Oxidant free rhodium-catalyzed C-C bond formation via C-H bond activation

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OXIDANT FREE RHODIUM-CATALYZED C-C BOND
FORMATION VIA C-H BOND ACTIVATION

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCE

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via C-H Bond Activation

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List of Abbreviations

δ	Chemical shift
$^{\circ}\text{C}$	Degree centigrade
Ac	Acetyl
Ad	Adamantyl
Ar	Aryl
BHT	2,6-di- <i>t</i> -butyl- <i>p</i> -cresol
BIPHEP	2,2'-bis(diphenylphosphino)biphenyl
Bn	Benzyl
BQ	1,4-benzoquinone
Bz	Benzoyl
calcd	Calculated
CH_2Cl_2	dichloromethane
CDCl_3	Deuterated chloroform
cm^{-1}	Inverse centimeter
Cp^*	Pentamethyl cyclopentadienyl
CSA	Camphorsulfonic acid
d	doublet
DIBAL-H	Diisobutylaluminum hydride
<i>d</i> -i-Prpf	1,1'-bis(diisopropylphosphino)ferrocene
dd	doublet of doublet
DCE	1,2-dichloroethane
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	Dimethyl sulfoxide
dt	doublet of triplets
equiv.	equivalent(s)
ESI	Electrospray ionization
Et	ethyl

EtOAc	ethyl acetate
FG	Functional group
FTIR	Fourier transform infrared spectrometry
g	gram
h	hour(s)
HRMS	High resolution mass spectrometry
Hz	hertz
IR	infrared
m	multiplet
m/z	Mass per charge ratio
M ⁺	Parent ion peak (mass spectrum)
Me	methyl
MeCN	acetonitrile
MeOH	methanol
min	minute(s)
mL	milliliter(s)
mmol	millimole
mol%	mole percent
MS	Mass spectrometry
<i>n</i> -Bu	<i>n</i> -butyl
NFSI	<i>N</i> -fluorobenzenesulfonimide
NMR	Nuclear magnetic resonance
NMP	<i>N</i> -methyl pyrrolidone
Ns	2-nitrobenzenesulfonate
OTf	Trifluoromethanesulfonate
Pcyp ₃	Tricyclopentylphosphine
Ph	Phenyl
Phth	Phthaloyl
PivOH	Pivalic acid
PMB	<i>P</i> -methoxybenzyl
PMP	4-methoxyphenyl

ppm	Parts per million
<i>p</i> -TSA	<i>p</i> -toluenesulfonic acid
Py	pyridine
q	Quartet
R _f	Retention factor
R.E.	Reductive elimination
rt	Room temperature
<i>t</i> -AmOH	2-methyl-2-butanol
TFA	Trifluoroacetic acid
TMS	Trimethylsilyl
TIPS	triisopropylsilyl
Ts	tosyl

Summary

This thesis demonstrated the rhodium-catalyzed direct C-C bond formation via C-H activation process and comprised five chapters:

Chapter 1

Transition metal-catalyzed inert C-H bond activation has become one of the most useful methods for the synthesis of precious molecules in modern organic chemistry. Among them, rhodium catalysis was proved to be efficient and sustainable for C-H bond functionalization. In the requirement of green chemistry and atom- and step-economy, many efforts have been made to realize an oxidant free C-H bond functionalization.

Chapter 2

The stereospecific construction of synthetically useful Z-type enyamides by Cp*Rh-catalyzed C-H olefinic alkynylation of enamides is described. With good functionality tolerance and operational simplicity, this protocol provides an alternative synthetic opportunity for the ease of access of specific 1,3-enyne derivatives.

Chapter 3

Cp*Rh-catalyzed C-H alkynylation of acrylamide derivative is realized using a hypervalent alkynyl iodine reagent. The use of a weakly coordinating directing group was proved to be of critical importance. The protocol is compatible with multiple functional groups and presents high reaction efficiency, which creates a new synthetic pathway to access functionalized 1,3-enyne skeletons.

Chapter 4

Cp*Rh-catalyzed directed aromatic C-H olefination with allyl acetate is described using *N,N*-disubstituted aminocarboxyl as the directing group. The catalytic cycle is redox-neutral, through which *trans*-products are obtained in high to excellent yields. The method exhibits a broad range of functional group compatibility due to the simplicity of reaction conditions adopted and offers a highly effective synthetic strategy in the arena of C-H olefination.

Chapter 5

Rhodium-catalyzed direct C-H allylation of acrylamides with allyl acetates is described. The high reaction efficiency, broad functionality tolerance and excellent γ -selectivity was obtained due to the use of weakly coordinating directing group, tosyl-imine, which demonstrates a new synthetic pathway for the access of 1,4-diene skeletons.

Chapter 1

[Cp*Rh]-complex Catalyzed C-H Functionalization

1.1 Transition-metal-catalyzed direct C-H bond functionalization

The carbon-hydrogen bond (abbreviated as C-H bond) is a most prevalent chemical bonds in organic compounds. Due to the inertness of C-H bond and its high bond dissociation energy,¹ for instance, 105 kcal/mol for H-CH₃ and 110 kcal/mol for H-C₆H₅, the formation of C-C or C-X bonds (X= S, O, N, Cl, Br, *etc.*) from inert C-H bonds under metal catalysis remains a great challenge nowadays. Normally, the functionalization of C-H bonds requires prefunctionalized materials to enhance the reactivity and selectivity of the reaction. Therefore, extensive attentions have been drawn to investigate a cheap and alternative method to solve the above issues. In modern catalysis research, transition-metal-catalyzed C-H bond activation has emerged as an important method due to its atom-economy and environmental friendly character in the synthesis of complex organic molecules and valuable building blocks.

In the realm of transition metal-catalyzed C-H activation,² palladium catalysts have already shown the magic power in C-H functionalization by achieving enormous advancements over past decades. However, to further the application of C-H bond activation in the synthetic chemistry, the focus to other transition metal catalysts is also in great demands. Despite the high cost of rhodium complexes, it was proved

¹ Weast, R. C. *hand book of chemistry and physics*. Sixty-seventh edition **1986**.

² For selected C-H functionalization reviews, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (c) Xu, L.-M.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712; (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (e) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (f) Giri, R.; Shi, B.-F.; Engle, K. M.; Mangel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (g) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (h) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208.

highly desirable and sustainable metal catalysts for C-H activation reactions, especially when the reaction system is inaccessible under other catalysis.

This chapter will serve to briefly summarize some recent developments in the field of rhodium-catalyzed C-C bond formation reactions *via* C-H activation process, which are directly related to this thesis.

1.2 Rh-catalyzed C-C bond formation *via* C-H bond activation

Within the past decades, the rhodium-catalyzed directed activation of C-H bonds has emerged as one of the most effective approaches for the synthesis of various complex molecules. It was found that a pendent heteroatom could function as a directing group to realize the regioselectivity of the aromatic C-H functionalization reactions. In these protocols, the advantageous reactivity is realized by the formation of a five-membered rhodacycle which undergo insertion or addition reactions with π -systems, such as alkenes and alkynes (Scheme 1.1).

Scheme 1.1 General mechanism for directing group-assisted *ortho*-C-H activation

1.2.1 Chelation-assisted C-H alkylation reactions

The generally accepted mechanism of Rh-catalyzed chelation-assisted C-H alkylation is outlined in Scheme 1.2. Initially, the coordination of transition metal to the chelating heteroatom of **1** triggered facile C-H bond activation, which provides metallacyclic intermediate **II**. Dissociation of one ligand, followed by hydride insertion and olefin binding, generates intermediate **IV**. Reductive elimination of intermediate **IV** produces the alkylation product **3** and closes the catalytic cycle.

Scheme 1.2 General mechanism for Rh-catalyzed chelation-assisted C-H alkylation

Using $\text{RhCl}(\text{PPh}_3)_3$ (Wilkinson's catalyst), the alkylation of aldimines were reported by Jun and co-workers, with essential catalytic amount of 2-amino-3-picoline subjected into the alkylation reaction.³ However, following acidic hydrolysis, instead of isolating the *ortho*-alkylated aldehyde, an additional equivalent of olefin was consumed to generate the alkylated ketone. Jun also further demonstrated that primary alcohols⁴ or amines⁵ could be used in hydroacylation transformations to generate the cooresponding ketones. (Scheme 1.3)

Scheme 1.3 Rh-catalyzed aromatic *ortho*-alkylation

³ (a) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem.-Eur. J.* **2002**, 8, 2423. For further examples of chelation-assisted hydroacylation, see the following and references therein. (b) Jun, C.-H.; Lee, H.; Hong, J.-B. *J. Org. Chem.* **1997**, 62, 1200. (c) Jun, C.-H.; Hong, J.-B.; Lee, D.-Y. *Synlett* **1999**, 1. (d) Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J.-B. *Angew. Chem., Int. Ed.* **2000**, 39, 3070. (e) Jun, C.-H.; Lee, H.; Hong, J.-B.; Kwon, B.-I. *Angew. Chem., Int. Ed.* **2002**, 41, 2146. (f) Jun, C.-H.; Moon, C. W.; Lim, S.-G.; Lee, H. *Org. Lett.* **2002**, 4, 1595. (g) Jun, C.-H.; Lee, J. H. *Pure Appl. Chem.* **2004**, 76, 577. (h) Jo, E.-A.; Jun, C.-H. *Eur. J. Org. Chem.* **2006**, 2504.

⁴ Jun, C.-H.; Hong, J.-B.; Kim, Y.-H.; Chung, K. Y. *Angew. Chem., Int. Ed.* **2000**, 39, 3440.

⁵ Jun, C.-H.; Chung, K.-Y.; Hong, J.-B. *Org. Lett.* **2001**, 3, 785.

More recently Jun also demonstrated that the aromatic alkylation was more efficient using electron-deficient functionalized olefins, such as α,β -unsaturated ester, amides, sulfones and nitriles, than unfunctionalized ones (Scheme 1.4).⁶ A solvent-free microwave protocol for aromatic alkylation was reported by Jun and co-workers as well, which obviates the long reaction time, high reaction temperature and the use of poisoning organic solvent (Scheme 1.4).⁷ In addition, a recyclable catalyst system for aromatic *ortho*-alkylation was reported by Jun, in which the catalyst was supported on a barbiturate additionally served as an H-bond acceptor (Scheme 1.5).⁸

Scheme 1.4 Rh-catalyzed aromatic *ortho*-alkylation under special conditions

⁶ Lim, S.-G.; Ahn, J.-A.; Jun, C.-H. *Org. Lett.* **2004**, 6, 4687.

⁷ (a) Vo-Thanh, G.; Lahrache, H.; Loupy, A.; Kim, I.-J.; Chang, D.-H.; Jun, C.-H. *Tetrahedron* **2004**, 60, 5539. (b) Jo, E.-A.; Ahn, J.-A.; Jun, C.-H. *Bull. Korean Chem. Soc.* **2007**, 28, 2020.

⁸ (a) Yoon, J. H.; Park, Y. J.; Lee, J. H.; Yoo, J.; Jun, C.-H. *Org. Lett.* **2005**, 7, 2889. For chelation-assisted hydroarylation, see: (b) Kim, D.-W.; Lim, S.-G.; Jun, C.-H. *Org. Lett.* **2006**, 8, 2937. (c) Chang, D.-H.; Lee, D.-Y.; Hong, B.-S.; Choi, J.-H.; Jun, C.-H. *J. Am. Chem. Soc.* **2004**, 126, 424. For use in hydroacylation reactions, see: (d) Park, J.-W.; Park, J.-H.; Jun, C.-H. *J. Org. Chem.* **2008**, 73, 5598. For a review on recyclable catalysts for C-H activation, see: (e) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, 41, 222.

Scheme 1.5 Rh-catalyzed alkylation under recyclable catalyst system

Jun also reported that the aryl ketimines will undergo *ortho*-alkenylation with diphenylacetylene and terminal alkynes using Wilkinson's catalyst, and functionalized isoquinolines would be obtained when increased the reaction temperature and prolonged reaction times (Scheme 1.6).⁹

Scheme 1.6 Rh-catalyzed aromatic *ortho*-alkenylation of aryl ketimines.

⁹ Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003**, 5, 2759.

1.2.2 Oxidative addition type reaction

Very recently, the (pentamethylcyclopentadienyl)rhodium (abbreviate as Cp*Rh)-complexes, such as [Cp*Rh(MeCN)₃][BF₄]₂, [Cp*Rh(MeCN)₃][SbF₆]₂, and [Cp*RhCl₂]₂, have been identified to be synthetically useful and highly efficient catalyst in the field of direct C-H bond functionalization. The pioneering works reported by Davies,¹⁰ Miura¹¹ and others¹² uncovered that the [Cp*Rh]-complex is able to mediate the directed C-H bond activation of aromatic C-H bonds and subsequent reaction with alkenes and alkynes for the synthesis of important structural moieties and heterocycles (Scheme 1.7).

Scheme 1.7 Cp*Rh-catalyzed aromatic C-H bond functionalization with alkynes and alkenes.

In addition, further extensive works were also investigated to the C-H functionalization with other π -systems. Recently, Ellman and Shi independently demonstrated several

¹⁰ Davies, D.L.; Al-Duaij, O.; Fawcett, J.; Giardiello, M.; Hilton, S. T.; Russell, D. R. *Dalton Trans.* **2003**, 21, 4132.

¹¹ (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, 9, 1407. (b) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, 74, 6295. (c) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, 16, 11212.

¹² (a) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, 130, 12414. (b) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, 130, 16474.

protocols about Cp*Rh-catalyzed arylation of imines (Scheme 1.8).¹³ By taking the advantage of the mild reaction condition and excellent functional group tolerance, this transformation displays an effective and convenient method for the synthesis of α -branched amines with simultaneous C-C bond formation.

Scheme 1.8 Cp*Rh-catalyzed arylation of imines

In 2011, Ellman and co-workers developed a novel Cp*Rh-catalyzed C-H amidation of anilide and enamide with isocyanates as the coupling partner (Scheme 1.9).¹⁴ Intriguingly, the activated [Cp*Rh(MeCN)₃][SbF₆]₂ was identified as the effective catalyst for this C-H amidation reaction of various anilides and enamides. Meanwhile, a broad range of isocyanates were also proved to be compatible in this protocol affording valuable *N*-acyl anthranilamides and enamine amides.

¹³ (a) Lian, Y.; Huber, T.; Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2013**, 52, 629. (b) Lian, Y.; Bergman, R. G.; Lavis, L. D.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, 135, 7122. (c) Tauchert, M. E.; Incarvito, C. D.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, 134, 1482. (d) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, 133, 1248. (e) Li, Y.; Zhang, X.-S.; Zhu, Q.-L.; Shi, Z.-J. *Org. Lett.* **2012**, 14, 4498. (f) Li, Y.; Zhang, X.-S.; Li, H.; Wang, W.-H.; Chen, K.; Li, B.-J.; Shi, Z.-J. *Chem. Sci.* **2012**, 3, 1634. (g) Li, Y.; Zhang, X.-S.; Chen, K.; He, K.-H.; Pan, F.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2012**, 14, 636. (h) Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W.-P.; Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, 50, 2115.

¹⁴ Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, 133, 11430.

Scheme 1.9 Cp*Rh-catalyzed amidation of anilide and enamide

Alternatively, the Cp*Rh-catalyzed acylations of aromatic C-H bond were also reported (Scheme 1.10).¹⁵ In 2012, Li and co-workers adopted the protected indole derivatives as the substrates, selectively generating the 2-aryloindole compounds with common aldehydes. Meanwhile, Rovis and co-workers demonstrated that the carbon monoxide was also an active coupling partner for carbonylation of aromatic amides *via* C-H/N-H activation to form phthalimides.

Scheme 1.10 Cp*Rh-catalyzed aromatic acylation reactions

¹⁵ (a) Zhou, B.; Yang, Y.; Li, Y. *Chem. Commun.* **2012**, 48, 5163. with CO: (b) Du, Y.; Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, 47, 12074.

1.2.3 Dehydrogenative cross-coupling reactions

While most of the twofold C-H oxidative cross-couplings between an arene and a heteroarene have been well developed through palladium-catalyzed strategies; several rhodium-catalyzed oxidative C-H dehydrogenative cross-coupling reactions were also reported. Although this type of reactions was still in its infancy, and the selectivity and reactivity issues remained to be addressed, many cross-coupling reactions of funan, thiophene and indole derivatives, and directing-group-containing arenes with alkenes or arenes had been disclosed (Scheme 1.11).¹⁶

Scheme 1.11 Cp*Rh-catalyzed oxidative dehydrogenative cross-coupling reactions

¹⁶ (a) Qin, X.; Liu, H.; Qin, D.; Wu, Q.; You, J.; Zhao, D.; Guo, Q.; Huang, X.; Lan, J. *Chem. Sci.* **2013**, 4, 1964. (b) Dong, J.; Long, Z.; Song, F.; Wu, N.; Guo, Q.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2013**, 52, 580. (c) Reddy, V. P.; Qiu, R.; Iwasaki, T.; Kambe, N. *Org. Lett.* **2013**, 15, 1290. (d) Wencel-Delord, J.; Nimphius, C.; Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, 51, 13001. (e) Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, 51, 2247. (f) Kuhl, N.; Hopkinson, M. N.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, 51, 8230.

1.2.4 Oxidant-free type reactions

Other than the aforementioned Rh-catalyzed oxidative addition type reactions and dehydrogenative cross-coupling reactions, recently, several [Cp*Rh]-catalyzed C-C bond formation through C-H activation process under external oxidant free conditions were also reported.¹⁷ A common characteristic of these protocols is the usage of an electrophilic reaction partner containing a leaving group which then undergoes a coupling process with the nucleophilic rhodacycle intermediate. Selected examples were described as follow.

As part of the efforts direct toward developing new applications of rhodium-catalysis chemistry, Yu and co-workers demonstrated the Cp*Rh-catalyzed C-H alkylation using diazocarbonyl compounds as the coupling partner (Scheme 1.7).¹⁸ In this carbenoid coupling reaction, various α -diazomalonates were proved to be active and efficient for alkylation of different synthetically useful benzene derivatives under mild reaction condition. Furthermore, Glorius and co-workers also developed the Cp*Rh-catalyzed C-H bond functionalization with diazocarbonyl compounds for the synthesis of quinoline and pyridine *N*-oxides (Scheme 1.12).¹⁹ In addition, several works shared the similar strategy were also reported independently by Rovis²⁰ and Cui.²¹

¹⁷ For the selected example of Rh-catalyzed C-H functionalization under oxidant free condition, see: (a) Gong, T.-J.; Xiao, B.; Cheng, W.-M.; Su, W.; Xu, J.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 10630. (b) Li, X.; Yu, S.; Wang, F.; Wan, B.; Yu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 2577. (c) Cui, S.; Zhang, Y.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3421. (d) Hyster, T. K.; Rovis, T. *Synlett* **2013**, *24*, 1842.

¹⁸ Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565.

¹⁹ Shi, Z.; Koester, D. C.; Bouladakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204.

²⁰ Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364.

²¹ Cui, S.; Zhang, Y.; Wang, D.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3912.

Scheme 1.12 Cp*Rh-catalyzed C-H functionalization with diazocarbonyl compounds

Moreover, in 2014, a unique Cp*Rh-catalyzed C-H olefination reaction with diazocarbonyl compounds was developed by Wang and co-workers (Scheme 1.13).²² Therein, the *N*-phenoxyacetamides were used as oxidizing/directing groups, affording *ortho*-alkenylated phenols in good yields and excellent stereoselectivity, which is inaccessible through Cp*Rh-catalyzed oxidative Mizoroki-Heck reaction of arenes with alkenes.

Scheme 1.13 Cp*Rh-catalyzed C-H olefination with diazocarbonyl compounds

²² Hu, F.; Xia, Y.; Ye, F.; Liu, Z.; Ma, C.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, 53, 1364.

Recently, the Rh-catalyzed redox-neutral biaryl synthesis was discovered by Li and co-workers (Schem 1.14).²³ The corresponding *meta*-substituted phenol and aniline products were afforded due to the rearomatization potential of dienones, which took effect as a driving force to furnish such C-C bond formation.

Scheme 1.14 Rh-catalyzed redox-neutral biaryl synthesis

In addition, the application of allylic substrates in Cp*Rh-catalyzed C-H bond functionalization was also reported. While, in 2013, Li and co-workers achieved the aromatic annulation reaction with oxa- and azanorbornadienes in good yields and high regioselectivity, recently, Cui and co-workers demonstrated the Rh-catalyzed C-H functionalization with diazabicycles for synthesis of functionalized cyclopentenes (Scheme 1.15).²⁴ In both works, the use of bicyclic allylic substrates offered the opportunity of introducing synthetically more useful motifs onto simple aromatic substrates.

²³ Zhang, X.; Wang, F.; Qi, Z.; Yu, S.; Li, X. *Org. Lett.* **2014**, *16*, 1586.

²⁴ (a) Qi, Z.; Li, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 8995. (b) Zhang, Y.; Wu, Q.; Cui, S. *Chem. Sci.* **2014**, *5*, 297.

Scheme 1.15 Rh-catalyzed C-H functionalization with bicyclic allyl substrates

Following with these achievements, another typical work of Cp*Rh-catalyzed allylic alkylation was described as well (Scheme 1.16).²⁵ In this reaction, the allylic alcohols were afforded through the cross coupling between simple directed aromatic compounds and 2-vinyloxirane. Further transformations of the corresponding allylic products were also presented, in particular the synthesis of valuable benzoazepane compounds.

Scheme 1.16 Cp*Rh-Catalyzed aromatic C-H alkylation with 2-vinyloxirane

²⁵ Yu, S.; Li, X. *Org. Lett.* **2014**, *16*, 1200.

1.3 Proposed work

The work of this thesis has been directed toward the development of oxidant-free Cp*Rh-catalyzed C-C bond formation *via* C-H activation process, which provides a wide range of reaction scope and enables high selectivities.

As many recent works has proved that the active hypervalent iodine reagents were adopted in rhodium-catalyzed C-H bond functionalization reactions,²⁶ it is envisioned that Cp*Rh-catalyzed C-H alkynylation of enamides could be approached by utilizing hypervalent alkynyl iodine reagents, 1-triisopropylsilylethynyl-1,2-benziodoxol-3(*1H*)-ones (TIPS-EBX), which obviates the preactivated alkyne substrates and relatively harsh reaction conditions (eq 1).

It is surmised that replacing the acetamide group with tosyl-imide group, the 1,3-enyne product could also be prepared by this Cp*Rh-catalyzed C-H alkynylation of alkenes strategy under very mild reaction condition, within which the employment of

²⁶ (a) Zhang, X.; Wang, F.; Qi, Z.; Yu, S.; Li, X. *Org. Lett.* **2014**, *16*, 1586. (b) Xie, F.; Qi, Z.; Li, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 11862. (c) Zhao, H.; Shang, Y.; Su, W. *Org. Lett.* **2013**, *15*, 5106.

weakly coordinating directing group proved to be critical for the achievement of this transformation (eq 2).

It is reasoned that the conjugated π -systems could also be synthesis by using Cp^*Rh -catalyzed C-H olefination of benzamides with allyl acetates. The mechanism scenario underwent β -OAc elimination instead of β -H elimination which is a general step for oxidative addition type of reactions (eq 3).

Finally, it is envisioned that the Cp^*Rh -catalyzed C-H allylation reaction of alkenes with allyl acetate as the coupling partner could be developed as well, which provides a new methods for the synthesis of 1,4-diene skeletons due to the weakly coordinating directing group (eq 4).

Chapter 2

Cp*Rh(III)-Catalyzed Olefinic C-H Alkynylation of enamides

2.1 Introduction

2.1.1 Transition-metal-catalyzed alkynylation reaction

Transition-metal-catalyzed alkynylation reaction has emerged as one of the most general and reliable methods in synthetic chemistry over past decades, which provides easy access for introducing alkynyl functionalities into naturally occurring compounds, advanced materials and pharmaceutic candidates.²⁷ In this regards, many chemists have putted efforts in this area and extraordinary strategies, including Sonogashira reaction, Cu-promoted Castro-Stephens reaction²⁸ and Pd-catalyzed Negishi reaction,²⁹ have been well established. Futhermore, with the surge of C-H functionalization methods, Pd-catalyzed Heck-type C-H alkynylation was also reported to be desirable in a number of cases (Scheme 2.1).

Scheme 2.1 Transition metal-catalyzed alkynylation of aromatic compounds

²⁷ (a) Brandsma, L.; Heus-Kloos, Y. A.; Van Der Heiden, R.; Verkuijsse, H. D. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: New York **1988**. (b) Brandsma, L.; Vasilevsky, S. F.; Verkuijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer-Verlag: New York **1998**. (c) Negishi, E.; Anastasia, L.; *Chem. Rev.* **2003**, 103, 1979.

²⁸ Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, 28, 3313.

²⁹ (a) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 42, 683. (b) King, A. O.; Negishi, E.; Villani, F. J., Jr.; Silveira, A., Jr. *J. Org. Chem.* **1978**, 43, 358.

2.1.2 Alkynylation reaction of alkenes

In the realm of Csp^2 - Csp bond formation, while much progress has been made in the area of aromatic alkynylations, relatively less success has been achieved in realizing the alkynylation of alkenes. Commonly, the most general and reliable methods are transition-metal-catalyzed cross-coupling between prefunctionalized alkenes,³⁰ such as vinyl halides or metal alkenes, and terminal alkynes or alkynylmetals (Scheme 2.2). In this context, the Pd-catalyzed Sonogashira reaction³¹ and Negishi cross-coupling³² are the most popular protocols among others. However, the indispensability of using pre-functionalization substrates and stoichiometric amount of metallic or halogenated wastes contradicts the principle of modern synthetic chemistry from the point of view of step and atom economy.

³⁰ For selected examples of olefinic alkynylation of other alkynylmetal see: (a) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138. (b) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (c) Margaretha, P.; Reichow, S.; Agosta, W. C. *J. Chem. Soc., Chem. Commun.* **1992**, 797. (d) Ley, S. V.; Redgrave, A. J.; Taylor, S. C.; Ahmed, S.; Ribbons, D. W. *Synlett* **1991**, 741. (e) Le Menez, P.; Farageas, V.; Bergue, I.; Poisson, J.; Ardisson, J.; Lallemand, J. Y.; Pancrazi, A. *J. Org. Chem.* **1995**, *60*, 3592. (f) Baldwin, J. E.; Bamford, S. J.; Fryer, A. M.; Rudolph, M. P. W.; Wood, M. E. *Tetrahedron* **1997**, *53*, 5233. (g) Siesel, D. A.; Staley, S. W. *Tetrahedron Lett.* **1993**, *34*, 3679. (h) Dang, H. P.; Linstumelle, G. *Tetrahedron Lett.* **1978**, 191. (i) Soderquist, J. A.; Matos, K.; Rane, A. M.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 2401. (j) Soderquist, J. A.; Rane, A. M.; Matos, K.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 6847. (k) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918. (l) Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chem. Lett.* **1997**, 1233. (m) Perez, I.; Perez Sestelo, J.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267. (n) Perez, I.; Perez Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155.

³¹ For selected examples of olefinic Sonogashira reaction see: (a) Lu, X.; Huang, X.; Ma, S. *Tetrahedron Lett.* **1992**, *33*, 2535. (b) Takeuchi, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem.* **2000**, *65*, 1558. (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (d) Sonogashira, K.; Tokai, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (e) Alami, M.; Ferri, F.; Linstumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403. (f) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 4107. (g) Hoshi, M.; Shirakawa, K. *Synlett* **2002**, 1101. (h) Bates, C. G.; Saejueng, P.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 1441. (i) Alami, M.; Linstumelle, G.; *Tetrahedron Lett.* **1991**, *32*, 6109. (j) Alami, M.; Crousse, B.; Ferri, F. *J. Organomet. Chem.* **2001**, *624*, 114.

³² For selected examples of olefinic Negishi cross-coupling see: (a) Hyuga, S.; Chiba, Y.; Yamashina, N.; Hara, S.; Suzuki, A. *Chem. Lett.* **1987**, 1757. (b) Andreini, B. P.; Carpita, A.; Rossi, R.; Scamuzzi, B. *Tetrahedron* **1989**, *45*, 5621. (c) Rossi, R.; Carpita, A.; Lippolis, V. *Synth. Commun.* **1991**, *21*, 333. (d) Stracker, E.; Zweifel, G. *Tetrahedron Lett.* **1991**, *32*, 3329. (e) Negishi, E.; Liu, F.; Choueiry, D.; Mohamud, M. M.; Silveira, A. Jr.; Reeves, M. *J. Org. Chem.* **1996**, *61*, 8325. (f) Tellier, F.; Sauvetre, R.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 3147. (g) Tellier, F.; Sauvetre, R.; Normant, J. F. *J. Organomet. Chem.* **1987**, *328*, 1.

Scheme 2.2 Transition-metal-catalyzed alkynylation reaction of alkenes

As an alternative strategy, the Pd-catalyzed Heck-type alkynylation of simple terminal alkene was also reported. In 1987, Jeffery's group developed the Pd-catalyzed cross-coupling reaction between acrylate derivatives and iodoalkynes (Scheme 2.3).³³ Following this work, in 2011, Huang and co-workers realized the synthesis of conjugated enynes by Pd-catalyzed cross-coupling between styrene derivatives and bromoalkynes (Scheme 2.3).³⁴ Although these protocols obviate the use of pre-activated alkenes, the relatively harsh reaction conditions and inaccessibility of *cis*-enynes skeleton, which is frequently found in natural products, limit its applicability. As such, the development of highly stereoselective and efficient method for olefin alkynylation is still desirable

Scheme 2.3 Pd-catalyzed Heck-type alkynylation reaction of terminal alkenes

³³ Jeffery, T. *Synthesis* **1987**, 70;

³⁴ Wen, Y.; Wang, A.; Jiang, H.; Zhu, S.; Huang, L. *Tetrahedron Lett.* **2011**, 52, 5736..

2.1.3 Alkynylation reactions with hypervalent alkynyl iodine reagent

The hypervalent iodine reagent 1-silylethynyl-1,2-benziodoxol-3(1H)-ones (TIPS-EBX) introduced by Zhdankin³⁵ has recently become an efficient alkynylation reagent, which is stable toward air and moisture as an oxidized and activated form of alkynes.³⁶ Since 2009, elegant works for C-H alkynylation of electron rich aromatic substrates, such as indole, pyrrole, furan, thiophene and anilines, enolates and, most recently thiols using TIPS-EBX as the electrophilic alkyne reagent by Au- or Pd-catalysis have been systematically reported by Waser and co-workers (Scheme 2.4).³⁷

Scheme 2.4 Au- or Pd-catalyzed alkynylation reactions

³⁵ (a) Zhdankin, V.V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927. (b) Zhdankin, V.V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (c) Zhdankin, V.V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Simonsen, A. J. *J. Org. Chem.* **1996**, *61*, 6547.

³⁶ The synthesis of EBXs was improved by Waser and co-workers; see ref 30d.

³⁷ (a) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 9346. (b) Brand, J. P.; Waser, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 7304. (c) Brand, J. P.; Waser, J. *Org. Lett.* **2012**, *14*, 744. (d) Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. *Chem. Eur. J.* **2012**, *18*, 5655. (e) Li, Y.; Brand, J. P.; Waser, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 6743. (f) Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013**, *15*, 112. (g) Brand, J. P.; Waser, J. *Synthesis* **2012**, *44*, 1155. (h) Frei, R.; Waser, J. *J. Am. Chem. Soc.* **2013**, *135*, 9620.

2.1.4 Enamide functionalization

Because of its dense functionality and the fact of being able to act as effective directing group, enamide represents a type of synthetically useful template in transition-metal-catalyzed direct C-H functionalizations.³⁸ Recently, our group reported a set of useful elaborations of enamides through C-H activation mode, such as arylation, trifluoromethylation as well as olefination (Scheme 2.5).³⁹

Scheme 2.5 Vinylic C(sp²)-H functionalization of enamides

³⁸ For a review on the synthetic applications of enamides, see: Carbery, D. R. *Org. Biomol. Chem.* **2008**, 6, 3455.

³⁹ (a) Zhou, H.; Xu, Y. H.; Chung, W. J.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2009**, 48, 5355. (b) Zhou, H.; Chung, W. J.; Xu, Y. H.; Loh, T.-P. *Chem. Commun.* **2009**, 3472. (c) Xu, Y. H.; Chok, Y. K.; Loh, T.-P. *Chem. Sci.* **2011**, 2, 1822. (d) Feng, C.; Loh, T.-P. *Chem. Sci.* **2012**, 3, 3458. (e) Pankajakshan, S.; Xu, Y. H.; Cheng, J. K.; Low, M. T.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2012**, 51, 5701.

As an extension of our former enamide functionalization works, in this chapter, a novel Rh-catalyzed alkynylation reaction of enamides with hypervalent alkynyl iodine reagents as the coupling partner is described (Scheme 2.6).

Scheme 2.6 Rh-catalyzed olefinic alkynylation of enamides

2.2 Result and discussion

At the outset of our study, the reaction condition was optimized using model coupling between *N*-(1-phenylvinyl)acetamide (**2a**) and the alkynylodonium reagent **1** with diverse parameters. It is found that with $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]_2$ as the catalyst and THF as the solvent, the reaction proceeded smoothly at room temperature to produce the desired alkynylation product in 50% yield (Table 2.1, Entry 1). It needs to be pointed out that in contrast to the Heck-type olefinic alkynylation of **2a**, which predominately presents the thermodynamically stable *trans*-products, this alkynylation occurs selectively on the *cis*-position with respect to the amido group, indicating the involvement of directing effect of amido group at the $\text{Csp}^2\text{-Csp}$ bond formation step within the catalytic cycle. The absolute structure of **3g** was unequivocally confirmed by single-crystal X-ray diffraction (Scheme 2.7).⁴⁰

⁴⁰ CCDC 980753 (**3g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.com.ac.uk/data_request/cif.

Scheme 2.7 Structure determination

To further optimize the reaction conditions, a systematic solvent-screening was conducted in order to yield the desired olefinic alkynylation with high efficiency. After extensive endeavors, it was found that acetone was the optimal solvent, which afforded the desired product **3a** in 83% yield, while other solvents such as 1,2-dichloroethane (DCE), acetonitrile, dioxane, 1,2-dimethoxyethane (DME), chlorobenzene, methanol and *t*-butanol gave product **3a** in lower yields (Table 2.1, Entries 2-9). With the optimal solvent identified, the effect of reaction additives was subsequently investigated, given that additives were commonly found to be of critical importance in diverse C-H activation reactions. It was discovered that while sodium acetate exerted obvious deleterious effect on the reaction efficiency (Table 2.1, Entry 10), the yield was further improved by pivalic acid which may help to abstract the H-atom during the C-H activation process (Table 2.1, Entry 11). Furthermore, when using $[\text{Cp}^*\text{RhCl}_2]_2$ as the catalyst and AgSbF_6 as the additive, the desired product was generated in moderate yield (Table 2.1, Entry 12). Moreover, no reaction occurred with CuCl or $\text{Pd}(\text{OAc})_2$ as the catalyst (Table 2.1, Entries 13, 14), which suggests the uniqueness of Rh(III) catalysts within this alkynylation reaction. Further control experiment clearly demonstrated the indispensability of rhodium catalyst in this reacti-

Table 2.1 Optimization of reaction condition.^a

Entry	Additive	Solvent	Yield (%) ^b
1	-	THF	50
2	-	DCE	52
3	-	MeCN	<10
4	-	Dioxane	<10
5	-	Acetone	83
6	-	DME	35
7	-	PhCl	59
8	-	MeOH	33
9	-	<i>t</i> -BuOH	81
10	NaOAc	Acetone	27
11	PivOH	Acetone	91
12	AgSbF ₆	Acetone	59 ^c
13	-	Acetone	NR ^d
14	-	Acetone	NR ^e
15	PivOH	Acetone	NR ^f

^a Unless otherwise noted, the reactions were carried out at room temperature using **2a** (0.1 mmol), **1** (0.11 mmol), catalyst (0.002 mmol), additive (0.01 mmol) in solvent (0.5 mL) for 12 h. ^b Isolated yields. ^c [Cp*RhCl₂]₂ (0.002 mmol) was used as the catalyst. ^d CuCl (0.01 mmol) was used as the catalyst. ^e Pd(OAc)₂ (0.005 mmol) was used as the catalyst. ^f No rhodium catalyst was added.

on (Table 2.1, Entry 15). It also needs to be pointed out that when halogenated (Br- or I-) ethynyltriisopropylsilane was utilized as the electrophilic alkynyl donor instead of alkynyliodonium reagents, a trace product was obtained.

With the optimized reaction condition in hand, various enamides were examined in order to explore the substrate scope of this alkylnylation reaction. With respect to aryl-substituted enamides, substrates containing both electron-donating and electron-withdrawing functional groups regardless of substitution position on the phenyl ring were all well tolerated (Table 2.2, **3b-3n**). Functional groups, such as methoxy (**3d**), trifluoromethyl (**3e**), cyano (**3f**), sulfonyl (**3j**) and acetyl (**3k**), which were of synthetic importance or amenable to further useful transformation, were proved to be well compatible with this reaction condition, affording corresponding products in high to excellent yields. It is noteworthy that halogen substituents, such as F, Cl and Br, were also well accommodated in such transformation, enabling further synthetic elaborations through conventional transition-metal-catalyzed coupling reactions (Table 2.2, **3h**, **3i**, **3n**). Moreover, *ortho*-substituents were innocuous to this C-H alkylnylation reaction as in the case of **2l**, **2m** and **2n**. Among these, the elegant performance of **2m** was much more intriguing, considering the ability for coordination as well as the sterics of *ortho*-piperidinyl substituent. Besides biphenyl and naphthyl based enamides, the heterocycle based enamide such as **2p** also participated in this alkylnylation reaction, albeit generating the product **3p** in relatively lower yield. Furthermore, this reaction is not limited to terminal olefin derived enamides, those transformed from indanone and chromanone were also effective, furnishing the desire-

Table 2.2 Reaction scope of enamide derivatives.^{a, b}

^a Unless otherwise noted, the reactions were carried out at room temperature using enamide **2** (0.1 mmol), **1** (0.11 mmol), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]_2$ (0.002 mmol), PivOH (0.01 mmol) in acetone (0.5 mL) for 12 h. ^b Isolated yields.

d products in good yields (Table 2.2, **3q**, **3r**).

In addition, this reaction is not limited to aryl substituted enamides, aliphatic counterparts, even those functionalized ones, were revealed to participate in this reaction without any complication (Table 2.2, **3s-3x**). Impressively, when substrate containing extra olefin pendent, such as **2t**, was submitted to the standard reaction condition, the C-H alkynylation chemoselectively and stereoselectively happened on the *cis*-position of enamide moiety to afford the product **3t** in 90% yield, with the olefin pendent being intact throughout the reaction. This result not only demonstrated the requirement of acetamido group for the occurrence of C-H activation but also the high reactivity of hypervalent alkynyl iodine reagent **1** in the downstream reaction processes. Furthermore, the sterical bulk of alkyl substituents did not exhibit any impediment on the reaction efficiency as displayed in the case of **2t**, **2u** and **2x**. Notably, pyruvate derived enamide **2y** was also proved to be applicable in this reaction to produce the product **3y** in moderate yield, which offers a new synthetic opportunity to access non-natural functionalized amino acid derivatives. The fact that *N*-vinylacetamide and *N*-benzoyl-*N*-(1-phenylvinyl)-acetamide did not provide any desired product indicates the critical role of the α -substituent and the N-H moiety in this reaction.

Olefinic alkynylation using other alkynyliodonium reagents.

Intermolecular KIE study of olefinic alkynylation of enamides.

Olefinic alkynylation using ^{13}C -labelled reagent **1-C¹³**.

Scheme 2.8 Alkynylation using *t*-butyl-based alkynyl reagent and isotope experiments

With the aim of examining reaction generality with respect to electrophilic alkynyliodonium reagents, the substituent effect on the alkynyl reagent was thus investigated. While *tert*-butyl based alkynyliodonium reagent reacted well with standard enamide **2a** to afford the desired product **4a** in 87% yield, the reaction with phenyl derived alkynyliodonium reagent turned out rather messy. The intermolecular KIE experiment was also conducted between **2a** and **2a-d₂** with alkynyliodonium reagent **1**, which produced a KIE value of 1.5 (refer to 2.4.2.). The KIE study partially

proved that the C-H activation process is the rate-limiting step of this alkynylation reaction. Furthermore, when ^{13}C labeled alkynyliodonium reagent **1-C¹³** was subjected to the standard reaction condition with **2a**, the desired product was obtained in 80% yield, indicating that no silyl-migration occurred during the catalytic cycle (Scheme 2.8).

Scheme 2.9 Plausible mechanism of Rh(III)-catalyzed C-H alkynylation of enamide

Based on the precedents of Rh(III)-catalyzed C-H activation involving directed insertion of unsymmetrical alkynes and the results of alkynylation of enamides, the reaction mechanism was plausibly proposed (Scheme 2.9). The reaction begins from

the coordination of active rhodium-catalyst to **2a** generating intermediate **I**, which undergoes reversible C-H bond activation through concerted metallation-deprotonation (CMD) pathway to afford rhodacycle **II**. Then the insertion of alkyne **1** forms the eight-membered intermediate **III**, which undergoes α -elimination to provide the rhodium vinylidene **IV** along with the extrusion of 2-iodobenzoic acid. The intermediate **IV** follows rearrangement and elimination through intermediate **V** reaching the intermediate **VI**. Finally, protonation of **VI** with another molecule of **2a** delivered the desired alkynylation product and regenerated intermediate **I**. It needs to be pointed out that the insertion of alkyne with reversed selectivity followed by β -elimination could also be a possible process for the generation of product **3a** and could not be firmly excluded at this stage.

Scheme 2.10 Synthetic transformations of enynamide **3a**.

In order to showcase the applicability of alkynylation products, further transformations by employing the alkynyl group were explored (Scheme 2.10). Desilylation of **3a** worked well with TBAF/HOAc system, which generated the terminal alkyne **6** in the 91% yield. In addition, desilylation/Sonogashira coupling between **3a** and 4-iodobenzonitrile also proceeded nicely, producing the corresponding product **5** in 78% yield. Furthermore, triazole product **7** could be generated in 88% yield without being compromised by the copper-catalyzed cycloaddition between terminal alkyne **6** and benzyl azide.

2.4 Conclusion

In conclusion, a novel protocol for Rh(III)-catalyzed C-H olefinic alkynylation of enamides for the synthesis of functionalized 1,3-enyne motifs was developed. By taking advantage of amide group's *ortho*-directing effect, this reaction underwent stereospecific activation of olefinic C-H bonds, thus providing a straightforward and efficient manner for the construction of *cis*-enamide frameworks. With the very mild reaction condition and highly reactive of hypervalent iodonium reagent, a large variety of synthetically useful functional groups were nicely accommodated. Furthermore, the enamide products that obtained through C-H alkynylation could be easily transformed into structurally relevant motifs by virtue of Sonogashira coupling or cycloaddition reactions.

2.4 Experimental Section

2.4.1 General Information

[Cp*Rh(MeCN)₃][SbF₆]₂, [Cp*RhCl₂]₂, CuCl, PivOH and solvents were purchased from commercial suppliers and were used as received unless otherwise noted. All reactions were carried out using 8mL sample vial or standard Schlenk technic. Reactions were monitored through thin layer chromatography [Merck 60 F254 precoated silica gel plate (0.2 mm thickness)]. Subsequent to elution, spots were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Alternative visualization was possible using basic solution of potassium permanganate. Flash chromatography was presented with Merck silica gel 60 with distilled solvents. HRMS spectra were recorded on a Waters Q-ToF Premier Spectrometer. ¹H NMR and ¹³C NMR spectra were recorded using Bruker Avance 400 MHz spectrometers. Chemical shifts for ¹H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of SiMe₄ (δ 0.00, singlet), methanol-*d*₄ (δ 3.31, quintet), DMSO-*d*₆ (δ 2.50, quintet). Multiplicities were given as: s (singlet); brs (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); td (triplet of doublet); m (multiplets); ddt (doublet of doublet of triplet) and etc. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (¹³C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.00, triplet), methanol-*d*₄ (δ 49.00, heptet), DMSO-*d*₆ (δ 40.00, heptet).

2.4.2 Experimental procedures

Scheme 2.11 Rh-catalyzed olefinic alkynylation of enamides

Experimental procedure A: The enamide **2** (0.1 mmol, 1 equiv.), hypervalent iodine reagent **1** (0.11 mmol, 1.1 equiv.), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]$ (0.002 mmol, 2 mol %), PivOH (0.01 mmol, 10 mol %) and acetone (0.5 mL) were placed in a 8 mL glass vial under air. After stirring at room temperature for 12 hours, saturated NaHCO_3 solution (5 mL) was added and the resulting mixture was extracted with dichloromethane (2x10mL). Removal of the solvent in vacuo and purified by column chromatography (Hexane:EtOAc = 2:1) afforded the desired product **3** (Scheme 2.11).

Scheme 2.12 Heck-type alkynylation reaction of enamide

Experimental procedure B: The enamide **2a** (0.1 mmol, 1 equiv.), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.005 mmol, 5 mol %) and K_2CO_3 (0.25 mmol, 2.5 equiv.) was stirred in DMF at room temperature under N_2 atmosphere for 5 min. Then, bromoethynyl triisopropylsilane (0.11 mmol, 1.1 equiv.) was slowly added into the system. The

reaction was then allowed to stir for 12 hours at 80 °C. After quenched with water, the mixture was extracted using ethylacetate. Then the organic layer was evaporated and the residue was directed subject to column chromatography (Hexane:EtOAc = 1:1) to afford the desired product 15.4 mg, 45% yield (Scheme 2.12).

Scheme 2.13 Sonogashira reaction between **3a** and 4-iodobenzonitrile

Experimental procedure C: The **3a** (0.1 mmol, 1 equiv.), 4-iodobenzonitrile (0.11 mmol, 1.1 equiv.), $\text{Pd(PPh}_3)_2\text{Cl}_2$ (0.002 mmol, 2 mol %) and CuI (0.001 mmol, 1 mol %) was stirred in THF under N_2 atmosphere. After cooling down to 0 °C, TBAF (0.12 mmol, 1.2 equiv.) was slowly added. The reaction was allowed to stir for 2 hours under room temperature. After quenched with water, the mixture was extracted using dichloromethane. Then the organic layer was evaporated and the residue was directed subject to column chromatography (Hexane:EtOAc = 2:1) to afford the product **5** 22.3 mg, 78% yield (Scheme 2.13).

Scheme 2.14 Desilylation reaction of **3a**

Experimental procedure D: The **3a** (0.2 mmol, 1 equiv.) was dissolved into 1 mL THF in a 10 mL RBF. Then, the mixture of TBAF (0.4 mmol, 4 equiv.), acetic acid (0.6 mmol, 6 equiv.) and 1 mL THF was added dropwisely. The reaction was allowed to stir for 0.5 hour at room temperature and quenched with saturated NaHCO₃ solution. After extracting with dichloromethane (2x10mL), the organic layer was evaporated and the residue was subjected to column chromatography (Hexane:EtOAc = 4:1) to deliver the product **6** 33.7 mg, 91% yield (Scheme 2.14).

Scheme 2.15 Cycloaddition reaction between **6** and benzyl azide

Experimental procedure E: The **6** (0.1 mmol, 1 equiv.) and BnN₃ (0.12 mmol, 1.2 equiv.) were dissolved into 1 mL CHCl₃ in a 5 mL RBF. Then the aqueous solution of CuSO₄·5H₂O (0.01 mmol, 0.1 equiv.) and sodium ascorbate (0.02 mmol, 0.2 equiv.) was added dropwisely. The reaction was allowed to stir for 36 hours under room temperature and quenched with saturated NH₃Cl solution. After extracting with dichloromethane (2x10mL), the organic layer was evaporated and the residue was

subjected to column chromatography (Hexane:EtOAc = 2:1) to deliver the product **7** 28.0 mg, 88% yield (Scheme 2.15).

2.4.3 Kinetic isotope effect study and ^{13}C labelling isotope experiment

Scheme 2.16 Kinetic isotope effect study

Experimental procedure: The *N*-(1-phenylvinyl)acetamide **2a** (0.1 mmol, 1 equiv.), **2a-d₂** (0.1 mmol, 1 equiv.), alkynyliodonium reagent **1** (0.1 mmol, 1 equiv.), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]$ (0.004 mmol, 2 mol %), PivOH (0.02 mmol, 10 mol %) and acetone (1 mL) were placed in a 8 mL glass vial under air. After stirring at room temperature for 12 hours, quenched with NaHCO_3 solution (10 mL) and extracted with dichloromethane (2x20mL), the resulting mixture was vacuoded and purified by column chromatography (Hexane:EtOAc = 2:1) affording the the mixture of **3a** and **3a-d₁** (Scheme 2.16). ^1H NMR (400 MHz, DMSO-d_6): δ 1.08 (m, 21H), 1.99 (s, 3H), 6.09 (s, 0.6H), 7.35-7.38 (m, 3H), 7.49-7.51(m, 2H), 9.39 (brs, 1H) ppm;

Figure 2.1 Intermolecular kinetic isotope effect study (^1H NMR in $\text{DMSO}-d_6$)

The **Figure 2.1** shows that the $[\text{P}_\text{H}] = 0.6$.

$$\text{KIE} = \text{P}_\text{H}/\text{P}_\text{D} = \text{P}_\text{H}/(1-\text{P}_\text{H}) = 0.6/0.4 = 1.5$$

Scheme 2.17 ^{13}C -labelling isotope experiment

Experimental procedure (Scheme 2.17): The *N*-(1-phenylvinyl)acetamide **2a** (0.2 mmol, 1 equiv.), ^{13}C labeled hypervalent alkynyliodonium reagent **1-C¹³** (0.22 mmol, 1.1 equiv.), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]$ (0.004 mmol, 2 mol %), PivOH (0.02 mmol, 10

mol %) and Acetone (1 mL) were placed in a 8 mL glass vial under air. After stirring at room temperature for 12 hours, saturated NaHCO_3 solution (10 mL) was added and the resulting mixture was extracted with dichloromethane (2x20mL). Removal of the solvent in vacuo and purified by column chromatography (Hexane:EtOAc = 2:1) afforded the desired product **3a-C¹³** 54.8 mg (80% yield). **¹H NMR (400 MHz, CD₃OD):** δ 1.13-1.14 (m, 21H), 2.12 (s, 3H), 6.03 (s, 1H), 7.34-7.49 (m, 5H) ppm; **¹³C NMR (100 MHz, CD₃OD):** δ 12.5, 19.1, 23.0, 99.4, 104.7, 126.8, 128.9, 129.6, 130.2, 137.5, 146.8, 171.7 ppm;

Figure 2.2 ¹³C-labelling isotope experiment (¹H NMR in CD₃OD)

Figure 2.3 ^{13}C -labelling isotope experiment (^{13}C NMR in CD_3OD)

Figure 2.4 ^{13}C -labelling isotope experiment (Hmbc in CD_3OD)

Scheme 2.18 Desilylation reaction of **3a-C¹³**

Experimental procedure (Scheme 2.18): The ¹³C labeled **3a-C¹³** (0.1 mmol, 1 equiv.) was dissolved into 0.5 mL THF in a 10 mL RBF. Then added the mixture of TBAF (0.2 mmol, 2 equiv.), AcOH(0.3 mmol, 3 equiv.) and 0.5 mL THF dropwisely. The reaction was allowed to stir for 0.5 hour under room temperature and quenched with saturated NaHCO₃ solution (10 mL). After the extraction with dichloromethane (2x10mL), the organic layer was evaporated and the residue was subjected to column chromatography (Hexane:EtOAc = 2:1) to deliver the product **6-C¹³** 16.7 mg (90% yield).

Figure 2.5 ¹³C-labelling isotope experiment desilylation (¹H NMR in CD₃OD)

Figure 2.6 ^{13}C -labelling isotope experiment desilylation (^{13}C NMR in CD_3OD)

Figure 2.7 ^{13}C -labelling isotope experiment desilylation (Dept 90 in CD_3OD)

Figure 2.8 ^{13}C -labelling isotope experiment desilylation (Dept 135 in CD_3OD)

Figure 2.9 ^{13}C -labelling isotope experiment desilylation (Hmqc in CD_3OD)

2.4.4 Characterization of alkynylation products

(Z)-N-(1-phenyl-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure A, **3a** was obtained as a white solid (31.0 mg, 0.091 mmol, Yield: 91%); m.p. = 78-80 °C; ^1H NMR (400 MHz, CD_3OD): δ 1.14 (m, 21H), 2.12 (s, 3H), 6.03 (s, 1H), 7.34-7.49 (m, 5H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5, 19.1, 23.0, 99.4, 104.7, 126.8, 129.6, 130.2, 137.5, 146.8, 171.65 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{32}\text{NOSi}$ $[\text{M}+\text{H}]^+$ 342.2253, found: 342.2246.

(Z)-N-(1-(*m*-tolyl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure A, **3b** was obtained as a white solid (32.7 mg, 0.092 mmol, Yield: 92%); m.p. = 67-69 °C; ^1H NMR (400 MHz, CD_3OD): δ 1.13 (m, 21H), 2.12 (s, 3H), 2.35 (s, 3H), 6.01 (s, 1H), 7.16-7.30 (m, 4H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5, 19.1, 21.5, 23.0, 99.3, 104.6, 104.8, 124.1, 127.4, 129.5, 131.0, 137.4, 139.4, 146.9, 171.6 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{34}\text{NOSi}$ $[\text{M}+\text{H}]^+$ 356.2410, found: 356.2413.

(Z)-N-(1-(*p*-tolyl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure A, **3c** was obtained as a white solid (31.8 mg, 0.089 mmol, Yield: 89%); m.p. = 140-142 °C; ^1H NMR (400 MHz, CD_3OD): δ 1.13 (m,

21H), 2.11 (s, 3H), 2.34 (s, 3H), 5.99 (s, 1H), 7.17 (d, $J = 8.0$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5, 19.1, 21.3, 23.0, 99.0, 103.9, 104.9, 126.8, 130.3, 134.6, 140.6, 146.7, 171.6 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{34}\text{NOSi}$ $[\text{M}+\text{H}]^+$ 356.2410, found: 356.2414.

(Z)-N-(1-(4-methoxyphenyl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl) acetamide:

Following the experimental procedure A, **3d** was obtained as a white solid (30.1 mg, 0.081 mmol, Yield: 81%); m.p. = 121-123 °C; ^1H NMR (400 MHz, CD_3OD): δ 1.13 (m, 21H), 2.11 (s, 3H), 3.80 (s, 3H), 5.93 (s, 1H), 6.91 (d, $J = 8.0$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.6, 19.1, 23.1, 55.8, 98.5, 102.8, 105.1, 115.0, 128.3, 129.8, 146.4, 162.2, 171.6 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{34}\text{NO}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 372.2359, found: 372.2365.

(Z)-N-(1-(4-(trifluoromethyl)phenyl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl) acetamide:

Following the experimental procedure A, **3e** was obtained as a white solid (37.6 mg, 0.092 mmol, Yield: 92%); m.p. = 112-114 °C; ^1H NMR (400 MHz, CD_3OD): δ 1.14 (m, 21H), 2.13 (s, 3H), 6.14 (s, 1H), 7.65 (m, 4H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5, 19.1, 23.0, 101.1, 104.2, 106.8, 125.6 (q, $J = 270.0$ Hz), 126.4, 127.4, 131.7 (q, $J = 30.0$ Hz), 141.3, 145.6, 171.8 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{31}\text{F}_3\text{NOSi}$ $[\text{M}+\text{H}]^+$ 410.2127, found: 410.2146.

(Z)-N-(1-(4-cyanophenyl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure A, **3f** was obtained as a white solid (35.4 mg, 0.097 mmol, Yield: 97%); m.p. = 139-141 °C; ¹H NMR (400 MHz, CD₃OD): δ 1.14 (m, 21H), 2.13 (s, 3H), 6.17 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H) ppm; ¹³C NMR (100 MHz, CD₃OD): δ 12.5, 19.1, 23.0, 101.9, 104.0, 107.6, 113.2, 119.5, 127.6, 133.4, 142.1, 145.4, 171.8 ppm; HRMS (ESI, *m/z*): calcd for C₂₂H₃₁N₂OSi [M+H]⁺ 367.2206, found: 367.2214.

(Z)-N-(1-([1,1'-biphenyl]-4-yl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl) acetamide:

Following the experimental procedure A, **3g** was obtained as a white solid (38.2 mg, 0.092 mmol, Yield: 92%); m.p. = 166-168 °C; ¹H NMR (400 MHz, CD₃OD): δ 1.13 (m, 21H), 2.14 (s, 3H), 6.08 (s, 1H), 7.31-7.35 (m, 1H), 7.41-7.44 (m, 2H), 7.54-7.62 (m, 6H) ppm; ¹³C NMR (100 MHz, CD₃OD): δ 12.5, 19.2, 23.1, 99.7, 104.7, 104.8, 127.3, 127.9, 128.1, 128.7, 129.9, 136.3, 141.5, 143.2, 146.4, 171.8 ppm; HRMS (ESI, *m/z*): calcd for C₂₇H₃₆NOSi [M+H]⁺ 418.2566, found: 418.2555.

(Z)-N-(1-(4-bromophenyl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure A, **3h** was obtained as a white solid (40.0 mg, 0.095 mmol, Yield: 95%); m.p. = 122-124 °C; ¹H NMR (400 MHz, CD₃OD): δ 1.13 (m, 21H), 2.11 (s, 3H), 6.05 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 2H),

7.51 (d, $J = 8.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5, 19.1, 23.0, 100.2, 104.5, 105.3, 124.1, 128.6, 132.7, 136.7, 145.9, 171.7 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{31}\text{BrNOSi}$ $[\text{M}+\text{H}]^+$ 420.1358, found: 420.1364.

(Z)-N-(1-(4-fluorophenyl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure A, **3i** was obtained as a white solid (32.1 mg, 0.089 mmol, Yield: 89%); m.p. = 81-83 °C; ^1H NMR (400 MHz, CD_3OD): δ 1.13 (m, 21H), 2.11 (s, 3H), 5.98 (s, 1H), 7.07-7.11 (m, 2H), 7.49-7.53 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5, 19.1, 23.0, 99.5, 104.6, 116.4 (d, $J = 22.0$ Hz), 129.0 (d, $J = 8.0$ Hz), 133.8 (d, $J = 3.0$ Hz), 145.9, 164.8 (d, $J = 247.0$ Hz), 171.7 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{31}\text{FNOSi}$ $[\text{M}+\text{H}]^+$ 360.2159, found: 360.2159.

(Z)-N-(1-(4-(methylsulfonyl)phenyl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure A, **3j** was obtained as a white solid (41.5 mg, 0.099 mmol, Yield: 99%); m.p. = 160-162 °C; ^1H NMR (400 MHz, CDCl_3): δ 1.13 (m, 21H), 2.14 (s, 3H), 3.06 (s, 3H), 5.44 (s, 1H), 7.54 (d, $J = 8.0$ Hz, 2H), 7.59 (s, 1H), 7.89 (d, $J = 8.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 11.1, 18.6, 23.7, 44.5, 100.2, 101.6, 102.5, 126.8, 127.4, 140.3, 141.0, 145.8, 168.2 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{34}\text{NO}_3\text{SSi}$ $[\text{M}+\text{H}]^+$ 420.2029, found: 420.2021.

(Z)-N-(1-(4-acetylphenyl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure A, **3k** was obtained as a white solid (36.7 mg, 0.096 mmol, Yield: 96%); m.p. = 150-152 °C; ^1H NMR (400 MHz, CD_3OD): δ 1.14 (m, 21H), 2.13 (s, 3H), 2.59 (s, 3H), 6.17 (s, 1H), 7.59-7.62 (m, 2H), 7.96-7.98 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5, 19.1, 23.0, 26.7, 101.3, 104.4, 106.9, 127.0, 129.7, 138.4, 142.1, 145.9, 171.7, 199.7 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{23}\text{H}_{34}\text{NO}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 384.2359, found: 384.2356.

(Z)-2-(1-acetamido-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)benzyl acetate:

Following the experimental procedure A, **3l** was obtained as colorless oil (37.6 mg, 0.091 mmol, Yield: 91%); ^1H NMR (400 MHz, CD_3OD): δ 1.15 (m, 21H), 2.02 (s, 3H), 2.07 (s, 3H), 5.15 (s, 2H), 5.41 (s, 1H), 7.33-7.42 (m, 4H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5, 19.1, 20.9, 23.3, 99.7, 103.7, 104.2, 129.3, 129.9, 130.3, 130.7, 135.1, 138.5, 146.6, 170.5, 172.4 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{24}\text{H}_{36}\text{NO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 414.2464, found: 414.2468.

(Z)-N-(1-(2-(piperidin-1-yl)phenyl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure A, **3m** was obtained as a white solid (40.7 mg, 0.096 mmol, Yield: 96%); m.p. = 79-81 °C; ^1H NMR (400 MHz, CD_3OD): δ 1.14 (m, 21H), 1.56-

1.59 (m, 2H), 1.67-1.72 (m, 4H), 2.04 (s, 3H), 2.91-2.94 (m, 4H), 5.87 (s, 1H), 6.96-7.06 (m, 2H), 7.22-7.27 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5, 19.2, 23.6, 25.3, 27.7, 99.8, 102.2, 104.9, 120.1, 123.5, 130.7, 131.3, 133.9, 147.1, 153.1, 170.0 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{26}\text{H}_{41}\text{N}_2\text{OSi}$ $[\text{M}+\text{H}]^+$ 425.2988, found: 425.2985.

(Z)-N-(1-(2-chlorophenyl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure A, **3n** was obtained as a white solid (35.1 mg, 0.094 mmol, Yield: 94%); m.p. = 89-91 °C; ^1H NMR (400 MHz, CD_3OD): δ 1.15 (m, 21H), 2.04 (s, 3H), 5.45 (s, 1H), 7.29-7.40 (m, 4H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5, 19.1, 23.0, 100.2, 103.5, 104.3, 128.0, 130.9, 131.0, 132.0, 133.3, 137.1, 146.0, 170.6 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{31}\text{ClNOSi}$ $[\text{M}+\text{H}]^+$ 376.1863, found: 376.1876.

(Z)-N-(1-(naphthalen-2-yl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl) acetamide:

Following the experimental procedure A, **3o** was obtained as a white solid (34.9 mg, 0.087 mmol, Yield: 87%); m.p. = 134-136 °C; ^1H NMR (400 MHz, CD_3OD): δ 1.15 (m, 21H), 2.18 (s, 3H), 6.19 (s, 1H), 7.46-7.49 (m, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.80-7.87 (m, 3H), 7.93 (s, 1H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5, 19.2, 23.1, 100.0, 104.9, 105.4, 124.3, 126.3, 127.6, 127.8, 128.6, 129.3, 129.6, 134.6, 135.2, 146.7, 171.8 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{25}\text{H}_{34}\text{NOSi}$ $[\text{M}+\text{H}]^+$ 392.2410, found: 392.2414.

(Z)-N-(1-(thiophen-2-yl)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure A, **3p** was obtained as a white solid (22.5 mg, 0.065 mmol, Yield: 65%); m.p. = 108-110 °C; ^1H NMR (400 MHz, CD_3OD): δ 1.12 (m, 21H), 2.10 (s, 3H), 6.05 (s, 1H), 7.02-7.04 (m, 1H), 7.23-7.24 (m, 1H), 7.39-7.40 (m, 1H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 11.2, 17.7, 21.5, 98.7, 102.8, 103.0, 125.3, 126.4, 127.6, 139.5, 140.8, 170.2 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{30}\text{NOSSi}$ $[\text{M}+\text{H}]^+$ 348.1817, found: 348.1820.

N-(3-((triisopropylsilyl)ethynyl)-2H-chromen-4-yl)acetamide:

Following the experimental procedure A, **3q** was obtained as a white solid (25.3 mg, 0.069 mmol, Yield: 69%); m.p. = 180-182 °C; ^1H NMR (400 MHz, CD_3OD): δ 1.13 (m, 21H), 2.14 (s, 3H), 4.79 (s, 2H), 6.82-6.96 (m, 2H), 7.16-7.20 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.4, 19.1, 22.9, 68.6, 101.6, 102.8, 112.4, 117.1, 122.2, 122.8, 124.6, 131.5, 136.2, 156.2, 172.1 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{32}\text{NO}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 370.2202, found: 370.2207.

N-(2-((triisopropylsilyl)ethynyl)-1H-inden-3-yl)acetamide:

Following the experimental procedure A, **3r** was obtained as a white solid (21.6 mg, 0.061 mmol, Yield: 61%); m.p. = 151-153 °C; ^1H NMR (400 MHz, CD_3OD): δ 1.14 (m, 21H), 2.17 (s, 3H), 3.56 (s, 2H), 7.27-7.42 (m, 4H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5,

19.1, 22.8, 41.0, 101.4, 103.2, 119.8, 120.8, 124.9, 127.7, 141.9, 142.7, 144.2, 171.7, 178.1 ppm; **HRMS (ESI, m/z)**: calcd for C₂₂H₃₂NOSi [M+H]⁺ 354.2253, found: 354.2254.

(Z)-N-(1-phenyl-6-(triisopropylsilyl)hex-3-en-5-yn-3-yl)acetamide:

Following the experimental procedure A, **3s** was obtained as colorless oil (30.6 mg, 0.083 mmol, Yield: 83%); **¹H NMR (400 MHz, CDCl₃)**: δ 1.11 (m, 21H), 2.10 (s, 3H), 2.79-2.99 (m, 4H), 4.69 (s, 1H), 7.18-7.29 (m, 5H), 7.77 (s, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃)**: δ 11.2, 18.7, 24.7, 34.9, 35.2, 90.3, 98.3, 102.0, 126.0, 128.3, 128.5, 141.2, 150.9, 167.5 ppm; **HRMS (ESI, m/z)**: calcd for C₂₃H₃₆NOSi [M+H]⁺ 370.2566, found: 370.2559.

(Z)-N-(5,5,6-trimethyl-1-(triisopropylsilyl)hepta-3,6-dien-1-yn-4-yl) acetamide:

Following the experimental procedure A, **3t** was obtained as colorless oil (32.5 mg, 0.090 mmol, Yield: 90%); **¹H NMR (400 MHz, CD₃OD)**: δ 1.09 (m, 27H), 1.75 (s, 3H), 2.06 (s, 3H), 2.18 (s, 2H), 4.69 (s, 1H), 4.87 (s, 1H), 5.63 (s, 1H) ppm; **¹³C NMR (100 MHz, CD₃OD)**: δ 12.5, 19.1, 23.0, 25.0, 26.5, 41.3, 96.2, 104.8, 106.6, 115.4, 143.9, 154.8, 171.2 ppm; **HRMS (ESI, m/z)**: calcd for C₂₁H₃₈NOSi [M+H]⁺ 348.2723, found: 348.2724.

(Z)-N-(2,2-dimethyl-1-phenyl-6-(triisopropylsilyl)hex-3-en-5-yn-3-yl) acetamide:

Following the experimental procedure A, **3u** was obtained as

colorless oil (38.4 mg, 0.097 mmol, Yield: 97%); ^1H NMR

(400 MHz, CD_3OD): δ 1.02 (s, 6H), 1.11 (m, 21H), 2.09 (s, 3H), 2.62 (1s, 2H), 5.48 (s, 1H), 7.13-7.26 (m, 5H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5, 19.1, 23.1, 25.7, 42.1, 46.7, 96.2, 104.7, 107.3, 127.3, 128.7, 131.8, 139.2, 154.4, 171.4 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{25}\text{H}_{40}\text{NOSi}$ $[\text{M}+\text{H}]^+$ 398.2879, found: 398.2881.

(Z)-4-acetamido-7-(triisopropylsilyl)hept-4-en-6-yn-1-yl acetate:

Following the experimental procedure A, **3v** was obtained

as colorless oil (30.0 mg, 0.082 mmol, Yield: 82%); ^1H

NMR (400 MHz, CDCl_3): δ 1.10 (m, 21H), 1.85 (t, 2H), 2.06 (d, $J = 8.0$ Hz, 6H), 2.77 (t, $J = 8.0$ Hz, 2H), 4.09 (t, $J = 8.0$ Hz, 2H), 4.71 (s, 1H), 7.74 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 11.2, 18.7, 21.0, 24.7, 27.1, 29.6, 63.7, 90.4, 98.5, 101.8, 150.3, 167.3, 171.1 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{36}\text{NO}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 366.2464, found: 366.2464.

(Z)-N-(1-(triisopropylsilyl)dec-3-en-1-yn-4-yl)acetamide:

Following the experimental procedure A, **3w** was

obtained as colorless oil (30.1 mg, 0.086 mmol, Yield:

86%); ^1H NMR (400 MHz, CDCl_3): δ 0.86-0.89 (m, 3H), 1.08 (m, 21H), 1.26-1.34 (m, 6H), 1.46-1.48 (m, 2H), 2.06 (s, 3H), 2.66-2.69 (m,

2H), 4.69 (s, 1H), 7.72 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 11.2, 14.0, 18.7, 22.6, 24.7, 28.1, 28.9, 31.6, 32.9, 89.5, 97.8, 102.3, 152.1, 167.4 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{40}\text{NOSi}$ $[\text{M}+\text{H}]^+$ 350.2879, found: 350.2876.

(Z)-N-(2,2-dimethyl-6-(triisopropylsilyl)hex-3-en-5-yn-3-yl)acetamide:

Following the experimental procedure A, **3x** was obtained as a white solid (26.7 mg, 0.083 mmol, Yield: 83%); m.p. = 122-124 °C ^1H NMR (400 MHz, CD_3OD): δ 1.10 (m, 30H), 2.04 (s, 3H), 5.67 (s, 1H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 12.5, 19.1, 22.9, 28.3, 38.2, 95.8, 104.6, 106.0, 156.0, 171.4 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{36}\text{NOSi}$ $[\text{M}+\text{H}]^+$ 322.2566, found: 322.2565.

(Z)-methyl 2-acetamido-5-(triisopropylsilyl)pent-2-en-4-ynoate:

Following the experimental procedure A, **3y** was obtained as colorless oil (20.1 mg, 0.062 mmol, Yield: 62%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.06 (m, 30H), 1.93 (s, 3H), 3.69 (s, 3H), 6.32 (s, 1H), 9.57 (s, 1H) ppm; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 11.1, 18.9, 22.7, 52.9, 101.9, 104.6, 111.6, 137.8, 164.6, 168.6 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{17}\text{H}_{30}\text{NO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 324.1995, found: 324.1986.

(E)-N-(1-phenyl-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure B, the compound was obtained as a white solid (15.4 mg, 0.045 mmol, Yield: 45%);

m.p. = 94-96 °C; **¹H NMR (400 MHz, CDCl₃):** δ 0.97 (m, 21H), 1.98 (s, 3H), 6.70 (s, 1H), 7.30-7.36 (m, 4H), 7.57-7.58 (m, 2H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 11.2, 18.5, 24.4, 95.2, 96.5, 104.2, 128.2, 128.4, 129.0, 136.0, 145.1, 169.2 ppm; **HRMS (ESI, m/z):** calcd for C₂₁H₃₂NOSi [M+H]⁺ 342.2253, found: 342.2249.

(Z)-N-(5,5-dimethyl-1-phenylhex-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure A, but using *t*-Bu-based hypervalent alkynyl iodine reagent, **4a** was obtained as a white solid (21.0 mg, 0.087 mmol, Yield: 87%); m.p. = 126-128 °C; **¹H NMR (400 MHz, CD₃OD):** δ 1.29 (m, 9H), 2.13 (s, 3H), 5.88 (s, 1H), 7.32-7.45 (m, 5H) ppm; **¹³C NMR (100 MHz, CD₃OD):** δ 22.8, 29.4, 31.4, 76.9, 105.0, 107.7, 126.6, 129.5, 129.7, 137.8, 144.6, 171.8 ppm; **HRMS (ESI, m/z):** calcd for C₁₆H₂₀NO [M+H]⁺ 242.1545, found: 242.1547.

(Z)-N-(4-(4-cyanophenyl)-1-phenylbut-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure C, **5** was obtained as a white solid (22.9 mg, 0.080 mmol, Yield: 80%); m.p. = 192-194 °C **¹H NMR (400 MHz, DMSO-*d*₆):** δ 2.07-2.09 (m, 3H), 6.09 (s, 1H), 7.38-7.40 (m, 3H), 7.50-7.52 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 2H), 9.78 (s, 1H) ppm; **¹³C NMR (100 MHz, DMSO-*d*₆):** δ 22.9, 91.8, 94.8, 99.6, 110.4, 118.5, 126.0, 127.9, 128.4, 129.2, 131.8, 132.5, 136.2, 147.4, 168.3 ppm; **HRMS (ESI, m/z):** calcd for C₁₉H₁₅N₂O [M+H]⁺ 287.1184, found: 287.1196.

(Z)-N-(1-phenylbut-1-en-3-yn-1-yl)acetamide:

Following the experimental procedure D, **6** was obtained as a white solid (17.0 mg, 0.092 mmol, Yield: 92%); m.p. = 162-164 °C ¹H NMR (400 MHz, CD₃OD): δ 2.13 (s, 3H), 3.74 (s, 1H), 5.81 (s, 1H), 7.34-7.35 (m, 3H), 7.44-7.45 (m, 2H) ppm; ¹³C NMR (100 MHz, CD₃OD): δ 22.9, 80.8, 86.4, 102.6, 126.9, 129.5, 130.2, 137.5, 147.8, 172.0 ppm; HRMS (ESI, m/z): calcd for C₁₂H₁₂NO [M+H]⁺ 186.0919, found: 186.0910.

(Z)-N-(2-(1-benzyl-1H-1,2,3-triazol-4-yl)-1-phenylvinyl)acetamide:

Following the experimental procedure E, **7** was obtained as a colorless oil (28.9 mg, 0.091 mmol, Yield: 91%); ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.10 (s, 3H), 5.67 (s, 2H), 6.79 (s, 1H), 7.29-7.42 (m, 8H), 7.50-7.52 (m, 2H), 8.16 (s, 1H), 9.59 (s, 1H) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆): δ 23.7, 53.2, 112.3, 123.9, 126.0, 128.4, 128.8, 129.2, 135.7, 136.5, 138.2, 143.7, 168.9 ppm; HRMS (ESI, m/z): calcd for C₁₉H₁₉N₄O [M+H]⁺ 319.1559, found: 319.1571.

Chapter 3

*Cp*Rh(III)-Catalyzed Olefinic C-H Alkynylation of Acrylamides Using Tosyl-Imide as Directing Group*

3.1 Introduction

3.1.1 Directing-group-assisted C-H bond functionalization

Directing-group assisted transition-metal-catalyzed C-H activation reactions, which allow site-selective manipulation of otherwise inert C-H bonds beyond their intrinsic electronic properties, offer alternatives to traditional methods for the construction of C-C and C-X bonds. From the viewpoint of atom-economy and sustainability, transition-metal-catalyzed C-H activation reactions have attracted increasing attention from the synthetic community. In this context, the past decade has witnessed an explosive advancement in this arena with a wide variety of chelating auxiliaries being devised as effective directing groups. Among these works, the weak coordination strategy, firstly raised by Yu, stood out as a competent and powerful mean, with broad application in a diverse range of synthetically useful C-H bond transformations.⁴¹ While much progress has been attained, this strategy, to some extent, was mainly restricted to the domain of palladium catalysis.⁴²

⁴¹ Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788.

⁴² For selected examples of palladium-catalyzed C-H activation using the strategy of weak coordination, see: (a) Zhang, X.-G.; Dai, H.-X.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 11948. (b) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387. (c) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J.-Q. *Nature Chem.* **2014**, *6*, 146. (d) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518. (e) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (f) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. (g) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676.

3.1.2 Rh-catalyzed C-H activation reactions

On the other hand, hypervalent Rh(III) salt has recently been recognized as the catalyst of choice for a large variety of C-H bond functionalization processes.⁴³

Elegant works from the groups of Miura, Fagnou, Glorius, Rovis, Ellman, Ma, Shi, Li and Chang, among others, not only substantially expanded this area but also demonstrated the high potential of Rh(III) catalyst in the process of C-H bond activation, thus drawing much attention from organic chemists.⁴⁴

⁴³ (a) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212. (b) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (c) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimica Acta.* **2012**, *45*, 31. (d) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (e) Kuhl, N.; Schroder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443.

⁴⁴ For selected recent examples of Rh(III)-catalyzed C-H functionalization, see: (a) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (b) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (c) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (d) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982. (e) Shroder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298. (f) Yu, D.-G.; Suri, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 8802. (g) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (h) Hyster, T. K.; Knorr, L.; Ward, T. R.; Rovis, T. *Science* **2012**, *338*, 500. (i) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2014**, *136*, 2735. (j) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 1248. (k) Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430. (l) Zeng, R.; Fu, C.; Ma, S. *J. Am. Chem. Soc.* **2012**, *134*, 9597. (m) Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W.-P.; Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2115. (n) Xie, F.; Qi, Z.; Li, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 11862. (o) Li, X.; Yu, S.; Wang, F.; Wan, B.; Yu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 2577. (p) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110. (q) Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565. (r) Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 2247. (s) Wencel-Delord, J.; Nimphius, C.; Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 13001.

3.1.3 The synthesis of 1,3-enynes

1,3-Enynes constitute a class of prevalent subunits widely found in naturally occurring compounds and pharmaceuticals and represent a key structural motif in synthetic chemistry because of their dense functionality, amenable to a diverse range of synthetic transformations.⁴⁵ Although considerable efforts have been made, currently reported methods suffer from either a necessity of substrate preactivation or reliance on harsh reaction conditions; therefore the development of a mild and step-economical pathway for the synthesis of a 1,3-enyne framework is still required (Scheme 3.1).⁴⁶

Scheme 3.1 General methods for synthesis of 1,3-enynes through transition metal-catalyzed cross coupling.

⁴⁵ (a) Fontana, A.; d'Ippolito, G.; D'Souza, L.; Mollo, E.; Parameswaram, P. S.; Cimino, G. *J. Nat. Prod.* **2001**, *64*, 131. (b) Gung, B. W.; Kumi, G. *J. Org. Chem.* **2004**, *69*, 3488. (c) Nicolaou, K. C.; Dai, M. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (d) El-Jaber, N.; Estevez-Braun, A.; Ravelo, A. G.; Munoz-Munoz, O.; Rodriguez-Afonso, A.; Murguia, J. R. *J. Nat. Prod.* **2003**, *66*, 722. (e) Zein, N.; Sinba, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198. (f) Ratovelomanana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917.

⁴⁶ (a) Trost, B. M.; Chan, C.; Ruhter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486. (b) Tsukada, N.; Ninomiya, S. Aoyama, Y.; Inoue, Y. *Org. Lett.* **2007**, *9*, 2919. (c) Nishimura, T.; Araki, H.; Maeda, Y.; Uemura, S. *Org. Lett.* **2003**, *5*, 2997. (d) Takeuchi, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem.* **2000**, *65*, 1558. (e) Katayama, H.; Yari, H.; Tanaka, M.; Ozawa, F. *Chem. Commun.* **2005**, 4336. (f) Wen, Y.; Wang, A.; Jiang, H.; Zhu, S.; Huang, L. *Tetrahedron Lett.* **2011**, *52*, 5736. (g) Bates, C. G.; Saejueng, P.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 1441.

3.1.4 Rh-catalyzed alkynylation reactions of aromatic compounds

Quite recently, in the field of rhodium-catalyzed direct C-H functionalization, the alkynylation of arenes using hypervalent iodine reagent as the alkynyl source was arised as an efficient method for installing alkynyl counterparts to normal aromatic motifs. By taking advantage of the electrophilic charater of hypervalent alkynyl iodine reagent,⁴⁷ the reaction circumvents relatively harsh reaction conditions as well as the employment of external oxidants, and presents a broad scope of substrates with excellent yields and outstanding selectivities.

In 2014, the directing-group assisted Rh-catalyzed alkynylation reaction of *N*-(pivaloyloxy)benzamide and its derivatives with extremely high efficiency generating only the mono alkynylation products in high to excellent yields under mild reaction conditions is described by our group (Scheme 3.2).⁴⁸ In addition, Glorius and co-workers presented that the Rh-catalyzed alkynylation reaction also worked with benzamide and acrylamide derivatives when raised up the load of catalysts and the

⁴⁷ For selected examples of alkynylation using hypervalent alkynylation iodine reagent, see: (a) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (b) Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7304. (c) Brand, J. P.; Waser, J. *Org. Lett.* **2012**, *14*, 744. (d) Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. *Chem. Eur. J.* **2012**, *18*, 5655. (e) Li, Y. Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6743. (f) Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013**, *15*, 112. (g) Huang, H.; Zhang, G.; Gong, L.; Zhang, S.; Chen, Y. *J. Am. Chem. Soc.* **2014**, *136*, 2280. (h) Wang, Z.; Li, X.; Huang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 14219.

⁴⁸ Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 2722.

reaction temperature (Scheme 3.2).⁴⁹ Intriguingly, $[\text{Cp}^*\text{IrCl}_2]$ was shown to be an effective catalyst for this transformation as well. Meanwhile, Li and co-workers demonstrated that a wide range of different directing groups could be adopted in this Rh-catalyzed alkynylation reaction when $\text{Zn}(\text{OTf})_2$ was employed as the additive (Scheme 3.2).⁵⁰ While much progress has been made, alkynylation of alkenes which operate under milder reaction condition and accommodate a broad range of functionalities are still highly desirable.

Scheme 3.2 Rh-catalyzed alkynylation reactions with hypervalent iodine reagents

We envisage that with the directing assistance of tosyl group, the Rh-catalyzed olefinic alkynylation reaction would be a very possible and applicable protocol for the synthesis of 1,3-enyne moieties. In this chapter, the novel rhodium-catalyzed C-H

⁴⁹ Collins, K. D.; Lied, F.; Glorius, F. *Chem. Commun.* **2014**, 50, 4459.

⁵⁰ Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, 136, 4780.

alkynylation of electron-deficient alkenes is described, wherein the employment of weakly coordinating directing group was proved to be critical for the accomplishment of this transformation (Scheme 3.3).

Scheme 3.3 Rh-catalyzed C-H olefinic alkynylation of acrylamides

3.2 Result and Discussion

We commenced our study by exploring effective directing groups in the olefinic alkynylation of 2-phenyl acrylamide derivatives with the hypervalent alkynyl iodine reagent **1**. Using $[\text{Cp}^*\text{RhCl}_2]_2$, NaOAc and DCE as the catalyst, the additive and the reaction solvent, respectively a series of different *N*-substituent were examined and the results are shown in Table 3.1. It was found that the nature of amide directing group is pivotal for the initiation of alkynylation reaction. When *N*-alkyl substituted or aniline derived substrates were employed, no reaction occurred (Table 3.1, entries 1-4). Moreover, 4-trifluoromethyl-2,3,5,6- tetrafluoroaniline based amide auxiliary, which was frequently employed by Yu as an effective weakly coordinating directing group in

palladium catalysis, was proved to be ineffective in this reaction (Table 3.1, entry 3).⁵¹ However, by changing alkyl- or aryl-substituted amide to *O*-pivaloyl hydroxylamide as the directing group, the C-H alkynylation product could be obtained in 35% yield (Table 3.1, entry 5). Further improvement was attained with *O*-methyl hydroxylamide as the directing group, which afforded the desired enyne product in 68% yield (Table 3.1, entry 6).⁵² Much to our surprise, the reaction efficiency was remarkably enhanced with the desired product being formed in 96% yield when Ts-imide was adopted as the directing group (**2a**, Table 3.1, entry 7). It is evident that the directing group with certain *pK*_a value had a critical impact on this reaction process. The remarkable effect of Ts-imide as the directing group was assumed to be due to its weakly coordinating ability, which rendered the formation of highly active ligated catalyst easy because of its weak σ -donation and the generation of thermodynamically labile metalacycle, making it more susceptible to the ensuing reaction steps. It is worth mentioning that the reaction still proceeded to a decent extent even in the absence of NaOAc, which is in sharp contrast with our previous finding in the alkynylation of arenes, thus further illustrating the competence of Ts-imide as the directing group in this reaction (Table 3.1, entry 8). As expected, the rhodium catalyst was found to be indispensable and the starting material **2a** remained intact with its absence (Table 3.1, entry 9). It needs to be

⁵¹ Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788.

⁵² Without the addition of NaOAc, no reaction occurred with acryl-NHOMe as substrate while 65% of **3a** was obtained in the case of **2a**.

emphasized that when **2a** was reacted with reagent **1-C¹³**, no silyl-migration product was observed (see the details at 3.4.2).

Table 3.1. Optimization of directing group.^a

Entry	R	Yield (%) ^b
1	Bn	NR
2	Ph	NR
3	C ₆ F ₄ CF ₃	NR
4	Me	NR
5	OPiv	35
6	OMe	68
7	Ts	96
8 ^c	Ts	67
9 ^d	Ts	NR
10 ^e	Ts	83

^a Unless otherwise noted, the reactions were carried out at room temperature using **2a** (0.1 mmol), hypervalent alkynylidonium reagent **1** (0.11 mmol), NaOAc (0.1 mmol), [Cp*RhCl₂]₂ (0.002 mmol) in DCE (0.5 mL) for 16 h. ^b Isolated yields. ^c No NaOAc. ^d No rhodium catalyst was added. ^e 1 g scale of TIPS-EBX.

Table 3.2. Substrate scope of acrylamides.^{a,b}

^a Unless otherwise noted, the reactions were carried out at room temperature using **2** (0.1 mmol), hypervalent aklynyliodonium reagent **1** (0.11 mmol), NaOAc (0.1 mmol), [Cp*RhCl₂]₂ (0.002 mmol) in DCE (0.5 mL) for 16 h. ^b Isolated yields.

With Ts-imide as the optimal directing group, the reaction generality with respect to electron-deficient alkenes was thus investigated and presented in Table 3.2. The α -aryl amides were first examined, showing that the electronic property of aryl substituents exerted negligible effect on the reaction, with both electron rich and deficient ones

being converted into the desired products in high to excellent yield. Halogen substituents, such as Cl, F were well tolerated, allowing further synthetic manipulation of the substrates. Furthermore, biphenyl and naphthalyl derived substrates were also amenable to this reaction condition, generating the products **3f**, **3g** in 98% and 87% yields, respectively. And present reaction was not limited to α -aryl amide derivatives, α -alkyl amides with a diverse range of functional groups were all nicely accommodated, highlighting the synthetic potential of this protocol. Particularly, linear alkyl based substrates such as **2h**, **2i** reacted smoothly with alkynyl reagent **1** to afford products **3h** and **3i** in 99% and 96% yields. In the case of acrylamides **2j** and **2k**, the reactions occurred selectively to produce 1,3-enyne products in excellent yield without the formation of alkene shift products, despite of the presence of π -conjugation of aryl units.

In addition, carbocycle-containing starting materials also engaged well in this transformation without any compromise in yield. Among those substrates, the result when using α -cyclopropyl acrylamide **2m** is more meaningful as it precludes the possibility of the involvement of radical pathway in the reaction process. When α -trimethylsilyl-methyl acrylamide **2n** was subjected to the standard reaction condition, the product **3n** was obtained in quantitative yield, with the silyl group remaining intact throughout the reaction, which indicated the C-H activation for the formation of metallacycle intermediate did not follow an electrophilic-metallation-deprotonation

pathway. The tolerance of alcohol and amine derived functionalities, such as those of in **2o**, **2p**, further expanded the reaction scope and indicated the synthetic potential of this reaction in the course of complicated molecule synthesis. Last but not the least, the present reaction was found to be highly stereoselective, with the alkynyl group incorporated into the *cis*-position with respect to the Ts-imide substituent. The structure of **3c** was unambiguously confirmed through a single-crystal X-ray diffraction analysis (Scheme 3.4).¹²

Scheme 3.4 Structure determination

In order to further extend the reaction scope, α,β -disubstituted acrylamide derivatives were subsequently examined (Table 3.3). After several attempts, it was revealed that using methanol as the reaction solvent in place of DCE was proved to be beneficial. With such slight alteration, the introduction of alkynyl group to a diverse range of α,β -disubstituted acrylamides, either cyclic or acyclic ones, could be successfully accomplished, thus generating the alkynylation products in moderate to good yields.

To be more specific, 1-cyclohexenyl derived substrate **2q** reacted smoothly to furnish product **3q** in 79% yield. Furthermore, the reaction of acyclic substrates (**2r-2u**) either containing alkyl/aryl or aryl/aryl substituents worked without any difficulty to afford related products in yields ranging from 42% to 61%. Heterocycle derived acrylamides such as **2v**, **2w** and **2x**, which possess Lewis basic heteroatoms, were also nicely engaged in this reaction to furnish desired products in good yield, thus further demonstrating the synthetic potential of this reaction.

Table 3.3. Substrate scope of acrylamides.^{a,b}

^a Unless otherwise noted, the reactions were carried out at room temperature using **2** (0.1 mmol), hypervalent aklynyliodonium reagent **1** (0.11 mmol), NaOAc (0.1 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (0.002 mmol) in MeOH (0.5 mL) for 16 h. ^b Isolated yields.

Scheme 3.5 Synthetic transformation of **3q**.

To showcase the synthetic utility of the structural motif obtained with this method, a set of synthetic derivatizations were conducted with **3q** as a representation (Scheme 3.5), the TIPS group could be readily removed with TBAF to afford the terminal alkyne, which, however, was unstable and simultaneously underwent intramolecular cyclization to generate the pyridinone **4q** in 97% yield. In addition, the palladium-catalyzed desilylative Sonogashira reaction/ intramolecular cyclization could be successfully applied without any compromise, delivering products **5q** and **6q** in 78% and 76% yields, respectively, when 4-cyanophenyl iodide and 4-acetylphenyl iodide

were employed. When **3q** was reacted with NBS in acetonitrile, bromonium induced electrophilic cyclization occurred nicely, giving rise to the product **7q** in 99% yield. Furthermore, with a sequence of methylation, desilylation and copper-catalyzed azide alkyne cycloaddition, triazole **8q** could be isolated in 83% yield.

3.3 Conclusion

In conclusion, the rhodium(III)-catalyzed olefinic C-H alkynylation of electron-deficient alkenes was developed. The weakly coordinating directing group Ts-imide was proved to be critical and was responsible for the occurrence of C-H alkynylation in a highly efficient and stereospecific manner. By taking advantage of C-H activation and high functional group tolerance, mild reaction conditions and operational simplicity, this protocol represents a straightforward and expedient method to access the functionalized 1,3-enyne structural motifs. Further transformations into a series of pyridinone and triazole were also attempted to show the synthetic potential of alkynylation products.

3.4 Experimental Section

3.4.1 General Information

[RhCp*Cl₂]₂, anhydrous DCE, methanol were purchased from commercial suppliers and used as received unless otherwise noted. All reactions were carried out under air without extra protection. Reactions were monitored through thin layer chromatography [Merck 60 F254 precoated silica gel plate (0.2 mm thickness)]. Subsequent to elution, spots were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible using basic solution of potassium permanganate or acidic solution of ceric molybdate as stain, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. HRMS spectra were recorded on a Waters Q-ToF Premier Spectrometer. ¹H NMR and ¹³C NMR spectra were recorded using Bruker Avance 400 MHz spectrometers. Chemical shifts for ¹H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of SiMe₄ (δ 0.00, singlet). Multiplicities were given as: s (singlet); brs (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); td (triplet of doublet); m (multiplets); ddt (doublet of doublet of triplet) and etc. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (¹³C NMR) are reported as δ in units of parts per

million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.00, triplet).

3.4.2 Experimental procedures

Scheme 3.6 Rh-catalyzed direct C-H olefinic alkynylation of acrylamides

Experimental procedure A (Scheme 3.6): To a 10mL RBF was successively charged with acrylamides **2** (0.1 mmol), hypervalent alkynyl iodine reagent **1** (0.11 mmol), NaOAc (0.1 mmol), $[\text{RhCp}^*\text{Cl}_2]_2$ (0.002 mmol) followed by adding anhydrous DCE (0.5 mL) through syringe and then closed tightly. After stirring at room temperature for 16 hours, the mixture was subjected to purification by silica gel column chromatography (Hexane:EtOAc = 2:1) afforded the desired product **3**.

Scheme 3.7 Desilylation/annulation of **3q**

Experimental procedure B (Scheme 3.7): To a solution of amide **3q** (0.1 mmol) in THF (1 mL) was added HOAc (0.3 mmol) and TBAF (0.2 mmol) at 0 °C. After addition, the solution was warmed up to room temperature and stirred for another 1h and quenched with water, extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over MgSO₄. The volatile compounds were removed in vacuo and the residue was subjected to column chromatography (Hexane:EtOAc = 4:1) to afford **4q** in 97% yield.

Scheme 3.8 Desilylation/Sonogashira reaction of **3q**

Experimental procedure C (Scheme 3.8): An oven-dried 5mL Schlenk tube was charged with amide **3q** (0.1 mmol), aryl iodide (0.12 mmol), PdCl₂(PPh₃)₂ (1 mg), CuCl (0.03 mmol) in sequence. The Schlenk tube was vacuumed and backfilled with

nitrogen for three times followed by adding anhydrous THF (1 mL). TBAF (0.2 mL, 1 M in THF) was added into the solution at 0 °C and under the protection of nitrogen through syringe and then the Schlenk tube was closed tightly. After warming up to room temperature and stirring for 1 hour, water was added and the resulting mixture was extracted with dichloromethane (2x20 mL). Removal of the solvent in vacuo and purification of the residue by silica gel column chromatography (Hexane:EtOAc = 4:1) afforded the desired product.

Scheme 3.9 Bromination/annulation of **3q**

Experimental procedure D (Scheme 3.9): To a solution of amides **3q** (0.1 mmol) in MeCN (1 mL) was added NBS (0.12 mmol) at room temperature. The solution was stirred for 2h and then quenched with water, extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was subjected to column chromatography (Hexane:EtOAc = 4:1) to afford **7q** in 99% yield.

Scheme 3.10 Desilylation & cycloaddition reaction of **3q** with benzyl azide

Experimental procedure E (Scheme 3.10): 1) To a solution of amides **3q** (0.1 mmol) in DMF (1 mL) was added K_2CO_3 (0.3 mmol), MeI (0.3 mmol) at room temperature. The solution was stirred overnight and then quenched with water, extracted with ethyl acetate. The combined organic layers were dried over MgSO_4 and concentrated in vacuo. The product was purified using column chromatography (Hexane:EtOAc = 8:1) on silica gel.

2) To a solution of intermediate obtained above in THF (1 mL) was added HOAc (0.3 mmol) and TBAF (0.2 mmol) at 0 °C. After addition, the solution was warmed up to room temperature and stirred for another 1h and quenched with water, extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over MgSO_4 . The volatile compounds were removed in vacuo and the residue was purified using column chromatography (Hexane:EtOAc = 10:1).

3) To a solution of intermediate obtained above and BnN_3 (0.12 mmol) in $t\text{-BuOH}/\text{H}_2\text{O}$ (1:1, 0.4 mL) in a 5 mL RBF was added $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.01 mmol) and sodium ascorbate (0.02 mmol). The reaction was stirred overnight at room temperature and quenched with saturated NH_4Cl solution. After extracting with

dichloromethane (2x10mL), the organic layer was evaporated and the residue was subjected to column chromatography (Hexane:EtOAc = 4:1) to deliver the product **8q** in a total yield of 83%.

3.4.3 ^{13}C -labelling isotope experiment

Scheme 3.11 ^{13}C -labelling isotope experiment

Experimental procedure (Scheme 3.11): To a 10mL RBF was successively charged with amides **2a** (0.1 mmol), 1-C^{13} (0.1 mmol), NaOAc (0.1 mmol), $[\text{RhCp}^*\text{Cl}]_2$ (0.002 mmol) followed by adding anhydrous DCE (0.5 mL) through syringe and then closed tightly. After stirring at room temperature for 16 h, the mixture was purified by silica gel column chromatography (Hexane:EtOAc = 2:1) to afford the desired product **3a-C¹³** (44 mg, 0.092 mmol, yield 92%). ^1H NMR (400 MHz, CDCl_3): δ 1.12-1.18 (m, 21H), 2.43 (s, 3H), 6.35 (s, 1H), 7.23-7.32 (m, 7H), 8.00 (d, J = 8.4 Hz, 2H), 9.58 (brs, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 11.2, 18.6, 21.6, 102.0, 108.4 (labelled 10 $\times$ more intensive), 115.5, 128.0, 128.4, 128.7, 129.2, 129.4, 135.6, 135.7,

143.8, 144.9, 162.6 ppm; **HRMS (ESI, m/z):** calcd for $C_{27}H_{36}NO_3SSi$ $[M+H]^+$
482.2185, found: 482.2181.

Figure 3.1 ^{13}C -labelling isotope experiment (1H NMR in CDCl₃)

Figure 3.2 ^{13}C -labelling isotope experiment (^{13}C NMR in CDCl₃)

Figure 3.3 ^{13}C -labelling isotope experiment (Hmhc in CDCl_3)

In ^{13}C NMR spectra, peak (^{13}C δ 108.4) is the ^{13}C labeled alkyne carbon peak. In the Hmhc NMR spectra, the ^{13}C labeled carbon peak (δ 108.4) has interactions with proton (δ 6.35) and protons (δ 1.15), which indicating the no carbon exchange in the alkynylation reaction.

3.4.4 Characterization of alkynylation products

(Z)-2-Phenyl-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3a** was obtained

as a white solid (46.2 mg, 0.096 mmol, Yield: 96%); m.p. =

117-119 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 1.12-1.18 (m, 21H), 2.43 (s, 3H), 6.35 (s, 1H), 7.23-7.32 (m, 7H), 8.00 (d, J = 8.4 Hz, 2H), 9.57 (brs, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 11.2, 18.6, 21.6, 102.0, 108.4, 115.5,

128.0, 128.4, 128.7, 129.2, 129.4, 135.6, 135.7, 143.8, 144.9, 162.6 ppm; **HRMS (ESI, m/z)**: calcd for $C_{27}H_{36}NO_3SSi$ $[M+H]^+$ 482.2185, found: 482.2181.

(Z)-2-(4-(Tert-butyl)phenyl)-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3b** was obtained as a white solid (46.5 mg, 0.086 mmol, Yield: 86%); m.p. = 138-140 °C; **1H NMR (400 MHz, $CDCl_3$)**: δ 1.12-1.19 (m, 21H), 1.29 (s, 9H), 2.43 (s, 3H), 6.32 (s, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.30-7.33 (m, 4H), 8.00 (d, J = 8.3 Hz, 2H), 9.49 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 11.2, 18.6, 21.6, 31.1, 34.7, 102.2, 107.8, 114.7, 125.5, 127.7, 128.8, 129.4, 132.6, 135.7, 143.8, 144.9, 152.5, 162.8 ppm; **HRMS (ESI, m/z)**: calcd for $C_{31}H_{44}NO_3SSi$ $[M+H]^+$ 538.2811, found: 538.2818.

(Z)-2-(4-Methoxyphenyl)-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3c** was obtained as a white solid (47.3 mg, 0.092 mmol, Yield: 92%); m.p. = 146-148 °C; **1H NMR (400 MHz, $CDCl_3$)**: δ 1.10-1.18 (m, 21H), 2.43 (s, 3H), 3.78 (s, 3H), 6.26 (s, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 8.00 (d, J = 8.3 Hz, 2H), 9.49 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 11.2, 18.6, 21.6, 55.3, 102.2, 107.1, 113.3,

113.9, 127.8, 128.7, 129.2, 129.4, 135.7, 143.5, 144.9, 160.4, 163.0 ppm; **HRMS (ESI, m/z)**: calcd for $C_{28}H_{38}NO_4SSi$ $[M+H]^+$ 512.2291, found: 512.2292.

(Z)-2-(4-Chlorophenyl)-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3d** was obtained as a white solid (48.5 mg, 0.094 mmol, Yield: 94%); m.p. = 141-143 °C; **1H NMR (400 MHz, $CDCl_3$)**:

δ 1.14-1.22 (m, 21 H), 2.43 (s, 3H), 6.36 (s, 1H), 7.19 (d, J = 8.5 Hz, 2H), 7.28-7.32 (m, 4H), 7.99 (d, J = 8.3 Hz, 2H), 9.77 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 11.1, 18.6, 21.6, 101.8, 109.7, 116.0, 128.6, 128.7, 129.5, 134.1, 135.3, 135.6, 142.6, 145.0, 162.3 ppm; **HRMS (ESI, m/z)**: calcd for $C_{27}H_{35}ClNO_3SSi$ $[M+H]^+$ 516.1795, found: 516.1799.

(Z)-2-(4-Fluorophenyl)-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3e** was obtained as a white solid (45.6 mg, 0.091 mmol, Yield: 91%); m.p. = 124-126 °C; **1H NMR (400 MHz, $CDCl_3$)**: δ

1.14-1.22 (m, 21H), 2.43 (s, 3H), 6.34 (s, 1H), 6.99 (t, J = 8.6 Hz, 2H), 7.22-7.24 (m, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.99 (d, J = 8.3 Hz, 2H), 9.79 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 11.2, 18.6, 21.6, 101.9, 109.3, 115.4 (d, J = 21.7 Hz), 115.7, 128.7, 129.5, 130.1 (d, J = 8.4 Hz), 131.8 (d, J = 3.6 Hz), 135.6, 142.6, 145.0, 162.4,

163.2 (d, $J = 248.4$ Hz) ppm; **HRMS (ESI, m/z)**: calcd for $C_{27}H_{35}FNO_3SSi$ $[M+H]^+$ 500.2091, found: 500.2098.

(Z)-2-([1,1'-Biphenyl]-4-yl)-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3f** was obtained as a white solid (54.7 mg, 0.098 mmol, Yield: 98%); m.p. = 149-151 °C; **1H NMR (400 MHz, $CDCl_3$)**:

δ 1.13-1.19 (m, 21H), 2.42 (s, 3H), 6.40 (s, 1H), 7.30-7.36 (m, 5H), 7.42 (t, $J = 7.8$ Hz, 2H), 7.51-7.56 (m, 4H), 8.01 (d, $J = 8.3$ Hz, 2H), 9.61 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 11.2, 18.6, 21.6, 102.1, 108.5, 115.1, 127.0, 127.1, 127.7, 128.4, 128.7, 128.8, 129.4, 134.4, 135.7, 140.1, 142.0, 143.5, 145.0, 162.7 ppm; **HRMS (ESI, m/z)**: calcd for $C_{33}H_{40}NO_3SSi$ $[M+H]^+$ 558.2498, found: 558.2496.

(Z)-2-(Naphthalen-2-yl)-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3g** was obtained as a white solid (46.1 mg, 0.087 mmol, Yield: 87%); m.p. = 160-162 °C; **1H NMR (400 MHz, $CDCl_3$)**:

δ 1.13-1.21 (m, 21H), 2.43 (s, 3H), 6.45 (s, 1H), 7.30 (d, $J = 8.2$ Hz, 2H), 7.35 (dd, $J_1 = 8.6$ Hz, $J_2 = 1.8$ Hz, 1H), 7.45-7.48 (m, 2H), 7.63 (s, 1H), 7.68-7.79 (m, 3H), 8.00 (d, $J = 8.4$ Hz, 2H), 9.53 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 11.2, 18.6, 21.6, 102.1, 108.2, 115.1, 124.9, 126.5, 126.9, 127.6, 128.1, 128.4, 128.7, 129.5, 132.8,

132.9, 133.3, 135.7, 144.0, 145.0, 163.0 ppm; **HRMS (ESI, m/z):** calcd for $C_{31}H_{38}NO_3SSi$ $[M+H]^+$ 532.2342, found: 532.2344.

(Z)-N- Tosyl-2-(3-(triisopropylsilyl)prop-2-yn-1-ylidene)octanamide:

Following the general reaction procedure A, **3h** was obtained as a white solid (48.3 mg, 0.099 mmol, Yield: 99%); m.p. = 46-48 °C; **1H NMR (400 MHz, $CDCl_3$):**

δ 0.85 (t, J = 6.8 Hz, 3H), 1.14-1.16 (m, 18H), 1.20-1.28 (m, 9H), 1.33-1.37 (m, 2H), 2.28 (td, J_1 = 7.6 Hz, J_2 = 0.9 Hz, 2H), 2.43 (s, 3H), 6.16 (t, J = 1.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 5H), 7.97 (d, J = 8.4 Hz, 2H), 10.26 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 11.1, 14.0, 18.6, 21.6, 22.4, 28.8, 28.9, 31.5, 33.0, 102.3, 107.9, 114.6, 128.6, 129.4, 135.9, 144.7, 144.8, 162.4 ppm; **HRMS (ESI, m/z):** calcd for $C_{27}H_{44}NO_3SSi$ $[M+H]^+$ 490.2811, found: 490.2813.

(Z)-2-(3-Phenylpropyl)-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3i** was obtained as colorless oil (50.4 mg, 0.096 mmol, Yield: 96%); **1H NMR (400 MHz, $CDCl_3$):** δ 1.14-1.26 (m,

21H), 1.67-1.75 (m, 2H), 2.33 (t, J = 7.5 Hz, 2H), 2.42 (s, 3H), 2.57 (t, J = 7.7 Hz, 2H), 6.14 (s, 1H), 7.09-7.17 (m, 3H), 7.22-7.26 (m, 2H), 7.31 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 10.25 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 11.1, 18.6, 21.6,

30.3, 32.7, 35.4, 102.1, 108.3, 115.0, 125.8, 128.3, 128.3, 128.6, 129.4, 135.9, 141.5, 144.1, 144.8, 162.3 ppm; **HRMS (ESI, m/z)**: calcd for $C_{30}H_{40}NO_3SSi$ $[M+H]^+$ 522.2498, found: 522.2488.

(Z)-2-Benzyl-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3j** was obtained as a white solid (47.7 mg, 0.096 mmol, Yield: 96%); m.p. = 103-105 °C; **1H NMR (400 MHz, $CDCl_3$)**: δ 1.12-1.26 (m, 21H),

2.44 (s, 3H), 3.63 (d, J = 0.9 Hz, 2H), 5.91 (t, J = 1.4 Hz, 1H), 7.07-7.09 (m, 2H), 7.22-7.33 (m, 5H), 7.97 (d, J = 8.4 Hz, 2H), 10.30 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 11.1, 18.6, 21.6, 38.1, 102.0, 109.4, 116.2, 126.8, 128.6, 128.7, 129.4, 129.4, 135.8, 137.3, 143.9, 144.8, 162.3 ppm; **HRMS (ESI, m/z)**: calcd for $C_{28}H_{38}NO_3SSi$ $[M+H]^+$ 496.2342, found: 496.2342.

(Z)-2-(4-Bromobenzyl)-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3k** was obtained as a white solid (54.1 mg, 0.094 mmol, Yield: 94%); m.p. = 150-152 °C; **1H NMR (400 MHz, $CDCl_3$)**:

δ 1.13-1.25 (m, 21H), 2.45 (s, 3H), 3.57 (d, J = 0.8 Hz, 2H), 5.95 (t, J = 1.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 2H), 7.31-7.38 (m, 4H), 7.94 (d, J = 8.4 Hz, 2H), 10.25 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 11.1, 18.6, 21.7, 37.7, 101.8, 109.8, 116.3,

120.8, 128.6, 129.4, 131.0, 131.8, 135.7, 136.3, 143.3, 144.9, 162.1 ppm; **HRMS (ESI, m/z)**: calcd for $C_{28}H_{37}BrNO_3SSi$ $[M+H]^+$ 574.1447, found: 574.1445.

(Z)-2-Cyclohexyl-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3l** was obtained as a white solid (48.2 mg, 0.099 mmol, Yield: 99%); m.p. = 1210-123 °C; **1H NMR (400 MHz, $CDCl_3$)**: δ 1.00-1.30 (m, 26H),

1.66-1.74 (m, 5H), 2.43 (s, 3H), 2.63 (t, $J = 11.7$ Hz, 1H), 6.06 (s, 1H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.98 (d, $J = 8.1$ Hz, 2H), 10.15 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 11.1, 18.6, 21.6, 26.0, 26.4, 32.7, 39.4, 102.4, 108.2, 112.8, 128.6, 129.4, 136.0, 144.8, 149.5, 162.9 ppm; **HRMS (ESI, m/z)**: calcd for $C_{27}H_{42}NO_3SSi$ $[M+H]^+$ 488.2655, found: 488.2649.

(Z)-2-Cyclopropyl-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3m** was obtained as a white solid (41.9 mg, 0.094 mmol, Yield: 94%); m.p. = 87-89 °C; **1H NMR (400 MHz, $CDCl_3$)**: δ 0.48-0.52 (m, 2H), 0.82-0.87 (m,

2H), 1.13-1.24 (m, 21H), 1.83-1.90 (m, 1H), 2.43 (s, 3H), 5.86 (d, $J = 0.8$ Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 2H), 7.99 (d, $J = 8.4$ Hz, 2H), 10.21 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 8.3, 11.1, 13.3, 18.6, 21.6, 102.1, 108.5, 111.2, 128.7, 129.4,

135.9, 144.8, 145.5, 162.5 ppm; **HRMS (ESI, m/z):** calcd for $C_{24}H_{36}NO_3SSi$ $[M+H]^+$ 446.2185, found: 446.2183.

(E)-N-Tosyl-5-(triisopropylsilyl)-2-((trimethylsilyl)methyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3n** was obtained as colorless oil (48.7 mg, 0.099 mmol, Yield: 99%); **1H NMR (400 MHz, $CDCl_3$):** δ -0.11 (s, 9H), 1.14-1.25 (m, 21H), 1.86

(d, J = 0.6 Hz, 2H), 2.41 (s, 3H), 5.96 (s, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 10.34 (s, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ -1.8, 11.1, 18.6, 21.6, 24.1, 102.7, 106.1, 110.8, 128.7, 129.3, 135.9, 143.7, 144.7 ppm; **HRMS (ESI, m/z):** calcd for $C_{25}H_{42}NO_3SSi_2$ $[M+H]^+$ 492.2424, found: 492.2424.

(Z)-2-(Ethoxymethyl)-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3o** was obtained as colorless oil (44.0 mg, 0.095 mmol, Yield: 95%); **1H NMR (400 MHz, $CDCl_3$):** δ 1.15-1.26 (m, 24 H), 2.43

(s, 3H), 3.51 (q, J = 7.0 Hz, 2H), 4.17 (d, J = 1.9 Hz, 2H), 6.49 (t, J = 1.9 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H), 10.36 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 11.1, 15.0, 18.6, 21.6, 66.7, 68.2, 102.0, 110.1, 115.5, 128.7, 129.4, 135.8, 139.8, 144.9, 161.5 ppm; **HRMS (ESI, m/z):** calcd for $C_{24}H_{38}NO_4SSi$ $[M+H]^+$ 464.2291, found: 464.2292.

(Z)-2-((1,3-Dioxoisindolin-2-yl)methyl)-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A, **3p** was obtained as a white solid (55.3 mg, 0.098 mmol, Yield: 98%); m.p. = 108-110 °C; ^1H NMR (400 MHz, CDCl_3):

δ 1.12-1.25 (m, 21H), 2.44 (s, 3H), 4.55 (d, J = 1.5 Hz, 2H), 6.06 (s, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.74-7.88 (m, 4H), 7.98 (d, J = 8.3 Hz, 2H), 10.36 (brs, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 11.0, 18.6, 21.6, 38.5, 101.1, 111.4, 115.7, 123.6, 128.7, 129.5, 131.7, 134.4, 135.6, 137.0, 145.0, 161.1, 167.5 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{30}\text{H}_{37}\text{N}_2\text{O}_5\text{SSi}$ $[\text{M}+\text{H}]^+$ 565.2192, found: 565.2187.

N-Tosyl-2-((triisopropylsilyl)ethynyl)cyclohex-1-enecarboxamide:

Following the general reaction procedure A but using MeOH as solvent, **3q** was obtained as a white solid (36.3 mg, 0.079 mmol, Yield: 79%); m.p. = 103-105 °C; ^1H NMR (400 MHz, CDCl_3): δ

1.14-1.26 (m, 21H), 1.58-1.60 (m, 4H), 2.32-2.33 (m, 2H), 2.40-2.42 (m, 5H), 7.31 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 8.1 Hz, 2H), 10.60 (brs, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 11.1, 18.6, 21.4, 21.5, 21.6, 25.1, 33.4, 105.5, 106.7, 127.7, 128.6, 129.3, 135.7, 136.1, 144.6, 163.3 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{25}\text{H}_{38}\text{NO}_3\text{SSi}$ $[\text{M}+\text{H}]^+$ 460.2342, found: 460.2346.

(Z)-3-(4-Methoxyphenyl)-2-methyl-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A but using MeOH as solvent, **3r** was obtained as colorless oil (29.5 mg, 0.058 mmol, Yield: 58%); **¹H NMR (400 MHz, CDCl₃):** δ 1.10-1.12 (m, 18H), 1.18-1.24 (m, 3H), 1.90 (s, 3H), 2.44 (s, 3H), 3.82 (s, 3H), 6.87-6.90 (m, 2H), 7.21-7.23 (m, 2H), 7.34 (d, J = 8.1 Hz, 2H), 8.02 (d, J = 8.3 Hz, 2H), 10.72 (brs, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 11.1, 16.9, 18.6, 21.7, 55.3, 105.7, 108.4, 113.7, 128.7, 129.0, 129.4, 129.9, 130.7, 135.2, 136.1, 144.7, 159.7, 164.2 ppm; **HRMS (ESI, m/z):** calcd for C₂₉H₄₀NO₄SSi [M+H]⁺ 526.2447, found: 526.2444.

(Z)-2-Methyl-3-phenyl-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general reaction procedure A but using MeOH as solvent, **3s** was obtained as colorless oil (30.3 mg, 0.061 mmol, Yield: 61%); **¹H NMR (400 MHz, CDCl₃):** δ 1.08-1.10 (m, 18H), 1.15-1.22 (m, 3H), 1.86 (s, 3H), 2.44 (s, 3H), 7.25-7.27 (m, 2H), 7.32-7.38 (m, 4H), 8.02 (d, J = 8.4 Hz, 2H), 10.70 (brs, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 11.1, 16.8, 18.6, 21.7, 105.4, 109.0, 128.2, 128.4, 128.5, 128.8, 129.2, 129.4, 135.9, 136.0, 138.5, 144.8, 164.0 ppm; **HRMS (ESI, m/z):** calcd for C₂₈H₃₈NO₃SSi [M+H]⁺ 496.2342, found: 496.2345.

(Z)-3-(4-Methoxyphenyl)-2-phenyl-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-**ynamide:**

Following the general reaction procedure A but using MeOH as solvent, **3t** was obtained as a white solid (24.7 mg, 0.042 mmol, Yield: 42%); m.p. = 141-143 °C; ¹H

NMR (400 MHz, CDCl₃): δ 1.09-1.14 (m, 21H), 2.44 (s, 3H), 3.72 (s, 3H), 6.61-6.63 (m, 2H), 6.93-6.95 (m, 2H), 7.05-7.07 (m, 2H), 7.15-7.18 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H), 9.02 (brs, 1H) ppm; ¹³C **NMR (100 MHz, CDCl₃):** δ 11.3, 18.7, 27.0, 55.1, 105.4, 106.1, 113.2, 128.3, 128.5, 128.7, 129.4, 129.4, 129.6, 130.3, 131.2, 135.1, 135.8, 138.2, 144.7, 159.6, 164.3 ppm; **HRMS (ESI, m/z):** calcd for C₃₄H₄₂NO₄SSi [M+H]⁺ 588.2604, found: 588.2604.

(Z)-3-(4-Fluorophenyl)-2-phenyl-N-tosyl-5-(triisopropylsilyl)pent-2-en-4-

Following the general reaction procedure A but using MeOH as solvent, **3u** was obtained as colorless oil (28.6 mg, 0.050 mmol, Yield: 50%); ¹H **NMR (400 MHz, CDCl₃):** δ

1.07-1.16 (m, 21H), 2.44 (s, 3H), 6.78-6.82 (m, 2H), 6.91-6.93 (m, 2H), 7.08-7.11 (m, 2H), 7.14-7.20 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 8.96 (brs, 1H) ppm; ¹³C **NMR (100 MHz, CDCl₃):** δ 11.2, 18.6, 21.7, 104.9, 106.7, 115.0 (d, *J* = 21.7 Hz), 128.5, 128.6, 128.7, 129.4, 130.2, 131.4, 131.5, 133.5 (d, *J* = 3.5 Hz),

134.4, 135.7, 139.5, 144.8, 162.3 (d, $J = 248.1$ Hz), 163.9 ppm; **HRMS (ESI, m/z)**: calcd for $C_{33}H_{39}FNO_3SSi$ $[M+H]^+$ 576.2404, found: 576.2399.

***N*-Tosyl-4-((triisopropylsilyl)ethynyl)-5,6-dihydro-2H-pyran-3-carboxamide:**

Following the general reaction procedure A but using MeOH as solvent, **3v** was obtained as a white solid (23.6 mg, 0.051 mmol, Yield: 51%); m.p. = 103-105 °C; **1H NMR (400 MHz, $CDCl_3$)**: δ

1.16-1.17 (m, 18H), 1.23-1.28 (m, 3H), 2.43-2.48 (m, 5H), 3.72 (t, $J = 5.6$ Hz, 2H), 4.34 (t, $J = 2.4$ Hz, 2H), 7.32 (d, $J = 8.4$ Hz, 1H), 7.95 (d, $J = 8.4$ Hz, 2H), 10.50 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 11.0, 18.6, 21.7, 31.7, 63.1, 64.9, 103.6, 108.6, 125.9, 128.6, 129.4, 133.9, 135.9, 144.9, 161.2 ppm; **HRMS (ESI, m/z)**: calcd for $C_{24}H_{36}NO_4SSi$ $[M+H]^+$ 462.2134, found: 462.2145.

***N*-Tosyl-4-((triisopropylsilyl)ethynyl)-2,5-dihydrofuran-3-carboxamide:**

Following the general reaction procedure A but using MeOH as solvent, **3w** was obtained as a white solid (33.9 mg, 0.076 mmol, Yield: 76%); m.p. = 99-101 °C; **1H NMR (400 MHz, $CDCl_3$)**: δ

1.15-1.17 (m, 18H), 1.22-1.26 (m, 3H), 2.44 (s, 3H), 4.79-4.82 (m, 2H), 4.87-4.90 (m, 2H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.95 (d, $J = 8.4$ Hz, 2H), 9.68 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 11.0, 18.6, 21.7, 75.8, 79.2, 96.2, 112.5, 127.7, 128.6, 129.5,

135.6, 136.2, 145.2, 158.0 ppm; **HRMS (ESI, m/z):** calcd for $C_{23}H_{34}NO_4SSi$ $[M+H]^+$ 448.1978, found: 448.1980.

tert-Butyl 3-(tosylcarbamoyl)-4-(((triisopropylsilyl)ethynyl)-2,5-dihydro-1H-pyrrole-1-carboxylate:

Following the general reaction procedure A but using MeOH as solvent, **3x** was obtained as colorless oil (38.8 mg, 0.071 mmol, Yield: 71%); **1H NMR (400 MHz, $CDCl_3$):** δ 1.15-1.18 (m, 18H), 1.22-1.27 (m, 3H), 1.43-1.46 (m, 9H), 2.44 (s, 3H), 4.36-4.42 (m, 4H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.96 (d, $J = 8.4$ Hz, 2H), 9.82 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 11.0, 18.6, 21.7, 28.3, 28.4, 52.9, 53.0, 57.6, 57.7, 80.4, 97.6, 111.0, 111.8, 125.9, 126.2, 128.7, 129.5, 135.1, 135.5, 145.2, 153.2, 153.5, 158.3, 158.5 ppm; **HRMS (ESI, m/z):** calcd for $C_{28}H_{43}N_2O_5SSi$ $[M+H]^+$ 547.2662, found: 547.2649.

2-Tosyl-5,6,7,8-tetrahydroisoquinolin-1(2H)-one:

Following the general reaction procedure B, **4q** was obtained as a white solid (29.2 mg, 0.097 mmol, Yield: 97%); m.p. = 147-149 °C; **1H NMR (400 MHz, $CDCl_3$):** δ 1.66-1.75 (m, 4H), 2.18-2.20 (m, 2H), 2.33-2.37 (m, 2H), 2.42 (s, 3H), 5.00 (m, 1H), 6.00 (m, 1H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.92 (d, $J = 8.0$ Hz, 2H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 19.8, 21.1, 21.4,

21.5, 21.6, 98.3, 127.8, 129.6, 130.2, 136.0, 141.2, 144.9, 148.6, 167.4 ppm; **HRMS**

(ESI, m/z): calcd for $C_{16}H_{18}NO_3S$ $[M+H]^+$ 304.1007, found: 304.1006.

4-(1-Oxo-2-tosyl-1,2,5,6,7,8-hexahydroisoquinolin-3-yl)benzonitrile:

Following the general reaction procedure C, **5q** was obtained as a white solid (31.4 mg, 0.078 mmol, Yield: 78%); m.p. = 181-183 °C; **1H NMR (400 MHz, $CDCl_3$):** δ

1.44-1.48 (m, 2H), 1.55-1.61 (m, 2H), 1.70-1.73 (m, 2H), 2.20-2.23 (m, 2H), 2.45 (s, 3H), 7.35 (d, $J = 7.7$ Hz, 4H), 7.66 (d, $J = 8.2$ Hz, 2H), 7.84 (s, 1H), 7.96 (d, $J = 8.4$ Hz, 2H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 20.4, 20.7, 21.7, 22.2, 26.1, 111.8, 116.2, 118.4, 128.0, 129.7, 130.1, 131.9, 133.3, 136.0, 137.5, 140.1, 145.2, 147.0, 167.0 ppm; **HRMS (ESI, m/z):** calcd for $C_{23}H_{21}N_2O_3S$ $[M+H]^+$ 405.1273, found: 405.1263.

3-(4-acetylphenyl)-2-tosyl-5,6,7,8-tetrahydroisoquinolin-1(2H)-one:

Following the general reaction procedure C, **6q** was obtained as a white solid (32.1 mg, 0.076 mmol, Yield: 76%); m.p. = 167-169 °C; **1H NMR (400 MHz, $CDCl_3$):** δ

1.41-1.47 (m, 2H), 1.56- 1.62 (m, 2H), 1.75- 1.79 (m, 2H), 2.22-2.25 (m, 2H), 2.47 (s, 3H), 2.66 (s, 3H), 7.34-7.38 (m, 4H), 7.90 (s, 1H), 7.98-8.00 (m, 4H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 20.4, 20.7, 21.7, 22.2, 26.1, 26.6, 117.4, 128.0, 128.2, 129.6,

129.7, 132.8, 136.1, 136.5, 137.1, 140.2, 145.1, 147.4, 167.1, 197.5 ppm; **HRMS (ESI, m/z)**: calcd for $C_{24}H_{24}NO_4S$ $[M+H]^+$ 422.1426, found: 422.1422.

4-Bromo-2-tosyl-3-(triisopropylsilyl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one:

Following the general reaction procedure D, **7q** was obtained as a white solid (53.3 mg, 0.099 mmol, Yield: 99%); m.p. = 164-166 °C; **¹H NMR (400 MHz, CDCl₃)**: δ 1.15-1.17 (m, 18H), 1.68-1.70 (m, 2H), 1.75-1.80 (m, 5H), 2.21-2.23 (m, 2H), 2.41 (s, 3H), 2.95-2.98 (m, 2H), 7.28 (d, *J* = 6.6 Hz, 2H), 7.86 (d, *J* = 6.6 Hz, 2H) ppm; **¹³C NMR (100 MHz, CDCl₃)**: δ 12.3, 18.7, 20.6, 21.1, 21.5, 22.1, 27.6, 117.5, 126.8, 129.2, 135.8, 139.3, 142.9, 149.3, 158.6, 163.9 ppm; **HRMS (ESI, m/z)**: calcd for $C_{25}H_{37}BrNO_3SSi$ $[M+H]^+$ 538.1447, found: 538.1449.

2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-N-methyl-N-tosylcyclohex-1-enecarboxamide:

Following the general reaction procedure E, **8q** was obtained as colorless oil (37.5 mg, 0.083 mmol, Yield: 83%); **¹H NMR (400 MHz, CDCl₃)**: δ 1.73-1.74 (m, 4H), 2.33 (m, 2H), 2.38 (s, 3H), 2.46 (m, 2H), 5.35 (s, 2H), 7.17-7.21 (m, 5H), 7.34-7.35 (m, 3H), 7.68 (d, *J* = 8.3 Hz, 2H) ppm; **¹³C NMR (100 MHz, CDCl₃)**: δ 21.6, 21.7, 27.0, 27.5, 53.9, 77.2, 120.8, 125.8, 127.9, 128.0, 128.7, 129.0, 129.1, 131.5, 134.5, 135.7, 144.3, 146.1, 172.6 ppm; **HRMS (ESI, m/z)**: calcd for $C_{24}H_{27}N_4O_3S$ $[M+H]^+$ 451.1804, found: 451.1810.

(Z)-N-Methoxy-2-phenyl-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general procedure A, the compound was obtained as a white solid (24.1 mg, 0.068 mmol, Yield: 68%); m.p. = 96-98 °C; **¹H NMR (400 MHz, CDCl₃):** δ 1.11 (m, 21H), 3.88 (s, 3H), 6.24 (s, 1H), 7.34-7.36 (m, 3H), 7.43-7.45 (m, 2H), 8.96 (brs, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 11.2, 18.6, 64.6, 102.4, 111.1, 126.7, 128.7, 129.2, 135.4, 144.7, 165.2 ppm; **HRMS (ESI, m/z):** calcd for C₂₁H₃₂NO₂Si [M+H]⁺ 358.2202, found: 358.2209.

(Z)-2-Phenyl-N-(pivaloyloxy)-5-(triisopropylsilyl)pent-2-en-4-ynamide:

Following the general procedure A, the compound was obtained as colorless oil (14.7 mg, 0.035 mmol, Yield: 35%); **¹H NMR (400 MHz, CDCl₃):** δ 1.11 (m, 21H), 1.34 (s, 9H), 6.30 (s, 1H), 7.34-7.37 (m, 3H), 7.47-7.49 (m, 2H), 9.58 (brs, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 11.2, 18.6, 27.0, 38.4, 102.5, 111.9, 126.9, 128.7, 129.3, 135.2, 144.5, 164.2, 175.7 ppm; **HRMS (ESI, m/z):** calcd for C₂₅H₃₈NO₃Si [M+H]⁺ 428.2621, found: 428.2618.

Chapter 4

Cp*Rh(III)-Catalyzed Direct C-H Olefination of Arenes with Allyl Acetates

4.1 Introduction

4.1.1 Transition metal-catalyzed aromatic olefination reactions

Over the past decades, the transition metal-catalyzed oxidative olefination of arenes through the activation of inert C-H bond has been proved to be an efficient and reliable synthetic method for introducing alkenyl functionality onto aromatic compounds (Scheme 4.1, i).⁵³ In this regards, plenty of efforts was drawn into this area and a large number of arene C-H olefination reactions catalyzed by varies of transition metal salts have been reported.⁵⁴ In these studies, the idea of using *ortho*-directing groups (DG) has been commonly adopted in order to improve the reaction efficiency as well as regioselectivity. Theoretically, an oxidant is required to regenerate the effective transition metal-catalyst. However, the forced using of external oxidants

⁵³ (a) Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, 69, 1221. (b) Ritleng, V.; Sirlin C.; Pfeffer, M. *Chem. Rev.* **2002**, 102, 1731. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, 34, 633. (d) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, 287, 1992.

⁵⁴ For palladium-catalyzed C-H olefination, see: (a) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, 133, 6541. (b) Lu, Y.; Wang, D.-H.; Engle K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, 132, 5916. (c) Wasa, M.; Engle K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, 132, 3680. (d) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, 327, 315. (e) Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, 132, 460. (f) Garcia-Rubia, A.; Arrayas, R. G.; Carretero, J. C.; *Angew. Chem., Int. Ed.* **2009**, 48, 6511. (g) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, 130, 10066. (h) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, 47, 6452. (i) Cho, S. H.; Hwang S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, 130, 9254. (j) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, 129, 7666. (k) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, 128, 2528. (l) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, 127, 4156. (m) Dams, M. D.; Vos, D. E. D.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, 42, 3512. (n) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, 125, 1476. For rhodium-catalyzed C-H olefination see: (a) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. *J. Am. Chem. Soc.* **2011**, 133, 2154. (b) Sturat, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, 132, 18326. (c) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, 132, 6908. (d) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, 133, 6449. (e) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, 131, 12050. (f) Tsai, A.S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, 133, 1248. (g) Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W.-P.; Zhang, X.-S.; Chen, K.; Shi, Z.-F. *Angew. Chem., Int. Ed.* **2011**, 50, 2115. (h) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, 130, 16474. (i) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, 132, 9585. For ruthenium-catalyzed C-H olefination, see: Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, 13, 706. For copper-catalyzed C-H olefination, see: Mousseau, J. J.; Bull, J. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2010**, 49, 1115.

unpleasantly produces stoichiometric amounts of related heavy metal wastes and presents relatively harsh reaction conditions.

Scheme 4.1 Transition-Metal-Catalyzed Oxidative Olefination

4.1.2 C-H bond functionalization using an oxidizing directing group

In the realm of C-H activation, one burgeoning method is the use of motifs which act as both a directing group and an internal oxidant(DG^{Ox}) (Scheme 4.1, ii). Several common directing groups, *N*-oxides,⁵⁵ oxime ester and *N*-methoxyamides,⁵⁶ were investigated to play a dual role in the C-H bond functionalization reactions.

In 2009, the Pd-catalyzed olefination of quinoline-*N*-oxides reported by Cui and Wu (Scheme 4.2),⁵⁷ gave the idea that the cleavage of N-O bonds could act as both an inducing counterpart and an internal oxidant within the catalytic cycle. Although a

⁵⁵ (a) Campeau, L. C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Leclerc, J. P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (c) Campeau, L. C.; Bertrand-Laperle, M.; Leclerc, J. P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (d) Campeau, L. C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276. (e) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872. (f) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254.

⁵⁶ (a) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (b) Wasa, M.; Yu, J.-Q.; *J. Am. Chem. Soc.* **2008**, *130*, 14058.

⁵⁷ Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009**, *131*, 13888.

high reaction temperature is required, it proposed the possibility of improving the atom efficiency and decreasing the toxic waste formation.

Scheme 4.2 Pd-Catalyzed olefination of quinoline-*N*-oxides *via* C-H activation under external-oxidant-free conditions

In 2011, Guimond et al. reported the rhodium(III)-catalyzed external-oxidant-free isoquinolines construction by C-H activation of *N*-methoxybenzamides and sequential coupling to internal alkynes (Scheme 4.3).⁵⁸ In contrast to the already known palladium-catalyzed C-H arylation and amination of *N*-methoxybenzamides in the presence of external oxidant with the integrity of N-O bond maintained,⁵⁹ the late stage cleavage of the N-O bond acted as an internal oxidant in this case.

Scheme 4.3 Rhodium(III)-catalyzed isoquinolone synthesis between *N*-methoxybenzamides and internal alkynes under external-oxidant-free condition

⁵⁸ Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908.

⁵⁹ (a) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (b) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (c) Tan, Y; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676.

Following this idea, in 2011, Glorius and co-workers developed an efficient Rh(III)-catalyzed oxidative C-H olefination of *N*-methoxybenzamides using the oxidizing directing groups (Scheme 4.4).⁶⁰ It needs to be mentioned that the selective formation of valuable tetrahydroisoquinolinone products were decided by the changing substituent of the directing/oxidizing group.

Scheme 4.4 Rh(III)-catalyzed C-H olefination and annulation of benzamides under external-oxidant-free condition

Meanwhile, an interesting allylation of arenes with allyl acetate was disclosed by Ellman (Scheme 4.5).⁶¹ While this transformation is proved to be redox neutral, the substoichiometric amount of copper salts is still needed to maintain the yield.

⁶⁰ Rakshit, S.; Grohmann, C.; Besset T.; Glorius F. *J. Am. Chem. Soc.* **2011**, *133*, 2350.

⁶¹ Tsai, S. A.; Brasse, M. Bergman, G. R.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 540.

Scheme 4.5 Rh(III)-catalyzed aromatic C-H allylation with allyl acetate.

We envisage that it is possible to find a protocol of Rh-catalyzed C-H bond functionalization under external-oxidant-free condition using substrates with non-oxidizing directing group. In this chapter, the oxidant-free Rh(III)-catalyzed C-H olefination reaction of directed benzamides with allyl acetate as the coupling partner is described (Scheme 4.6).

Schem 4.6 Rh-catalyzed direct aromatic C-H olefination with allyl acetates

4.2 Result and Discussion

At the outset of our studies, the reaction condition was optimized using *N,N*-dimethylbenzamide (**1a**) and allyl acetate (**2a**) as the model substrates. After extensive trials, it was pleased to find that 62% yield of the desired olefination product could be obtained. Guided by the dramatic solvent effect observed in our previous works, a series of solvents was subsequently examined, and DCE was proved to be the optimal

Table 4.1 Reaction Conditions Optimization ^a

Entry	Catalyst	Additive	Solvent	Yield ^b (%)
1	[Cp [*] RhCl ₂] ₂	AgSbF ₆	DME	62
2	[Cp [*] RhCl ₂] ₂	AgSbF ₆	Dioxane	58
3	[Cp [*] RhCl ₂] ₂	AgSbF ₆	DCE	92
4	[Cp [*] RhCl ₂] ₂	AgSbF ₆	THF	74
5	[Cp [*] RhCl ₂] ₂	AgSbF ₆	<i>t</i> -AmOH	53
6	[Cp [*] RhCl ₂] ₂	AgSbF ₆	Acetone	80
7	[Cp [*] RhCl ₂] ₂	AgSbF ₆	MeCN	NR
8	[Cp [*] RhCl ₂] ₂	AgOAc	DCE	NR
9	[Cp [*] RhCl ₂] ₂	-	DME	NR
10	-	AgSbF ₆	DME	NR
11	[Cp [*] RhCl ₂] ₂	AgSbF ₆	DME	NR ^c

^a Unless otherwise noted the reactions were carried out at 110 °C using **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (0.0025 mmol), additive (0.01mmol) in solvent (1 mL) stirred for 16 h. ^b Isolated yields. ^c K₂CO₃ (0.2 mmol) was added.

choice (Table 4.1, entries 1-7). Much to our surprise, when AgOAc was added instead of AgSbF₆, no reaction occurred, which indicates the vital role of cationic rhodium catalyst in the catalytic cycle (Table 4.1, entry 8). Not surprisingly, the reaction did

not proceed in the absence of either Rh(III) catalyst or silver additive (Table 4.1, entries 9, 10). In addition, when stoichiometric amount of K_2CO_3 was added, the reaction was totally suppressed (Table 4.1, entry 11).

With the optimized reaction condition in hand, we turned our attention to the exploration of the reaction scope of various *N,N*-disubstituted benzamide derivatives with allyl acetate (**2a**) as the model coupling partner. The relatively results were shown in Table 4.2. In this olefination reaction, both electron-withdrawing and electron-donating functional groups at the *para*-position of *N,N*-dimethyl amide group were well adapted, obtaining the corresponding olefination products in high yields (**3b-3l**). Notably, methoxy (**3c**), TMS (**3d**), trifluoromethyl (**3e**), bromo (**3i**), acetal (**3j**) and ester (**3k**), which are valuable functional groups amenable for further derivatization were all well tolerated. In addition, 2-naphthamide was also a suitable substrate, giving the *C3*-olefination product in 82% yield (**3m**). As HOAc is formed throughout this catalytic cycle, the weak acidity of the reaction media would lead to decomposition of dioxole group, which gave a moderate yield of 64% (**3n**). With regard to *meta*-methyl substituted substrate, the reaction selectively happened at sterically more accessible site, thus delivering the desired product in high yield (**3o**). However, for the *meta*-Cl substituted analogue, the reaction tended to afford a mixture of two regio-isomers (**3p**, **3p'**). When *ortho*-methyl substituted substrate **1q** was engaged in such olefination reaction, an inseparable mixture of allylation and alkenylation products was obtained with the isomeric ratio of 1:1 (**3q**, **3q'**).

Table 4.2. Scope of *N,N*-Dimethylbenzamide Derivatives^{a,b}

^a Unless otherwise noted the reactions were carried out at 110 °C using **1a** (0.2 mmol), **2a** (0.24 mmol), [Cp*RhCl₂]₂ (0.0025 mmol), AgSbF₆ (0.01 mmol) in DCE (1 mL) stirred for 16 h. ^b Isolated yields. ^c Catalyst (0.005 mmol) was used. DCE = 1,2-dichloroethane.

Scheme 4.7. Alkene Counterpart Comparison: Terminal vs. Internal.

In order to have a better understanding of this protocol, the exploration of the allyl electrophilic coupling partners was proceeded. Whilst linear allyl acetates, such as cinnamyl acetate, were proved inaccessible to this olefination reaction (Scheme 4.7, iii), the branched isomer 2-phenylallyl acetate, showed relatively acceptable reactivity to afford the *trans*-product (Scheme 4.7, iv). The low yield was attributed to the steric hinderance of the bulky phenyl group. Meanwhile, high yields were obtained with the 1-substituted allyl acetates, of which the products were observed to be mixtures of isomers (Table 4.3). In order to simplify the characterization of the products, further hydrogenation was adopted. The reaction proceeded readily with complete γ -selectivity, and no terminal alkene product was formed. Compared to aliphatic substituted allyl acetates, those with aromatic substituents afforded the desired product in relatively higher yield.

Table 4.3. Scope of Allyl Acetate Derivatives^a

entry	allyl acetate derivatives	product	yield (%) ^b
1			90%
2			85%
3			70% ^c
4			69% ^c
5			74% ^d
6			80%

^a Unless otherwise noted the reactions were carried out at 110 °C using **1a** (0.2 mmol), **2** (0.24 mmol), [Cp*RhCl₂]₂ (0.0025 mmol), AgSbF₆ (0.01 mmol) in DCE (1 mL) stirred for 16 h. ^b Isolated over two step yields. ^c [Cp*RhCl₂]₂ (0.005 mmol) and AgSbF₆ (0.02 mmol) was used. ^d Reaction temperature is 140 °C.

Scheme 4.8. Kinetic Isotope Effects.

Attempting to obtain more detailed information about the mechanism of the present olefination reaction, the following experiments were conducted as shown in Scheme 4.8. Significant isotope effects were observed either in the intramolecular or intermolecular studies, thus indicating the rationality of C-H bond cleavage being the rate-determining step. In combination with the high reactivity of highly electron-deficient substrates, a concerted-metalation-deprotonation is most likely the plausible mechanistic pathway.

Scheme 4.9. Plausible Catalytic Mechanism.

On the basis of aforementioned experimental results, a plausible mechanism is proposed in Scheme 4.9. Precomplexation of amide substrate with active Rh(III) catalyst would trigger *ortho* C-H bond activation to form the metallacycle *via* a concerted-metalation-deprotonation pathway to deliver the intermediate **I**. After migratory insertion by the incoming alkene, a seven-membered rhodium (III) species **II** is formed with carbonate oxygen chelating to the metal. Then β -OAc elimination¹⁷ would happen to give the product **IV** and regenerate the active Rh(III) catalyst. The final product is obtained after the migratory isomerization of double bond, which may due to the effect of trace [Rh-H] complex. Due to the conformational restriction, the β -H elimination with the benzylic hydrogen atom would be prevented by the coordination of the directing group. During the whole catalytic cycle, the Rh(III)

catalyst undergoes a redox neutral process, which indicates an oxidant free strategy with the acetate anion as a leaving group.

4.3 Conclusion

In conclusion, a novel cationic Rh(III)-catalyzed olefination of *N,N*-disubstituted benzamides with allyl acetate derivatives is described, which delivers *trans*-products in high to excellent yields without the need of an external oxidant. The ambient condition and high efficiency of this reaction shows tolerance of a range of functionalities.

4.4 Experimental Section

4.4.1 General Information

[Cp*RhCl₂]₂, AgSbF₆, and Cu(OAc)₂ were purchased from commercial suppliers and used as received unless otherwise noted. Benzamide and allyl acetate derivatives are synthesized according to the reported procedure.⁶² All reactions were carried out under air unless otherwise stated. Commercial solvents and reagents were used without further purification. Reactions were monitored through thin layer chromatography [Merck 60 F254 precoated silica gel plate (0.2 mm thickness)]. Subsequent to elution, spots were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible using basic solution of potassium

⁶² For synthesis of benzamides, see: Ju, J.; Jeong, M.; Moon, J.; Hyun, M. J.; Lee, S. *Org. Lett.* **2007**, *9*, 4615. For synthesis of allyl acetates, see: Guerinot, A.; Serra-Muns, A.; Bensoussan, C.; Reymond, S.; Cossy, J. *Tetrahedron*, **2011**, *67*, 5024.

permanganate or acidic solution of ceric molybdate as stain, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. HRMS spectra were recorded on a Waters Q-ToF Premier Spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded using Bruker Avance 300, 400 and 500 MHz spectrometers. Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.260, singlet). Multiplicities were given as: *s* (singlet); *brs* (broad singlet); *d* (doublet); *t* (triplet); *q* (quartet); *dd* (doublets of doublet); *ddd* (doublets of doublets of doublet); *td* (triplet of doublet); *m* (multiplets); *ddt* (doublet of doublet of triplet) and etc. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.00, triplet).

4.4.2 Experimental procedures

Scheme 4.10 Rh-catalyzed direct C-H olefination of arenes

Experimental procedure A: The benzamide **1** (0.2 mmol, 1 equiv.), $[\text{Cp}^*\text{RhCl}_2]_2$ (0.0025 mmol, 1.25 mol %), AgSbF_6 (0.01 mmol, 5 mol %) and DCE (1 mL) were placed in a 8 mL glass vial under air. Allyl acetate **2a** (0.24 mmol, 1.2 equiv.) was

then added and the reaction was heated to 110 °C for 16 h. The crude mixture was then directly purified by column chromatography (Hexane:EtOAc = 2:1) (Scheme 2.10).

4.4.3 Deuterium labeling and kinetic isotope effect studies

Scheme 4.11 Intramolecular KIE determination

Experimental procedure: a) **1a-d₁** (0.2 mmol, 1 equiv.), [Cp*RhCl₂]₂ (0.0025 mmol, 0.0125 equiv.), AgSbF₆ (0.01 mmol, 0.05 equiv.) and 1,2-dichloroethane (1 mL) were placed in a glass vial under air. Allyl acetate (0.1 mmol, 0.5 equiv.) was then added and the reaction was heated to 110 °C for 5 min. The mixture was then filtered and concentrated *in vacuo* to give a crude product that was purified by column chromatography (Hexane:EtOAc = 2:1) to afford **3a/3a-d₁**.

b) In a 10 mL RBF, catalytic amount of Pd/C (0.02 mmol, 10 mol %) was added, followed with the addition of **3a/3a-d₁** in 5 mL ethanol. The air in the flask was exchanged to hydrogen, using pump and hydrogen balloon for three times. Another hydrogen balloon was connected to the flask and the mixture was stirred vigorously for 12 hours. After the reaction was finished, the crude mixture was filtered,

concentrated in *vacuo* and purified by column chromatography (Hexane:EtOAc = 2:1) (Scheme 2.11).

Figure 4.1 Intramolecular KIE study (^1H NMR in CDCl_3)

The **Figure 4.1** shows that the $[\text{P}_\text{D}] = 0.97 + 2.29 - 3 = 0.26 \approx 0.3$.

$$\text{KIE} = \text{P}_\text{H}/\text{P}_\text{D} = (1 - \text{P}_\text{D})/\text{P}_\text{D} = (1 - 0.3)/0.3 = 2.33$$

Scheme 4.12 Intermolecular KIE determination

Experimental procedure: **1a** (0.1 mmol, 1 equiv.), **1a-d₅** (0.1 mmol, 1 equiv.) $[\text{Cp}^*\text{RhCl}_2]_2$ (0.0025 mmol, 0.025 equiv.), AgSbF_6 (0.01 mmol, 0.1 equiv.) and 1,2-dichloroethane (1 mL) were placed in a glass vial under air. Allyl acetate (0.1 mmol, 1 equiv.) was then added and the reaction was heated to 110 °C for 5 min. The reaction was then filtered and concentrated *in vacuo* to give a crude product that was purified by column chromatography (Hexane:EtOAc = 2:1) (Scheme 2.12).

Figure 4.2 Intermolecular KIE study (^1H NMR in CDCl_3)

The **Figure 4.2** shows that $[\text{P}_\text{H}] = 0.79 + 0.68 = 1.47 \approx 1.5$

$$\text{KIE} = \text{P}_\text{H}/\text{P}_\text{D} = 1.5/(2-1.5) = 3.00$$

4.4.4 Characterization of Products

(*E*)-*N,N*-dimethyl-2-(prop-1-en-1-yl)benzamide

Following the general procedure A, **3a** was obtained as colorless oil,

Yield: 92%; ^1H NMR (400 MHz, CDCl_3): δ 1.86 (d, $J = 6.4$ Hz, 3H),

2.78 (s, 3H), 3.14 (s, 3H), 6.19~6.28 (m, 1H), 6.36 (d, $J = 15.6$ Hz,

1H), 7.16~7.25 (m, 2H), 7.27~7.34 (m, 1H), 7.49 (d, $J = 7.6$, 1H) ppm;

^{13}C NMR (100 MHz, CDCl_3): δ 18.7, 34.6, 38.4, 125.3, 126.2, 126.8, 127.5, 128.2, 128.8, 134.4, 134.9, 171.3 ppm; **HRMS (ESI, m/z):** calculated for $\text{C}_{12}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]^+$: 193.1434, found: 193.1450.

(*E*)-*N,N*,4-trimethyl-2-(prop-1-en-1-yl)benzamide

Following the general procedure A, **3b** was obtained as colorless oil, **Yield:** 90%; **^1H NMR (400 MHz, CDCl_3):** δ 1.86 (d, J = 6.4 Hz, 3H), 2.34 (s, 3H), 2.78 (s, 3H), 3.12 (s, 3H), 6.17~6.26 (m, 1H), 6.34 (d, J = 15.6 Hz, 1H), 7.02~7.13 (m, 2H), 7.30 (s, 1H) ppm; **^{13}C NMR (100 MHz, CDCl_3):** δ 18.7, 21.3, 34.7, 38.5, 125.9, 126.2, 127.5, 127.6, 128.0, 132.2, 134.3, 138.5, 171.5 ppm; **HRMS (ESI, m/z):** calculated for $\text{C}_{13}\text{H}_{17}\text{NO}$ $[\text{M}+\text{H}]^+$: 204.1388, found: 204.1388.

(*E*)-4-methoxy-*N,N*-dimethyl-2-(prop-1-en-1-yl)benzamide

Following the general procedure A, **3c** was obtained as colorless oil, **Yield:** 88%; **^1H NMR (400 MHz, CDCl_3):** δ 1.85 (d, J = 6.4 Hz, 3H), 2.78 (s, 3H), 3.12 (s, 3H), 3.81 (s, 3H), 6.17~6.26 (m, 1H), 6.34 (d, J = 15.6 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.98 (s, 1H), 7.10 (d, J = 8.4 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl_3):** δ 18.7, 34.7, 38.5, 55.2, 110.2, 112.7, 127.6, 127.7, 127.8, 128.5, 136.2, 159.9, 171.3 ppm; **HRMS (ESI, m/z):** calculated for $\text{C}_{13}\text{H}_{17}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 220.1338, found: 220.1340.

(E)-N,N-dimethyl-2-(prop-1-en-1-yl)-4-(trimethylsilyl)benzamide

Following the general procedure A, **3d** was obtained as colorless oil, **Yield:** 83%; **¹H NMR (400 MHz, CDCl₃):** δ 0.27 (s, 9H), 1.87 (d, J = 6.4 Hz, 3H), 2.79 (s, 3H), 3.13 (s, 3H), 6.21~6.29 (m, 1H), 6.38 (d, J = 15.6 Hz, 1H), 7.14~7.46(m, 2H), 7.60 (s, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ -1.2, 18.7, 34.7, 38.5, 125.4, 127.8, 128.3, 130.4, 131.8, 133.4, 135.3, 141.3, 171.3 ppm; **HRMS (ESI, m/z):** calculated for C₁₅H₂₃NOSi [M+H]⁺: 262.1627, found: 262.1629.

(E)-N,N-dimethyl-2-(prop-1-en-1-yl)-4-(trifluoromethyl)benzamide

Following the general procedure A, **3e** was obtained as colorless oil, **Yield:** 77%; **¹H NMR (400 MHz, CDCl₃):** δ 1.90 (d, J = 4.4 Hz, 3H), 2.79 (s, 3H), 3.16 (s, 3H), 6.34~6.40 (m, 2H), 7.29 (t, J = 16.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.75 (s, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 18.7, 34.7, 38.3, 122.4, 123.5, 126.3, 126.9, 130.7, 130.9, 131.2, 135.3, 138.1, 169.9 ppm; **HRMS (ESI, m/z):** calculated for C₁₃H₁₄NOF₃ [M+H]⁺: 258.1106, found: 258.1112.

(E)-N,N-dimethyl-3-(prop-1-en-1-yl)-[1,1'-biphenyl]-4-carboxamide

Following the general procedure A, **3f** was obtained as colorless oil, **Yield:** 75%; **¹H NMR (400 MHz, CDCl₃):** δ 1.89 (d, J = 6.4 Hz, 3H), 2.84 (s, 3H), 3.16 (s, 3H), 6.29~6.36 (m, 1H), 6.43 (d, J = 16 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.36 (t, J = 13.6 Hz,

1H), 7.44 (t, $J = 13.6$ Hz, 3H), 7.59 (d, $J = 7.6$ Hz, 2H), 7.70 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 18.7, 34.7, 38.5, 124.2, 125.7, 126.8, 126.9, 127.0, 127.6, 128.8, 133.8, 134.9, 140.6, 141.7, 171.2 ppm; HRMS (ESI, m/z): calculated for $\text{C}_{18}\text{H}_{19}\text{NO}$ $[\text{M}+\text{H}]^+$: 266.1545, found: 266.1545.

(*E*)-4-hydroxy-*N,N*-dimethyl-2-(prop-1-en-1-yl)benzamide

Following the general procedure A, **3g** was obtained as colorless oil, **Yield:** 89%; ^1H NMR (400 MHz, CDCl_3): δ 1.76 (d, $J = 6.8$ Hz, 3H), 2.78 (s, 3H), 3.12 (s, 3H), 5.95~6.01 (m, 1H), 6.20 (d, $J = 15.6$ Hz, 1H), 6.52 (d, $J = 8.4$ Hz, 1H), 6.78 (s, 1H), 6.90 (d, $J = 8.4$ Hz, 1H), 8.67 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 18.6, 35.0, 38.8, 112.2, 114.7, 125.5, 127.3, 127.5, 128.4, 136.0, 157.6, 172.8 ppm; HRMS (ESI, m/z): calculated for $\text{C}_{13}\text{H}_{15}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 218.1181, found: 218.1185.

(*E*)-4-chloro-*N,N*-dimethyl-2-(prop-1-en-1-yl)benzamide

Following the general procedure A, **3h** was obtained as colorless oil, **Yield:** 89%; ^1H NMR (400 MHz, CDCl_3): δ 1.87 (d, $J = 6.8$ Hz, 3H), 2.78 (s, 3H), 3.12 (s, 3H), 6.26~6.33 (m, 2H), 7.11 (d, $J = 8.0$ Hz, 1H), 7.20 (d, $J = 8.0$ Hz, 1H), 7.47 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 18.7, 34.8, 38.5, 125.4, 126.5, 126.9, 127.7, 130.0, 133.3, 134.8, 136.4, 170.3 ppm; HRMS (ESI, m/z): calculated for $\text{C}_{12}\text{H}_{14}\text{NOCl}$ $[\text{M}+\text{H}]^+$: 224.0842, found: 224.0840.

(E)-4-bromo-N,N-dimethyl-2-(prop-1-en-1-yl)benzamide

Following the general procedure A, **3i** was obtained as colorless oil, **Yield:** 73%; **¹H NMR (400 MHz, CDCl₃):** δ 1.87 (d, *J* = 4.8 Hz, 3H), 2.78 (s, 3H), 3.12 (s, 3H), 6.26~6.33 (m, 2H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 18.7, 34.8, 38.5, 123.1, 126.4, 127.9, 128.4, 129.8, 130.2, 133.8, 136.7, 170.3 ppm; **HRMS (ESI, m/z):** calculated for C₁₂H₁₄NOBr [M+H]⁺: 268.0337, found: 268.0334.

(E)-4-acetyl-N,N-dimethyl-2-(prop-1-en-1-yl)benzamide

Following the general procedure A, **3j** was obtained as colorless oil, **Yield:** 87%; **¹H NMR (400 MHz, CDCl₃):** δ 1.89 (d, *J* = 4.8 Hz, 3H), 2.61 (d, *J* = 5.2 Hz, 3H), 2.78 (s, 3H), 3.16 (s, 3H), 6.36~6.39 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 8.08 (s, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 18.7, 26.7, 34.7, 38.3, 125.4, 126.6, 130.2, 135.0, 137.3, 139.1, 170.3, 197.7 ppm; **HRMS (ESI, m/z):** calculated for C₁₄H₁₇NO₂ [M+H]⁺: 232.1338, found: 232.1326.

(E)-methyl 4-(dimethylcarbamoyl)-3-(prop-1-en-1-yl)benzoate

Following the general procedure A, **3k** was obtained as colorless oil, **Yield:** 83%; **¹H NMR (400 MHz, CDCl₃):** δ 1.89 (d, *J* = 4.8 Hz, 3H), 2.77 (d, *J* = 5.2 Hz, 3H), 3.15 (s, 3H), 3.93 (s, 3H), 6.36~6.39 (m, 2H), 7.27 (t, *J* = 16.0 Hz, 1H),

7.88 (d, $J = 8.0$ Hz, 1H), 8.18 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 18.7, 34.7, 38.3, 52.2, 126.4, 126.6, 126.7, 127.7 130.0, 130.5.0, 134.8, 138.9, 166.5, 170.3 ppm; HRMS (ESI, m/z): calculated for $\text{C}_{14}\text{H}_{17}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 248.1287, found: 248.1283.

(*E*)-(4-fluoro-2-(prop-1-en-1-yl)phenyl)(pyrrolidin-1-yl)methanone

Following the general procedure A, **3l** was obtained as colorless oil,

Yield: 85%; ^1H NMR (400 MHz, CDCl_3): δ 1.82~1.88 (m, 5H), 1.92~1.97 (m, 2H), 3.10 (t, $J = 13.2$ Hz, 2H), 3.66 (t, $J = 14.0$ Hz, 2H), 6.24~6.31 (m, 1H), 6.40 (d, $J = 16.0$ Hz, 1H), 6.89~6.94 (m, 1H), 7.16~7.22 (m, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 18.7, 24.5, 25.9, 45.5, 48.3, 111.8, 113.8, 126.8, 128.1, 129.8, 132.2, 136.8, 164.1, 168.9 ppm; HRMS (ESI, m/z): calculated for $\text{C}_{14}\text{H}_{16}\text{NOF}$ $[\text{M}+\text{H}]^+$: 234.1294, found: 234.1293.

(*E*)-*N,N*-dimethyl-3-(prop-1-en-1-yl)-2-naphthamide

Following the general procedure A, **3m** was obtained as

colorless oil, **Yield:** 82%; ^1H NMR (400 MHz, CDCl_3): δ 1.91 (d, $J = 6.4$ Hz, 3H), 2.79 (s, 3H), 3.19 (s, 3H), 6.33~6.38 (m, 1H), 6.50(d, $J = 16.0$ Hz, 1H), 7.44~7.49 (m, 2H), 7.68 (s, 1H), 7.75~7.81 (m, 2H), 7.92 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 18.9, 34.8, 38.6, 124.5, 125.6, 126.1, 127.7, 127.7, 127.8 128.9, 132.0, 132.6, 133.5, 134.0, 171.2 ppm; HRMS (ESI, m/z): calculated for $\text{C}_{16}\text{H}_{17}\text{NO}$ $[\text{M}+\text{H}]^+$: 240.1388, found: 240.1387.

(E)-N,N-dimethyl-6-(prop-1-en-1-yl)benzo[d][1,3]dioxole-5-carboxamide

Following the general procedure A, **3n** was obtained as colorless oil, **Yield:** 64%; **¹H NMR (400 MHz, CDCl₃):** δ 1.87 (d, *J* = 6.8 Hz, 3H), 2.81 (s, 3H), 3.12 (s, 3H), 6.00 (s, 2H), 6.17 (d, *J* = 15.6 Hz, 1H), 6.54~6.60 (m, 1H), 6.68 (s, 2H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 19.4, 34.8, 38.6, 101.0, 106.6, 117.8, 120.0, 122.8, 129.4, 132.8, 144.9, 147.7, 170.8 ppm; **HRMS (ESI, m/z):** calculated for C₁₃H₁₅NO [M+H]⁺: 202.1232, found: 202.1220.

(E)-N,N,5-trimethyl-2-(prop-1-en-1-yl)benzamide

Following the general procedure A, **3o** was obtained as colorless oil, **Yield:** 75%; **¹H NMR (400 MHz, CDCl₃):** δ 1.85 (d, *J* = 6.4 Hz, 3H), 2.31 (s, 3H), 2.78 (s, 3H), 3.12 (s, 3H), 6.15~6.22 (m, 1H), 6.31 (d, *J* = 16.0 Hz, 1H), 7.00 (s, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 18.7, 21.0, 34.7, 38.5, 125.3, 126.7, 127.4, 127.4, 129.7, 131.6, 134.9, 136.7, 171.5 ppm; **HRMS (ESI, m/z):** calculated for C₁₃H₁₇NO [M+H]⁺: 204.1388, found: 204.1389.

(E)-5-chloro-N,N-dimethyl-2-(prop-1-en-1-yl)benzamide

Following the general procedure A, **3p** was obtained as colorless oil, **Yield:** 54%; **¹H NMR (400 MHz, CDCl₃):** δ 1.86 (d, *J* = 5.6 Hz, 3H), 2.80 (s, 3H), 3.13 (s, 3H), 6.20~6.32 (m, 2H), 7.17 (s, 1H), 7.26~7.28 (m, 2H), 7.42 (d, *J* = 8.8 Hz, 1H) ppm; **¹³C NMR**

(100 MHz, CDCl₃): δ 18.8, 34.7, 38.4, 126.3, 126.5, 126.8, 129.0, 129.3, 132.6, 133.0, 136.3, 169.7 ppm; **HRMS (ESI, m/z)**: calculated for C₁₂H₁₄NOCl [M+H]⁺: 224.0842, found: 224.0840.

(E)-3-chloro-N,N-dimethyl-2-(prop-1-en-1-yl)benzamide

Following the general procedure A, **3p'** was obtained as colorless oil,

Yield: 31%; **¹H NMR (400 MHz, CDCl₃):** δ 1.87 (d, J = 6.4 Hz, 3H), 2.74 (s, 3H), 3.06 (s, 3H), 6.04~6.10 (m, 1H), 6.55 (d, J = 16.0 Hz, 1H), 7.13~7.21 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H) ppm; **¹³C NMR (100**

MHz, CDCl₃): δ 19.2, 34.7, 38.1, 125.1, 125.4, 127.9, 128.4, 129.8, 133.1, 133.5, 137.2, 170.1 ppm; **HRMS (ESI, m/z)**: calculated for C₁₂H₁₄NOCl [M+H]⁺: 224.0842, found: 224.0843.

(E)-N,N,2-trimethyl-6-(prop-1-en-1-yl)benzamide

Following the general procedure A, **3q** was obtained as colorless oil,

Yield: 37%; **¹H NMR (400 MHz, CDCl₃):** δ 1.84 (d, J = 5.6 Hz, 3H), 2.25 (s, 3H), 2.74 (s, 3H), 3.12 (s, 3H), 6.18~6.30 (m, 2H), 7.15~7.20 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):**

δ 18.7, 34.1, 37.5, 122.6, 127.6, 127.9, 128.3, 133.7, 134.2, 135.9, 136.6, 171.2 ppm;

HRMS (ESI, m/z): calculated for C₁₃H₁₇NO [M+H]⁺: 204.1388, found: 204.1387.

2-allyl-N,N,6-trimethylbenzamide

Following the general procedure A, **3q'** was obtained as colorless oil,

Yield: 37%; **¹H NMR (400 MHz, CDCl₃):** δ 1.84 (d, *J* = 5.6 Hz, 3H), 2.25 (s, 3H), 2.76 (s, 3H), 3.16 (s, 3H), 5.03~5.08 (m, 2H), 5.85~5.95 (m, 1H) 7.03~7.07 (m, 3H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ

18.9, 34.3, 37.7, 122.6, 127.6, 127.9, 128.3, 133.7, 134.2, 135.9, 136.6, 171.2 ppm;

HRMS (ESI, *m/z*): calculated for C₁₃H₁₇NO [*M*+H]⁺: 204.1388, found: 204.1387.

***N,N*-dimethyl-2-(3-phenylpropyl)benzamide**

Following the general procedure A and hydrogenation, **4b** was

obtained as colorless oil, **Yield:** 90%; **¹H NMR (400 MHz, CDCl₃):** δ 1.94 (m, 2H), 2.61~2.68 (m, 4H), 2.75 (s, 3H), 3.06

(s, 3H), 7.13~7.28 (m, 9H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 32.2, 32.4, 34.5, 35.7, 38.6, 125.7, 126.0, 128.2, 128.4, 128.7, 129.3, 136.4, 138.5, 142.0, 171.3 ppm;

HRMS (ESI, *m/z*): calculated for C₁₈H₂₁NO [*M*+H]⁺: 268.1701, found: 268.1700.

***N,N*-dimethyl-2-(5-phenylpentyl)benzamide**

Following the general procedure A and hydrogenation, **4c**

was obtained as colorless oil, **Yield:** 85%; **¹H NMR (400 MHz, CDCl₃):** δ 1.36~1.40 (m, 2H), 1.60~1.65 (m, 4H),

2.57~2.61 (m, 4H), 2.80 (s, 3H), 3.11 (s, 3H), 7.15~7.28

(m, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 29.2, 30.6, 31.2, 32.8, 34.6, 35.8, 38.7, 125.5, 125.8, 125.9, 128.2, 128.3, 128.7, 129.4, 136.3, 138.9, 142.6, 170.3 ppm; HRMS (ESI, m/z): calculated for $\text{C}_{20}\text{H}_{25}\text{NO}$ $[\text{M}+\text{H}]^+$: 296.2014, found: 296.2013.

N,N-dimethyl-2-octylbenzamide

Following the general procedure A and hydrogenation, **4d** was obtained as colorless oil, **Yield:** 70%; ^1H NMR (400 MHz, CDCl_3): δ 0.86~0.88 (m, 3H), 1.26~1.29 (m, 10H), 1.59 (m, 2H), 2.57 (m, 2H), 2.83 (s, 3H), 3.13 (s, 3H), 7.13~7.30 (m, 4H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 14.1, 22.7, 29.2, 29.4, 29.6, 30.8, 31.9, 33.0, 34.6, 38.8, 125.8, 126.0, 128.7, 129.4, 136.3, 139.2, 171.8 ppm; HRMS (ESI, m/z): calculated for $\text{C}_{16}\text{H}_{25}\text{NO}$ $[\text{M}+\text{H}]^+$: 262.2014, found: 262.2012.

2-(3-cyclohexylpropyl)-*N,N*-dimethylbenzamide

Following the general procedure A and hydrogenation, **4e** was obtained as colorless oil, **Yield:** 69%; ^1H NMR (400 MHz, CDCl_3): δ 0.84~0.89 (m, 2H), 1.14~1.22 (m, 6H), 1.61~1.70 (m, 7H), 2.55 (m, 2H), 2.82 (s, 3H), 3.13 (s, 3H), 7.13~7.30 (m, 4H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 26.4, 26.7, 28.0, 33.2, 33.3, 34.5, 37.3, 37.4, 38.7, 125.8, 125.9, 128.7, 129.4, 136.3, 139.2, 171.5 ppm; HRMS (ESI, m/z): calculated for $\text{C}_{18}\text{H}_{27}\text{NO}$ $[\text{M}+\text{H}]^+$: 274.2171, found: 274.2174.

2-(4,4-dimethylpentyl)-*N,N*-dimethylbenzamide

Following the general procedure A and hydrogenation, **4f** was obtained as colorless oil, **Yield:** 74%; **¹H NMR (400 MHz, CDCl₃):** δ 0.86 (s, 9H), 1.20~1.26 (m, 2H), 1.56 (m, 2H), 2.57 (m, 2H), 2.83 (s, 3H), 3.13 (s, 3H), 7.13~7.30 (m, 4H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 25.8, 29.4, 30.3, 33.8, 34.6, 38.8, 44.1, 125.8, 126.0, 128.8, 129.4, 136.4, 139.2, 171.8 ppm; **HRMS (ESI, m/z):** calculated for C₁₆H₂₅NO [M+H]⁺: 248.2014, found: 248.2013.

***N,N*-dimethyl-2-(3-(4-(trifluoromethyl)phenyl)propyl)benzamide**

Following the general procedure A and hydrogenation, **4g** was obtained as colorless oil, **Yield:** 80%; **¹H NMR (400 MHz, CDCl₃):** δ 1.96 (m, 2H), 2.60 (m, 2H), 2.71 (t, $J=14.8$ Hz, 2H), 2.76 (s, 3H), 3.06 (s, 3H), 7.14~7.30 (m, 6H), 7.53 (d, $J = 7.6$ Hz, 2H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 32.0, 32.4, 34.5, 35.4, 38.6, 125.1, 125.2, 126.1, 126.2, 128.7, 128.8, 129.3, 136.3, 138.1, 146.2, 171.3 ppm; **HRMS (ESI, m/z):** calculated for C₁₉H₂₀NOF₃ [M+H]⁺: 336.1575, found: 336.1571.

(E)-N,N-dimethyl-2-(2-phenylprop-1-en-1-yl)benzamide

Following the general procedure A, the compound was obtained

as colorless oil, **Yield:** 28%; **¹H NMR (400 MHz, CDCl₃):** δ 2.21

(s, 3H), 2.77 (s, 3H), 3.09 (s, 3H), 6.81 (s, 1H), 7.29~7.40 (m, 7H),

7.47 (d, *J* = 7.6 Hz, 2H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ

17.4, 34.7, 38.3, 124.5, 126.0, 126.4, 127.1, 127.5, 128.4, 128.5, 129.7, 134.9, 137.0,

143.1, 171.3 ppm; **HRMS (ESI, *m/z*):** calculated for C₁₈H₁₉NO [M+H]⁺: 266.1545,

found: 266.1546.

Chapter 5

Cp*Rh(III)-Catalyzed Olefinic C-H Allylation with Allyl Acetates

5.1 Introduction

5.1.1 Transition metal-catalyzed allylic alkylation reaction.

In recent years, allylic alkylation has become one of the most important C-C bond formation methods in synthetic chemistry, which is widely applied to the synthesis of naturally occurring molecules and pharmaceuticals.⁶³ In this context, the allylic substitution reactions catalyzed by various transition metals have been extensively studied. Among these reactions, the Pd-catalysis was proved competent for the regio- and stereoselectively allylation reactions of aromatic compounds, organic boronic acids and organic halides, which proceeded *via* β -OAc elimination rather than β -H elimination.⁶⁴ Alternatively, Cu-catalyzed asymmetric allylation using nonstabilized nucleophiles such as Grignard, organoaluminum, organoborane and organozinc reagents were also well established, within which the stereogenic centers was created because of the high S_N2' regioselectivity.⁶⁵

⁶³ For the related reviews, see: (a) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (b) Schobert, R.; Gordon, G. J. *Curr. Org. Chem.* **2002**, *6*, 1181.

⁶⁴ For the selected examples of Pd-catalyzed allylic substitution *via* β -OAc elimination process, see: (a) Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 17276. (b) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384. (c) Miyaura, N.; Yamada, K.; Suginome, K.; Suzuli, A. *J. Am. Chem. Soc.* **1985**, *107*, 972. (d) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013. (e) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1990**, *31*, 7453. (f) Bouyssi, D.; Gerusz, V.; Balme, G. *Eur. J. Org. Chem.* **2002**, 2445. (g) Lautens, M.; Tayama, E.; Herse, C. *J. Am. Chem. Soc.* **2005**, *127*, 72. (h) Mariampillai, B.; Herse, C.; Lautens, M. *Org. Lett.* **2005**, *7*, 4745. (i) Cheng, J. C.-Y.; Daves, G. D. Jr. *Organometallics* **1986**, *5*, 1753. (j) Zhu, G.; Lu, X. *Organometallics* **1995**, *14*, 4899. (k) Zhang, Q.; Lu, X. *J. Am. Chem. Soc.* **2000**, *122*, 7604. (l) Lu, X. *Top. Catal.* **2005**, *35*, 73. For the selected examples of Pd-catalyzed allylic substitution *via* β -H elimination process, see: (m) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076. (n) Ruan, J.; Li, X.; Saidi, O.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 2424. (o) Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980. (p) Zhang, Y.; Li, Z.; Liu, Z.-Q. *Org. Lett.* **2012**, *14*, 226. (q) Li, Z.; Zhang, Y.; Liu, Z.-Q. *Org. Lett.* **2012**, *14*, 74.

⁶⁵ For the selected examples of Cu-catalyzed asymmetric allylic alkylation reaction, see: (a) Dubner, F.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 379. (b) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446. (c) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856. (d) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 15572. (e) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554. (f) Shido, Y.; Yoshida, M.; Tanabe, M.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 18573.

5.1.2 Rh(III)-catalyzed allylation reactions of C(sp²)-H bond

In the field of transition metal-catalyzed C-C bond formation *via* C-H activation process, rhodium catalysts have attracted more and more attentions of modern chemists for their high catalytic efficiency and broad functional group tolerance. Therefore, plenty of elegant works on rhodium-catalyzed C-H bond functionalization have been developed over the past decades.

Quite recently, using allene derivatives as the coupling partner, the Rh(III)-catalyzed C-H allylation of arenes and alkenes were disclosed by Ma and Cramer, independently (Scheme 5.1).⁶⁶ In both works, lower reaction temperature was adopted to minimize the diallylation products. The chiral products were generated by taking the advantage of utilizing a chiral version Cp ligand of rhodium catalysis in Cramer's work (Condition B).

Scheme 5.1 Rh(III)-catalyzed allylation reaction of benzamide with allenes.

⁶⁶ (a) Zeng, R.; Fu, C.; Ma, S. *J. Am. Chem. Soc.* **2012**, *134*, 9597. (b) Ye, B.; Cramer, N. *J. Am. Chem. Soc.* **2013**, *135*, 636.

Intriguingly, one example of Rh(III)-catalyzed allylation of arenes was disclosed by Ellman and co-workers, when using allyl acetate as the allyl source (Scheme 5.2).⁶⁷ Although the catalytic amount of copper(II) acetate was needed to maintain the yield, this discovery did set the stage for the allyl esters acting as the electrophilic coupling partner in the rhodium-catalyzed C-H allylation reaction.

Scheme 5.2 Rh(III)-catalyzed allylation of arenes with allyl acetate.

In 2013, Glorius and co-workers reported the Rh(III)-catalyzed allylation of benzamides with allyl carbonates (Scheme 5.3).⁶⁸ The allyl carbonate was adopted as coupling partner, which maintained a high isomeric ratio and presented robust reactivity than other allyl substrates.

Scheme 5.3 Rh-catalyzed direct C-H allylation reaction of arenes.

⁶⁷ Tsai, S. A.; Brasse, M.; Bergman, G.R.; Ellman, J. A. *Org. Lett.* **2011**, 13, 540.

⁶⁸ (a) Wang, H.; Schroder, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, 52, 5386 (b) Wang, H.; Beiring, B.; Yu, D.-G.; Collins, K. D.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, 52, 12430.

Almost the same time, an external oxidant-free olefination reaction of arenes with allyl acetate was developed by our group, within which allyl substitution intermediate with excellent γ -selectivity was formed through β -OAc elimination process (see the details in Chapter 4).

Since much effort was made in the arena of rhodium-catalyzed aromatic C-H allylation reaction, the relatively more active alkenes,⁶⁹ however, was not adopted in such reaction process. With our continue interest in rhodium catalysis and olefinic C-H bond functionalization, we envisaged that the application of Rh(III)-catalyzed direct olefinic C-H allylation would be a efficient and fascinating method for the synthesis of functionalized 1,4-diene skeletons. In this chapter, the Rh(III)-catalyzed olefinic C-H allylation with allyl acetates is described, wherein the weakly coordinating directing group tosyl-imide is proved to be the crux to the success of this protocol (Scheme 5.4).

Scheme 5.4 Rh-catalyzed direct C-H allylation of acrylamide with allyl acetates

⁶⁹ For selected examples of Rh(III)-catalyzed C-H functionalization of alkenes, see: (a) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.*, 2010, **132**, 18326. (b) Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X. *Org. Lett.*, 2010, **12**, 5462. (c) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.*, 2010, **132**, 9585. (d) Kuhl, N.; Schroder, N.; Glorius, F. *Org. Lett.*, 2013, **15**, 3860. (e) Wang, H.; Beiring, B.; Yu, D.-G.; Collins, K. D.; Glorius, F. *Angew. Chem., Int. Ed.*, 2013, **52**, 12430. (f) Hyster, T. K.; Rovis, T. *Chem. Commun.*, 2011, **47**, 11846. (g) Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. *Chem. Asian J.*, 2012, **7**, 1208. (h) Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem. Eur. J.*, 2011, **17**, 7167.

5.2 Result and Discussion

In the beginning of our study, the influence of different allyl electrophiles was explored. Using 2-phenyl-*N*-tosylacrylamide (**1a**) as the model substrate, [Cp*RhCl₂]₂ as the catalyst, and NaOAc as the additive, the reaction was conducted in DCE at 80 °C (Table 5.1, Entry 1 & 2). To our delight, both allyl esters afforded the allylation product (**3a**) without any migration of the double bond. The absolute *cis*-structure was confirmed by the NOESY NMR analysis of **3k** (see the details in 5.4.3), which demonstrated the amido group's directing effect at the C-C bond formation step within the catalytic cycle.

Table 1.1 Reaction Conditions Optimization^a

Entry	R	Additive	Solvent	Yield ^b (%)
1	OCOOMe (2a)	NaOAc	DCE	58
2	OAc (2b)	NaOAc	DCE	63
3	2b	NaOAc	MeOH	84
4	2b	NaOAc	<i>t</i> -AmOH	19
5	2b	NaOAc	Acetone	31
6	2b	NaOAc	PhCl	39
7	2b	NaOAc	MeCN	23
8	2b	NaOAc	Dioxane	27

Entry	R	Additive	Solvent	Yield ^b (%)
9	2b	NaOAc	DME	30
10	2b	NaOAc	DMSO	NR
11	2b	CsOAc	MeOH	77
12	2b	Cs ₂ CO ₃ & PivOH	MeOH	45
13	2b	NaHCO ₃	MeOH	Trace
14	2b	Na ₂ CO ₃	MeOH	24
15	2b	K ₂ CO ₃	MeOH	30
16	2b	NaOAc	MeOH	51 ^c
17	2b	-	MeOH	13 ^d
18	2b	NaOAc	MeOH	NR ^e
19	2b	NaOAc	MeOH	73 ^f

^a unless otherwise noted the reactions were carried out at 80 °C using **1a** (0.1 mmol), **2** (0.4 mmol), [Cp*RhCl₂]₂ (0.002 mmol), additive (0.1 mmol) in solvent (0.5 mL) stirred for 12 h. ^b Isolated yields. ^c [Cp*Rh(MeCN)₃][SbF₆]₂ was used as catalyst. ^d No NaOAc was added. ^e No rhodium catalyzed was added. ^f 1 g scale.

Since allyl acetate (**2b**) performed slightly better than allyl carbonate (**2a**) in this protocol, we examined a series of solvents to further improve the reaction yield. It was found that methanol was the optimal solvent (Table 5.1, Entry 3-9). And the reaction was totally suppressed, when the apolar aprotic solvent, DMSO, was adopted (Table 5.1, Entry 10). After the identification of the optimal solvent, we turned our attention to the effect of reaction additives. When sodium acetate was replaced by cesium acetate, the yield was slightly decreased (Table 5.1, Entry 11). The obvious deleterious

effect was discovered when a combination of cesium carbonate and pivalic acid was utilized as the additive (Table 5.1, Entry 12). Similar results were obtained when sodium and potassium carbonate were introduced (Table 5.1, Entry 14 & 15). Moreover, when sodium bicarbonate was applied as the additive, only trace product was observed throughout the reaction process (Table 5.1, Entry 13). When the cationic $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]_2$ catalyst was introduced into the reaction in place of $[\text{Cp}^*\text{RhCl}_2]_2$ catalyst, inferior yield was obtained, indicating the importance of this type of rhodium catalyst (Table 5.1, Entry 16). Furthermore, the reaction gave a lower yield without an additive, inferring the importance of the additive and the efficiency of the rhodium catalyst. In addition, the reaction did not proceed when no rhodium catalyst was added (Table 5.1, Entry 18). In order to show the robustness of this catalytic system, a gram-scale reaction was also conducted with a yield of 73% obtained (Table 5.1, Entry 19).

In order to verify the dramatic effect of the directing groups, several different acrylamides were adopted into this allylation reaction. While *N*-methyl substituted acrylamides provides moderated yield of desired product, other substrates, beside **2a**, were proved to be inaccessible for this allylation reaction, which would explain the reason why such allylation reaction of olefin was not carried out in the past (Table 5.2).

Table 5.2 Optimization of directing group ^a

Entry	R	Yield ^b (%)
1	NHTs (1a)	84
2	NMe ₂	N. R.
3	NiPr ₂	N. R.
4	NHBn	N. R.
5	NHMe	36
6	NHPh	N. R.

^a Unless otherwise noted the reactions were carried out at 80 °C using acrylamides (0.1 mmol), **2a** (0.4 mmol), [Cp*RhCl₂]₂ (0.002 mmol), NaOAc (0.1mmol) in MeOH (0.5 mL) stirred for 12 h. ^b Isolated yields.

With the optimal reaction conditions in hand, the reaction limitations and generality were then investigated with respect to the acrylamides (Table 5.3). The α -aryl substituted acrylamides were examined firstly under standard reaction condition using allyl acetate **2b** as the coupling partner. Functional groups, such as methyl, methoxy, methylthio, chloro and fluoro, substituted at the *para*-position of the α -substituted phenyl ring were shown to be no influence in this allylation reaction, thus giving corresponding *cis*-product in high yields (Table 5.3, **3b-3h**). It is noteworthy that the sulfur-containing substrate **1h** did not show any deleterious effect stem from catalyst deactivation. Furthermore, the *meta*-dimethyl substituted phenyl acrylamide **1i** was

also well accommodated with this reaction, providing the desired product in 79% isolated yield (Table 5.3, **3i**). Moreover, the desired 1,4-diene product was generated smoothly in 87% isolated yield, when substrate **1j**, derived from 2-naphthyl acrylate, was employed (Table 5.3, **3j**). In addition, this olefinic allylation protocol is not limited to α -aryl substituted substrates, those with α -aliphatic substituents were also effectively participate in the olefinic allylation reaction, affording 1,4-diene products in high to excellent yields (Table 5.3, **3k-3p**). Intriguingly, when α -methyl substituted acrylamide **1k** was employed as the substrate, besides the desired allylation product **3k** was generated, an unexpected and inseparable conjugated diene isomer **3k'** was also observed with the ratio of **3k:3k'** as 83:17. When hexyl and benzyl substituted acrylamide were submitted to the standard reaction condition, the formation of a small amount of diene isomers was noticed as well (Table 5.3, **3l-3n**). However, when substrates derived from 2-cycloalkylacrylate was employed, the formation of conjugated diene was not obviously observed, and thus generating the olefinic allylation products in 75% and 77% yields (Table 5.3, **3o** & **3p**). To further extend the reaction scope, several α,β -disubstituted acrylamide derivatives were subsequently investigated as well. When, 1-cyclohexenyl derived substrate **1q** was introduced in this reaction, the allylation product **3q** was obtained in 82% yield. In addition, the heterocycle-derived acrylamide **1r**, possessing Lewis basic heteroatoms, was also nicely engaged in this reaction, obtaining the desired product in 81% yield. Furthermore, albeit generating the product **3s** in relatively low yield, the cinnamamide **1s** was also found to be a viable substrate.

Table 5.3 Reaction scope of acrylamide derivatives ^{a,b}

^a Unless otherwise noted the reactions were carried out at 80 °C using **1** (0.1 mmol), **2b** (0.4 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (0.002 mmol), NaOAc (0.1mmol) in MeOH (0.5 mL) stirred for 12 h. ^b Isolated yields. ^c Ratio for **3**:**3'** given in brackets were determined by ¹H NMR.

Table 5.4 Reaction scope of allyl acetate derivatives ^{a,b}

Entry	Allyl acetate derivatives	Desired product	Yield (%) (E/Z)
1			35% (77/23)
2			61% (99/1)
3			67% (87/13)
4			59% (83/17)
5			37% (-)
6			57% (-)
7			47% (-)

^a Unless otherwise noted the reactions were carried out at 80 °C using **1a** (0.2 mmol), **2** (0.4 mmol), [Cp*RhCl₂]₂ (0.004 mmol), NaOAc (0.2 mmol) in MeOH (1 mL) stirred for 16 h. ^b Isolated yields.

To further demonstrate the generality of this olefinic C-H allylation reaction, allyl acetate derivatives were explored subsequently under the optimal reaction condition. With respect to α -substituted allyl acetates studied, excellent γ -selectivity along with moderated to high stereoselectivity and synthetically useful chemical yields were obtained (Table 5.4, entries 1-4). Although not very effective, the adoption of α -vinyl allyl acetate did provide a straightforward introduction of 1,3-diene moiety to the alkene skeleton (Table 5.4, entry 1). Furthermore, the substitutions on the β - or γ -carbon of allyl acetates were also allowed with lowered reaction efficiency, due to the steric interaction in the process of carboration. For instance, the allylic substitution proceeded smoothly affording the desired product **3g** and **3h** in 37% and 57% yields, respectively, when 2-methylallyl acetate **2g** and but-2-en-1-yl acetate **2h** were submitted to the standard reaction condition with **1a** (Table 5.4, entries 5, 6). In addition, cyclohex-2-en-1-yl acetate **2i** was also adapted in this reaction, providing the corresponding product in 47% yields.

To gain mechanistic details of this allylic alkylation reaction, a possible reaction pathway was proposed in Scheme 5.5. At first, the imide directed C-H activation of acrylamide **1** by the *in situ* formed rhodium catalyst [Rh^{III}-OAc] delivering the intermediate **I** via a concerted-metalation-deprotonation (CMD) process, thus initiated the catalytic cycle. Then, the seven-membered rhodacycle **II** was formed by the migratory insertion of the allyl C-C double bond to the Rh-C bond. The induction of β -OAc elimination was believed to be a better choice with the coordination carbonyl of acetoxyl to the metal center, thus affording the desired allylation product **3** and

regenerating the active rhodium catalyst to complete the catalytic cycle. Alternatively, for the formation of dienes **3'**, intermediate **I** is hypothesized to undergo insertion of **2b** with reversed regioselectivity, forming the intermediate **II'**. Followed by hydride elimination/ reinsertion through intermediates **III'** and **IV'**, finally undergoes β -OAc elimination to get the target.

Scheme 5.5 Plausible catalytic mechanism.

5.3 Conclusion

In conclusion, a novel Rh(III)-catalyzed intermolecular direct olefinic C-H allylation of electron-deficient alkenes with commercial available allyl acetates as electrophile coupling partner was described. With respect to acrylamide and allyl acetate, a wide

range of functionalities and substitution patterns were well adapted to this protocol. The preparation of synthetically useful 1,4-diene motifs was provided through the straightforward and efficient allylic alkylation of alkene substrates with the assistance of a weak-coordinating directing group.

5.4 Experiment Section

5.4.1 General information

[RhCp*Cl₂]₂, anhydrous solvents were purchased from commercial suppliers and used as received unless otherwise noted. All reactions were carried out under air without extra protection. Reactions were monitored through thin layer chromatography [Merck 60 F254 precoated silica gel plate (0.2 mm thickness)]. Subsequent to elution, spots were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible using basic solution of potassium permanganate or acidic solution of ceric molybdate as stain, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. HRMS spectra were recorded on a Waters Q-Tof Premier Spectrometer. ¹H NMR and ¹³C NMR spectra were recorded using Bruker Avance 400 MHz spectrometers. Chemical shifts for ¹H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of SiMe₄ (δ 0.00, singlet). Multiplicities were given as: s (singlet); brs (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); td (triplet of doublet); m (multiplets); ddt (doublet of doublet of triplet) and

etc. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform- d (δ 77.00, triplet).

5.4.2 Experimental procedures

Scheme 5.6 Rh-catalyzed C-H allylation reaction of acrylamides with allyl acetates

Experiment procedure A: To an 8mL glass sample vial was successively charged with amides **1** (0.1 mmol), allyl acetate **2c** (0.4 mmol), NaOAc (0.1 mmol), $[\text{RhCp}^*\text{Cl}_2]_2$ (0.002 mmol) followed by adding anhydrous MeOH (0.5 mL) through syringe and then closed tightly. After stirring at $80\text{ }^\circ\text{C}$ for 12 hours, the mixture was washed with saturated NH_4Cl (5 mL) and extracted with dichloromethane (2x5mL). The organic layers were combined and vacuo, then subjected to purification by silica gel column chromatography (Hexane: EtOAc = 2:1)afforded the desired product **3** (Scheme 5.6).

Scheme 5.7 Large scale experiment

Experiment procedure (Scheme 5.7): To a 50mL RBF was successively charged with amides **1** (1 g, 3.3 mmol), allyl acetate **2c** (1.4 mL, 13.2 mmol), NaOAc (0.27 g, 3.3 mmol), $[\text{RhCp}^*\text{Cl}_2]_2$ (40 mg, 0.066 mmol) followed by adding anhydrous MeOH (20 mL) through syringe and then closed tightly. After stirring at 80 °C for 12 hours, the mixture was washed with saturated NH_4Cl (50 mL) and extracted with dichloromethane (2x20mL). The organic layers were combined and vacuo, then subjected to purification by silica gel column chromatography (Hexane:EtOAc = 2:1) afforded the desired product **3a** (0.83g, 73%).

5.4.3 Characterization of products

(Z)-2-phenyl-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3a** was obtained as a white solid, 28.7 mg, Yield: 84%; ^1H NMR (400 MHz, CDCl_3): δ 2.46 (s, 3H), 3.06-3.10 (m, 2H), 5.03-5.07 (m, 2H), 5.75-5.85 (m, 1H), 6.14 (t, J = 8.0 Hz, 1H), 7.14-7.16 (m, 2H), 7.31-7.37 (m, 5H), 7.94 (d, J = 8.0 Hz, 2H), 8.01 (brs, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 21.7, 33.7, 116.5, 127.2, 128.5, 128.7,

129.0, 129.6, 134.9, 135.5, 135.6, 135.9, 138.0, 145.2, 164.9 ppm; **HRMS (ESI, m/z):** calcd for $C_{19}H_{20}NO_3S$ $[M+H]^+$ 342.1164, found: 342.1160.

(Z)-2-(p-tolyl)-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3b** was obtained as a white solid, 28.8 mg, Yield: 81%; **1H NMR (400 MHz, $CDCl_3$):** δ 2.34 (s, 3H), 2.46 (s, 3H), 3.06-3.09 (m, 2H), 5.02-5.06 (m, 2H), 5.75-5.83 (m, 1H), 6.10 (t, $J = 8.0$ Hz, 1H), 7.03 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 8.0$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.94 (d, $J = 8.0$ Hz, 2H), 8.01 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 21.1, 21.7, 33.7, 116.4, 127.2, 128.5, 129.5, 129.7, 133.1, 135.0, 135.4, 135.5, 137.6, 138.7, 145.1, 165.0 ppm; **HRMS (ESI, m/z):** calcd for $C_{20}H_{22}NO_3S$ $[M+H]^+$ 356.1320, found: 356.1322.

(Z)-2-(4-methoxyphenyl)-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3c** was obtained as a white solid, 27.9 mg, Yield: 75%; **1H NMR (400 MHz, $CDCl_3$):** δ 2.46 (s, 3H), 3.06-3.10 (m, 2H), 3.80 (s, 3H), 5.01-5.06 (m, 2H), 5.75-5.83 (m, 1H), 6.05 (t, $J = 8.0$ Hz, 1H), 6.82-6.84 (m, 2H), 7.07-7.09 (m, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.94 (d, $J = 8.0$ Hz, 2H), 8.01 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 21.7, 33.7, 55.3, 114.4, 116.3, 128.3, 128.5, 129.5, 135.1, 135.5, 136.6, 145.1, 159.9, 165.2 ppm; **HRMS (ESI, m/z):** calcd for $C_{20}H_{22}NO_4S$ $[M+H]^+$ 372.1270, found: 372.1281.

(Z)-2-(4-(*tert*-butyl)phenyl)-*N*-tosylhexa-2,5-dienamide:

Following the general procedure A, **3d** was obtained as a white solid, 30.2 mg, Yield: 76%; **¹H NMR (400 MHz, CDCl₃):** δ 1.32 (s, 9H), 2.47 (s, 3H), 3.08-3.11 (m, 2H), 5.02-5.06 (m, 2H), 5.75-5.85 (m, 1H), 6.12 (t, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.33-7.38 (m, 4H), 7.95-7.97 (m, 3H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 21.7, 31.2, 33.7, 34.6, 116.4, 126.0, 127.1, 128.5, 129.6, 133.1, 135.0, 135.2, 135.6, 138.2, 145.1, 151.9, 164.9 ppm; **HRMS (ESI, *m/z*):** calcd for C₂₃H₂₈NO₃S [M+H]⁺ 398.1790, found: 398.1791.

(Z)-2-(4-chlorophenyl)-*N*-tosylhexa-2,5-dienamide:

Following the general procedure A, **3e** was obtained as a white solid, 31.2 mg, Yield: 83%; **¹H NMR (400 MHz, CDCl₃):** δ 2.47 (s, 3H), 3.00-3.04 (m, 2H), 5.02-5.07 (m, 2H), 5.74-5.82 (m, 1H), 6.12 (t, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 12.0 Hz, 2H), 7.26-7.28 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 8.14 (brs, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 21.7, 33.8, 116.7, 128.3, 128.5, 129.2, 129.6, 134.2, 134.6, 134.7, 134.9, 135.3, 137.2, 145.4, 164.8 ppm; **HRMS (ESI, *m/z*):** calcd for C₁₉H₁₉ClNO₃S [M+H]⁺ 376.0774, found: 376.0773.

(Z)-2-(4-fluorophenyl)-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3f** was obtained as a white solid, 29.1 mg, Yield: 81%; **¹H NMR (400 MHz, CDCl₃):** δ 2.47 (s, 3H), 3.02-3.06 (m, 2H), 5.02-5.07 (m, 2H), 5.75-5.85 6.09 (t, *J* = 8.0 Hz, 1H), 6.98-7.02 (m, 2H), 7.12-7.15 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 2H), 8.08 (brs, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 21.7, 33.7, 116.0 (d, *J* = 22.0 Hz), 116.6, 128.5, 128.9, 129.0, 129.6, 131.9 (d, *J* = 4.0 Hz), 134.7 (d, *J* = 7.0 Hz), 135.4, 137.3, 145.3, 164.3 (d, *J* = 247.0 Hz), 164.8 ppm; **HRMS (ESI, m/z):** calcd for C₁₉H₁₉FO₃S [M+H]⁺ 360.1070, found:360.1075.

(Z)-2-([1,1'-biphenyl]-4-yl)-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3g** was obtained as a white solid, 35.5 mg, Yield: 85%; **¹H NMR (400 MHz, CDCl₃):** δ 2.45 (s, 3H), 3.06-3.10 (m, 2H), 5.04-5.08 (m, 2H), 5.77-5.87 (m, 1H), 6.19 (t, *J* = 8.0 Hz, 1H), 7.21-7.25 (m, 2H), 7.34-7.38 (m, 3H), 7.43-7.46 (m, 2H), 7.52-7.57 (m, 4H), 7.95 (d, *J* = 8.0 Hz, 2H), 8.14 (brs, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 21.7, 33.8, 116.5, 127.0, 127.6, 127.7, 127.7, 128.5, 128.9, 129.6, 134.7, 134.9, 135.4, 135.5, 137.4, 140.1, 141.5, 145.2, 165.0 ppm; **HRMS (ESI, m/z):** calcd for C₂₅H₂₃NO₃SNa [M+Na]⁺ 440.1296, found: 440.1305.

(Z)-2-(4-(methylthio)phenyl)-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3h** was obtained as a white solid, 30.2 mg, Yield: 78%; **¹H NMR (400 MHz, CDCl₃):** δ 2.47 (s, 3H), 2.48 (s, 3H), 3.02-3.06 (m, 2H), 5.01-5.06 (m, 2H), 5.74-5.84 (m, 1H), 6.10 (t, *J* = 8.0 Hz, 1H), 7.05-7.07 (m, 2H), 7.15-7.18 (m, 2H), 7.35-7.37 (m, 2H), 7.92-7.96 (m, 3H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 15.4, 21.7, 33.7, 116.5, 126.6, 127.5, 128.5, 129.6, 132.3, 134.9, 135.2, 135.4, 136.8, 139.7, 145.2, 165.0 ppm; **HRMS (ESI, *m/z*):** calcd for C₂₀H₂₂NO₃S₂ [M+H]⁺ 388.1041, found: 388.1053.

(Z)-2-(3,5-dimethylphenyl)-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3i** was obtained as a white solid, 29.2 mg, Yield: 79%; **¹H NMR (400 MHz, CDCl₃):** δ 2.26 (s, 6H), 2.46 (s, 3H), 3.07-3.11 (m, 2H), 5.03-5.08 (m, 2H), 5.76-5.84 (m, 1H), 6.10 (t, *J* = 8.1 Hz, 1H), 6.71 (s, 2H), 6.95 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 2H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 21.2, 21.7, 33.7, 116.4, 125.0, 128.5, 129.5, 130.3, 135.1, 135.7, 135.8, 135.9, 137.6, 138.6, 145.1, 165.2 ppm; **HRMS (ESI, *m/z*):** calcd for C₂₁H₂₄NO₃S [M+H]⁺ 370.1477, found: 370.1475.

(Z)-2-(naphthalen-2-yl)-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3j** was obtained as a white solid, 34.1 mg, Yield: 87%; **¹H NMR (400 MHz, CDCl₃):** 2.46 (s, 3H), 3.08-3.12 (m, 2H), 5.05-5.10 (m, 2H), 5.80-5.86 (m, 1H), 6.25 (t, *J* = 8.0 Hz, 1H), 7.27-7.34 (m, 3H), 7.48-7.50 (m, 3H), 7.65-7.68 (m, 1H), 7.76-7.81 (m, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 8.14 (brs, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 21.7, 33.9, 116.6, 124.2, 126.5, 126.7, 127.6, 128.1, 128.5, 128.8, 129.6, 132.9, 133.0, 133.2, 134.8, 135.4, 135.8, 137.2, 145.2, 165.2 ppm; **HRMS (ESI, m/z):** calcd for C₂₃H₂₂NO₃S [M+H]⁺ 392.1320, found: 392.1324.

(Z)-2-methyl-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3k** was obtained as colorless oil, 22.3 mg, Yield: 80%; **¹H NMR (400 MHz, CDCl₃):** δ 1.90 (s, 3H), 2.45 (s, 3H), 2.93-2.96 (m, 2H), 5.02-5.08 (m, 2H), 5.74-5.83 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 2H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 20.2, 21.7, 33.5, 116.3, 118.3, 128.5, 128.6, 129.4, 129.6, 129.9, 135.4, 135.6, 136.5, 145.1, 165.9 ppm; **HRMS (ESI, m/z):** calcd for C₁₄H₁₈NO₃S [M+H]⁺ 280.1007, found: 208.1007.

(Z)-2-benzyl-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3l** was obtained as a white solid, 27.7 mg, Yield: 78%; **¹H NMR (400 MHz, CDCl₃):** δ 2.45 (s, 3H), 2.96-2.99 (m, 2H), 3.50 (s, 2H), 5.03-5.10 (m, 2H), 5.77-

5.85 (m, 2H), 7.02-7.05 (m, 2H), 7.21-7.27 (m, 5H), 7.74 (d, $J = 8.0$ Hz, 2H), 8.01 (brs, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 21.7, 33.4, 40.4, 116.4, 126.9, 128.3, 128.5, 128.9, 129.5, 134.8, 135.2, 135.4, 135.5, 137.3, 144.9, 165.7 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$ 356.1320, found: 356.1315.

(Z)-2-(4-bromobenzyl)-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3m** was obtained as a white solid, 34.7 mg, Yield: 80%; ^1H NMR (400 MHz, CDCl_3): δ 2.47 (s, 3H), 2.97-3.00 (m, 2H), 3.45 (s, 2H), 5.05-5.12 (m, 2H), 5.77-5.87 (m, 2H), 6.86 (d, $J = 8.0$ Hz, 2H), 7.23-7.30 (m, 4H), 7.71 (d, $J = 8.0$ Hz, 2H), 8.23 (brs, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 21.7, 33.4, 39.9, 116.6, 120.7, 128.2, 129.4, 129.5, 130.3, 130.6, 134.8, 135.0, 135.0, 135.1, 136.3, 145.1, 165.4 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{24}\text{H}_{36}\text{NO}_3\text{SSi}$ $[\text{M}+\text{H}]^+$ 434.0426, found: 434.0425.

(Z)-2-(but-3-en-1-ylidene)-N-tosyloctanamide:

Following the general procedure A, **3n** was obtained as a white solid, 30.1 mg, Yield: 86%; ^1H NMR (400 MHz, CDCl_3): δ 0.83-0.86 (m, 3H), 1.19-1.27 (m, 8H), 2.15-2.19 (m, 2H), 2.82-2.86 (m, 2H), 5.02-5.09 (m, 2H), 5.67 (t, $J = 8.1$ Hz, 1H), 5.77-5.84 (m, 1H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.97 (d, $J = 8.3$ Hz, 2H), 8.32 (brs, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 14.0, 21.6, 22.4, 28.1, 28.6, 31.4, 33.3, 34.3, 116.2,

128.4, 129.5, 132.4, 135.5, 136.3, 145.1, 166.5 ppm; **HRMS (ESI, m/z):** calcd for $C_{19}H_{28}NO_3S$ $[M+H]^+$ 350.1790, found: 350.1790.

(Z)-2-cyclopropyl-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3o** was obtained as a white solid, 22.9 mg, Yield: 75%; **1H NMR (400 MHz, $CDCl_3$):** δ 0.50-0.53 (m, 2H), 0.79-0.83 (m, 2H), 1.43-1.49 (m, 1H), 2.44 (s, 3H), 3.05-3.09 (m, 2H), 4.96-5.02 (m, 2H), 5.70-5.88 (m, 2H), 7.35 (d, $J = 8.2$ Hz, 2H), 7.99 (d, $J = 8.4$ Hz, 2H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 6.18, 14.2, 21.7, 33.3, 116.1, 128.5, 129.6, 133.2, 135.4, 135.7, 139.4, 145.0, 164.8 ppm; **HRMS (ESI, m/z):** calcd for $C_{16}H_{20}NO_3S$ $[M+H]^+$ 306.1164, found: 306.1166.

(Z)-2-cyclohexyl-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3p** was obtained as a white solid, 26.8 mg, Yield: 77%; **1H NMR (400 MHz, $CDCl_3$):** δ 1.02-1.13 (m, 3H), 1.17-1.24 (m, 2H), 1.62-1.72 (m, 6H), 2.13-2.15 (m, 1H), 2.45 (s, 3H), 2.69-2.72 (m, 2H), 4.98-5.08 (m, 2H), 5.52 (t, $J = 8.0$ Hz, 1H), 5.75-5.82 (m, 1H), 7.35 (d, $J = 8.2$ Hz, 2H), 7.97 (d, $J = 8.3$ Hz, 2H), 8.19 (brs, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 21.7, 25.8, 26.2, 31.8, 33.1, 41.6, 116.0, 127.6, 128.5, 129.5, 135.6, 142.5, 145.2, 167.4 ppm; **HRMS (ESI, m/z):** calcd for $C_{19}H_{26}NO_3S$ $[M+H]^+$ 348.1633, found: 348.1632.

2-allyl-*N*-tosylcyclohex-1-enecarboxamide:

Following the general procedure A, **3q** was obtained as a white solid, 26.2 mg, Yield: 82%; **¹H NMR (400 MHz, CDCl₃):** δ 1.57-1.59 (m, 4H), 2.06 (m, 2H), 2.17 (m, 2H), 2.44 (s, 3H), 2.79-2.81 (m, 2H), 5.00-5.11 (m, 2H), 5.76- 5.86 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.1 Hz, 2H), 8.29 (brs, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 21.6, 21.8, 21.9, 26.3, 29.9, 39.1, 116.5, 128.1, 128.4, 128.5, 129.3, 129.5, 135.5, 135.8, 142.3, 144.9, 167.3 ppm; **HRMS (ESI, m/z):** calcd for C₁₇H₂₂NO₃S [M+H]⁺ 320.1320, found: 320.1325.

5-allyl-*N*-tosyl-3,4-dihydro-2*H*-pyran-6-carboxamide:

Following the general procedure A, **3r** was obtained as a white solid, 26.0 mg, Yield: 81%; **¹H NMR (400 MHz, CDCl₃):** δ 1.81-1.83 (m, 2H), 2.10-2.13 (m, 2H), 2.43 (s, 3H), 3.20-3.22 (m, 2H), 3.95-3.98 (m, 2H), 4.94-5.02 (m, 2H), 5.66-5.76 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 8.1 Hz, 2H), 8.96 (brs, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 21.6, 21.9, 26.2, 36.3, 66.1, 116.0, 126.4, 128.4, 129.5, 135.4, 135.9, 138.3, 144.8, 159.7 ppm; **HRMS (ESI, m/z):** calcd for C₁₆H₁₉NO₄SN_a [M+Na]⁺ 344.0932, found: 344.0939.

(E)-3-phenyl-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **3s** was obtained as colorless oil, 8.5 mg, Yield: 25%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 2.41 (s, 3H), 4.55-4.56 (m, 2H), 5.26-5.37 (m, 2H), 5.91-5.99 (m, 1H), 7.18-7.22 (m, 1H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.37-7.39 (m, 3H), 7.47-7.49 (m, 2H), 7.65-7.69 (m, 1H), 7.84 (d, $J = 8.4$ Hz, 2H), ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 21.6, 48.6, 118.0, 118.3, 127.8, 128.3, 128.9, 129.7, 130.6, 132.9, 134.5, 136.9, 144.8, 146.1, 165.8 ppm; **HRMS** (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$ 342.1164, found: 342.1166.

(2Z)-2-phenyl-N-tosylocta-2,5,7-trienamide:

Following the general procedure A, **4c** was obtained as colorless oil, 12.9 mg, Yield: 35%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 2.47 (s, 3H), 3.13-3.17 (m, 2H), 5.01-5.04 (m, 1H), 5.11-5.15 (m, 1H), 5.63-5.70 (m, 1H), 6.03-6.15 (m, 2H), 6.24-6.33 (m, 1H), 7.14-7.16 (m, 2H), 7.32-7.38 (m, 5H), 7.95-7.98 (m, 2H) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 21.7, 28.5, 30.9, 32.7, 116.4, 127.4, 128.5, 128.8, 129.1, 129.6, 130.4, 132.8, 135.3, 135.5, 136.0, 136.6, 138.7, 145.2, 164.7 ppm; **HRMS** (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{22}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$ 368.1320, found: 368.1327.

(2Z,5E)-2,8-diphenyl-N-tosylocta-2,5-dienamide:

Following the general procedure A, **4d** was obtained as a white solid, 27.2 mg, Yield: 61%; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 2.30-2.34 (m, 2H), 2.46 (s, 3H), 2.64-2.68 (m,

2H), 2.99-3.03 (m, 2H), 5.37-5.53 (m, 2H), 6.08 (t, $J = 8.0$ Hz, 1H), 7.11-7.16 (m, 5H), 7.24-7.36 (m, 7H), 7.94-7.96 (m, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 21.7, 32.8, 34.3, 35.7, 125.8, 126.9, 127.3, 128.3, 128.4, 128.5, 128.6, 129.0, 129.6, 131.9, 135.0, 135.5, 136.0, 139.1, 141.8, 145.2, 164.9 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{27}\text{H}_{28}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$ 446.1790, found: 446.1792.

(2Z)-2-phenyl-*N*-tosylundeca-2,5-dienamide:

Following the general procedure A, **4e** was obtained as a white solid, 27.6 mg, Yield: 67%; ^1H NMR (400 MHz, CDCl_3): δ 0.86-0.90 (m, 3H), 1.24-1.36 (m, 6H), 1.95-2.00 (m, 2H), 2.47 (s, 3H), 2.99-3.02 (m, 2H), 5.34-5.48 (m, 2H), 6.12 (t, $J = 8.4$ Hz, 1H), 7.14-7.16 (m, 2H), 7.30-7.37 (m, 5H), 7.96 (d, $J = 8.8$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 14.0, 21.7, 22.5, 29.0, 31.4, 32.5, 32.8, 126.0, 127.2, 128.5, 128.6, 129.0, 129.0, 129.6, 133.1, 134.9, 135.6, 136.1, 139.1, 145.1, 165.0 ppm; HRMS (ESI, m/z): calcd for $\text{C}_{24}\text{H}_{30}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$ 412.1946, found: 412.1934.

(2Z)-6-cyclohexyl-2-phenyl-*N*-tosylhexa-2,5-dienamide:

Following the general procedure A, **4f** was obtained as a white solid, 25.0 mg, Yield: 59%; ^1H NMR (400 MHz, CDCl_3): δ 1.01-1.27 (m, 6H), 1.57-1.72 (m, 4H), 1.85-1.93 (m, 1H), 2.47 (s, 3H), 2.99-3.02 (m, 2H), 5.31-5.41 (m, 2H), 6.13 (t, $J = 8.4$ Hz, 1H), 7.14-7.17 (m, 2H), 7.31-7.38 (m, 5H), 7.97 (d, $J = 8.0$ Hz, 2H), 7.94 (brs, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 21.7, 26.0, 26.1, 32.9, 33.0, 40.7, 123.6, 127.3, 128.6, 129.0, 129.6,

135.0, 135.6, 136.1, 138.9, 139.2, 145.2, 165.0 ppm; **HRMS (ESI, m/z):** calcd for $C_{25}H_{30}NO_3S$ $[M+H]^+$ 424.1946, found: 424.1956.

(Z)-5-methyl-2-phenyl-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **4g** was obtained as colorless oil, 13.2 mg, Yield: 37%; **1H NMR (400 MHz, $CDCl_3$):** δ 1.73 (s, 3H), 2.47 (s, 3H), 3.01-3.03 (m, 2H), 4.70 (s, 1H), 4.80 (s, 1H), 6.20 (t, J = 8.1 Hz, 1H), 7.16-7.18 (m, 2H), 7.32-7.38 (m, 5H), 7.94-7.97 (m, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 21.7, 22.8, 37.5, 111.7, 127.2, 128.6, 128.7, 129.1, 129.6, 135.5, 135.9, 136.1, 137.7, 143.4, 145.2, 164.9 ppm; **HRMS (ESI, m/z):** calcd for $C_{20}H_{22}NO_3S$ $[M+H]^+$ 356.1320, found: 356.1309.

(Z)-4-methyl-2-phenyl-N-tosylhexa-2,5-dienamide:

Following the general procedure A, **4h** was obtained as colorless oil, 20.3 mg, Yield: 57%; **1H NMR (400 MHz, $CDCl_3$):** δ 1.13 (d, J = 8.0 Hz, 3H), 2.47 (s, 3H), 3.40-3.46 (m, 1H), 4.97-5.02 (m, 2H), 5.72-5.81 (m, 1H), 5.94 (d, J = 8.0 Hz, 1H), 7.13-7.15 (m, 2H), 7.31-7.32 (m, 3H), 7.37 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 10.2 Hz, 2H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 20.2, 21.7, 37.7, 114.2, 127.2, 128.5, 128.7, 129.0, 129.6, 134.0, 135.5, 135.8, 140.9, 143.0, 145.2, 165.0 ppm; **HRMS (ESI, m/z):** calcd for $C_{20}H_{22}NO_3S$ $[M+H]^+$ 356.1320, found: 356.1324.

(Z)-3-(cyclohex-2-en-1-yl)-2-phenyl-*N*-tosylacrylamide:

Following the general procedure A, **4i** was obtained as a white solid, 17.9 mg, Yield: 47%; **¹H NMR (400 MHz, CDCl₃):** δ 1.37-1.40 (m, 1H), 1.52-1.57 (m, 2H), 1.70-1.81 (m, 2H), 1.98-1.99 (m, 2H), 2.47 (s, 3H), 3.30-3.35 (m, 2H), 5.43-5.46 (m, 1H), 5.74-5.78 (m, 1H), 5.97 (d, *J* = 11.0 Hz, 1H), 7.11- 7.13 (m, 2H), 7.30-7.32 (m, 3H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 8.2 Hz, 2H), 7.86 (brs, 1H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 20.33, 21.7, 24.7, 28.8, 35.9, 127.3, 128.0, 128.6, 128.9, 129.0, 129.6, 133.9, 135.5, 136.0, 144.6, 145.2, 165.0 ppm; **HRMS (ESI, *m/z*):** calcd for C₂₂H₂₄NO₃S [M+H]⁺ 382.1477, found: 382.1472.

(Z)-3-(cyclohex-2-en-1-yl)-2-phenyl-*N*-tosylacrylamide:

Following the general procedure A, the compound was obtained as a white solid, 7.2 mg, Yield: 36%; **¹H NMR (400 MHz, CDCl₃):** δ 2.91 (s, 3H), 3.13-3.18 (m, 2H), 5.05-5.15 (m, 2H), 5.59 (brs, 1H), 5.87-5.95 (m, 1H), 6.05 (t, *J* = 8.1Hz, 1H), 7.28-7.39 (m, 5H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 26.20, 34.0, 115.7, 126.8, 127.9, 128.6, 131.4, 136.1, 137.5, 138.8, 169.2 ppm; **HRMS (ESI, *m/z*):** calcd for C₂₂H₂₄NO₃S [M+H]⁺ 202.1154, found: 202.1149.

5.4.4 NOESY NMR analysis of **3k**

Figure 5.1 NOSEY NMR analysis of **3k** (in DMSO- d_6)

The NOE correlation from H (δ 5.56, t, J = 8.0 Hz, 1H) to H (δ 1.78, s, 3H) indicated the Z-geometry for the double bond.

List of Publications

1. *Oxidant-Free Rh(III)-Catalyzed Direct C-H Olefination of Arenes with Allyl Acetates*, Chao Feng, **Daming Feng**, Teck-Peng Loh*, *Org. Lett.* **2013**, *15*(14), 3670-3673. (First author equally contribution)
2. *Rhodium(III)-Catalyzed Olefinic C-H Alkynylation of Enamides at Room Temperature*, Chao Feng, **Daming Feng**, Teck-Peng, Loh*, *Chem. Commun.* **2014**, *50*, 9865-9868. (First author equally contribution)
3. *Rhodium(III)-Catalyzed C-H Allylation of Eletron-Deficient Alkenes with Allyl Acetates*, Chao Feng, **Daming Feng**, Teck-Peng, Loh*, *Chem. Commun.* **2015**, *51*, 342-345. (First author equally contribution)
4. *Rhodium(III)-Catalyzed Olefinic C-H Alkynylation of Acrylamides Using Tosyl-Imide as Directing Group*, Chao Feng, **Daming Feng**, Yang Luo, Teck-Peng Loh*, *Org. Lett.* **2014**, *16*(22), 5956-5959. (Second author)

Conferences:

- Daming Feng, Teck-Peng Loh*, 2nd International Syposium on C-H Activation, June 30th – July 3rd, 2014, Rennes, France, poster presentation.