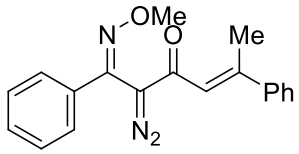
The title compound was prepared according to the general procedure. The product was obtained as yellow oil in a *cis* : *trans* ratio of 37 : 63. Yield 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.58 (m, 2H), 7.42 - 7.35 & 5.70 (m & d, *J* = 10.0 Hz, 3H & 1H), 6.24 - 6.19 & 6.63 - 6.60 (m & m, 1H), 5.45 & 5.32 (s & s, 1H), 4.07 (s, 3H), 2.94 - 2.91 & 2.04 - 2.01 (m & m, 2H), 2.17 - 2.13 (m, 2H), 1.67 - 1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5, 183.3, 152.0, 150.1, 144.6, 144.5, 139.5, 139.2, 134.1, 130.3, 130.1, 130.0, 128.7, 128.7, 127.8, 127.7, 125.8, 119.8, 118.3, 62.7, 32.4, 26.9, 26.2, 25.6, 22.6, 21.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{18}N_3O_2$: 296.1399. Found: 296.1407.

(1*Z*,4*E*)-2-Diazo-1-(methoxyimino)-5-methyl-1,7-diphenylhept-4-en-6-yn-3-one (71j):



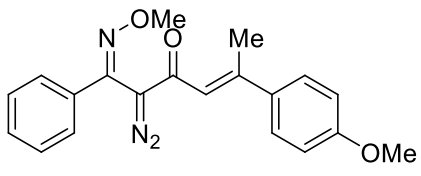
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 - 7.61 (m, 2H), 7.43 - 7.39 (m, 3H), 7.37 - 7.30 (m, 5H), 6.07 (s, 1H), 4.08 (s, 3H), 2.33 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 143.9, 135.5, 133.7, 131.9, 130.3, 129.1, 128.9, 128.4, 128.0, 127.7, 122.3, 93.6, 91.7, 62.8, 20.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{18}N_3O_2$: 344.1399. Found: 344.1391.

(1*Z*,4*E*)-2-Diazo-1-(methoxyimino)-1,5-diphenylhex-4-en-3-one (71k):



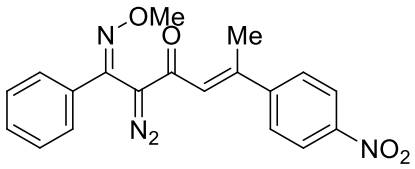
The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 61 - 62 ℃. Yield 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 - 7.65 (m, 2H), 7.44 - 7.42 (m, 3H), 7.25 - 7.23 (m, 1H), 7.20 - 7.19 (m, 2H), 6.85 (d, J = 7.2 Hz, 2H), 5.94 (s, 1H), 4.08 (s, 3H), 2.48 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 152.6, 144.3, 142.2, 134.4, 130.2, 128.9, 128.9, 128.3, 128.0, 126.2, 122.5, 62.8, 18.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{18}N_3O_2$: 320.1399. Found: 320.1395.

(1*E*,4*E*)-1-(Methoxyimino)-5-(4-methoxyphenyl)-1-phenylhex-4-en-3-one (71l):



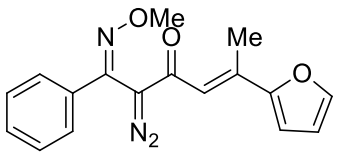
The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 - 7.65 (m, 2H), 7.43 - 7.42 (m, 3H), 6.83 (d, *J* = 7.2 Hz, 2H), 6.70 (dd, J_1 = 6.8 Hz, J_2 = 2.4 Hz, 2H), 5.91 (s, 1H), 4.08 (s, 3H), 3.77 (s, 3H), 2.48 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 160.4, 152.2, 144.5, 134.5, 134.3, 130.1, 128.9, 128.0, 127.7, 120.8, 113.6, 62.8, 55.3, 18.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{19}N_2O_4$: 339.1345. Found: 339.1342.

(1*Z*,4*E*)-2-Diazo-1-(methoxyimino)-5-(4-nitrophenyl)-1-phenylhex-4-en-3-one (71m):



The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 123 - 124 ℃. Yield 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 - 8.02 (m, 2H), 7.67 - 7.64 (m, 2H), 7.46 - 7.45 (m, 3H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.92 (d, *J* = 1.2 Hz, 1H), 4.10 (s, 3H), 2.46 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.3, 149.1, 148.6, 147.7, 143.8, 134.5, 130.3, 129.1, 128.1, 127.0, 125.3, 123.5, 62.9, 18.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{17}N_4O_4$: 365.1250. Found: 365.1245.

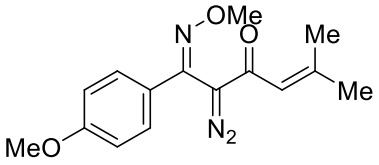
(1*Z*,4*E*)-2-Diazo-5-(furan-2-yl)-1-(methoxyimino)-1-phenylhex-4-en-3-one (71n):



The title compound was prepared according to the general procedure. The product was

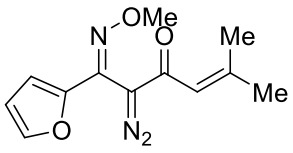
obtained as yellow oil. Yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 - 7.62 (m, 2H), 7.38 - 7.36 (m, 3H), 7.28 (d, J = 1.2 Hz, 1H), 6.47 (d, J = 3.2 Hz, 1H), 6.36 (dd, J_1 = 3.2 Hz, J_2 = 1.6 Hz, 1H), 6.28 (s, 1H), 4.08 (s, 3H), 2.40 (d, J = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.3, 154.4, 144.5, 143.8, 139.8, 134.1, 130.0, 128.7, 127.8, 117.0, 112.0, 111.7, 62.7, 15.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{16}N_3O_3$: 310.1192. Found: 310.1197.

(*Z*)-2-Diazo-1-(methoxyimino)-1-(4-methoxyphenyl)-5-methylhex-4-en-3-one (71o):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 6.90 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 5.62 (s, 1H), 4.04 (s, 3H), 3.83 (s, 3H), 2.10 (d, J = 1.2 Hz, 3H), 1.65 (d, J = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 161.1, 154.2, 144.0, 129.1, 126.4, 121.2, 114.1, 62.6, 55.4, 27.5, 20.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{18}N_3O_3$: 288.1348. Found: 288.1361.

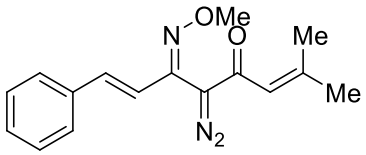
(*E*)-2-Diazo-1-(furan-2-yl)-1-(methoxyimino)-5-methylhex-4-en-3-one (71p):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J_1 = 2.0 Hz, J_2 = 0.8 Hz, 1H), 6.67 (dd, J_1 = 3.6 Hz, J_2 = 0.8 Hz, 1H), 6.47 (dd, J_1 = 3.6 Hz, J_2

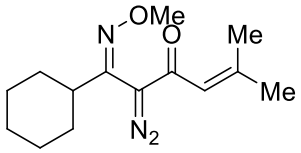
= 2.0 Hz, 1H), 5.71 (s, 1H), 4.07 (s, 3H), 2.15 (d, *J* = 1.2 Hz, 3H), 1.76 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.2, 154.7, 147.4, 144.4, 135.9, 120.4, 112.5, 111.8, 63.0, 27.6, 20.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{14}N_3O_3$: 248.1035. Found: 248.1041.

(6*Z*,7*E*)-5-Diazo-6-(methoxyimino)-2-methyl-8-phenylocta-2,7-dien-4-one (71q):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.43 (m, 2H), 7.37 - 7.30 (m, 3H), 6.92 (d, *J* = 16.4 Hz, 1H), 6.86 (d, *J* = 16.4 Hz, 1H), 5.91 (s, 1H), 4.03 (s, 3H), 2.20 (d, *J* = 0.8 Hz, 3H), 1.81 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 154.9, 144.0, 136.5, 135.8, 128.9, 128.8, 127.1, 122.9, 120.6, 62.8, 27.7, 20.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{18}N_3O_2$: 314.1116. Found: 314.1111.

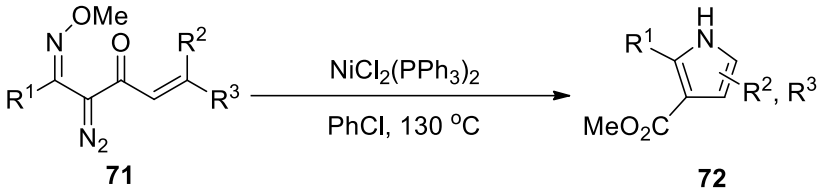
(*Z*)-1-Cyclohexyl-2-diazo-1-(methoxyimino)-5-methylhex-4-en-3-one (71r):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (t, *J* = 1.2 Hz, 1H), 3.88 (s, 3H), 2.67 - 2.61 (m, 1H), 2.13 (d, *J* = 0.8 Hz, 3H), 1.94 - 1.90 (m, 2H), 1.90 (d, *J* = 1.2 Hz, 3H), 1.79 - 1.76 (m, 2H), 1.69 - 1.66 (m, 1H), 1.41 - 1.18 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.9, 154.3, 148.7, 120.0, 61.9, 41.5, 31.3, 27.5, 26.3,

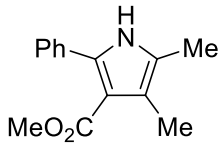
26.1, 20.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{22}N_3O_2$: 264.1712. Found: 264.1714.

General procedure for pyrroles:



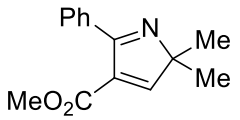
A solution of diazo compound **71** (0.2 mmol) and $NiCl_2(PPh_3)_2$ (0.02 mmol, 10 mol%) in chlorobenzene (2.0 mL) was stirred at 130 ℃ until the starting material was fully consumed. The reaction mixture was concentrated under reduced pressure to give the crude material which was purified by column chromatography using hexane : ethyl acetate = 9 : 1 to give the corresponding product.

Methyl 4,5-dimethyl-2-phenyl-1*H*-pyrrole-3-carboxylate (72a):



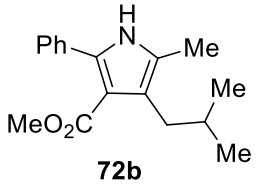
The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 168 - 170 ℃. Yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.48 - 7.45 (m, 2H), 7.40 - 7.30 (m, 3H), 3.69 (s, 3H), 2.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 135.3, 133.1, 128.8, 128.1, 127.7, 124.6, 117.6, 111.3, 50.5, 10.9, 10.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{16}NO_2$: 230.1181. Found: 230.1178.

Methyl 2,2-dimethyl-5-phenyl-2*H*-pyrrole-4-carboxylate (72a'):

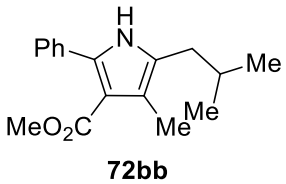


The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 6%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.68 - 7.66 (m, 2H), 7.42 - 7.40 (m, 3H), 3.78 (s, 3H), 1.46 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.2, 164.0, 134.4, 131.3, 129.7, 128.5, 127.9, 127.8, 76.7, 51.9, 22.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{16}NO_2$: 230.1181. Found: 230.1176.

Methyl 4-isobutyl-5-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate (72b) & Methyl 5-isobutyl-4-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate (72bb):



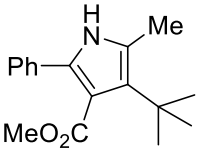
72b



72bb

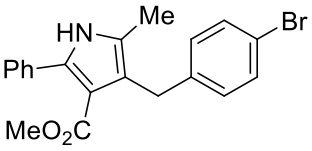
The title compound was prepared according to the general procedure. The product was obtained as yellow oil in a ratio of **72b** : **72bb** = 1.7 : 1. Yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 & 7.91 (s & s, 1H), 7.48 - 7.44 (m, 2H), 7.40 - 7.29 (m, 3H), 3.68 & 3.66 (s & s, 3H), 2.52 & 2.43 (d & d, *J* = 6.8 Hz & 7.2 Hz, 2H), 2.21 & 2.20 (s & s, 1H), 1.86 - 1.83 (m, 1H), 0.93 & 0.91 (d & d, *J* = 6.8 Hz & 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 166.4, 135.3, 135.3, 133.2, 133.2, 128.8, 128.7, 128.1, 128.0, 127.7, 127.6, 125.3, 121.8, 118.1, 111.2, 111.0, 50.5, 50.5, 34.7, 34.3, 30.3, 29.6, 22.6, 22.4, 11.2, 11.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{22}NO_2$: 272.1651. Found: 272.1653.

Methyl 4-*tert*-butyl-5-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate (72c):



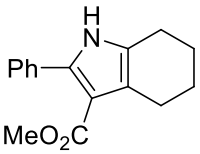
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.35 - 7.33 (m, 4H), 7.26 - 7.25 (m, 1H), 3.69 (s, 3H), 2.39 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 132.5, 129.7, 128.6, 127.7, 127.0, 126.7, 123.3, 114.2, 51.7, 32.6, 31.6, 15.4 ; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{22}NO_2$: 272.1651. Found: 272.1656.

Methyl 4-(4-bromobenzyl)-5-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate (72d):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.48 - 7.45 (m, 2H), 7.40 - 7.33 (m, 5H), 7.09 - 7.07 (m, 2H), 4.03 (s, 2H), 3.58 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 141.3, 135.8, 132.9, 131.1, 130.0, 128.8, 128.1, 127.9, 125.8, 120.0, 119.1, 110.9, 50.5, 30.4, 11.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{19}NO_2Br$: 384.0599. Found: 384.0594.

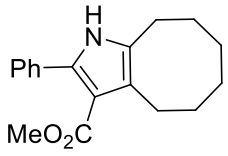
Methyl 5-phenyl-2-(phenylethynyl)-1*H*-pyrrole-3-carboxylate (72e):



The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 126 - 127 ℃. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ

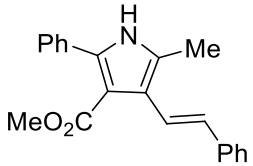
7.94 (s, 1H), 7.52 - 7.50 (m, 2H), 7.40 - 7.36 (m, 2H), 7.34 - 7.31 (m, 1H), 3.70 (s, 3H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.58 (t, *J* = 6.0 Hz, 2H), 1.84 - 1.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 135.8, 133.0, 128.9, 128.1, 127.8, 127.8, 120.2, 109.9, 50.5, 23.4, 23.4, 22.9, 22.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{18}NO_2$: 292.1338. Found: 292.1343.

Methyl 2-phenyl-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[b]pyrrole-3-carboxylate (72f):



The title compound was prepared according to general procedure. The product was obtained as white solid, mp: 129 - 130 ℃. Yield 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.50 - 7.47 (m, 2H), 7.40 - 7.36 (m, 2H), 7.33 - 7.31 (m, 1H), 3.69 (s, 3H), 2.86 (t, *J* = 6.0 Hz, 2H), 2.68 (t, *J* = 6.0 Hz, 2H), 1.72 - 1.70 (m, 2H), 1.69 - 1.61 (m, 2H), 1.53 - 1.48 (m, 2H), 1.42 - 1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 134.7, 133.2, 130.3, 128.7, 128.1, 127.6, 121.9, 110.6, 50.5, 30.7, 29.8, 26.0, 25.9, 25.8, 23.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{22}NO_2$: 284.1651. Found: 284.1651.

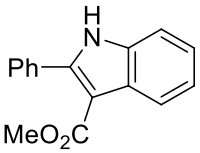
(*E*)-Methyl 5-methyl-2-phenyl-4-styryl-1*H*-pyrrole-3-carboxylate (72g):



The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 174 - 175 ºC. Yield 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ

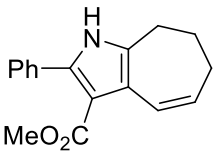
8.10 (s, 1H), 7.56 (d, *J* = 16.4 Hz, 1H), 7.51 - 7.47 (m, 4H), 7.42 - 7.40 (m, 2H), 7.38 - 7.32 (m, 3H), 7.24 - 7.20 (m, 1H), 6.65 (d, *J* = 16.8 Hz, 1H), 3.71 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 138.5, 135.4, 132.6, 129.1, 128.8, 128.6, 128.2, 128.1, 126.8, 126.1, 122.9, 120.1, 110.8, 50.9, 13.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{20}NO_2$: 318.1494. Found: 318.1497.

Methyl 2-phenyl-1*H*-indole-3-carboxylate (72h):



The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 150 - 151 ℃. Yield 44%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.23 - 8.21 (m, 1H), 7.69 - 7.66 (m, 2H), 7.48 - 7.46 (m, 3H), 7.42 - 7.39 (m, 1H), 7.30 - 7.28 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 144.5, 135.1, 132.0, 129.5, 129.3, 128.2, 127.6, 123.3, 122.2, 122.2, 110.9, 104.6, 50.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{14}NO_2$: 252.1025. Found: 252.1025.

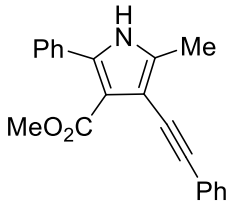
Methyl 2-phenyl-1,6,7,8-tetrahydrocyclohepta[b]pyrrole-3-carboxylate (72i):



The title compound was prepared according to the general procedure (reaction at 60 °C). The product was obtained as yellow solid, mp: 134 - 135 ℃. Yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.42 - 7.39 (m, 2H), 7.37 - 7.35 (m, 3H), 6.93 (d, *J* = 12.0 Hz, 1H), 5.74 - 5.69 (m, 1H), 3.65 (s, 3H), 2.87 (t, *J* = 6.0 Hz, 2H), 2.47 - 2.43 (m, 2H), 2.00 - 1.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 135.2, 132.8, 131.6, 128.7, 128.1, 127.8, 127.4, 121.5, 119.4, 110.5, 50.8, 30.9, 29.1, 23.3; HRMS

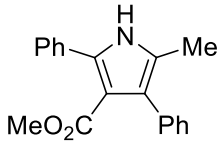
(ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{18}NO_2$: 268.1338. Found: 268.1333.

Methyl 5-methyl-2-phenyl-4-(phenylethynyl)-1*H*-pyrrole-3-carboxylate (72j):



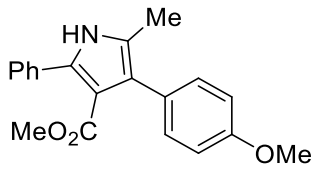
The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 180 - 181 °C. Yield 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.54 - 7.51 (m, 4H), 7.43 - 7.27 (m, 6H), 3.79 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 135.8, 133.6, 131.8, 131.3, 128.8, 128.4, 128.3, 128.2, 127.5, 124.4, 112.5, 104.7, 92.5, 83.7, 51.1, 12.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{18}NO_2$: 316.1338. Found: 316.1333.

Methyl 5-methyl-2,4-diphenyl-1*H*-pyrrole-3-carboxylate (72k):



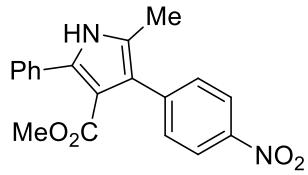
The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 206 - 208 °C. Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.55 - 7.54 (m, 2H), 7.43 - 7.39 (m, 5H), 7.38 - 7.27 (m, 3H), 3.51 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 135.6, 134.9, 132.5, 130.1, 128.6, 128.3, 127.9, 127.7, 126.2, 125.8, 123.7, 111.5, 50.7, 11.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{18}NO_2$: 292.1338. Found: 292.1336.

Methyl 4-(4-methoxyphenyl)-5-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate (72l):



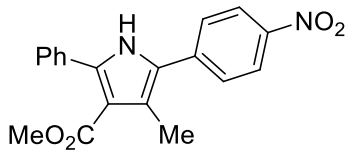
The title compound was prepared according to general procedure. The product was obtained as yellow solid, mp: 186 - 187 ℃. Yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 8.54 - 7.52 (m, 2H), 7.40 - 7.39 (m, 2H), 7.26 - 7.26 (m, 1H), 7.25 - 7.23(m, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 3.53 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 158.1, 134.8, 132.7, 131.1, 129.6, 128.5, 128.2, 127.9, 125.6, 123.3, 114.7, 113.1, 111.5, 55.2, 50.7, 11.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{17}N_2O_4$ 337.1188. Found: 337.1194.

Methyl 5-methyl-4-(4-nitrophenyl)-2-phenyl-1*H*-pyrrole-3-carboxylate (72m):



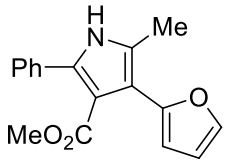
The title compound was prepared according to general procedure. The product was obtained as yellow solid, mp: 220 - 221 ℃. Yield 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.24 (d, *J* = 8.8 Hz, 2H), 7.55 - 7.53 (m, 2H), 7.48 - 7.36 (m, 5H), 3.52 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 146.2, 143.1, 136.1, 132.0, 130.8, 128.8, 128.4, 128.3, 126.7, 123.0, 121.8, 50.9, 11.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{17}N_2O_4$ 337.1188. Found: 337.1194.

Methyl 4-methyl-5-(4-nitrophenyl)-2-phenyl-1H-pyrrole-3-carboxylate (72mm):



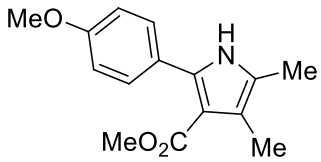
The title compound was prepared according to General procedure. The product was obtained as yellow solid, mp: 199 - 201 ℃. Yield 32%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.29 (d, *J* = 8.8 Hz, 2H), 7.60 - 7.58 (m, 2H), 7.52 - 7.51 (m, 2H), 7.43 - 7.41 (m, 3H), 3.72 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 146.0, 138.9, 132.1, 128.9, 128.7, 128.3, 127.4, 127.1, 124.3, 122.2, 113.9, 50.9, 12.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{17}N_2O_4$ 337.1190. Found: 337.1194.

Methyl 4-(furan-2-yl)-5-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate (72n):



The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 165 - 166 ºC. Yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.47 - 7.44 (m, 3H), 7.38 - 7.31 (m, 3H), 6.44 (d, J_1 = 3.2 Hz, J_2 = 1.6 Hz 1H), 6.38 (d, *J* = 3.2 Hz, 1H), 3.60 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 149.1, 141.2, 134.9, 132.2, 128.4, 128.3, 128.0, 127.9, 113.1, 111.2, 110.7, 107.6, 51.1, 12.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{16}NO_3$: 282.1130. Found: 282.1133.

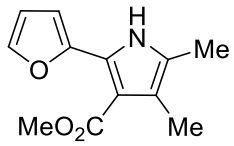
Methyl 2-(4-methoxyphenyl)-4,5-dimethyl-1H-pyrrole-3-carboxylate (72o):



The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 159 - 160 ºC. Yield 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.69 (s,

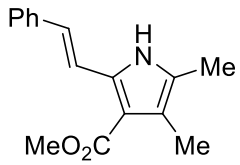
3H), 2.21 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 159.3, 135.4, 130.1, 125.6, 124.1, 117.3, 113.5, 110.8, 55.3, 50.5, 11.0, 10.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{18}NO_3$: 260.1287. Found: 260.1286.

Methyl 2-(furan-2-yl)-4,5-dimethyl-1*H*-pyrrole-3-carboxylate (72p):



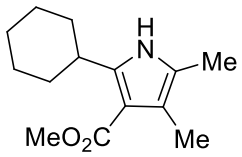
The title compound was prepared according to the general procedure. The product was obtained as green oil. Yield 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.37 (d, *J* = 1.2 Hz, 1H), 7.23 (d, *J* = 3.6 Hz, 1H), 6.48 (dd, J_1 = 3.2 Hz, J_2 = 1.6 Hz, 1H), 3.85 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 146.6, 140.8, 125.8, 124.7, 117.6, 112.1, 110.3, 109.1, 50.7, 11.2, 10.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{14}NO_3$: 220.0974. Found: 220.0973.

(*E*)-Methyl 4,5-dimethyl-2-styryl-1*H*-pyrrole-3-carboxylate (72q):



The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 150 - 151 ^{o}C. Yield 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.80 (d, *J* = 16.8 Hz, 1H), 7.48 - 7.46 (m, 2H), 7.35 - 7.31 (m, 2H), 7.25 - 7.21 (m, 1H), 6.68 (d, *J* = 16.8 Hz, 1H), 3.86 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 137.2, 133.0, 128.7, 127.5, 126.3, 125.8, 125.5, 118.5, 118.0, 113.1, 50.8, 11.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{18}NO_2$: 256.1338. Found: 256.1335.

Methyl 2-cyclohexyl-4,5-dimethyl-1*H*-pyrrole-3-carboxylate (72r):



The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 127 - 129 °C. Yield 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, *J* = 16.0 Hz, 1H), 3.79 (s, 3H), 3.44 - 3.36 (m, 1H), 2.13 (s, 6H), 1.98 - 1.95 (m, 2H), 1.83 - 1.73 (m, 3H), 1.48 - 1.41 (m, 2H), 1.40 - 1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 143.2, 121.9, 115.8, 109.2, 50.3, 36.0, 32.9, 26.6, 26.2, 11.1, 10.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{22}NO_2$: 236.1651. Found: 236.1646.

CHAPTER 3

Novel Approaches to Multi-Substitued Pyridines by Ring-Expansion of 2H-Azirines

CHAPTER 3 NOVEL APPROACHES TO MULTI-SUBSTITUTED PYRIDINES BY RING-EXPANSION OF 2*H*-AZIRINES

3.1 OVERIEW

Pyridine is an important *N*-heterocycle which is structurally related to benzene in structure, with one methine group replaced by a nitrogen atom. They are widespread in many pharmaceuticals, natural products, and functional materials, and are valuable ligands in synthetic science.[84] Due to the importance of the pyridines, there are constant advancements in the development of methodologies to prepare pyridines in the last few decades.[85] While traditional methods largely rely on condensation of carbonyl compounds with ammonia,[86] modern strategies turn to transition-metal catalysis, C-H functionalization, and cycloaddition reactions.[87] Despite this progress, it is still highly desirable to develop more flexible, operationally simple methods with br-

[84] a) Pozharskii, A. F.; Soldatenkov, A.; Katritzky, A. R.; Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications, Wiley, Hoboken, **2011**; b) Michael, J. P.; *Nat. Prod. Rep.* **2005**, *22*, 627; c) Hagan, D. O. *Nat. Prod. Rep.* **2000**, 17, 435; d) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043; e) Chen, M. Z.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 1352.

[85] a) Kral, K.; Hapke, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2434; b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, Wiley, Hoboken, **2010**, pp. 115-175; c) Hill, M. D. *Chem. Eur. J.* **2010**, *16*, 12052; d) Keller, P. A. in *Comprehensive Heterocyclic Chemistry III, Vol. 7* (Eds.: A. R. Katritzky, A. R. Christopher, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Oxford, **2008**, pp. 217-308; e) Zeni, G.; Larock, R. L. *Chem. Rev.* **2006**, *106*, 4644; f) Varela, J.; Saa, C. *Chem. Rev.* **2003**, *103*, 3787; g) Groenendaal, B.; Ruijter, E.; Orru, R. V. A. *Chem. Commun.* **2008**, 5474; h) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085; i) Boger, D. L. *Chem. Rev.* 1986, 86, 781.

[86] a) Frederic, L. M.; Allais, C.; Constantieux, T.; Rodriguez, J. *Chem. Commun.* **2008**, 4207; b) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957; c) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 269.

[87]; b) Loy, N. S. Y.; Singh, A.; Xu, X.; Park, C.-M. *Angew. Chem. Int. Ed.* **2013**, *52*, 2212; c) Gati, W.; Rammah, M. M.; Rammah, M. B.; Couty, F.; Evano, G. *J. Am. Chem. Soc.* **2012**, *134*, 9078; d) Ohashi, M.; Takeda, I.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2011**, *133*, 18018; e) Nakamura, I; Zhang, D.; Terada, M. *J. Am. Chem. Soc.* **2010**, *132*, 7884; f) Wang, Y.-F.; Chiba, S. *J. Am. Chem. Soc.* **2009**, *131*, 12570; g) Chiba, S.; Xu, Y.-J.; Wang, Y.-F. *J. Am. Chem. Soc.* **2009**, *131*, 12886; h) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918; i) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096; j) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 4592; k) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030; l) Yamamoto, Y.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2001**, *123*, 6189.

-oad functional group tolerance. In this chapter, we described two different methods to construct multi-substituted pyridines by intramolecular ring-expansion of 2*H*-azirine derivtives in the presence of rhodium catalyst or transition-metal free condition, respectively. For rhodium-catalyzed pyridine synthesis, we found that the 2-vinyl-2*H*-azirines could be easily from *α*-diazo-*β*-keto oxime ethers generated *in-situ*, following amination of sp^3 C-H bond of allylic carbon to afford the pyridine derivatives. In the second part, we developed an efficient method for the synthesis of multi-substituted pyridines from ring expansion of 2-allyl-2*H*-azirines promoted by DBU (1,8-diazabicyclo [5.4.0] undec-7-ene) promotion.

3.2 RHODIUM(II)-CATALYZED SYNTHESIS OF PYRIDINES THROUGH AMINATION OF SP^3 C–H BOND

3.2.1 INTRODUCTION

Nitrogen-containing heterocycles are among the important scaffolds that are ubiquitous in numerous natural products and many biologically active pharmaceuticals. It is reported that 18 of the top 20 small-molecule drugs involved at least one *N*-heterocycle in 2010. Pyridines are the most remarkable example of them which are prevalently found in drugs.[88] The most renowned ones are the vitamin B6, the proton pump inhibitor esomeprazole and the Nexium (Figure 3.1, **a-c**).[89] The pyridine

[88] a) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive heterocyclic chemistry II: a review of the literature 1982-1995: the structure, reactions, synthesis, and uses of heterocyclic compounds*; 1st ed.; Pergamon: Oxford; New York, 1996. b) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043. c) Joule, J. A.; Mills, K. *Heterocyclic chemistry*; 4th ed.; Blackwell Science: Malden, MA, 2000. d) Michael, J. P. *Nat. Prod. Rep*. **2005**, *22*, 627. e) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. f) Triggle, D. J. *Cell. Mol. Neurobiol.* **2003**, *23*, 293.

[89] a) Lukevitz, É. *Chem. Heterocycl. Compd.* **1995**, *31*, 639; b) Jones, G. *In Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; McKillop, A., Eds.; Pergamon: Oxford, U.K., **1996**, Vol. *5*, p 167; c) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043; d) Spitzner, D. *Sci. Synth.* **2004**, *15*, 11.

moieties are also found in many natural products. Amythaiamicin D (Figure 3.1, **d**)[90] and Diploclidine (Figure 3.1, **e**)[91] are two examples of recently isolated natural products containing a pyridine core.

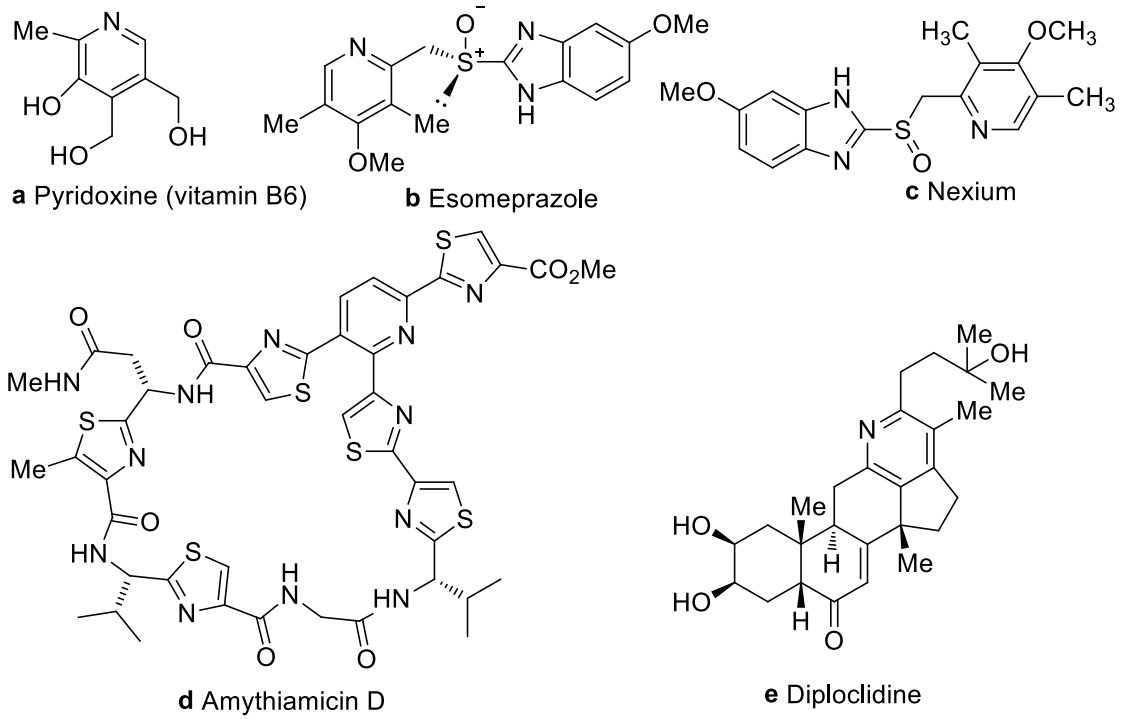
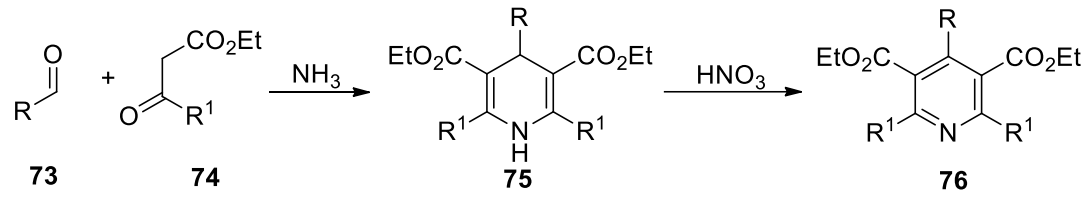


Figure 3.1 Natural products and drugs containing multi-substituted pyridines

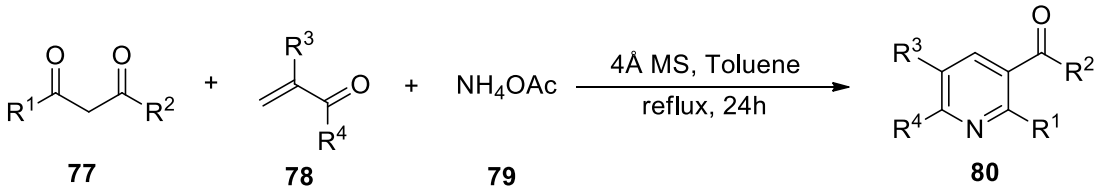
Considering the values of pyridine core in natural products and drugs, organic chemists have spent great efforts to develop new strategies to construct them which could accommodate a wider substrate scope, operationally simpler procedures, as well as attaching environmental sustainability. Hantzsch pyridine synthesis is a known conventional method to afford multi-substituted pyridines through condensation of amines with carbonyl compounds (Scheme 3.1).[92]

[90] Kubota, T.; Nishi, T.; Fukushi, E.; Kawabata, J.; Fromont, J.; Kobayashi, J. *Tetrahedron Lett.* **2007**, *48*, 4983.
[91] Hughes, R. A.; Thompson, S. P.; Alcaraz, L.; Moody, C. J. *J. Am. Chem. Soc.* **2005**, *127*,15644
[92] a) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *1*, 215; b) Lavilla, R. *J. Chem. Soc. Perkin Trans. 1* **2002**, 1141; c) Moreau, J.; Hurvois, J.-P.; Mbaye, M. D.; Renaud, J.-L.; *Targets. Heterocycl. Syst.* **2009**,



Scheme 3.1 Hantzsch pyridine synthesis

Multicomponent reactions (MCRs) are reactions whereby more than two reactants combine in a sequential manner to give highly selective products with retainment of majority of the atoms of the starting material.[93] Rodriguez developed a simple metal-free, step-economic and selective pathway to access pyridines **80** from readily available substrates, involving a 1,3-dicarbonyl **77**, a Michael acceptor **78** and a synthetic equivalent of nitrogen source **79** (Scheme 3.2).[94]



Scheme 3.2 Multicomponent reactions for pyridine synthesis

Ring-closing metathesis (RCM) is a powerful method to construct C–C double bond that has also been extended to the synthesis of substituted pyridine derivatives.[95] A multistep synthesis of polysubstituted pyridines using RCM as the key step was reported by Donohoe and co-workers recently (Scheme 3.3).[96]

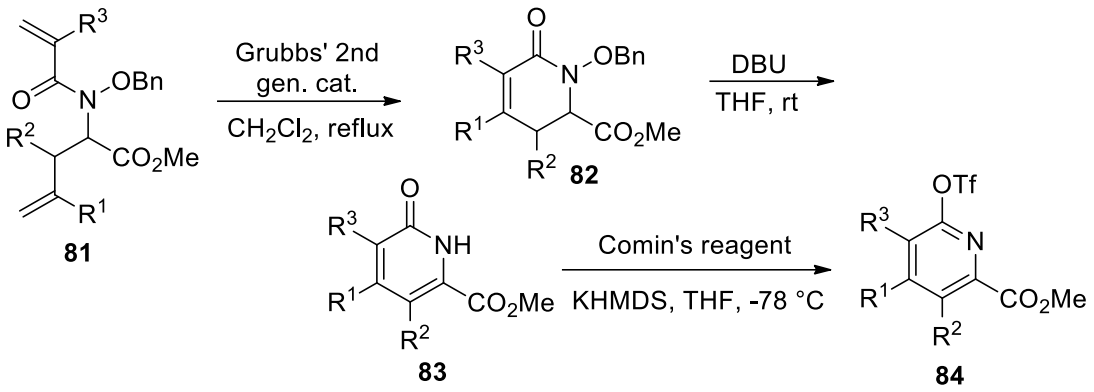
13, 201.

[93] For a book, see: a) Zhu, J.; Bienaymé, H. (Eds.), *Multicomponent Reactions*, Wiley-VCH, Weinheim, **2005**; for selected recent reviews, see: b) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439; c) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6234; d) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083; e) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508; f) Marson, C. M. *Chem. Soc. Rev.* **2012**, *41*, 7712.

[94] Allais, C.; Frédéric, L. M.; Jean, R.; Thierry, C. *Eur. J. Org. Chem.* **2013**, 4131.

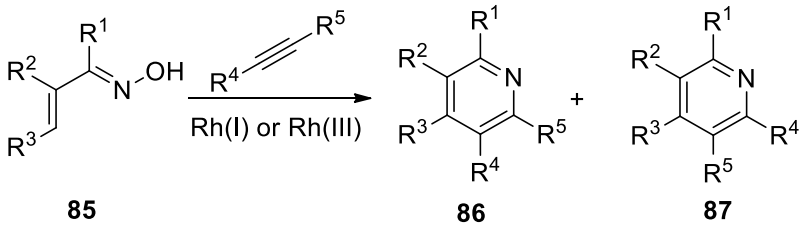
[95] a) Otterlo, van W. A. L.; de Koning, C. B. *Chem. Rev.* **2009**, *109*, 3743. b) Sato, A.; Sugimoto, O.; Tanji, K. I. *Heterocycles* **2009**, *78*, 2067.

[96] Donohoe, T. J.; Bower, J. F.; Basutto, J. A.; Fishlock, L. P.; Procopiou, P. A.; Callens, C. K. A. *Tetrahedron* **2009**, *65*, 8969.



Scheme 3.3 Ring-closing metathesis to the synthesis of pyridines

Transition-metal catalyzed C–H activation reactions have drawn great attention in the past several years. Cheng, Chiba and Rovis independently demonstrated the Rh(I) or Rh(III)-catalyzed synthesis of polysubstituted pyridines (**86**, **87**) from *α*, *β*-unsaturated oximes **85** and symmetrical internal alkynes.[97] Several terminal alkynes, which were historically avoided because of their propensity to undergo side reactions, were reported by Bergman and Ellman to be competent substrates with a Rh(I)/phosphite system (Scheme 3.4).[98]

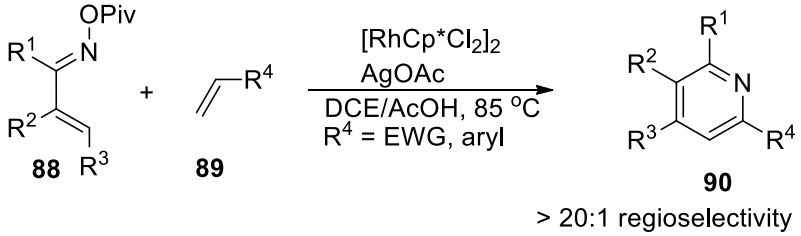


Scheme 3.4 Synthesis of polysubstituted pyridines from *α*, *β*-unsaturated oximes

In connection with previous work, Rovis reported Rh(III)-catalyzed synthesis of substituted pyridines **90** from the coupling of *α*, *β*-unsaturated *O*-pivaloyl oximes **88**

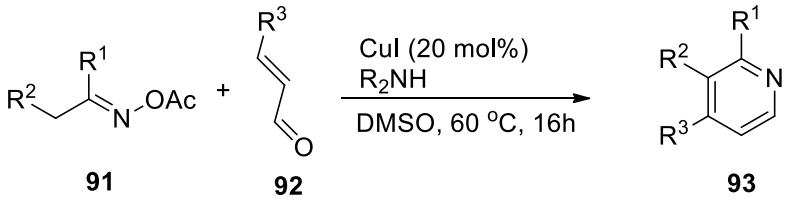
[97] a) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, *10*, 325; b) Parthasarathy, K.; Cheng, C.-H. *Synthesis* **2009**, 1400; c) Too, P. C.; Noji, T.; Lim, Y. J.; Li, X.; Chiba, S. *Synlett* **2011**, 2789; d) Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 11846.
[98] Martin, R. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2012**, *77*, 2501.

with activated alkenes **89** in 2012 (Scheme 3.5).[99] This reaction is performed with high regioselectivitiy and excellent yield. Mechanistic studies revealed the involvement of reversible C–H activation, alkene insertion, and a C–N bond formation/N–O bond cleavage in the pyridine formation process.



Scheme 3.5 Synthesis of pyridines from alkenes and *α*, *β*-unsaturated oxime esters

In 2012, Yoshikai group developed a [3 + 3]-type condensation reaction of *O*-acetyl ketoximes **91** and *α*, *β*-unsaturated aldehydes **92** under mild reaction conditions in the presence of copper (I) catalyst and a secondary ammonium salt (or amine) (Scheme 3.6).[100]

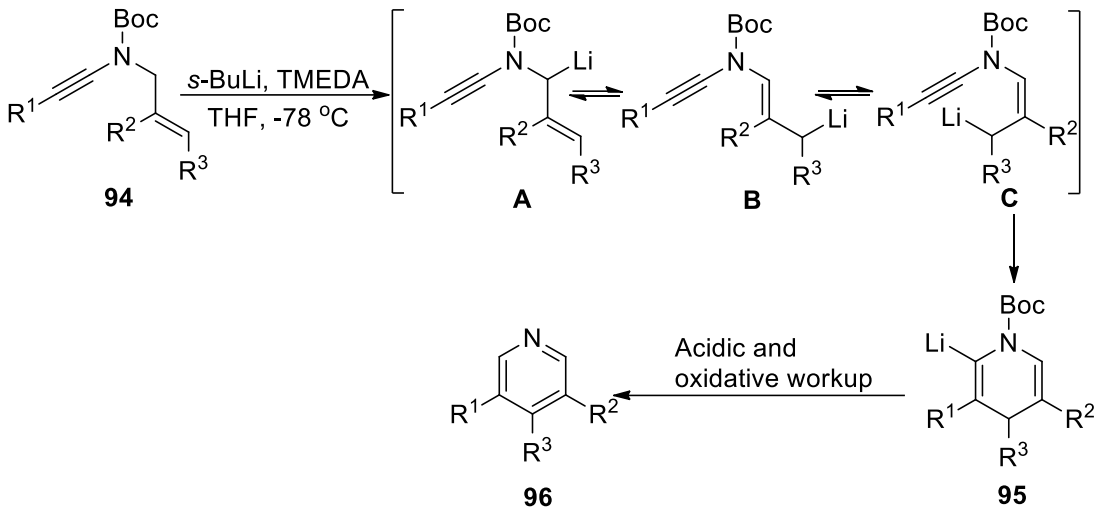


Scheme 3.6 Synthesis of pyridines from condensation of oximes and enals

Evano and co-workers described an efficient and general method for the synthesis of pyridines based on a lithiation/isomerization/intramolecular carbolithiation sequence in 2012 (Scheme 3.7).[101] This method offers an efficient, divergent, and straightforward access to a wide range of polysubstituted pyridines **96**

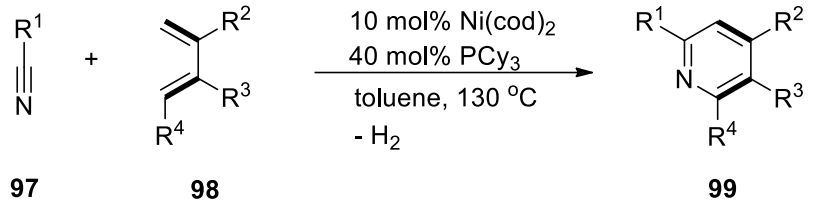
[99] Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.*, **2013**, *135*, 66.
[100] Wei, Y.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 3756.
[101] Gati, W.; Rammah, M. M.; Rammah, M. B.; François, C.; Gwilherm, E. *J. Am. Chem. Soc.* **2012**, *134*, 9078.

starting from readily available *N*-allyl-ynamides **94**.



Scheme 3.7 Synthesis of pyridines from *N*-allyl-ynamides

The transition metal-catalyzed [2 + 2 + 2] cycloaddition reaction of a nitrile and two alkynes is a versatile method for preparing highly substituted pyridine derivatives.[102] In 2011, Ogoshi group developed the Ni(0)-catalyzed intermolecular [4 + 2] cycloaddition reaction of nitriles **97** with 1,3-butadienes **98** to afford a variety of pyridines **99** regioselectively (Scheme 3.8).[103]

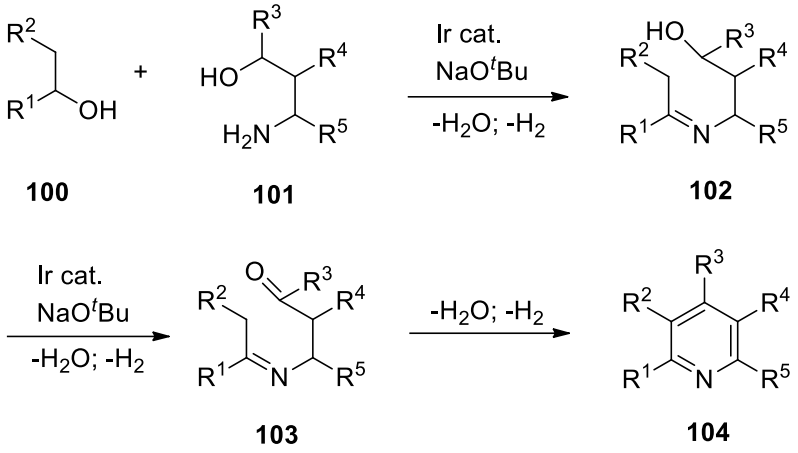


Scheme 3.8 Synthesis of pyridines from dienes and nitriles

[102] For reviews, see: a) J. A. Varela, C. Saá, *Chem. Rev.* **2003**, *103*, 3787; b) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127; c) B. Heller, M. Hapke, *Chem. Soc. Rev.* **2007**, *36*, 1085; for recent examples with various metals, see: d) C. Brändli, T. R. Ward, *J. Comb. Chem.* **2000**, *2*, 42; e) Y. Zhou, J. A. Porco Jr., J. K. Snyder, *Org. Lett.* **2007**, *9*, 393; f) H. T. Chang, M. Jeganmohan, C.-H. Cheng, *Org. Lett.* **2007**, *9*, 505; g) K. Kase, A. Goswami, K. Ohtaki, E. Tanabe, N. Saino, V. Okamoto, *Org. Lett.* **2007**, *9*, 931; h) A. Wada, K. Nogushi, M. Hirano, K. Tanaka, *Org. Lett.* **2007**, *9*, 1295; i) K. Parthasarathy, M. Jeganmohan, C.-H. Cheng, *Org. Lett.* **2008**, *10*, 325; i) Komine, Y.; Tanaka, K. *Org. Lett.* **2010**, *12*, 1312; j) Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.* **2006**, 3917; k) Senaiar, R. S.; Young, D. D.; Deiters, A. *Chem. Commun.* **2006**, 1313; l) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605.

[103] Ohashi, M.; Takeda, I.; Masashi.; Ogoshi, S. *J. Am. Chem. Soc.* **2011**, *133*, 18018.

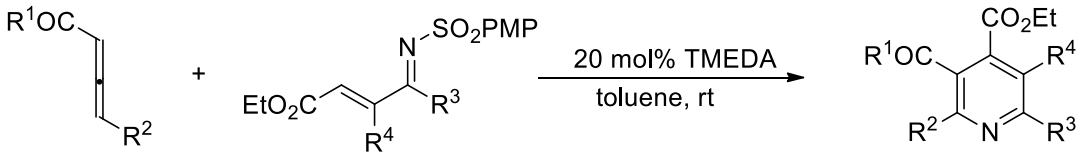
In 2013, Kempe has presented a novel iridium catalyzed pyridine synthesis from simple alcohol substrates (**100**, **101**) (Scheme 3.9).[104] This reaction proved to exhibit high regioselectivity, even for the conventionally challenging unsymmetrically substituted pyridines. A broad spectrum of functional groups was also tolerated.



100 **101** **102** **103** **104**

Scheme 3.9 Iridium catalyzed pyridine synthesis

Recently, Loh group reported an organic base catalyzed aza-Rauhut-Currier /cyclization/desulfonation cascade reaction under a mild, environmentally benign protocol for the synthesis of pyridines **107** by 2,3-butadienoate **105** and *N*-sulfonyl-1-aza-1,3-dienes **106** (Scheme 3.10).[105]



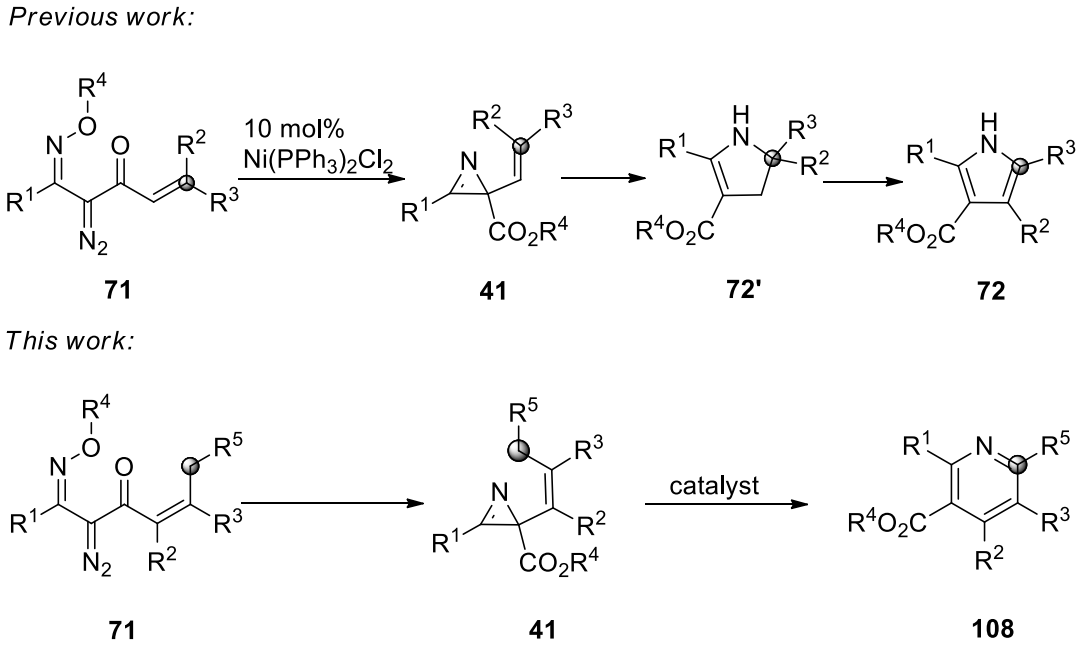
105 **106** **107**

Scheme 3.10 Organic base catalyzed pyridine synthesis

[104] Stefan, M.; Rhett, K. *Angew. Chem., Int. Ed.* **2013**, *10*, 6326.
[105] Shi, Z.-G.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2013**, *52*, 8584.

3.2.2 RESULT AND DISCUSSION

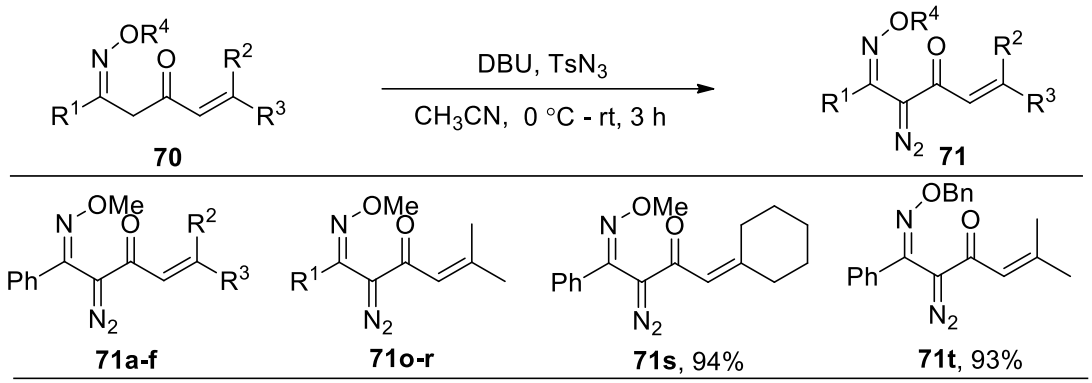
In the chapter 2, we have already discussed the synthesis of fully substituted pyrroles from common substrates *α*-diazo-*β*-keto oxime ethers **71** in the presence of nickel catalyst. The nitrenes derived from 2*H*-azirines **41** added selectively to C–C double bond leading to 2*H*-pyrroles **72'**, which subsequently rearranged to fully substituted pyrroles **72**. On the other hand, we envisaged that the same azirine intermediates **41** could probably insert into allylic sp^3 C–H bond which would finally afford the pyridine derivatives **108**.



Scheme 3.11 Synthesis of *N*-heterocycles from *α*-diazo oxime ethers

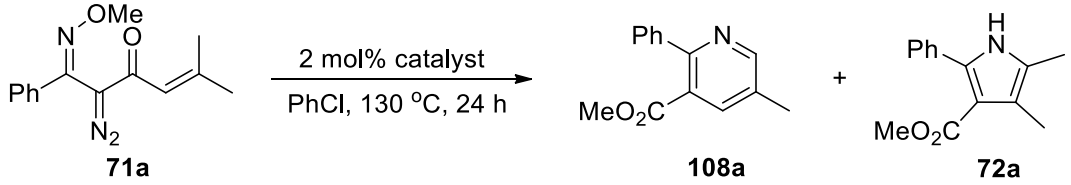
The *α*-diazo oxime ethers **71a-f** and **71o-r** could easily be prepared and have been studied to yield fully substituted pyrroles in Chapter 2, Table 2-3. **71s** and **71t** were synthesized from carbonyl derivatives by diazo transfer reactions under mild conditions (Table 3-1).

Table 3-1 Preparation of *α*-diazo-*β*-keto oxime ethers



We started our exploration for the synthesis of pyridines by employing *α*-diazo oxime ether **71a** as model substrate to screen various metal salts (Table 3-2). The reaction with $(Cu(OTf))_2$.benzene gave pyridine **108a** in moderate yield, while Ag and Co catalysts gave a mixture of pyridine **108a** and pyrrole **72a** with poor selectivity

Table 3-2 Optimization of reaction conditions for pyridine synthesis

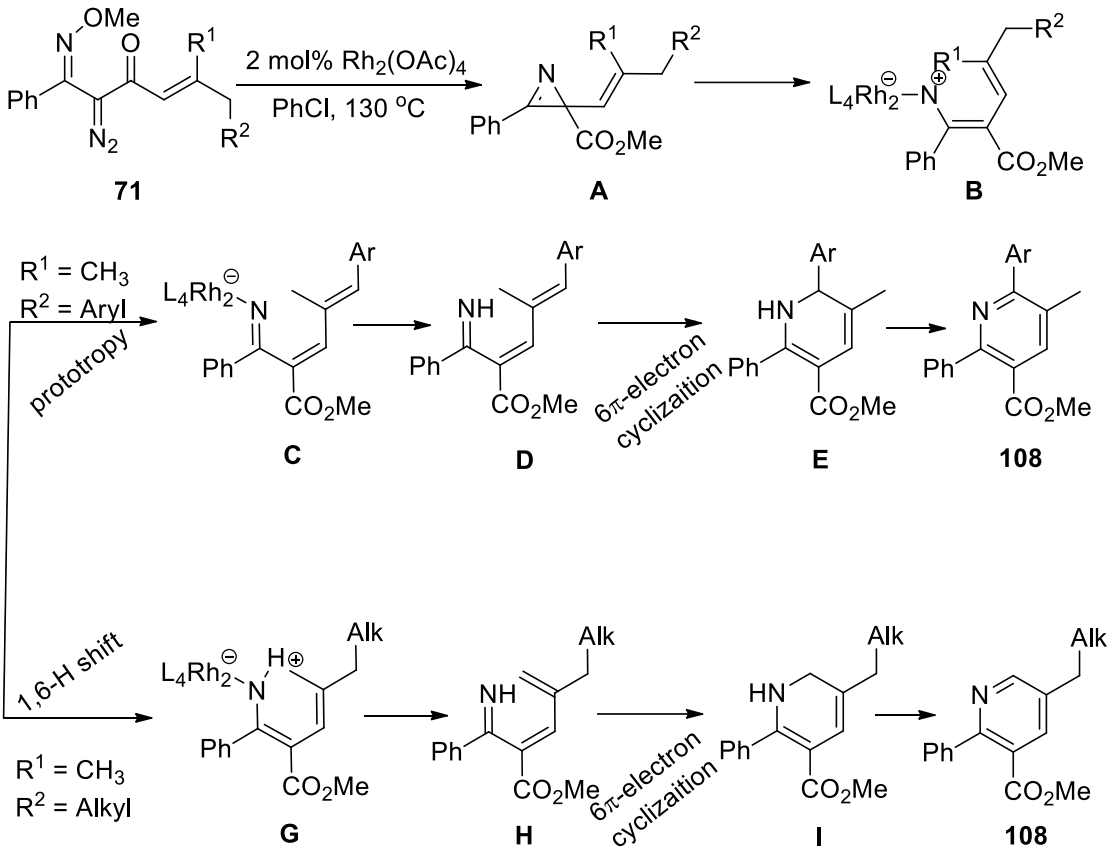


Entry	Catalyst[a]	Yield[b] (%)	
		108a	**72a**
1	$(Cu(OTf))_2$.benzene	53	-
2	AgOAc	25	38
3	$Co(OAc)_2$	28	31
4	$Rh_2(pfb)_4$	45	-
5	$Rh_2(OPiv)_4$	57	-
6	$Rh_2(esp)_2$	61	-
7	$Rh_2(OAc)_4$	73	-

[a]Reaction conditions: **14a** (0.1 mmol), catalyst (2 mol%), PhCl (1.0 mL), 130 ℃, 24 h. [b]NMR yields. [c]methyl 2,2-dimethyl-5-phenyl-2*H*-pyrrole-4-carboxylate (16%). pfb = perfluorobutyrate, TFA = trifluoroacetate, Piv = pivalate, esp = α,α,α',α'-tetra methyl-1,3-benzenedipropionate.

(Table 3-2, entries 1-3). To further improve the selectivity for pyridine, we tested Rh(II) complexes bearing ligands with different steric and electronic attributes (Table 3-2, entries 4-7) and found that Rh(II) complexes with both electron-withdrawing and sterically bulky ligands gave moderate yields. Gratifyingly, $Rh(OAc)_2$ provided pyridine **108a** in 73% yield. We did not observe the dihydropyridine intermediate probably due to the rapid oxidation step.

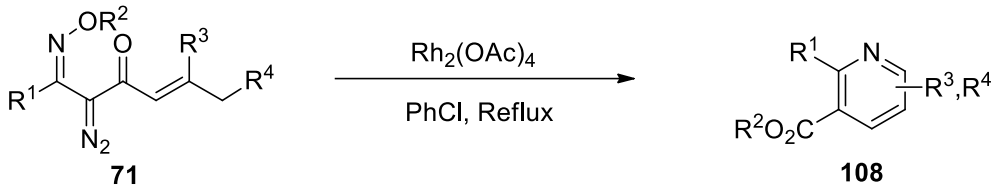
With the optimized reaction conditions in hand, we turned our attention to survey the scope of the reaction (Table 3-3). Initially, we examined the regioselectivity of the reaction by employing substrate **71b** bearing two different substituents (R^3 and R^4). Reaction of **71b** bearing methyl and isobutyl groups led to the construction of **108b** as a single isomer in which C–N bond formation occurred at the methyl group rather than isobutyl group, which is *syn* to the nitrene. Surprisingly, **71d** bearing *p*-bromobenzyl group instead of isobutyl group afforded **108d** which arises from the reaction at the benzylic site. This observation indicates that the reaction mechanism did not involve direct C–H insertion due to the geometric constraint, which prevents the nitrene from reacting at the benzylic site without prior isomerization. The plausibility of isomerization of the alkene during the formation of 2*H*-azirine intermediate was ruled out by examination of the configuration. Based on these experimental results, we propose that the reaction mechanism is divided into thermodynamic and kinetic pathways depending on the properties of substituents for R^2 (Scheme 3.12). For substrates with R^2 = aryl group, the nitrene intermediate **B** was isomerized to **C** *via* prototropic isomerization of the benzylic proton affording the thermodynamically more stable 1-azatriene **D**. On the other hand, for those with R^2 = alkyl group, 1,6-hydride shift is preferred from the substituents *syn* to the nitrenes to afford kinetic 1-azatriene **H**.

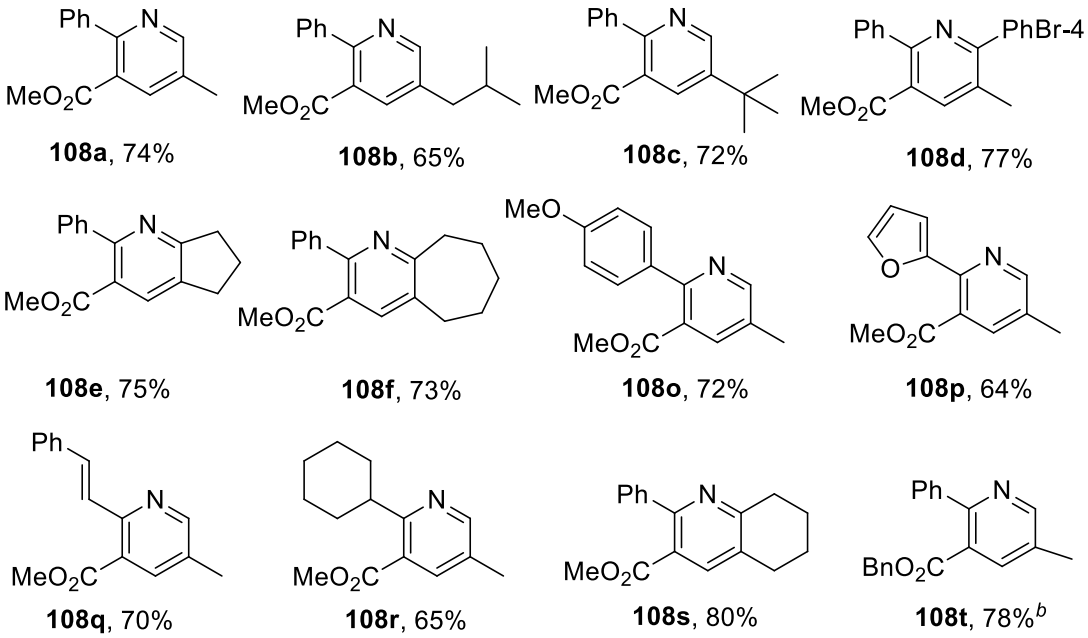


Scheme 3.12 Proposed reaction pathway

A variety of fused bicyclic pyridines are readily obtained in good yields by incorporating desired size of rings onto alkenes (Table 3-3, **108e-f** and **108s**). We also studied the scope of R^1 group and found that various types of substituents could be well tolerated (**108o**-**t**). The reaction with substrates bearing electron-rich aryl (**108o**) and heteroaryl (**108p**) groups reacted smoothly to afford the corresponding pyridines in 72% and 64%, respectively. Also, those with vinyl and alkyl groups proceeded well to give pyridines (**108q** and **108r**, respectively). Different esters can be installed by using corresponding oxime ethers. Thus, pyridine with benzyl ester (**108t**) could be accessed in good yield by employing benzyl oxime ether.

Table 3-3 Substrate scope of pyridine synthesis[a]





[a]Reaction conditions: **71** (0.2 mmol), $Rh_2(OAc)_4$ (2 mol %), PhCl (2.0 mL), 130 °C, 24 h
[b]benzyl oxime ether

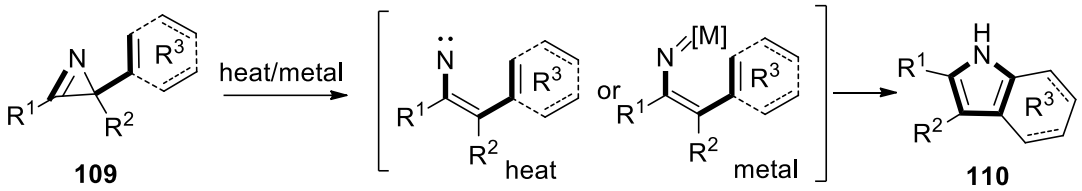
3.2.3 SUMMARY

In summary, a novel reaction manifold that allows chemoselective synthesis of pyridines from common substrates *α*-diazo-*β*-keto oxime ethers has been developed. Mechanistic study indicates that the pyridine formation is initiated by 1,6-hydride shift or prototropic isomerization depending on the type of substituents. The reaction tolerance of these transformations demonstrates that the diverse structures of these important *N*-heterocycles are readily accessible from *α*-diazo-*β*-keto oxime ethers with high efficiency.

3.3 TRANSION-METAL-FREE SYNTHESIS OF PYRIDINES THROUGH AMINATION OF sp^2 C–H BOND

3.3.1 INTRODUCTION

2*H*-Azirines are the smallest unsaturated aza-heterocycles. Their unique property has been extensively explored for synthetic and biological applications. Due to its inherent ring-strain, 2*H*-azirines possess the potential to ring-open and serve as a versatile source of nitrenes, electrophiles, dienophiles, and dipolarophiles and are further applied in the construction of various *N*-heterocycles such as indoles, pyrroles, isoxazoles, and pyrazolo[1,5-*a*]pyridines. Among them, indoles and pyrroles **110** are the most well studied from ring-expansion of 2-aryl-2*H*-azirines (**109**, R^3 = Ar) and 2-vinyl-2*H*-azirines (**109**, R^3 = vinyl) *via* nitrene intermediates upon thermolysis and transition metal catalysis (Scheme 3.13).[106]

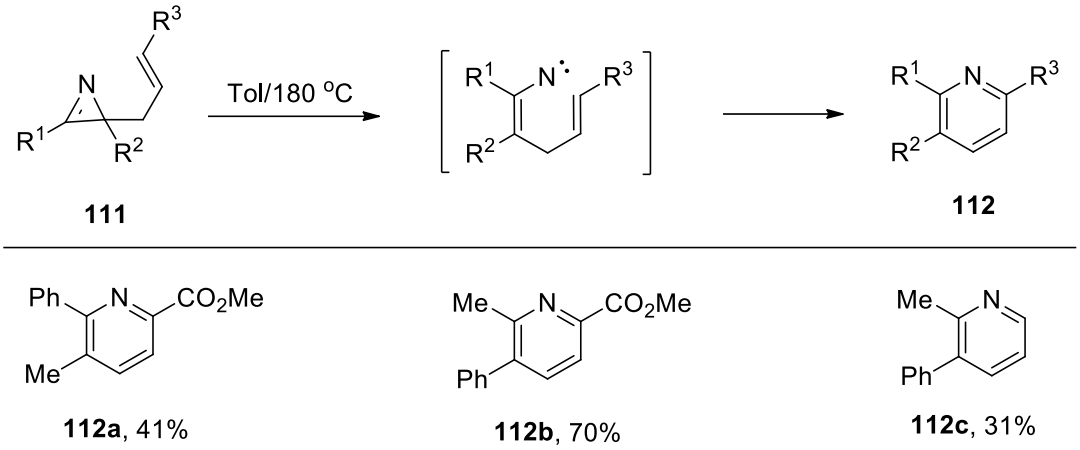


Scheme 3.13 Synthesis of pyrroles and indoles from 2*H*-azirines

However, different from aryl and vinyl-substituted azirines, few examples of successful *N*-heterocycle synthesis involving 2-allyl-2*H*-azirines which contain remote double bonds have been reported. Padwa and co-workers reported in a limited number of examples (**112a-c**) that thermal generation of nitrenes from 2-allyl-2*H*-azirines **111**

[106] a) Jana, S.; Clements, M. D.; Sharp, B. K.; Zheng, N. *Org. Lett.* **2010**, *12*, 3736; b) Chiba, S.; Hattoti, G.; Narasaka, K. *Chem. Lett.* **2007**, *36*, 52; c) Taber, D. F.; Tian, W. *J. Am. Chem. Soc.* **2006**, *128*, 1058; d) Padwa, A.; Smolanoff, J.; Tremper, A. *J. Am. Chem. Soc.* **1975**, *97*, 4682–4691.

leads to the formation of mixtures of pyridines, pyrroles, and indoles (Scheme 3.14).[107]

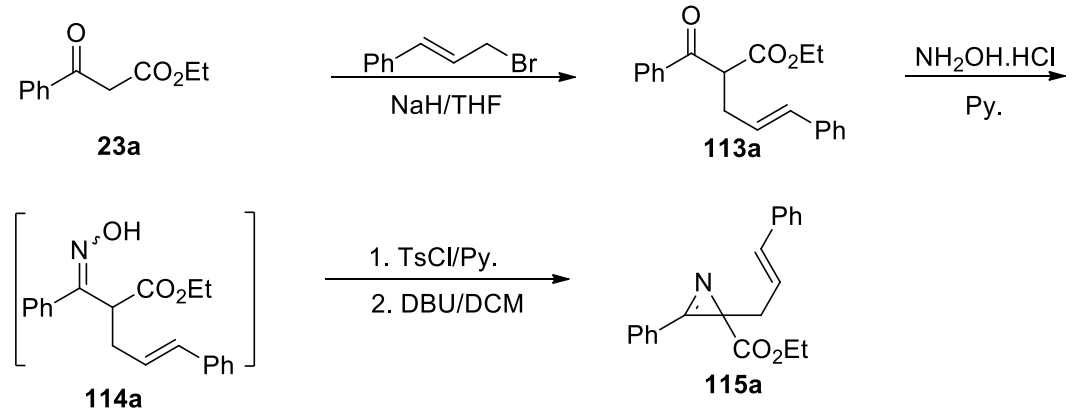


Scheme 3.14 Synthesis of pyridines from 2-allyl-2*H*-azirines

In continuation of our interests in pyridine synthesis, we developed an efficient access to the synthesis of multi-substituted pyridines from common substrates 2-allyl-2*H*-azirines by organic base DBU (1, 8-diazabicyclo [5.4.0] undec-7-ene) promoted intramolecular electrocyclization.

3.3.2 RESULT AND DISCUSSION

The substrate 2-allyl-2*H*-azirine **115a** was readily accessed based on Neber



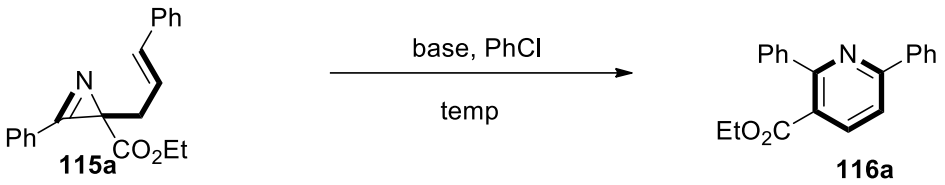
Scheme 3.15 General procedure for preparing 2-allyl-2*H*-azirines

[107] Padwa, A.; Carlsen, P. H. J. *Tetrahedron Lett.* **1978**, *19*, 433.

reactions. Firstly, the *α*-allyl-*β*-keto-ester **113a** was prepared by nucleophilic substitution of *β*-keto-ester **23a** with allyl bromide. After condensation with hydroamine, the oxime intermediate **114a** was treated directly with *p*-toluenesulfonyl chloride without isolation and organic base was added consecutively to give the desired azirine substrates **115a** (Scheme 3.15).

With the substrates in hand, various conditions were investigated for pyridine formation by employing 2-allyl-2*H*-azirine **115a** as the model substrate. When **115a**

Table 3-4 Base promoted synthesis of multi-substituted pyridines

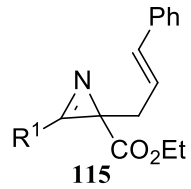


Entry	Base	Sovlent	Yield[b] (%)
1	TMEDA	PhCl	17
2	DMAP	PhCl	0
3	DABCO	PhCl	17
4	Quinine	PhCl	16
5	TEA	PhCl	13
6	**DBU**	**PhCl**	**95**
7	DBU	PhCl	0
8	DBU	DCE	26
9	DBU	PhCl	75
10	DBU	PhCl	77
11	$FeBr_2$	PhCl	23
12	$Rh_2(OAc)_4$	PhCl	25

[a]Unless otherwise noted, the reactions were carried out using 2-phenoxyacetophenone (**115a**) (0.1 mmol), base (0.3 mmol) in solvents (0.1 M, 1 mL) at 130 ℃ for 48 h under an nitrogen atmosphere (1 atm). [b]Yields determined by NMR *vs.* standard. [c]The reaction was performed with 2.2 equiv DBU. TMEDA = Tetramethylethylenediamine, DMAP = 4-Dimethylaminopyridine, DABCO = 1, 4-diazabicyclo-[2.2.2]octane, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

treated with TMEDA in chlorobenzene at 130 ℃, **115a** afforded ethyl 2,6-diphenylnicotinate **116a** in poor yield (Table 3-4, entry 1). We also employed other bases in an attempt to improve the yield but turned out unsuccessful. The use of DMAP failed to provide any product (Table 3-4, entry 2), while quinine, DABCO and TEA gave similar results as TMEDA (Table 3-4, entries 3-5). Gratifyingly, the yield

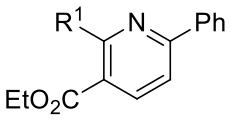
Table 3-5 Substrate Scope of Pyridine Synthesis[a]



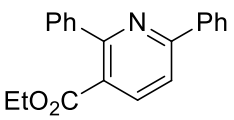
115

3 equiv DBU

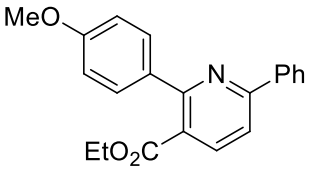
PhCl, 130 °C



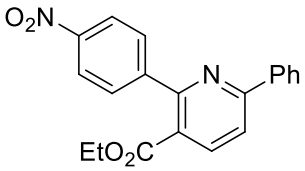
116



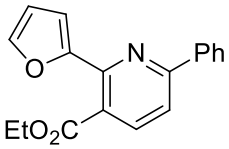
116a, 95%/90%[d]



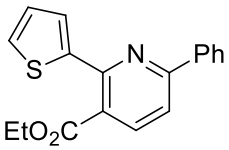
116b, 92%



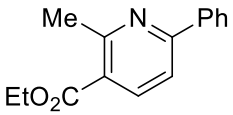
116c, 45%[c]



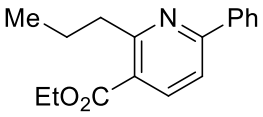
116d, 54%[c]



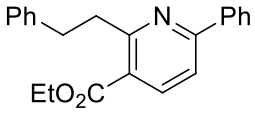
116e, 54%[c]



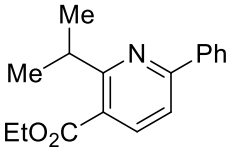
116f, 92%/84%[d]



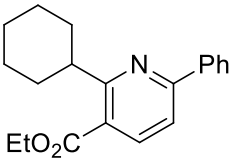
116g, 88%



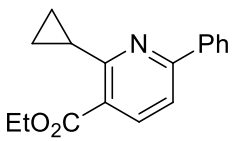
116h, 96%



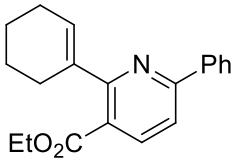
116i, 80%



116j, 96%



116k, 94%

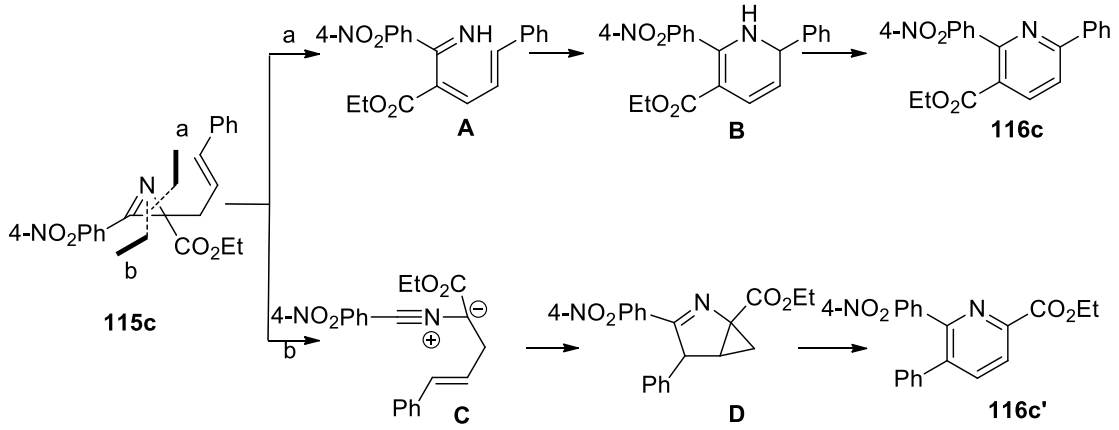


116l, 90%

[a]Unless otherwise noted, reactions were carried out using **115a - 115l** (0.2 mmol), DBU (0.6 mmol) in chlorobenzene (0.1 M, 2 mL) at 130 °C for 48 h under nitrogen atmosphere. [b]Isolated yields. [c]**116c'** = ethyl 6-(4-nitrophenyl)-5-phenylpicolinate (38%); **116d'** = ethyl 6-(furan-2-yl)-5-phenyl picolinate (32%); **116e'** = ethyl 5-phenyl-6-(thiophen-2-yl)picolinate (23%). [d]Reactions were carried out using **115** (1.0 mmol), DBU (3.0 mmol) in chlorobenzene (0.1 M, 10 mL) at 130 °C for 48 h under nitrogen atmosphere.

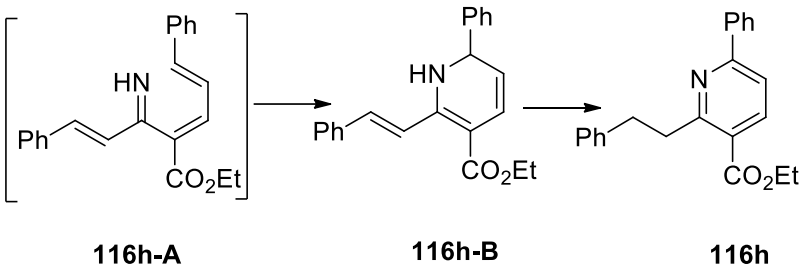
could be improved dramatically to 95% when DBU was selected as the base (Table 3-4, entry 6). In contrast, there is completely no conversion in the absence of DBU, which rules out the possibility of simple thermal promotion (Table 3-4, entry 7). Reduction of the amount of base or reaction temperature led to decreased yields (Table 3-4, entries 8-10). Interestingly, metal complexes commonly employed for the generation of nitrenes gave **116a** in poor yields (Table 3-4, entries 11-12).

Encouraged by the results, we examined the substrate scope of the reaction (Table 3-5). Overall, the reaction tolerated a broad range of substitutions to give multi-substituted pyridines in good to excellent yields. In order to investigate the electronic effect on the R^1 substituent, substrates with aryl groups bearing electron-donating and withdrawing groups were subjected to the reaction conditions. While those with phenyl and electron-rich aryl groups led to pyridines in excellent yiel-ds (**116a** and **116b**, respectively), a competing reaction was observed with a substrate bearing electron-deficient aryl group that provided a mixture of regioisomers **116c** and **116c'**. We proposed that the formation of the minor isomer **116c'** proceeds through 1,3-dipolar cycloaddition of the nitrile ylide intermediate arising from C–C bond cleavage of the azirine ring (Scheme 3.16).



Scheme 3.16 Proposed pathway for pyridines

Similarly, C–C bond cleavage was also observed with heteroaryl-substituted substrates **115d**and **115e**. On the other hand, the competing nitrile ylide pathway was completely suppressed with alkyl-substituted substrates providing single regioisomers in excellent yields (**116f-k**). Substituents with cyclopropyl and vinyl groups could be tolerated during the reaction (**116k** and **116l**); however, styryl substitution led to an unexpected product **116h** in which the double bond was saturated, presumably due to the isomerization of the alkene **116h-B** into the dihydropyridine (Scheme 3.17).

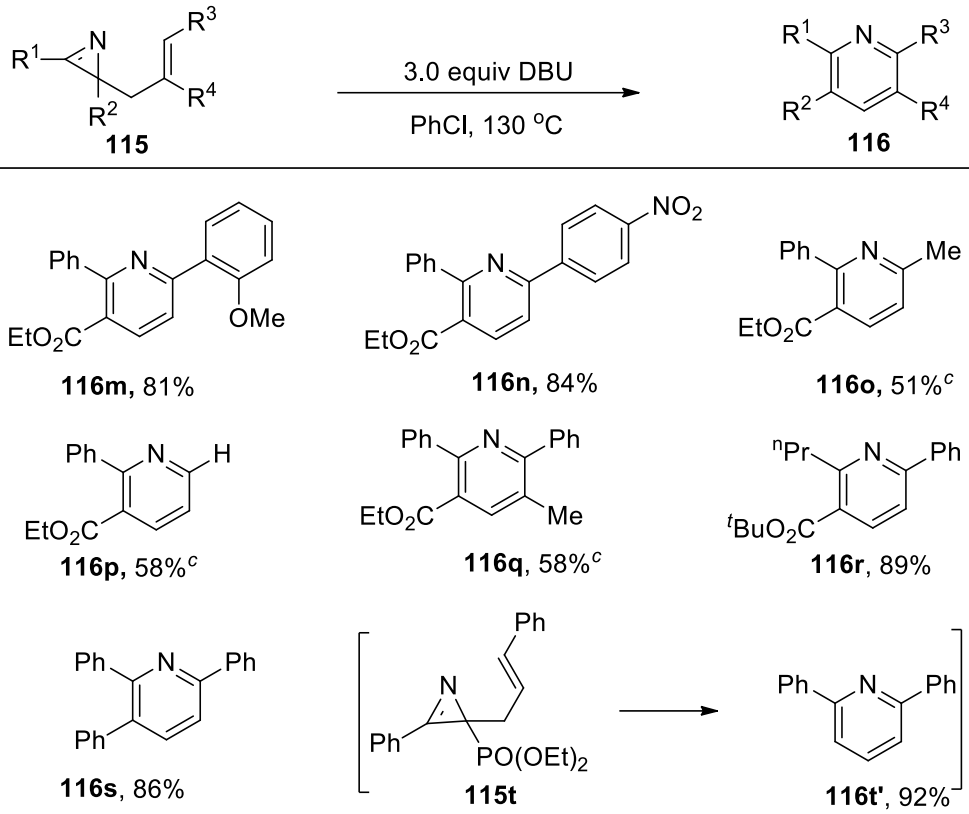


116h-A **116h-B** **116h**

Scheme 3.17 Probable pathway for saturated alkenyl moiety

Next, we turned our attention to examine the influence of the substituents at 2-position of 2*H*-azirines (Table 3-6). Different from the substitution at R^1, substrates with both electron-rich and deficient aryl groups at the terminal position of the allyl groups (R^3) underwent the reaction smoothly to provide single regioisomers (**116m** and **116n**). However, the competing nitrile ylide pathway was again observed when aryl group at R^3 was replaced with methyl group in a mixture of **116o** and **116o'**. Likewise, **116p** bearing unsubstituted allyl group provided a regioisomeric mixture. Interestingly, employing a methyl group at R^4 (**115q**) also promoted the nitrile ylide pathway to give a mixture of **116q** and **116q'**, even in the presence of an aryl substituent at R^3. Other than the ester group, we also studied other functional groups for R^2. Reaction of **115s** bearing a phenyl group proceeded smoothly to give **116s** in excellent yield. When phosphonate

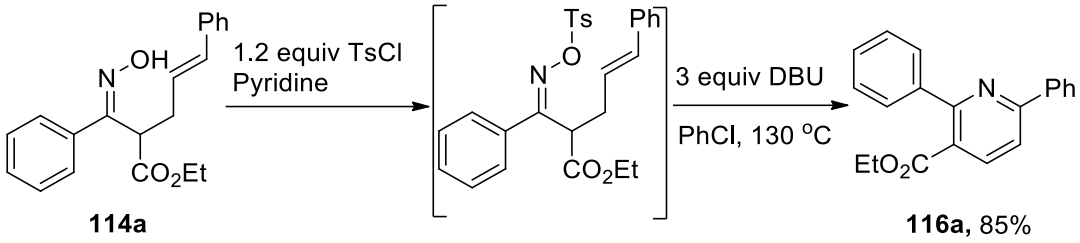
Table 3-6 Substrate scope for highly-substituted pyridines[a, b]



[a]Unless otherwise noted, reactions were carried out using **115m - 115t** (0.2 mmol), DBU (0.6 mmol) in chlorobenzene (0.1 M, 2 mL) at 130 °C for 48 h under an nitrogen atmosphere (1 atm). [b]Isolated yields. [c]**116o'** = ethyl 5-methyl-6-phenylpicolinate (37%); **116p'** = ethyl 6-phenylpicolinate (27%); **116q'** = ethyl 3-methyl-5,6-diphenylpicolinate (24%).

group was introduced as R^2, elimination is favored over oxidation to provide 3-unsubstituted pyridine **116t** in 92% yield.

Since the Neber reaction normally employs DBU as base in the preparation of 2*H*-azirine substrates **115**, we envisaged that a one-pot synthesis of pyridines from oximes *via in situ* formation of 2*H*-azirines could be achieved. To our delight, **116a** was obtained in 85% from oxime **114a** by using 3 equivalent of DBU (Scheme 3.18).



114a **116a,** 85%

Scheme 3.18 One-pot synthesis of pyridine

3.3.3 SUMMARY

In summary, we have developed a novel method for the synthesis of highly substituted pyridines through DBU-mediated ring opening reaction of 2-allyl-2*H*-azirines. 6π-Electrocyclization of the resulting 1-azatrienes provides pyridines in good yields.

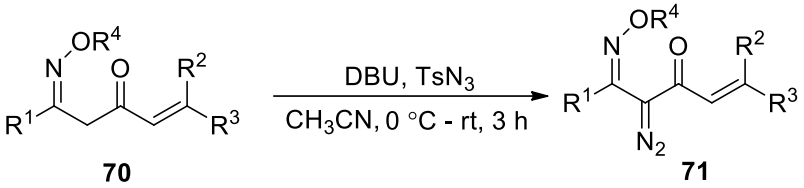
3.4 CONCLUSION

In this chapter, we have described two methodologies to synthesize multi-substituted pyridines from rhodium-catalyzed nitrene reaction and DBU-mediated ring opening of 2-allyl-2*H*-azirines. *α*-Diazo oxime ethers underwent cascade rearrangement to yield 2-vinyl-2*H*-azirines as key intermediates, which further underwent ring-opening in the presence of Rh(II) catalyst to achieve amination of sp^3 C-H bond of allylic carbon. This reaction tolerated a variety of functional groups and provided a new access to multi-substituted pyridines. On the other hand, we prepared the 2-allyl-2*H*-azirines according to the known Nebel reaction, and found that in the absence of metal catalysts, only commercially available base DBU could successfully promote small ring opening and the resulting 1-azatrienes formed pyridines in good yields *via* 6π-electrocyclization.

3.5 EXPERMENTAL SECTION

3.5.1 Rhodium(II)-catalyzed synthesis of pyridines through amination of sp^3 C–H bond

General procedure for *α*-diazo-*β*-keto oxime ethers:

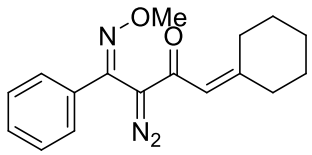


70 **71**

To a solution of *β*-oximino ketones **70** (0.5 mmol, 1.0 eq.) and 4-methylbenzenesulfonyl azide (0.55 mmol, 1.1 eq.) in CH_3CN (5 mL) was added DBU (0.55 mmol, 1.1 eq.) dropwise at 0 ℃. The resulting orange color solution was stirred at 0 ℃ for 3 h and slowly brought up to room temperature. Upon completion of reaction as indicated by TLC, the solvent was removed under reduced pressure, and the crude mixture was purified by flash chromatography using hexane : ethyl acetate = 19 : 1.

The data and procedure for **71a-f** and **71o-r** was involved in Chapter 2.

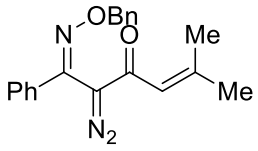
(*Z*)-1-Cyclohexylidene-3-diazo-4-(methoxyimino)-4-phenylbutan-2-one (71s):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.57 (m, 2H), 7.41 - 7.35 (m, 3H), 5.46 (s, 1H), 4.07 (s, 3H), 2.67 (t, J = 5.6 Hz, 2H), 1.84 (t, J = 7.5 Hz, 2H), 1.55 - 1.50 (m, 4H), 1.41 - 1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

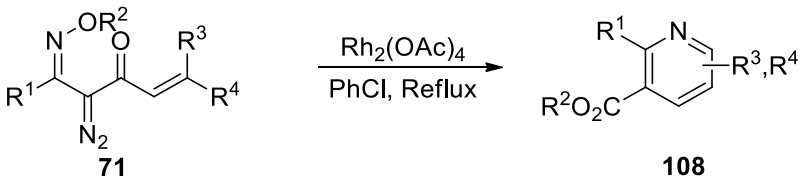
184.4, 160.6, 144.6, 134.2, 129.9, 128.6, 127.9, 119.0, 62.7, 37.8, 30.3, 28.5, 27.8, 26.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{20}N_3O_2$: 298.1556. Found: 298.1555.

(*Z*)-1-((Benzyloxy)imino)-2-diazo-5-methyl-1-phenylhex-4-en-3-one (71t):



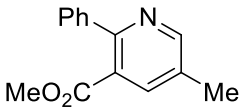
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.56 (m, 2H), 7.40 - 7.33 (m, 8H), 5.56 (s, 1H), 5.28 (s, 2H), 2.05 (d, J = 0.8 Hz, 3H), 1.59 (d, J = 2.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 154.2, 144.8, 136.9, 134.1, 130.0, 128.6, 128.5, 128.4, 128.2, 127.8, 121.3, 76.7, 27.4, 20.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{20}N_3O_2$: 334.1556. Found: 334.1551.

General procedure for pyridine-3-carboxylic ester:



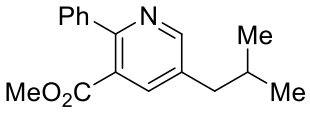
A solution of diazo compound **71** (0.2 mmol) and $Rh_2(OAc)_4$ (0.004 mmol, 2 mol%) in chlorobenzene (2.0 mL) was stirred at 130 ℃ until the starting material was fully consumed. The reaction mixture was concentrated under reduced pressure to give the crude material which was purified by flash chromatography using hexane : ethyl acetate = 9 : 1 to give desired product **108**.

Methyl 5-methyl-2-phenylnicotinate (108a):



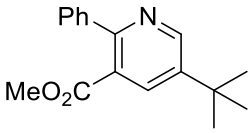
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 1.6 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.53 - 7.50 (m, 2H), 7.45 - 7.39 (m, 3H), 3.68 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 156.1, 151.8, 140.0, 138.2, 131.3, 128.5, 128.1, 126.4, 52.3, 17.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{14}NO_2$: 228.1025. Found: 228.1027.

Methyl 5-isobutyl-2-phenylnicotinate (108b):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 2.4 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.54 - 7.52 (m, 2H), 7.45 - 7.40 (m, 3H), 3.70 (s, 3H), 2.56 (d, J = 6.8 Hz, 2H), 1.97 - 1.91 (m, 1H), 0.96 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 156.4, 152.0, 140.0, 138.2, 135.0, 128.5, 128.1, 126.4, 52.3, 41.7, 30.0, 22.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{20}NO_2$: 270.1494. Found: 270.1498.

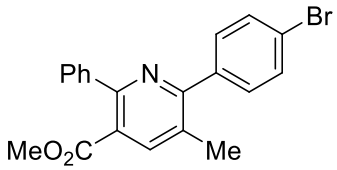
Methyl 5-tert-butyl-2-phenylnicotinate (108c):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 2.4

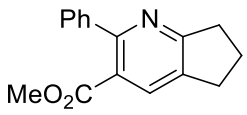
Hz, 1H), 8.06 (d, *J* = 2.4 Hz, 1H), 7.54 - 7.52 (m, 2H), 7.43 - 7.41 (m, 3H), 3.69 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.1, 155.9, 149.2, 144.2, 140.0, 134.7, 128.5, 128.1, 126.2, 52.3, 33.6, 30.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{20}NO_2$: 270.1494. Found: 270.1492.

Methyl 6-(4-bromophenyl)-5-methyl-2-phenylnicotinate (108d):



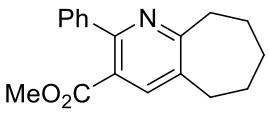
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 77%. 1H NMR (400 MHz, CDCl3) δ 8.00 (d, *J* = 0.4 Hz, 1H), 7.60 - 7.57 (m, 4H), 7.56 - 7.49 (m, 2H), 7.42 - 7.40 (m, 3H), 3.71 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) *δ* 168.6, 158.9, 156.1, 140.6, 139.9, 138.7, 131.4, 130.9, 128.9, 128.7, 128.6, 128.1, 125.3, 122.9, 52.3, 19.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{17}NO_2Br$: 382.0443. Found: 382.0447.

Methyl 2-phenyl-6,7-dihydro-5*H*-cyclopenta[b]pyridine-3-carboxylate (108e):



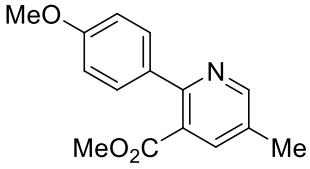
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.91 (s, 1H), 7.50 - 7.41 (m, 2H), 7.39 - 7.38 (m, 3H), 3.65 (s, 3H), 3.10 (t, *J* = 7.6 Hz, 2H), 3.02 (t, *J* = 7.6 Hz, 2H), 2.22 - 2.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.2, 168.5, 157.7, 140.7, 135.3, 133.6, 128.5, 128.2, 128.1, 124.6, 52.2, 34.6, 30.3, 23.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{16}NO_2$: 254.1181. Found: 254.1188.

Methyl 2-phenyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine-3-carboxylate (108f):



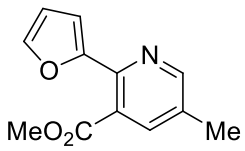
The title compound was prepared according to the general procedure. The product was obtained as colorles oil. Yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.53 - 7.50 (m, 2H), 7.43 - 7.35 (m, 3H), 3.67 (s, 3H), 3.13 (t, J = 5.6 Hz, 2H), 2.86 (dd, J_1 = 6.8 Hz, J_2 = 4.0 Hz, 2H), 1.91 - 1.89 (m, 2H), 1.74 - 1.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 165.8, 155.6, 140.4, 138.1, 136.3, 128.6, 128.3, 128.1, 124.0, 52.1, 39.6, 34.7, 32.4, 27.9, 26.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{20}NO_2$: 282.1494. Found: 282.1496.

Methyl 2-(4-methoxyphenyl)-5-methylnicotinate (108o):



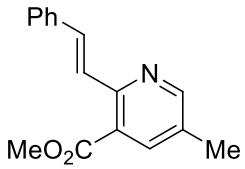
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 1.2 Hz, 1H), 7.86 (d, J = 1.2 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.72 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 160.0, 155.6, 151.7, 138.2, 132.4, 130.8, 129.9, 126.1, 113.6, 55.3, 52.3, 17.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{16}NO_3$: 258.1130. Found: 258.1128.

Methyl 2-(furan-2-yl)-5-methylnicotinate (108p):



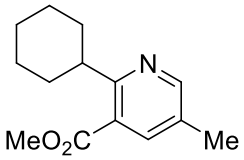
The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 96 - 97 ℃. Yield: 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 2.0 Hz, 1H), 7.70 (d, J = 1.2 Hz, 1H), 7.51 (d, J = 0.8 Hz, 1H), 6.98 (d, J = 3.2 Hz, 1H), 6.52 (dd, J_1 = 3.6 Hz, J_2 = 2.0 Hz, 1H), 3.90 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 152.3, 151.4, 144.3, 143.6, 137.1, 131.4, 125.2, 111.9, 110.5, 52.6, 18.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{12}NO_3$: 218.0817. Found: 218.0820.

(*E*)-Methyl 5-methyl-2-styrylnicotinate (108q):



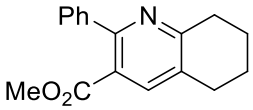
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 2.0 Hz, 1H), 8.10 (d, J = 15.6 Hz, 1H), 8.01 (d, J = 0.8 Hz, 1H), 7.87 (d, J = 15.6 Hz, 1H), 7.64 - 7.62 (m, 2H), 7.39 - 7.35 (m, 2H), 7.31 - 7.26 (m, 1H), 3.96 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 152.8, 138.9, 137.0, 135.0, 131.2, 128.6, 128.4, 127.5, 125.0, 123.5, 52.4, 18.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{16}NO_2$: 254.1181. Found: 254.1179.

Methyl 2-cyclohexyl-5-methylnicotinate (108r):



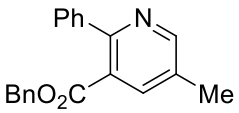
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 1.6 Hz, 1H), 7.88 (d, J = 2.0 Hz, 1H), 3.94 (s, 3H), 3.47 - 3.40 (m, 1H), 2.35 (s, 3H), 1.88 - 1.82 (m, 4H), 1.74 - 1.64 (m, 3H), 1.48 - 1.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 163.7, 152.2, 138.3, 129.8, 124.7, 52.3, 42.3, 32.5, 26.7, 26.1, 17.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{20}NO_2$: 234.1494. Found: 234.1490.

Methyl 2-phenyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (108s):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.50 - 7.40 (m, 2H), 7.39 - 7.37 (m, 3H), 3.66 (s, 3H), 3.02 - 2.99 (m, 2H), 2.86 - 2.83 (m, 2H), 1.95 - 1.91 (m, 2H), 1.88 - 1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 160.1, 156.2, 140.5, 138.5, 130.5, 128.5, 128.2, 128.1, 124.0, 52.1, 32.9, 28.3, 22.9, 22.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{18}NO_2$: 268.1338. Found: 268.1336.

Benzyl 5-methyl-2-phenylnicotinate (108t):

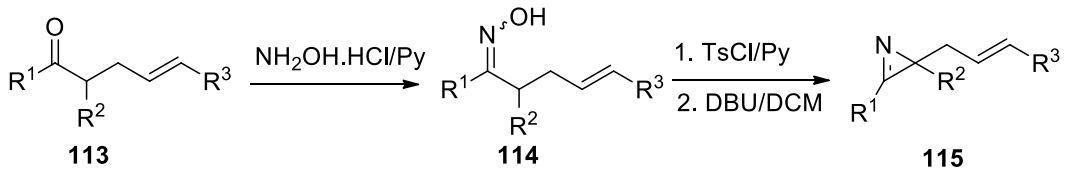


The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 2.0 Hz, 1H), 7.91 (d, J = 1.6 Hz, 1H), 7.50 - 7.48 (m, 2H), 7.39 - 7.36 (m, 3H), 7.28 - 7.25 (m,

3H), 7.03 - 7.00 (m, 2H), 5.12 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 156.2, 151.8, 140.1, 138.2, 134.9, 131.4, 128.5, 128.4, 128.3, 128.3, 128.3, 126.5, 67.4, 17.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{18}NO_2$: 304.1338. Found: 304.1334.

3.5.2 Transition-metal-free synthesis of pyridines through amination of *sp*^{2} C–H bond

General procedure for allyl-*2H*-azirines:



113 **114** **115**

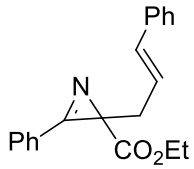
To a solution of $NH_2OH·HCl$ (2eq.) in pyridine (12 eq.) was added β-allyl ketone **113** (1.0 eq.) dropwise. The solution was stirred for 1-20 h, and the solvent was removed under reduced pressure. The residue was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give ketoxime, which was used for the next step without purification.

To the ketoxime **114** was added TsCl (1.5 eq.) and pyridine (12 eq.). The solution was stirred for 20 h and quenched with saturated aqueous NH_4Cl. The mixture was extracted three times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography using hexane : ethyl acetate = 4 : 1.

To a solution of ketoximetosylate in DCM was added DBU (1.5 eq.) dropwise, and the mixture was stirred at room temperature for 3h. Upon completion of the reaction as indicated by TLC, the reaction mixture was quenched with H_2O, and the

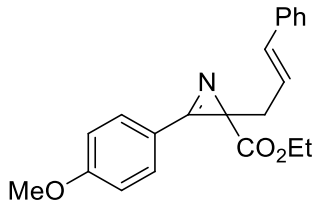
layers were separated. The aqueous layer was extracted with ethyl acetate, and the combined layers were washed with water, brine and dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography using hexane : ethyl acetate = 6 : 1.

Ethyl 2-cinnamyl-3-phenyl-2*H*-azirine-2-carboxylate (115a):



The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield: 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 - 7.83 (m, 2H), 7.61 - 7.59 (m, 1H), 7.58 - 7.55 (m, 2H), 7.26 - 7.25 (m, 4H), 7.23 - 7.17 (m, 1H), 6.43 (d, J = 15.6 Hz, 1H), 6.20 - 6.13 (m, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.13 - 3.07 (m, 1H), 2.83 - 2.77 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 163.0, 137.3, 133.6, 132.9, 130.2, 129.3, 128.4, 127.1, 126.1, 125.3, 122.8, 61.4, 39.4, 35.1, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{20}NO_2$: 306.1494. Found: 306.1495.

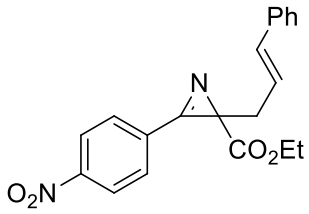
Ethyl 2-cinnamyl-3-(4-methoxyphenyl)-2*H*-azirine-2-carboxylate (115b):



The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 - 7.77 (m, 2H), 7.27 - 7.17 (m, 5H), 7.04 - 7.01 (m, 2H), 6.42 (d, J = 16.0 Hz, 1H), 6.21 - 6.14 (m, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 3.11 - 3.05 (m, 1H), 2.80 - 2.74 (m, 1H), 1.21 (t,

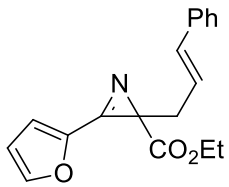
J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 163.8, 161.6, 137.4, 132.8, 132.3, 128.4, 127.1, 126.1, 125.6, 115.0, 114.8, 61.3, 55.6, 39.0, 35.3, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{22}NO_3$: 336.1600. Found: 336.1597.

Ethyl 2-cinnamyl-3-(4-nitrophenyl)-2*H*-azirine-2-carboxylate (115c):



The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 - 8.37 (m, 2H), 8.05 - 8.01 (m, 2H), 7.29 - 7.19 (m, 5H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.14 - 6.06 (m, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.23 - 3.18 (m, 1H), 2.82 - 2.76 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 163.2, 150.6, 136.9, 133.6, 130.9, 128.5, 127.5, 126.1, 124.5, 61.9, 40.8, 34.8, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{19}N_2O_4$: 351.1345. Found: 351.1347.

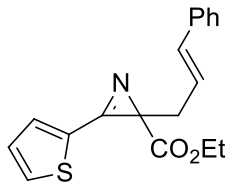
Ethyl 2-cinnamyl-3-(furan-2-yl)-2*H*-azirine-2-carboxylate (115d):



The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield: 56%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.79 (d, *J* = 1.2 Hz, 1H), 7.28 - 7.25 (m, 4H), 7.21 - 7.17 (m, 2H), 6.65 - 6.63 (m, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.17 - 6.12 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.14 - 3.08 (m, 1H), 2.75 - 2.69 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.7, 153.1, 148.9, 139.8, 137.3, 133.0, 128.4, 127.2, 126.1, 124.9, 121.0, 112.9, 61.6, 39.0, 35.0, 14.2;

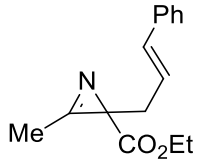
HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{18}NO_3$: 296.1287. Found: 296.1286.

Ethyl 2-cinnamyl-3-(thiophen-2-yl)-2*H*-azirine-2-carboxylate (115e):



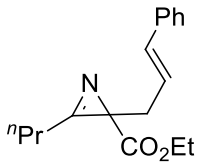
The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield: 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 - 7.79 (d, J = 1.2 Hz, 1H), 7.64 - 7.63 (m, 1H), 7.28 - 7.18 (m, 6H), 6.44 (d, J = 16.0 Hz, 1H), 6.22 - 6.14 (m, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.16 - 3.10 (m, 1H), 2.76 - 2.70 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 156.3, 137.2, 135.0, 134.7, 133.0, 128.4, 128.3, 127.1, 126.0, 125.1, 125.0, 61.4, 40.0, 35.1, 14.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{18}NO_2S$: 312.1058. Found: 312.1057.

Ethyl 2-cinnamyl-3-methyl-2*H*-azirine-2-carboxylate (115f):



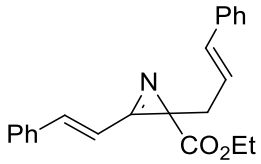
The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 - 7.27 (m, 4H), 7.22 - 7.19 (m, 1H), 6.39 (d, J = 16.0 Hz, 1H), 6.09 - 6.01 (m, 1H), 4.19 - 4.13 (m, 2H), 2.98 - 2.92 (m, 1H), 2.73 - 2.67 (m, 1H), 2.46 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 163.6, 137.1, 132.7, 128.5, 127.2, 126.1, 125.0, 61.3, 37.7, 34.4, 14.2, 12.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{18}NO_2$: 244.1338. Found: 244.1340.

Ethyl 2-cinnamyl-3-propyl-2*H*-azirine-2-carboxylate (115g):



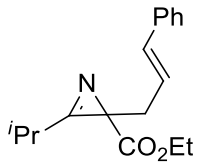
The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 - 7.26 (m, 4H), 7.22 - 7.20 (m, 1H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.10 - 6.02 (m, 1H), 4.20 - 4.10 (m, 2H), 2.95 - 2.89 (m, 1H), 2.76 - 2.69 (m, 3H), 1.79 - 1.73 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 166.4, 137.2, 132.7, 128.4, 127.2, 126.1, 125.1, 61.2, 37.8, 34.7, 28.8, 18.0, 14.2, 13.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{22}NO_2$: 272.1651. Found: 272.1651.

Ethyl 2-cinnamyl-3-((E)-styryl)-2*H*-azirine-2-carboxylate (115h):



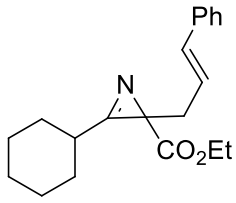
The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield: 71%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.50 - 7.48 (m, 2H), 7.41 - 7.38 (m, 3H), 7.32 - 7.28 (m, 5H), 7.25 - 7.24 (m, 1H), 7.21 - 7.20 (m, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.24 - 6.16 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.09 - 3.04 (m, 1H), 2.79 - 2.74 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.3, 161.5, 148.6, 137.3, 134.0, 132.9, 131.0, 129.0, 128.4, 128.3, 127.2, 126.1, 125.5, 109.9, 61.4, 38.5, 35.0, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{22}H_{22}NO_2$: 332.1651. Found: 332.1648.

Ethyl 2-cinnamyl-3-isopropyl-2*H*-azirine-2-carboxylate (115i):



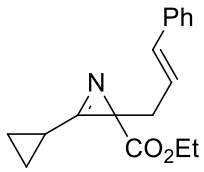
The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 - 7.26 (m, 4H), 7.22 - 7.20 (m, 1H), 6.40 (d, *J* = 15.6 Hz, 1H), 6.12 - 6.04 (m, 1H), 4.22 - 4.09 (m, 2H), 3.07 - 3.02 (m, 1H), 2.94 - 2.88 (m, 1H), 2.76 - 2.70 (m, 1H), 1.31 - 1.27 (m, 6H), 1.24 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 166.4, 137.2, 132.7, 128.4, 127.2, 126.1, 125.1, 61.2, 37.8, 34.7, 28.8, 18.0, 14.2, 13.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{22}NO_2$: 272.1651. Found: 272.1645.

Ethyl 2-cinnamyl-3-cyclohexyl-2*H*-azirine-2-carboxylate (115j):



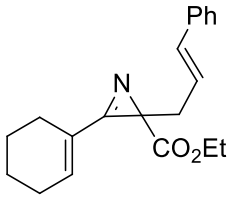
The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield: 71%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.33 - 7.26 (m, 4H), 7.22 - 7.18 (m, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 6.12 - 6.05 (m, 1H), 4.21 - 4.09 (m, 2H), 2.88 - 2.82 (m, 2H), 2.77 - 2.71 (m, 1H), 1.98 - 1.93 (m, 2H), 1.77 - 1.75 (m, 2H), 1.62 - 1.57 (m, 1H), 1.54 - 1.51 (m, 2H), 1.41 - 1.32 (m, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.9, 168.9, 137.3, 132.6, 128.4, 127.2, 126.1, 125.4, 61.2, 38.1, 36.2, 35.0, 28.2, 28.2, 25.6, 24.9, 24.9, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{26}NO_2$: 312.1964. Found: 312.1969.

Ethyl 2-cinnamyl-3-cyclopropyl-2*H*-azirine-2-carboxylate (115k):



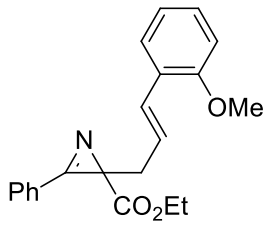
The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield: 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 - 7.26 (m, 4H), 7.22 - 7.20 (m, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 6.12 - 6.06 (m, 1H), 4.22 - 4.09 (m, 2H), 2.88 - 2.82 (m, 1H), 2.71 - 2.65 (m, 1H), 2.17 - 2.13 (m, 1H), 1.26 - 1.09 (m, 5H), 1.09 - 1.04 (m, 1H), 0.99 - 0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 168.2, 137.2, 132.6, 128.5, 127.2, 126.1, 125.3, 61.2, 38.0, 34.8, 14.2, 8.4, 8.1, 7.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{20}NO_2$: 270.1494. Found: 270.1495.

Ethyl 2-cinnamyl-3-(cyclohex-1-en-1-yl)-2*H*-azirine-2-carboxylate (115l):



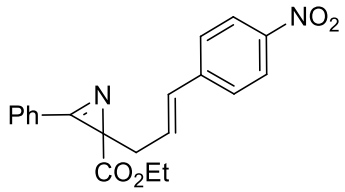
The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield: 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.26 (m, 4H), 7.21 - 7.19 (m, 1H), 6.56 - 6.55 (m, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 6.16 - 6.10 (m, 1H), 4.19 - 4.14 (m, 2H), 2.91 - 2.87 (m, 1H), 2.75 - 2.69 (m, 1H), 2.51 - 2.45 (m, 2H), 2.28 - 2.27 (m, 2H), 1.77 - 1.67 (m, 4H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 162.8, 145.3, 137.5, 132.6, 128.4, 127.1, 126.1, 125.7, 124.3, 61.2, 38.9, 35.0, 26.2, 24.2, 21.6, 21.5, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{24}NO_2$: 310.1807. Found: 310.1805.

(*E*)-Ethyl 2-(3-(2-methoxyphenyl)allyl)-3-phenyl-2*H*-azirine-2-carboxylate (115m):



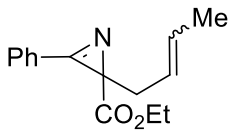
The title compound was prepared according to General procedure. The product was obtained as yellow oil. Yield: 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 - 7.86 (m, 2H), 7.60 - 7.55 (m, 1H), 7.54 - 7.51 (m, 2H), 7.29 - 7.26 (m, 1H), 7.17 - 7.15 (m, 1H), 6.87 - 6.80 (m, 2H), 6.74 (d, *J* = 16.0 Hz, 1H), 6.16 - 6.12 (m, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 3.21 - 3.16 (m, 1H), 2.80 - 2.74 (m, 1H), 1.22 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 163.2, 156.5, 133.4, 130.3, 129.2, 128.2, 127.9, 126.8, 126.5, 126.1, 123.0, 120.6, 110.8, 61.4, 55.4, 39.7, 35.5, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{22}NO_3$: 336.1600. Found: 336.1601.

(*E*)-Ethyl 2-(3-(4-nitrophenyl)allyl)-3-phenyl-2*H*-azirine-2-carboxylate (115n):



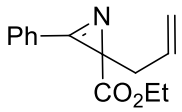
The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield: 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 - 8.11 (m, 2H), 7.86 - 7.83 (m, 2H), 7.66 - 7.62 (m, 1H), 7.58 - 7.55 (m, 2H), 7.40 - 7.38 (m, 2H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.43 - 6.36 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.99 - 2.97 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 162.8, 146.8, 143.7, 133.9, 131.1, 130.6, 130.2, 129.4, 126.6, 123.9, 122.5, 61.6, 38.9, 35.2, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{19}N_2O_4$: 351.1345. Found: 351.1350.

Ethyl 2-(but-2-en-1-yl)-3-phenyl-2*H*-azirine-2-carboxylate (115o):



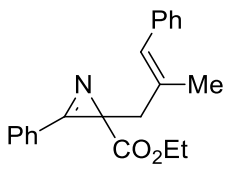
The title compound was prepared according to general procedure. The product was obtained as yellow oil in a *cis* : *trans* ratio of 24 : 76. Yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 - 7.83 (m, 2H), 7.64 - 7.54 (m, 3H), 5.52 - 5.44 (m, 1H), 5.40 - 5.39 (m, 1H), 4.18 - 4.12 (m, 2H), 3.00 - 2.98 & 2.90 - 2.84 (m, 1H), 2.72 - 2.64 & 2.63 - 2.59 (m, 1H), 1.59 - 1.54 (m, 3H), 1.22 - 1.18 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 163.1, 133.4, 133.4, 130.1, 130.1, 129.2, 128.6, 126.8, 126.0, 125.1, 123.0, 61.3, 61.3, 39.6, 34.4, 28.5, 17.9, 14.1, 12.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{18}NO_2$: 244.1338. Found: 244.1341.

Ethyl 2-allyl-3-phenyl-2*H*-azirine-2-carboxylate (115p):



The title compound was prepared according to general procedure. The product was obtained as colorless oil. Yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 - 7.84 (m, 2H), 7.62 - 7.54 (m, 3H), 5.79 - 5.70 (m, 1H), 5.12 - 5.01 (m, 2H), 4.16 (q, J = 7.2 Hz, 2H), 2.99 - 2.93 (m, 1H), 2.72 - 2.66 (m, 1H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 163.0, 133.6, 133.5, 130.1, 129.2, 122.8, 117.9, 61.3, 39.1, 35.7, 14.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{16}NO_2$: 230.1181. Found: 230.1176.

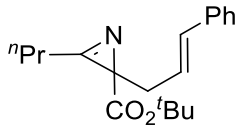
(*E*)-Ethyl 2-(2-methyl-3-phenylallyl)-3-phenyl-2*H*-azirine-2-carboxylate (115q):



The title compound was prepared according to general procedure. The product was

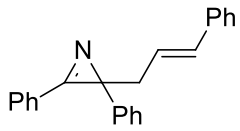
obtained as yellow oil. Yield: 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 - 7.84 (m, 2H), 7.60 - 7.51 (m, 3H), 7.26 - 7.21 (m, 2H), 7.15 - 7.12 (m, 1H), 7.01 - 6.99 (m, 2H), 6.26 (s, 1H), 4.21 - 4.16 (m, 2H), 3.11 - 3.07 (m, 1H), 2.88 - 2.84 (m, 1H), 1.81 (d, J = 1.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 162.0, 138.0, 134.5, 133.4, 130.0, 129.2, 128.7, 128.6, 127.9, 126.0, 123.0, 61.4, 41.1, 39.5, 41.1, 39.5, 18.9, 14.2 ; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{22}NO_2$: 320.1651. Found: 320.1642.

tert-Butyl 2-cinnamyl-3-propyl-2*H*-azirine-2-carboxylate (115r):



The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 - 7.18 (m, 5H), 6.38 (d, J = 15.6 Hz, 1H), 6.10 - 6.02 (m, 1H), 2.91 - 2.85 (m, 2H), 2.75 - 2.70 (m, 2H), 2.69 - 2.63 (m, 1H), 1.78 - 1.64 (m, 2H), 1.44 (s, 9H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 166.6, 137.3, 132.4, 128.5, 127.1, 126.1, 125.6, 81.3, 38.5, 34.9, 28.8, 28.0, 18.0, 13.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{26}NO_2$: 300.1964. Found: 300.1958.

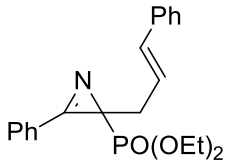
2-Cinnamyl-2,3-diphenyl-2*H*-azirine (115s):



The title compound was prepared according to general procedure. The product was obtained as yellow oil. Yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 - 7.87 (m, 2H), 7.57 - 7.52 (m, 3H), 7.30 - 7.17 (m, 10H), 6.50 (d, J = 15.6 Hz, 1H), 6.26 - 6.18 (m,

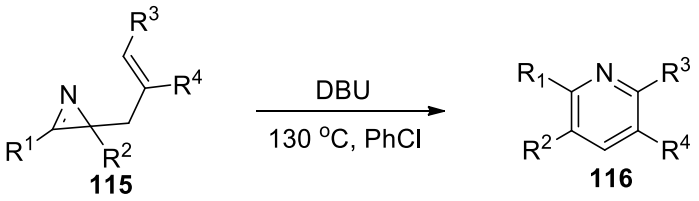
1H), 3.33 - 3.27 (m, 1H), 3.09 - 3.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 142.8, 137.4, 133.0, 132.6, 129.6, 129.2, 128.4, 128.3, 127.1, 126.7, 126.4, 126.3, 126.1, 124.6, 41.4, 38.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{23}H_{20}N$: 310.1596. Found: 310.1593.

(*E*)-Ethyl 2-(2-methyl-3-phenylallyl)-3-phenyl-2*H*-azirine-2-carboxylate (115t):



The title compound was prepared according to general procedure. The product was obtained as colorless oil. Yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 - 7.89 (m, 2H), 7.60 - 7.52 (m, 3H), 7.26 - 7.20 (m, 5H), 6.11 - 6.06 (m, 1H), 6.38 (d, J = 15.6 Hz, 1H), 4.20 - 4.08 (m, 4H), 3.02 - 2.94 (m, 1H), 2.80 - 2.72 (m, 1H), 1.34 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 137.2, 133.7, 133.2, 130.2, 129.3, 128.4, 127.2, 126.1, 124.7, 124.6, 123.4, 62.5 (J = 7.0 Hz), 62.3 (J = 7.0 Hz), 35.7 (J = 6.0 Hz), 35.4, 33.7, 16.5 (J = 7.0 Hz), 16.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{25}NO_3P$: 370.1572. Found: 370.1577.

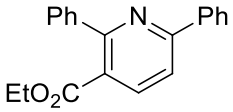
General procedure for pyridines:



A solution of azirine compound (0.2 mmol) and DBU (0.6 mmol, 3.0 eq.) in chlorobenzene (2.0 mL) was stirred at 130 ℃ until the starting material was fully

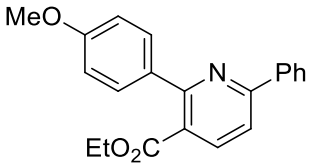
consumed (18 - 48 h). The reaction mixture was concentrated under reduced pressure to give the crude material which was purified by flash chromatography using hexane : ethyl acetate = 9 : 1 to give desired product.

Ethyl 2,6-diphenylnicotinate (116a):



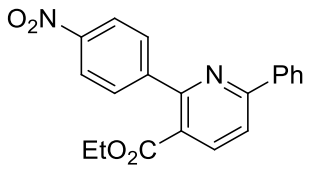
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.0 Hz, 1H), 8.14 - 8.11 (m, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.65 - 7.62 (m, 2H), 7.51 - 7.42 (m, 6H), 4.17 (q, J = 7.2 Hz, 2H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 158.4, 140.5, 138.3, 129.7, 128.8, 128.8, 128.6, 128.0, 127.3, 125.3, 117.8, 61.4, 13.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{18}NO_2$: 304.1337. Found: 304.1338.

Ethyl 2-(4-methoxyphenyl)-6-phenylnicotinate (116b):



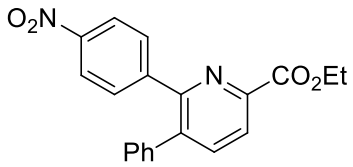
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 - 8.11 (m, 3H), 7.72 (d, J = 8.0 Hz, 1H), 7.64 - 7.61 (m, 2H), 7.48 - 7.44 (m, 3H), 6.99 - 6.97 (m, 2H), 4.22 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 1.50 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 160.2, 158.3, 158.1, 138.9, 138.4, 132.9, 130.3, 129.6, 128.7, 127.3, 124.9, 117.3, 113.5, 61.4, 55.3, 13.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{20}NO_3$: 334.1443. Found: 334.1440.

Ethyl 2-(4-nitrophenyl)-6-phenylnicotinate (116c):



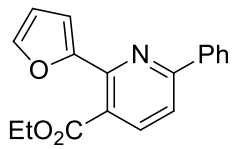
The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 96 - 97 ℃. Yield: 45%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 -8.30 (m, 3H), 8.12 - 8.10 (m, 2H), 7.86 (d, J = 8.0 Hz, 1H), 7.79 - 7.77 (m, 2H), 7.52 - 7.48 (m, 3H), 4.22 (q, J = 6.8 Hz, 2H), 1.50 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 159.0, 157.0, 147.8, 147.0, 139.5, 137.7, 130.2, 129.9, 128.9, 127.3, 125.0, 123.2, 119.0, 61.7, 13.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{17}N_2O_4$: 349.1188. Found: 349.1178.

Ethyl 6-(4-nitrophenyl)-5-phenylpicolinate (116c'):



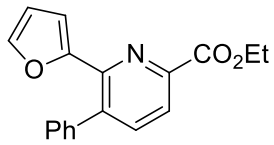
The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 100 - 101 ℃. Yield: 38%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.0 Hz, 1H), 8.12 - 8.09 (m, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.60 - 7.57 (m, 2H), 7.36 - 7.31 (m, 3H), 7.18 - 7.16 (m, 2H), 4.52 (q, J = 7.2 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 154.9, 147.5, 147.3, 145.8, 139.7, 139.7, 138.1, 131.1, 129.3, 128.9, 128.4, 124.4, 123.2, 62.1, 14.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{17}N_2O_4$: 349.1188. Found: 349.1195.

Ethyl 2-(furan-2-yl)-6-phenylnicotinate (116d):



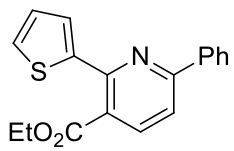
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 - 8.08 (m, 2H), 7.97 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.54 - 7.45 (m, 4H), 7.19 - 7.18 (m, 1H), 6.57 - 6.56 (m, 1H), 4.39 (q, J = 6.8 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 158.1, 153.1, 146.7, 143.6, 138.2, 137.9, 129.7, 128.8, 127.2, 124.1, 117.8, 111.9, 111.2, 61.6, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{16}NO_3$: 294.1130. Found: 294.1136.

Ethyl 2-(furan-2-yl)-6-phenylnicotinate (116d'):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 32%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.44 - 7.39 (m, 4H), 7.31 - 7.29 (m, 2H), 6.30 - 6.28 (m, 1H), 6.12 - 6.11 (m, 1H), 4.51 (q, J = 7.2 Hz, 2H), 1.48 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 151.5, 147.2, 143.5, 139.6, 139.0, 137.8, 132.7, 128.7, 128.6, 128.2, 122.7, 113.0, 111.3, 62.1, 14.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{16}NO_3$: 294.1130. Found: 294.1125.

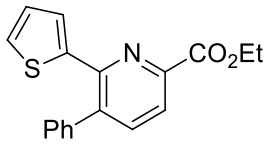
Ethyl 6-phenyl-2-(thiophen-2-yl)nicotinate (116e):



The title compound was prepared according to the general procedure. The product was

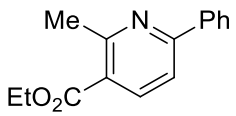
obtained as colorless oil. Yield: 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 - 8.12 (m, 2H), 8.01 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.52 - 7.45 (m, 5H), 7.10 - 7.08 (m, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 157.9, 150.5, 143.5, 138.6, 137.9, 129.8, 128.8, 128.8, 128.5, 127.8, 127.5, 127.2, 124.0, 117.3, 61.7, 14.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{16}NO_2S$: 310.0902. Found: 310.0900.

Ethyl 5-phenyl-6-(thiophen-2-yl)picolinate (116e'):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 23%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.45 - 7.43 (m, 3H), 7.34 - 7.32 (m, 2H), 7.30 - 7.29 (m, 1H), 6.83 - 6.80 (m, 1H), 6.70 - 6.68 (m, 1H), 4.49 (q, J = 7.2 Hz, 2H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 150.6, 146.8, 143.4, 139.7, 139.2, 137.7, 129.0, 128.8, 128.4, 128.2, 127.4, 122.4, 61.9, 14.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{16}NO_2S$: 310.0902. Found: 310.0902.

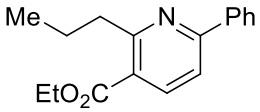
Ethyl 2-methyl-6-phenylnicotinate (116f):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.4 Hz, 1H), 8.07 - 8.05 (m, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.51 - 7.42 (m, 3H), 4.40 (q, J = 7.2 Hz, 2H), 2.92 (s, 3H), 1.42 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7,

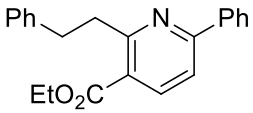
159.9, 159.1, 139.3, 138.5, 129.6, 128.8, 127.3, 123.7, 117.3, 61.1, 25.3, 14.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{16}NO_2$: 242.1181. Found: 242.1180.

Ethyl 6-phenyl-2-propylnicotinate (116g):



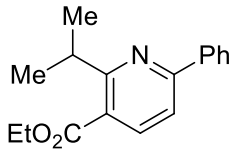
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.4 Hz, 1H), 8.09 - 8.06 (m, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.50 - 7.44 (m, 3H), 4.40 (q, J = 7.2 Hz, 2H), 3.24 - 3.20 (m, 2H), 1.87 - 1.82 (m, 2H), 1.42 (t, J = 7.2 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 163.3, 158.8, 139.3, 138.7, 129.6, 128.8, 127.3, 123.7, 117.1, 61.1, 39.1, 23.0, 14.3, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{20}NO_2$: 270.1494. Found: 270.1493.

Ethyl 2-phenethyl-6-phenylnicotinate (116h):



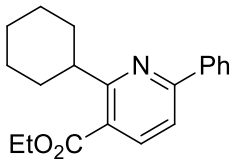
The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.4 Hz, 1H), 8.08 - 8.06 (m, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.51 - 7.45 (m, 3H), 7.32 - 7.27 (m, 4H), 7.20 - 7.19 (m, 1H), 4.38 (q, J = 7.2 Hz, 2H), 3.60 - 3.55 (m, 2H), 3.17 - 3.13 (m, 2H), 1.40 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 162.3, 158.9, 142.2, 139.4, 138.5, 129.7, 128.8, 128.6, 128.3, 127.3, 125.7, 123.7, 117.3, 61.2, 38.8, 35.7, 14.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{22}H_{22}NO_2$: 332.1651. Found: 332.1650.

Ethyl 2-isopropyl-6-phenylnicotinate (116i):



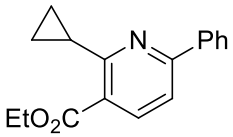
The title compound was prepared according to the general procedure. The product was obtained as colorles oil. Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 - 8.13 (m, 3H), 7.61 (d, J = 8.0 Hz, 1H), 7.51 - 7.43 (m, 3H), 4.39 (q, J = 7.2 Hz, 2H), 3.95 - 3.92 (m, 1H), 1.42 (t, J = 7.2 Hz, 3H), 1.37 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 167.2, 158.3, 138.9, 138.7, 129.6, 128.7, 127.2, 123.3, 116.5, 61.2, 32.6, 22.4, 14.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{20}NO_2$: 270.1494. Found: 270.1494.

Ethyl 2-cyclohexyl-6-phenylnicotinate (116j):



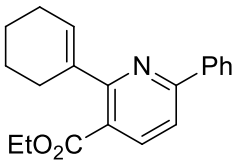
The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 77 - 78 ℃. Yield: 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 - 8.12 (m, 3H), 7.60 (d, J = 8.0 Hz, 1H), 7.51 - 7.43 (m, 3H), 4.40 (q, J = 7.2 Hz, 2H), 3.59 - 3.54 (m, 1H), 1.92 - 1.78 (m, 7H), 1.47 - 1.41 (m, 5H), 1.33 - 1.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.4, 158.2, 139.0, 138.8, 129.5, 128.7, 127.2, 123.4, 116.4, 61.2, 43.1, 32.5, 26.7, 26.2, 14.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{24}NO_2$: 310.1807. Found: 310.1803.

Ethyl 2-cyclopropyl-6-phenylnicotinate (116k):



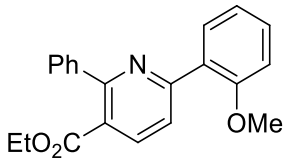
The title compound was prepared according to the general procedure. The product was obtained as colorless solid, mp: 79 - 80 ℃. Yield: 94%. 1H NMR (400 MHz, CDCl3) δ 8.17 (d, *J* = 8.0 Hz, 1H), 8.06 - 8.03 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.48 - 7.42 (m, 3H), 4.41 (q, *J* = 7.2 Hz, 2H), 3.18 - 3.12 (m, 1H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.34 - 1.28 (m, 2H), 1.07 - 1.05 (m, 2H); ^{13}C NMR (100 MHz, CDCl3) *δ* 167.2, 163.4, 158.4, 138.9, 138.5, 129.6, 128.7, 127.1, 123.5, 115.6, 61.1, 14.4, 14.3, 11.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{18}NO_2$: 268.1338. Found: 268.1334.

Ethyl 2-(cyclohex-1-en-1-yl)-6-phenylnicotinate (116l):



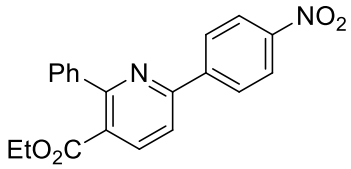
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.07 - 8.04 (m, 2H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.49 - 7.42 (m, 3H), 5.83 - 5.81 (m, 1H), 4.33 (q, *J* = 6.8 Hz, 2H), 2.62 - 2.58 (m, 2H), 2.21 - 2.17 (m, 2H), 1.85 - 1.81 (m, 2H), 1.75 - 1.71 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.7, 161.3, 157.9, 138.9, 138.7, 138.3, 129.5, 128.7, 128.7, 127.3, 125.0, 117.4, 61.3, 27.8, 25.7, 22.8, 22.0, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{22}NO_2$: 308.1651. Found: 308.1647.

Ethyl 6-(2-methoxyphenyl)-2-phenylnicotinate (116m):



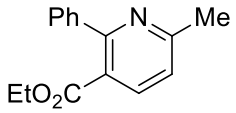
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.0 Hz, 1H), 7.98 - 7.93 (m, 2H), 7.62 - 7.60 (m, 2H), 7.44 - 7.37 (m, 4H), 7.10 - 7.06 (m, 1H), 7.02 - 7.00 (m, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.90 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 158.5, 157.5, 157.3, 140.8, 137.6, 131.6, 130.6, 128.8, 128.4, 128.2, 127.9, 124.9, 122.8, 121.2, 111.5, 61.3, 55.7, 13.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{20}NO_3$: 334.1443. Found: 334.1440.

Ethyl 6-(4-nitrophenyl)-2-phenylnicotinate (116n):



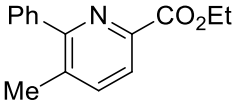
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 - 8.29 (m, 4H), 8.24 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.65 - 7.63 (m, 2H), 7.49 - 7.47 (m, 3H), 4.19 (q, J = 7.2 Hz, 2H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 159.1, 155.7, 148.6, 144.1, 140.0, 139.2, 128.9, 128.8, 128.1, 126.9, 124.0, 118.6, 61.6, 13.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{17}N_2O_4$: 349.1188. Found: 349.1181.

Ethyl 6-methyl-2-phenylnicotinate (116o):



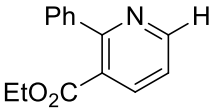
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 1H), 7.51 - 7.49 (m, 2H), 7.42 - 7.40 (m, 3H), 7.19 (d, J = 8.0 Hz, 1H), 4.12 (q, J = 6.8 Hz, 2H), 2.65 (s, 3H), 1.02 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 160.8, 158.7, 140.6, 138.2, 128.5, 128.4, 128.0, 124.4, 121.2, 61.2, 24.8, 13.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{16}NO_2$: 242.1181. Found: 242.1183.

Ethyl 5-methyl-6-phenylpicolinate (116o'):



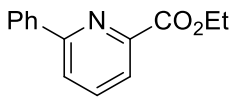
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 37%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.56 - 7.54 (m, 2H), 7.47 - 7.40 (m, 3H), 4.46 (q, J = 7.2 Hz, 2H), 2.41 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 159.0, 145.9, 139.8, 139.2, 135.0, 129.2, 128.3, 128.2, 123.4, 61.7, 20.4, 14.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{16}NO_2$: 242.1181. Found: 242.1177.

Ethyl 2-phenylnicotinate (116p):



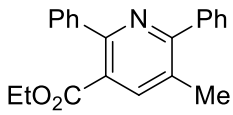
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 - 8.76 (m, 1H), 8.12 - 8.10 (m, 1H), 7.55 - 7.52 (m, 2H), 7.44 - 7.42 (m, 3H), 7.36 - 7.33 (m, 1H), 4.15 (d, J = 7.2 Hz, 2H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 158.9, 151.2, 140.2, 137.8, 128.6, 128.5, 128.1, 127.4, 121.5, 61.5, 13.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{14}NO_2$: 228.1025. Found: 228.1028.

Ethyl 6-phenylpicolinate (116p'):



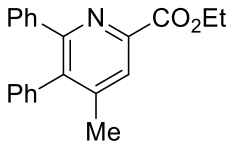
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 27%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 - 8.04 (m, 3H), 7.92 - 7.88 (m, 2H), 7.51 - 7.42 (m, 3H), 4.49 (q, J = 6.8 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 157.6, 148.4, 138.5, 137.6, 129.4, 128.8, 127.2, 123.5, 123.3, 61.8, 14.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{14}NO_2$: 228.1025. Found: 228.1027.

Ethyl 5-methyl-2,6-diphenylnicotinate (116q):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.61 - 7.57 (m, 4H), 7.47 - 7.39 (m, 6H), 4.17 (q, J = 7.2 Hz, 2H), 2.45 (s, 3H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 160.0, 156.0, 140.3, 139.9, 129.2, 129.0, 128.8, 128.4, 128.3, 128.2, 128.0, 125.5, 61.4, 19.6, 13.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{20}NO_2$: 318.1494. Found: 318.1499.

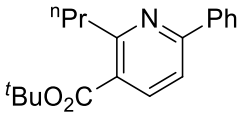
Ethyl 4-methyl-5,6-diphenylpicolinate (116q'):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 24%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.29

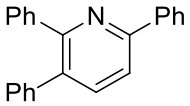
- 7.27 (m, 5H), 7.16 - 7.14 (m, 3H), 7.07 - 7.05 (m, 2H), 4.49 (q, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 158.0, 147.4, 146.7, 140.0, 139.3, 137.7, 130.1, 129.8, 128.3, 127.6, 127.5, 127.4, 125.2, 61.8, 20.8, 14.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{20}NO_2$: 318.1494. Found: 318.1487.

***tert*-Butyl 6-phenyl-2-propylnicotinate (116r):**



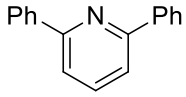
The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 1H), 8.07 - 8.05 (m, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.50 - 7.43 (m, 3H), 3.20 - 3.16 (m, 2H), 1.87 - 1.81 (m, 2H), 1.62 (s, 9H), 1.04 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 162.5, 158.3, 139.1, 138.8, 129.4, 128.7, 127.2, 125.6, 117.1, 81.8, 39.1, 28.2, 23.1, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{19}H_{24}NO_2$: 298.1807. Found: 298.1810.

2,3,6-Triphenylpyridine (116s):



The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 111 - 112 ℃. Yield: 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 - 8.14 (m, 2H), 7.78 - 7.77 (m, 2H), 7.51 - 7.42 (m, 5H), 7.30 - 7.21 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 155.6, 140.4, 140.0, 139.4, 139.1, 134.4, 130.2, 129.5, 129.0, 128.7, 128.3, 127.8, 127.1, 127.0, 118.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{23}H_{18}N$: 308.1439. Found: 308.1439.

2,6-Diphenylpyridine (116t):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 - 8.14 (m, 4H), 7.84 - 7.80 (m 1H), 7.71 - 7.69 (m, 2H), 7.52 - 7.48 (m, 4H), 7.45 - 7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 139.5, 137.5, 129.0, 128.7, 127.0, 118.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{14}N$: 231.1048. Found: 238.1051.

CHAPTER 4

Catalytic and Direct Methyl Sulfonylation of Alkenes and Alkynes Using Methyl Sulfonyl Radical Generated from DMSO, Dioxygen and Copper System

Chapter 4 CATALYTIC AND DIRECT METHYL SULFONYLATION OF ALKENES AND ALKYNES USING METHYL SULFONYL RADICAL GENERATED FROM DMSO, DIOXYGEN AND COPPER SYSTEM

4.1 OVERIEW

Dimethyl sulfoxide (DMSO) is produced from dimethyl sulfide (DMS) in the wood industry. As a common solvent, it has been widely used in chemistry and related science due to its rather low toxicity, relative stability and low cost.[108] At the meantime, biologists have also employed DMSO as a hydroxyl radical scavenger to trap the highly reactive oxygen species present in biological system.[109] It is worth to note that reactive oxygen species have been regarded to be the causative factors of many diseases.[110] Detailed mechanistic studies have revealed that DMSO reacts with the OH radicals present in the biological system to form methane, ethylene and methyl sulfonyl radical species.[111] To the best of our knowledge, these radical species derived from DMSO have not been applied in synthetic chemistry.[112] We envisage that the methyl sulfonyl radical species generated from DMSO using this strategy may react with alkenes or alkynes to construct C–S bonds, generating interesting and synthetically useful methyl sulfones. In this chapter, we describe a novel method for

[108] a) Soroko, I.; Bhole, Y.; Livingston, A. G. *Green Chem.* **2011**, *13*, 162; b) Doble, M.; Kumar, *A. Green Chemistry and Engineering*; Elsevier Inc.: New York, **2007**; Chapter 5 pp 93-104; c) Nelson, W. M. *Green solvents for chemistry: Perspectives and practice in Green Chemistry*, 1st ed.; Oxford University Press: USA, **2003**; Chapter 3 pp 60-62 and Chapter 5 pp 116-132; d) Dimethyl Sulfoxide Producers Association, US Environmental Protection Agency. IUCLID Data Set; Leesburg, VA, September 8, **2003**; report number 201-14721A; e) Trofimov, B. A. *Sulfur Rep*. **1992**, *74*, 207.

[109] a) Baptista, L.; Silva, E. C.; Arbilla, G. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6867; b) Eberhardt. M. K.; Colina, R. *J. Org. Chem.* **1988**, *53*, 1071.

[110] Christine, C. W. *Biochem. J.* **1981**, *198*, 125.

[111] a) Veltwisch, D.; Janata, E.; Asmus, K. D. *J. Chem. Soc. Perkin Trans. 2*. **1980**, 146; b) Repine, J. E.; Eaton, J. W.; Anders, M. W.; Hoidal, J. R.; Fox, R. B. *J. Clin. Invest.* **1979**, *64*, 1642; c) Gilbert, B. C.; Norman, R. O. C.; Sealy, R. C. *J. Chem. Soc., Perkin Trans. 2*. **1976**, 303.

[112] During our manuscript under revision, Huang reported DMSO as sulfonyl radical source: Shi, X.; Ren, X.; Ren, Z.; Li, J.; Wang, Y.; Yang, S.; Gu, J.; Gao, Q.; Huang, G. *Eur. J. Org. Chem.* **2014**, 5083.

the synthesis of *β*-keto methyl sulfones and (*E*)-vinyl methyl sulfones from alkenes and alkynes respectively using methyl sulfonyl radical generated from DMSO. This methyl sulfonation method is found to be highly chemo- and regio-selective. The mechanism study including D-labeling and $^{18}O_2$ experiments support that a radical process is involved in the reaction. Furthermore, the *β*-keto methyl sulfones and (*E*)-vinyl methyl sulfones derived from our methodology were applied in transformation to many useful compounds.

4.2 SYNTHESIS OF *β*–KETO METHYL SULFONES BY METHYL SULFONYLATION OF ALKENES WITH DMSO

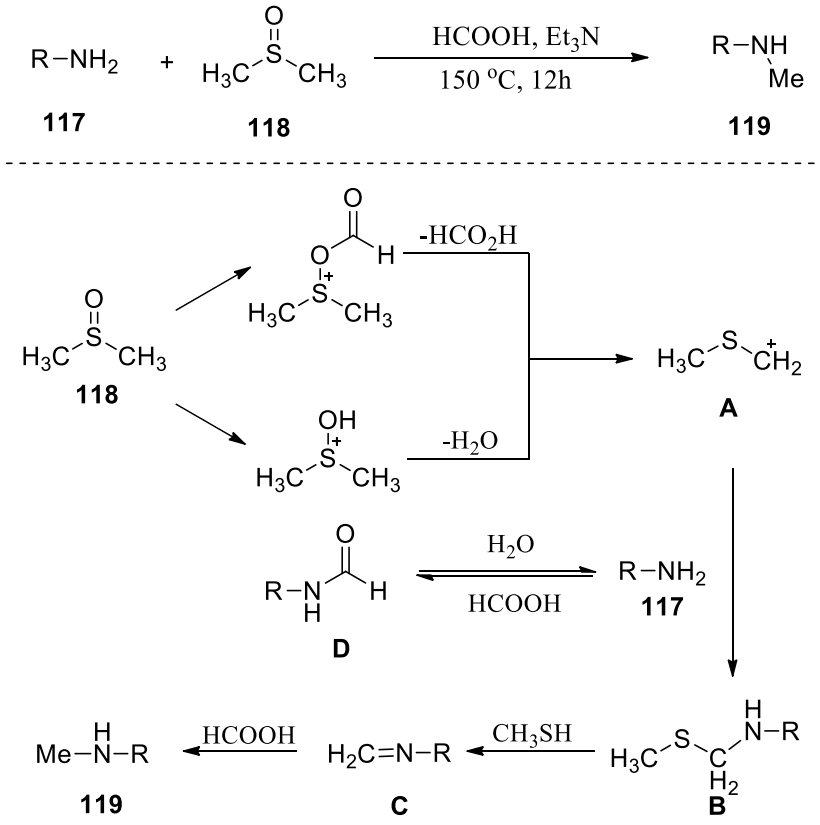
4.2.1 INTRODUCTION

Dimethyl sulfoxide (DMSO) is well known as a common solvent in organic chemistry and related science; it has also been explored as medicine or involved as an important component in some medicines.[113] In view of the stability of the molecule, there are only limited reports of its applications as reactant in organic synthesis.[114] Recently, organic chemists committee has growing interest to employ DMSO as reaction partner to construct valuable C–C and C–S bonds. Compared to other analogous reagents, DMSO possesses distinctive advantages such as low cost, availability, low toxicity and ease of handling. Herein, we summarized a few examples of recently progress in using DMSO as reactant reactions.

Xiao group in 2013 reported using DMSO **118** as methylation reagent to

[113] Roy, K.-M. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. *Sulfones and Sulfoxides.* **2012**, pp 25-487.
[114] Oda, R.; Hayashi, Y. *Bull. Inst. Chem. Res. Kyoto Univ.* **1970**, *47*, 480.

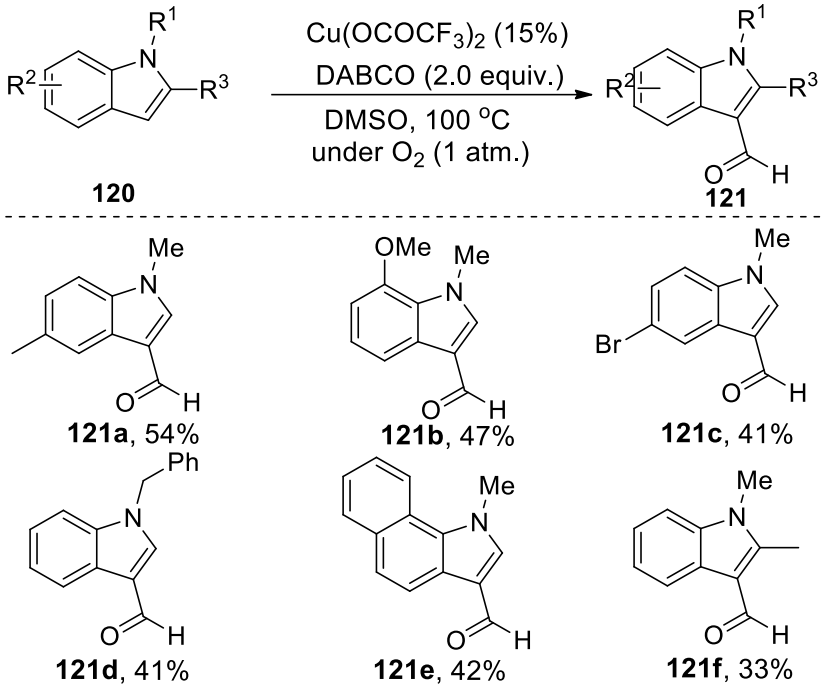
construct of C–N bonds with amines **117** and nitro compounds.[115] They believed that DMSO might be initially acylated by formic acid, or protonated by formic acid, which both lead to the formation of intermediate **A** (Scheme 4.1). Subsequently, **A** is attacked by an amine to generate intermediate **B**. The elimination of methane thiol from **B** gives to the imine intermediate **C**, which might be reduced by formic acid, providing the methylated amine product **119**.



Scheme 4.1 Using DMSO as methylation reagent

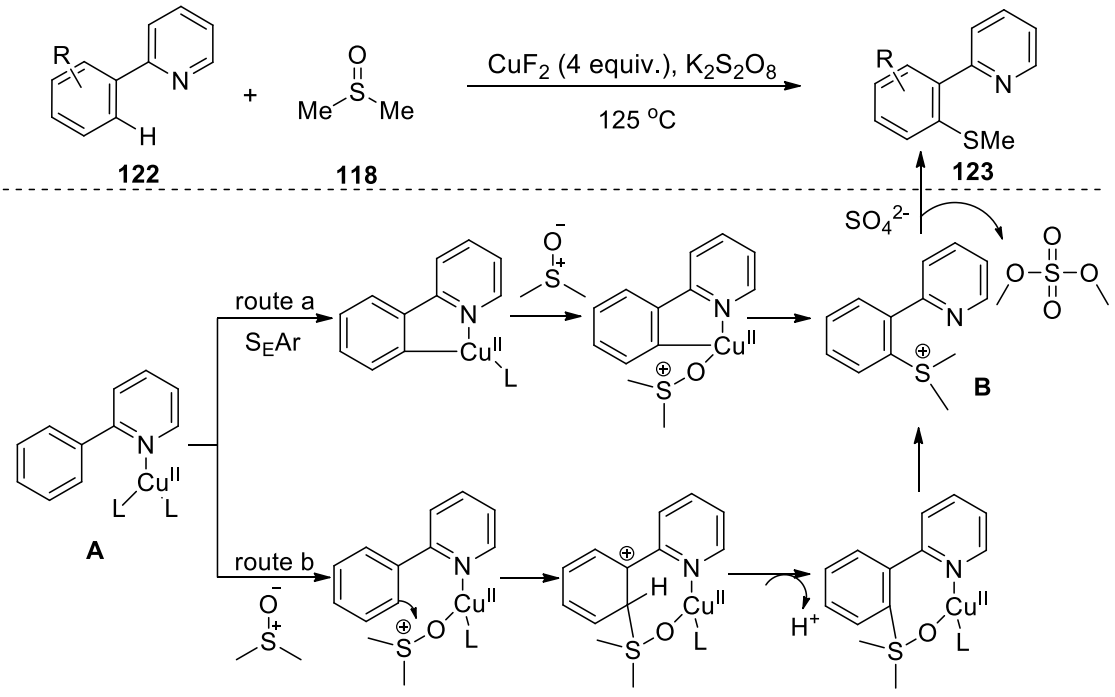
In 2012, Chiba group reported that copper-catalyzed direct C–H aerobic formylation of C(3) on indoles **120** in moderate yields using 1,4-diazabicyclo [2.2.2] octane (DABCO) as an additive in dimethyl sulfoxide (DMSO).[116] In this case, the carbon of formyl group was most likely introduced from DMSO (Scheme 4.2).

[115] a) Russell, G. A.; Weiner, S. A. *J. Org. Chem.* **1966**, *31*, 248; b) Jiang, X.; Wang, C.; Wei, Y.; Xue, D. C; Liu, Z.; Xiao, J. *Chem. Eur. J.* **2014**, *20*, 58.
[116] Wang, Y. F.; Zhang, F. L.; Chiba, S. *Synthesis.* **2012**, *44*, 1526



Scheme 4.2 Using DMSO as methylation reagent

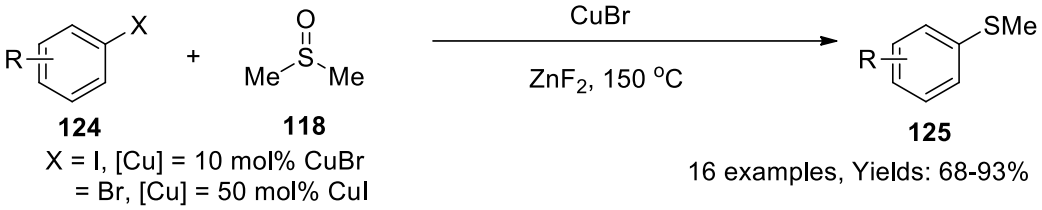
In 2010, Qing and co-workers reported an unprecedented Cu(II)-mediated methylthiolation of aryl C–H bonds with pyridine as directing group **122** under oxidat-



Scheme 4.3 Using DMSO as methylthiolation reagent

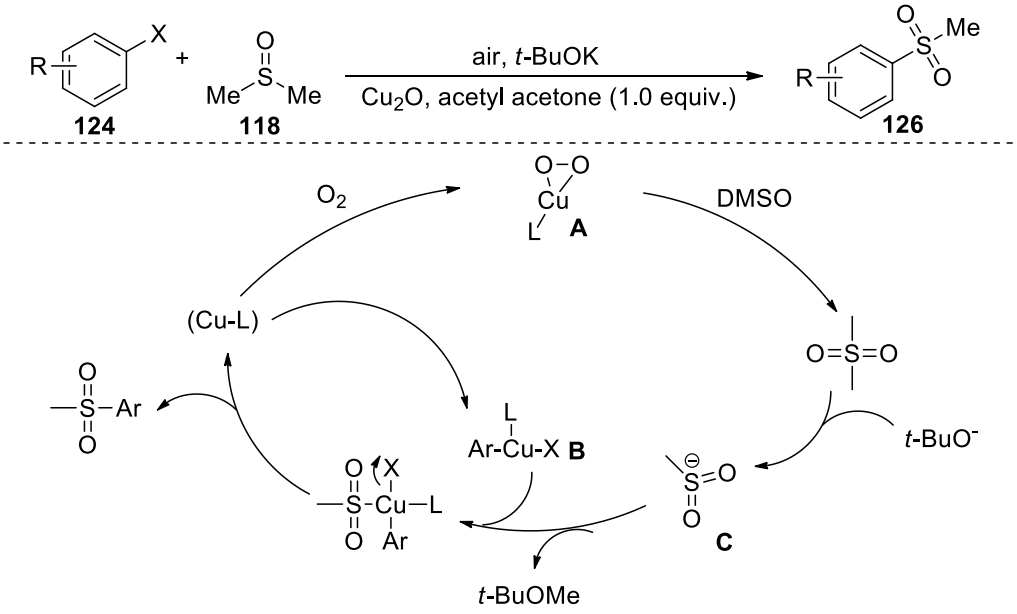
-ive condition that employed the widely available DMSO **118** as the methylthiolation reagent.[117] They also proposed two reaction pathways and both of them involved key intermediate **B**, which was probably captured by the sulfate ion generated by the decomposition of $K_2S_2O_8$ to afford the desired product (Scheme 4.3).

Later, Cheng Jiang group demonstrated a copper-mediated methylthioylation of aryl halides **124** with DMSO at 150 ℃ to afford the aryl sulfides **125** in good to excellent yields (Scheme 4.4).[118]



Scheme 4.4 Using DMSO as methylthiolation reagent

Yuan and co-workers recently reported a novel copper (I)-catalyzed strategy to synthesize aryl methyl sulfones **126** from aryl halides **124** and widely available DMSO

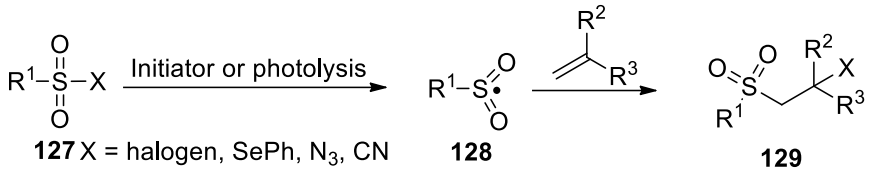


Scheme 4.5 Using DMSO as methyl sulfonylation reagent

[117] Chu, L.; Yue, X.; Qing, F. L. *Org. Lett.* **2010**, *12*, 1644.
[118] Luo, F.; Pan, C.; Li, L.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, *47*, 5304.

under basic condition using atmospheric oxygen as the sole oxidant (Scheme 4.5).[119] They believed that methyl sulfonyl anion intermediate **C** takes the important role in this transformation.

It is important to note that sulfonyl radicals generated using various sulfonyl compounds have been well studied.[120] For example, sulfonyl halides,[121] selenides,[122] cyanides, [123] azides,[124] and sodium sulfinates [125] **127** have been found to be useful starting materials for the generation of the corresponding sulfonyl radicals **128** to access a variety of sulfonyl compounds (Scheme 4.6).



Scheme 4.6 Generations and reactions of sulfonyl radicals

Biologically, scientists have employed DMSO **118** as a hydroxyl radical scavenger to trap the highly reactive oxygen species present in biological system (Scheme 4.7).[126] In the process, DMSO **118** reacts with the OH radicals present in the biological system to generate methane, ethylene and methyl sulfonyl radical species.

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[119] Yuan, G.; Zheng, J.; Gao, X.; Li, X.; Huang, L.; Chen, H.; Jiang, H. *Chem. Commun.* **2012**, *48*, 7513.

[120] a) M. P. Bertrand and C. Ferreri, in Radicals in Organic Synthesis, Vol. 2 (ed., P. Renaud and M. Sibi), Wiley-VCH, Weinheim, **2001**, pp. 485-504; b) Bertrand, M. *Organic Preparations and Proced-ures Int.*, **1994**, *26*, 257.

[121] a) Gilmore, K.; Gold, B.; Clark, R. J.; Alabugin I. V. *Australian Journal of Chemistry*. **2013**, *66*, 336; b) Nair, R. P.; Kim, T. H.; Frost, B. J. *Organometallics*. **2009**, *28*, 4681; c) Xi, C.; Lia, C.; Chen, C.; Wang, R. *Synlett*. **2004**, 1595; d) Kang, S. K.; Seo, H. W.; Ha, Y. H. *Synthesis*. **2001**, 1321; e) Craig, D. C.; Edwards, G. L.; Muldoon, C. A. *Tetrahedron*. **1997**, *53*, 6171.

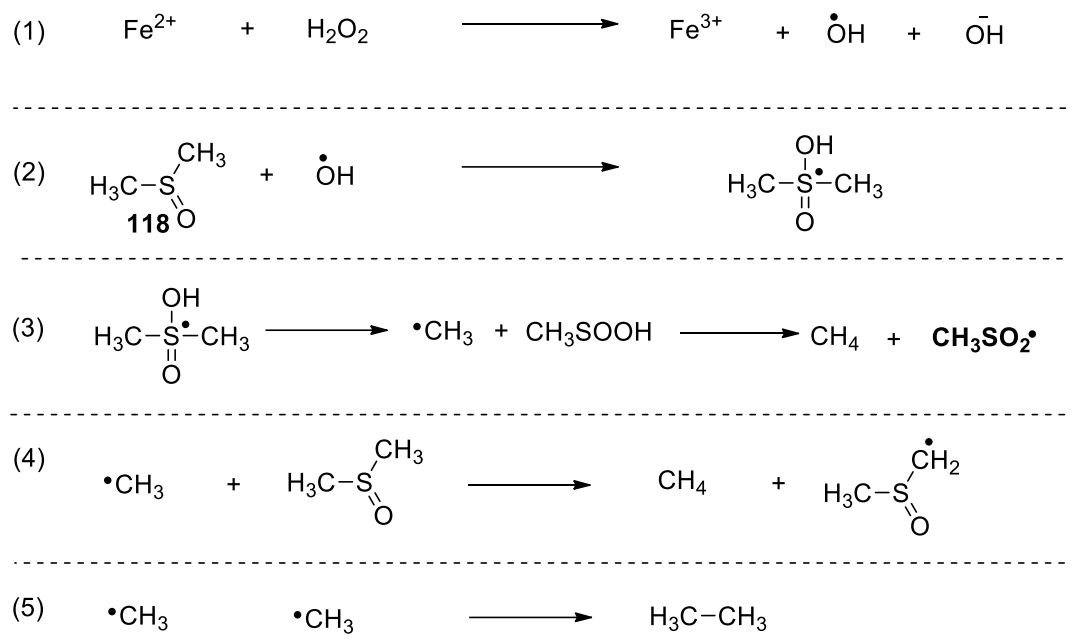
[122] a) Yoshimatsu, M.; Hayashi, M.; Tanabe, G.; Muraoka, O. *Tetrahedron Lett.* **1996**, *37*, 4161; b) Barton, D. H. R.; Csiba, M. S.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1994**, *35*, 2869.

[123] Fang J. M.; Chen, M. Y. *Tetrahedron Lett.* **1987**, *28*, 2853.

[124] Mantrand N.; Renaud, P. *Tetrahedron*. **2008**, *64*, 11860-11864.

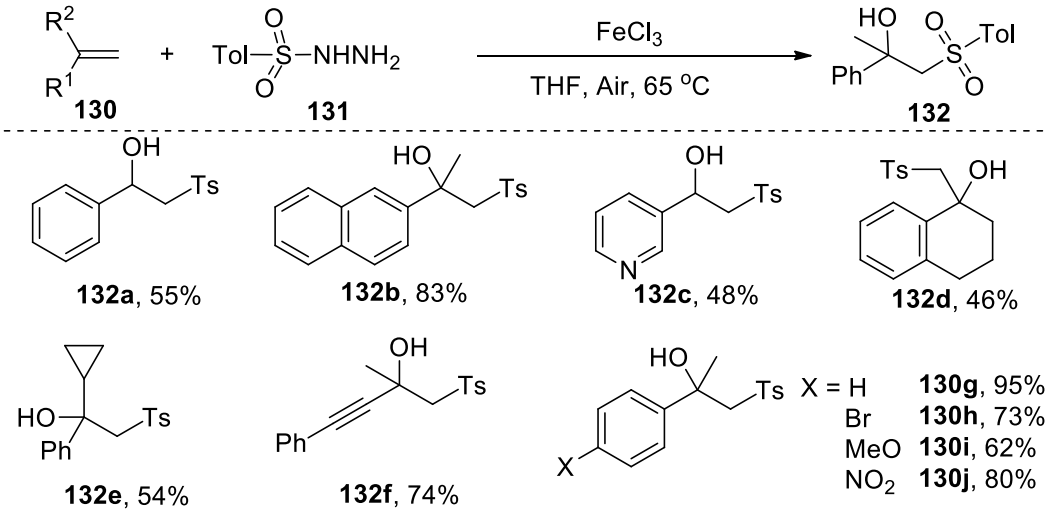
[125] a) Li, H. S.; Liu, G. *J. Org. Chem.* **2014**, *79*, 509; b) Chawla, R.; Singh, A. K.; Yadav, L. D. S. *Eur. J. Org. Chem.* **2014**, 2032; c) Xiao, F.; Chen, H.; Xie, H.; Chen, S.; Yang, L.; Deng, G. J. *Org. Lett.* **2014**, *16*, 50; d) Kariya, A.; Yamaguchi, T.; Nobuta, T.; Tada, N.; Miura, T.; Itoh, A. *RSC Adv.* **2014**, *4*, 13191; e) Xi, Y; Dong, B.; McClain, E. J.; Wang, Q.; Gregg, T. L.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Angew. Chem. Int. Ed.* **2014**, *53*, 4657; f) Tang, X.; Huang, L.; Xu, Y.; Yang, J.; Wu, W.; Jiang, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 4205.

[126] Eberhardt. M. K.; Colina, R. *J. Org. Chem.* **1988**, *53*, 1071.



Scheme 4.7 Using DMSO as methyl sulfonylation reagent

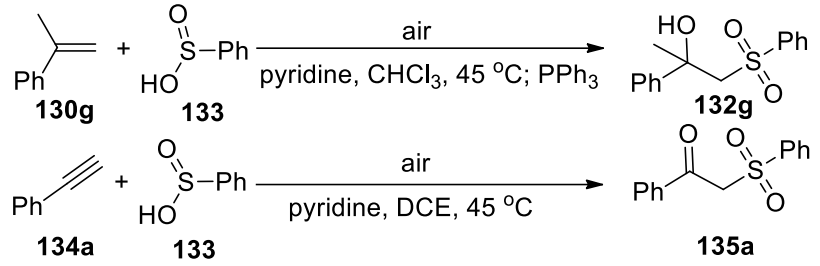
Recently, Taniguchi has shown that sulfonyl radicals generated from the corresponding hydrazine compounds **131** can be used to functionalize alkenes **130**.[127] The reaction is revealed to be promoted by environmentally benign iron catalysts under mild conditions and the experimental procedure is very easy to handle and safe (Scheme 4.8).



Scheme 4.8 Generations and reactions of sulfonyl radicals

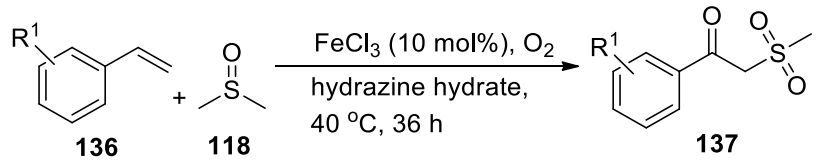
[127] Taniguchi, T.; Idota, A.; Ishibashi, H. *Org. Biomol. Chem.* **2011**, *9*, 3151.

Furthermore, Lei reported that sulfonyl radicals generated from the corresponding sulfinic acids **133** are useful for the oxidative difunctionalization of alkenes **130g** and alkynes **134** to generate tertiary *β*-hydroxysulfones **132a** and *β*-keto sulfones **135a** (Scheme 4.9).[128]



Scheme 4.9 Difunctionalization of alkenes and alkynes

While our manuscript was being revised, Huang reported an iron (III)-catalyzed synthesis of *β*-oxo methyl sulfones **137** which employs aryl alkenes **136** and readily available dimethyl sulfoxide **118** with hydrazine and oxygen as the oxidant (Scheme 4.10).[112] The reaction is believed to undergo a radical pathway as our proposed, though they are using hydrazine hydrate as reducant.



Scheme 4.10 Using DMSO as methyl sulfonylation reagent

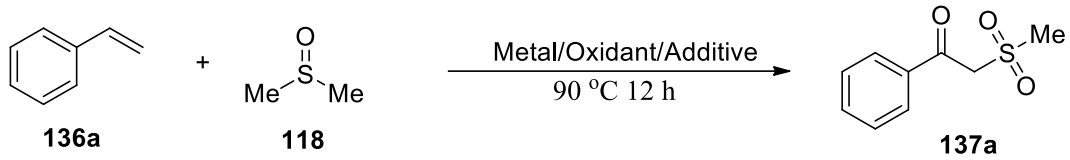
Herein, we describe a novel method for the synthesis of *β*-keto methyl sulfones from alkenes and alkynes respectively using methyl sulfonyl radical generated from DMSO. This methyl sulfonation method is found to be highly chemo- and regioselective.

[128] (a) Lu, Q.; Zhang, J.; Wei, F.; Qi, Y.; Wang, H.; Liu, Z.; Lei, A. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 7156; b) Lu, Q.; Zhang, J.; Zhao, G.; Qi, Y.; Wang, H.; Lei, A. *J. Am. Chem. Soc.* **2013**, *135*, 11481.

4.2.2 RESULT AND DISCUSSION

As we have discussed in the previous section, the hydroxyl radical is able to react with DMSO to generate active methyl sulfonyl radical (Table 4-1). On the other hand, the well-known iron-catalyzed reactions could effeciently promote the generation of highly reactive hydroxyl radical from hydrogen peroxide under thermal condition.[129]

Table 4-1 Optimization of reaction conditions for difunctionalization of alkenes[a]



136a **118** **137a**

Entry	Solvent	Catalyst	Additive[f]	Oxidant	Yield[b]
1	DMSO	$FeCl_2$	D-1[d]	H_2O_2	15[c]
2	DMSO	CuBr	D-1[d]	H_2O_2	27[c]
3	DMSO	CuBr	D-1[d]	O_2	24[c]
4	DMSO	CuBr	D-2[e]	O_2	50
5	DMSO	CuBr	D-2	O_2	86(82[c])
6	DMSO	Cu_2O	D-2	O_2	54
7	DMSO	Cu(OTf).Benzene	D-2	O_2	77
8	DMSO	$Cu(OTf)_2$	D-2	O_2	36
9	DMSO	CuBr	D-3	O_2	80
10	DMSO	CuBr	D-4	O_2	64
11	DMSO	CuBr	D-2	air	73
12	DCE[g]	CuBr	D-2	O_2	5
13	DMSO	$CuBr_2/FeBr_3$[h]	-	O_2	-

[a]Conditions: 0.25 mmol **136a** and 10 mol% metal catalyst with 3.0 equiv additives were added to 1 mL **118** under oxidant (10.0 equiv H_2O_2 or 1 atm. O_2 balloon). [b]GC yields. [c]Isolated yields. [d]20 mol% additives. [e]1.5 equiv additives. [f]D-1: 1,10-phenanthroline; D-2: $HPO(OEt)_2$; D-3: $HPO(OMe)_2$; D-4: $HP(O^iBu)_2$. [g]5 mmol **2** in 1 mL DCE. [h]$CuBr_2$ (2.5 mol%), $FeBr_3$ (5 mol%).

Thus, we began our investigation by treating styrene **136a** with DMSO **118** in the catalytic system of $FeCl_2$ and H_2O_2 with 1,10-phenanthroline as ligand at 90 °C (Table 4-1, entry 1). Delightedly, we detected the product after 12 hours albeit in low yield (15%). The structure was confirmed as 2-(methylsulfonyl)-1-phenylethanone

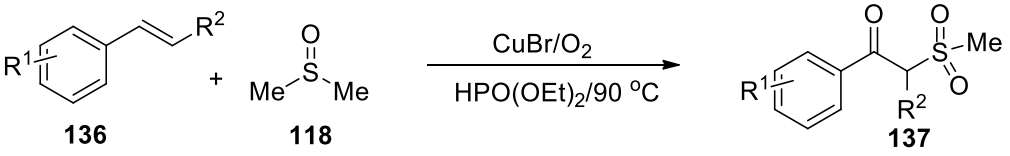
[129] a) Halliwell, B.; Clement M. V.; Long, L. H. *FEBS Letters.* **2000**, *486*, 10; b) Winterbourn, C. C. *Biochem. J.* **1981**, *198*, 125; c) Fenton, H. J. H. *J. Chem. Soc., Trans.* **1894**, *65*, 899.

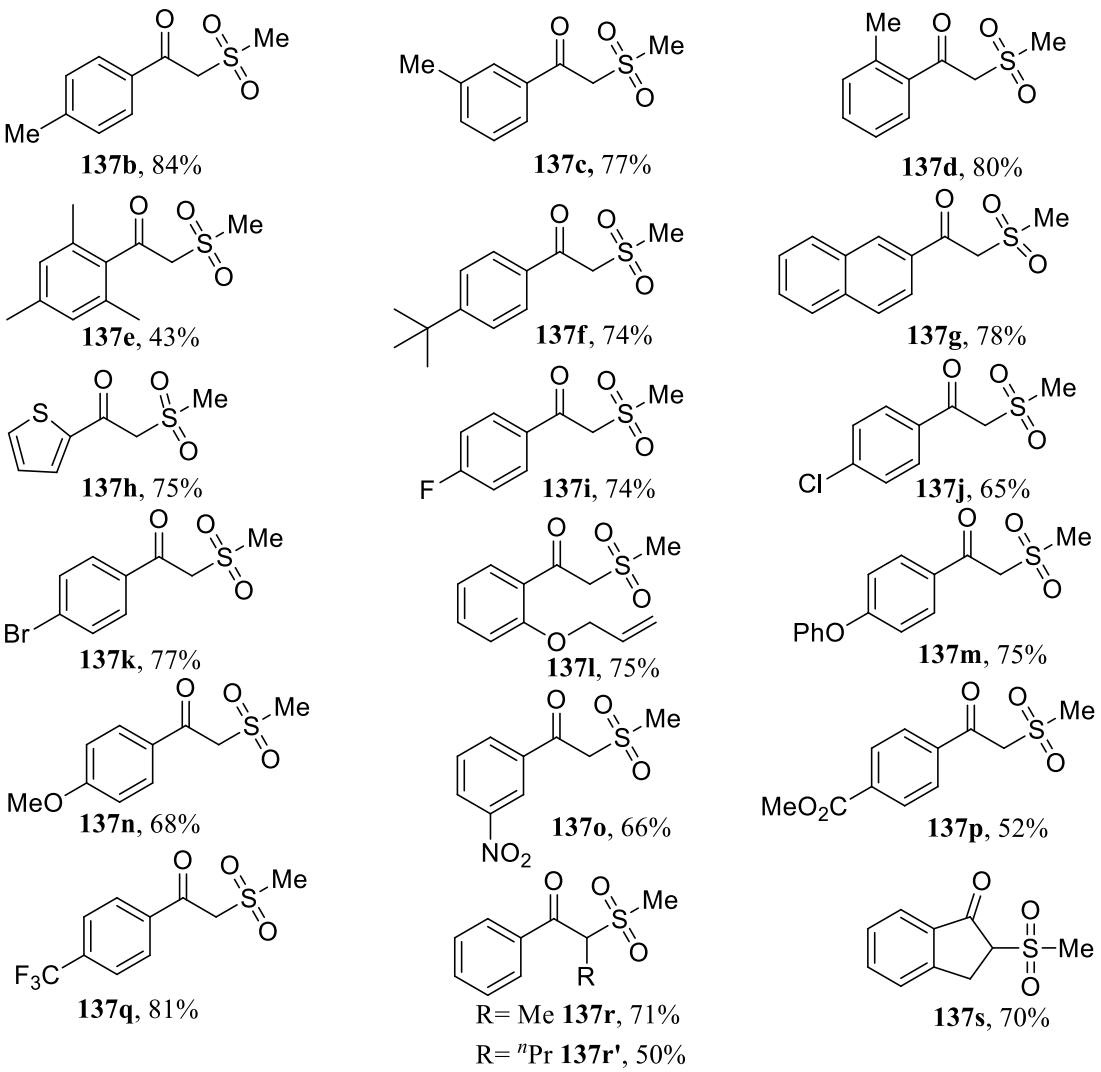
137a with reported spectra data. Copper catalyst such as CuBr could improve the yield to 27% (Table 4-1, entry 2). A more environmentally-friendly and convenient oxidant such as O_2 could exert a positive effect on the reaction, providing the desired product in 24% yield (Table 4-1, entry 3). The amount of diethyl phosphite is crucial to the outcome of reaction. It was found that when stoichiometric amount of additive was employed, the yield was improved dramatically (Table 4-1, entries 4-5). Generally, copper catalysts with different counterions all promoted the reaction with fluctuating yields (see **Experimental section**). Copper (I) performed more efficiently in the reaction system compared to copper (II) catalysts (Table 4-1, entries 7-8). Simple substituents phosphite like methyl, ethyl, gave better results compared to the bulky ones (Table 4-1, entries 5 and 9-10). It is worth to note that air also promoted the reaction acting as common oxidant (Table 4-1, entry 11). Employing DCE as solvent failed to enhance the reaction efficiency and only trace amount of product was obtained (Table 4-1, entry 12). Interestingly, when we employed Ji's Cu/Fe catalytic system without triethylamine, the reaction was completely suppressed without phosphorylation or sulfonylation of alkene (Table 4-1, entry 13). Also, no desired product was found when the reaction was performed using Lei's reaction conditions (**136a** reacted with DMSO **118** with pyridine under air atmosphere).

With the optimized reaction conditions in hand, we turned attention to survey the substrate scope of the reaction (Table 4-2). Generally, a broad range of substituted aryl alkenes proceeded well to give the corresponding *β*-keto methyl sulfones in good to excellent yields. *Ortho*, *meta*- and *para*-substituted phenyl alkenes (**137b**-**137d**) proceeded smoothly under optimized conditions leading to the corresponding products in good to excellent yields (77-84%). Studying the steric effect revealed that a hindered 2,4,6-trimethyl groups slightly reduced the yield (**137e**, 43%). On the other hand,

4-*t*-butyl group substituted phenyl alkene worked well with DMSO **118** affording the product in good yield (**137f**). Naphthyl and heteroaryl substrates were compatible with the reaction condition (**137g-137h**), and a diverse range of halogen substituents (F, Cl, Br) at the *para*-position of phenyl group could also be well tolerated (**137i-137k**). It is worth to note that the functionalities of chloro and bromo at the *para*-position of phen-

Table 4-2 Substrate scope for reaction of alkenes with DMSO[a, b]





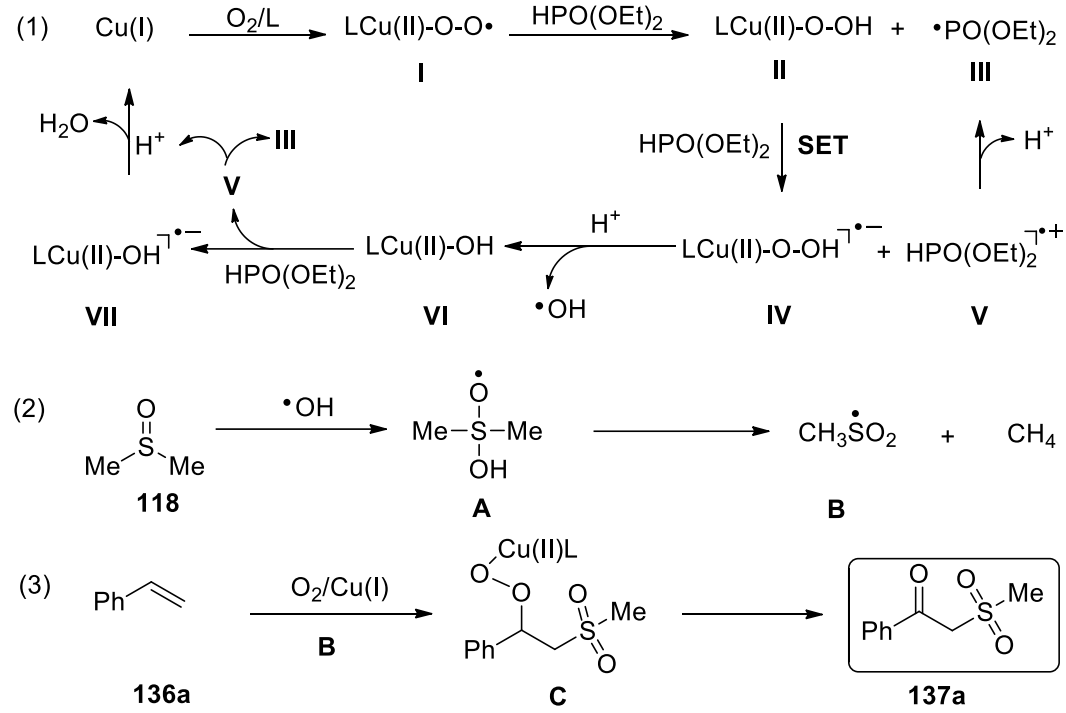
[a]Conditions: 0.25 mmol **136** and 10 mol% CuBr with 3.0 equiv $HPO(OEt)_2$ were stirred in 1 mL DMSO under 1 atm. O_2 balloon. [b]Isolated yields.

-yl group could also be further transformed in coupling reactions. Unfortunately, when alkyl substituted alkenes were explored in the reaction condition; the desired product was not detected and the starting material was recovered. The negative result turned our interest in exploring the chemoselectivity of compound bearing both the alkyl and aryl substituted alkene moieties (**136l**). The result revealed that the alkyl alkene moiety remained intact while the aryl alkene proceeded smoothly to provide the 1-(2-(allyloxy) phenyl)-2-(methylsulfonyl)ethanone (**137l**) in 75% yield. Examination of the electronic effect on the phenyl group revealed that both of electron-rich and electron-deficient groups afforded promising results (**137m-137q**). Furthermore, internal and cyclic alkenes were also tested under the standard condition to afford the corresponding methyl sulfones in 71% and 70% yield, respectively (**137r-137s**).

Based on these initial results, a possible reaction pathway was proposed for the alkene derivatives **136** reacting with DMSO **118** in $CuBr/O_2/HPO(OEt)_2$ conditions (Scheme 4.11). Initially, copper complex-**I** may be generated from $CuBr/O_2/HPO(OEt)_2$.[130] Then, a radical process takes place to generate the metal complex-**II** and phosphonic radical-**III**, respectively. One more equivalent of phosphite acts as reductant to take part in the SET (Single Electron Transfer) process to give radical anion **IV** and cation **V**. While **V** probably changes to the phosphonic radical-**III** by deprotonation, copper (II) complex-**IV** generates the important hydroxyl radical and Cu(II)-OH (**VI)** which may be further reduced by phosphite through SET process to regenerate Cu(I). As reported,[20] hydroxyl radical could react with DMSO to give several radical species, one of which is the methyl sulfonyl radical **B** from the demethylation of dimethyl sulfinic acid radical **A**. Styrene was attacked by radical

[130] a) He, C.; Guo, S.; Huang, L.; Lei, A. W. *J. Am. Chem. Soc.* **2010**, *132*, 8273; b) Wei, W.; Ji, J. X. *Angew. Chem. Int. Ed.* **2011**, *50*, 9097; c) Jensen, M. P.; Que, E. L.; Shan, X.; Akimova, E. R.; Jr, L. Q. *Dalton Trans.* **2006**, 3523; d) Zhang, N.; Samanta, S. R.; Rosen, B. M.; Percec, V. *Chem. Rev.* **2014**, *114*, 5848.

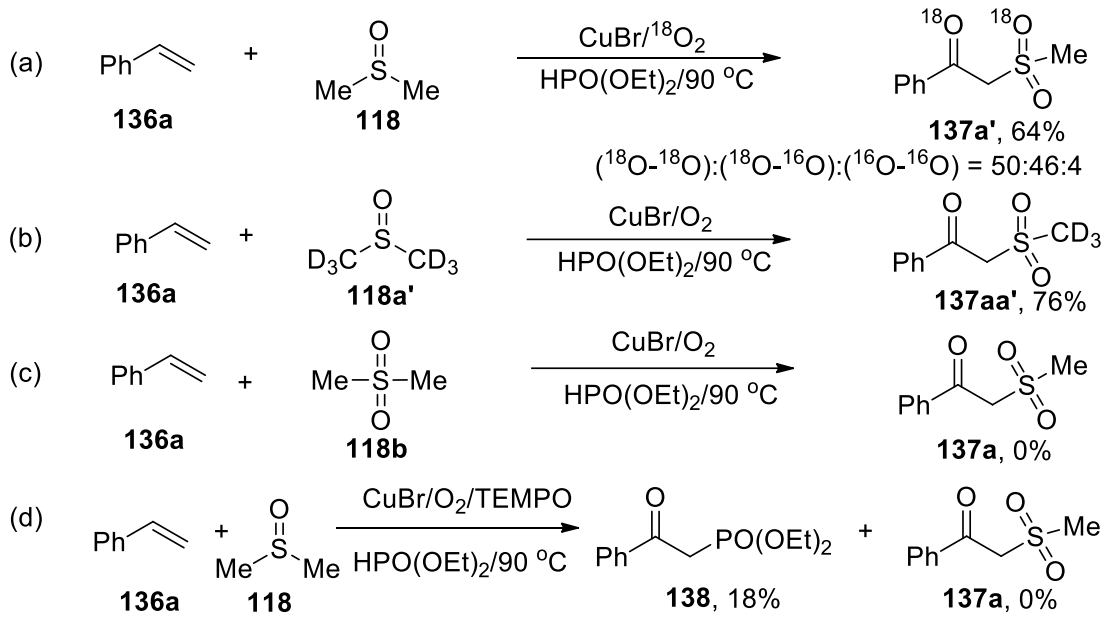
species **B** to form hydroperoxyl complex-**C**, which is finally oxidized to give *β*-keto methyl sulfones.



Scheme 4.11 Proposed mechanism for difunctionalization of alkenes

To further understand the reaction mechanism, the isotopic labeling experiments with $^{18}O_2$ and *d*-DMSO were performed. The results indicated that two additional oxygen atoms present in the product originated from $^{18}O_2$ (Scheme 4.12 (a)) and demethylation of DMSO occurred facilely (Scheme 4.12 (b)). Furthermore, no reaction was detected by GC analyzing when dimethyl sulfone **118b** was employed to react with styrene **136a** under the same reaction conditions (Scheme 4.12 (c)). This reaction demonstrated that active methyl sulfonyl ($MeSO_2$) radical species were implicated rather than dimethyl sulfone **118b** reacting with alkene directly. D_2O exchange experiment was also performed and no D-labeling product was detected (See experimental section). When using TEMPO as radical scavenger in the reaction, the formation of desired product **137a** was completely suppressed and only a small

amount of *β*-keto-diethyl phosphonate **138** was obtained (Scheme 4.12 (d)). The reaction was hindered when subjecting the *β*-keto diethyl phosphonate instead of the aryl alkene in the reaction system, indicating that *β*-keto phosphonate is not the intermediate of this reaction. Therefore, we may conclude that a DMSO/•OH radical process is the most likely pathway in our reaction system.

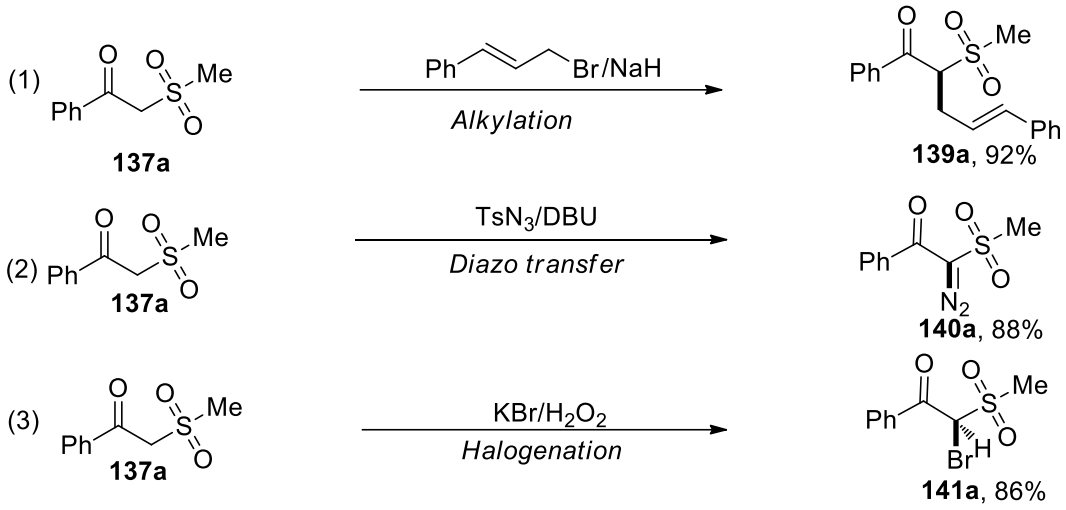


Scheme 4.12 Mechanistic studying

β-Keto methyl sulfones are very useful synthetic intermediates in construction of pharmaceuticals and natural products. Especially, the active methylene has potential to be functionalized to generate useful compounds. For instance, the *β*-keto methyl sulfone **137a** could be either alkylated with allyl bromide or diazo transferred with tosyl azide in presence of suitable base conditions (Scheme 4.13, eq 1 and 2).[131] It can also easily be halogenated in presence of H_2O_2 and KBr to provide 2-bromo-2-(methylsulf-onyl)-1-phenyl-ethanone **141a** (Scheme 4.13, eq 3), which is the key intermediate for one step synthesis of biological active molecule

[131] Illger, W.; Liedhegener, A.; Regitz, M. *Liebigs Ann. Chem.* **1972**, *760*, 1.

2-(methylsulfonyl)-3-phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole.[132]



Scheme 4.13 Diverse transformations of *β*-keto methyl sulfones

4.2.3 SUMMARY

In summary, a novel method for the synthesis of *β*-keto methyl sulfones from common substrates aryl alkenes and DMSO was described. We developed a new catalytic system including copper, oxygen and $HPO(OEt)_2$ to generate the hydroxyl radical *in situ* which promoted a cascade radical reactions. DMSO was activated by hydroxyl radical in the reaction system to give methyl sulfonyl radical, which further functionalized the aryl alkenes. Isotopic labelling and $^{18}O_2$ experiments were performed to examine the reaction mechanism.

[132] a) Suryakiran, N.; Prabhakar, P.; Reddy, T. S.; Mahesh, K. C.; Rajesh, K.; Venkateswarlu, Y. *Tetrahedron Lett.* **2007**, *48*, 877; b) Powers, L. J.; Fogt, S. W.; Ariyan, Z. S.; Rippin, D. J.; Heilman, R. D. *J. Med. Chem.* **1981**, *24*, 604.

4.3 SYNTHESIS OF (*E*)-VINYL METHYL SULFONES BY METHYL SULFONYLATION OF ALKYNES WITH DMSO

4.3.1 INTRODUCTION

The C–S bonds formation reactions play an important role in organic synthesis.[133] Organosulfur compounds are very useful synthetic intermediates that contain fundamental functional groups, such as thiol, sulfide, or disulfide units.[134] Furthermore, they are also occurred widely in biological systems ranging from small natural metabolites to proteins. Among them, vinyl sulfones as an interesting sulfur-containing compounds, have found valuable applications in biological research such as covalent protease inhibitors[135] or substrates for bioconjugation.[136] Vinyl sulfones are also widely used as synthetic intermediates that serve as both Michael acceptors and reaction partners in cycloaddition reaction in organic synthesis. In the interest of the significance of these compounds, many methods have been developed to synthesize them. The general methods for the preparation of vinyl sulfones involve a) the oxidation of vinyl sulfides, b) the elimination from α- or β substituted sulfones, or c) olefination reactions, which normally involve multiple-step synthesis from either

[133] a) Vigalok, A.; C-X Bond Formation, Springer, Heidelberg, **2010**; b) Yudin, A. K. Catalyzed Carbon-Heteroatom Bond Formation, Wiley-VCH, Weinheim, **2012**; c) Liu, H.; Jiang, X. *Chem. Asian J.* **2013**, *8*, 2546.

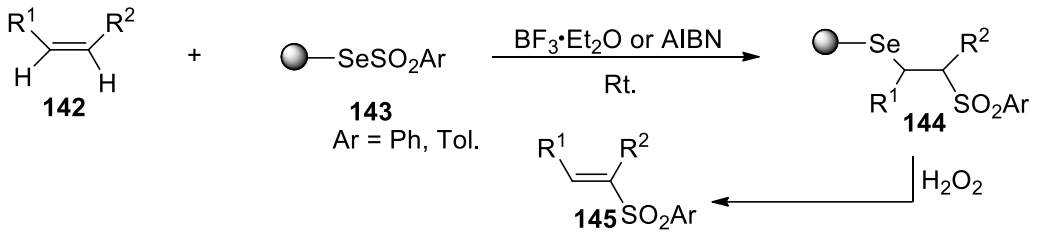
[134] Dénès, F.; Pichowicz, M.; Povie, G.; Renaud, P. *Chem. Rev.* **2014**, *114*, 2587.

[135] a) Palmer, J. T.; Rasnick, D.; Klaus, J. L.; Bromme, D. *J. Med. Chem.* **1995**, *38*, 3193; b) Santos, M. M. M.; Moreira, R. *Mini-Rev. Med. Chem.* **2007**, *7*, 1040; c) Kerr, I. D.; Lee, J. H.; Farady, C. J.; Marion, R.; Rickert, M.; Kailash, M. S.; Pandey, C.; Caffrey, C. R.; Legac, J.; Hansell, E.; McKerrow, J. H.; Craik, C. S.; Rosenthal, P. J.; Brinen, L. S. *J. Biol. Chem.* **2009**, *284*, 25697; d) Kisselev, A. F.; Linden, van der W. A.; Overkleeft, H. S. *Chem. Biol.* **2012**, *19*, 99; e) Ni, L.; Zheng, X. S.; Somers, P. K.; Hoong, L. K.; Hill, R. R.; Marino, E. M.; Suen, K.-L.; Saxena, U.; Meng, C. Q. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 745.

[136] a) Morales-Sanfrutos, J.; Lopez-Jaramillo, J.; Ortega-Munoz, M.; Megia-Fernandez, A.; Perez-Balderas, F.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Org. Biomol. Chem.* **2010**, *8*, 667; b) Lopez-Jaramillo, F. J.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. Integrative Proteomics (Ed.: H.-C. E. Leung), InTech, Rijeka, **2012**, pp. 301-327.

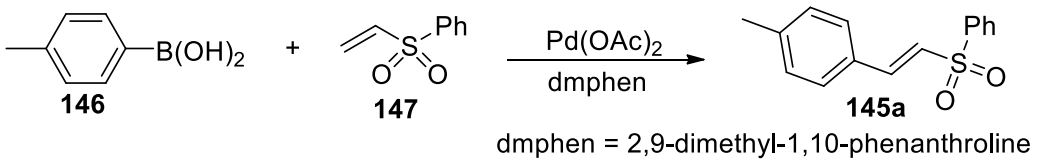
toxic or unstable starting materials.[137]

Herein, we briefly introduce the recent development in the synthesis of vinyl sulfones. In 2011, Huang group reported a novel polystyrene-supported addition of selenosulfonates reagents **143** to olefins **142** in the presence of boron trifluoride or AIBN to prepare vinyl sulfones **145** in good regioselectivity (Scheme 4.14).[138]



Scheme 4.14 Selenosulfonations of olefins to vinyl sulfones

Mizoroki-Heck reaction is an instrumental method to obtain direct C–C bond formation.[139] Recently, Mats Larhed reported a palladium-catalyzed reaction of arylboronic acid **146** with vinyl sulfones **147** to give the trans-configured *β*-substituted products **145a** exclusively (Scheme 4.15).[140]



Scheme 4.15 Arylation of olefins to alkenyl sulfones

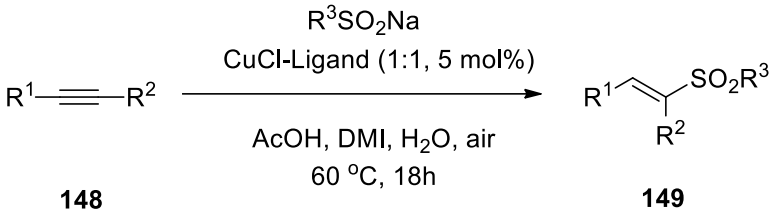
[137] a) Nair, V.; Augustine, A.; Suja, T. D. *Synthesis* **2002**, 2259; b) Meadows, D. C.; Gervay-Hague, J.; *Med. Res. Rev.* **2006**, *26*, 793; d) Huang, X.; Duan, D.; Zheng, W. *J. Org. Chem.* **2003**, *68*, 1958; c) Xu, W. M.; Tang, E.; Huang, X. *Synthesis* **2004**, 2094; d) Guan, Z.-H.; Zuo, W.; Zhao, L.-B.; Ren, Z.-H.; Liang, Y.-M. *Synthesis* **2007**, 1465; e) Signore, G.; Malanga, C.; Menicagli, R. *Tetrahedron* **2008**, *64*, 11218; f) Das, B.; Lingaiah, M.; Damodar, K.; Bhunia, N. *Synthesis* **2011**, 2941; g) Liang, S.; Zhang, R.-Y.; Wang, G.; Chen, S.-Y.; Yu, X.-Q. *Eur. J. Org. Chem.* **2013**, 7050.

[138] Qian, H.; Huang, X. *Synlett* **2001**, 1913.

[139] a) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320; b) Heck, R. F. *Synlett* **2006**, 2855; c) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581; For reviews, see: d) Heck, R. F. Acc. Chem. Res. **1979**, *12*, 146; e) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009; f) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442; g) Br äse, S.; Meijere, de A. in *Metal-Catalyzed Cross-coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, pp.217; h) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644.

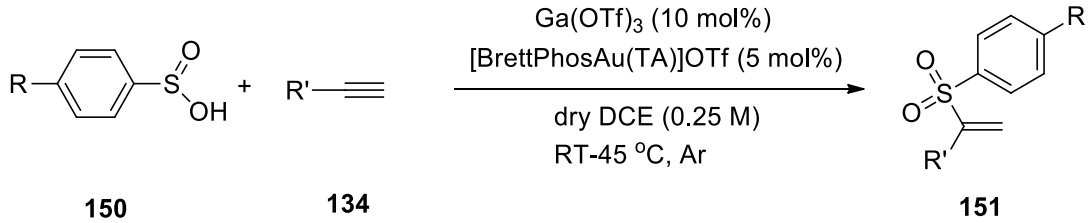
[140] Lindh, J.; Enquist, P. A.; Pilotti, Å.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2007**, *72*, 7957.

In 2014, a copper-catalyzed sulfonylation of alkynes **148** was reported by Taniguchi, using sodium sulfinates in air to provide (*E*)-alkenyl sulfones **149** regio- and stereoselectively (Scheme 4.16).[141]



Scheme 4.16 Sulfonylation of alkynes to (*E*)-alkenyl sulfones

Shi and co-workers recently reported a general method for the synthesis of *α*-substituted vinyl sulfones **151** in the presence of a triazole gold complex and gallium triflate (Scheme 4.17).[142] In contrary to the previous examples, this efficient C–S bond formation between simple terminal alkynes **134** and sulfinic acids **150** provided access to anti-Markovnikov vinyl sulfones.



Scheme 4.17 Sulfonylation of alkynes to anti-Markovnikov sulfonal adducts

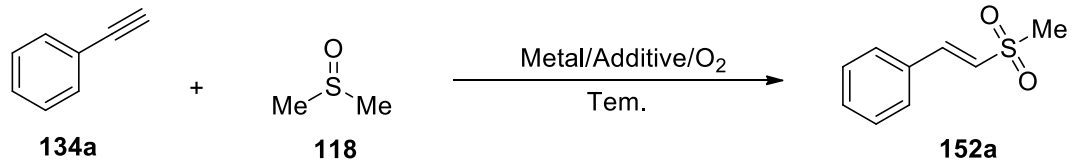
In view of our continuous interests in methyl sulfonyl radical generation from DMSO/CuBr catalytic system, we turned our attention to synthesize of (*E)*-vinyl methyl sulfones by methyl sulfonylation of alkynes *via* a radical process.

[141] Taniguchi, N. *Tetrahedron* **2014**, *70*, 1984.
[142] Xi, Y.; Dong, B.; McClain, E. J.; Wang, Q.; Gregg, T. L.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 4657.

4.3.2 RESULT AND DISCUSSION

At the outset, we performed the reaction of phenyl acetylene **134a** with DMSO **118** under the same condition as styrenes **136** and after the reaction we detected a major product **152a** in moderate yield after analyzing the spectra data (Table 4-3, entry 1). Encouraged by this result, we explored the reaction with aryl alkynes under various conditions. Increasing the reaction temperature was found to be beneficial to the reaction to give **152a** in 75% yield (Table 4-3, entry 2). Further effort to increase the yield of the reaction was employed organic base and acid, the result found that the triethylamine suppressed the reaction completely, while acetic acid reduced the yield

Table 4-3 Optimization of reaction conditions for (*E)*-vinyl methyl sulfones[a]



134a **118** **152a**

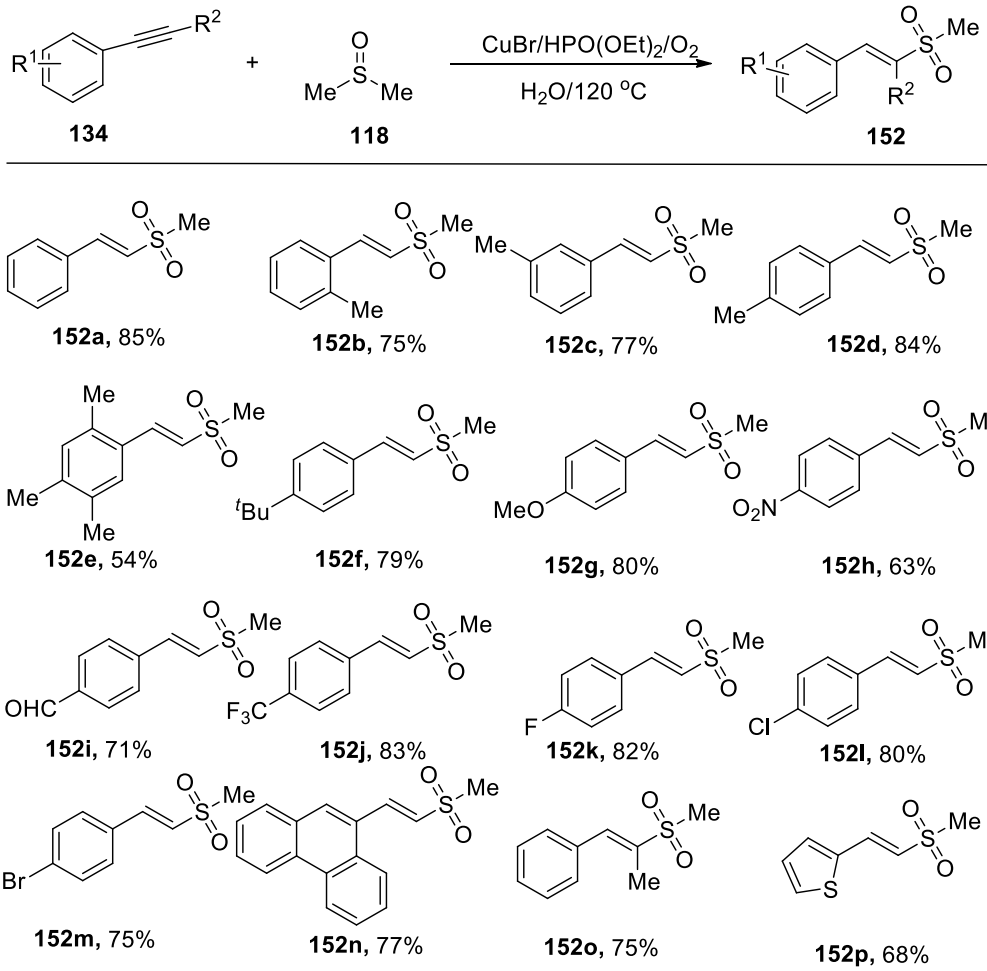
Entry	Catalyst	Additives[f]	Temp.	Yield(%)[b]
1	CuBr	D-2 (3.0 eq.)	90	64
2	CuBr	D-2 (3.0 eq.)	120	75
3	CuBr	D-2 (3.0eq.)+TEA[c]	120	-
4	CuBr	D-2 (3.0eq.)+HOAc[c]	120	45
5	CuBr	D-2 (3.0eq.)+Ag(OTf)[d]	120	54
6	CuBr	D-2 (3.0eq.)+$NiCl_2$[d]	120	-
7	CuBr	D-2 (3.0eq.)+$ZnBr_2$[d]	120	-
8	CuBr	D-2 (3.0eq.)+$FeBr_2$[d]	120	-
9	CuBr	D-2 (3.0eq.)+H_2O (10 eq.)	120	88 (85[e])
10	CuBr	D-2 (3.0eq.)+H_2O (20 eq.)	120	83

[a]Conditions: **134a (**0.25 mmol, 27.5 μL), catalyst (10 mol%) and additive were stirred in 1 mL DMSO under 1 atm. O_2 balloon for about 24 h. [b]GC yields. [c]3.0 eq. [d]20 mol%. [e]Isolated yield. [f]D-2: $HPO(OEt)_2$.

to 45% (Table 4-3, entries 3-4). It was found that using bimetallic catalysts system like silver, nickel, zinc and iron together with copper also failed to improve the reaction efficiency (Table 4-3, entries 5-8). Gratifyingly, the reaction proceeded smoothly with up to 85% isolated yield after adding 10 equiv. of water (Table 4-3, entry 9). Further increment in the amount of water had negligible effect on this reaction (Table 4-3, entry 10).

When we extended the optimized conditions to other substrates, all aryl alkynes reacted smoothly to afford the desired vinyl methyl sulfones in good to excellent yields giving the *E*-isomer exclusively. *Ortho*, *meta*- and *para*-substituted phenyl alkynes re-

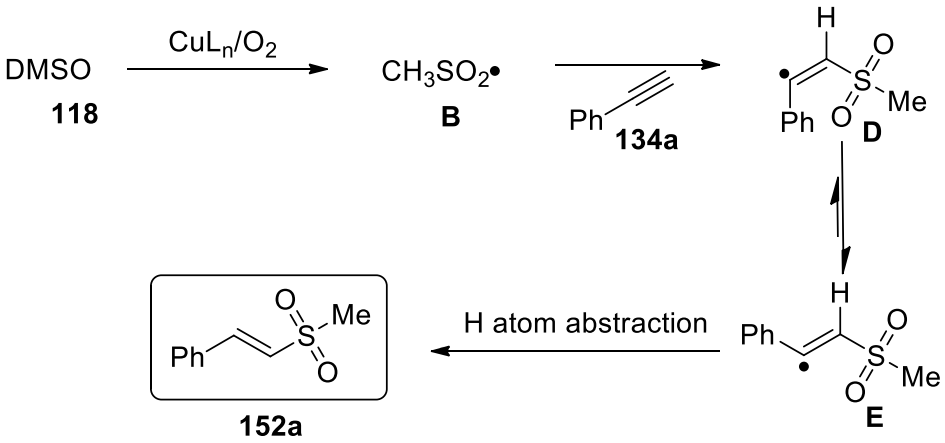
Table 4.4 Substrates scope for reaction of alkynes with DMSO[a, b]



[a]Conditions: 0.25 mmol **134** and 10 mol% CuBr with 3.0 equiv $HPO(OEt)_2$ were stirred in 10 eq. H_2O and 1 mL DMSO under 1 atm. O_2 balloon. [b]Isolated yields.

-acted well under optimized conditions leading to the corresponding *E*-vinyl methyl sulfones in good to excellent yields (**152b**-**152d**). Steric effect reduced the yield slightly when 1-ethynyl-2,4,5-trimethylbenzene (**152e**) was tested, while substrate with phenyl bearing tertiary butyl group at *para* position had less influence on the reaction (**152f**). A study of electronic effect showed that alkynes with both electron-donating (**152g**) and electron-withdrawing (**152h**-**152j**) substituents gave products in moderate to excellent yields (63%-83%). It is noteworthy that aldehyde, as useful functional group, could be well tolerated without oxidation to acid. Substrates bearing halogens (F, Cl, Br) at the *para*-position of phenyl group also proceeded smoothly to provide the corresponding products in good yields (**152k**-**152m**). Because of these functionalities renders the products to be amenable for further transformation through coupling reactions. Reactions of fused rings (**152n**) as well as heterocyclic compounds (**152o**) were performed and the corresponding (*E*)-vinyl methyl sulfones were obtained in good yields of 77% and 68%, respectively. Finally, internal alkynes is also an effective substrate to give (*E*)-(2-(methylsulfonyl)prop-1-en-1-yl)benzene in 75% yield (**152p**).

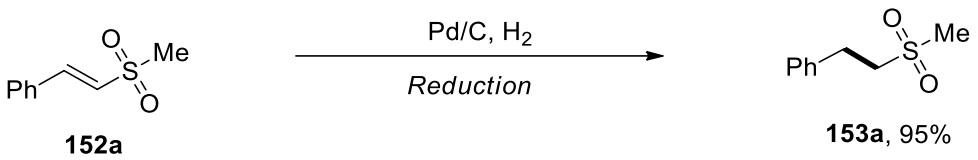
On the basis of these results, a proposed reaction mechanism which is similar to the alkene system is described in Scheme 4.18. Methyl sulfonyl radical **B** was prob-



Scheme 4.18 Proposed mechanistic rationalization

-ably generated through the pathway as shown in Scheme 4.17, and subsequently reacted with the alkyne **134a** to form complex-**D**. After the hydrogen atom abstraction process, only *E* isomer **152a** was detected.

An example of applications of vinyl methyl sulfones was also explored. The methyl sulfonyl group could be well tolerated in reductive condition to afford (2-(methylsulfonyl)ethyl)benzene **153a** in excellent yield from (*E*)-(2-(methylsulfonyl)vinyl)benzene **152a** (Scheme 4.19).



Scheme 4.19 Transformation of (*E*)-vinyl methyl sulfones

4.3.3 SUMMARY

In summary, a simple and direct methodology for the synthesis of (*E*)-vinyl methyl sulfones from common substrates aryl alkynes and DMSO was described. High temperature and small amount of water were shown to improve the reaction efficiency compared to the reaction system for alkenes. Mechanistically, DMSO was activated by hydroxyl radical in the reaction system to give methyl sulfonyl radical, which further functionalized the aryl alkynes leading to (*E*)-vinyl methyl sulfones regioselectively.

4.4 CONCLUSION

In this chapter, we have described a radical strategy promoted by copper, oxygen and $HPO(OEt)_2$ for difunctionalization of alkenes to synthesis of β-keto methyl sulfones; meanwhile, we have also demonstrated that alkynes could be directly

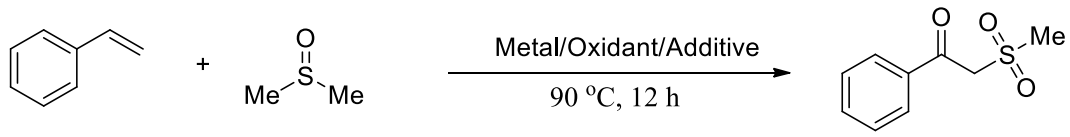
methyl sulfonylation to afford (*E*)-vinyl methyl sulfones through modification of the reaction condition. We demonstrated a new catalytic system that involves copper, oxygen and $HPO(OEt)_2$ to generate the hydroxyl radical *in situ* which initiates a cascade radical reactions. DMSO was activated in the reaction system to afford methyl sulfonyl radical that can functionalize both the aryl alkenes and alkynes. Isotopic labeling and $^{18}O_2$ experiments were performed to investigate the reaction mechanism.

4.5 EXPERMENTAL SECTION

4.5.1 Synthesis of *β*-keto methyl sulfones by methyl sulfonylation of alkenes with DMSO

4.5.1.1 Optimization of reaction conditions and general procedure for mechanism study:

Table 4.4 Optimization of reaction conditions for *β*-keto methyl sulfones[a]



136a 118 137a

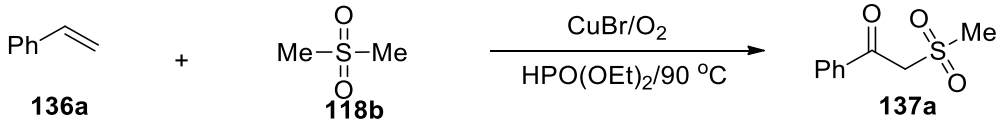
Entry	Solvent	Catalyst	Additive[f]	Temp.	Yield[b]
1	DCE[c]	CuBr (10%)	D-2 (2.0 eq.)	90	5
2	DMF[c]	CuBr (10%)	D-2 (2.0 eq.)	90	4
3	Tol[c]	CuBr (10%)	D-2 (2.0 eq.)	90	-
4	ACN[c]	CuBr (10%)	D-2 (2.0 eq.)	90	-
5	DMSO	CuBr (10%)	D-2 (2.0 eq.)	90	52
6	DMSO	CuBr (5%)	D-2 (2.0 eq.)	90	47
7	DMSO	-	D-2 (2.0 eq.)	90	-
8[d]	DMSO	-	Pyridine (2.0 eq.)	90	-
9	DMSO	CuBr (20%)	D-2 (2.0 eq.)	90	42

10	DMSO	CuBr (10%)	D-2 (2.0 eq.)	55	10
11	DMSO	CuBr (10%)	D-2 (2.0 eq.)	70	48
12	DMSO	CuBr (10%)	D-2 (2.0 eq.)	110	45
13	DMSO	CuBr (10%)	D-2 (3.0 eq.)	90	86(82[e])
14	DMSO	CuBr (10%)	D-2 (2.2 eq.)	90	71
15	DMSO	CuBr (10%)	D-2 (1.5 eq.)	90	50
16	DMSO	CuBr (10%)	D-2 (0.5 eq.)	90	15
17	DMSO	CuBr (10%)	-	90	-
18	DMSO	CuBr (10%)	D-3 (3.0 eq.)	90	75
19	DMSO	CuBr (10%)	D-4 (3.0 eq.)	90	80
20	DMSO	CuBr (10%)	D-5 (3.0 eq.)	90	64
21	DMSO	CuBr (10%)	D-6 (3.0 eq.)	90	-
22	DMSO	CuCl (10%)	D-2 (3.0 eq.)	90	25
23	DMSO	CuI (10%)	D-2 (3.0eq.)	90	55
24	DMSO	Cu(OTf).Benzene(10%)	D-2 (3.0eq.)	90	77
25	DMSO	Cu(OAc) (10%)	D-2 (3.0eq.)	90	54
26	DMSO	CuCN (10%)	D-2 (3.0eq.)	90	47
27	DMSO	CuTC (10%)	D-2 (3.0eq.)	90	73
28	DMSO	$Cu(OTf)_2$ (10%)	D-2 (3.0eq.)	90	36
29	DMSO	$Cu(hfacac)_2$ (10%)	D-2 (3.0eq.)	90	52
30	DMSO	Cu_2O (10%)	D-2 (3.0eq.)	90	69
31	DMSO	$Cu(OAc)_2$ (10%)	D-2 (3.0eq.)	90	64
32	DMSO	$CuBr_2$ (10%)	D-2 (3.0eq.)	90	28
33	DMSO	$FeBr_2$ (10%)	D-2 (3.0eq.)	90	-
34	DMSO	$NiCl_2$ (10%)	D-2 (3.0eq.)	90	-
35	DMSO	$CoBr_2$ (10%)	D-2 (3.0eq.)	90	-
36[g]	DMSO	CuBr (10%)	D-2 (3.0eq.)	90	73

[a]Conditions: **136a (**0.25 mmol), catalyst and additive were stirred in 1 mL DMSO under 1 atm. O_2 balloon for about 12h. [b]GC yields. [c]5 mmol DMSO in 1 mL referred solvent. [d]Lei's condition. [e]Isolated yield. [f] D-2: $HPO(OEt)_2$; D-3: $HPO(OMe)_2$; D-4: $HP(O^nBu)_2$; D-5: $HP(O^iBu)_2$; D-6: $HPO(OPh)_2$. [g]The same condition under 1 atm. air balloon.

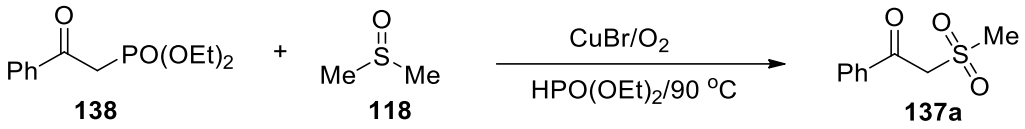
General procedure for mechanism study:

1. Styrene reacted with dimethyl sulfone:



A mixture of alkene **136a** (0.25 mmol), dimethyl sulfone **118b** (5 mmol), $HPO(OEt)_2$ (0.75 mmol) and CuBr (0.025 mmol) in 0.1 mL DCE in an oven-dried tube, which was stirred at 90 °C under 1 atm. O_2 atmosphere for 24h. After cooling down, the reaction mixture was diluted with 10 mL ethyl acetate (EA) and washed with water (2 mL) for 3 times. The water solution was extracted with EA twice and combined top layer with previous organic mixtures. After dried with Na_2SO_4, the mixture was concentrated under reduced pressure to give the crude material, there is no product **137a** was detected by GC analysis.

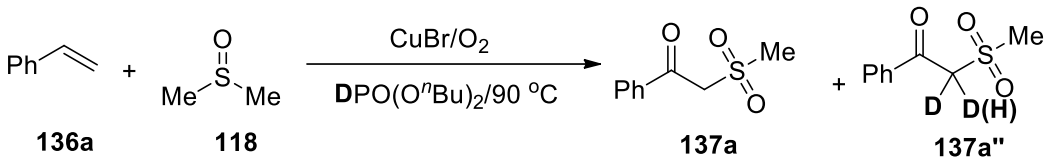
2. *β*-Keto phosphonate reacted with DMSO:



A mixture of phosphonate **138** (0.25 mmol), $HPO(OEt)_2$ (0.75 mmol) and CuBr (0.025 mmol) in 1 mL DMSO in an oven-dried tube, which was stirred at 90 °C under 1 atm. O_2 atmosphere for 24h. After cooling down, the reaction mixture was diluted with 10 mL ethyl acetate (EA) and washed with water (2 mL) for 3 times. The water solution was extracted with EA twice and combined top layer with previous organic mixtures. After dried with Na_2SO_4, the mixture was concentrated under reduced pressure to give the crude material, there is no product **137a** was detected by

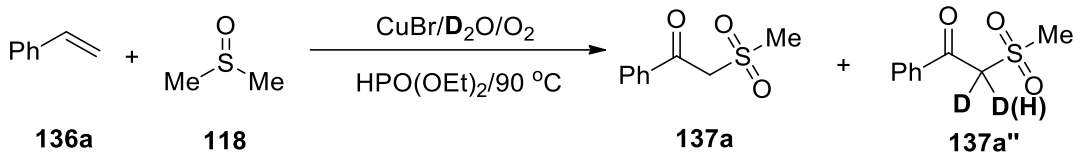
GC analysis.

3. Styrene reacted with DMSO with D-labeling of dibutyl phosphite:



A mixture of alkene **136a** (0.25 mmol), $DPO(O^nBu)_2$ (0.75 mmol) and CuBr (0.025 mmol) in 1 mL DMSO in an oven-dried tube, which was stirred at 90 °C under O_2 atmosphere for 24h. After cooling down, the reaction mixture was diluted with 10 mL ethyl acetate (EA) and washed with water (2 mL) for 3 times. The water solution was extracted with EA twice and combined top layer with previous organic mixtures. After dried with Na_2SO_4, the mixture was concentrated under reduced pressure to give the crude material which was purified by flash chromatography using hexane : ethyl acetate = 1 : 1 to give **137a** in 80% isolated yield, there is no D-labeling product **137a"** was detected.

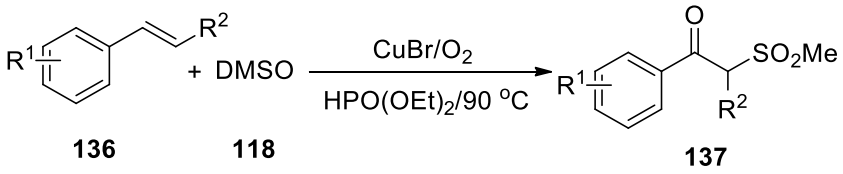
4. Styrene reacted with DMSO within D_2O:



A mixture of alkene **136a** (0.25 mmol), D_2O (5 mmol), $HPO(OEt)_2$ (0.75 mmol) and CuBr (0.025 mmol) in 1 mL DMSO in an oven-dried tube, which was stirred at 90 °C under 1atm. O_2 atmosphere for 24h. After cooling down, the reaction mixture was diluted with 10 mL ethyl acetate (EA) and washed with water (2 mL) for 3 times. The water solution was extracted with EA twice and combined top layer with previous

organic mixtures. After dried with Na_2SO_4, the mixture was concentrated under reduced pressure to give the crude material which was purified by flash chromatography using hexane : ethyl acetate = 1 : 1 to give **137a** in 83% isolated yield, there is no D-labeling product **137a** was detected.

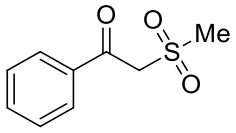
4.5.1.2 General procedure for *β*-keto methyl sulfones and their spectra data:



136 **118** **137**

A mixture of alkene **136** (0.25 mmol), DMSO **118** (1 mL), $HPO(OEt)_2$ (0.75 mmol, 96.6 μL) and CuBr (0.025 mmol, 3.6 mg) in an oven-dried tube, which was stirred at 90 ^oC under 1atm. O_2 atmosphere until the starting material was fully consumed (12 - 24 h). The reaction mixture was diluted with 10 mL ethyl acetate (EA) and washed with water (2 mL) for 3 times. The water solution was extracted with EA twice and combined top layer with previous organic mixtures. After dried with Na_2SO_4, the mixture was concentrated under reduced pressure to give the crude material which was purified by flash chromatography using hexane : ethyl acetate = 1 : 1 to give desired product **137**.

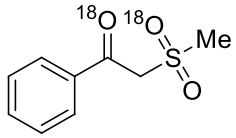
2-(Methylsulfonyl)-1-phenylethanone (137a):



The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 104 - 105 ℃. Yield: 82%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 - 7.99 (m, 2H), 7.68 - 7.64 (m, 1H), 7.55 - 7.51 (m, 2H), 4.61 (s, 2H), 3.16 (s, 3H);

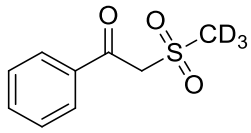
^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2, 135.6, 134.6, 129.2, 129.0, 61.2, 41.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{11}O_3S$: 199.0429. Found: 199.0424.

2-(Methylsulfonyl)-1-phenylethanone (137a'):



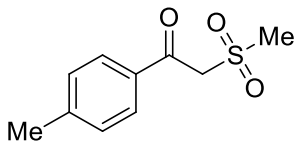
The title compound was prepared according to the general procedure with using 1atm. $^{18}O_2$ instead of O_2. The product was obtained as white solid, mp: 109 - 110 ℃. Yield: 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 - 7.99 (m, 2H), 7.68 - 7.64 (m, 1H), 7.55 - 7.51 (m, 2H), 4.61 (s, 2H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2, 189.2, 135.6, 134.7, 129.2, 129.0, 61.3, 41.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{11}O_3S$: 203.0514. Found: 203.0516.

2-(Methylsulfonyl)-1-phenylethanone (137aa'):



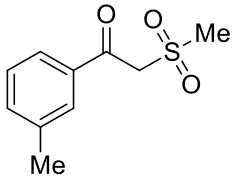
The title compound was prepared according to the general procedure with using *d*-DMSO instead. The product was obtained as white solid, mp: 114 - 115 ℃. Yield: 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 - 7.99 (m, 2H), 7.68 - 7.64 (m, 1H), 7.55 - 7.51 (m, 2H), 4.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2, 135.6, 134.7, 129.2, 129.0, 61.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_8D_3O_3S$: 202.0617. Found: 202.0617.

2-(Methylsulfonyl)-1-(p-tolyl)ethanone (137b):



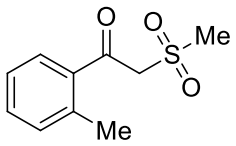
The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 116 - 117 ℃. Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.57 (s, 2H), 3.14 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 146.0, 133.2, 129.7, 129.4, 61.2, 41.8, 21.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{13}O_3S$: 213.0585. Found: 213.0591.

Ethyl 2-isopropyl-6-phenylnicotinate (137c):



The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 65 - 66 ℃. Yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 - 7.89 (m, 2H), 7.48 - 7.39 (m, 2H), 4.59 (m, 2H), 3.15 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4, 139.0, 135.7, 135.5, 129.6, 128.9, 126.5, 61.3, 41.8, 21.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{13}O_3S$: 213.0585. Found: 213.0578.

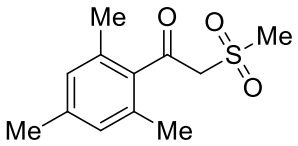
2-(Methylsulfonyl)-1-(o-tolyl)ethanone (137d):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.6 Hz, 1H), 7.49 - 7.45 (m, 1H), 7.36 - 7.29 (m, 2H), 4.56 (m, 2H), 3.17 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 140.1, 135.7, 133.1, 132.5, 130.2, 126.1, 63.4,

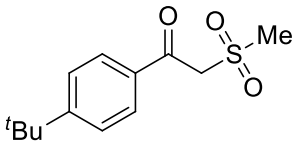
42.0, 21.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{13}O_3S$: 213.0585. Found: 213.0591.

1-Mesityl-2-(methylsulfonyl)ethanone (137e):



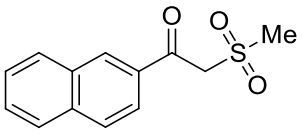
The title compound was prepared according to the general procedure. The product was obtained as colorless solid, mp: 136 - 137 ℃. Yield: 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 2H), 4.34 (d, J = 0.8 Hz, 2H), 3.23 (s, 3H), 2.29 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 140.5, 137.1, 133.9, 129.2, 65.6, 42.6, 21.1, 19.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{17}O_3S$: 241.0898. Found: 241.0899.

1-(4-(*tert*-Butyl)phenyl)-2-(methylsulfonyl)ethanone (137f):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 4.58 (s, 2H), 3.14 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 158.9, 133.1, 129.3, 126.0, 61.2, 41.7, 35.3, 30.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{19}O_3S$: 255.1055. Found: 255.1055.

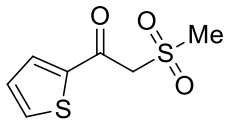
2-(Methylsulfonyl)-1-(naphthalen-2-yl)ethanone (137g):



The title compound was prepared according to the general procedure. The product was

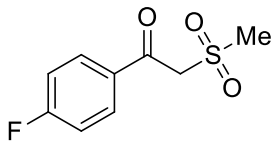
obtained as yellow solid, mp: 99 - 100 ℃. Yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.04 - 7.93 (m, 2H), 7.91 - 7.87 (m, 2H), 7.67 - 7.57 (m, 2H), 4.73 (s, 2H), 3.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1, 136.1, 133.0, 132.3, 132.1, 130.0, 129.5, 129.0, 127.8, 127.3, 123.7, 61.3, 41.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{13}O_3S$: 249.0585. Found: 249.0579.

2-(Methylsulfonyl)-1-(thiophen-2-yl)ethanone (137h):



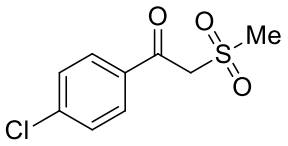
The title compound was prepared according to the general procedure. The product was obtained as brown solid, mp: 121 - 122 ℃. Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 - 7.81 (m, 2H), 7.23 - 7.21 (m, 1H), 4.50 (s, 2H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2, 143.0, 137.0, 135.4, 128.9, 62.3, 41.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_7H_9O_3S_2$: 204.9993. Found: 204.9993.

1-(4-Fluorophenyl)-2-(methylsulfonyl)ethanone (137i):



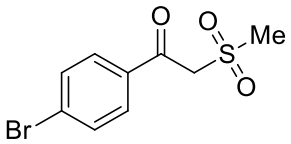
The title compound was prepared according to the general procedure. The product was obtained as colorless solid, mp: 89 - 90 ℃. Yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 - 8.04 (m, 2H), 7.22 - 7.18 (m, 2H), 4.58 (s, 2H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 168.0, 165.4, 132.2 (J = 9.8 Hz), 116.3 (J_1 = 22.2 Hz, J_2 = 1.3 Hz), 61.4 (J = 2.8 Hz), 41.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{10}O_3SF$: 217.0335. Found: 217.0337.

1-(4-Chlorophenyl)-2-(methylsulfonyl)ethanone (137j):



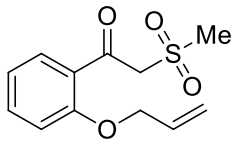
The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 149 - 150 ℃. Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 - 7.94 (m, 2H), 7.52 - 7.50 (m, 2H), 4.57 (s, 2H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 141.5, 133.9, 130.7, 129.4, 61.3, 41.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{10}O_3SCl$: 233.0039. Found: 233.0033.

1-(4-Bromophenyl)-2-(methylsulfonyl)ethanone (137k):



The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 160 - 161 ℃. Yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 - 7.86 (m, 2H), 7.69 - 7.67 (m, 2H), 4.56 (s, 2H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 134.3, 132.4, 130.7, 130.4, 61.3, 41.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{10}O_3SBr$: 276.9534. Found: 276.9535.

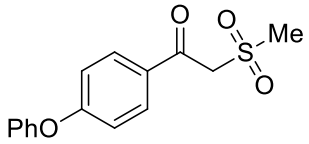
1-(2-(Allyloxy)phenyl)-2-(methylsulfonyl)ethanone (137l):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 - 7.81 (m, 1H), 7.55 - 7.51 (m, 1H), 7.07 - 7.03 (m, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.16 - 6.06 (m, 1H), 5.47 - 5.37 (m, 2H), 4.78 (s, 2H), 4.71 - 4.69 (m, 2H), 3.15 (s, 3H); ^{13}C NMR (100

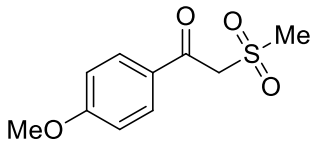
MHz, $CDCl_3$) δ 190.2, 158.3, 135.5, 131.9, 131.3, 126.4, 121.3, 119.4, 113.1, 69.9, 65.4, 42.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{15}O_4S$: 255.0691. Found: 255.0702.

2-(Methylsulfonyl)-1-(4-phenoxyphenyl)ethanone (137m):



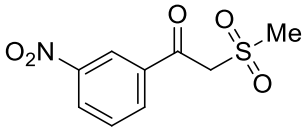
The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 124 - 125 ℃. Yield: 75%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 - 7.97 (m, 2H), 7.44 - 7.40 (m, 2H), 7.26 - 7.22 (m, 1H), 7.10 - 7.07 (m, 2H), 7.04 - 7.02 (m, 2H), 4.55 (s, 2H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 163.6, 154.8, 131.8, 130.2, 125.1, 120.5, 117.3, 61.2, 41.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{15}O_4S$: 291.0691. Found: 291.0686.

1-(4-Methoxyphenyl)-2-(methylsulfonyl)ethanone (137n):



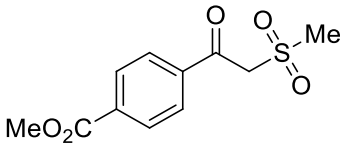
The title compound was prepared according to the general procedure. The product was obtained as colorless solid, mp: 139 - 140 ℃. Yield: 68%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J_1 = 6.8 Hz, J_2 = 2.4 Hz, 2H), 6.98 (dd, J_1 = 7.2 Hz, J_2 = 2.4 Hz, 2H), 4.55 (s, 2H), 3.89 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 164.8, 131.8, 128.7, 114.2, 61.2, 55.6, 41.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{13}O_4S$: 229.0535. Found: 229.0529.

2-(Methylsulfonyl)-1-(3-nitrophenyl)ethanone (137o):



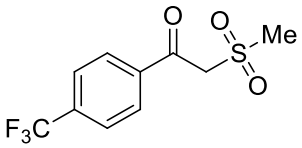
The title compound was prepared according to the general procedure. The product was obtained as colorless solid, mp: 104 - 105 ℃. Yield: 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 - 8.84 (m, 1H), 8.53 - 8.50 (m, 1H), 8.37 - 8.34 (m, 1H), 7.79 - 7.75 (m, 1H), 4.67 (s, 2H), 3.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 148.7, 136.9, 134.7, 130.4, 128.7, 124.1, 61.5, 41.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{10}NO_5S$: 244.0280. Found: 244.0285.

Methyl 4-(2-(methylsulfonyl)acetyl)benzoate (137p):



The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 129 - 130 ℃. Yield: 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 - 8.17 (m, 2H), 8.08 - 8.06 (m, 2H), 4.63 (s, 2H), 3.97 (s, 3H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 165.8, 138.6, 135.2, 130.1, 129.2, 61.6, 52.6, 41.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{13}O_5S$: 257.0484. Found: 257.0489.

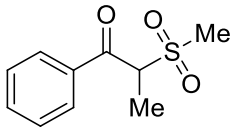
2-(Methylsulfonyl)-1-(4-(trifluoromethyl)phenyl)ethanone (137q):



The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 100 - 101 ℃. Yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 4.64 (s, 2H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 138.2, 135.8 (J = 32.8 Hz), 129.6, 126.1 (J = 3.5 Hz),

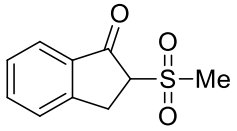
123.3 (J = 271.3 Hz), 61.5, 41.8; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{10}O_3SF_3$: 267.0303. Found: 267.0311.

2-(Methylsulfonyl)-1-phenylpropan-1-one (137r):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 - 8.02 (m, 2H), 7.68 - 7.64 (m, 1H), 7.55 - 7.51 (m, 2H), 4.96 (q, J = 7.2 Hz, 1H), 2.98 (s, 3H), 1.75 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 135.7, 134.5, 129.2, 129.0, 64.0, 36.9, 13.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{13}O_3S$: 213.0585. Found: 213.0591.

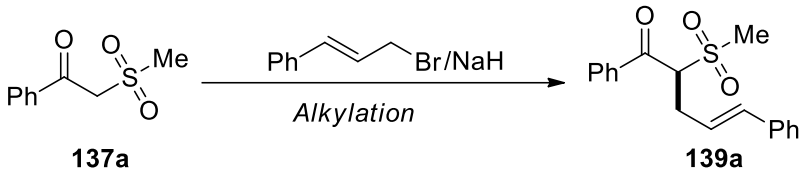
2-(Methylsulfonyl)-2,3-dihydro-*1H*-inden-1-one (137s):



The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 157 - 158 ℃. Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.6 Hz, 1H), 7.70 - 7.66 (m, 1H), 7.56 - 7.54 (m, 1H), 7.46 - 7.42 (m, 1H), 4.15 (dd, J_1 = 8.4 Hz, J_2 = 3.6 Hz, 1H), 3.80 (dd, J_1 = 18.0 Hz, J_2 = 3.6 Hz, 1H), 3.51 (dd, J_1 = 18.0 Hz, J_2 = 8.4 Hz, 1H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 152.5, 136.3, 135.4, 128.4, 126.6, 125.1, 67.0, 40.2, 26.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{11}O_3S$: 211.0429. Found: 211.0428.

Applications of *β*-keto methyl sulfones:

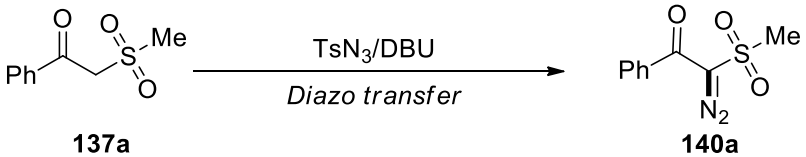
(*E*)-2-(Methylsulfonyl)-1,5-diphenylpent-4-en-1-one (139a):



137a **139a**

The title compound was prepared according to the following procedure: To a solution of NaH (0.24 mmol) in 5 mL THF, **137a** (0.20 mmol) in 1 mL THF solution was added dropwise, the resulted mixture was stirred for 0.5 h, then (*E*)-(3-bromoprop-1-en-1-yl)benzene (0.24 mmol) in 1 mL THF solution was added at 0 ^{o}C. The reaction mixture was allowed at 50 ^{o}C for around 6 h until the **137a** was consumed completely. It quenched with 5 mL NH_4Cl, and extracted with ethyl acetate for 3 times. The combined organic lay was concentrated under reduced pressure to give the crude material which was purified by flash chromatography using hexane : ethyl acetate = 2 : 1 to give desired product as yellow solid, mp: 133 - 135 ^{o}C. Yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.6 Hz, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.26 - 7.20 (m, 5H), 6.50 (d, J = 15.6 Hz, 1H), 6.03 - 5.95 (m, 1H), 5.00 (dd, J_1 = 10.0 Hz, J_2 = 4.4 Hz, 1H), 3.22 - 3.13 (m, 2H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 136.7, 136.3, 134.5, 134.5, 129.2, 129.0, 128.5, 127.8, 126.3, 122.6, 68.7, 37.7, 32.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{19}O_3S$: 315.1055. Found: 315.1059.

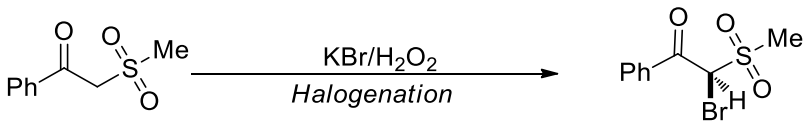
2-Diazo-2-(methylsulfonyl)-1-phenylethanone (140a):



137a **140a**

The title compound was prepared according to the following procedure: **137a** (0.20 mmol) and tosyl azide (0.24 mmol, 47.3 mg) was added to 5 mL dry CH_3CN, the resulting mixture was cooled at 0 ^oC. DBU (0.24 mmol, 36.5 mg) was then added dropwisely and the mixture was stirred for around 2h until the **137a** was consumed completely based on TLC. The reaction mixture was concentrated directly under reduced pressure to give the crude material which was purified by flash chromatography using hexane : ethyl acetate = 2 : 1 to give desired product as yellow oil. Yield: 88%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 - 7.66 (m, 2H), 7.64 - 7.60 (m, 1H), 7.53 - 7.49 (m, 2H), 3.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.3, 135.5, 133.4, 129.1, 127.4, 45.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{10}N_2O_3S$: 225.0334. Found: 225.0338.

2-Bromo-2-(methylsulfonyl)-1-phenylethanone (141a):



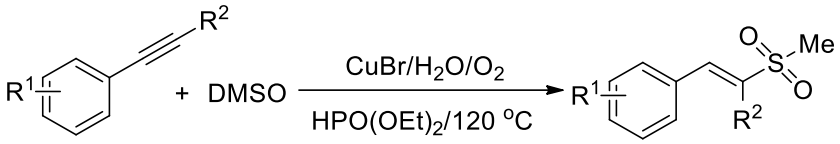
137a **141a**

The title compound was prepared according to the reported procedure.[132a] **3a** (0.20 mmol, 39.6 mg) and KBr (0.24 mmol, 28.6 mg) was added to 2 mL acetic acid, the resulting mixture was cooled at 0 ^oC. H_2O_2 (1.6 mmol, 48.0 μL) was then added slowly and the mixture was stirred for overnight at room temperature until the **3a** was consumed completely based on TLC. The reaction mixture was concentrated directly under reduced pressure to give the crude material which was purified by flash chromatography using hexane : ethyl acetate = 4 : 1 to give desired product as white solid, mp: 80 - 82 ^oC. Yield: 86%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01- 7.98 (m, 2H), 7.72 - 7.68 (m, 1H), 7.57 - 7.53 (m, 2H), 6.00 (s, 1H), 3.35 (s, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 187.8, 135.1, 133.8, 129.3, 129.2, 55.9, 37.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{10}BrO_3S$: 276.9534. Found: 276.9536.

4.5.2 Synthesis of (*E*)-vinyl methyl sulfones by methyl sulfonylation of alkynes with DMSO

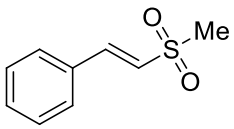
General procedure for (*E*)-vinyl methyl sulfones:



134 **118** **152**

A mixute of alkyne compound **134** (0.25 mmol), DMSO **118** (1 mL), $HPO(OEt)_2$ (0.75 mmol), H_2O (2.5 mmol) and CuBr (0.025 mmol) in an oven-dried tube, which was stirred at 120 °C under 1atm. O_2 atmosphere until the starting material was fully consumed. The reaction mixture was diluted with 10 mL ethyl acetate (EA) and washed with water (2 mL) for 3 times. The water solution was extracted with EA twice and combined top layer with previous organic mixtures. After dried with Na_2SO_4, the mixture was concentrated under reduced pressure to give the crude material which was purified by flash chromatography using hexane : ethyl acetate = 1 : 1 to give desired product **152**.

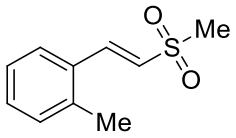
(*E*)-(2-(Methylsulfonyl)vinyl)benzene (152a):



The title compound was prepared according to the general procedure. The product was obtained as yellow oil. Yield: 85%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 15.2 Hz,

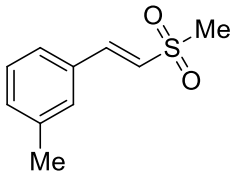
1H), 7.54 - 7.51 (m, 2H), 7.46 - 7.43 (m, 3H), 6.92 (d, *J* = 15.2 Hz, 1H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 132.0, 131.3, 129.1, 128.5, 126.2, 43.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{11}O_2S$: 183.0480. Found: 183.0476.

(*E*)-1-Methyl-2-(2-(methylsulfonyl)vinyl)benzene (152b):



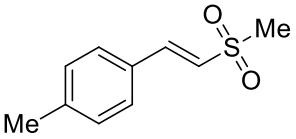
The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 85 - 86 ℃. Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 15.2 Hz, 1H), 7.52 - 7.50 (m, 1H), 7.36 - 7.32 (m, 1H), 7.26 - 7.23 (m, 2H), 6.84 (d, *J* = 15.2 Hz, 1H), 3.04 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 138.3, 131.1, 131.0, 127.1, 126.8, 126.6, 43.3, 19.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{13}O_2S$: 197.0636. Found: 197.0639.

(*E*)-1-Methyl-3-(2-(methylsulfonyl)vinyl)benzene (152c):



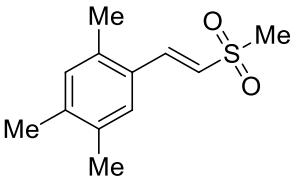
The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 65 - 66 ℃. Yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 15.2 Hz, 1H), 7.32 - 7.27 (m, 4H), 6.91 (d, *J* = 15.2 Hz, 1H), 3.03 (m, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 138.9, 132.2, 132.1, 129.2, 129.0, 126.0, 125.8, 43.3, 21.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{13}O_2S$: 197.0636. Found: 197.0630.

(*E*)-1-Methyl-4-(2-(methylsulfonyl)vinyl)benzene (152d):



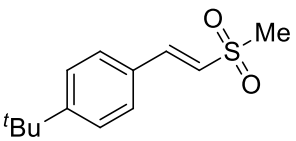
The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 116 - 117 ℃. Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 15.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 15.6 Hz, 1H), 3.03 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 142.1, 129.9, 129.3, 128.6, 125.0, 43.4, 21.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{13}O_2S$: 197.0636. Found: 197.0638.

(*E*)-1,2,4-Trimethyl-5-(2-(methylsulfonyl)vinyl)benzene (152e):



The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 97 - 98 ℃. Yield: 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 15.2 Hz, 1H), 7.29 (s, 1H), 7.01 (s, 1H), 6.80 (d, J = 15.2 Hz, 1H), 3.03 (s, 3H), 2.38 (s, 3H), 2.25 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 140.5, 135.8, 134.7, 132.4, 128.3, 127.9, 125.5, 43.4, 19.7, 19.2, 19.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{17}O_2S$: 225.0949. Found: 225.0953.

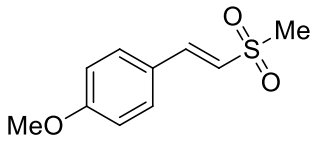
(*E*)-1-(*tert*-Butyl)-4-(2-(methylsulfonyl)vinyl)benzene (152f):



The title compound was prepared according to the general procedure. The product was obtained as colorless solid, mp: 87 - 88 ℃. Yield: 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ

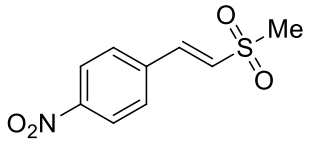
7.61 (d, *J* = 15.2 Hz, 1H), 7.48 - 7.43 (m, 4H), 6.88 (d, *J* = 15.6 Hz, 1H), 3.03 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 144.0, 129.3, 128.4, 126.1, 125.1, 43.4, 35.0, 31.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{19}O_2S$: 239.1106. Found: 239.1104.

(*E*)-1-Methoxy-4-(2-(methylsulfonyl)vinyl)benzene (152g):



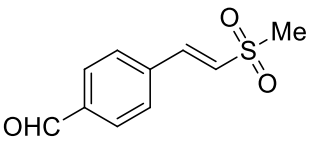
The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 119 - 120 ℃. Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 15.6 Hz, 1H), 7.47 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 6.94 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 6.76 (d, *J* = 15.6 Hz, 1H), 3.86 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 143.7, 130.4, 124.7, 123.4, 114.6, 55.5, 43.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{13}O_3S$: 213.0585. Found: 213.0583.

(*E*)-1-(2-(Methylsulfonyl)vinyl)-4-nitrobenzene (152h):



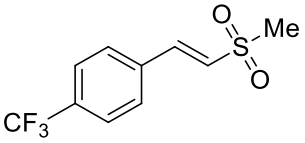
The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 189 - 190 ℃. Yield: 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 - 8.28 (m, 2H), 7.71 - 7.67 (m, 3H), 7.08 (d, *J* = 15.6 Hz, 1H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 141.1, 138.1, 130.5, 129.3, 124.4, 43.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{10}NO_4S$: 228.0331. Found: 228.0333.

(*E*)-4-(2-(Methylsulfonyl)vinyl)benzaldehyde (152i):



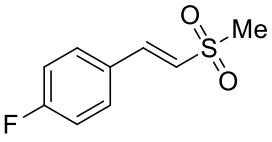
The title compound was prepared according to the general procedure. The product was obtained as colorless solid, mp: 140 - 141 ℃. Yield: 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 15.2 Hz, 1H), 7.05 (d, J = 15.6 Hz, 1H), 3.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 142.3, 137.9, 137.6, 130.3, 129.3, 129.1, 43.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{11}O_3S$: 211.0429. Found: 211.0425.

(*E*)-1-(2-(Methylsulfonyl)vinyl)-4-(trifluoromethyl)benzene (152j):



The title compound was prepared according to the general procedure. The product was obtained as yellow solid, mp: 142 - 143 ℃. Yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 - 7.63 (m, 5H), 7.02 (d, J = 15.6 Hz, 1H), 3.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 135.5, 132.9 (J = 32.5 Hz), 128.9, 128.7, 126.2 (J = 3.7 Hz), 123.6 (J = 270.8 Hz), 43.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{10}O_2SF_3$: 251.0354. Found: 251.0352.

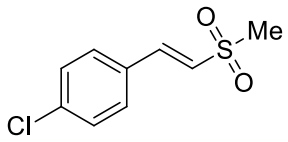
(*E*)-1-Fluoro-4-(2-(methylsulfonyl)vinyl)benzene (152k):



The title compound was prepared according to the general procedure. The product was obtained as colorless solid, mp: 126 - 127 ℃. Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 15.2 Hz, 1H), 7.54 - 7.51 (m, 2H), 7.15 - 7.10 (m, 2H), 6.86 (d, J = 15.6

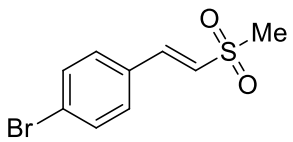
Hz, 1H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (J = 251.9 Hz), 142.7, 130.6 (J = 34.5 Hz), 128.3, 125.9, 116.4 (J = 22.1 Hz), 43.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{10}O_2SF$: 201.0386. Found: 201.0382.

(*E*)-1-Chloro-4-(2-(methylsulfonyl)vinyl)benzene (152l):



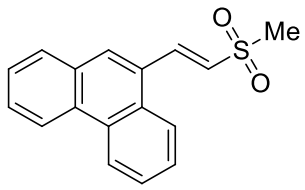
The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 149 - 150 ℃. Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 15.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 15.2 Hz, 1H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 137.5, 130.6, 129.7, 129.5, 126.8, 43.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{10}O_2SCl$: 217.0090. Found: 217.0096.

(*E*)-1-Bromo-4-(2-(methylsulfonyl)vinyl)benzene (152m):



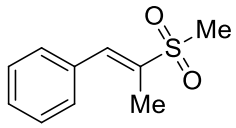
The title compound was prepared according to the general procedure. The product was obtained as white solid, mp: 160 - 161 ℃. Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 - 7.56 (m, 2H), 7.57 (d, J = 15.2 Hz, 1H), 7.38 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 15.6 Hz, 2H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 132.5, 131.0, 129.9, 126.9, 125.9, 43.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{10}O_2SBr$: 260.9585. Found: 260.9584.

(*E*)-9-(2-(Methylsulfonyl)vinyl)phenanthrene (152n):



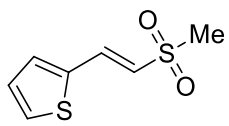
The title compound was prepared according to the general procedure. The product was obtained as dark solid, mp: 122 - 123 ℃. Yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 8.0 Hz, 1H), 8.68 (d, J = 8.4 Hz, 1H), 8.48 (d, J = 15.2 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.76 - 7.72 (m, 4H), 7.11 (d, J = 15.2 Hz, 1H), 3.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 131.5, 130.8, 130.5, 129.6, 129.4, 129.3, 128.6, 128.3, 127.6, 127.4, 127.3, 127.3, 124.1, 123.4, 122.7, 43.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{15}O_2S$: 283.0793. Found: 283.0799.

(*E*)-(2-(Methylsulfonyl)prop-1-en-1-yl)benzene (152o):



The title compound was prepared according to the general procedure. The product was obtained as colorless oil. Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.46 - 7.39 (m, 5H), 2.98 (s, 3H), 2.34 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 136.8, 133.6, 129.6, 129.5, 128.8, 40.4, 13.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{13}O_2S$: 197.0636. Found: 197.0639.

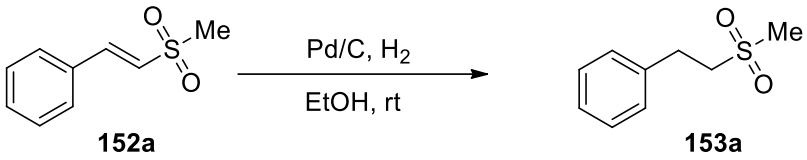
(*E*)-2-(2-(Methylsulfonyl)vinyl)thiophene (152p):



The title compound was prepared according to the general procedure. The product was obtained as brown oil. Yield: 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 15.2 Hz, 1H), 7.48 (d, J = 5.2 Hz, 1H), 7.33 (d, J = 3.6 Hz, 1H), 7.11 - 7.09 (m, 1H), 6.70 (d, J

= 15.2 Hz, 1H), 3.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 136.5, 132.7, 130.1, 128.4, 124.2, 43.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_7H_9O_2S_2$: 189.0044. Found: 189.0047.

(2-(Methylsulfonyl)ethyl)benzene (153a):



152a **153a**

The title compound was prepared according to the following procedure. **152a** (0.20 mmol, 36.4 mg) and Pd/C (10%, 4 mg) was added to 2 mL anhydrous ethanol, the resulting mixture was stirred under 1 atm. H_2 balloon for overnight at room temperature until the **152a** was consumed completely based on TLC (the product is positive to $KMnO_4$ solution on TLC). The reaction mixture was concentrated directly under reduced pressure to give the crude material which was purified by flash chromatography using hexane: ethyl acetate = 2:1 to give desired product as white solid, mp: 88 - 89 ^{o}C. Yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.28 (m, 2H), 7.26 - 7.23 (m, 3H), 3.32 - 3.28 (m, 2H), 3.19 - 3.15 (m, 2H), 2.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 129.0, 128.4, 127.1, 56.2, 41.0, 28.6; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{13}O_2S$: 185.0636. Found: 185.0637.

LIST OF PUBLICATIONS

1. Y. Jiang, T.-P. Loh. *Chem. Sci.* **2014**, *5*, 4939–4943. Catalytic and Direct Methyl Sulfonylation of Alkenes and Alkynes Using Methyl Sulfonyl Radical Generated from DMSO, Dioxygen and Copper System.
2. Y. Jiang, C.-M. Park, T.-P. Loh. *Org. Lett.* **2014**, *16*, 3432–3435. Transition Metal-Free Synthesis of Substituted Pyridines *via* Ring-Expansion of 2-Allyl-2*H*-Azirines.
3. Y. Jiang, C.-M. Park. *Chem. Sci.* **2014**, *5*, 2347–2351. A Catalyst-Controlled Selective Synthesis of Pyridines and Pyrroles.
4. Y. Jiang, W. C. Chan, C.-M. Park. *J. Am. Chem. Soc.* **2012**, *134*, 4104–4107. Expedient Synthesis of Highly Substituted Pyrroles *via* Tandem Rearrangement of α-Diazo Oxime Ethers.
5. Y. Jiang, V. Y. K. Zhong, L. Emmanuvel, C.-M. Park. *Chem. Commun.* **2012**, *48*, 3133–3135. Synthesis of 2-Aminofurans and 2-Unsubstituted Furans *via* Carbenoid-Mediated [3 + 2] Cycloaddition.
6. X. Qi$^{\Psi}$, Y. Jiang$^{\Psi}$, C.-M. Park. *Chem. Commun.* **2011**, *47*, 7848–7850 ($^{\Psi}$*Equally Contribution*). Divergent Reactivity of α-Oximino Carbenoids: Facile Access to 2-Isoxazolines and 2*H*-Azirines.
7. Patent: Method for Preparing 2*H*-Azirine Carboxylic Esters **2013**: WO2013081549 A1. Cheol-Min Park, Yaojia Jiang.
8. Y. Jiang, T.-P. Loh. *EUCHEM Conference on Organic Free Radicals & Annual Meeting COST Action CM 1201*, **2014**, PA113, Prague, Czech Republic. Catalytic and Direct Methyl Sulfonylation of Alkenes and Alkynes Using Methyl Sulfonyl Radical Generated from DMSO, Dioxygen and Copper System.