NANYANG TECHNOLOGICAL UNIVERSITY

HECK REACTION OF ALKYL HALIDES AND A-SELECTIVE HECK REACTION OF STYRENES

ZOU YINJUN

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2014

Heck Reaction of Alkyl Halides and α-Selective Heck Reaction of Styrenes

ZOU YINJUN

School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological University
in partial fulfillment of the requirement for the degree of
Doctor of Philosophy

2014

Acknowledgement

I would like to thank my supervisor, Nanyang Assistant Professor Zhou Jianrong (Steve), for recruiting me into his group and giving me the opportunity to conduct my study with abundant resources. His devotion to the chemistry, mastery of the knowledge, scrutinization of experimental procedures and scientific manuscripts, and joy of discovery in new reactions always challenged me and inspired me to explore deeper and further in chemistry. I will be always grateful for the opportunity of working in his laboratory.

I would like to thank my colleagues in the past four years who have been my band of brothers and who made me laugh and cry. In particular, I must thank Dr. Huang Zhiyan and Dr. Hu Jian, from whom I learned and benefited so much as a mentor and a friend. Their enthusiasm to chemistry, diligence to experiment, in-depth knowledge, and patience affected me greatly. I thank Dr. Yang Junfeng, with whom I went through the whole program of choppy waves. I thank Dr. Yang Junfeng, Dr. Yang Peng, Mr. Wu Chunlin, and Mr. Wu Xiaojin for proofreading my thesis. Many thanks to the technical support staffs in CBC, Dr. Li Yongxin, Ms. Goh Ee Ling and Ms. Zhu Wen Wei.

I would like to thank the fellows in RHC for their constant tenderness, aspiration and encouragement. I thank my old and new friends who shared numerous memorable and cherishable moments in these years.

I am forever indebted to my parents who raise me up with their all-out efforts, who teach me how to walk steady and stand firm, who support me without any delay, and who love me with all their hearts and minds.

Thanks be to God!

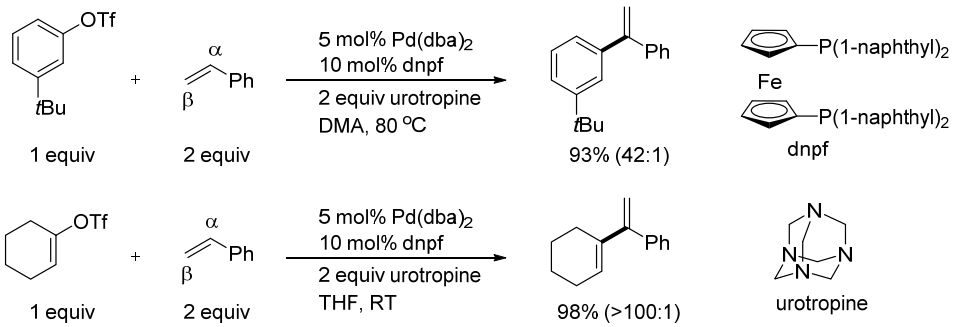
Table of Contents

Abstract

My graduate study has been focused on the development of transition metal-catalyzed reactions, especially Pd-catalyzed coupling reactions. In this thesis, we described two catalytic systems that solved challenging problems in the intermolecular Heck reaction.

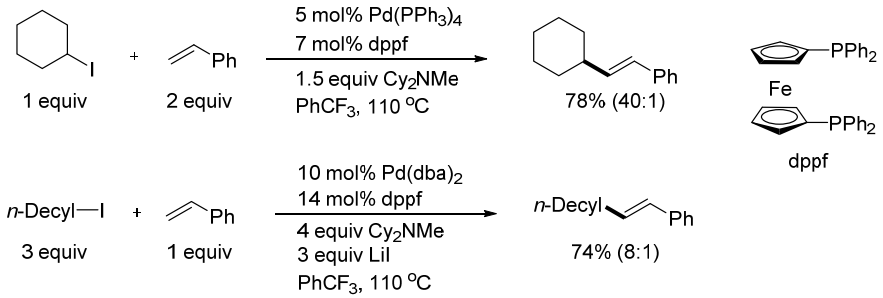
In the first part, we disclosed a new catalyst – Pd/dnpf can efficiently catalyze the Heck reaction of aryl and vinyl triflates with aromatic olefins. For example, *m-tert*-butylphenyl triflate furnished the internal insertion product in 93% yield with 42:1 α/β regioselectivity. Cyclohexyl triflate furnished the desire product in 98% yield with almost exclusively internal insertion selectivity. In most cases, the aryl or vinyl groups insert selectively at α position in >95% purity and the minor isomers can be removed after purification by flash chromatography.

We conducted both experimental and computational study to probe the origin of high internal selectivity. The study revealed that the generality and selectivity is attributed to the combination of electronic and steric effects derived from our new ligand – dnpf. The resulting rigid and congested coordination sphere sterically disfavors the terminal insertion. The initial results of aryl bromides unfolded the potential of the newly-developed ligand for more reactions.



In the second part, we disclosed an efficient catalyst – Pd/dppf for the intermolecular Heck reaction of alkyl halides, which is a challenging problem in palladium catalysis. The simple and easily accessible Pd/dppf catalyst showed good reactivity as well as good selectivity. For example, the coupling reaction of cyclohexyl iodide with styrene furnished the *trans*-Heck product in 78% yield with 40:1 selectivity. *n*-Decyl iodide furnished the coupling product in 74% yield with 8:1 isomeric ratio.

The use of dppf as supporting ligand was crucial for our success in this reaction as other ligands failed to afford the product in a satisfactory yield. It can be applied to a broad spectrum of electrophiles including alkyl iodides, bromides and chlorides. Both primary and secondary alkyl halides bearing functional groups such as esters, amides and nitriles were tolerated in the catalytic system. Concerning the scope of olefins, vinylarenes of steric and electronic perturbations coupled well. We conducted mechanistic study to probe the reaction mechanism and the experimental data suggested that the reaction was initiated by a single electron transfer from Pd^0-complex to alkyl halides.



List of Abbreviations

δ	chemical shift (ppm)
°C	degree centigrade
Ac	acetyl
AIBN	azobisisobutylonitrile
Ar	aryl (substituted aromatic ring)
(*R*)-BINAP	(*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
*n*Bu	*n*-butyl
$n\text{Bu}_2\text{O}$	dibutyl ether
*t*Bu	*t*-butyl
cod	1,5-cyclooctadiene
conv.	conversion
Cy_2NMe	*N,N*-dicyclohexylmethylamine
DABCO	1,4-diazabicyclo[2.2.2]octane
Dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DMA	*N,N*-dimethylacetamide
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dippf	1,1′-bis(diisopropylphosphino)ferrocene
dnpf	1,1′-bis[di(1-naphthyl)phosphino]ferrocene

dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1-bis(diphenylphosphino)ferrocene
dppbz	1,2-bis(diphenylphosphino)benzene
EA	ethyl acetate
ESR	electron spin resonance
ee	enantiomeric excess
eq	equation
equiv	equivalent
GC	gas chromatography
h	hour
Hz	hertz
*i*Pr	isopropyl
*i*Pr$_2$NMe	*N,N*-diisopropylethylamine
J	coupling constant
2,6-lutidine	2,6-dimethylpyridine
2-MeTHF	2-methyltetrahydrofuran
mg	milligram
MHz	megahertz
mL	millilitre
mmol	millimole
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
OTf	trifluoromethane sulfonate
Ph	phenyl

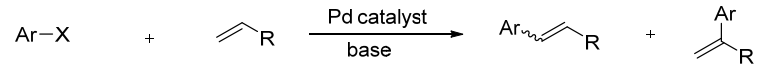
PhH	benzene
$PhCF_3$	α,α,α-trifluorotoluene
Piv	pivalic
PMDETA	*N,N,N′,N″,N″*-pentamethyldiethylenetriamine
proton sponge	1,8-bis(dimethylamino)naphthalene
refl.	reflux
RT	room temperature
TBME	*tert*-butyl methyl ether
temp.	temperature
THF	tetrahydrofuran
THP	tetrahydropyran
TMEDA	tetramethylethylenediamine
Tol.	toluene
Triglyme	triethylene glycol dimethyl ether
Ts	*p*-toluenesulfonyl
urotropine	1,3,5,7-tetraazatricyclo[3.3.1.$1^{3,7}$]decane
veratrol	1,2-dimethoxybenzene

Chapter 1 Selective Arylation and Vinylation at the α Position of Vinylarenes

1.1 Introduction

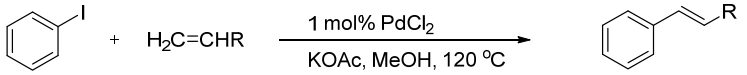
1.1.1 General introduction of Heck reaction

The Mizoroki-Heck reaction, or more often the Heck reaction, refers to Pd-catalyzed arylation and vinylation of olefins with aryl or vinyl halides and sulfonates (eq 1.1). In the early 1970s, Mizoroki *et al.* reported the coupling reactions of iodobenzene with olefins and *trans*-products were obtained in good yields (eq 1.2).[1] Almost at the same time, Heck *et al.* reported the coupling reaction of aryl halides including aryl iodides, benzyl chloride and alkenyl bromide (eq 1.3).[2] Since then, numerous precatalysts and supporting ligands such as phosphines and *N*-heterocyclic carbenes have been developed and indeed successfully applied for the synthesis of useful compounds.



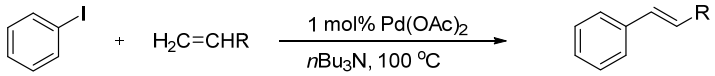
(1.1)

X = halides, OTf, OTs



(1.2)

R = H, 72%
R = Me, 73%
R = Ph, 90%
R = COOMe, 97%



(1.3)

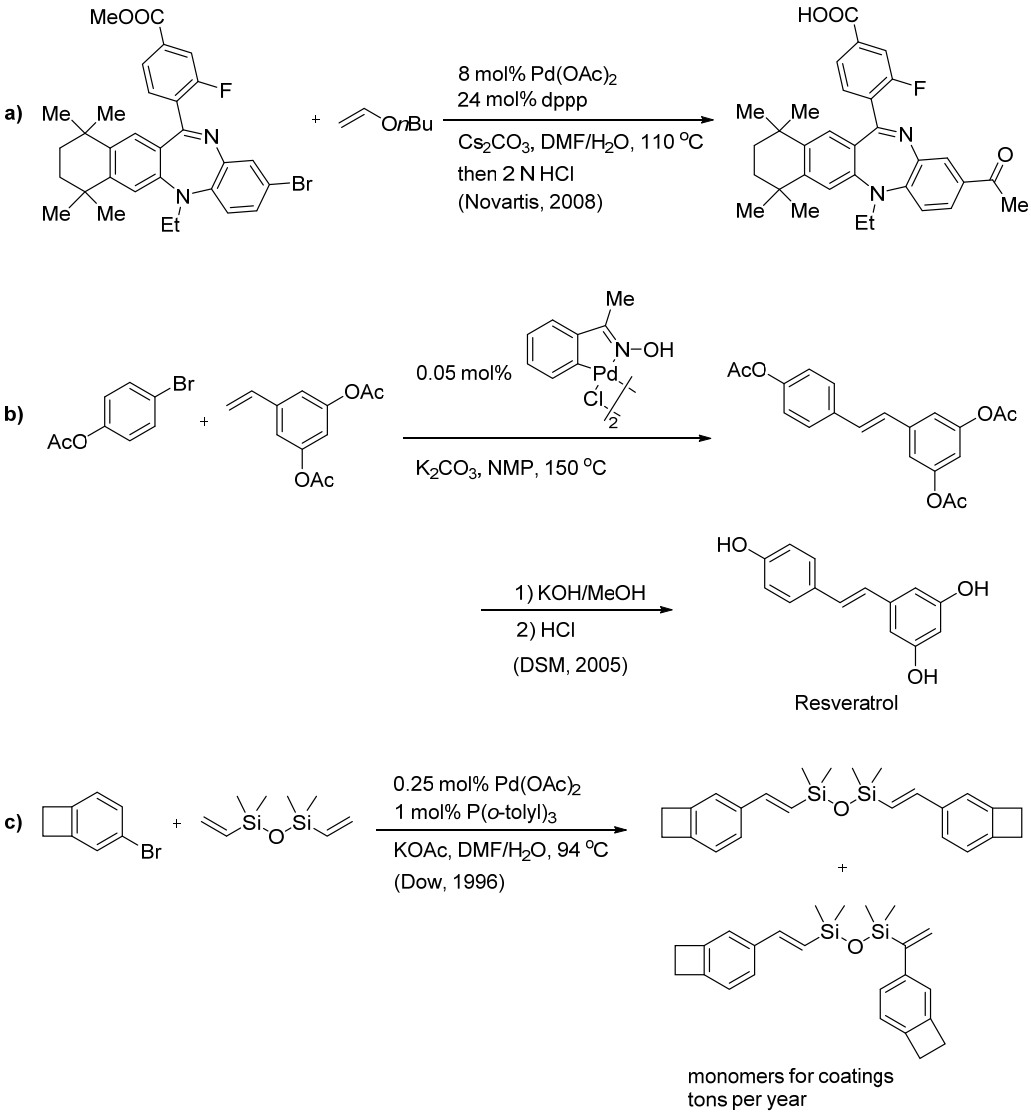
R = Ph, 75%
R = *p*-NO_2Ph, 85%
R = COOMe, 81%

Generally, for aryl iodides and activated aryl bromides, the Heck reaction proceeds very efficiently even without phosphine ligands and many ligandless processes have been applied in industry. Unactivated aryl chlorides and bromides usually require electron rich and steric bulky phosphines such as

$P(tBu)_3$ as ligand. For aryl triflates or aryl halides with scavengers, bidentate bisphosphines are commonly served as chelating ligands. Other reaction parameters such as substrate structure, nature of the base and solvent are all important for the success of the transformation. There is no such common catalytic system for the Heck reaction and reaction conditions differ from each other. Researchers are continuously dedicating great effort to invent more active and selective catalysts.[3]

Today, Heck reaction has become an important tool for construction of carbon-carbon bonds. Large scale processes have been developed in industry for the preparation of active pharmaceutical ingredients, agrochemicals and advanced materials.[3a,4] For instance, Novartis developed an efficient one-pot synthesis using Heck reaction as a key step to prepare diazepinylbenzoic acid, which is a retinoid X receptor antagonist for the treatment of diabetes and other metabolic diseases (Scheme 1.1, **a**).[5] Resveratrol is an antioxidant commonly found in grapes, *polygonum cuspidatum* and red wine, which is beneficial to human health in a number of ways such as cardiovarscular protective effects and lifespan extension.[6] DSM applies the Heck reaction as a key step for the total synthesis of resveratrol which is commercialized as *resVida*® in the market (Scheme 1.1, **b**).[7] The key monomers for the production of Dow's CYCLOTENE™ advanced electronics resins are also produced based on Heck reaction (Scheme 1.1, **c**). These resins have been applied in commercial electronic devices such as printed circuit boards, multilayer interconnects and high-aperture active-matrix liquid crystal displays.[4g,8] For the significance of Heck reaction in organic synthesis, Professor Richard Heck shared the Nobel Prize in Chemistry 2010, along with Professors Ei-ichi Negishi and Akira

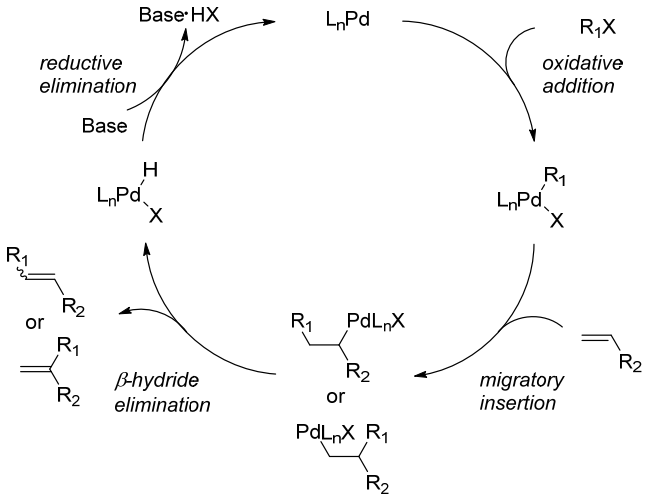
Suzuki.[9]



Scheme 1.1. Applications of Heck reaction in synthesis.

As well as numerous new catalysts being developed for the Heck reaction in the past decades, extensive experimental and computational studies have been performed to illustrate the catalytic cycle.[10] The commonly accepted mechanism is through the Pd^0/Pd^{II} cycle consisting of four elemental steps as depicted in Scheme 1.2. Oxidative addition of the active L_nPd^0 species into the C-X bond initiates the catalytic cycle. It is followed by *syn* migratory insertion of the L_nPd^{II} species into an alkene after coordination. Then the newly generated alkylpalladium species undergoes *syn* β-hydride elimination to afford

the alkene product. After that, base-assisted reductive elimination of $L_nPd^{II}(H)X$ occurs to regenerate the active L_nPd^0 which enters into a new catalytic cycle. Throughout the cycle, palladium is bound with its ligands and the catalytic reactivity is profoundly influenced by the steric and electronic properties of binding ligands. It is frequently assumed that oxidative addition is the rate-determining step, although it has been challenged.[3b,4e] New studies on the mechanism are undergoing to guide the design and optimization of reaction conditions. [4e]

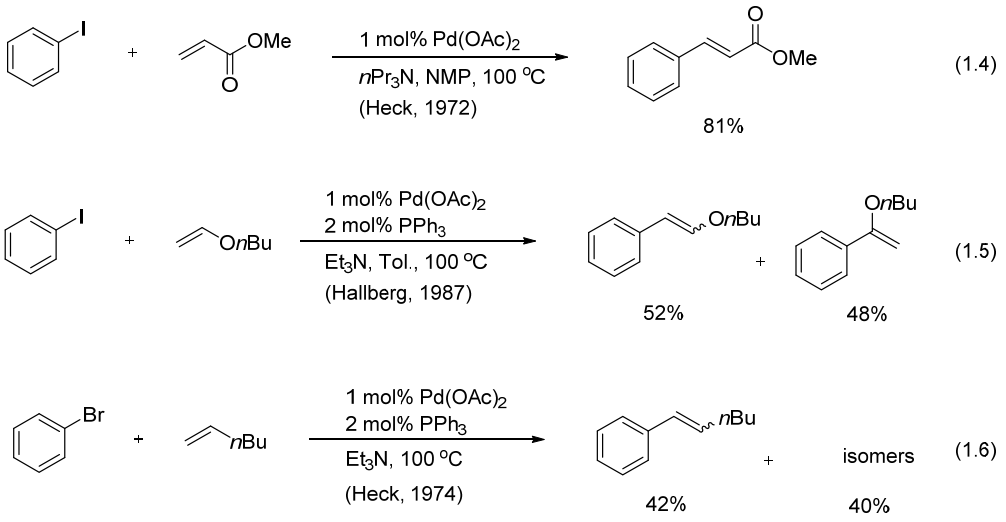


Scheme 1.2. Generally accepted catalytic cycle of Heck reaction.

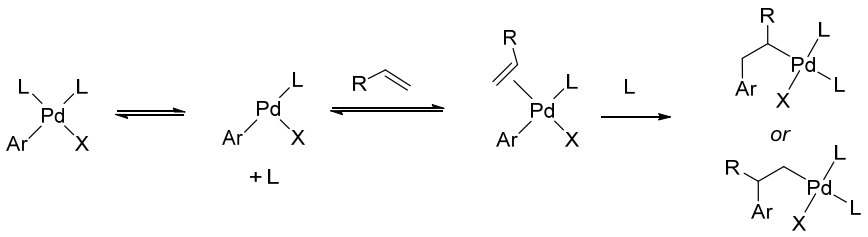
1.1.2 Regioselective Heck reaction of common olefins involving neutral pathway

In intermolecular Heck reactions, a key issue is to control the regioselectivity at which vinylic site was added aryl groups. For olefins bearing significant electronic difference between two vinylic sites, such as acrylates and *N*-vinylphthalimide, high regioselectivity can readily be obtained by manipulating catalysts and reaction conditions.[4a,11] In the very early study by Heck, the coupling of iodobenzene with methyl acrylate afforded the terminal insertion product – *trans*-methyl cinnamate exclusively (eq 1.4).[2] When the

olefins are less electronic biased, the regioselectivity decreased dramatically. For example, Hallberg *et al.* reported the coupling of iodobenzene with *n*-butyl vinyl ether which gave 1:1 β/α selectivity in the immediate Heck products (eq 1.5). They improved the β/α selectivity to 10:1 by using 1-chloro-4-nitrobenzene as the arylating agent which is of lower electron density.[12] The reaction of bromobenzene with *n*-hexene also furnished a mixture of Heck products (eq 1.6). The ratio of terminal insertion products versus other isomers was almost 1:1.[13]

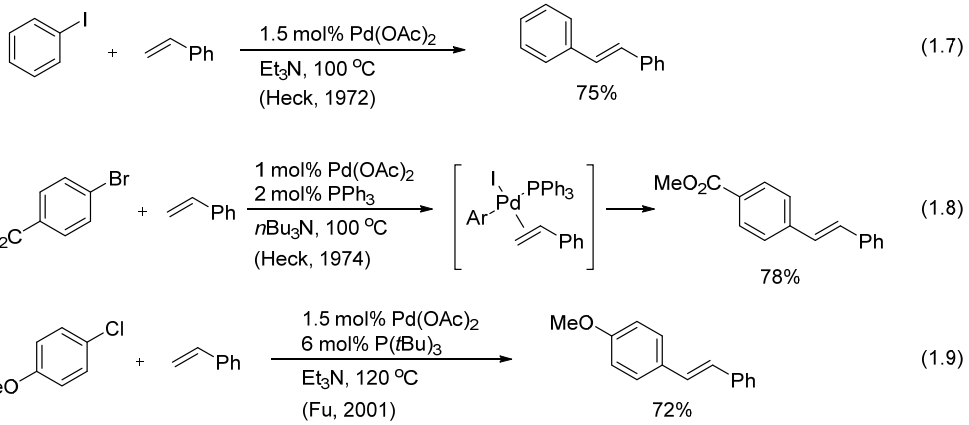


It is understood that these reactions proceeded through a neutral pathway. A weak Pd-P bond or Pd-solvent bond in the oxidative addition complex dissociates to provide a vacant coordination site for the olefin to undergo migratory insertion (Scheme 1.3). The organo group generally added to the less hindered site of the olefin. If the electronic effect dominates over the steric effect, the organic group would add to the more electronic deficient site. Thus, good terminal selectivity was achieved based on the steric and electronic property of the olefin substrates, as well as the properties of ligands and halide additives.[4a,12-14]



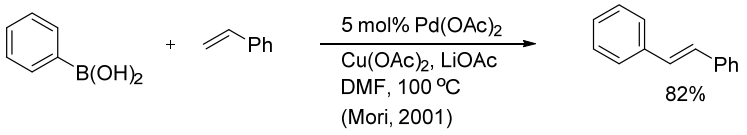
Scheme 1.3. A neutral pathway for olefin insertion.

In Heck reaction of aryl halides with styrene, terminal insertion products are usually observed. In 1972, Heck *et al.* first reported the coupling reaction of iodobenzene with styrene that led to the exclusively formation of (*E*)-stibene (eq 1.7).[2] Later, Heck *et al.* reported the coupling reaction of methyl 4-bromobenzoate with styrene with the aid of PPh_3 as supporting ligand and terminal insertion product was obtained in good yield (eq 1.8).[13] By applying a more bulky and electron-rich ligand P(*t*Bu)$_3$, Fu *et al.* reported that the coupling reaction of aryl chloride to afford the (*E*)-stibenes (eq 1.9).[11b] These reactions proceeded through the neutral pathway that involves Pd complexes of styrene with a phosphine ligand or an anionic ligand before insertion (eq 1.8). The transition state for styrene insertion is believed to be relatively late, which could lead to more stable Pd-benzyl complexes favouring terminal selectivity.

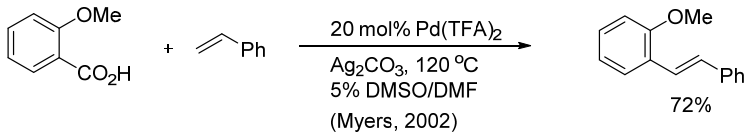


In many Heck variant conditions such as oxidative, decarbonylative and decarboxylative conditions, terminal selectivity was also ubiquitously

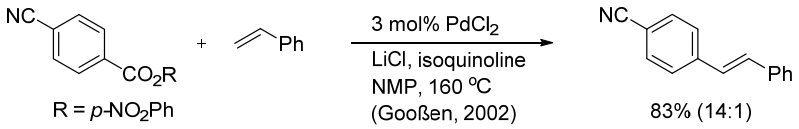
observed.[15] For example, Mori *et al.* reported the coupling reaction of organoboron compounds and olefins through a Pd^{II}-mediated pathway promoted by $Cu(OAc)_2$ as an oxidant (eq 1.10).[15d] Myers *et al.* developed the Pd-catalyzed decarboxylative coupling reaction of aryl carboxylic acids with olefins that required Ag_2CO_3 as an oxidant (eq 1.11).[16] Gooßen *et al.* reported the decarbonylative olefination reaction of aryl esters that led to the formation of terminal insertion products (eq 1.12).[17] In these reactions, an anionic ligand such as halide or acetate would occupy the position of the phosphine in the key styrene-complex intermediate as in eq 1.8. The same reason based on the late transition state can be applied to explain the observed β selectivity in the ionic pathway.



(1.10)



(1.11)

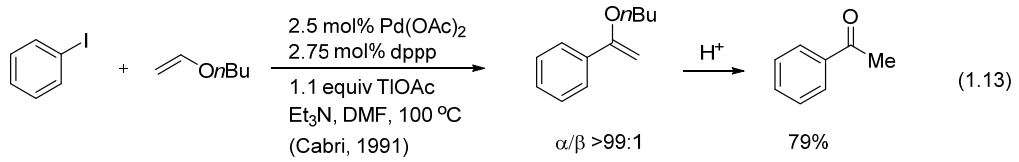


(1.12)

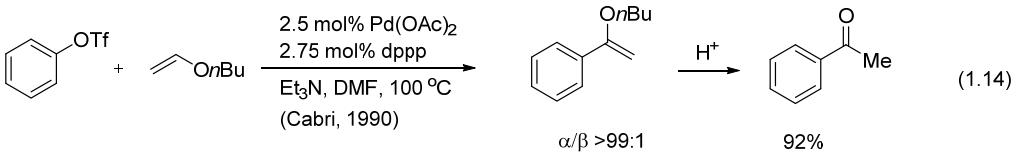
1.1.3 Regioselective Heck reaction of common olefins involving cationic pathway

In early 1990s, Cabri *et al.* made a significant advance in promoting internal selectivity by careful evaluation of ligands and leaving groups of the aryl substrates.[11a] By addition of silver or thallium salts as halide scavengers or replacement of halides with triflates as nucleophiles, excellent internal selectivity was obtained for different types of olefins.[18] For example, when 1.1

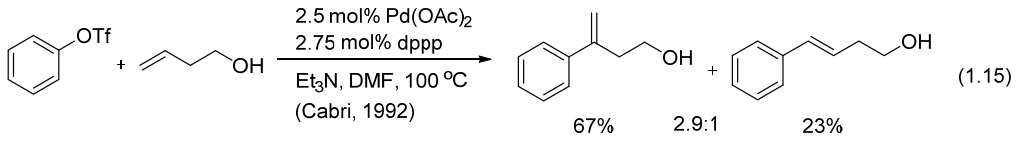
equiv of TlOAc was added into the reaction of iodobenzene with *n*-butyl vinyl ether, the α insertion product was obtained almost exclusively with trace amount of β insertion product (eq 1.13).[19] When phenyltriflate was used in the place of iodobenzene, the Heck reaction proceeded well with excellent yield and α/β selectivity as >99:1 (eq 1.14).[11c,18a] However, the internal selectivity dropped drastically if the olefin was not electronically biased. For instance, homoallylic alcohol of which the inductive effect diminished over the bonds only furnished the isomers in 2.6:1 α/β selectivity (eq 1.15).[18b] Methyl acrylate and acrylonitrile that intrinsically favor *β*-selecitivity gave the usual terminal insertion products (eq 1.16).



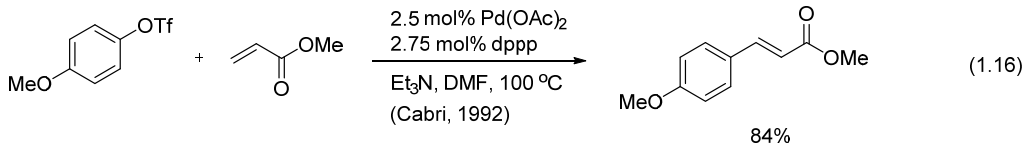
(1.13)



(1.14)



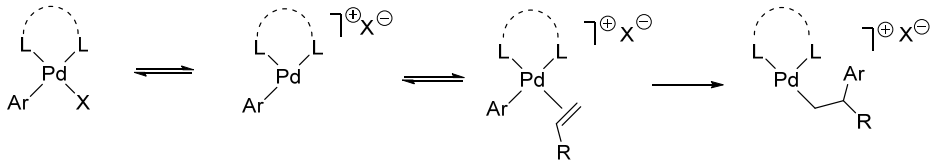
(1.15)



(1.16)

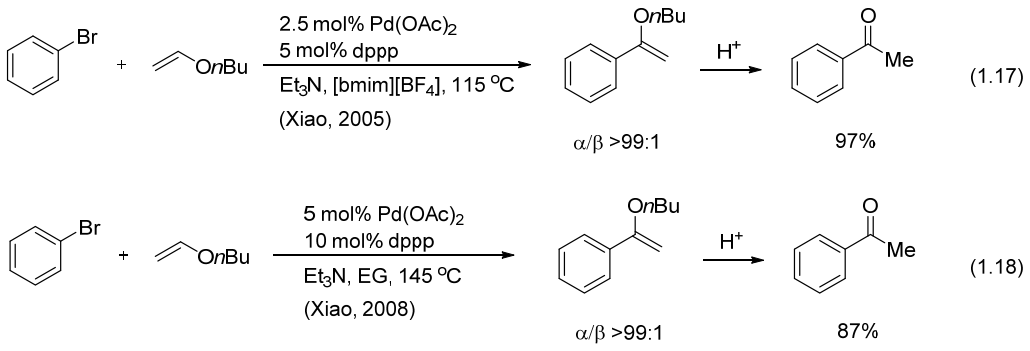
It is explained that these reactions proceeded through a cationic pathway (Scheme 1.4). In the cationic pathway, rather than one coordinating ligand in the neutral pathway, the halide dissociates from the oxidative addition complex to generate a cationic Pd complex. The olefin then coordinates to the

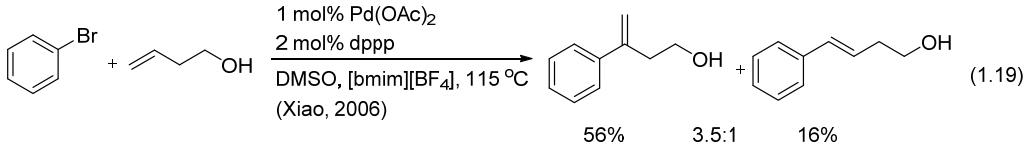
unoccupied vacant d-orbital to undergo migratory insertion. The increased polarization in the cationic Pd complex governs the aryl nucleophile to add onto the carbon with lower charge density.[11a,18b,20]



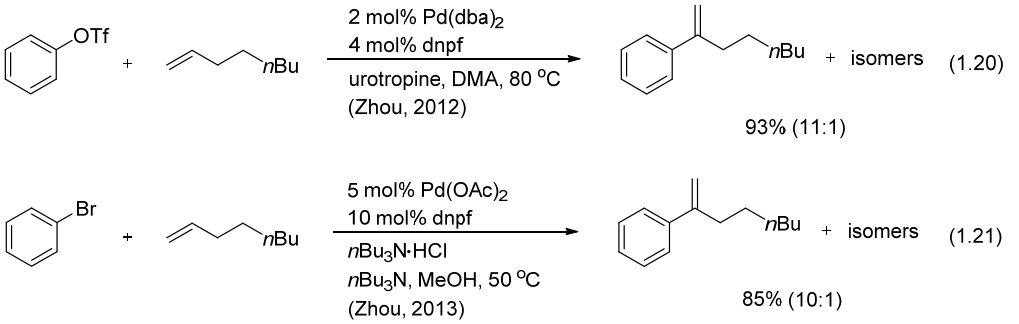
Scheme 1.4. A cationic pathway for olefin insertion.

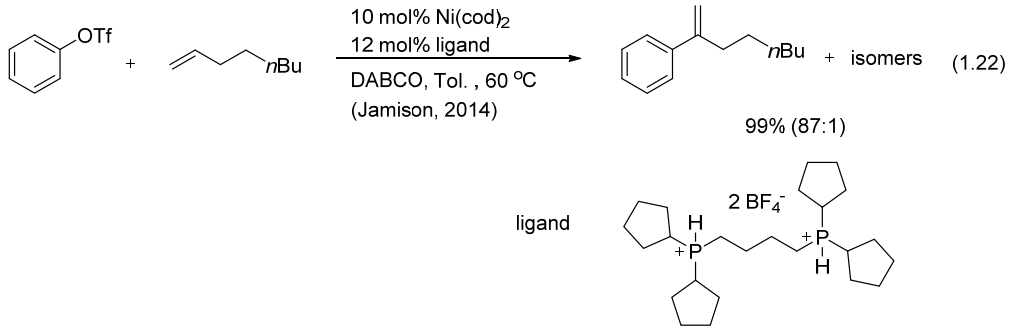
Following Cabri's work on promoting the internal selectivity via cationic pathway, Xiao *et al.* developed the Heck reaction of aryl halides in ionic liquids that accomplished highly regioselective internal arylation.[11e,21] For example, the Heck reaction of bromobenzene with *n*-butyl vinyl ether furnished almost exclusively the α insertion product (eq 1.17).[22] The strong electrostatic interaction resulting from the ionic liquid could facilitate the dissociation of halides from the oxidative addition complexes without additional halide scavengers. Hydrogen bonding with the halide anions may also contribute to enhance the formation of cationic Pd intermediate. Indeed, they successfully achieved high internal selectivity in protic solvents, of which ethylene glycol proved to be the best (eq 1.18).[23] However, the α/β selectivity dropped to 3.5:1 when homoallylic alcohol was used which lacks electronic bias (eq 1.19).[24]



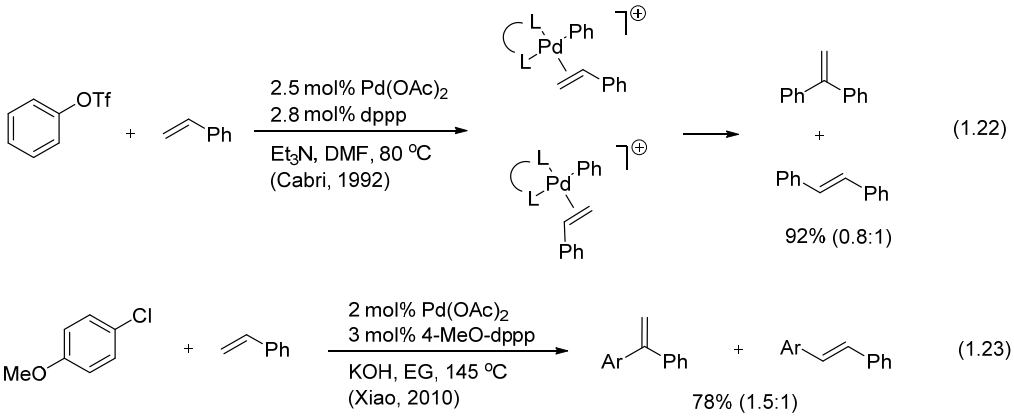


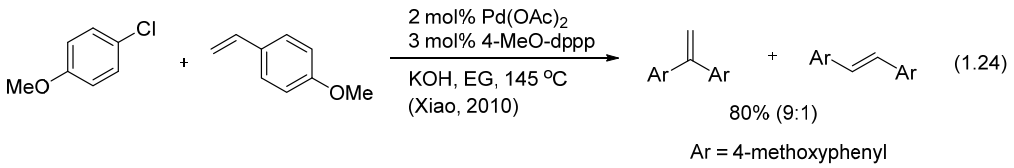
Along with this work, our group reported the intermolecular Heck reaction between aryl triflates and aliphatic olefins with high internal selectivity (eq 1.20).[25] By employing a series of ferrocene-based bisphophines, namely dippf, dppf and dnpf, terminal olefins with or without electronic bias coupled with aryl trifaltes in good yields and isomeric selectivity. The rigid backbone conformation of the ligand would direct the olefin inserted preferentially at α position in migratory insertion step and eventually led to high regioselectivity. Later, by promoting the hydrogen bonding to assist the formation of cationic Pd intermediate, our group developed the Heck reaction of aryl halides with olefin favoring internal selectivity in the presence of nBu$_3$N·HCl as activator and MeOH as solvent (eq 1.21).[26] Very recently, Jamison *et al.* reported the Ni-catalyzed Heck reaction of electronically unbiased olefins that afforded high α/β selectivity (eq 1.22). In the presence of triethylsilyl trifluoromethanesulfonate, aryl chlorides, mesylates, tosylates, and sulfamates were compatible to give the products with high internal selectivity.[27]





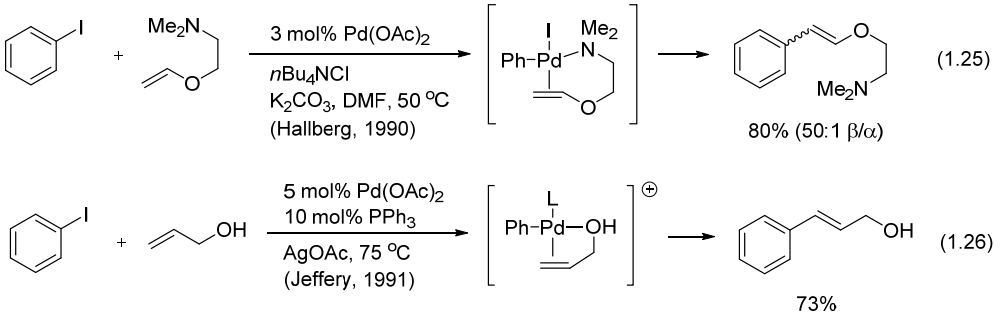
Reversal of β selectivity in insertion of styrene and other aryl olefins proved to be very difficult.[28] For example, Cabri *et al.* reported that in reactions of aryl triflates and styrene, cationic (dppp)Pd(aryl)(styrene) complexes were responsible for olefin insertion. Due to the relatively early insertion transition state of this cationic complex, the α-insertion transition state will have significant partial positive charge established at the benzylic position, which is resonance-stabilized. Indeed, some α-insertion product was obtained in the reaction, but the α/β selectivity was only of 0.8:1 (eq 1.22).[18b] We speculated that the electronic effect alone was insufficient to bias the insertion predominantly at the α position in the cationic pathway. Xiao *et al.* also reported the reaction of 4-chloroanisole with styrene in the protic solvent, which gave a similar α/β selectivity of 1.5:1 (eq 1.23).[29] When the olefin was changed from styrene to 4-methoxystyrene, the α/β selectivity could be improved to 9:1, which was the best of this type (eq 1.24).





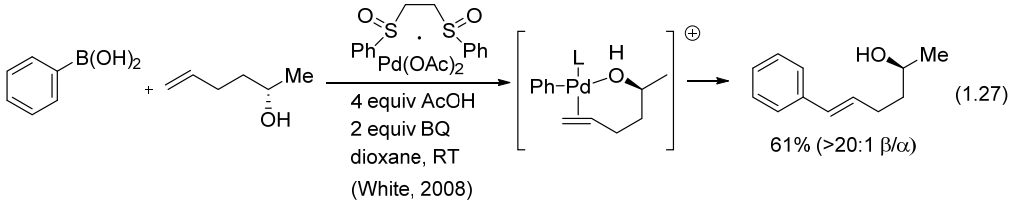
1.1.4 Regioselective Heck reaction of olefins containing directing groups

Besides the above methods to control the regioselectivity in olefin insertion step, modifying the olefin structures to induce chelating effect with the catalyst is another practical strategy. For example, the β/α selectivity was only 1:1 in the reaction of iodobenzene and *n*-butyl vinyl ether as shown in eq 1.5 previously.[12] After *β*-amino substituent was introduced, of which the N atom can coordinate to Pd-center in the organopalladium intermediates, the β/α selectivity increased sharply to 50:1 (eq 1.25).[30] In the case of allylic alcohols, the OH group could coordinate with Pd cation to obtain the terminal insertion product exclusively (eq 1.26).[31] Other heteroatom-containing functional groups such as phosphino and 2-pyridyl can serve as directing groups to enhance the regioselectivity.[32]

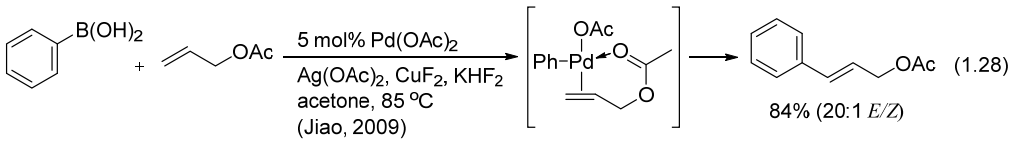


In the oxidative Heck variants, White *et al.* reported Pd/sulfoxide-catalyzed coupling reaction that favored the terminal insertion product (eq 1.27).[33] The chelation effect between cationic Pd^{II} complex and functional groups that could form 5- and 6-membered rings gave excellent selectivity. Allylic carbonyl, homoallylic carbonyl, bishomoallylic carbonyl, alcohol, thiol, and amino acid-

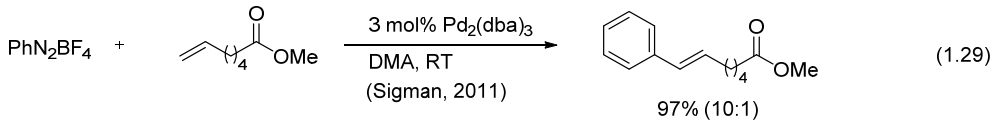
derived carbonyl groups could serve as active chelation counterparts. However, the selectivity decreased when chelation required more than 7-membered rings.

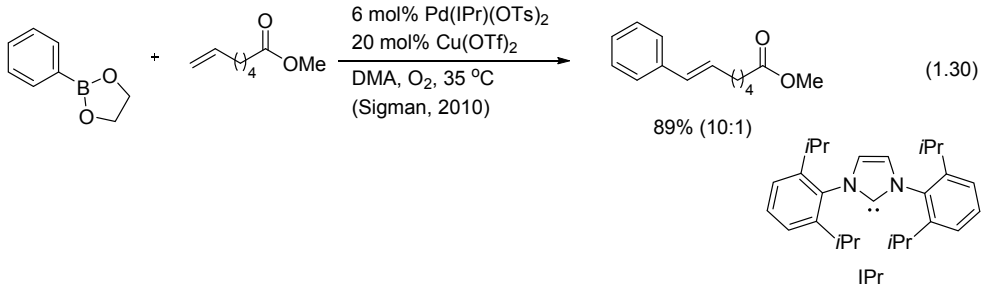


Jiao *et al.* reported the ligand-free oxidative Heck reaction of arylboronic acid with allylic acetate (eq 1.28).[15i,34] The chelation between the Pd^{II} and O atom of the carbonyl group would direct the terminal insertion. The steric hindrance of the resulting intermediate favored the formation of *trans*-products. Substituents such as formyl, nitrile and halogen groups on the arylboronic acids were well tolerated. Alkenylboronic ester could couple with allylic acetate.



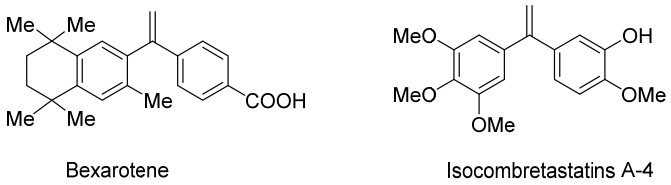
More recently, Sigman *et al.* made an advance in promoting terminal insertion products in intermolecular Heck reaction of electronically non-biased olefins (eq 1.29).[35] By using aryldiazonium tetrafluoroborates as electrophiles, which could undergo facile oxidative addition to Pd^0-complex and the resulting Pd^{II}-complex would undergo selectively *β*-hydride elimination to afford the styryl Heck products. They also reported the oxidative Heck reaction of arylboronic esters with non-biased olefins that afforded preferentially terminal insertion products (eq 1.30).[36] In these transformations, carbonyl groups may serve as directing groups to afford the terminal insertion products.





1.1.5 Applications of 1,1-diarylethylenes in synthesis

The corresponding Heck products – 1,1-diarylethylenes are common core structures in medicinal chemistry, for example anticancer agents bexarotene and isocombretastatins A (Scheme 1.5). Bexarotene is a selective agonist for retinoid X receptors and it has been used for the treatment of T-cell lymphoma, lung cancer, breast cancer, and Kaposi's sarcoma.[37] Recent studies also revealed its potency to ameliorate memory deficits of Alzheimer's disease.[38] Combretastatins A are natural products of (*Z*)-1,2-diarylethene structures that can effectively inhibit tubulin polymerization. Structural isomers Isocombretastatins A exhibited similar or higher potency.[39] The 1,1-diarylethylenes are also key intermediates in synthesis of bioactive natural products[40] and other potential therapeutics.[11e,41] Some of these compounds were prepared by cross-coupling using α-halogenated or α-metalated vinylarenes. Our Heck reaction can serve as an alternative way to access these compounds.

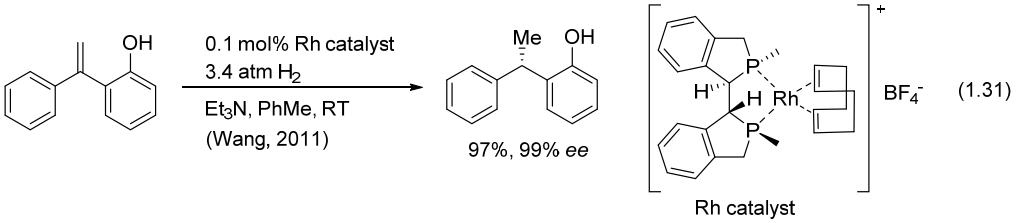


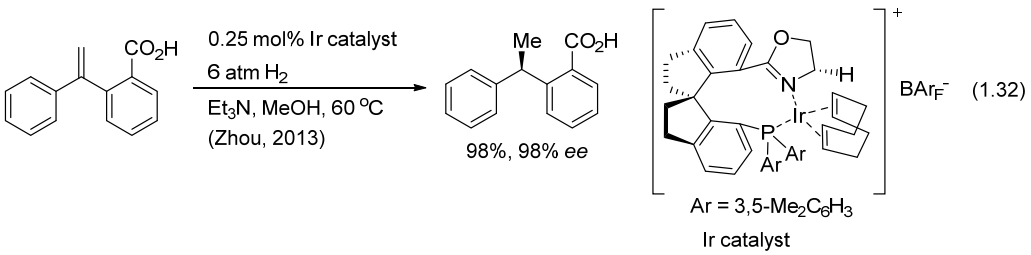
Bexarotene Isocombretastatins A-4

Scheme 1.5. Anticancer agents containing 1,1-diarylethylene motif.

Furthermore, the 1,1-diarylethene can be used to prepare chiral compounds via readily available asymmetric catalysis such as hydrogenation reaction.[42] For

example, Wang *et al.* reported the Rh-catalyzed asymmetric hydrogenation of 1,1-diarylethene to access the chiral 1,1-diarylmethine in excellent enantioselectivity (eq 1.31).[42d] Zhou *et al.* reported the Ir-catalyzed asymmetric hydrogenation of 1,1-diarylethene containing carboxylic acid as directing group. The carboxyl group can be removed by decarboxylation without any deterioration of *ee* (eq 1.32).[42b]





In this project, we aimed to realize the intermolecular Heck reaction of aromatic olefins with high internal selectivity, which is very challenging. The new method would provide an efficient way for the preparation of 1,1-diarylethenes.

1.2 Results and discussion

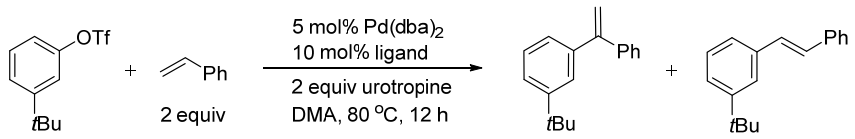
By carefully surveying Cabri's work on Heck reaction of aryl triflates and olefins,[18b] we speculated that dppp could play a crucial role as supporting ligand to obtain the α-selective products. In some cases, the α selectivity was even better when dppf was used as supporting ligand. We envisioned that in the cationic pathway, the cone angle and steric effect derived from the supporting ligand could discriminate the α- and β-position carbon in the transition state and thus determine the regioselectivity. If a supporting ligand could form a rigid and crowded environment in the coordination sphere that sterically disfavors β insertion, high α selectivity could be achieved. Herein, we are happy to present the solution that could afford high α selectivity in intermolecular Heck reaction of styrenes.

1.2.1 Condition optimizations of the model reaction

Bearing the idea in mind, we synthesized several bisphophines of ferrocene core structure with different aryl groups on the phosphorus atoms. We chose the model reaction of *m*-*t*-butylphenyl triflate and styrene to search for suitable bisphosphines, commercially available or home-made, that could induce a high level of α selectivity. From the result as summarized in Table 1.1, a new ferrocene bisphosphine carrying 1-naphthyl groups, 1,1'-bis[di(1-naphthyl)phosphino]ferrocene (dnpf), proved to be exceptionally active and selective. The Heck product was obtained almost quantitatively, 96% yield, after 12 h at 80 ^{o}C (entry 10). The ratio of the desired 1,1-diarylethene to (*E*)-1,2-diarylethene was determined to be 36:1. (*Z*)-1,2-Diarylethene was not detected by GC. In comparison, most bisphosphines including dppe, dppb,

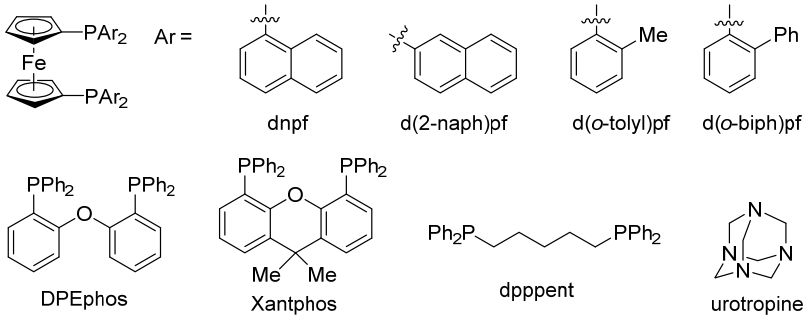
dpppent, dppbz, (*R*)-BINAP, DPEphos, Xantphos, d(2-naph)pf and dippf gave low yield of the desired Heck product. Although a moderate yield of 57% was obtained when dppf was used as ligand, the selectivity was 7:1. Other bisphosphines such as dppp, d(*o*-tolyl)pf and d(*o*-biph)pf provided much lower α selectivity.

Table 1.1. Influence of chelating ligands on the model Heck reaction.



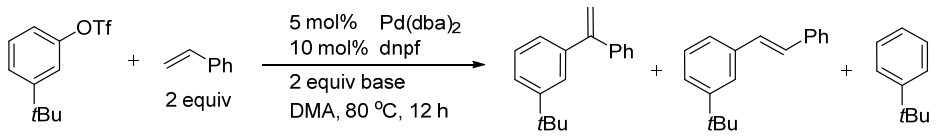
Entry	Ligand	Conv. (%)[a]	Yield (%)[a]	Selectivity[b]
1	dppe	19	3	1:4
2	dppp	97	34	1:1
3	dppb	23	5	2:1
4	dpppent	35	5	1:4
5	dppbz	10	2	1:4
6	(*R*)-BINAP	48	3	1:4
7	DPEphos	70	4	1:6
8	Xantphos	6	1	1:1
9	dppf	100	57	7:1
10	dnpf	100	96	36:1
11	d(2-naph)pf	21	25	5:1
12	d(*o*-tolyl)pf	89	53	6:1
13	d(*o*-biph)pf	100	56	2:1
14	dippf	23	1	1:3

[a] Reaction condition: *m*-*t*BuPhOTf (0.10 mmol), styrene (0.20 mmol), $Pd(dba)_2$ (0.005 mmol), ligand (0.010 mmol), urotropine (0.20 mmol), DMA (0.20 mL). Conversion and yield were determined by GC versus a calibrated internal standard. [b] Selectivity was determined by GC. ^{1}H NMR spectroscopy was unsuitable for the determination of selectivity due to low signal intensity of the minor isomer.



The choice of base was also important. From the result of base study as summarized in Table 1.2, a significant amount of the reduction byproduct, *t*-butylbenzene was detected when common trialkylamines were used. For example, in the reaction of Et_3N was used, the reduction byproduct rose to 18% (entry 6).[43] Other amines of rigid structures, such as urotropine, 2,6-lutidine and proton sponge did not give any reduction byproduct (entries 1-3). In the case of urotropine, its nitrogens are located at bridgeheads of the tricyclic structures. The α-hydrogens are not in the right geometry to eliminate and to donate hydrides to Pd according to Bredt's rule. In the case 2,6-lutidine, no α-hydrogen atoms are available to donate the Pd center a hydride. For proton sponge, its sterically congested nitrogens cannot bind to the Pd center and cannot donate a hydride. However, DABCO almost inhibited the reaction (entry 8). Furthermore, some weak inorganic bases worked very well for the transformation and can replace urotropine. Alkali carbomates such as Li_2CO_3 and Na_2CO_3 gave quantitative yields with good α selectivity (entries 9-11). But alkali acetates were not effective for this transformation at all (entries 12-14).

Table 1.2. Influence of bases on the model Heck reaction.

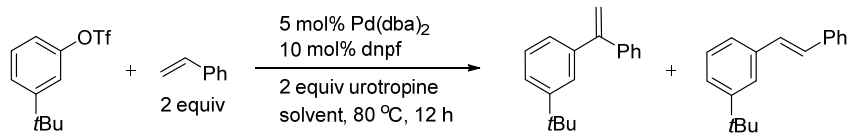


Entry	Base	Conv. (%)[a]	Yield (%)[a]	Selectivity[b]	*t*BuPh (%)[a]
1	urotropine	100	96	36:1	0
2	2,6-lutidine	100	86	43:1	0
3	proton sponge	100	88	33:1	0
4	iPr$_2$NMe	100	74	26:1	7
5	Cy$_2$NMe	100	76	23:1	6
6	Et$_3$N	100	56	21:1	18
7	nBu$_3$N	100	65	30:1	7
8	DABCO	2	0	NA	2
9	Li_2CO_3	100	94	34:1	0
10	Na_2CO_3	100	97	42:1	0
11	K_2CO_3	100	89	43:1	0
12	LiOAc	4	0	NA	4
13	NaOAc	4	0	NA	4
14	KOAc	4	0	NA	4

[a] Reaction condition: *m*-*t*BuPhOTf (0.10 mmol), styrene (0.20 mmol), Pd(dba)$_2$ (0.005 mmol), dnpf (0.010 mmol), base (0.20 mmol), DMA (0.20 mL). Conversion and yield were determined by GC versus a calibrated internal standard. [b] Selectivity was determined by GC. ^{1}H NMR spectroscopy was unsuitable for the determination of selectivity due to low signal intensity of the minor isomer.

Judged from the solvent screening result as summarized in Table 1.3, the model reaction worked very well in many ethereal solvents (THF, dioxane, DME and Triglyme) and amide solvents (DMA, DMF and NMP). In general, >90% yield and >20:1 selectivity were obtained. For example, in DMA and THF (entries 1 and 5), the selectivity was 36:1 and 42:1, respectively. In toluene and 1,2-dichloroethane (entries 9 and 10), the model reaction was much slower.

Table 1.3. Effect of solvents on the model Heck reaction.

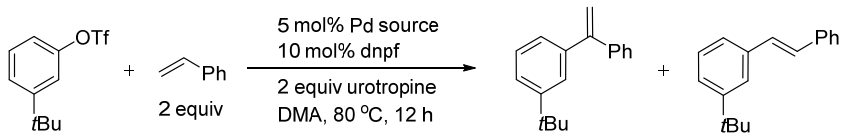


Entry	Solvent	Conv. (%)[a]	Yield (%)[a]	Selectivity[b]
1	DMA	100	96	36:1
2	DMF	100	97	24:1
3	NMP	100	93	25:1
4	DMSO	100	96	17:1
5	THF	100	94	42:1
6	1,4-dioxane	97	86	33:1
7	DME	97	96	39:1
8	Triglyme	100	100	35:1
9	Tol.	53	47	27:1
10	DCE	26	26	42:1

[a] Reaction condition: *m*-*t*BuPhOTf (0.10 mmol), styrene (0.20 mmol), $Pd(dba)_2$ (0.005 mmol), dnpf (0.010 mmol), urotropine (0.20 mmol), solvent (0.20 mL). Conversion and yield were determined by GC versus a calibrated internal standard. [b] Selectivity was determined by GC. ^{1}H NMR spectroscopy was unsuitable for the determination of selectivity due to low signal intensity of the minor isomer.

With regard to the choice of Pd source, $Pd(dba)_2$, $Pd_2(dba)_3$ and $Pd(OAc)_2$ gave very similar results regardless of the initial oxidation state (entries 1-5). However, $Pd(TFA)_2$ and $Pd(acac)_2$ gave lower yield and α selectivity (entries 6-7). Furthermore, when the amount of styrene was decreased to 1.2 equiv, the yield and the selectivity in DMA dropped slightly to 82% yield and 28:1 respectively (entry 2).

Table 1.4. Effect of Pd sources on the model Heck reaction.



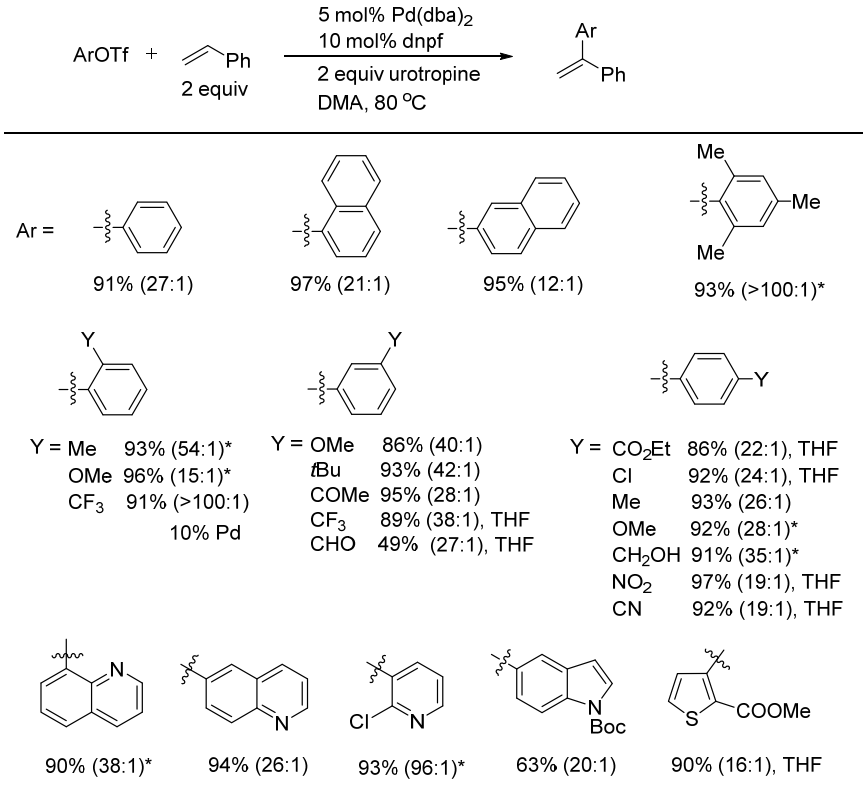
Entry	Pd source	Conv. (%)[a]	Yield (%)[a]	Selectivity[b]
1	$Pd(dba)_2$	100	96	36:1
2[c]	$Pd(dba)_2$	99	82	28:1
3[d]	$Pd(dba)_2$	100	91	28:1
4	$Pd_2(dba)_3$	100	95	34:1
5	$Pd(OAc)_2$	100	96	33:1
6	$Pd(OCOCF_3)_2$	63	59	24:1
7	$Pd(acac)_2$	87	70	5:1

[a] Reaction condition: *m*-*t*BuPhOTf (0.10 mmol), styrene (0.20 mmol), $Pd(dba)_2$ (0.005 mmol), dnpf (0.010 mmol), urotropine (0.20 mmol), DMA (0.20 mL). Conversion and yield were determined by GC versus a calibrated internal standard. [b] Selectivity was determined by GC. ^{1}H NMR spectroscopy was unsuitable for the determination of selectivity due to low signal intensity of the minor isomer. [c] 1.2 equiv of styrene was used. [d] 5 mol% Pd and 6 mol% dnpf were used.

1.2.2 Substrate scope of the Heck reaction

Next, we examined the scope of aryl triflates in Pd/dnpf-catalyzed Heck reactions of styrene. Most reactions proceeded smoothly in good yield and >20:1 selectivity (Scheme 1.6). Both electron-donating and electron-withdrawing groups, such as methoxy and trifluoromethyl groups respectively, on aryl triflates can be present. For most aryl triflates carrying electron-withdrawing groups, such as ester and nitro groups, we found THF was a better solvent than DMA. Polar groups such as nitrile, nitro, ester, aldehyde, ketone and even free alcohol can be tolerated. In addition, an aromatic chloride remained intact in the catalytic condition in the presence of ArOTf. Some heteroaryl triflates derived from pyridine, quinoline, thiophene and indole also worked well. For some aryl triflates containing *ortho*-substituent, dippf was

found to be more active than dnpf. For the coupling reactions of 8-quinolinyl triflate and 2-chloro-3-pyridyl triflate, we found dippf performed better than dnpf in regard to α/β selectivity. Pd/dippf can catalyze Heck reaction of sterically hindered 2-mesityl triflate to furnish the 1,1-diarylethene product almost exclusively.

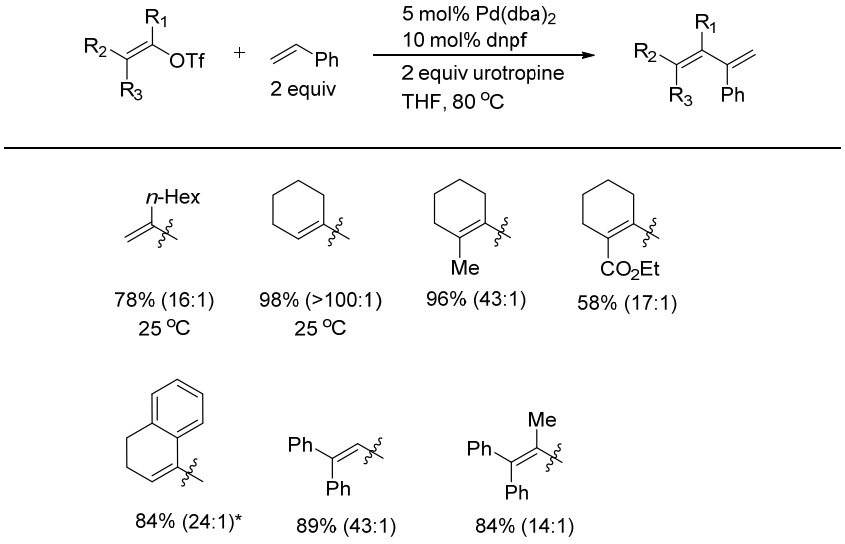


Reaction condition: organic triflate (0.50 mmol), styrene (1.0 mmol), $Pd(dba)_2$ (0.025 mmol), dnpf (0.50 mmol), urotropine (1.0 mmol), DMA (1.25 mL). Isolated yield after purification was reported. Selectivity in crude mixture was determined by GC (in parentheses).
* 10 mol% $Pd(dba)_2$ and 12 mol% dippf.

Scheme 1.6. Aryl and heteroaryl triflates in Heck reaction with styrene

The same conditions can be well applied to catalyze Heck reaction of vinyl triflates with styrene to afford multiple-substituted 1,3-dienes (Scheme 1.7), which otherwise require cross-couplings using *α*-metalated vinylarenes. Vinyl electrophiles with sterical perturbation such as 1-(2-methyl)cyclohexenyl and 1-(1-methyl-2,2-diphenyl)vinyl triflates proceeded the reaction to afford desired tetra-substituted olefin in good yields with excellent α selectivity. Vinyl

electrophiles with electronical perturbation such as 1-(2-ethylcarbonyl)cyclohenyl triflate can also efficiently couple with styrene in good yield and selectivity. Notablely, 2-octenyl and 1-cyclohexenyl triflates even coupled with styrene at room temperature. The α selectivity was satisfactory in most cases. Furthermore, the minor isomers can be removed by flash chromatography.

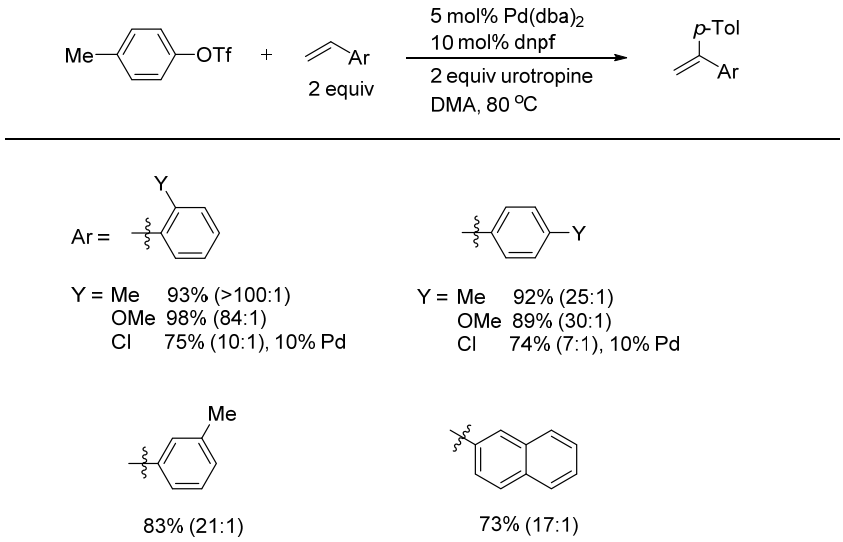


Reaction condition: vinyl triflate (0.50 mmol), styrene (1.0 mmol), $Pd(dba)_2$ (0.025 mmol), dnpf (0.50 mmol), urotropine (1.0 mmol), THF (1.25 mL). Isolated yield after purification was reported. Selectivity in crude mixture was determined by GC (in parentheses).
* DMA was used as solvent.

Scheme 1.7. Vinyl triflates in Heck reaction of styrene

Then we examined the scope of vinylarenes using *p*-tolyl triflate as the model aryl electrophile (Scheme 1.8). The Pd/dnpf catalyst can tolerate *ortho*-substituents on vinylarenes. For electron-neutral and electron-rich vinylarenes, methyl and methoxy groups respectively, the α/β selectivity remained >20:1 in most cases. However, for electron-poor vinylarenes such as *o*- and *p*-chlorostyrene the selectivity dropped to about 10:1. It can be understood by considering the involvement of partial positive charge at the benzylic position in the transition states leading to internal insertion.[29,44] The insertion transition

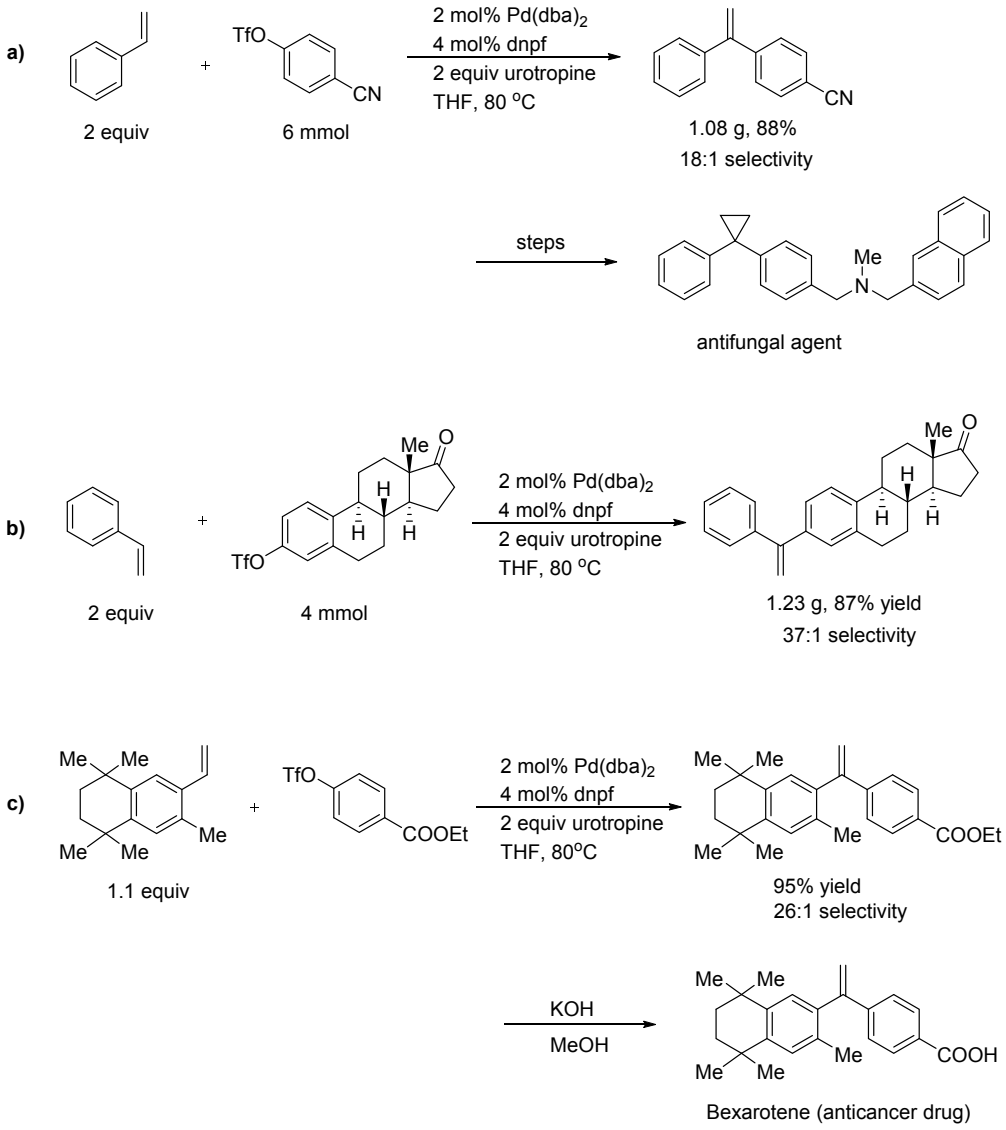
state will be destabilized in the presence of electron-withdrawing groups and thus results a lower α/β selectivity.



Reaction condition: *p*-OMePhOTf (0.50 mmol), vinylarene (1.0 mmol), $Pd(dba)_2$ (0.025 mmol), dnpf (0.50 mmol), urotropine (1.0 mmol), DMA (1.25 mL). Isolated yield after purification was reported. Selectivity in crude mixture was determined by GC(in parentheses).

Scheme 1.8. Heck reaction of various vinylarenes.

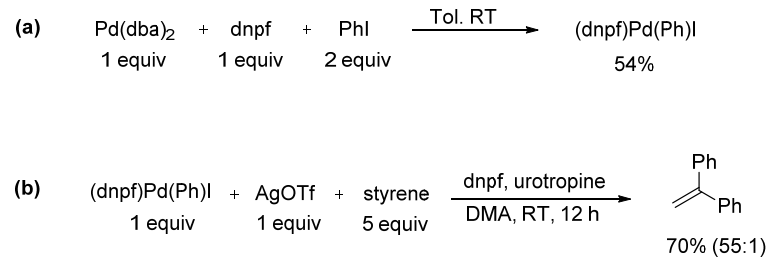
The new method can be readily scaled up without much modification of conditions. In the presence of 2 mol% of Pd/dnpf catalyst, *p*-cyano-1,1-diphenylethene can be prepared in a gram scale and 18:1 selectivity (Scheme 1.10, **a**). The product was an intermediate for the preparation of an antifungal agent.[45] Similarly, with 2 mol% of Pd/dnpf catalyst, the Heck reaction of 3-estrone triflate and styrene afforded 1.2 gram of the desired isomer in 37:1 selectivity (Scheme 1.9, **b**). The minor isomer can be completely removed by flash chromatography. Bexarotene, marketed as Targretin is an anticancer drug. It can be assembled via our Heck method from respective triflate and vinylarene in good yield and α/β selectivity (95%, 26:1). After subsequent hydrolysis of the ester group, the drug can be obtained (Scheme 1.9, **c**).



Scheme 1.9. Applications of regioselective Heck reaction.

1.2.3 Mechanistic study on the origin of regioselectivity

To probe the origin of high internal selectivity by using the new Pd/dnpf catalyst, we prepared the oxidative addition complex of PhI with the catalyst (Scheme 1.10, **a**). Treatment of (dnpf)Pd(Ph)I with AgOTf in the presence of 5 equiv of styrene at room temperature led to 70% yield of the Heck product in 55:1 selectivity (Scheme 1.10, **b**).[46] It suggested the Pd/dnpf catalyst could readily afford the Heck product in a high α selectivity via the cationic pathway, either by using triflates or by addition of halide scavengers.



Scheme 1.10. (a) Synthesis of (dnpf)Pd(Ph)I complex; (b) Stoichiometric reaction of styrene insertion into the cationic (dnpf)Pd(Ph) complex.

Single-crystal X-ray diffraction analysis of the complex (dnpf)Pd(Ph)I provided valuable information on the structural features to understand the origin of high α selectivity (Figure 1.1).[47] Firstly, the ferrocene backbone of dnpf adopts an almost eclipsed conformation, unlike the staggered conformtion which is commonly observed in related dppf complexes.[48] This unusual conformation seems to be stabilized by edge-to-edge π-interaction between two neighbouring naphthyl groups of dnpf, which is not observed in related dppf complexes. Secondly, phenyl ring and iodine atom are forced ca. 15^{o} above and below the coordination plane defined by P1-Pd-P2, respectively. It is a unique feature of (dnpf)Pd(Ph)I complex which was not oberved in the related dppf complex. This deviation is caused by the steric repulsion with neighbouring naphthyl groups of dnpf. In transition state of aryl insertion at β position, styrene would occupy the position of the iodide and experience severe steric repulsion with the naphthyl groups.

(a) (b)

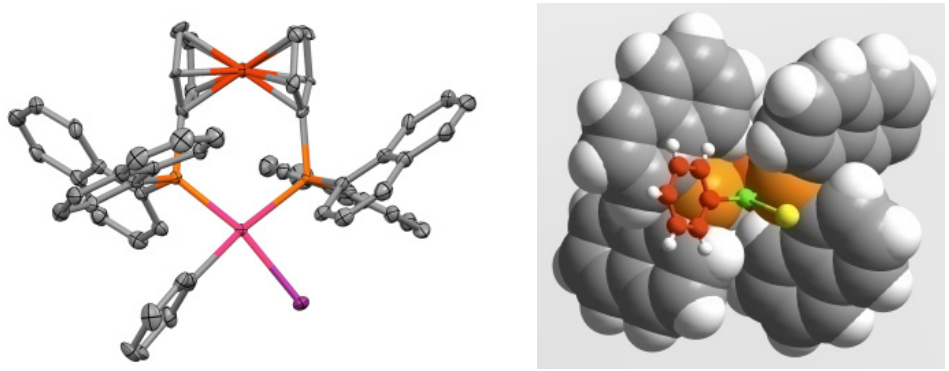


Figure 1.1. (a) ORTEP of (dnpf)Pd(Ph)I (top view) with 50% thermal ellipsoid probability with hydrogen omitted for clarity. (b) Front view with dnpf ligand in space-filling representation and Pd(Ph)I fragment in ball-and-stick. Key bond angles: <P1(right)–Pd–P2(left) = 103°; <I–Pd–C(Ph) = 82°; <P1–Pd–C(Ph) = 164°; <P2–Pd–I = 165°.

In collaboration with Dr. Lu Yunpeng, we have conducted DFT calculation using PBE1PBE method on the insertion step of cationic (dnpf)Pd(Ph)(styrene) conformers. We indentified all four ground-state (GS) structures for the styrene complexes (Figure 1.2). In the optimized structure, the nearly-eclipsed ferrocene backbone and distortion of square planarity were reproduced. In all cases, the C=C double bond was oriented perpendicular to the coordination plane. GS(b) and GS(d) were destabilized by the steric repulsion between the phenyl ring of styrene and naphthyl groups of dnpf.

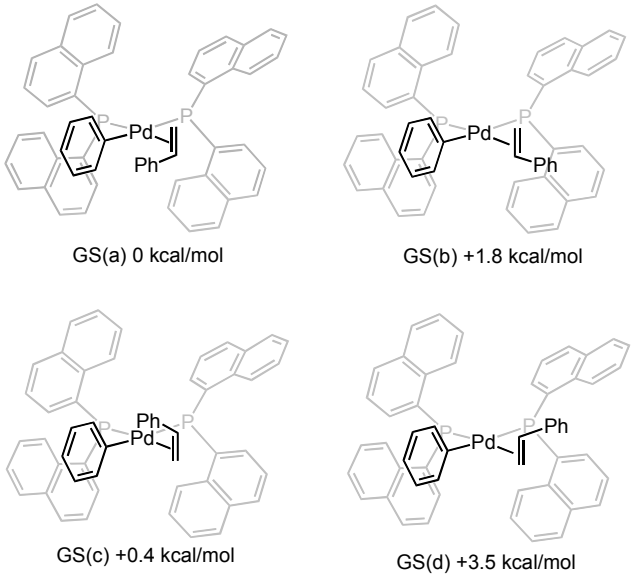


Figure 1.2. Four ground state structures of cationic (dnpf)Pd(Ph)(styrene) complexes and their relative energy. The positive charge of structures and the ferrocene backbone are omitted for clarity.

We have also located transition states (TSs) for aryl insertion of cationic (dnpf)Pd(Ph)(styrene) complexes (Figure 1.3). Assuming fast pre-equilibrium between the olefin complexes, the regioselectivity of the Heck reaction would be determined by the relative energy of TSs rather than insertion barriers. All four insertion TSs were located, two for internal insertion and another two for terminal insertion. The two TSs for terminal insertion were greatly destabilized by the steric repulsion between the phenyl ring of styrene and naphthyl groups of dnpf. In addition, TS(internal) was 3.5 kcal/mol lower in energy than TS(terminal)', which matches reasonably well with the observed α/β selectivity.

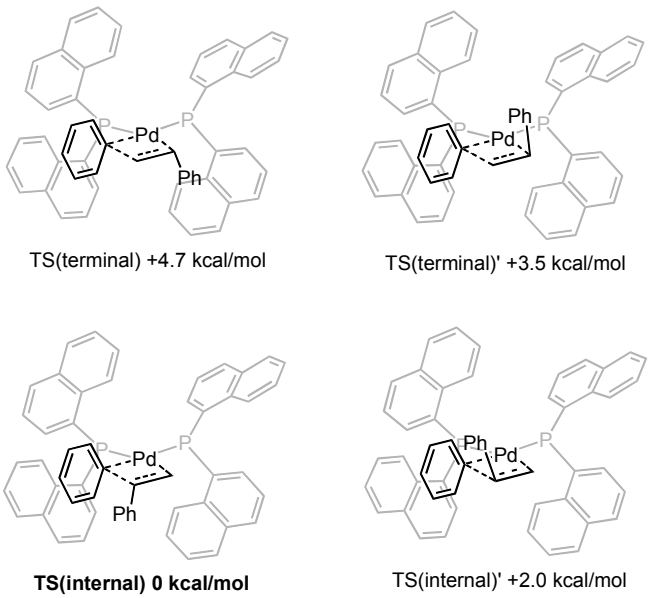


Figure 1.3. Four transition states for styrene insertion in cationic (dnpf)Pd(Ph)(styrene) complexes and their relative energy. The positive charge and ferrocene backbone are omitted for clarity.

Put together, the predominant pathway for aryl insertion starts from styrene complex GS(c) in Figure 1.2. A counterclockwise rotation of styrene results in TS(internal) in Figure 1.3. The corresponding insertion barrier was determined to be relatively low (8.9 kcal/mol), which is consistent with the observed α/β selectivity in the stoichiometric reaction at room temperature (Scheme 1.5). We suspect that the rate limiting step of the catalytic cycle may be oxidative addition of aryl triflates with (dnpf)Pd^0. In the presence of dba ligand, which is known to bind strongly to active catalyst, the actual concentration of active (dnpf)Pd^0 catalyst may be lower.[49]

From the natural bond orbital (NBO) analysis of TS(internal) as shown in Figure 1.3, we found that the positive charge was highly delocalized in the entire structure rather than on a few atoms. In TS(internal), the Pd center carries a partial charge of +0.09, α-(CH) fragment of styrene +0.13 and β-(CH_2)

fragment -0.04. The small, but significant, amount of partial positive charge at the benzylic site provides electronic bias for internal insertion in the cationic pathway of Heck reaction.

In ligand screening, dppf was found to be less selective than dnpf in our model Heck reaction (Table 1.1). Our calculation also supported the experimental observation. All four insertion TSs for cationic (dppf)Pd(Ph)(styrene) complexes and their relative energy were shown in Figure 1.4. The energy difference between TS(internal) and TS(terminal)' was 0.5 kcal/mol, which is much smaller than 3.5 kcal/mol as calculated for dnpf as ligand in Figure 1.3.

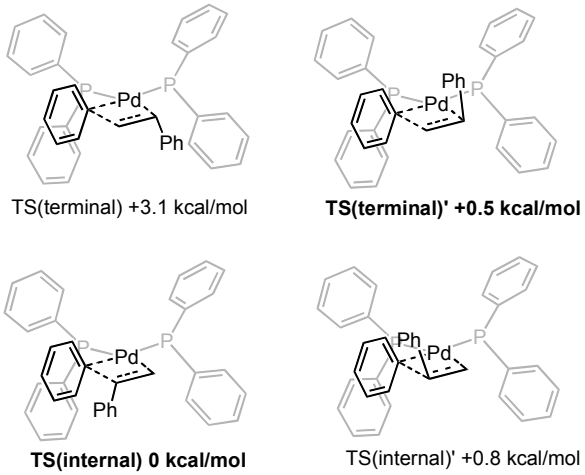
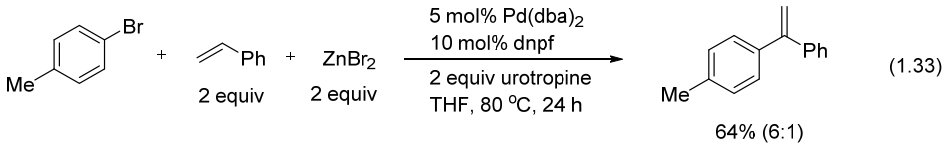


Figure 1.4. Four transition states for styrene insertion in cationic (dppf)Pd(Ph)(styrene) complexes and their relative energy. Positive charge and ferrocene backbone are omitted for clarity.

Thus, the higher α selectivity obtained with the Pd/dnpf catalyst can be attributed to two factors. One is the electronic stabilization of TS for internal insertion in the cationic pathway. The other is the steric destabilization of TS for terminal insertion by the rigid dnpf ligand.

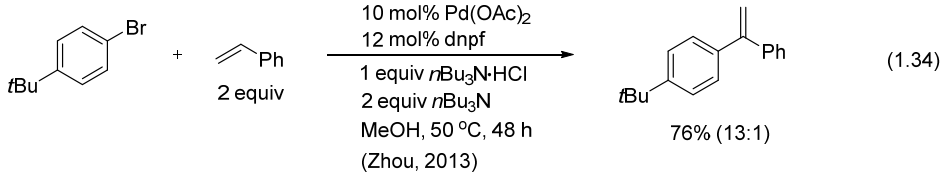
1.2.4 Heck reaction of aryl bromides with styrene

We noted that $ZnBr_2$ is able to abstract a halogen atom from nickel benzylic complex to form a cationic intermediate in THF which has been characterized by X-ray diffraction analyses.[50] We introduced the $ZnBr_2$ as additive into our catalyst system to check the compatibility. To our delight, we successfully obtained the desired 1,1-diarylethene product from *p*-bromotoluene and styrene without further optimization in moderate yield of 64% with 6:1 α/β selectivity (eq 1.33).



(1.33)

Later, by using the combination of methanol and nBu$_3$N·HCl which can facilitate the dissociation of bromide to promote the reaction through the cationic pathway, our group reported the coupling reaction of 1-bromo-4-*tert*-butylbenzene with styrene in good yield and α selectivity (eq 1.34).[26a]

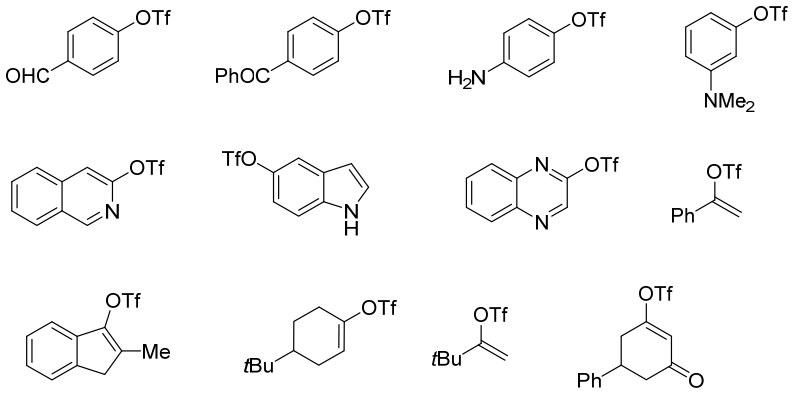


(1.34)

1.2.5 Unsuccessful examples of Heck reaction

We successfully developed the intermolecular Heck reaction of aryl and vinyl triflates with styrenes favoring internal insertion products. However, our method has its limitation. Some aryl triflates such as 4-formylphenyl triflate and 4-benzophenyl triflate only gave 5:1 α/β selectivity. Amino-substituted aryl triflates were unsuccessful which were of low conversion and trace products. Heteroaryl triflates such as 3-isoquinolinyl triflate and 5-indolyl triflate

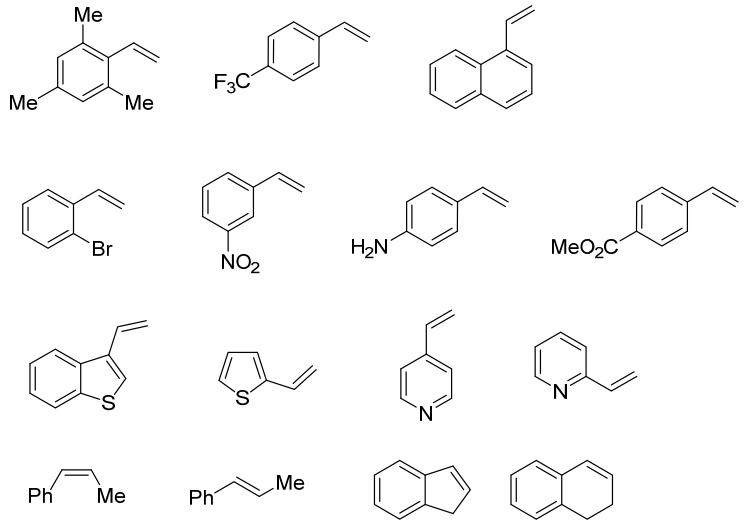
afforded the products in low yield and low selectivity (~5:1). Benzopyrazine triflate did not give the coupling product despite of full conversion. α-Styryl triflate formed the homo-coupling product from the triflate itself. 4-*tert*-Butyl cyclohexenyl triflate gave low α/β selectivity of 3:1 despite of full conversion. Some other vinyl triflates did not afford coupling products, neither.



Scheme 1.11. Additional triflates tested in the Heck reaction.

In the scope of vinylarenes, we encountered more problems. 2,4,6-Trimethylstyrene and 4-(trifluoromethyl)styrene indeed coupled with *p*-tolyl triflate, however, the α/β selectivity is only of 1:1 and 5:1, respectively. The coupling reaction of 1-vinylnaphthalene stopped with 50% conversion of triflate even using 10 mol% Pd/dnpf catalyst. Some functional groups such as bromo, nitro, amino, and methoxycarbonyl groups on styrenes were not tolerated. No coupling products were observed even at a higher temperature using 10 mol% Pd/dnpf catalyst. These functional groups may poison the active catalyst in the reaction. Some heteroaryl olefins such as 3-vinylbenzothiophene and 2-vinylthiophene gave very low α/β selectivity (1:1 and 3:1, respectively). 2-Vinylpyridine and 4-vinylpyridine both failed to afford the coupling products which might be caused by the facile polymerization of themselves. We also attempted to couple α,β-disubstituted olefins, such as indene, 1,2-

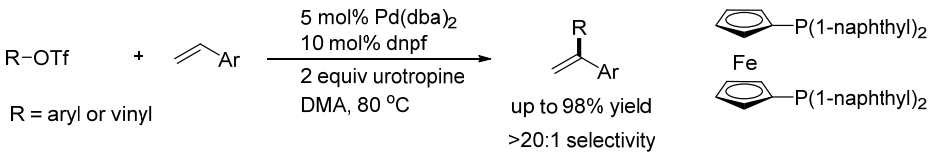
dihydronaphthalene, (*E*)-*β*-methylstyrene and (*Z*)-*β*-methylstyrene, but they failed to react.



Scheme 1.12. Additional aryl olefins tested in the Heck reaction.

1.3 Conclusion

In summary, we have developed a general method for Heck reaction of aromatic olefins, in which the aryl or vinyl groups insert selectively at α position. In most cases, the desired isomers were produced in >95% purity and the minor isomers can be removed by flash chromatography. We have applied the new catalyst in the synthesis of bio-active molecules for the demonstration. The initial result of 4-bromotoluene revealed that the catalyst could be extended for the coupling reaction of other aryl halides. The use of bisphosphine dnpf was the key to the unprecedented generality and selectivity. Our mechanistic study and DFT calculation revealed that the high α selectivity originated from a combination of electronic and steric effects. Unlike dppf ligand, dnpf can form a rigid and crowded environment in the coordination sphere, which sterically disfavors insertion at β position.



1.4 Experimental section

1.4.1 General and preparation of substrates

^{1}H NMR spectra were acquired on Bruker Avance 500 (500 MHz), 400 (400 MHz) or 300 (300MHz) spectrometers and chemical shifts were recorded relative to tetramethylsilane (δ 0.00) or residual protiated solvent (δ 7.26 for $CDCl_3$ and δ 5.30 for CD_2Cl_2). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH. Coupling constants were reported as a *J* value in Hz. ^{13}C NMR spectra were obtained on Bruker Avance 500 (125 MHz), 400 (100 MHz) or 300 (75 MHz) spectrometers and chemical shifts were recorded relative to solvent resonance (δ 77.16 for $CDCl_3$ and δ 53.52 for CD_2Cl_2). ^{19}F[51] NMR spectra were obtained at Bruker Avance 400 (376 MHz) spectrometers. ^{31}P[51] NMR spectra were obtained at Bruker Avance 500 (202 MHz) or 400 (162 MHz) spectrometers. Proof of purity of new compounds was demonstrated with copies of ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectra.

Glassware was dried in an oven at 120 ^{o}C for at least 4 hours before use. Dry *N,N*-dimethylacetamide (Acros) was degassed by argon bubbling and then stored over activated 4 Å molecular sieve beads in the glove box. Dry toluene, hexanes, diethyl ether and DCM were collected from a solvent purification system containing a column of activated alumina (1 m x 2) under argon. Dry THF was freshly distilled from sodium/benzophenone under argon before use. All of anhydrous solvents were stored in Schlenk tubes in the glove box.

Unless noted otherwise, commercially available chemicals were used without further purification. 3-Methoxyphenol[52] and 3′-hydroxyacetophenone[53] were prepared according to reported procedures. The ferrocene 1,1′-

bisphosphines were prepared according to established procedures in our lab.[25] Styrene was passed through a short plug of basic aluminum oxide in the glove box to remove 4-*t*-butylcatecholstabilizer before use. Urotropine was purified by vacuum sublimation and stored in the glove box. Dry *N,N,N′,N′*-tetramethylethlenediamine (TMEDA), diisopropylethylamine (DIPEA), triethylamine, and tributylamine were distilled from CaH_2 under argon before use. The GC internal standard, *n*-dodecane was degassed by argon bubbling and dried over activated 4 Å molecular sieve beads before use.

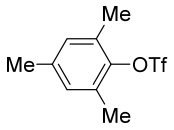
Thin-layer chromatography (TLC) was conducted with Merck 60 F254 coated silica gel plate (0.2 mm thickness). Flash chromatography was performed using Merck silica gel 60 (0.040-0.063 mm) or SiliCycle silica gel F60 (0.040-0.063mm).

Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010instrument with Agilent J&W GC column DB-5MS-UI. GC/MS analysis was conducted on a Thermo Scientific DSQ II single quadrupole GC/MS instrument with Agilent J & W GC column DB-5MS-UI. ESI/MS analysis was conducted on a ThermoFinnigan LCQ Fleet MS spectrometer. X-ray crystallographic analysis of single crystals was performed on a Bruker X8 APEX X-Ray diffractometer.

General Procedure for preparation of aryl triflates: Under argon, parent or substituted phenol (5.0 mmol), dry DCM (10 mL) and analytical grade pyridine (0.8 mL, 10.0 mmol) were added successively into a 100-mL Schlenk flask containing a magnetic stirring bar. After the solution was chilled to 0 ^{o}C in an ice/water bath, triflic anhydride (1.0 mL, 6.0 mmol) was added dropwise over 10 minutes. The resulting mixture was slowly warmed up to room

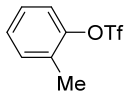
temperature and kept stirring for 12 hours. At the end of the reaction (monitored by TLC), the mixture was concentrated on a rotary evaporator under reduced pressure and the residue was directly subjected to flash chromatography to afford the desired aryl triflate.

The general procedure was used for all the preparation of triflates on 5.0 mmol scale (substituted phenol) unless stated otherwise.



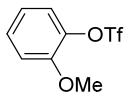
2-Mesityl trifluoromethanesulfonate [125261-32-7]. The titled compound was obtained as colorless oil (1.14 g, 85%) after flash chromatography using 1:40 ethyl acetate (EA) /hexanes as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (s, 2H), 2.35 (s, 6H), 2.29 (s, 3H).



***o*-Tolyl trifluoromethanesulfonate [66107-34-4].** The titled compound was obtained as colorless oil (1.00 g, 83%) after flash chromatography using 1:40 EA/hexanes as eluent.

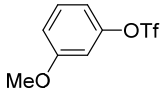
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.23 (m, 4H), 2.38 (s, 3H).



***o*-Anisyl trifluoromethanesulfonate [59099-58-0].** The titled compound was obtained as colorless oil (1.25 g, 96%) after flash chromatography using 1:20 EA/hexanes as eluent.

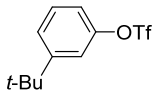
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, J = 8.4, 8.0, 1.6 Hz, 1H), 7.22 (dd, J = 8.1, 1.5 Hz, 1H), 7.04 (dd, J = 8.4, 1.4 Hz, 1H), 6.98 (pseudotriplet of

doublet, J = 8.0, 1.5 Hz, 1H), 3.91 (s, 3H).



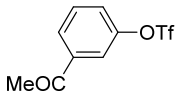
***m*-Anisyl trifluoromethanesulfonate [66107-33-3].** *m*-Methoxyphenol (2.48 g, 20 mmol) was used and the titled compound was obtained as colorless oil (4.75 g, 93%) after flash chromatography using 1:20 EA/hexanes as eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (ψt, J = 8.3 Hz, 1H), 6.93 (dd, J = 8.4, 2.3 Hz, 1H), 6.87 (dd, J = 8.3, 2.2 Hz, 1H), 6.81 (ψt, J = 2.3 Hz, 1H), 3.83 (s, 3H).



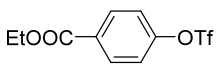
***m-tert*-Butylphenyl trifluoromethanesulfonate [201851-06-1].** The titled compound was obtained as colorless oil (1.33 g, 94%) after flash chromatography using 1:20 EA/hexanes as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.34 (m, 2H), 7.26-7.24 (m, 1H), 7.09-7.07 (m, 1H), 1.33 (s, 9H).



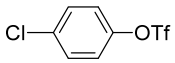
***m*-Acetylphenyl trifluoromethanesulfonate [138313-22-1].** The titled compound was obtained as light yellow oil (710 mg, 87%) after flash chromatography using 1:10 EA/hexanes as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 7.8 Hz, 1H), 7.84 (s, 1H), 7.60-7.56 (m, 1H), 7.47 (d, J = 8.2 Hz, 1H), 2.62 (s, 3H).



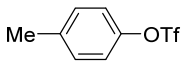
***p*-(Ethoxycarbonyl)phenyl trifluoromethanesulfonate [125261-30-5].** *p*-Hydroxy-benzoate (332 mg, 2 mmol) was used and the titled compound was obtained as white solid (539 mg, 90%) after flash chromatography using 1:10 EA/hexanes as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-8.13 (m, 2H), 7.37-7.33 (m, 2H), 4.40 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H).



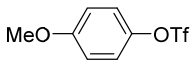
***p*-Chlorophenyl trifluoromethanesulfonate [29540-84-9].** *p*-Chlorophenol (256mg, 2.0 mmol) was used and the titled compound was obtained as colorless oil (426mg, 82%) after flash chromatography using 1:30 EA/hexanes as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.41 (m, 2H), 7.25-7.21 (m, 2H).



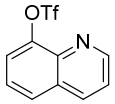
***p*-Tolyl trifluoromethanesulfonate [29540-83-8].** *p*-Cresol (2.16 g, 20 mmol) was used and the titled compound was obtained as colorless oil (4.31 g, 90%) after flash chromatography using 1:20 EA/hexanes as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.23 (m, 2H), 7.17-7.15 (m, 2H), 2.38 (s, 3H).



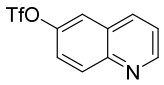
***p*-Anisyl trifluoromethanesulfonate [66107-29-7].** *p*-Methoxyphenol (2.48 g, 20 mmol) was used and the titled compound was obtained as colorless oil (4.55 g, 89%) after flash chromatography using 1:20 EA/hexanes as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.18 (m, 2H), 6.93-6.91 (m, 2H), 3.82 (s, 3H).



8-Quinolinyl trifluoromethanesulfonate [108530-08-1]. The titled compound was obtained as light yellow solid (1.40 g, 100%) after flash chromatography using 1:5 EA/hexanes as eluent.

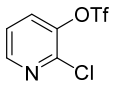
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.23 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.63 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.59-7.51 (m, 2H).



6-Quinolinyl trifluoromethanesulfonate [173089-80-0]. 6-Hydroxyquinoline (363 mg, 2.5 mmol) was used and the titled compound was obtained as white light brown solid (546 mg, 79%) after flash chromatography using 1:5 EA/hexanes as eluent.

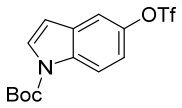
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (d, *J* = 2.8 Hz, 1H), 8.22-8.19 (m, 2H), 7.75 (d, *J* = 2.2 Hz, 1H), 7.60 (dd, *J* = 9.3, 2.5 Hz, 1H), 7.50 (dd, *J* = 8.4, 4.2 Hz, 1H).

^{19}F NMR (376 MHz, $CDCl_3$): δ 72.7.



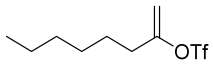
2-Chloro-3-pyridyl trifluoromethanesulfonate [163083-47-4]. The titled compound was obtained as yellowish oil (1.26 g, 96%) after flash chromatography using 1:8 EA/hexanes as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.72 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.38 (dd, *J* = 8.2, 4.7 Hz, 1H).



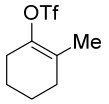
***N*-(*t*-Butoxycarbonyl)-5-indolyl trifluoromethanesulfonate [1247868-60-5].** The compound was prepared according to a reported procedure with some modification.[54] Under argon, 4-(*N,N*-dimethylamino)pyridine (24.4 mg, 0.20 mmol), 5-indolyl trilfate (530 mg, 2.0 mmol) and dry THF (10 mL) were added into a 20-mL vial containing a magnetic stir bar. Then Boc anhydride (480 mg, 2.2 mmol) was added dropwise and the reaction mixture was kept stirring for additional 14 hours. At the conclusion of the reaction, the solvent was removed under reduced pressure and the residue was directly subjected to flash chromatography (1:9 Et_2O/hexanes as eluent). The titled compound was obtained as white solid (716 mg, 97 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 3.6 Hz, 1H), 7.47 (d, J = 2.5 Hz, 1H), 7.21 (dd, J = 9.0, 2.5 Hz, 1H), 6.60 (dd, J = 3.8, 0.6 Hz, 1H), 1.68 (s, 9H).



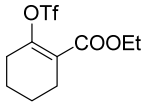
2-Octenyl trifluoromethanesulfonate [98747-02-5]. The compound was prepared according to a reported procedure.[55] Under argon, to a solution of 1-octyne (3.30 g, 30 mmol) in analytic-grade pentane (10 mL) was added TfOH (3.00 g, 20 mmol) at -30 ^{o}C. The resulting mixture was stirred for 10 min and then warmed up to RT over 30 min. After quenching with saturated $NaHCO_3$, the organic phase was washed with saturated $NaHCO_3$ twice and then dried over K_2CO_3. The filtrate was concentrated and purified by distillation (54-56 ^{o}C, 3.5 mmHg) to give the titled compound as colorless oil (2.46 g, 86%). The ratio of desired product to its regioisomer was determined to be 19:1 by GC.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.09 (d, *J* = 3.4 Hz, 1H), 4.92 (d, *J* = 3.4 Hz, 1H), 2.36-2.31 (t, *J* = 7.4 Hz, 2H), 1.56-1.49 (m, 2H), 1.37-1.31 (m, 6H), 0.91-0.87 (m, 3H).



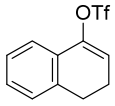
2-Methyl-1-cyclohexenyl trifluoromethanesulfonate [32363-21-6]. The compound was prepared according to a reported procedure.[56] Under argon, to a dry 100-mL Schlenk flask were charged Mg turnings (240 mg, 10 mmol), dry Et_2O (10 mL) and EtBr (1.09 g, 10 mmol) dropwise via a syringe at RT. The resulting mixture was stirred at RT for 2 h. The Grignard solution was then transferred into a solution of *i*-Pr_2NH (1.01 g, 10 mmol) in dry Et_2O (10 mL) maintained at 0 ^oC. After warmed up to RT, the solution was stirred at RT for 18 h. Then the resulting mixture was cooled to 0 ^oC. Dry HMPA (3.5 mL, 20 mmol) was added dropwise via a syringe, followed by 2-methylcyclohexanone (1.12 g, 10 mmol). After stirred for 6 h at RT, $PhNTf_2$ (3.57 g, 10 mmol) was added in one portion. The resulting mixture was stirred at RT for 15 h and then refluxed for 6 h. After cooling down to RT, 10% aq. HCl (20 mL) was added to quench the reaction. The organic phase was successively washed with 10% aq. HCl, saturated $NaHCO_3$ and brine. The organic layer was then dried over anhydrous $MgSO_4$, concentrated and purified by bulb-to-bulb distillation (60 ^oC, 1 mmHg) to give the titled compound as colorless oil (0.97 g, 40% yield). The ratio of desired product to its regioisomer was determined to be 48:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31-2.29 (m, 2H), 2.13-2.12 (m, 2H), 1.78-1.72 (m, 5H), 1.62-1.59 (m, 2H).



2-Ethoxycarbonyl-1-cyclohexenyl trifluoromethanesulfonate [98747-02-5]. The compound was prepared according to a reported procedure.[57] Under argon, to a suspension of NaH (288 mg, 12 mmol) in dry DCM (40 ML) was added ethyl cyclohexanone-2-carboxylate (1.70 g, 10 mmol) at 0 ^{o}C. After stirring at RT for 30 min, the mixture was cooled down to -78 ^{o}C and Tf_2O (3.38 g, 12 mmol) was added dropwise via a syringe. The resulting mixture was then warmed up to RT and stirred for 14 h. At the end of the reaction, the mixture was quenched with water. The organic phase was washed with brine and then dried over Na_2SO_4. The filtrate was purified by flash chromatography to give the titled compound as colorless oil (2.80 g, 93%). The purity was >99% judged by GC.

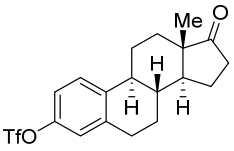
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.27 (q, J = 7.2 Hz, 2H), 2.50-2.45 (m, 2H), 2.42-2.37 (m, 2H), 1.81-1.73 (m, 2H), 1.71-1.64 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H).



3,4-Dihydro-1-naphthyl trifluoromethanesulfonate [123994-49-0]. The compound was prepared according to a reported procedure with some modification.[58] Under argon, α-tetralone (511 mg, 3.5 mmol), 2,6-di-(*tert*-butyl)-4-methylpyridine (790 mg, 3.85 mmol) and dry DCM (12 mL) were added into a 20-mL round-bottom flask containing a magnetic stir bar. Triflic anhydride (0.65 mL, 3.85 mmol) was then added dropwise via a syringe and the reaction mixture was kept stirring for additional 15 hours. At the conclusion of

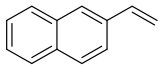
the reaction, the solvent was removed under reduced pressure and the residue was directly subjected to flash chromatography using hexanes as eluent. The titled compound was obtained as colorless oil (847 mg, 87%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.34 (m, 1H), 7.28-7.25 (m, 2H), 7.18-7.16 (m, 1H), 6.01 (t, J = 4.8 Hz, 1H), 2.87 (t, J = 8.1 Hz, 2H), 2.51 (td, J = 8.4, 4.8 Hz, 2H).



3-(Trifluoromethanesulfonyl)estrone [92817-04-4]. The compound was prepared according to a reported procedure with some modification.[59] Under argon, estrone (2.00 g, 7.4 mmol), triethylamine(2.1 mL, 14.8 mmol) and dry DCM (40 mL) were added into a 100-mL round bottom flask containing a magnetic stir bar. After the reaction mixture was chilled to 0 ^{o}C in an ice/water bath, triflic anhydride (1.40 mL, 8.14 mmol) was added dropwise. The reaction mixture was stirred for additional 2 hours and then quenched by addition of saturated $NaHCO_3$ solution (40 mL). The aqueous phase was extracted with DCM (2 x 40 mL) and the combined organic phases were washed by brine and dried over anhydrous Na_2SO_4. After filtration, the crude product was concentrated under reduced pressure and purified by flash chromatography using 1:4 EA/hexanes as eluent to give the titled compound as white solid (2.40 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 8.7 Hz, 1H), 7.03 (dd, J = 8.7, 2.6 Hz, 1H), 6.99 (d, J = 2.6 Hz, 1H), 2.96-2.93 (m, 2H), 2.52 (dd, J = 19.2, 9.0 Hz, 1H), 2.42-2.38 (m, 1H), 2.33-2.27 (m, 1H), 2.20-1.99 (m, 4H), 1.66-1.49 (m, 6H), 0.92 (s, 3H).



2-Vinylnaphthalene [827-54-3]. The compound was prepared according to a reported procedure with some modification.[60] In an argon-filled glove box, a 25-mL reaction tube containing a magnetic stir bar was charged with $PdCl_2$ (7.1 mg, 0.040 mmol), PPh_3 (31 mg, 0.12 mmol), 2-bromonaphthalene (414 mg, 2.0 mmol), potassium vinyltrifluoroborate[61] (268 mg, 2.0 mmol), Cs_2CO_3 (1.95 g, 6.0 mmol) and 4 mL of 9:1 THF/H_2O. Then it was sealed with a rubber septum and heated in an 80 ^oC oil bath for 22 hours until the 2-bromonaphthalene was fully consumed. The reaction mixture was passed through a pad of Celite and washed with diethyl ether. The filtrate was concentrated under reduced pressure and the residue was subjected to flash chromatography with hexanes as eluent. The titled compound was obtained as white solid (262 mg, 85%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.85-7.80 (m, 3H), 7.76 (s, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.49-7.43 (m, 2H), 6.90 (dd, J = 17.5, 10.9 Hz, 1H), 5.89 (d, J = 17.5 Hz, 1H), 5.35 (d, J = 10.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 135.1, 133.7, 133.3, 128.3, 128.2, 127.8, 126.5, 126.4, 126.1, 123.3, 114.3.

1.4.2 Condition optimization of Heck reaction

Typical procedure for condition optimization: In an argon-filled glove box, a dry 4-mL vial containing a magnetic stir bar was sequentially charged with $Pd(dba)_2$ (2.8 mg, 0.005 mmol), ligand (0.010 mmol) and dry DMA (0.2 mL). After stirring at room temperature for 15 minutes, *m*-*t*-butylphenyl triflate (28.2 mg, 0.10 mmol), styrene (20.8 mg, 0.20 mmol), GC standard *n*-dodecane (10 μL) and urotropine (28 mg, 0.20 mmol) were added sequentially. The vial

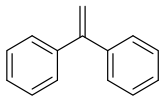
was capped tightly and the reaction mixture was heated with stirring at 80 ^{o}C for 12 hours. Samples of reaction mixture were subjected to GC analysis to determine the conversion of aryl triflate, yield and selectivity of the Heck reaction products and amount of reduction byproduct of aryl triflate. The major isomer, 1,1-diarylethene and the minor isomer, substituted (*E*)-stilbene were assigned based on ^{1}H NMR spectroscopy of the crude mixture and confirmed by GCMS. The ratio of the two isomers was determined by GC. Substituted (*Z*)-stilbene was not detected. *Note: ^{1}H NMR spectroscopy was unsuitable for the determination of the ratio of the two isomers due to low signal intensity of the minor isomer in the spectra.*

1.4.3 Isolation of 1,1-diarylethene Heck products

General procedure for products isolation: In an argon-filled glove box, a dry 25-mL reaction tube containing a magnetic stir bar was sequentially charged with $Pd(dba)_2$ (14.3 mg, 0.025 mmol), 1,1'-bis[di(1-naphthyl)phosphino]ferrocene (dnpf) (37.7 mg, 0.050 mmol) and 1.25 mL of dry DMA. After stirring at room temperature for 15 minutes, organic triflate (0.50 mmol), vinylarene (1.0 mmol), *n*-dodecane (GC internal standard, 50 μL) and urotropine (140 mg, 1.0 mmol) were added sequentially via syringe. The reaction tube was capped tightly and the mixture was heated with vigorous stirring in an 80 ^{o}C oil bath (external temperature). After the aryl triflate was fully consumed (monitored by GC), the reaction mixture was cooled to room temperature and passed through a pad of silica gel to remove DMA with diethyl ether washings in most cases. The filtrate was concentrated under reduced pressure and the residue was directly subjected to silica gel flash chromatography for purification. The major isomer was assigned based on ^{1}H

NMR spectroscopy of purified sample. The ratio of two isomers which were identified by GCMS was determined by GC analysis. *Note: ^1H NMR spectroscopy was unsuitable for the determination of the ratio of the two isomers due to low signal intensity of the minor isomer in the spectra.*

The general procedure was used for all the isolation using 0.50 mmol of organic triflate unless stated otherwise.

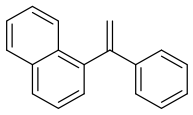


1,1-Diphenylethene [530-48-3]. $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours at 80 ^oC. The titled compound was obtained as colorless oil (82 mg, 91% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 27:1 by GC.

^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.36 (m, 10H), 5.53 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 141.6, 128.4, 128.3, 127.8, 114.4.

GCMS (EI): calcd for $C_{14}H_{12}$ M: 180.09. Found: 180.09.



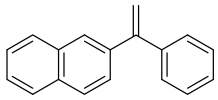
α-(1-Naphthyl)styrene [28358-65-8]. $Pd(dba)_2$ (28.7 mg, 0.050 mmol) and dnpf (45.2 mg, 0.060 mmol) were used and the reaction finished after 13 hours at 80 ^oC. The titled compound was obtained as white solid (112 mg, 97% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 21:1 by GC.

^1H NMR (400 MHz, $CDCl_3$): δ 7.95-7.92 (m, 2H), 7.88 (d, J = 8.5 Hz, 1H),

7.60 (ψt, J = 7.0 Hz, 1H), 7.54-7.49 (m, 2H), 7.43-7.39 (m, 3H), 7.37-7.33 (m, 3H), 6.08 (d, J = 1.3 Hz, 1H), 5.49 (d, J = 1.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 141.2, 139.9, 133.8, 132.0, 128.5, 128.3, 128.1, 127.8, 127.4, 126.7, 126.6, 126.0, 125.8, 125.6, 116.4.

GCMS (EI): calcd for $C_{18}H_{14}$ M: 230.11. Found: 230.13.

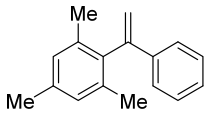


α-(2-Naphthyl)styrene [28358-66-9]. $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours at 80 ^{o}C. The titled compound was obtained as light yellow oil (110 mg, 95% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 12:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90-7.88 (m, 4H), 7.60-7.54 (m, 3H), 7.49-7.44 (m, 5H), 5.70 (s, 1H), 5.66 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 141.6, 139.0, 133.4, 133.1, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.4, 126.5, 126.3, 126.1, 115.0.

GCMS (EI): calcd for $C_{18}H_{14}$ M: 230.11. Found: 230.12.



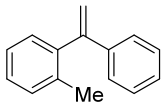
α-Mesitylstyrene [1667-02-3]. $Pd(dba)_2$ (28.7 mg, 0.050 mmol) and dippf (25.1 mg, 0.060 mmol) were used and the reaction was stopped after 48 hours at 80 ^{o}C. The titled compound was obtained as light yellow oil (99 mg, 93% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be >100:1

by GC. When dnpf was used as ligand, the rate of the reaction was slightly slower.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.23 (m, 5H), 6.91 (s, 2H), 5.95 (s, 1H), 5.09 (s, 1H), 2.32 (s, 3), 2.11 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 139.7, 138.3, 136.5, 136.2, 128.5, 128.3, 127.7, 126.0, 114.6, 21.2, 20.2.

GCMS (EI): calcd for $C_{17}H_{18}$ M: 222.14. Found: 222.06.

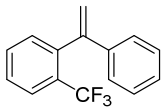


***α*-(*o*-Tolyl)styrene [947-77-3].** $Pd(dba)_2$ (28.7 mg, 0.050 mmol) and dippf (25 mg, 0.060 mmol) were used and the reaction finished after 13 hours at 80 ^{o}C. The titled compound was obtained as colorless oil (90 mg, 93% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity in the crude products was determined to be 54:1 by GC. When dnpf was used as ligand, the selectivity was lower (11:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.29 (m, 9H), 5.87 (d, J = 1.4 Hz, 1H), 5.30 (d, J = 1.4 Hz, 1H), 2.16 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 141.7, 140.7, 136.2, 130.2, 130.1, 128.5, 127.69, 127.66, 126.6, 125.8, 115.0, 20.2.

GCMS (EI): calcd for $C_{15}H_{14}$ M: 194.11. Found: 194.00.

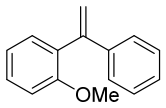


***α*-(*o*-Trifluoromethyl)styrene [191867-93-3].** $Pd(dba)_2$ (28.7 mg, 0.050 mmol) and dippf (25.1 mg, 0.060 mmol) were used and the reaction finished after 80 hours at 80 ^{o}C. The titled compound was obtained as colorless oil (113

mg, 91% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be >100:1 by GC. When dnpf was used as ligand, the reaction was very slower at 80 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.8 Hz, 1H), 7.53 (ψt, *J* = 7.5 Hz, 1H), 7.44 (ψt, *J* = 7.6 Hz, 1H), 7.30-7.23 (m, 6H), 5.88 (s, 1H), 5.23 (s, 1H).

GCMS (EI): calcd for $C_{15}H_{11}F_3$ M: 248.08. Found: 248.07.

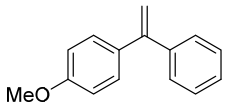


α-(*o*-Anisyl)styrene [24892-80-6]. $Pd(dba)_2$ (28.7 mg, 0.050 mmol) and dnpf (45.2 mg, 0.060 mmol) were used and the reaction finished after 13 hours at 80 ^{o}C. The titled compound was obtained as light yellow oil (106 mg, 96% yield) after flash chromatography using 1:40 EA/hexanes as eluent. The internal/terminal selectivity in the crude products was determined to be 15:1by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 7H), 7.03 (ψt,*J* =7.4 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 1H), 5.78 (d, *J* = 1.2 Hz, 1H), 5.37 (d, *J* = 1.2 Hz, 1H), 3.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 147.1, 141.2, 131.4, 131.2, 129.1, 128.1, 127.4, 126.5, 120.7, 115.5, 111.4, 55.7.

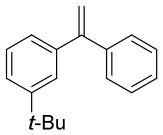
GCMS (EI): calcd for $C_{15}H_{14}O$ M: 210.10. Found: 210.03.



α-(*m*-Anisyl)styrene[34564-79-9]. $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours

at 80 °C. The titled compound was obtained as colorless oil (90 mg, 86% yield) after flash chromatography using 1:40 EA/hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 40:1 by GC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.30 (m, 5H), 7.24 (d, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.89-6.86 (m, 2H), 5.46 (s, 2H), 3.78 (s, 3H).

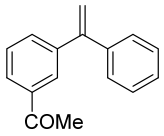


***α*-(*m*-*tert*-Butylphenyl)styrene.** $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours at 80 °C. The titled compound was obtained as colorless oil (111 mg, 93% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 42:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.33 (m, 8H), 7.24-7.22 (m, 1H), 5.56-5.55 (m, 2H), 1.41 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 150.6, 141.7, 141.3, 128.4, 128.2, 127.9, 127.8, 125.7, 125.5, 124.8, 114.1, 34.8, 31.5.

GCMS (EI): calcd for $C_{18}H_{20}$ M: 236.16. Found: 236.14.



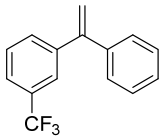
1-(*m*-Acetylphenyl)-1-phenylethene [953422-19-0]. $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours at 80 °C. The titled compound was obtained as light yellow oil (106 mg, 95% yield) after flash chromatography using 1/20

EA/hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 28:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (ψt, J = 1.6 Hz, 1H), 7.93 (dψt, J = 7.6, 1.3 Hz, 1H), 7.53 (dψt, J = 7.7, 1.5 Hz, 1H), 7.44 (dd, J = 7.7, 7.6 Hz, 1H), 7.36-7.31 (m, 5H), 5.55 (d, J = 0.8 Hz, 1H), 5.51(d, J = 0.9 Hz, 1H), 2.60 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 149.4, 142.2, 140.9, 137.3, 133.1, 128.6, 128.5, 128.2, 128.13, 128.12, 127.7, 115.4, 26.8.

GCMS (EI): calcd for $C_{16}H_{14}O$ M: 222.10. Found: 222.11.

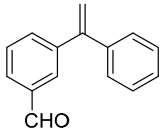


***α*-(*m*-Trifluoromethylphenyl)styrene[395-10-8].** $Pd(dba)_2$ (14.4 mg, 0.025 mmol), dnpf (37.7 mg, 0.050 mmol) and dry THF (1.25 mL) were used and the reaction finished after 12 hours at 80 ^{o}C (monitored by GC). The titled compound was obtained as colorless oil (110 mg, 89% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 38:1 by GC. When DMA was used as solvent, the conversion of triflate was 40% after 12 h and the selectivity were lower (15:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.48-7.44 (m, 1H), 7.40-7.31 (m, 5H), 5.57 (s, 1H), 5.12 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1, 142.5,140.8, 131.7, 130.8 (q, J = 32.2 Hz), 128.8, 128.6, 128.27, 128.25, 125.1 (q, J = 3.9 Hz), 124.6 (q, J = 3.8 Hz), 124.3 (q, J = 272.4 Hz), 115.8.

GCMS (EI): calcd for $C_{15}H_{11}F_3$ M: 248.08. Found: 248.03.

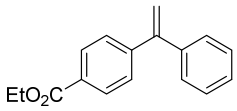


α-(*m*-Formylphenyl)styrene [85366-55-8]. $Pd(dba)_2$ (14.4 mg, 0.025 mmol), dnpf (37.7 mg, 0.050 mmol) and dry THF (1.25 mL) were used and the reaction finished after 24 hours at 80 ^oC (monitored by GC). The titled compound was obtained as colorless oil (51 mg, 49% yield) after flash chromatography using 1:20 Et_2O/hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 27:1 by GC. When DMA was used as solvent, the conversion of triflate was low (10%) after 12 h.

^1H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.87-7.84 (m, 2H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.51 (dd, *J* = 7.6 Hz, 1H), 7.38-7.32 (m, 5H), 5.57 (s, 1H), 5.54 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 149.0, 142.6, 140.8, 136.6, 134.3, 129.7, 129.0, 128.9, 128.5, 128.23, 128.21, 115.7.

GCMS (EI): calcd for $C_{15}H_{12}O$ M: 208.09. Found: 208.08.



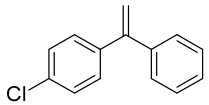
α-(*p*-(Ethoxycarbonyl)phenyl)styrene [679390-82-0]. $Pd(dba)_2$ (14.4 mg, 0.025 mmol), dnpf (37.7 mg, 0.050 mmol) and dry THF (1.25 mL) were used and the reaction finished after 18 hours at 80 ^oC. The titled compound was obtained as white solid (108 mg, 86% yield) after flash chromatography using 1:30 EA/hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 22:1 by GC. When DMA was used

as solvent, 10% Pd was necessary to have full conversion of aryl triflate and selectivity was 15:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.36-7.30 (m, 5H), 5.55 (s, 1H), 5.54 (s, 1H), 4.39 (q, *J*= 7.2 Hz, 2H), 1.40 (t, *J*= 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 149.5, 146.1, 141.0, 129.9, 129.6, 128.5, 128.4, 128.1, 115.9, 61.1, 14.5.

GCMS (EI): calcd for $C_{17}H_{16}O_2$ M: 252.12. Found: 252.07.

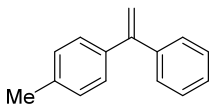


***α*-(*p*-Chloropheny)styrene[18218-20-7].** $Pd(dba)_2$ (14.4 mg, 0.025 mmol), dnpf (37.7 mg, 0.050 mmol) and dry THF (1.25 mL) were used and the reaction finished after 18 hours at 80 ^{o}C. The titled compound was obtained as colorless oil (99 mg, 92% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 24:1 by GC. When DMA was used as solvent, 10% Pd was necessary to have full conversion of aryl triflate and the selectivity was 24:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.31 (m, 9H), 5.52 (s, 1H), 5.50 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1, 141.1, 140.1, 133.7, 129.7, 128.5, 128.4, 128.3, 128.0, 114.8.

GCMS (EI): calcd for $C_{14}H_{11}Cl$ M: 214.05. Found: 214.07.



***α*-(*p*-Tolyl)styrene [948-55-0].** $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours at 80

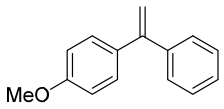
^{o}C. The titled compound was obtained as colorless oil (90 mg, 93% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 26:1 by GC.

For *p*-bromotoluene (86 mg, 0.5 mmol), $Pd(dba)_2$ (14.3 mg, 0.025 mmol), dnpf (37.7 mg, 0.050 mmol), $ZnBr_2$ (135 mg, 0.6 mmol) and THF as solvent were used. The reaction stopped after 48 hours at 80 ^{o}C with 96% conversion of *p*-bromotoluene. The titled compound was obtained as colorless oil (62 mg, 64% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 6:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.39 (m, 5H), 7.33 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 5.52 (s, 1H), 5.49 (s, 1H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 141.8, 138.8, 137.6, 129.0, 128.4, 128.29, 128.25, 127.8, 113.7, 21.3.

GCMS (EI): calcd for $C_{15}H_{14}$ M: 194.11. Found: 194.11.

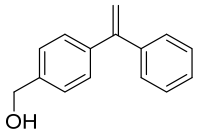


α-(*p*-Anisyl)styrene[4333-75-9]. $Pd(dba)_2$ (28.7 mg, 0.050 mmol) and dnpf (45.2 mg, 0.060 mmol) were used and the reaction finished after 20 hours at 80 ^{o}C. The titled compound was obtained as white solid (97 mg, 92% yield) after flash chromatography using 1:40 EA/hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 28:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.29 (m, 7H), 6.90-6.88 (m, 2H), 5.43 (s, 1H), 5.38 (s, 1H), 3.84 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 149.6, 141.9, 134.1, 129.5, 128.4, 128.2, 127.8, 113.7, 113.1, 55.4.

GCMS (EI): calcd for $C_{15}H_{14}O$ M: 210.10. Found: 210.08.

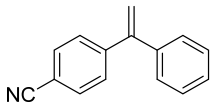


***α*-[*p*-(Hydroxymethyl)phenyl]styrene.** $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours at 80 ^{o}C. The titled compound was obtained as white solid (96 mg, 91% yield) after flash chromatography using 1:4 EA/hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 35:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.32 (m, 9H), 5.46 (ψs, 2H), 4.72 (s, 2H), 1.78 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 141.5, 141.1, 140.5, 128.6, 128.4, 128.3, 127.9, 127.0, 114.5, 65.3.

GCMS (EI): calcd for $C_{15}H_{14}O$ [M]: 210.10. Found: 210.12.



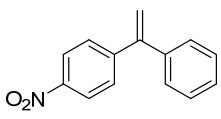
***α*-(*p*-Cyanophenyl)styrene [81329-28-4].** $Pd(dba)_2$ (5.7 mg, 0.010 mmol), dnpf (15.1 mg, 0.020 mmol) and dry THF (1.25 mL) were used and the reaction finished after 36 hours at 80 ^{o}C. The titled compound was obtained as colorless oil (94 mg, 92% yield) after flash chromatography using 1:20 Et_2O/hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 19:1 by GC. When DMA was used as solvent, the conversion of triflate was very low (3%) after 12 h.

Gram-scale procedure. In an argon-filled glove box, a dry 25-mL Schlenk tube containing a magnetic stir bar was sequentially charged with $Pd(dba)_2$ (69 mg, 0.12 mmol, 2 mol%), dnpf (180 mg, 0.24 mmol, 4 mol%) and dry THF (15 mL). After stirring at room temperature for 15 minutes, *p*-cyanophenyl triflate (1.51 g, 6.0 mmol), styrene (1.25 g, 12 mmol), *n*-dodecane (GC standard, 100 μL) and urotropine (1.68 g, 12 mmol) were added sequentially. The Schlenk tube was capped tightly and the reaction mixture was heated with stirring in an oil bath maintained at 80 ^{o}C. After 24 hours, an aliquot was taken from the reaction mixture under argon. GC analysis indicated that the full conversion of the aryl triflate and that the selectivity of Heck products was 18:1. The resulting mixture was passed through a short pad of silica gel and eluted with Et_2O. The filtrate was concentrated and purified by flash chromatography (1:20 Et_2O/hexanes) to give the titled compound as colorless oil (1.08 g, 88% yield). The minor isomer was completely removed by flash chromatography (checked by GC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.38-7.34 (m, 3H), 7.30-7.28 (m, 2H), 5.60 (s, 1H), 5.55 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 146.2, 140.3, 132.2, 128.9, 128.6, 128.4, 128.2, 118.9, 116.8, 111.4.

GCMS (EI): calcd for $C_{15}H_{11}N$ M: 205.09. Found: 205.08.



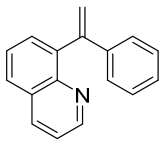
α-(*p*-Nitrophenyl)styrene [395-10-8]. $Pd(dba)_2$ (14.4 mg, 0.025 mmol), dnpf (37.7 mg, 0.050 mmol) and dry THF (1.25 mL) were used and the reaction finished after 24 hours at 80 ^{o}C (monitored by GC). The titled compound was

obtained as light yellow oil (109 mg, 97% yield) after flash chromatography using 1:20 EA/hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 19:1 by GC. When DMA was used as solvent, the conversion of triflate was lower (36%) after 12 h.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.40-7.37 (m, 3H), 7.31-7.29 (m, 2H), 5.64 (s, 1H), 5.60 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 148.2, 147.5, 140.3, 129.1, 128.6, 128.5, 128.3, 123.7, 117.4.

GCMS (EI): calcd for $C_{14}H_{11}NO_2$ M: 225.08. Found: 225.04.

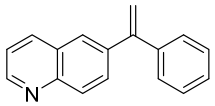


α-(8-Quinolinyl)styrene. $Pd(dba)_2$ (28.7 mg, 0.050 mmol) and dnpf (45.2 mg, 0.060 mmol) were used and the reaction finished after 13 hours at 80 ^{o}C. The titled compound was obtained as light yellow solid (104 mg, 90% yield) after flash chromatography using 1:5 EA/hexanes as eluent. The internal/terminal selectivity of Heck products was determined to be 38:1 in the crude mixture by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (dd, J = 4.1, 1.8 Hz, 1H), 8.15 (dd, J = 8.3, 1.8 Hz, 1H), 7.83 (dd, J = 8.1, 1.4 Hz, 1H), 7.69 (dd, J = 7.1, 1.5 Hz, 1H), 7.57 (dd, J = 8.1, 8.0 Hz, 1H), 7.36-7.33 (m, 3H), 7.29-7.23 (m, 3H), 6.07 (d, J = 1.3 Hz, 1H), 5.49 (d, J = 1.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 147.9, 146.8, 141.5, 141.4, 136.1, 130.6, 128.5, 128.1, 127.9, 127.3, 126.6, 126.3, 121.0, 116.1.

GCMS (EI): calcd for $C_{17}H_{13}N$ M: 231.10. Found: 231.17.

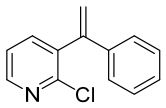


***α*-(6-Quinolinyl)styrene.** $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours at 80 ^oC. The titled compound was obtained as white solid that rapidly changed to brownish (108 mg, 94% yield) after flash chromatography using 1:5 EA/hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 26:1 by GC.

^1H NMR (400 MHz, $CDCl_3$): δ 8.89 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.00-8.05 (m, 2H), 7.74-7.72 (m, 2H), 7.38-7.34 (m, 6H), 5.61 (d, *J* = 0.9 Hz, 1H), 5.58 (d, *J* = 0.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 149.4, 148.0, 141.2, 139.7, 136.2, 130.0, 129.3, 128.38, 128.36, 128.1, 128.0, 127.0, 121.4, 115.6.

GCMS (EI): calcd for $C_{17}H_{13}N$ M: 231.10. Found: 231.12.



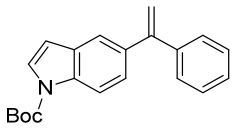
***α*-(2-Chloro-3-pyridyl)styrene.** $Pd(dba)_2$ (28.7 mg, 0.050 mmol) and dippf (25.1 mg, 0.060 mmol) were used and the reaction finished after 72 hours at 80 ^oC. The titled compound was obtained as light yellow oil (99 mg, 93% yield) after flash chromatography using DCM as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 96:1 by GC. When dnpf was used as ligand, the reaction was very slower at 80 ^oC.

^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.66 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.34-7.24 (m, 6H), 5.88 (s, 1H), 5.34 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 148.9, 145.9, 140.1, 139.0, 137.2,

128.6, 128.3, 126.6, 122.5, 117.6.

GCMS (EI): calcd for $C_{13}H_{10}ClN$ M: 215.05. Found: 215.01.

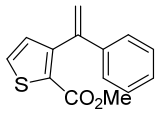


***N*-(*t*-Butoxycarbonyl)-5-indolyl-1-phenylethene.** $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours at 80 ^oC. The titled compound was obtained as colorless oil (100 mg, 63% yield) after flash chromatography using 1:20 EA/hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 20:1 by GC. The major byproduct was the Heck product with 1-naphthyl as transferred aryl group. The 1-naphthyl group was derived from dnpf ligand.

^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 8.2, Hz, 1H), 7.61 (d, J = 3.4 Hz, 1H), 7.53 (s, 1H), 7.39-7.31 (m, 6H), 6.55 (d, J = 3.7 Hz, 1H), 5.49 (s, 1H), 5.47 (s, 1H), 1.69 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 149.9, 142.2, 136.4, 134.9, 130.7, 128.5, 128.3, 127.8, 126.5, 125.0, 120.9, 114.8, 113.9, 107.6, 83.9, 28.3.

GCMS (EI): calcd for $C_{16}H_{13}N$ [M-Boc+H]: 219.10. Found: 219.13.



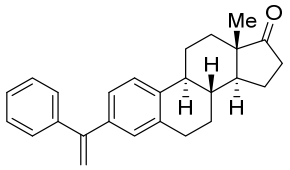
Methyl 3-(α-styrenyl)-2-thiophencarboxylate. $Pd(dba)_2$ (14.4 mg, 0.025 mmol), dnpf (37.7 mg, 0.050 mmol) and dry THF (1.25 mL) were used and the reaction finished after 36 hours at 80 ^oC. The titled compound was obtained as colorless oil (110 mg, 90% yield) after flash chromatography using 1:20 EA/hexanes as eluent, which was solidified upon standing at room temperature.

The internal/terminal selectivity of Heck products in the crude mixture was determined to be 16:1 by GC. When DMA was used as solvent, the conversion of the triflate was only 40% after 12 h and the selectivity was 6:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 5.0 Hz, 1H), 7.29-7.23 (m, 5H), 7.03 (d, *J* = 5.0 Hz, 1H), 5.77 (d, *J* = 1.2 Hz, 1H), 5.31 (d, *J* = 1.2 Hz, 1H), 3.61 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 148.2, 144.2, 140.6, 131.9, 130.3, 129.0, 128.4, 127.7, 126.4, 115.7, 51.9.

GCMS (EI): calcd for $C_{14}H_{12}O_2S$ M: 244.06. Found: 244.01.



3-(α-Styryl)estrone. The reaction was set up with $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) in the argon-filled glove box and the reaction finished after 13 hours at 80 ^{o}C. The titled compound was obtained as white solid (160 mg, 90% yield) after flash chromatography using 1:15 EA/hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 33:1 by GC.

Large-scale procedure using a Schlenk manifold: A 25-mL dry Schlenk tube containing a magnetic stir bar was charged with $Pd(dba)_2$ (46 mg, 0.080 mmol) and dnpf (121 mg, 0.16 mmol). The atmosphere was switched to argon via three cycles of evacuation and refilling and degassed dry DMA (10 mL) wasadded. After stirring for 15 minutes at rt, the mixture was treated with styrene (833 mg, 8.0 mmol), 3-(trifluoromethanesulfonyl)estrone (1.61 g, 4.0 mmol), GC standard *n*-dodecane (0.40 mL) and urotropine (1.12 g, 8.0 mmol). The reaction

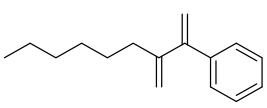
tube was sealed with a rubber septum and the mixture was heated with vigorous stirring in an 80 ^{o}C oil bath (external temperature). The aryl triflate was fully consumed after 11 hours (monitored by GC). The reaction mixture was quenched with 30 mL of water and extracted with ethyl acetate (40 mL x 4). The organic extracts were washed with brine (40 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was subjected to flash chromatography using 1:15 to 1:10 EA/hexanes as eluent. Some fractions contained a small amount of dba, which was removed by washing the solid with 10 mL of hexanes. The titled compound was obtained as pure white solid (1.23 g, 87% yield). The internal/terminal selectivity of Heck products in the crude mixture was determined to be 37:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.32 (m, 5H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 7.08 (s, 1H), 5.43 (s, 1H), 5.40 (s, 1H), 2.91-2.88 (m, 2H), 2.54-2.41 (m, 2H), 2.35-2.31 (m, 1H), 2.19-1.96 (m, 4H), 1.68-1.43 (m, 6H), 0.92 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 221.0, 149.9, 141.7, 139.5, 139.1, 136.4, 128.9, 128.4, 128.2, 127.8, 125.9, 125.3, 114.0, 50.7, 48.1, 44.6, 38.3, 36.0, 31.7, 29.5, 26.7, 25.8, 21.7, 14.0.

GCMS (EI): calcd for $C_{16}H_{28}O$ [M]: 356.21. Found: 356.17.

The procedure for vinylation of styrene was same with the one for arylation of styrene.

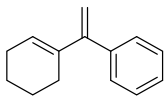


2-Octyl-3-phenyl-1,3-butadiene [145642-48-4]. $Pd(dba)_2$ (14.4 mg, 0.025 mmol), dnpf (37.7 mg, 0.050 mmol) and dry THF (1.25 mL) were used. After 12 hours at RT, 80% of vinyl triflate was consumed and the reaction was terminated. The titled compound was obtained as light yellow oil (84 mg, 78% yield) after flash chromatography using pentane as eluent. The selectivity of Heck products in the crude mixture was determined to be 16:1 by GC. If the reaction was allowed to reach full conversion, the selectivity dropped to 11:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.27 (m, 5H), 5.27 (d, J = 1.5 Hz, 1H), 5.17 (s, 1H), 5.06 (s, 1H), 4.94 (d, J = 2.0 Hz, 1H), 2.25 (t, J = 7.5 Hz, 2H), 1.46-1.41 (m, 2H), 1.33-1.24 (m, 6H), 0.88 (t, J = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 149.4, 141.5, 128.3, 128.1, 127.4, 115.3, 113.6, 34.7, 31.9, 29.2, 28.3, 22.8, 14.2.

GCMS (EI): calcd for $C_{16}H_{22}$ M: 214.17. Found: 214.18.



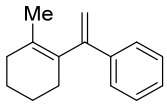
1-(α-Styryl)cyclohexene [96748-61-7]. $Pd(dba)_2$ (14.4 mg, 0.025 mmol), dnpf (37.7 mg, 0.050 mmol) and dry THF (1.25 mL) were used. The reaction finished after 24 hours at RT. The titled compound was obtained as colorless oil (90 mg, 98% yield) after flash chromatography using pentane as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be >100:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.24 (m, 5H), 5.63-5.61 (m, 1H), 5.19 (d, J = 0.7 Hz, 1H), 4.98 (d, J = 0.7 Hz, 1H), 2.26- 2.22 (m, 2H), 2.11-2.08 (m, 2H), 1.75-1.69 (m, 2H), 1.63-1.53 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 142.3, 137.3, 129.1, 128.9, 127.9,

127.1, 111.1, 26.6, 26.0, 23.1, 22.3.

GCMS (EI): calcd for $C_{14}H_{16}$ M: 184.13. Found: 184.12.

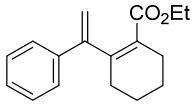


1-Methyl-2-(α-styryl)cyclohexene. $Pd(dba)_2$ (14.4 mg, 0.025 mmol), dnpf (37.7 mg, 0.050 mmol) and dry THF (1.25 mL) were used. The reaction finished after 12 hours at 80 ^oC. The titled compound was obtained as colorless oil (95 mg, 96% yield) after flash chromatography using pentane as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 43:1 by GC.

^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (m, 2H), 7.32-7.28 (m, 2H), 7.26-7.22 (m, 1H), 5.52 (d, J = 0.7 Hz, 1H), 4.97 (d, J = 0.7 Hz, 1H), 2.08- 2.06 (m, 2H), 2.02-1.98 (m, 2H), 1.71-1.59 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 140.1, 132.4, 129.9, 128.5, 127.5, 126.4, 112.6, 31.5, 30.6, 23.5, 23.4, 20.8.

GCMS (EI): calcd for $C_{15}H_{18}$ M: 198.14. Found: 198.13.



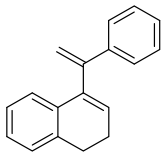
1-Ethoxycarbonyl-2-(α-styryl)cyclohexene. $Pd(dba)_2$ (14.4 mg, 0.025 mmol), dnpf (37.7 mg, 0.05 mmol) and dry THF (1.25 mL) were used. After 42 hours at 80 ^oC, 71% of vinyl triflate was consumed and the reaction was terminated. The titled compound was obtained as colorless oil (74 mg, 58% yield) after flash chromatography (1:2 DCM/hexanes). The selectivity of Heck products in the crude mixture was determined to be 17:1 by GC. When 10% Pd

and 12% dnpf were used as catalyst, 80% conversion and 9:1 selectivity was observed after 40 h at 80 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.38 (m, 2H), 7.32-7.29 (m, 2H), 7.27-7.23 (m, 1H), 5.37 (d, *J* = 1.0 Hz, 1H), 5.01 (d, *J* = 1.0 Hz, 1H), 3.96 (q, *J* = 7.1 Hz, 2H), 2.43- 2.40 (m, 2H), 2.17-2.14 (m, 2H), 1.74-1.64 (m, 4H), 1.02 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 150.9, 145.6, 139.2, 128.9, 128.3, 127.7, 126.8, 111.6, 60.3, 31.1, 26.4, 22.4, 22.2, 13.8.

GCMS (EI): calcd for $C_{17}H_{20}O_2$ M: 256.15. Found: 256.14.

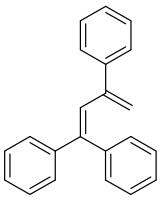


α-(3,4-Dihydro-1-naphthyl)styrene [162111-49-1]. $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours at 80 ^{o}C. The titled compound was obtained as colorless oil (98 mg, 84% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 24:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.9 Hz, 2H), 7.27-7.19 (m, 3H), 7.13 (d, *J* = 7.3 Hz, 1H), 7.06 (ψt, *J* = 7.3 Hz, 1H), 6.98 (ψt, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.13 (t, *J* = 4.5 Hz, 1H), 5.64 (s, 1H), 5.33 (s, 1H), 2.86 (t, *J* = 7.8 Hz, 2H), 2.40 (td, *J* = 7.8, 4.5 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 140.2, 139.6, 136.3, 134.5, 128.8, 128.4, 127.7, 127.5, 126.9, 126.7, 126.4, 125.7, 115.0, 28.4, 23.5.

GCMS (EI): calcd for $C_{18}H_{16}$ M: 232.13. Found: 232.12.

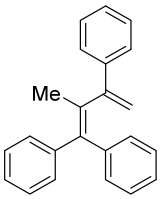


1,1,3-Triphenyl-1,3-butadiene. $Pd(dba)_2$ (8.6 mg, 0.015 mmol), dnpf (22.6 mg, 0.030 mmol), dry THF (0.75 mL), vinyl triflate (98.5 mg, 0.3 mmol), styrene (62.4 mg, 0.6 mmol) and urotropine (84.0 mg, 0.6 mmol) were used. The reaction finished after 12 hours at 80 ^{o}C. The titled compound was obtained as colorless oil (75 mg, 89% yield) after flash chromatography using hexanes as eluent (yellow spots on TLC plate under UV light). The internal/terminal selectivity of Heck products in the crude mixture was determined to be 43:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.13 (m, 15H), 6.74 (s, 1H), 5.38 (d, *J* = 1.0 Hz, 1H), 5.03 (d, *J* = 1.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 144.8, 143.3, 140.9, 140.2, 130.3, 128.5, 128.3, 128.2, 128.09, 128.05, 127.7, 127.5, 127.2, 126.8, 117.5.

GCMS (EI): calcd for $C_{22}H_{18}$ M: 282.14. Found: 282.13.



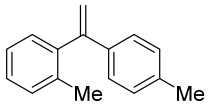
2-Methyl-1,1,3-triphenyl-1,3-butadiene. $Pd(dba)_2$ (14.4 mg, 0.025 mmol), dnpf (37.7 mg, 0.050 mmol) and dry THF (1.25 mL) were used. The reaction finished after 12 hours at 80 ^{o}C. The titled compound was obtained as colorless oil (125 mg, 84% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 14:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.00 (m, 15H), 5.39 (d, *J* = 1.4 Hz, 1H), 5.02 (d, *J* = 1.4 Hz, 1H), 1.90 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 143.13, 143.09, 140.7, 140.2, 136.0, 130.0, 129.5, 128.4, 128.2, 127.6, 127.5, 126.9, 126.7, 126.2, 115.3, 22.0.

GCMS (EI): calcd for $C_{23}H_{20}$ M: 296.16. Found: 296.14.

The procedure for Heck reaction of vinylarens was same with the one for arylation of styrene.

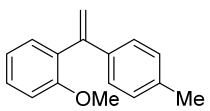


1-(*o*-Tolyl)-1-(*p*-tolyl)ethene [2919-22-4]. $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours at 80 ^{o}C. The titled compound was obtained as colorless oil (97 mg, 93% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be >100:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.15 (m, 6H), 7.08-7.07 (m, 2H), 5.73 (d, *J* = 1.2 Hz, 1H), 5.13 (d, *J*= 1.2 Hz, 1H), 2.33 (s, 3H), 2.06 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 142.0, 137.9, 137.5, 136.3, 130.15, 130.11, 129.2, 127.6, 126.5, 125.8, 114.1, 21.3, 20.2.

GCMS (EI): calcd for $C_{16}H_{16}$ M: 208.13. Found: 208.08.



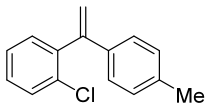
1-(*o*-Anisyl)-1-(*p*-tolyl)ethene [124998-41-0]. $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished

after 13 hours at 80 ^{o}C. The titled compound was obtained as light yellow oil (110 mg, 98% yield) after flash chromatography using 1:40 EA/hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 84:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.7 Hz, 1H), 7.24-7.18 (m, 3H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 5.70 (s, 1H), 5.25 (s, 1H), 3.65 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 146.9, 138.3, 137.1, 131.42, 131.38, 129.00, 128.86, 126.4, 120.7, 114.6, 111.3, 55.8, 21.3.

GCMS (EI): calcd for $C_{16}H_{16}O$ M: 224.12. Found: 224.06.

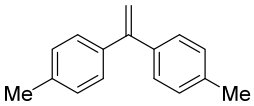


1-(*o*-Chlorophenyl)-1-(*p*-tolyl)ethene. $Pd(dba)_2$ (28.7 mg, 0.050 mmol) and dnpf (45.2 mg, 0.060 mmol) were used and the reaction finished after 20 hours at 80 ^{o}C. The titled compound was obtained as colorless oil (86 mg, 75% yield) after flash chromatography using hexanes as eluent. The minor isomer, substituted (*E*)-stilbene cannot be separated from the major isomer. The internal/terminal selectivity of Heck products was determined to be 10:1 in the crude mixture by GC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.38 (m, 1H), 7.32-7.27 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.80 (s, 1H), 5.22 (s, 1H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 141.0, 137.7, 137.0, 133.4, 131.7, 129.8, 129.2, 128.9, 126.8, 126.4, 115.4, 21.3.

GCMS (EI): calcd for $C_{15}H_{13}Cl$ M: 228.07. Found: 228.05.

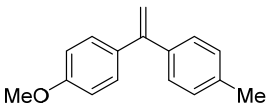


1,1-Di(*p*-tolyl)ethene[2919-20-2]. $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours at 80 ^oC. The titled compound was obtained as colorless oil (96 mg, 92% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 25:1 by GC.

^1H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, *J* = 7.9 Hz, 4H), 7.13 (d, *J* = 7.9 Hz, 4H), 5.38 (s, 2H), 2.36 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9, 138.9, 137.5, 128.9, 128.3, 113.1, 21.3.

GCMS (EI): calcd for $C_{16}H_{16}$ M: 208.13. Found: 208.08.



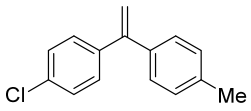
1-(*p*-Anisyl)-1-(*p*-tolyl)ethene [13392-76-2]. $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours at 80 ^oC. The titled compound was obtained as colorless oil (100 mg, 89% yield) after flash chromatography using 1:40 EA/hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 30:1 by GC.

^1H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* =8.0 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.34 (s, 1H), 5.33 (s, 1H), 3.82 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 149.5, 139.1, 137.6, 134.3, 129.5,

129.0, 128.3, 113.6, 112.4, 55.4, 21.3.

GCMS (EI): calcd for $C_{16}H_{16}O$ M: 224.12. Found: 224.14.

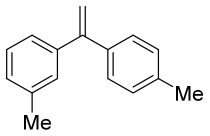


1-(*p*-Chlorophenyl)-1-(*p*-tolyl)ethene [69416-93-9]. $Pd(dba)_2$ (28.7 mg, 0.050 mmol) and dnpf (45.2 mg, 0.060 mmol) were used and the reaction finished after 20 hours at 80 ^oC. The titled compound was obtained as white solid (85 mg, 74% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 7:1 by GC.

^1H NMR (400 MHz, $CDCl_3$): δ 7.32-7.27 (m, 4H), 7.22 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 5.45 (s, 1H), 5.40 (s, 1H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 140.3, 138.3, 137.9, 133.6, 129.7, 129.1, 128.4, 128.2, 114.1, 21.3.

GCMS (EI): calcd for $C_{15}H_{13}Cl$ M: 228.07. Found: 228.05.

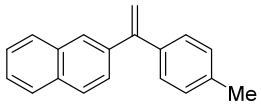


1-(*m*-Tolyl)-1-(*p*-tolyl)ethene [22057-87-0]. $Pd(dba)_2$ (14.3 mg, 0.025 mmol) and dnpf (37.7 mg, 0.050 mmol) were used and the reaction finished after 13 hours at 80 ^oC. The titled compound was obtained as colorless oil (86 mg, 83% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 21:1 by GC.

^1H NMR (400 MHz, $CDCl_3$): δ 7.24-7.09 (m, 8H), 5.40 (s, 1H), 5.37 (s, 1H), 2.35 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 141.8, 138.9, 137.8, 137.5, 129.1, 129.0, 128.5, 128.3, 128.2, 125.6, 113.6, 21.5, 21.3.

GCMS (EI): calcd for $C_{16}H_{16}$ M: 208.13. Found: 208.08.



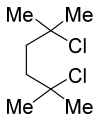
1-(2-Naphthyl)-1-(*p*-tolyl)ethene[1147123-33-8]. $Pd(dba)_2$ (28.7 mg, 0.050 mmol) and dnpf (45.2 mg, 0.060 mmol) were used and the reaction finished after 13 hours at 80 ^oC. The titled compound was obtained as yellowish oil (95 mg, 73% yield) after flash chromatography using hexanes as eluent. The internal/terminal selectivity of Heck products in the crude mixture was determined to be 17:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.75 (m, 4H), 7.48-7.41 (m, 3H), 7.27 (d, J = 7.2 Hz, 2H), 7.14 (d, J = 7.2 Hz, 2H), 5.52-5.51 (m, 2H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 139.2, 138.8, 137.7, 133.4, 133.1, 129.1, 128.4, 128.3, 127.8, 127.7, 127.4, 126.6, 126.3, 126.1, 114.3, 21.3.

GCMS (EI): calcd for $C_{19}H_{16}$ M: 244.13. Found: 244.06.

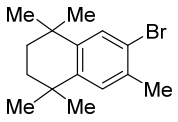
1.4.3 Synthesis of bexarotene



2,5-Dichloro-2,5-dimethylhexanes [6223-78-5]. The compound was prepared according to a reported procedure with some modification.[62] In air, 2,5-dimethyl-2,5-hexanesdiol (20.0 g, 137 mmol) and conc. HCl (100 mL, 1.20 mol) were charged into a 250-mL round bottom flask containing a magnetic stir bar. The resulting slurry was stirred vigorously at RT for 48 h. Then water (80 mL) was added and the mixture was extracted with diethyl ether (100 mL x 3).

The combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. After filtration, the crude product was concentrated and crystallized from hot diethyl ether to give the titled compound as white solid (18.24 g, 73% yield).

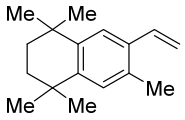
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 4H), 1.60 (s, 12H).



2-Bromo-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalene [119999-22-3]. The compound was prepared according to a reported procedure with some modification.[63] Under argon, 2,5-dimethyl-2,5-dichlorohexanes (5.50 g, 30.0 mmol) , *o*-bromotoluene (10.26 g, 60.0 mmol) and dry DCM (60 mL) were charged into a 100-mL Schlenk flask containing a magnetic stir bar. Then $AlCl_3$ (0.40 g, 3.0 mmol) was added in three portions over 15 min at RT. The resulting brown solution was stirred for 1 h and then quenched with water (50 mL). The aqueous layer was extracted with hexanes (50 mL x 3) and organic extracts were dried over anhydrous $MgSO_4$. After filtration, the crude product was concentrated and crystallized from hot methanol to give the titled compound as white solid (7.10 g, 84 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.16 (s, 1H), 2.36 (s, 3H), 1.68 (ψs, 4H), 1.28 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 144.3, 134.8, 130.3, 129.1, 122.3, 35.10, 35.08, 34.2, 34.1, 31.93, 31.88, 22.7.

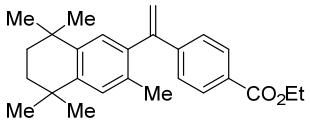


2,5,5,8,8-Pentamethyl-3-vinyl-5,6,7,8-tetrahydronaphthalene. The compound was prepared using a reported procedure.[60] In an argon-filled glove box, a 25-mL reaction tube containing a magnetic stir bar was charged with $PdCl_2$ (17.7 mg, 0.10 mmol), PPh_3 (78.7 mg, 0.30 mmol), 2-bromo-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalene (1.41 g, 5.0 mmol), potassium vinyltrifluoroborate[61] (736.7 mg, 5.5 mmol), Cs_2CO_3 (5.21 g, 15.0 mmol) and 9:1 THF/H_2O (10 mL). The tube was sealed with a screw cap and the reaction was heated in an 80 ^oC oil bath for 24 hours with stirring. The reaction mixture was passed through a pad of Celite® and washed with diethyl ether. The filtrate was concentrated on a rotary evaporator and the residue was subjected to flash chromatography with hexanes as eluent. The titled compound was obtained as colorless oil (805 mg, 70%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 1H), 7.08 (s, 1H), 6.90 (dd, J = 17.5, 11.0 Hz, 1H), 5.60 (dd, J = 17.5, 1.5 Hz, 1H), 5.24 (dd, J = 11.0, 1.5 Hz, 1H), 2.32 (s, 3H), 1.68 (ψs, 4H), 1.31 (s, 6H), 1.28 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 142.8, 135.3, 134.5, 132.7, 128.4, 123.7, 114.4, 35.4, 35.3, 34.2, 34.1, 32.1, 32.0, 19.6.

GCMS (EI): calcd for $C_{17}H_{24}$ M: 228.19. Found: 228.13.



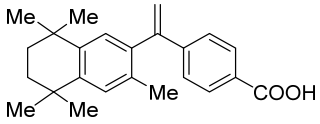
Ethyl ester of bexarotene [1346970-00-0]. In an argon-filled glove box, $Pd(dba)_2$ (5.7 mg, 0.01 mmol, 2 mol%), dnpf (15.1 mg, 0.02 mmol, 4 mol%) and dry THF (1.25 mL) were sequentially charged into a dry 25-mL reaction tube containing a stir bar. After stirring for 15 minutes, *p*-(ethoxycarbonyl)phenyl triflate (149 mg, 0.50 mmol), 2,5,5,8,8-pentamethyl-3-

vinyl-5,6,7,8-tetrahydronaphthalene (228 mg, 1.0 mmol), GC standard *n*-dodecane (50 μL) and urotropine (140 mg, 1.0 mmol) were added sequentially. The reaction tube was sealed tightly with a screw cap and the reaction was heated with vigorous stirring in an 80 ^{o}C oil bath. The reaction was complete after 24 h at 80 ^{o}C (check by GC) and the α/β selectivity of Heck products in the crude mixture was determined to be 26:1. The resulting mixture was then passed through a short pad of silica gel with ether washing. The filtrate was concentrated and purified by flash chromatography (1:15 EA/hexanes as eluent) to give the titled compound as white solid (180 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97(d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.13 (s, 1H), 7.08 (s, 1H), 5.81 (d, *J* = 1.1 Hz, 1H), 5.32 (d, *J* = 1.1 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.95 (s, 3H), 1.70 (ψs, 4H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.31 (s, 6H), 1.28 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 149.4, 145.6, 144.5, 142.5, 138.2, 132.9, 129.7, 129.5, 128.21, 128.17, 126.7, 116.8, 61.0, 35.37, 35.36, 34.1, 34.0, 32.1, 32.0, 20.1, 14.5.

GCMS (EI): calcd for $C_{26}H_{32}O_2$ M: 376.24. Found: 376.19.



Bexarotene [153559-49-0]. The compound was prepared according to a reported procedure with some modification.[64] Under argon, ethyl ester of bexarotene (150 mg, 0.4 mmol) was added into a 10-mL reaction tube containing a stir bar. Then 2.0 mL of degassed methanol and 0.2 mL of 5 N KOH were added into the reaction tube. The reaction mixture was heated to reflux in an oil bath with stirring and the reaction was completed after 2 h

(monitored by TLC). The reaction mixture was cooled down to RT and acidified to pH = 2 by slow addition of 1 N HCl. Methanol was evaporated on a rotary evaporator and the residue was then extracted with 10 mL of ethyl acetate. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by flash chromatography using 1:1 EA/hexanes as eluent to give the titled compound as white solid (110 mg, 89%). Some product might be lost on the silica gel during purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.03 (br s, 1H), 8.04 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.14 (s, 1H), 7.09 (s, 1H), 5.84 (d, *J* = 1.1 Hz, 1H), 5.35 (d, *J* = 1.1 Hz, 1H), 1.95 (s, 3H), 1.71 (ψs, 4H), 1.31 (s, 6H), 1.28 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 149.3, 146.6, 144.6, 142.5, 138.1, 132.9, 130.5, 128.2 (3 overlapping signals), 126.8, 117.3, 35.36, 35.35, 34.2, 34.1, 32.1, 32.0, 20.1.

ESI/MS: calcd for $C_{24}H_{27}O_2$ [M^-]: 347.20. Found: 347.16.

1.4.4 Mechanistic study

Synthesis of (dnpf)Pd(Ph)I. The complex was prepared by modifying a reported procedure for (dppf)Pd(Ar)Br.[48a] In an argon-filled glove box, a 20-mL vial containing a magnetic stir bar was charged with $Pd(dba)_2$ (115 mg, 0.20 mmol), dnpf (150 mg, 0.20 mmol) and dry toluene (2.0 mL). After stirring for 15 min at RT, phenyl iodide (82 mg, 0.40 mmol; pretreated by passing through a short plug of basic alumina) was added. After stirring at RT for 3 hours, the reaction was completed (monitored by ^{31}P NMR spectroscopy). The solvent was removed under reduced pressure and the residue was subjected to flash chromatography with 1:2 hexanes/DCM as eluent. The titled compound was

obtained as yellow powder in 97% purity (108 mg, 54%). Brown single crystals suitable for X-ray crystallographic analysis were obtained by vapor diffusion of diethyl ether into a concentrated solution in DCM at RT.

^{1}H NMR (400 MHz, CD_2Cl_2): δ 9.81-9.72 (m, 3H), 9.48 (d, *J* =7.7 Hz, 1H), 8.24-8.20 (m, 2H), 8.06-7.99 (m, 3H), 7.96-7.92 (m, 2H), 7.82-7.77 (m, 2H), 7.70-7.66 (m, 3H), 7.43-7.31 (m, 6H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 7.09-7.00 (m, 2H), 6.95-6.91 (m, 1H), 6.72-6.68 (m, 1H), 6.43-6.39 (m, 2H), 6.22-6.19 (m, 1H), 5.86-5.83 (m, 1H), 5.66-5.62 (m, 1H), 4.56 (s, 1H), 4.39 (s, 1H), 4.17 (s, 1H), 4.15 (s, 1H), 4.00-3.98 (m, 4H)

^{13}C NMR (100 MHz, CD_2Cl_2): δ 148.8 (d, *J* = 124.2 Hz), 145.3 (d, *J* =32.9 Hz), 143.3 (d, *J* = 31.0 Hz), 139.8, 135.9 (d, *J* = 3.4 Hz), 135.0-134.8 (m), 134.2, 134.1, 133.84, 133.77, 133.6, 133.4, 133.0 (d, *J* = 2.5 Hz), 132.9, 132.2, 130.5, 129.9, 129.6-129.3 (m), 128.8, 128.6, 128.3, 128.2, 128.1, 126.9, 126.4, 126.3, 126.1, 126.0, 125.9, 125.8, 125.6 (d, *J* = 6.3 Hz), 125.3, 125.2 (d, *J* = 8.1 Hz), 125.0, 124.8, 124.7, 124.6, 124.5, 124.2 (d, *J* = 7.8 Hz), 121.3, 92.3 (dd, *J* = 41.5, 9.6 Hz), 87.3 (dd, *J* = 31.0, 3.1 Hz), 76.7 (d, *J* = 4.9 Hz), 75.7 (d, *J* = 10.9 Hz), 75.4 (d, *J* = 3.6 Hz), 74.7 (d, *J* = 9.8 Hz), 70.5 (d, *J* = 4.6 Hz), 70.2 (d, *J* = 5.9 Hz), 69.5 (d, *J* = 2.4 Hz), 69.4 (d, *J* = 4.1 Hz). Some doublets may have been recorded as singlets.

^{31}P NMR (162 MHz, CD_2Cl_2): δ 24.3 (d, *J* = 30.0 Hz), 13.5 (d, *J* = 30.0 Hz)

ESI/MS: calcd for $C_{56}H_{42}FeP_2Pd$ [M-I+1]: 938.11. Found: 938.93.

Stoichiometric study of styrene insertion into (dnpf)Pd(Ph)I in the presence of AgOTf. In an argon-filled glove box, a 4-mL vial containing a magnetic stir bar was charged with (dnpf)Pd(Ph)I (19 mg, 0.020 mmol), dnpf (15.1 mg, 0.020 mmol) and dry DMA (0.5 mL). After stirring at rt for 5 min, styrene (5 equiv,

10 mg, 0.10 mmol), *n*-dodecane (10 μL), AgOTf (5.2 mg, 0.020 mmol) and urotropine (5.6 mg, 0.040 mmol) were sequentially added. The reaction mixture was covered with aluminum foil and was vigorously stirred at room temperature. At intervals, an aliquot was removed and passed through a short plug of silica gel. The filtrate was subjected to GC analysis to determine yield and selectivity of the Heck products. The calibrated GC yields of the Heck product after 1, 2 and 12 hours were determined to be 63%, 68% and 70%, respectively. The selectivity of 1,1-diphenylethene versus (*E*)-stilbene was determined to 55:1 and remained constant during the course of the reaction. The isomers of the Heck product were confirmed by GCMS.

1.5 References

(1) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

(2) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.

(3) (a) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062. (b) Beletskaya, I. P.; Cheprakov, A. V. In *The Mizoroki–Heck Reaction*; John Wiley & Sons, Ltd: 2009, p 51.

(4) (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (e) Bräse, S.; Meijere, A. D. In *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH Verlag GmbH: 2008, p 217. (f) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177. (g) de Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086.

(5) Jiang, X.; Lee, G. T.; Prasad, K.; Repič, O. *Org. Process Res. Dev.* **2008**, *12*, 1137.

(6) (a) Gliemann, L.; Schmidt, J. F.; Olesen, J.; Biensø, R. S.; Peronard, S. L.; Grandjean, S. U.; Mortensen, S. P.; Nyberg, M.; Bangsbo, J.; Pilegaard, H.; Hellsten, Y. *The Journal of Physiology* **2013**, *591*, 5047. (b) Hubbard, B. P.; Gomes, A. P.; Dai, H.; Li, J.; Case, A. W.; Considine, T.; Riera, T. V.; Lee, J. E.; E, S. Y.; Lamming, D. W.; Pentelute, B. L.; Schuman, E. R.; Stevens, L. A.; Ling, A. J. Y.; Armour, S. M.; Michan, S.; Zhao, H.; Jiang, Y.; Sweitzer, S. M.; Blum, C. A.; Disch, J. S.; Ng, P. Y.; Howitz, K. T.; Rolo, A. P.; Hamuro, Y.; Moss, J.; Perni, R. B.; Ellis, J. L.; Vlasuk, G. P.; Sinclair, D. A. *Science* **2013**, *339*, 1216.

(7) (a) Haerter, R.; Lemke, U.; Radspieler, A.; WO/2005/023740: 2005. (b)

Bonrath, W.; Eggersdorfer, M.; Netscher, T. *Catal. Today* **2007**, *121*, 45. (c) Vries, J. In *Organometallics as Catalysts in the Fine Chemical Industry*; Beller, M., Blaser, H.-U., Eds.; Springer Berlin Heidelberg: 2012; Vol. 42, p 1.

(8) (a) DeVries, R. A.; Vosejpka, P. C.; Ash, M. L. *Catalysis of Organic Reactions* **1998**, *75*, 467. (b) Foster, P. S.; Ecker, E. L.; Rutter Jr, E. W.; Moyer, E. S.; US Patent 5,854,302: 1998. (c) Stark, E. J.; Schultz, J. A.; Ecker, E. L.; Devries, R. A.; US Patent 5,491,250: 1996.

(9) The Nobel Prize in Chemistry 2010, http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/.

(10) (a) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314. (b) von Schenck, H.; Åkermark, B.; Svensson, M. *J. Am. Chem. Soc.* **2003**, *125*, 3503. (c) Deeth, R. J.; Smith, A.; Brown, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7144. (d) Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5*, 31.

(11) (a) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (c) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1990**, *55*, 3654. (d) Vallin, K. S. A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 4340. (e) Ruan, J.; Xiao, J. *Acc. Chem. Res.* **2011**, *44*, 614. (f) Nilsson, P.; Olofsson, K.; Larhed, M. In *The Mizoroki–Heck Reaction*; John Wiley & Sons, Ltd: 2009, p 133. (g) Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2949.

(12) Andersson, C. M.; Hallberg, A.; Daves, G. D. *J. Org. Chem.* **1987**, *52*, 3529.

(13) Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133.

(14) Daves, G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433.

(15) (a) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**,

37, 481. (b) Reetz, M. T.; Westermann, E.; Lohmer, R.; Lohmer, G. *Tetrahedron Lett.* **1998**, *39*, 8449. (c) Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 155. (d) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H. F.; Fugami, K.; Kosugi, M. *Org. Lett.* **2001**, *3*, 3313. (e) Zheng, C.; Wang, D.; Stahl, S. S. *J. Am. Chem. Soc.* **2012**, *134*, 16496. (f) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 79. (g) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (h) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (i) Su, Y.; Jiao, N. *Curr. Org. Chem.* **2011**, *15*, 3362.

(16) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250.

(17) Gooßen, L. J.; Paetzold, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1237.

(18) (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481. (b) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558.

(19) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *Tetrahedron Lett.* **1991**, *32*, 1753.

(20) (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, *19*, 1953. (b) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417.

(21) Xu, L.; Chen, W.; Ross, J.; Xiao, J. *Org. Lett.* **2000**, *3*, 295.

(22) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2004**, *127*, 751.

(23) Hyder, Z.; Ruan, J.; Xiao, J. *Chem. Eur. J.* **2008**, *14*, 5555.

(24) Mo, J.; Xu, L.; Ruan, J.; Liu, S.; Xiao, J. *Chem. Commun.* **2006**, 3591.

(25) Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5915.

(26) (a) Qin, L.; Hirao, H.; Zhou, J. *Chem. Commun.* **2013**, *49*, 10236. (b) Liu, S.; Zhou, J. *Chem. Commun.* **2013**.

(27) Tasker, S. Z.; Gutierrez, A. C.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 1858.

(28) (a) Nadri, S.; Joshaghani, M.; Rafiee, E. *Organometallics* **2009**, *28*, 6281. (b) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2002**, *43*, 2191. (c) Tobrman, T.; Dvorak, D. *Tetrahedron Lett.* **2004**, *45*, 273.

(29) Ruan, J.; Iggo, J. A.; Berry, N. G.; Xiao, J. *J. Am. Chem. Soc.* **2010**, *132*, 16689.

(30) Andersson, C. M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757.

(31) Jeffery, T. *Tetrahedron Lett.* **1991**, *32*, 2121.

(32) Itami, K.; Yoshida, J.-I. In *The Mizoroki–Heck Reaction*; John Wiley & Sons, Ltd: 2009, p 259.

(33) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 11270.

(34) Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980.

(35) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 9692.

(36) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 13981.

(37) (a) Boehm, M. F.; Zhang, L.; Badea, B. A.; White, S. K.; Mais, D. E.; Berger, E.; Suto, C. M.; Goldman, M. E.; Heyman, R. A. *J. Med. Chem.* **1994**, *37*, 2930. (b) Faul, M. M.; Ratz, A. M.; Sullivan, K. A.; Trankle, W. G.; Winneroski, L. L. *J. Org. Chem.* **2001**, *66*, 5772. (c) Büttner, M. W.; Nätscher, J. B.; Burschka, C.; Tacke, R. *Organometallics* **2007**, *26*, 4835.

(38) (a) Cramer, P. E.; Cirrito, J. R.; Wesson, D. W.; Lee, C. Y. D.; Karlo, J. C.; Zinn, A. E.; Casali, B. T.; Restivo, J. L.; Goebel, W. D.; James, M. J.; Brunden,

K. R.; Wilson, D. A.; Landreth, G. E. *Science* **2012**, *335*, 1503. (b) Fitz, N. F.; Cronican, A. A.; Lefterov, I.; Koldamova, R. *Science* **2013**, *340*, 924.

(39) (a) Messaoudi, S.; Treguier, B.; Hamze, A.; Provot, O.; Peyrat, J.-F.; De Losada, J. R.; Liu, J.-M.; Bignon, J.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *J. Med. Chem.* **2009**, *52*, 4538. (b) Alvarez, R.; Alvarez, C.; Mollinedo, F.; Sierra, B. G.; Medarde, M.; Pelaez, R. *Bioorg. Med. Chem.* **2009**, *17*, 6422.

(40) (a) Nicolaou, K. C.; Snyder, S. A.; Huang, X. H.; Simonsen, K. B.; Koumbis, A. E.; Bigot, A. *J. Am. Chem. Soc.* **2004**, *126*, 10162. (b) Jeong, J. H.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 2309.

(41) (a) Hamze, A.; Giraud, A.; Messaoudi, S.; Provot, O.; Peyrat, J.-F.; Bignon, J.; Liu, J.-M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *Chemmedchem* **2009**, *4*, 1912. (b) Botteghi, C.; Corrias, T.; Marchetti, M.; Paganelli, S.; Piccolo, O. *Org. Process Res. Dev.* **2002**, *6*, 379. (c) Cee, V. J.; Frohn, M.; Lanman, B. A.; Golden, J.; Muller, K.; Neira, S.; Pickrell, A.; Arnett, H.; Buys, J.; Gore, A.; Fiorino, M.; Horner, M.; Itano, A.; Lee, M. R.; McElvain, M.; Middleton, S.; Schrag, M.; Rivenzon-Segal, D.; Vargas, H. M.; Xu, H.; Xu, Y.; Zhang, X.; Siu, J.; Wong, M.; Bürli, R. W. *ACS Med. Chem. Lett.* **2011**, *2*, 107.

(42) (a) Bess, E. N.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 646. (b) Song, S.; Zhu, S.-F.; Yu, Y.-B.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 1556. (c) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B. n.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344. (d) Wang, X.; Guram, A.; Caille, S.; Hu, J.; Preston, J. P.; Ronk, M.; Walker, S. *Org. Lett.* **2011**, *13*, 1881.

(43) (a) Saa, J. M.; Dopico, M.; Martorell, G.; Garciaraso, A. *J. Org. Chem.* **1990**, *55*, 991. (b) Cabri, W.; Candiani, I.; Debernardinis, S.; Francalanci, F.; Penco, S.; Santi, R. *J. Org. Chem.* **1991**, *56*, 5796.

(44) Fristrup, P.; Le Quement, S.; Tanner, D.; Norrby, P.-O. *Organometallics* **2004**, *23*, 6160.

(45) Nussbaumer, P.; Dorfstatter, G.; Grassberger, M. A.; Leitner, I.; Meingassner, J. G.; Thirring, K.; Stutz, A. *J. Med. Chem.* **1993**, *36*, 2115.

(46) (a) Ludwig, M.; Stromberg, S.; Svensson, M.; Akermark, B. *Organometallics* **1999**, *18*, 970. (b) Hii, K. K.; Claridge, T. D. W.; Giernoth, R.; Brown, J. M. *Adv. Synth. Catal.* **2004**, *346*, 983.

(47) CCDC 873139 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.cam.ac.uk /data_request/cif.

(48) (a) Sergeev, A. G.; Artamkina, G. A.; Khrustalev, V. N.; Antipin, M. Y.; Beletskaya, I. P. *Mendeleev Commun.* **2007**, *17*, 142. (b) Czauderna, C.; Wurziger, H.; Sun, Y.; Thiel, W. R. *Z. Anorg. Allg. Chem.* **2008**, *634*, 2380.

(49) Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178*, 511.

(50) (a) Ascenso, J. R.; de C.T. Carrondo, M. A. A. F.; Dias, A. R.; Gomes, P. T.; Fátima, M.; Piedade, M.; Romao, C. C.; Revillon, A.; Tkatchenko, I. *Polyhedron* **1989**, *8*, 2449. (b) Albers, I.; Álvarez, E.; Cámpora, J.; Maya, C. M.; Palma, P.; Sánchez, L. J.; Passaglia, E. *J. Organomet. Chem.* **2004**, *689*, 833. (c) Anderson, T. J.; Vicic, D. A. *Organometallics* **2004**, *23*, 623.

(51) Taylor, M. J. W.; Eckenhoff, W. T.; Pintauer, T. *Dalton Trans.* **2010**, *39*, 11475.

(52) Frlan, R.; Gobec, S.; Kikelj, D. *Tetrahedron* **2007**, *63*, 10698.

(53) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694.

(54) Im, G. Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H. Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933.

(55) Senboku, H.; Fujimura, Y.; Kamekawa, H.; Tokuda, M. *Electrochimica Acta* **2000**, *45*, 2995.

(56) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500.

(57) Li, S.; Dieter, R. K. *J. Org. Chem.* **2003**, *68*, 969.

(58) Stang, P.; Treptow, W. *Synthesis* **1980**, 283.

(59) Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662.

(60) Molander, G. A.; Brown, A. R. *J. Org. Chem.* **2006**, *71*, 9681.

(61) Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, *1999*, 1875.

(62) Price, C. J.; Zeits, P. D.; Reibenspies, J. H.; Miller, S. A. *Organometallics* **2008**, *27*, 3722.

(63) Boehm, M. F.; Heyman, R. A.; U.S. 7655699: 2010.

(64) Wagner, C. E.; Jurutka, P. W.; Marshall, P. A.; Groy, T. L.; van der Vaart, A.; Ziller, J. W.; Furmick, J. K.; Graeber, M. E.; Matro, E.; Miguel, B. V.; Tran, I. T.; Kwon, J.; Tedeschi, J. N.; Moosavi, S.; Danishyar, A.; Philp, J. S.; Khamees, R. O.; Jackson, J. N.; Grupe, D. K.; Badshah, S. L.; Hart, J. W. *J. Med. Chem.* **2009**, *52*, 5950.

Chapter 2 Palladium-Catalyzed Intermolecular Heck Reaction of Alkyl Halides

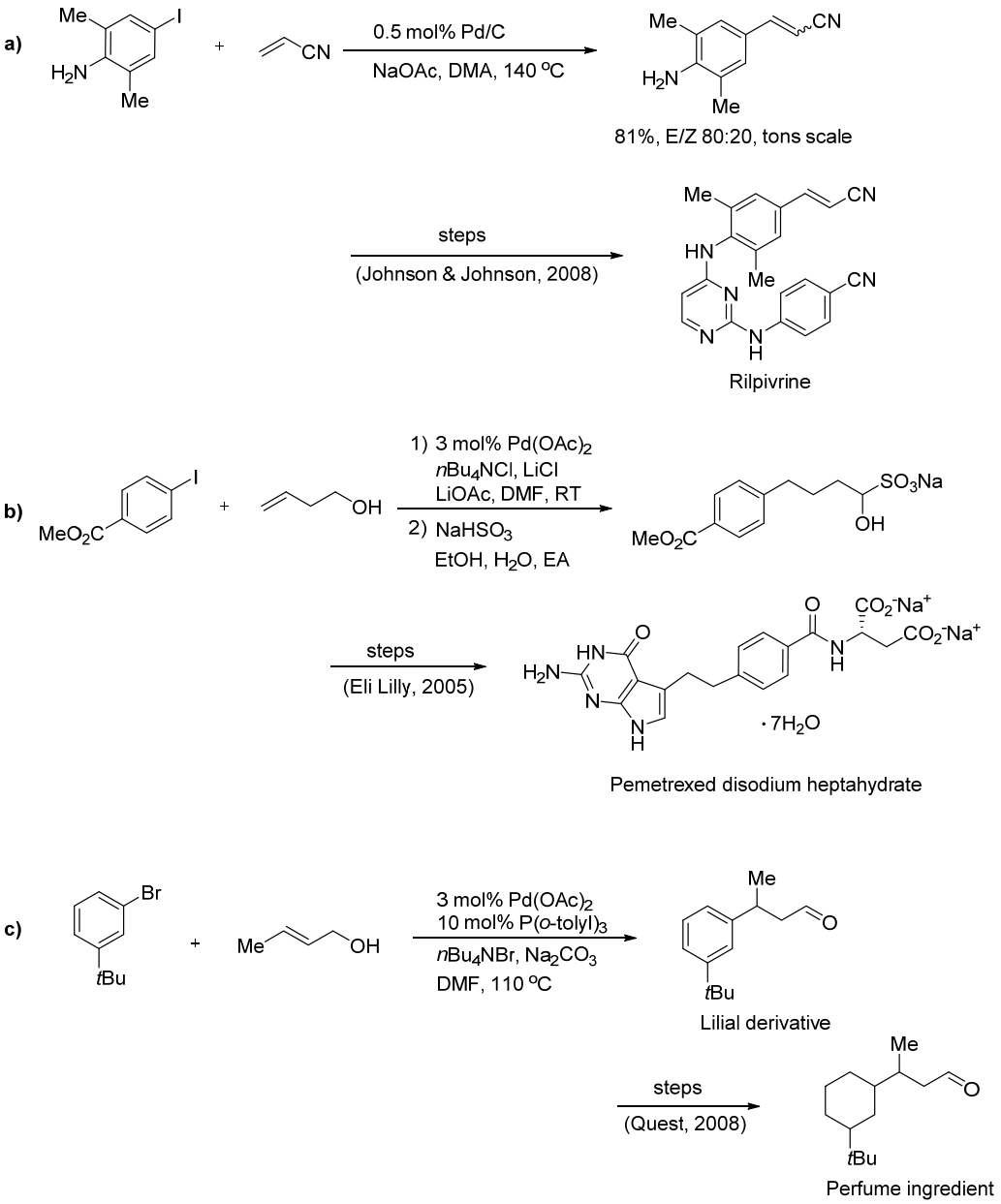
2.1 Introduction

2.1.1 General introduction of Heck reaction

Since its discovery by Heck[1] and Mizoroki[2], the Heck reaction has become an important tool for the construction of carbon-carbon bonds in organic synthesis.[3] It has been widely applied for the preparation of intermediates in industry. For example, Johnson & Johnson developed a Heck process for the production of Rilpivirine, which is a non-nucleoside reversed transcriptase inhibitor for the treatment of HIV-1 infection (Scheme 2.1, **a**).[4] Eli Lilly uses the Heck reaction to produce the feedstock en route to pemetrexed disodium heptahydrate (tradename *Alimta*®), which is a chemotherapy drug for the treatment of non-squamous non-small cell lung cancer and malignant pleural mesothelioma (Scheme 2.1, **b**).[5] Quest international (acquired by Givaudan) used Heck reaction as a key step to access novel fragrance compounds (Scheme 2.1, **c**).[6] Perfumes containing these ingredients showed strong and pleasant odour, good substantivity to hair and cloth, antibacterial and antimicrobial properties, *etc*. The significance of Heck reaction has been highlighted by the award of Nobel Prize in Chemistry in 2010.[7]

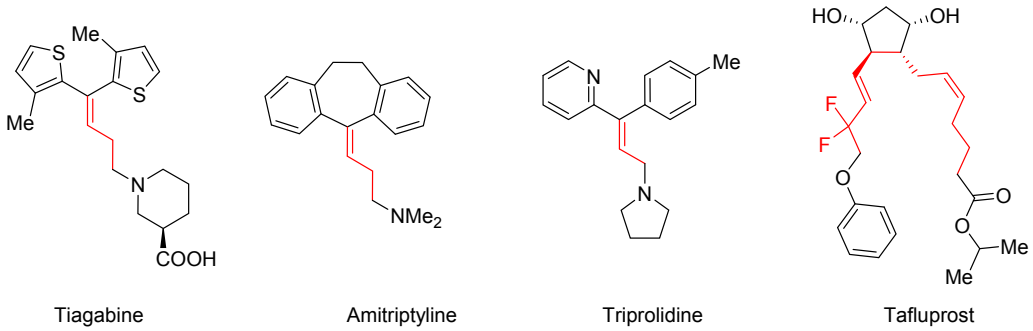
The Heck reaction of aryl and vinyl halides has been well developed and widely applied.[3] Generally, the nature of halides does not only change the reaction rate as oxidative addition is assumed to be the rate-determining step, but also determines the reaction pathway. Less substituted olefins are more reactive than more substituted ones. The Heck reaction is best applied to the terminal olefins which undergo a faster reaction rate and now both internal and

terminal insertion products can be obtained in excellent selectivity. Electron deficient olefins give higher yields than electron rich olefins. The ligand is important regarding to both reactivity and selectivity of the reaction outcome. Bulky electron rich phosphines can catalyze unactivated aryl chlorides. The reaction can be performed in various solvents including both polar and non-polar solvents. Although the Heck reaction is sensitive to oxygen, it is tolerant with water.



Scheme 2.1. Selected examples of Heck reaction in industry.

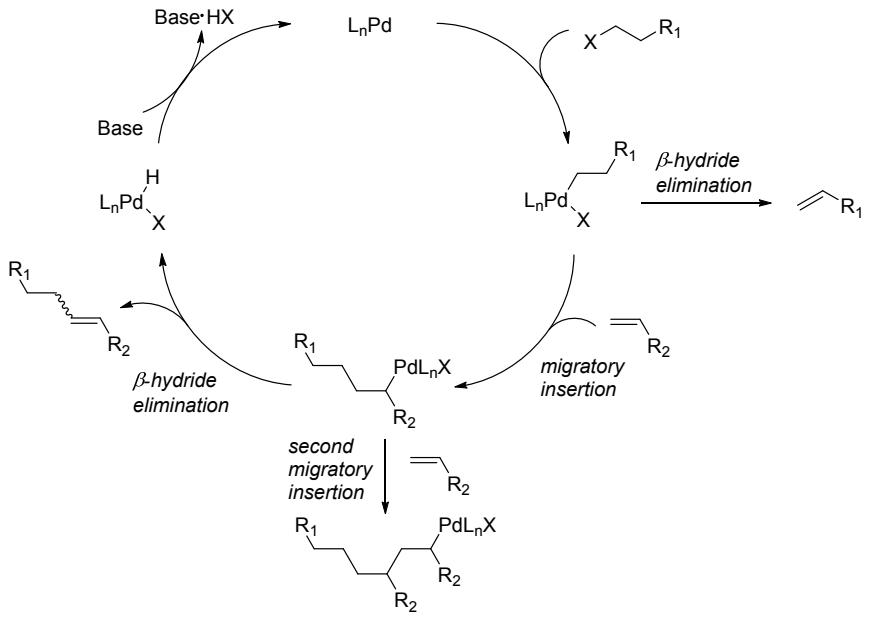
However, even after more than 40 years since the initial discovery, Heck reaction of common alkyl halides still remains a great challenge. Industrial processes are limited to aryl halides. Alkenes with alkyl groups are common core structure presented in many drugs (Scheme 2.2).[8] For example, amitriptyline is widely used for the treatment of depressive disorder, which is on the World Health Organization's List of Essential Medicines.[9] Heck reaction of alkyl halides and olefins would provide alternative ways to synthesize bioactive compounds and aid in the development of drug discoveries.



Tiagabine Amitriptyline Triprolidine Tafluprost

Scheme 2.2. Selected drug molecules of alkenes with alkyl groups.

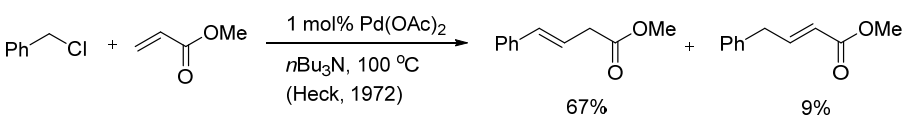
Generally, alkyl halides are more difficult than aryl and vinyl halides to undergo oxidative addition to a low-valent metal center, as the C(sp^3)-X bond is more electron rich than the C(sp^2)-X bond. The subsequently resulting alkyl-metal complex is highly reactive due to the lacking of stabilization with empty d orbitals of the metal and predominantly led to side reactions such as β-hydride elimination and hydrodehalogenation.[10] Meanwhile, a second olefin is possible to insert into the alkyl-metal complex, which further complicates the reaction as shown in the generalized catalytic cycle for Heck reaction of alkyl halides (Scheme 2.3). More and more studies are undergoing to develop active catalysts for the alkyl halides.



Scheme 2.3. A possible catalytic cycle for Heck reaction of alkyl halides.

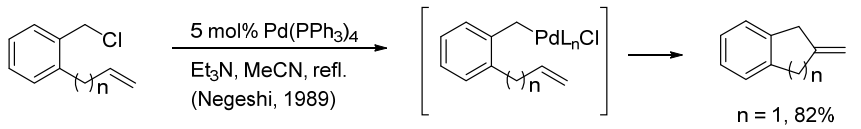
2.1.2 Heck reaction of benzyl halides without β-hydrogen atoms

In the past decades, alkyl halides without β-hydrogen atoms were used in Heck reaction to circumvent the undesirable β-hydride elimination. Among them, benzyl halides are the most common and well-studied electrophiles. In 1972, Heck *et al.* discovered the first example of coupling reaction of benzyl chloride with methyl acrylate in moderate yield. The major olefinic product *trans*-methyl-4-phenyl-3-butenoate was obtained due to double bond migration of the immediate Heck product, which became the minor product, at high temperature (eq 2.1).[1] Although Heck suggested $Pd(OAc)_2$ was reduced by the olefin, later studies revealed that α-hydrogen containing amine bases or phosphine ligands would be responsible for the reduction of Pd^{II} to Pd^0.[11] Then oxidative addition between benzyl chloride and in situ generated Pd^0 occurred to enter into the catalytic cycle as depicted in Scheme 2.3.

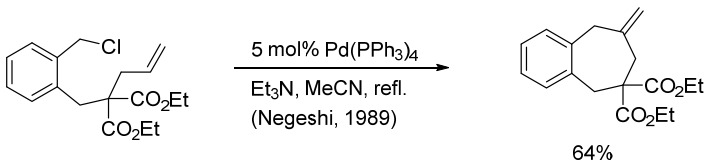


(2.1)

Later, Negeshi *et al.* developed a Pd-catalyzed cyclization of benzyl halides, including Cl, Br, I, OMs, and OCO_2Me, with tethered alkenes to form five- to seven-membered carbocycles (eq 2.2 – 2.3).[12] They suggested the catalytic reaction most likely proceeded through a benzylpalladation intermediate after oxidative addition, rather than via radical cyclization. Treatment with typical radical cyclization condition, which was 6 mol% AIBN and 1.2 equiv nBu$_3$SnH with benzene as solvent, only led to hydrostannation products without any formation of desired cyclization products. It is arguable that common radical initiator did not catalyze the cyclization reaction could rule out the involvement of free radicals in the reaction condition.



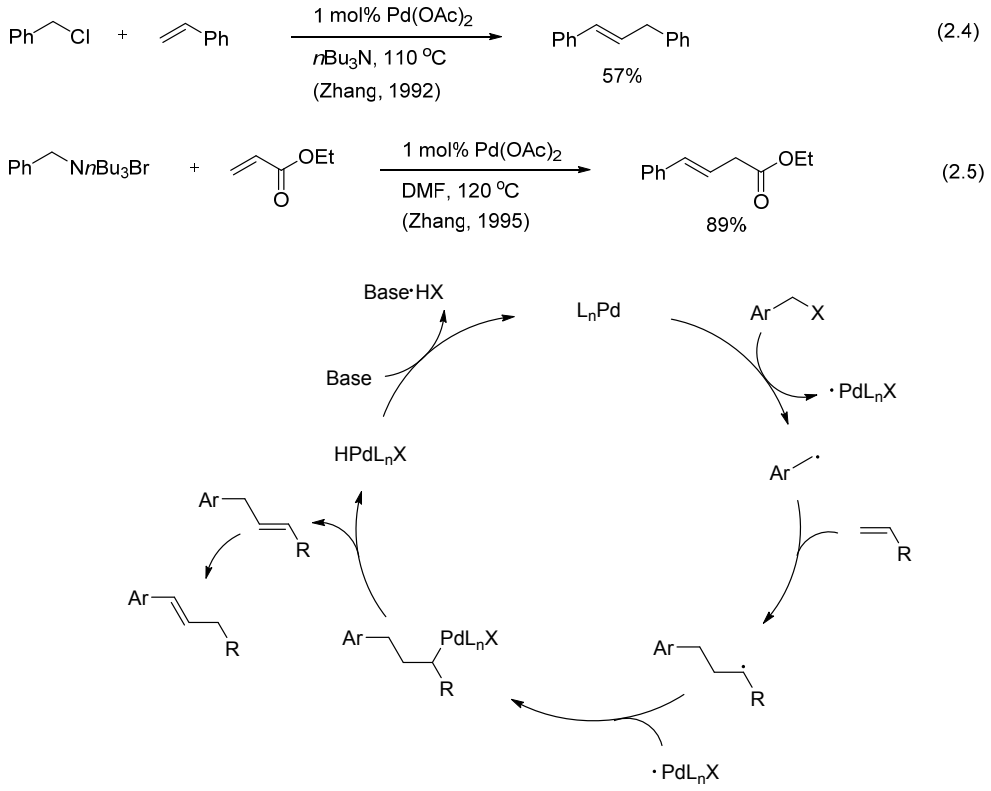
(2.2)



(2.3)

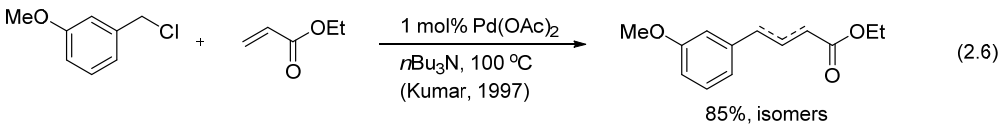
Zhang *et al.* further developed the intermolecular Heck reaction of benzyl chlorides as well as benzyl tributylammonium bromides with various olefins that afforded the coupling products in moderate to good yield (eq 2.4 – 2.5).[13] The conjugated products were obtained due to isomerization catalyzed Pd-hydride at high temperature. It was noteworthy that the above reactions were totally inhibited after the addition of radical scavenger – 1,4-dinitrobezene. When they conducted the spin trapping experiments for the reaction using *tert*-nitrosobutane, the ESR spectra showed clear signals of benzyl *tert*-butyl nitroxide radical which indicated the involvement of free radicals in the catalytic reactions. According to the observation, they proposed a catalytic

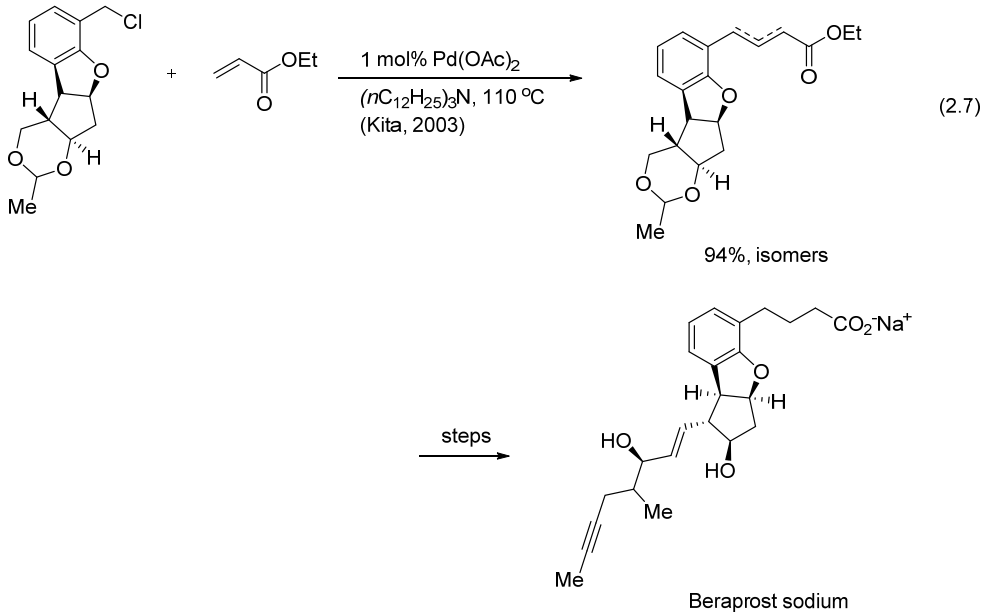
cycle via single electron transfer process as shown in Scheme 2.4.



Scheme 2.4. A plausible catalytic cycle via free radical process.

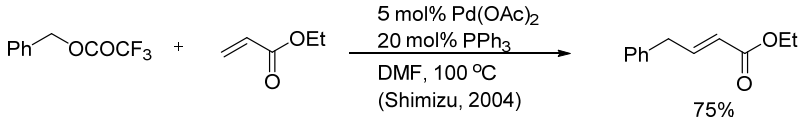
Similar conditions for Heck reactions of benzyl chlorides were also developed for the preparation of synthetic intermediates. For example, Kumar *et al.* used the Heck reaction of benzyl chloride with ethyl acrylate as a key step to prepare substituted 1-tetralones (eq 2.6).[14] Kita *et al.* developed the Heck reaction of benzyl chloride for the synthesis of Beraprost intermediate, of which the sodium salt is an anti-platelet drug candidate (eq 2.7).[15]



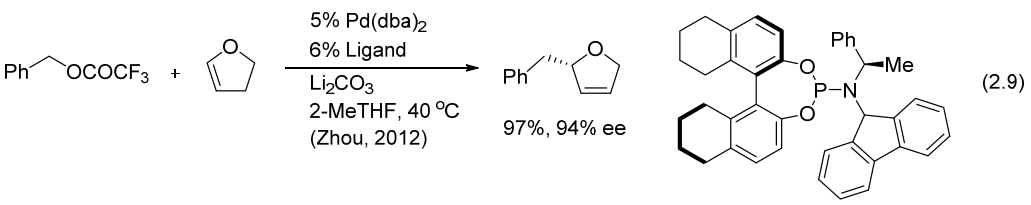


(2.7)

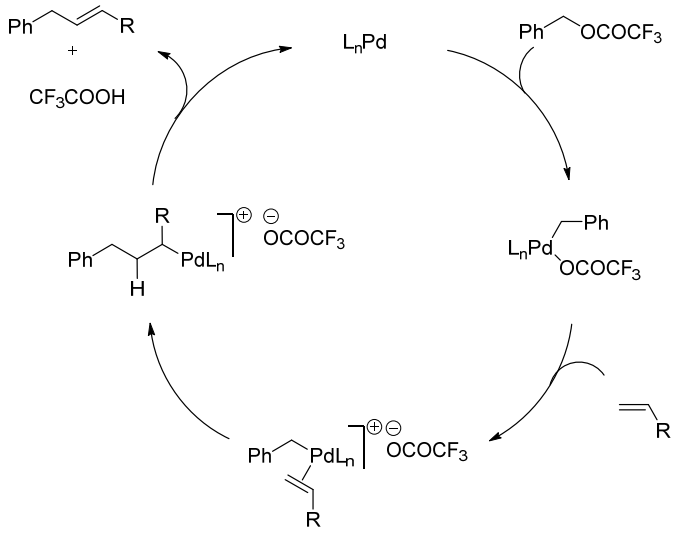
Shimizu *et al.* reported benzyl trifluoroacetates could be used as effective electrophiles to couple with various olefins (eq 2.8).[16] They successfully managed to obtain the immediate Heck product without olefin isomerization. Recently, our group reported the first asymmetric Heck reaction of benzyl trifluoroacetates with cyclic olefins in excellent stereoselectivity under mild reaction condition (eq 2.9).[17] For these reactions, a cationic Pd-benzyl species was probably involved in the catalytic cycle, as evidenced by ^{1}H NMR study on the reaction intermediates by Shimizu and Yamamoto (Scheme 2.5).[18]



(2.8)



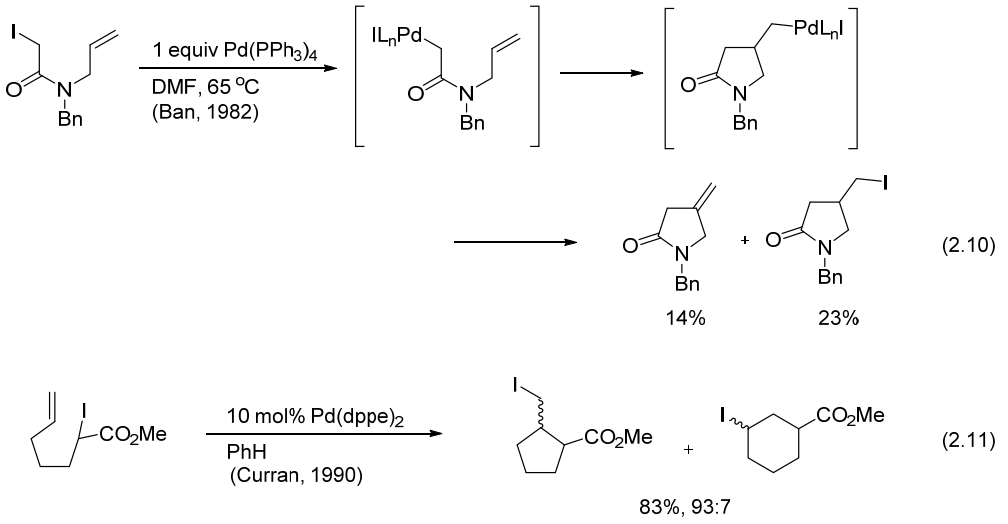
(2.9)



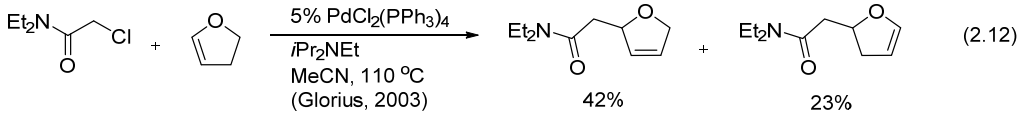
Scheme 2.5. A plausible catalytic cycle via cationic Pd intermediate.

2.1.3 Heck reaction of α-halocarbonyl compounds without β-hydrogen atoms

α-Halocarbonyl compounds are also often used electrophiles without bearing β-hydrogen atoms. In 1982, Ban *et al.* reported the ene-halogenocyclization of primary α-iodoamide in the presence of stoichiometric amount of $Pd(PPh_3)_4$ which was the first example of this type (eq 2.10).[19] They proposed that the olefinic product was obtained through β-hydride elimination from the σ-alkylmetal complex after oxidative addition, while the iodide was formed via directly reductive elimination of Pd-species. Curran *et al.* revealed that this transformation may proceed through an atom transfer process after they conducted a series of control experiments for the mechanistic study.[20] The outcome of control experiments using ditin $(n\text{Bu}_3\text{Sn})_2$ or $Pd(dppe)_2$ as catalyst was almost identical regarding of both yield and isomeric selectivity. Thus they suggested free radicals were involved in the reaction (eq 2.11).[20-21] Jiang's recent study on cyclization of unactivated alkyl iodides also suggested an atom transfer process was accounted for the Heck products.[22]

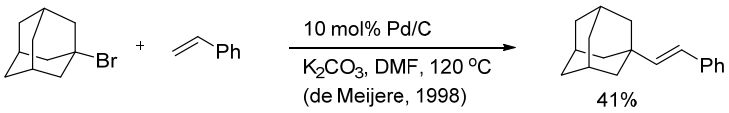


In 2003, Glorius reported palladium-catalyzed intermolecular Heck reaction of α-chloroamides with olefins in moderate to good yield. The ubiquitously observed α-insertion products of 2,3-dihydrofuran pointed out that the involvement of palladium enolates was highly likely as the free radical process would lead to the formation of β-substituted dihyrofuran (eq 2.12).[23]



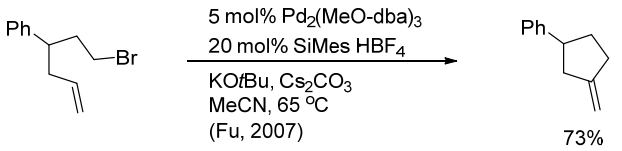
2.1.4 Heck reaction of common alkyl halides containing β-hydrogen atoms

Alkyl halides that carry β-hydrogens have been also studied for Heck reaction. de Meijere *et al.* reported the coupling reactions of 1-bromoadamantane with various styrenes (eq 2.13).[24] It was interesting that when *trans*-styrene-(β)-d was used, both *trans*-β-adamantylstyrene and *trans*-β-adamantylstyrene-(β)-d were obtained in 1:1 ratio. It indicated that the reaction might proceed via a free radical pathway or a cationic Pd-intermediate, as *syn*-addition of adamantylpalladium bromide to styrene and subsequent *syn*-β-hydride elimination would only lead to *trans*-β-adamantylstyrene.

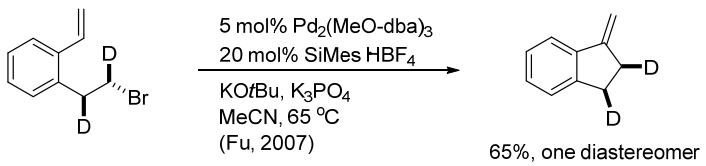


(2.13)

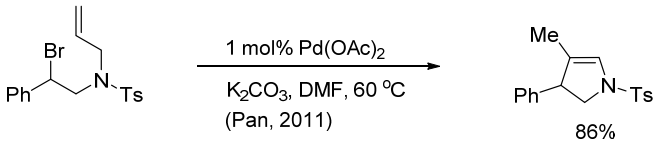
For those alkyl halides bearing eliminable β-hydrogen atoms, intramolecular cyclization onto pedant olefins can proceed efficiently to form five- or six-membered rings. In 2007, Fu *et al.* reported the intramolecular Heck reaction of unactivated alkyl bromides and chlorides using a palladium/*N*-heterocyclic carbene catalyst to afford five-membered methylenecyclpentanes in good yield (eq 2.14).[25] The coupling reaction of a secondary alkyl bromide was not tolerated under their standard condition, neither was a disubstituted olefin. The formation of a six-membered carbocyle was not successful. Later, Pan *et al.* reported a ligand-free palladium-catalyzed cyclization of secondary bromides affording pyrroline derivatives in good yield and regioselectivity (eq 2.16).[26] In both above works, only one diastereomeric configuration was detected in the products from stereospecific starting materials under catalytic reaction conditions (eq 2.15 and 2.17). Thus, those reactions proceeded via alkylpalladium intermediates with an S_N2 mechanism for oxidative addition, as diastereomers would emerge if free radicals were involved.



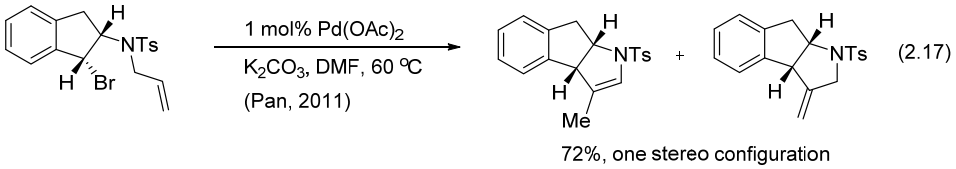
(2.14)



(2.15)

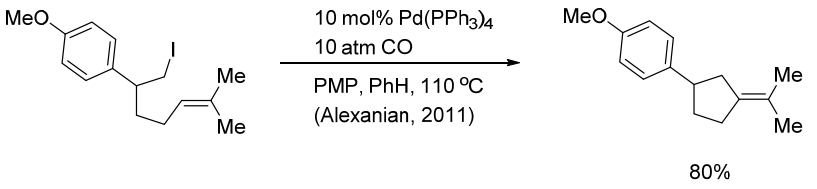


(2.16)

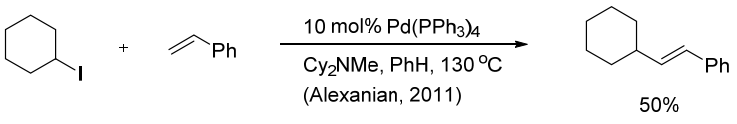


(2.17)

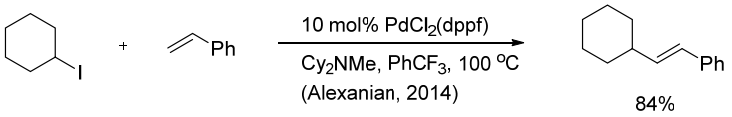
Recently, Alexanian *et al.* disclosed an efficient palladium-catalyzed carbocyclization of alkyl iodides to generate both five- and six-membered rings (eq 2.18).[27] The catalysis can be applied to olefins bearing multiple substituents, which are more difficult to undergo Heck reaction than terminal alkenes. They trapped the reaction intermediate with TEMPO, a common radical trapping reagent, under catalytic reaction condition, which indicated the involvement of free radicals. The CO atmosphere possibly led to the formation of a $Pd(PPh_3)_x(CO)_y$ species that could stabilize the intermediate to increase the yield. They suggested a hybrid organometallic-radical process as illustrated in Scheme 2.6. Three examples of Heck reactions of cyclohexyl iodide with styrenes were reported, which gave around 50% yield (eq 2.19). During the preparation of this thesis, the group reported an improved catalyst for Heck reaction of alkyl halides (eq 2.20).[28]



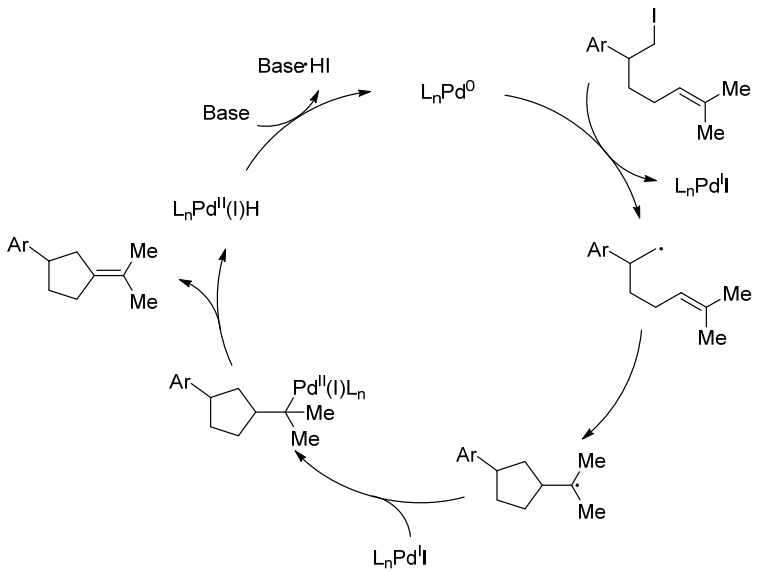
(2.18)



(2.19)



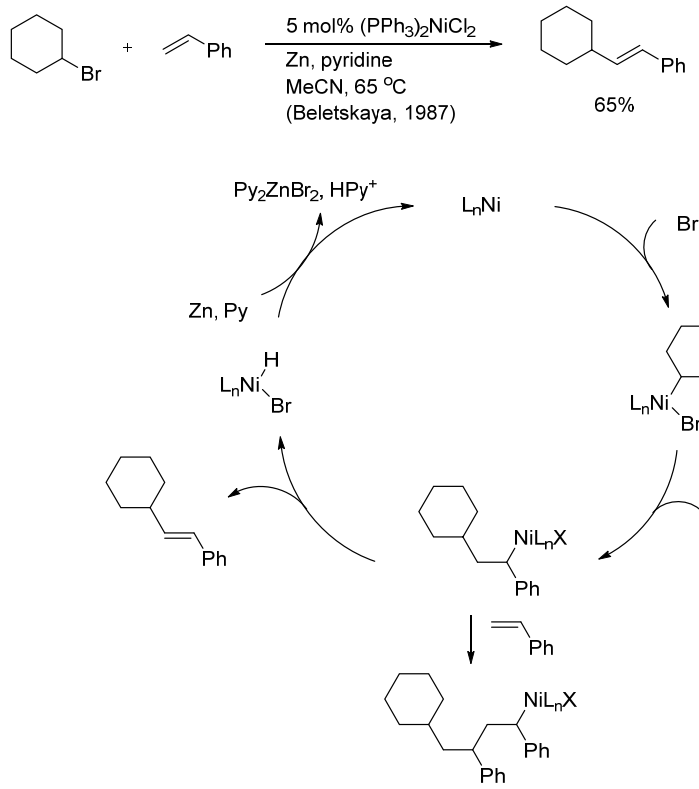
(2.20)



Scheme 2.6. Proposed catalytic cycle of carbocyclization.

2.1.5 Heck reaction of alkyl halides catalyzed by other metals

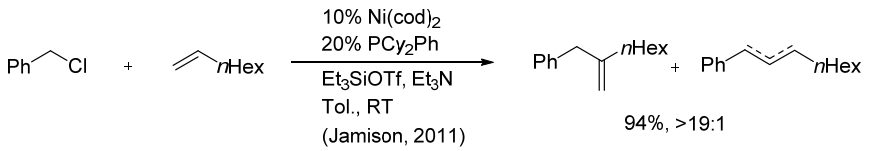
Back in 1988, Beletskaya *et al.* reported six examples of Ni-catalyzed Heck reaction of alkyl halides with styrene which gave yields ranging from 11% to 65% (eq 2.21).[29] Originally, they suggested a similar reaction pathway to the general catalytic cycle of Pd catalysis that involved an alkylnickel intermediate (Scheme 2.7). Zinc was required as a reductant for the regeneration of Ni^0 from $HNiBrL_2$.[30] Pyridine was critical as a base, as other bases such as Et_3N inhibited the reaction completely. Pyridine also served as a ligand on Ni. They also observed the double insertion of styrene byproduct.[31] When methyl acrylate was used as olefin, the coupling product was obtained in good yield without formation of double insertion byproduct. Coupling reactions of primary alkyl halides suffered from low yield due to the fast β-hydride elimination of alkylnickel intermediates. In retrospect, a radcial-type oxidative addition and radical addition to styrene were probably involved.



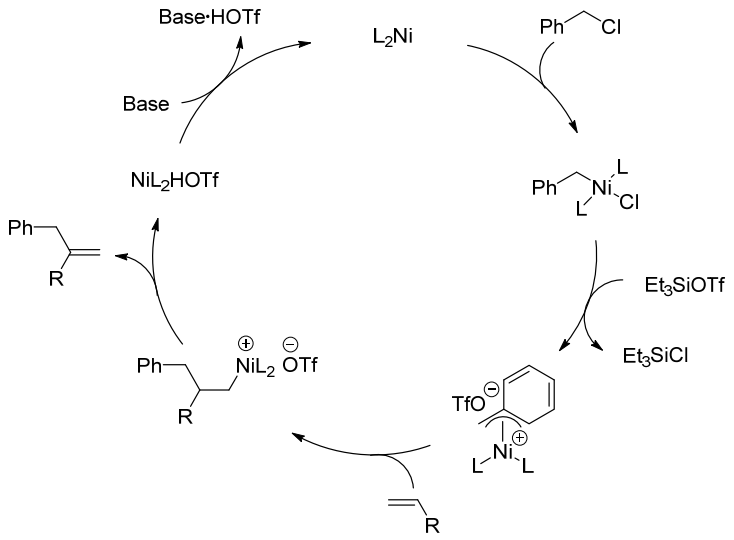
(2.21)

Scheme 2.7. Proposed catalytic cycle of Heck reaction by Ni in the presence of zinc.

Ni catalysts have been developed for the alkenylation of benzyl halides. Jamison *et al.* reported the nickel catalyst for the Heck reaction of benzyl chlorides with various electronically unbiased aliphatic olefins in excellent yield and regioselectivity (eq 2.22).[32] The additive Et_3SiOTf promoted the formation of a cationic η^3-Ni-benzyl complex after oxidative addition of benzyl chloride. The cationic Ni^{II} intermediate would preferentially lead to the internal insertion product due to steric hindrance of bulky phosphines (Scheme 2.8).



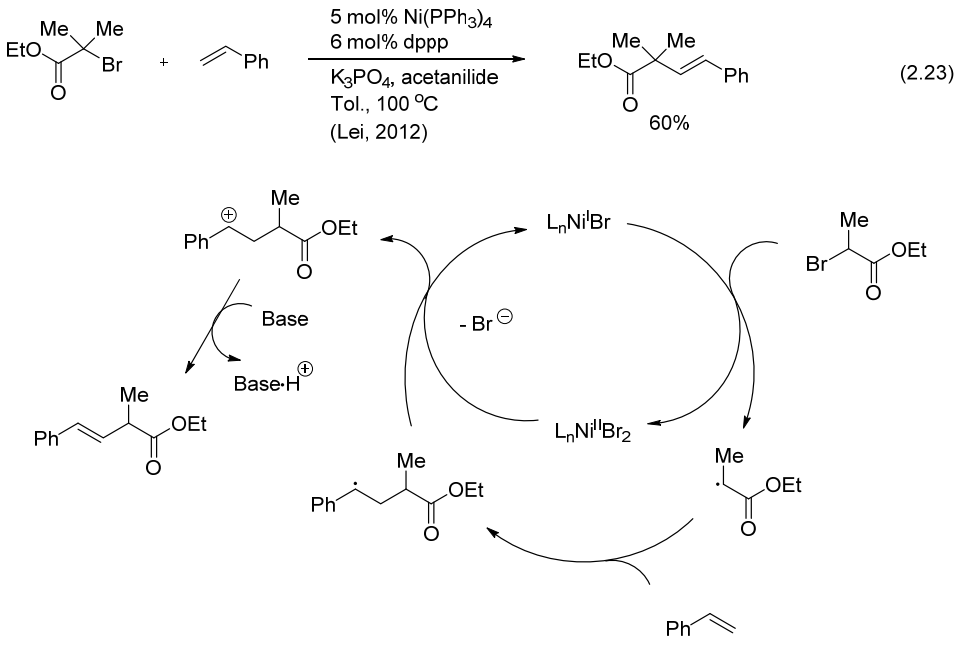
(2.22)



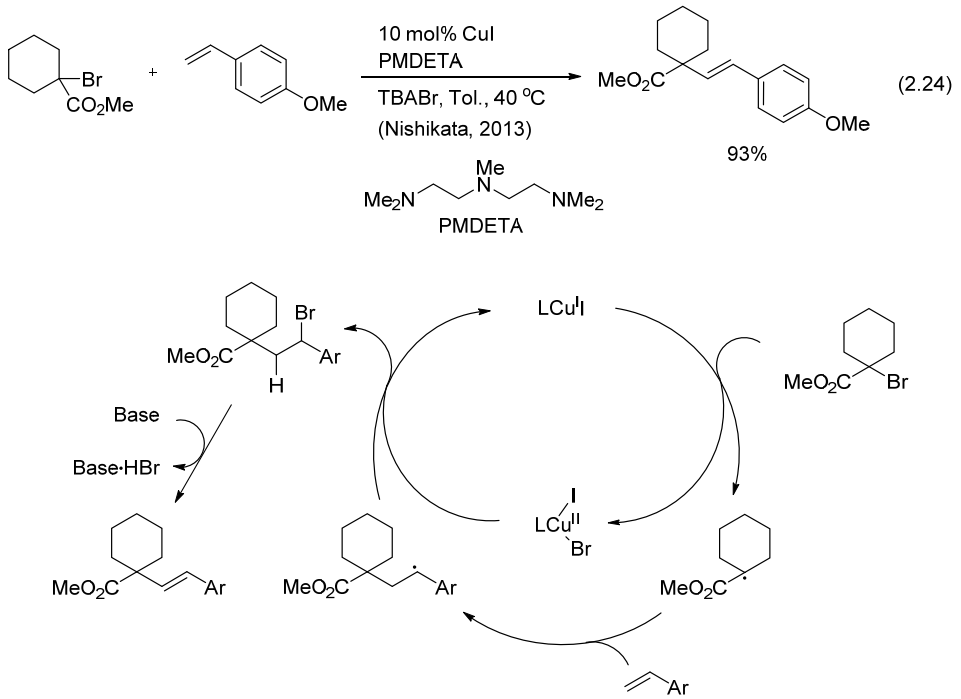
Scheme 2.8. Proposed catalytic cycle involving of η^3-Ni intermediate.

More recently, Lei *et al.* reported a nickel catalysis for intermolecular Heck reaction of secondary and tertiary bromoesters and amides with aromatic olefins (eq 2.23).[33] Based on their mechanistic study, they suggested a catalytic cycle involving a single electron transfer process (Scheme 2.9). $(PPh_3)_3Ni^{I}Br$ species generated from $Ni(PPh_3)_4$ and bromoesters was the active catalyst. The resulting α-carbonyl radical then added up to the styrene to form a benzyl radical, which would be oxidized by $(PPh_3)_2Ni^{II}Br_2$ species to a benzyl cationic intermediate. The final base-assisted deprotonation afforded the Heck product.

Nishikata *et al.* reported a copper catalysis for the Heck-type coupling reaction of tertiary α-bromoesters with styrenes (eq 2.24).[34] The catalytic cycle was initiated by the Cu^{I} complex via atom transfer radical addition to generate the tertiary alkyl radical and Cu^{II} complex. The resulting alkyl radical added onto styrene to form a benzylic radical, which was oxidized by Cu^{II} complex. Base-assisted deprotonation afforded the alkene product. The choice of PMDETA was crucial for this transformation which served as both a ligand[35] and a base (Scheme 2.10).



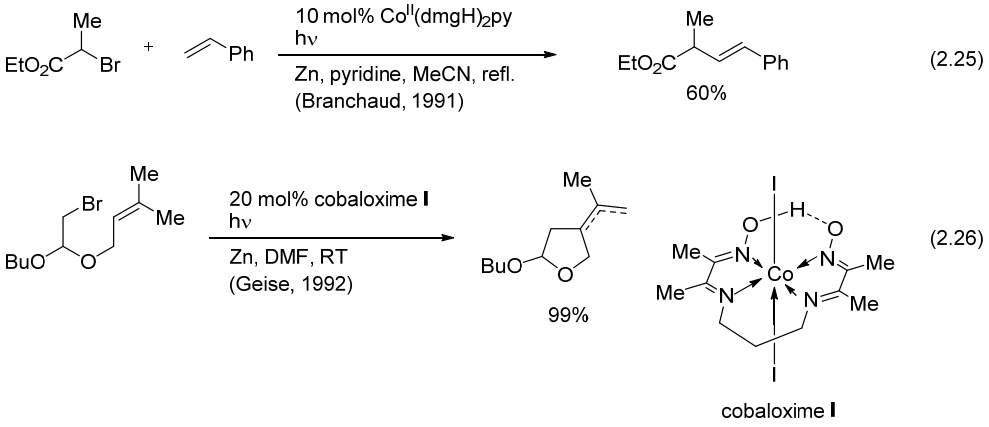
Scheme 2.9. Proposed catalytic cycle involving Ni^{I} and Ni^{II} complexes.

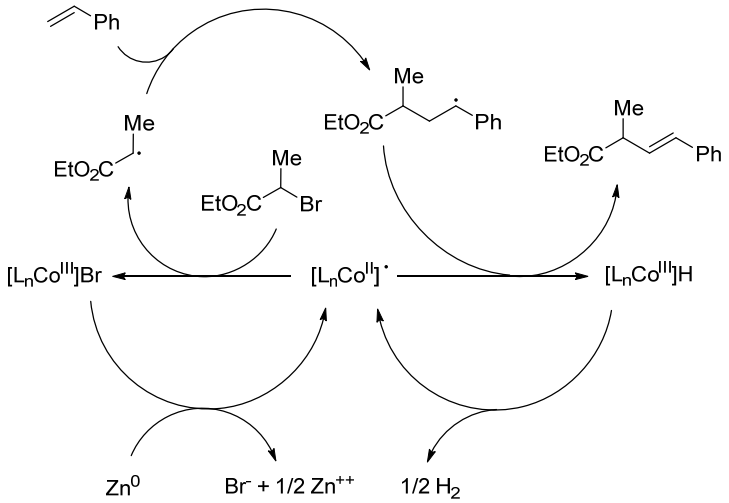


Scheme 2.10. Proposed catalytic cycle by Cu-complex.

Cobalt-catalyzed coupling reaction of alkyl halides has been well studied. In early 1990s, Branchaud *et al.* reported the coupling reaction of α-bromoesters with styrene using cobaloxime as catalyst under the irradiation (eq 2.25).[36] The

reaction of $Co^{II}(dmgH)_2py$ (dmgH = dimethylglyoxime monoanion) with α-bromoesters under the visible light generated the alkyl radical, which was trapped by the styrene. The resulting benzylic radical underwent β-hydrogen abstraction by Co^{II} radical complex to afford the coupling product (Scheme 2.11). Zn served as a reductant to regenerate Co^{II} radical complex from Co^{III}. Giese *et al.* reported the cyclization of bromoacetals catalyzed cobaloxime **I** by under irradiation (eq 2.26).[37]

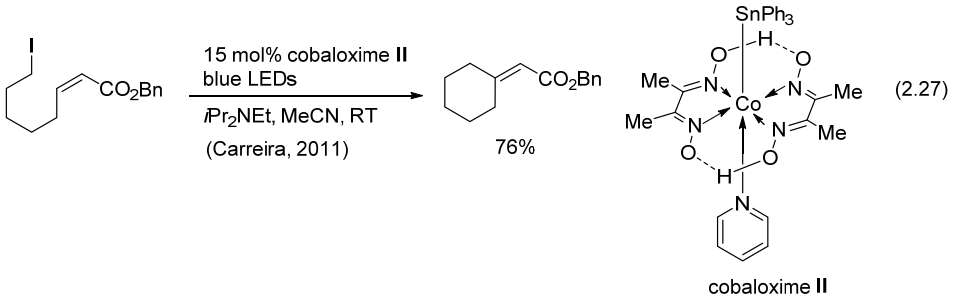


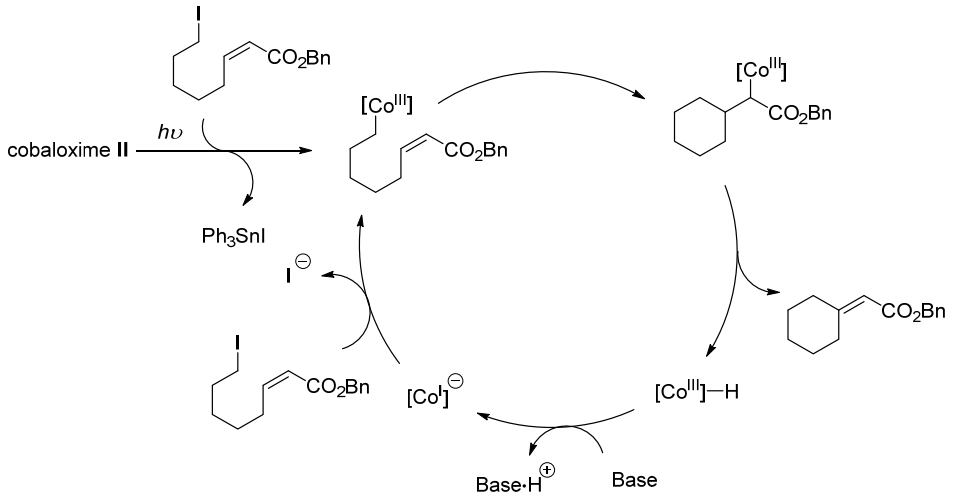


Scheme 2.11. Proposed catalytic cycle by cobaloxime.

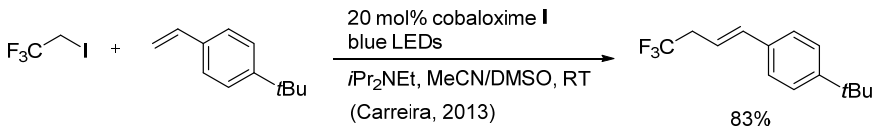
Carreira *et al.* developed cobalt-catalyzed Heck reaction of alkyl iodides with tethered olefins (eq 2.27).[38] The reaction of cobaloxime **II** and alkyl iodide

under irradiation of visible light would generate a Co^{III}-alkyl complex that underwent intramolecular addition to the olefin. The resulting adduct afforded the product and a putative Co^{III}-H intermediate which would be deprotonated by the amine base to generate the catalytically active Co^{I}-species (Scheme 2.12). A wild range of functional groups such as esters, amides, ketones, and aldehydes were tolerated. Later, they also reported the trifluoroethylation of styrene using cobaloxime **II** as photocatalyst (eq 2.28). The reaction was developed in the flow reactor which afforded the product with high efficiency (eq 2.29).[39]

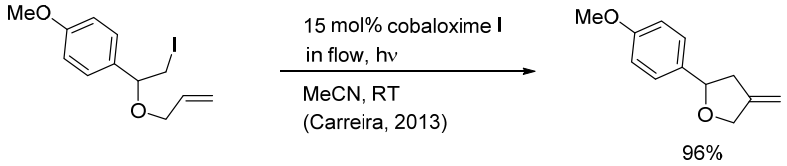




Scheme 2.12. Proposed catalytic cycle of Co-catalyzed intramolecular Heck reaction.

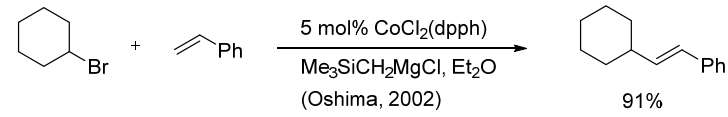


(2.28)

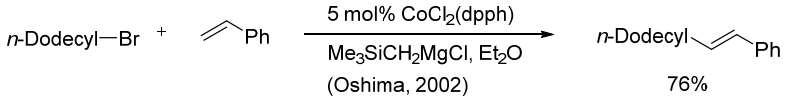


(2.29)

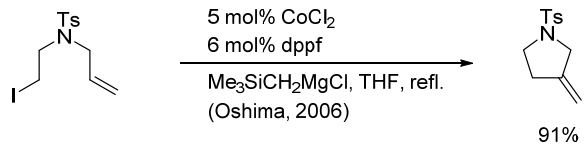
In 2002, Oshima *et al.* reported cobalt-catalyzed coupling reactions of secondary halides with styrenes in good yields (eq 2.30).[40] The bidentate ligand – 1,6-bis(diphenylphosphino)hexane (dpph) was crucial as the supporting ligand to furnish the products in good yield, while other mono- and bis-phospines generally gave a rise of the double insertion of styrene byproducts. In the proposed catalytic cycle, the highly reactive Grignard reagent was also critical to generate the active Co^0-complex at initiation step and trap the electron deficient 12-electron cationic $Co^I(dpph)^+$-complex after alkyl halide underwent the single electron transfer process (Scheme 2.13). The catalyst also coupled primary halides with styrene in good yield (eq 2.31). Under elevated temperature, intramolecular Heck reaction proceeded well to afford six-membered ring products (eq 2.32).



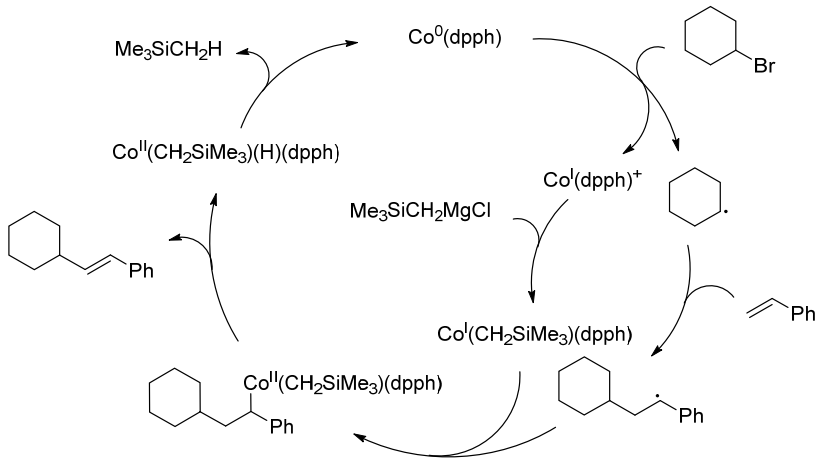
(2.30)



(2.31)

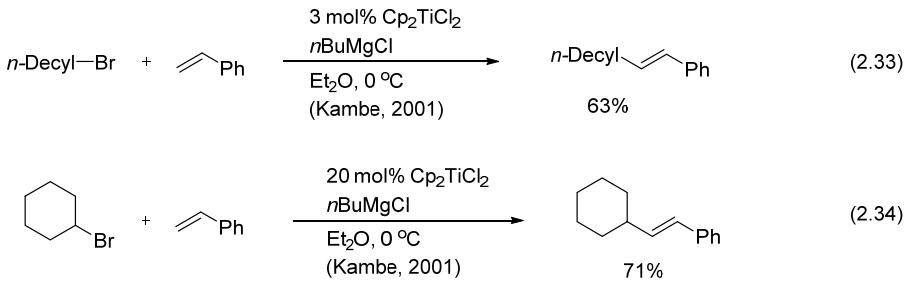


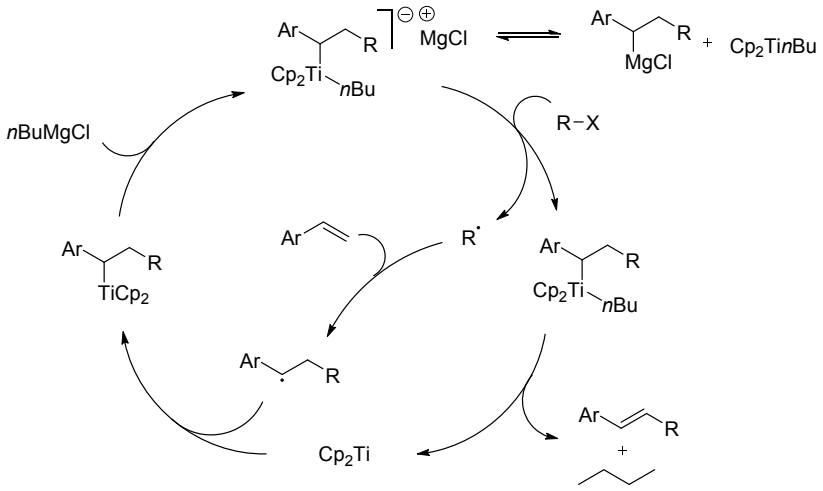
(2.32)



Scheme 2.13. Proposed catalytic cycle of Co-catalyzed Heck reaction.

Kambe *et al.* reported the coupling reactions of primary and secondary alkyl halides with styrenes using Cp_2TiCl_2 as a catalyst in the presence of Grignard reagent (eq 2.33 – 2.34).[41] In the ether solvent, Grignard reagent served to generate the active titanocene ate complex. The ate complex would transfer one electron to alkyl halide resulting an alkyl radical, which reacted with styrene to form a benzyl radical species, and a benzylbutyltitanocene complex, which underwent β-hydride elimination to afford the product and regeneration of Cp_2Ti. The benzyl radical species and Cp_2Ti then entered into another catalytic cycle (Scheme 2.14).





Scheme 2.14. Proposed catalytic cycle of Ti-catalyzed Heck reaction.

2.1.6 Summary of Heck reaction of alkyl halides

As described, many transition metal catalysts have been developed for the Heck reaction of alkyl halides. Benzyl halides and α-carbonyl halides are most common electrophiles as they do not contain eliminable β-hydrogen atoms. Although alkyl halides containing eliminable β-hydrogen atoms are more challenging, many breakthroughs have been made in recent years. Along with Pd catalysts, other transition metal catalysts such as Ni, Cu, Co and Ti are explored to furnish the products. However, excess amount of halides are commonly required to obtain satisfactory yields. Stoichiometric amounts of alkylmetal reductants such as Grignard reagents were needed in Co- or Ti-catalyzed coupling reactions. Ester or amide groups at α-carbon of alkyl halides were universally presented in Ni- or Co-catalyzed coupling reactions, which limited the general applicability of these coupling reactions. Premature β-hydride elimination remains a great problem and very limited examples of Pd-catalyzed Heck reaction of alkyl halides were reported. We aimed to realize the

Pd-catalyzed intermolecular Heck reaction of common alkyl halides under mild reaction condition.

2.2 Results and discussion

Pd-catalyzed intermolecular Heck reaction of common alkyl halides remained a great challenge. Encouraged by Alexanian's work on cyclization of unactivated alkyl halides, we proposed that incorporation of proper ligands, such as bisphosphines of large cone angles and more steric hindered ligands, into the catalyst would slow down the rate of β-hydride elimination and enhance the rate of migratory insertion. Thus, the intermolecular Heck reaction of common alkyl halides could be achieved. Herein, we are delighted to disclose the Pd catalysis for the coupling reaction of alkyl halides with styrenes.

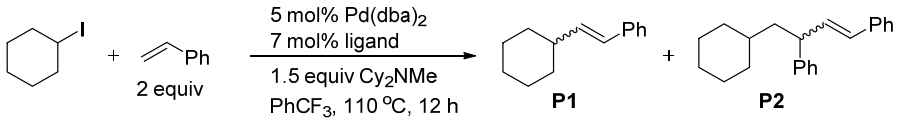
The products – *trans*-β-alkylstyrenes are common structures in organic synthesis. They used to be prepared from cross-couplings of *trans*-vinylmetals or vinyl halides.[42] Wittig reaction of aryl-substituted triphenylphosphine ylides typically gave a mixture of *trans*- and *cis*-isomers.[43] To form selectively *trans*-olefins, modified *P*-ylides reagents, arylaldimine or Schlosser modification was needed.[44] Ruthenium-catalyzed olefin metathesis are also often used to construct *trans*-β-alkylstyrenes.[45]

2.2.1 Condition optimizations of model reactions

We chose a model reaction of cyclohexyl iodide with styrene to search for an active Pd catalyst. After many trials, we found that NHC, BOX and PyBOX were not effective for this transformation. To our delight, dppf was a quite active ligand (entry 1, Table 2.1). The desired *trans*-isomer was obtained in 70% yield and in good *E*/*Z* ratio (14:1). Other mono- and bis-phosphines were much worse, which mainly led to β-hydride elimination byproduct. For example, dppp, an effective ligand in Lei's procedure[33a] gave no desired product (entry 6). (*R*)-BINAP and DPEphos only furnished 40% and 56% yield, respectively,

despite of full conversion of cyclohexyl iodide (entries 7 and 10). Reactions with other phosphines were of low conversion and gave trace desired products. We also conducted the study of ligands for *n*-decyl iodide and styrene and found out that dppf still served as the best ligand.

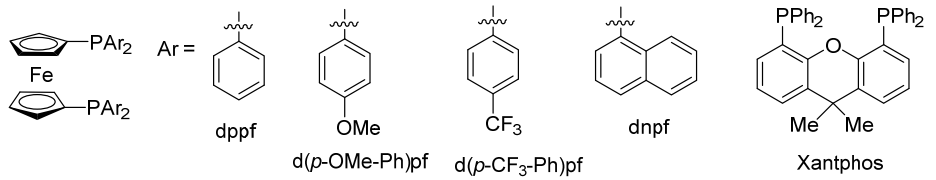
Table 2.1. Effect of phosphorus ligands on Heck reaction

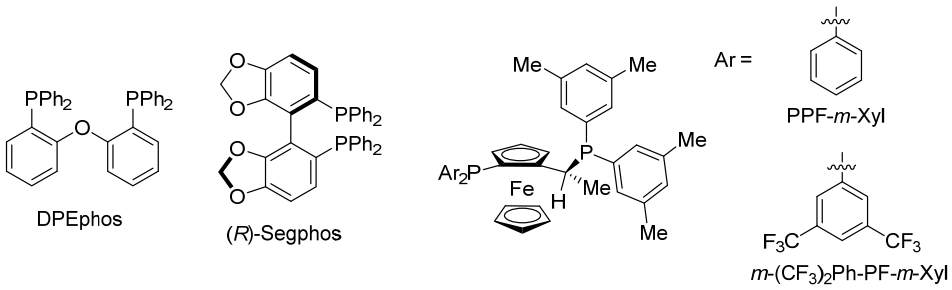


Entry	Ligand	Conv. (%)[a]	P1		P2	
			Yield of *E* (%)[a]	*E*/*Z*[b]	Yield of *E* (%)[a]	*E*/*Z*[b]
1	dppf	100	**70**	14	9	8
2	d(*p*-OMe-Ph)pf	100	58	6	13	5
3	d(*p*-CF_3-Ph)pf	100	48	6	11	5
4	dnpf	57	12	38	5	28
5	dippf	18	2	7	2	-
6	dppp	15	0	-	0	-
7	dppe	14	0	-	0	-
8	dppb	23	0	-	0	-
9	(*R*)-BINAP	96	40	4	10	4
10	(*R*)-Segphos	59	10	3	4	3
11	Xantphos	14	3	-	-	-
12	DPEphos	96	56	9	11	5
13	*m*-$(CF_3)_2$Ph-PF-*m*-Xyl	56	1	6	-	-
14	PPF-*m*-Xyl	20	0	-	0	-
15	P(*o*-tolyl)$_3$	5	0	-	0	-
16	P(2-furyl)$_3$	14	4	9	4	10
17	PCy_3	26	1	-	0	-
18	P(*t*Bu)$_3$	28	1	-	5	-

[a] Reaction condition: CyI (0.10 mmol), styrene (0.20 mmol), $Pd(dba)_2$ (0.005 mmol), ligand (0.007 mmol), Cy_2NMe (0.15 mmol), $PhCF_3$ (0.40 mL). Conversion and yield were determined by GC versus a calibrated internal standard. [b] Selectivity

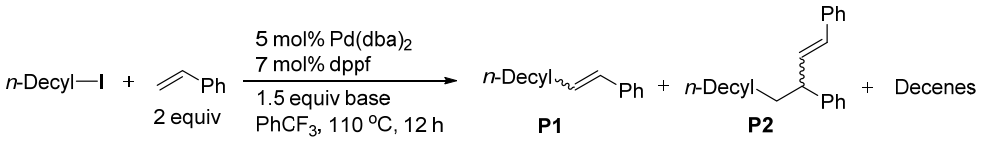
was determined by GC. ^{1}H NMR spectroscopy was unsuitable for the determination of selectivity due to low signal intensity of the minor isomer.





We then chose the model reaction of *n*-decyl iodide with styrene to study the effect of bases and solvents for two considerations: 1) *n*-decyl iodide is much more challenging in this transformation as it is so prone to undergo β-hydride elimination. 2) The β-hydride elimination byproduct, decenes from *n*-decyl iodide can be detected and quantified by GC, while cyclohexene from cyclohexyl iodide is too volatile for quantification. As summarized in Table 2.2, we found that most of the bases were ineffective. Inorganic salts such as alkali phosphates, acetates and pivolates only afforded <15% yield of desired product with less than 50% conversion of *n*-decyl iodide (entries 1-5). The organic bases generally gave better yields than the inorganic bases, probably due to the better solubility in non-polar solvent $PhCF_3$. While Et_3N, nBu_3N and iPr_2NMe furnished around 20% yield (entries 6-8), we are delighted that Cy_2NMe gave the best yield of 54% with 5:1 isomeric ratio (entry 9). In some reported examples, Cy_2NMe can have a significant impact in regard of reactivity and selectivity in Heck reaction.[46] With the best base in hand, we then continued to look into the effect of solvents.

Table 2.2. Influence of bases on the model Heck reaction.



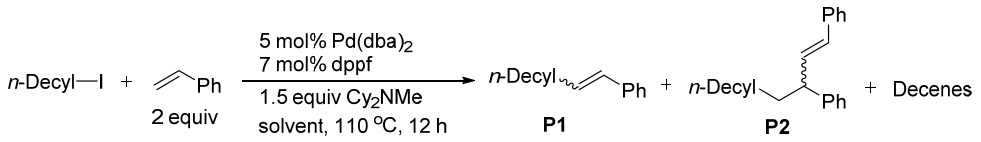
Entry	Base	Conv. (%)[a]	P1		P2		Decenes
			Yield of *E* (%)[a]	*E*/*Z*[b]	Yield of *E* (%)[a]	*E*/*Z*[b]	Yield (%)[a]
1	K_3PO_4	44	9	3	2	5	3
2	LiOAc	18	5	3	1	5	2
3	NaOAc	25	4	2	1	5	2
4	KOAc	51	14	3	3	6	5
5	LiOPiv	43	13	3	3	5	7
6	Et_3N	68	20	3	4	5	7
7	nBu$_3$N	75	20	3	4	5	7
8	iPr$_2$NMe	75	25	3	5	5	8
9	Cy$_2$NMe	100	**54**	5	4	6	15
10	2,6-lutidine	18	4	2	1	6	1

[a] Reaction condition: *n*-decyl-I (0.10 mmol), styrene (0.20 mmol), $Pd(dba)_2$ (0.005 mmol), dppf (0.007 mmol), base (0.15 mmol), $PhCF_3$ (0.40 mL). Conversion and yield were determined by GC versus a calibrated internal standard. [b] Selectivity was determined by GC.

The model reaction indeed proceeded in various solvents as summarized in Table 2.3. In general, ethereal solvents such as THF, THP, 2-MeTHF and nBu$_2$O afforded ~30% yield of desired product (entries 1-4). In dioxane, DME and Triglyme, an increased yield was observed which is higher than 40% (entries 5-7). In amide solvents such as DMA and NMP, the reaction afforded the product in ~40% yield (entries 9 and 10). In aromatic hydrocarbon solvents such as toluene, *p*-xylene and *m*-xylene, the reaction furnished around 40% yield (entries 11-15). Among them, we found that $PhCF_3$ was the best solvent, which afforded the desired product in 54% yield and 5:1 selectivity (entry 12).

From the table, we concluded that the formation of decenes via the β-hydride elimination was the major side reaction.

Table 2.3. Effect of solvents on the model Heck reaction.



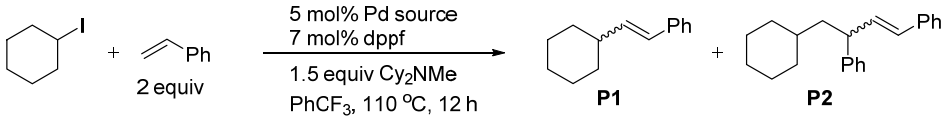
Entry	Solvent	Conv. (%)	P1		P2		Decenes
			Yield of *E* (%)	*E/Z*	Yield of *E* (%)	*E/Z*	Yield (%)
1	THF	73	25	3	4	6	15
2	THP	80	32	4	5	7	16
3	2-MeTHF	77	30	4	5	6	17
4	nBu$_2$O	80	30	4	7	7	13
5	1,4-Dioxane	98	43	5	5	7	25
6	DME	100	46	7	4	10	30
7	Triglyme	100	47	6	5	9	19
8	TBME	55	19	4	5	6	6
9	DMA	99	39	4	4	7	30
10	NMP	100	33	4	4	6	33
11	Veratrol	100	52	7	6	9	19
12	PhCF$_3$	100	**54**	5	4	6	15
13	Toluene	91	40	5	5	7	22
14	*o*-Xylene	90	39	4	6	7	20
15	*p*-Xylene	90	37	3	6	7	20

[a] Reaction condition: *n*-decyl-I (0.10 mmol), styrene (0.20 mmol), Pd(dba)$_2$ (0.005 mmol), ligand (0.007 mmol), Cy$_2$NMe (0.15 mmol), solvent (0.40 mL). Conversion and yield were determined by GC versus a calibrated internal standard.
[b] Selectivity was determined by GC.

Then we studied the effect of Pd sources on the model reactions. For cyclohexyl iodide, all Pd^0 complexes performed well to furnish the products in good yield and selectivity, more than 70% and 10:1 *E*/*Z* ratio in general. In

contrast, $Pd(dppf)Cl_2$ afforded the products in 36% yield and 4:1 selectivity (entry 4, Table 2.4). When $Pd(dba)_2$ was switched to $Pd(PPh_3)_4$, the yield was improved from 70% to 79% with satisfactory selectivity (entry 1 and 5). $Pd(dppf)_2$ was highly active by itself (entry 9). Under these conditions, some byproduct, about 10%, derived from insertion of two styrene molecules was detected. The inclusion of additional 2 equiv of LiI did not improve the yield much (entry 6), which was very effective for primary alkyl halides as described in later. In the dark, the catalysis also proceeded with the same efficiency, which excluded the involvement of photocatalytic process (entry 7).

Table 2.4. Effect of Pd sources on the model Heck reaction of cyclohexyl iodide.

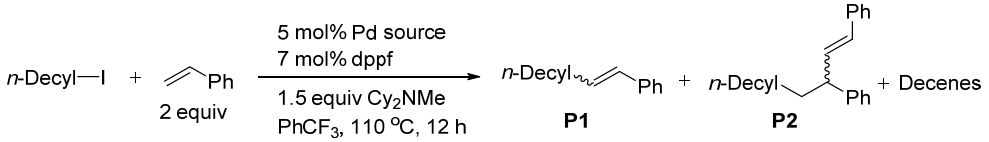


Entry	Pd source	Conv. (%)[a]	P1		P2	
			Yield of *E* (%)[a]	*E*/*Z*[b]	Yield of *E* (%)[a]	*E*/*Z*[b]
1	$Pd(dba)_2$	100	**70**	14	9	8
2	$Pd_2(dba)_3$	99	75	10	11	6
3	$Pd(PtBu_3)_2$	100	48	6	11	5
4[c]	$Pd(dppf)Cl_2$	86	36	4	10	4
5	$Pd(PPh_3)_4$	100	**79**	19	11	8
6[d]	$Pd(PPh_3)_4$	100	**80**	35	11	9
7[e]	$Pd(PPh_3)_4$	100	**79**	20	10	8
8[c]	Pd(dppf)(dba)	100	**76**	32	8	11
9[c]	$Pd(dppf)_2$	100	**81**	62	7	28

[a] Reaction condition: CyI (0.10 mmol), styrene (0.20 mmol), $Pd(dba)_2$ (0.005 mmol), dppf (0.007 mmol), Cy_2NMe (0.15 mmol), $PhCF_3$ (0.40 mL). Conversion and yield were determined by GC versus a calibrated internal standard. [b] Selectivity was determined by GC. ^1H NMR spectroscopy was unsuitable for the determination of selectivity due to low signal intensity of the minor isomer. [c] No added dppf. [d] 2 equiv LiI. [e] In the dark.

For *n*-decyl iodide, all Pd^0 sources furnished the products in moderate yield and selectivity with a significant amount of decenes (entries 1-3, Table 2.5). $Pd(dba)_2$ was slightly more effective than other Pd^0 complexes, which gave 54% yield and 5:1 olefinic selectivity (entry 1). Similar to the observation in Heck reaction of cyclohexyl iodide, $Pd(dppf)_2$ itself was highly active (entry 5). Some byproduct, <10%, derived from insertion of two styrene molecules was detected. To our surprise, the inclusion of additional 2 equiv of LiI improved the yield about 10% to 65% with 8:1 olefinic selectivity (entry 6). We reasoned that the additional halide ions may stabilize the alkylpalladium intermediate which might lead to a relative faster rate of migratory insertion.[47] By changing the molar ratio of *n*-decyl iodide and styrene from 1:2 to 3:1, we managed to further improve the yield to 81% (entry 3, Table 2.6). When 5 mol% Pd/dppf catalyst was used, the conversion of styrene was much lower. We tested some nickel complexes such as $Ni(cod)_2$ and $Ni(PPh_3)_4$ for the catalytic reaction and did not observe the desired products.

Table 2.5. Effect of Pd sources on the model Heck reaction of *n*-decyl iodide.

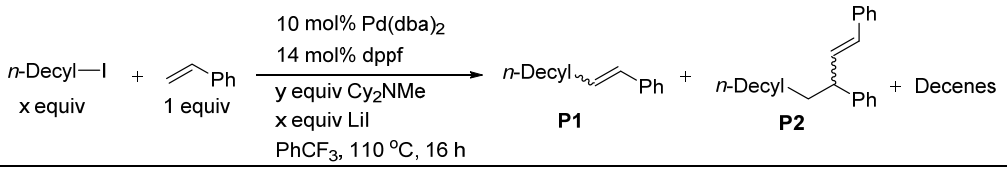


Entry	Pd source	Conv. (%)[a]	P1		P2		Decenes
			Yield of *E* (%)[a]	*E*/*Z*[b]	Yield of *E* (%)	*E*/*Z*[b]	Yield (%)[a]
1	$Pd(dba)_2$	100	54	5	4	6	15
2	$Pd(PtBu_3)_2$	100	50	8	4	11	32
3	$Pd(PPh_3)_4$	100	51	8	6	8	22
4[c]	Pd(dba)(dppf)	100	54	5	7	7	23

5[c]	$Pd(dppf)_2$	100	55	6	5	8	30
6[d]	$Pd(dba)_2$	100	**65**	8	8	7	19
7[e]	Pd(dba)(dppf)	100	**64**	9	8	16	24
8[e]	$Pd(dppf)_2$	100	55	8	4	13	34

[a] Reaction condition: *n*-decyl-I (0.10 mmol), styrene (0.20 mmol), $Pd(dba)_2$ (0.005 mmol), dppf (0.007 mmol), Cy_2NMe (0.15 mmol), $PhCF_3$ (0.40 mL). Conversion and yield were determined by GC versus a calibrated internal standard. [b] Selectivity was determined by GC. [c] No added dppf. [d] 2 equiv LiI. [e] No added dppf and 2 equiv LiI.

Table 2.6. Further optimization on the model Heck reaction of *n*-decyl iodide.



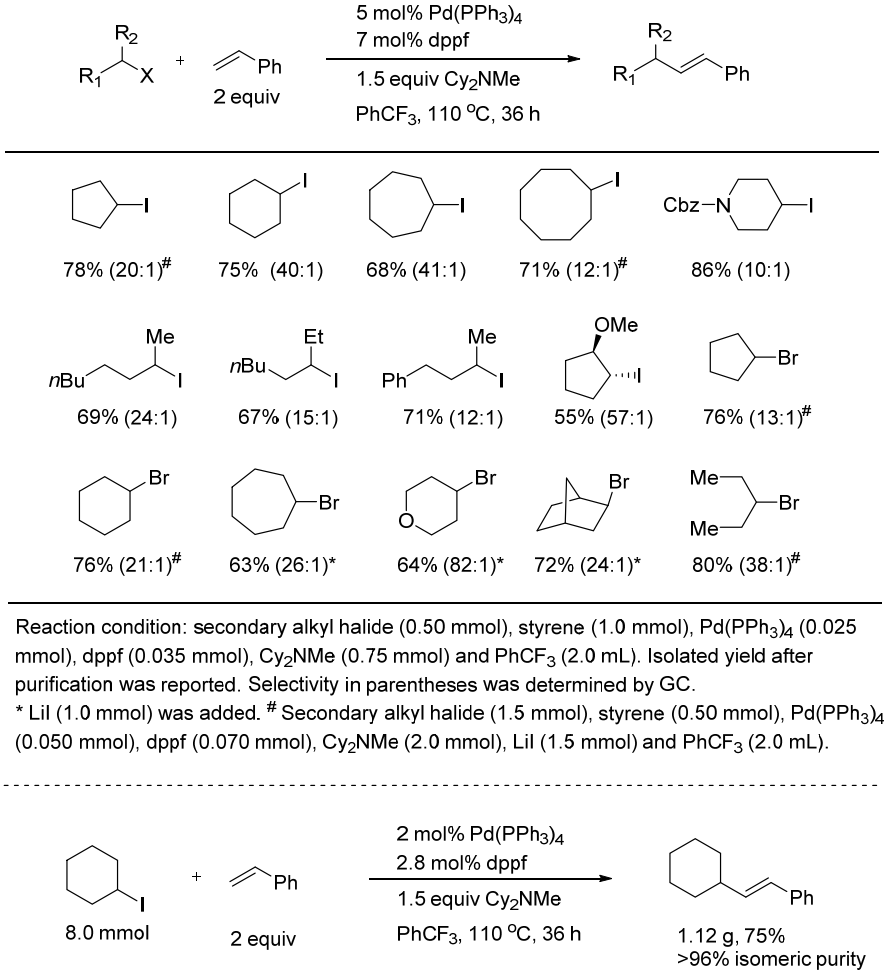
Entry	RI (x equiv)	Cy_2NMe (y equiv)	LiI (x equiv)	Conv. of styrene (%)[a]	**P1**(%)[a]	*E*/*Z*[b]	**P2** (%)[a]	Decenes
1	2.0	2.5	2.0	79	68	9	< 5	N.D.
2	2.5	3.0	2.5	86	77	8	< 5	N.D.
3	3.0	4.0	3.0	90	81	8	< 5	N.D.

[a] Reaction condition: styrene (0.10 mmol), *n*-decyl-I (x mmol), $Pd(dba)_2$ (0.010 mmol), ligand (0.014 mmol), Cy_2NMe (y mmol), LiI (x mmol), $PhCF_3$ (0.40 mL). Conversion and yield were determined by GC versus a calibrated internal standard. [b] Selectivity was determined by GC. N.D. = not determined

2.2.2 Scope of alkyl halides and olefins

With optimized condition in hand, we studied the scope of substrates. Under optimized conditions using 1:2 stoichiometric ratio of RX and styrene and 5% Pd catalyst, most secondary alkyl halides can couple in good yield (Scheme 2.15). In most cases, only two isomers were produced, the *trans* and *cis* olefins with the ratio shown in parentheses. The inclusion of LiI can improve the yields for alkyl bromides, about 10% in most cases. Cyclic iodide of five- to eight-membered rings underwent the Heck reaction efficiently. The incorporation of oxygen and nitrogen atoms into the rings did not affect the coupling process.

Notably, *exo*-2-norbornyl bromide gave exclusively the *exo*-product, while *trans*-1-iodo-2-methoxycyclopentane afforded the *trans*-isomer. Both examples indicated that alkyl radicals were probably involved. In cases of cyclopentyl iodide and bromide, cyclohexyl bromide, cylcooctyl iodide, and 3-pentyl bromides, the yields were only around 50%. By using an alternative procedure, 3:1 ratio of RX and styrene with 10 mol% Pd/dppf catalyst, the yields improved to more than 70%. The reaction of CyI and styrene was scaled up with 2 mol% Pd/dppf catalyst and 1.12 gram Heck product was obtained in good yield of 75%.

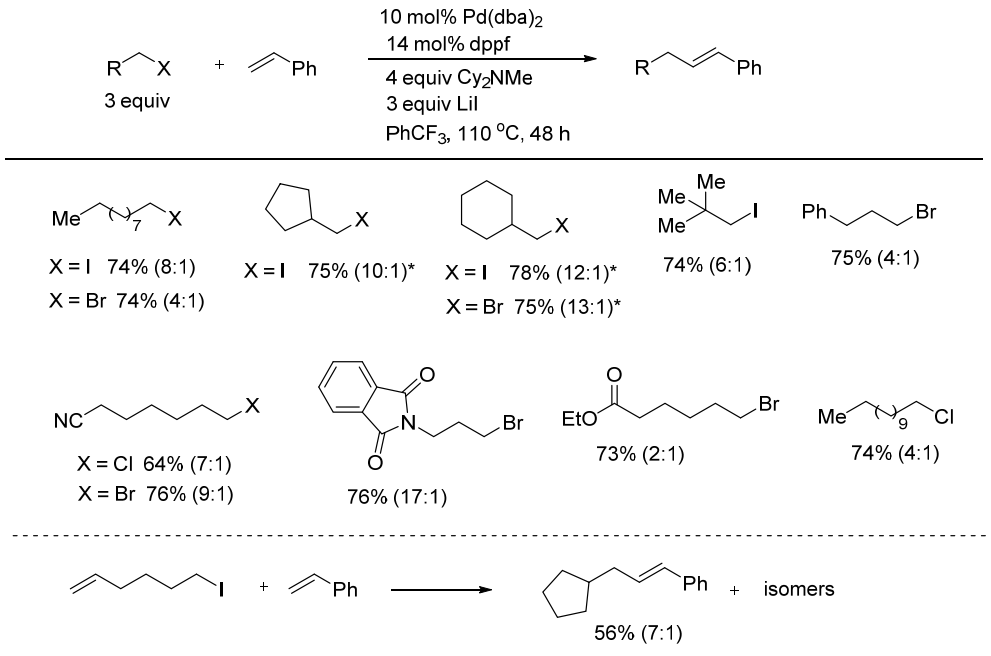


Reaction condition: secondary alkyl halide (0.50 mmol), styrene (1.0 mmol), $Pd(PPh_3)_4$ (0.025 mmol), dppf (0.035 mmol), Cy_2NMe (0.75 mmol) and $PhCF_3$ (2.0 mL). Isolated yield after purification was reported. Selectivity in parentheses was determined by GC.
* LiI (1.0 mmol) was added. # Secondary alkyl halide (1.5 mmol), styrene (0.50 mmol), $Pd(PPh_3)_4$ (0.050 mmol), dppf (0.070 mmol), Cy_2NMe (2.0 mmol), LiI (1.5 mmol) and $PhCF_3$ (2.0 mL).

Scheme 2.15. Heck reaction of secondary alkyl halides.

For most of the Heck reaction of primary alkyl halides, $Pd(dba)_2$ and dppf

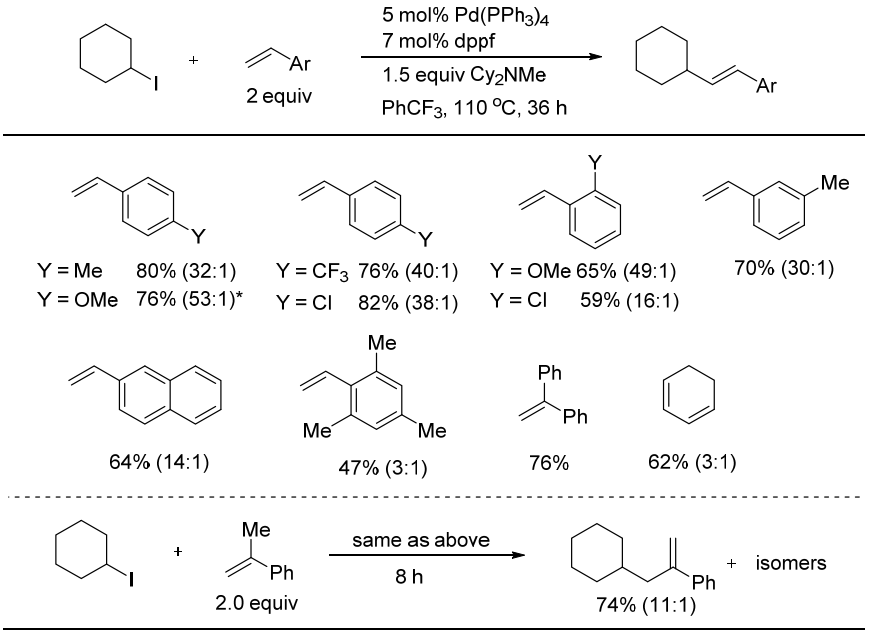
formed the most active catalyst (Scheme 2.16). The main side reaction was Pd-assisted premature β-hydride elimination of alkyl halides to corresponding olefins.[48] In a control experiment without the Pd catalyst, *N*-alkylation of Cy_2NMe became the major side reaction at 110 ^oC. We used 3:1 ratio of primary alkyl halides and styrene to obtain good yields and good isomeric selectivity. If 1:2 ratio of primary alkyl halides and styrene was used, the yield of coupling products was ranging from 50% to 63%. In most cases, the coupling products were obtained in more than 70% yields and 10:1 olefinic selectivity. Hindered neopentyl iodide coupled well. Polar groups such as esters, nitriles and phthalimides were tolerated. 6-Iodo-1-hexene afforded the cyclised Heck product in 56% yield and 7:1 selectivity versus several other isomers. Primary alkyl chlorides can also couple via intermediary of alkyl iodides from reactions of alkyl chlorides with LiI in situ.



Reaction condition: primary alkyl halide (1.5 mmol), styrene (0.50 mmol), $Pd(dba)_2$ (0.050 mmol), dppf (0.070 mmol), Cy_2NMe (2.0 mmol), LiI (1.5 mmol) and $PhCF_3$ (2.0 mL). Isolated yield after purification was reported. Selectivity in parentheses was determined by GC.
* $Pd(PPh_3)_4$ was used

Scheme 2.16. Heck reaction of primary alkyl halides.

With regard to the scope of olefins, electron-donating and -withdrawing substituents such as OMe and CF_3 groups on styrenes were well tolerated (Scheme 2.17). Most of them furnished the coupling product in good yield and selectivity. Hindered 2-vinylmesitylene also coupled in moderate yield. On α–position of styrene, alkyl and aryl groups can be present, but β-substitutions were not tolerated. The coupling of α-methylsytrene afforded the Heck products in 74% yield with 11:1 selectivity after 8 h, as longer reaction time would decrease the selectivity. A conjugated diene, 1,3-cyclohexadiene also coupled in reasonable yield with 3:1 selectivity of the desired isomer versus several others.



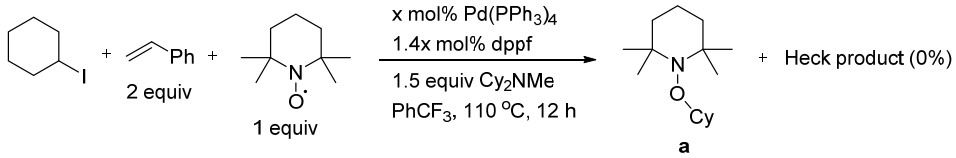
Reaction condition: CyI (0.50 mmol), styrene (1.0 mmol), $Pd(PPh_3)_4$ (0.025 mmol), dppf (0.035 mmol), Cy_2NMe (0.75 mmol) and $PhCF_3$ (2.0 mL). Isolated yield after purification was reported. Selectivity in parentheses was determined by GC.
* $Pd(dba)_2$ was used

Scheme 2.17. Examples of aromatic olefins and a conjugated diene.

2.2.3 Mechanistic probing of the catalytic reaction

We speculated that our Heck reaction may involve radicals in the catalytic cycle. To confirm that, we included 1 equiv TEMPO, a radical trap in the model Heck reaction (Scheme 2.18). No Heck product was detected and *N*-cyclohexyl-

TEMPO **a** was formed in 2:1 molar ratio with respect to the Pd^0 catalyst (Scheme 2.18). Therefore, it is possible that during oxidative addition of $(dppf)Pd^0$, two consecutive single electron transfer events (SET) occurred to generate two alkyl radicals and $(dppf)PdI_2$.

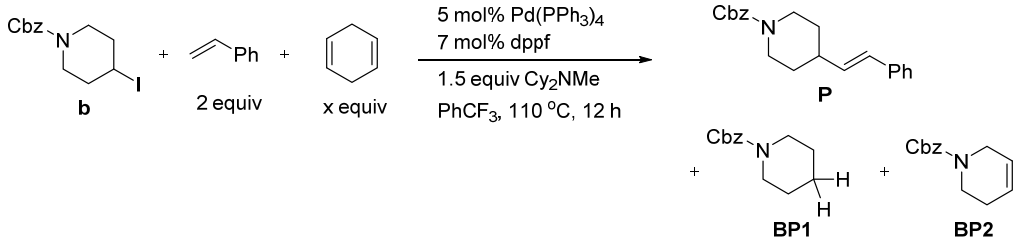


Entry	Pd cat. (x mol%)	Conv. of CyI (%)	Yield of **a** (%)
1	10	23	20
2	20	44	41
3	50	100	100

GC yield on **a** 0.10 mmol scale.

Scheme 2.18. Trapping experiment using 1 equiv of TEMPO.

In another trapping experiment, the alkyl radical from *N*-Cbz-4-iodopiperidine **b** was partially intercepted by 1,4-cyclohexadiene via hydrogen atom abstraction (Scheme 2.19).



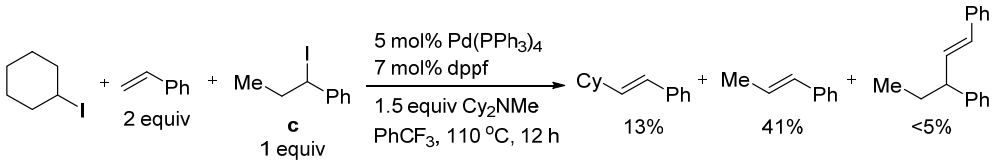
Entry	x (equiv)	Conv. of **b** (%)	Yield of **P** (%)	Yield of **BP1** (%)	Yield of **BP2** (%)
1	0	100	91%	1%	7%
2	5	100	46%	26%	13%

GC yield on **a** 0.10 mmol scale.

Scheme 2.19. Trapping experiment using 1,4-cyclohexadiene.

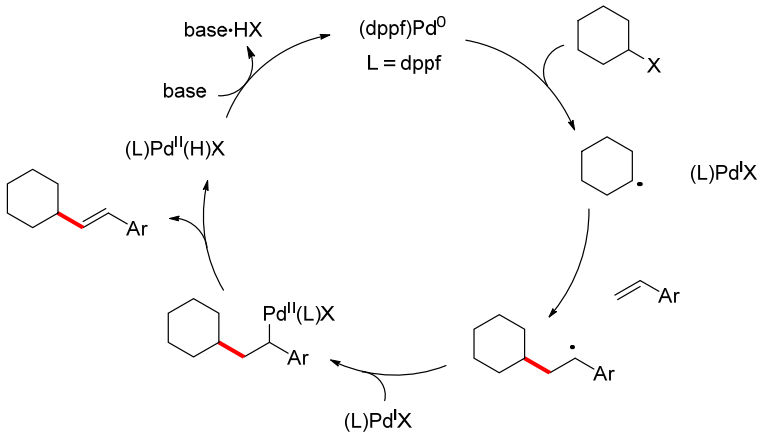
We also excluded the possibility of atom transfer radical addition to styrene followed by HX elimination (Scheme 2.20).[22,34,49] When a benzylic iodide **c**

was subjected to active Heck reaction of CyI and styrene, **c** was fully consumed but only gave the elimination product, β-methylstyrene in moderate yield (41%). Little Heck product derived from insertion of **c** into styrene was observed (<5%). Furthermore, the presence of **c** inhibited the Heck reaction of CyI and the yield of the latter process was reduced from 74% to 13%.



Scheme 2.20. Elimination of 1-iodo-1-phenylpropane in model Heck reaction.

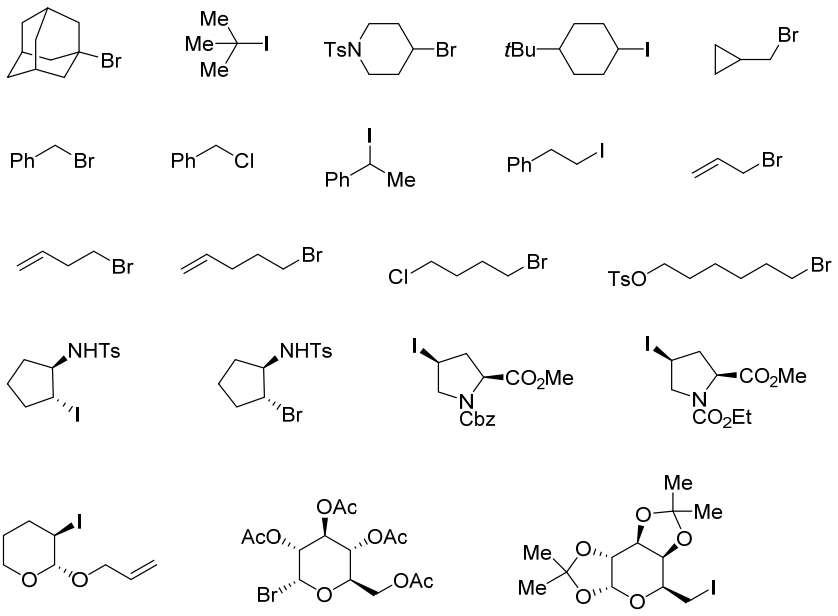
Based on the mechanistic probes, we proposed a tentative catalytic cycle starts from a SET oxidative addition of (dppf)Pd^0 and alkyl halide followed by alkyl radical addition to styrene (Scheme 2.21).[50] Recombination of the benzylic radical and (dppf)$Pd^{I}X$ forms (dppf)Pd^{II}(alkyl)X species which undergoes β-hydride elimination to afford the Heck product. Base-assisted reductive elimination regenerates the active (dppf)Pd^0 to start a new catalytic cycle.



Scheme 2.21. A possible catalytic cycle of Heck reaction.

2.2.4 Unsuccessful examples of Heck reaction

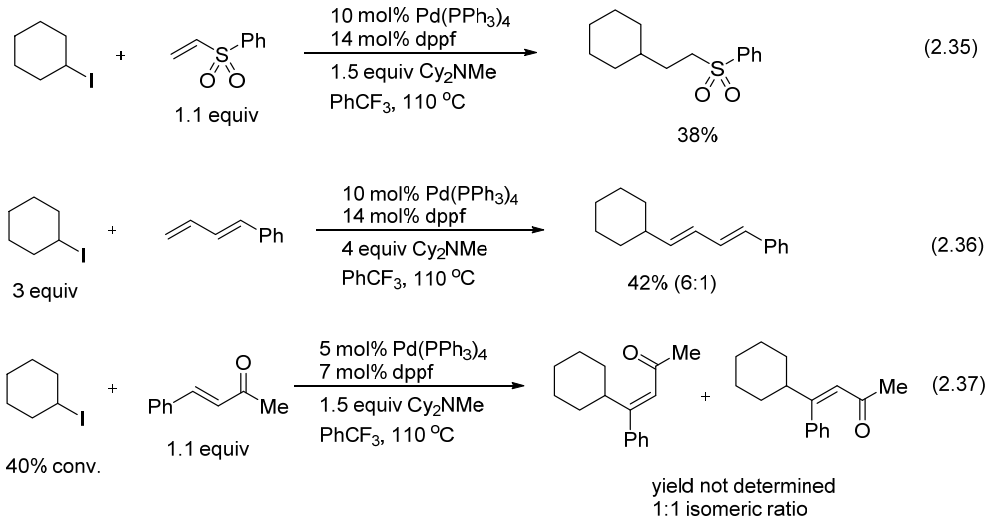
We attempted to couple tertiary halides such as 1-bromoadamatane and *tert*-butyl iodide with styrene, but failed to obtain desired products. 4-Bromo-*N*-tosylpiperidine did not afford the coupling products. 4-*tert*-Butyl cyclohexyl iodide did give the *trans*-product together with several olefinic isomers of Heck products. Cyclopropylmethyl bromide failed to give the coupling product. Benzylic and allylic halides gave trace Heck product. Two proline-derived iodies gave complex products in moderate yields. We also tried some glucose derivatives, but they failed to couple.



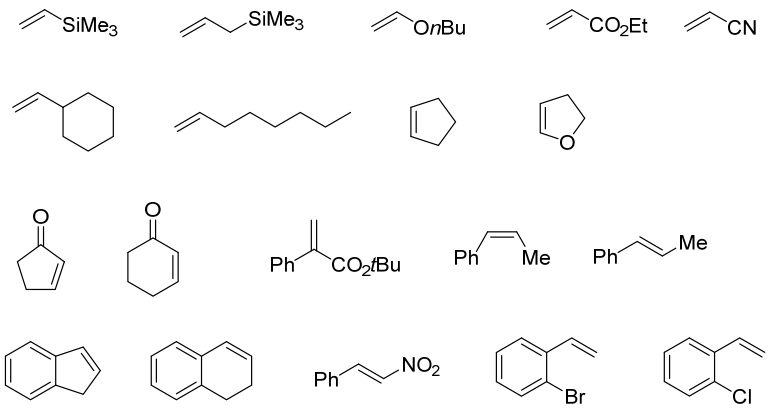
Scheme 2.22. Additional halides tested in Heck reaction.

With regard to the scope of olefins, the coupling of phenyl vinyl sulfone furnished the hydroalkylation product in 38% yield (eq 2.35). The catalytic reaction stopped as longer reaction time did not improve the conversion of phenyl vinyl sulfone. The coupling reaction of *trans*-1-phenyl-1,3-butadiene afforded the Heck product in 42% yield with 6:1 selectivity (eq 2.36). We obtained initial result of *trans*-4-Phenyl-3-buten-2-one, however, the isomeric

ratio was only of 1:1 (eq 2.37).



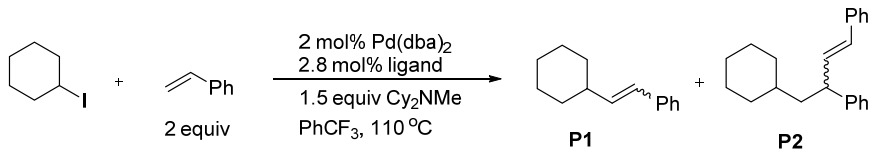
Coupling reactions of vinyl silanes and vinyl ethers gave trace products. Attempts to couple methyl acrylate and acrylonitrile were not successful probably due to the facile polymerization. Vinylcyclohexane, 1-octene, cyclopentene and 1,2-dihydrofuran failed to react, neither did cyclopentenone and cyclohexenone. We also attempted to couple α,β-disubstituted olefins, such as *cis*-β-methylstyrene, *trans*-β-methylstyrene, indene, 1,2-dihydronaphthalene and *trans*-β-nitrostyrene, but they failed to react. *Ortho* halogen-substituted styrenes also failed to afford the coupling products, as the halogens were reactive in the reaction condition.



Scheme 2.23. Additional olefins tested in Heck reaction.

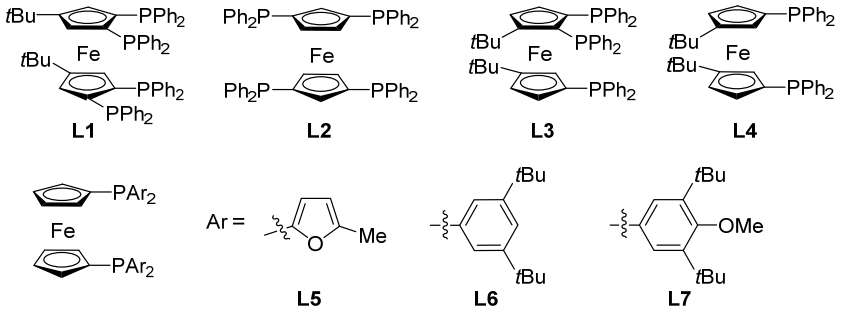
In collaboration with Prof. Jean-Cyrille Hierso, we tested some ligands for the Heck reaction of cyclohexyl iodide (Table 2.7). From the table, dppf is the better than other phosphine ligands. **L2** and **L4** that have similar structure to dppf also showed slight lower yield and selectivity. Other aryl groups rather than phenyl gave lower yield. Phosphines bearing unsymmetric phosphorus atoms or two on the same Cp ring deteriorated the catalytic acitivity. In some conditions using Hierso's ligands, we speculated the polymerization occurred as partial of styrene was consumed.

Table 2.7. Result of additional test ligands.[a]



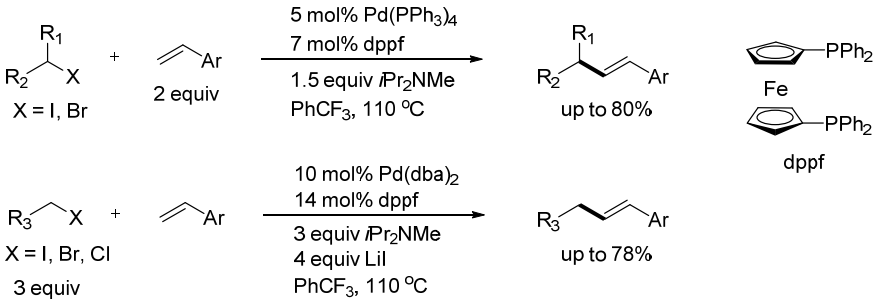
Entry	Ligand	Time	Conv. of CyI (%)[a]	**P1**	
				Yield of *E* (%)[a]	*E*/*Z*[b]
1	dppf	12 h	98	57	5
		36 h	100	64	49
2	**L1**	12 h	25	-	-
		36 h	55	-	-
3	**L2**	12 h	95	36	4
		36 h	100	43	10
4	**L3**	12 h	11	-	-
		36 h	62	-	-
5	**L4**	12 h	98	44	4
		36 h	100	54	9
6	**L5**	12 h	47	9	-
		36 h	95	10	-
7	**L6**	12 h	60	7	-
		36 h	100	26	-
8	**L7**	12 h	40	1	-
		36 h	99	19	-

[a] Reaction condition: CyI (0.10 mmol), styrene (0.20 mmol), $Pd(dba)_2$ (0.005 mmol), ligand (0.007 mmol), Cy_2NMe (0.15 mmol), $PhCF_3$ (0.40 mL). Conversion and yield were determined by GC versus a calibrated internal standard. [b] Selectivity was determined by GC. ^1H NMR spectroscopy was unsuitable for the determination of selectivity due to low signal intensity of the minor isomer. Yield of **P2** not determined.



2.3 Conclusion

In conclusion, we disclose herein an efficient method for intermolecular Heck reaction of alkyl halides, which was an unsolved problem for many years in palladium catalysis. The simple, easily available Pd/dppf catalyst showed good reactivity. Both primary and secondary alkyl halides including iodides, bromides and chlorides were tolerated in the catalytic system. Various vinyl arenes proceeded the Heck reaction with cyclohexyl iodide in good yield and isomeric ratio. Our mechanistic investigation points to a radical-type oxidative addition of alkyl halides.



2.4 Experimental section

2.4.1 General

General considerations are same to the section 1.4.1. Unless noted otherwise, commercially available chemicals were used without further purification. 2-Iodooctane, 3-iodooctane, iodocycloheptane, iodocylooctane, 6-iodo-1-hexene, cyclopentylmethyl iodide, cyclohexylmethyl iodide, 2-bromo-4-phenylbutane and 2-iodo-4-phenylbutane were prepared from the corresponding alcohols via reported procedures.[51] *N*-Cbz-4-iodo-piperidine was prepared according to reported procedure.[52] *trans*-1-Iodo-2-methoxycyclopentane was prepared according to reported procedure.[53] The ferrocene 1,1′-bisphosphines were prepared using our reported procedure.[54] $Pd(dppf)_2$[55] and Pd(dba)(dppf)[56] were prepared by using reported procedures. Styrene was passed through a short plug of basic aluminum oxide in an argon-filled glove box to remove 4-*tert*-butylcatechol (radical stabilizer) before use. *N,N*-Dicyclohexylmethylamine (Fluka) was degassed by argon bubbling before use in the glove box.

2.4.2 Condition optimization for Heck reaction of alkyl halides

Typical procedure: In an argon-filled glove box, a dry 8-mL culture tube containing a magnetic stir bar was charged with $Pd(dba)_2$ (2.9 mg, 0.005 mmol), dppf (3.9 mg, 0.007 mmol) and 0.40 mL of dry $PhCF_3$. After stirring at room temperature for 30 minutes, cyclohexyl iodide (21.0 mg, 0.10 mmol) or *n*-decyl iodide (26.8 mg, 0.10 mmol), styrene (20.8 mg, 0.20 mmol), GC standard *n*-dodecane (10 μL) and Cy_2NMe (29.3 mg, 0.15 mmol) were added sequentially. The tube was capped tightly and the reaction mixture was heated with stirring in a heating block maintained at 110 ^oC. After 12 hours, aliquots were taken from the reaction mixture in the glove box and passed through a short plug of

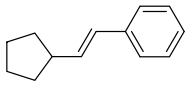
silica gel with diethyl ether washings. The filtrates were subjected to GC analysis to determine the conversion of alkyl iodide, the yield and selectivity of the Heck isomers and yield of a byproduct with double styrene insertion. The structures of the major isomer, (*E*)-β-alkylstyrene and its minor (*Z*)-isomer in the crude mixture were assigned by ^{1}H NMR spectroscopy and confirmed by GCMS. The ratio of the two isomers was determined by GC analysis. *Note: ^{1}H NMR spectroscopy was unsuitable to determine the ratio of the two isomers due to low signal intensity of the minor isomer.*

2.4.3 Isolation of Heck products

General procedure for Heck reaction of secondary alkyl halides using 1:2 RX and styrene: In an argon-filled glove box, a dry 10-mL reaction tube containing a magnetic stir bar was charged sequentially with $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol, 5 mol%), dppf (19.4 mg, 0.035 mmol, 7 mol%) and 2.0 mL of dry $PhCF_3$. After stirring at room temperature for 30 minutes, alkyl halide (0.50 mmol, 1.0 equiv), vinylarene (1.0 mmol, 2.0 equiv), *n*-dodecane (GC standard, 20 μL) and Cy_2NMe (146 mg, 0.75 mmol, 1.5 equiv) were added sequentially via syringes. For reactions of alkyl bromides, LiI (1.0 mmol, 134 mg, 2.0 equiv) was added to improve the yield by about 10%. The reaction tube was capped tightly and the mixture was heated with vigorous stirring in a110 ^{o}C oil bath for 36 h, unless stated otherwise. At the end of the reaction, the mixture was cooled to room temperature. It was diluted with diethyl ether and then passed through a short pad of silica gel to remove insoluble salts with diethyl ether washings. The filtrate was concentrated under reduced pressure and the residue was directly subjected to silica gel flash chromatography for isolation. The ratio of the amount of (*E*)-isomer to (*Z*)-isomer was determined by GC in both the

crude mixtures and isolated samples. In most cases, the ratio did not change after flash chromatography. In some cases, additional minor isomers were detected and the olefinic ratio was determined as the amount of (*E*)-isomer to the sum of other isomers by GC.

An alternative procedure using 3:1 RX and styrene for some examples: In an argon-filled glove box, a dry 10-mL reaction tube containing a magnetic stir bar was charged sequentially with $Pd(PPh_3)_4$ (57.8 mg, 0.050 mmol, 10 mol%), dppf (38.8 mg, 0.070 mmol, 14 mol%) and 2.0 mL of dry $PhCF_3$. After stirring at room temperature for 30 minutes, alkyl halide (1.50 mmol, 3.0 equiv), styrene (52 mg, 0.5 mmol, 1.0 equiv), *n*-dodecane (GC standard, 20 μL), Cy_2NMe (390 mg, 2.0 mmol, 4.0 equiv) and LiI (201 mg, 1.5 mmol, 3.0 equiv) were added sequentially. The reaction tube was capped tightly and the mixture was heated with vigorous stirring in a 110 ^oC oil bath for 48 h, unless stated otherwise. At the end of the reaction, the mixture was cooled to room temperature. It was diluted with diethyl ether and then passed through a short pad of silica gel to remove insoluble salts with diethyl ether washings. The filtrate was concentrated under reduced pressure and the residue was directly subjected to silica gel flash chromatography for isolation.



(*E*)-*β*-Cyclopentylstyrene [40132-68-1]. General procedure using iodocyclopentane (98 mg, 0.5 mmol): the titled compound was obtained as colorless oil (44 mg, 51% yield) after flash chromatography using hexanes as eluent. The *trans/cis* selectivity of the isolated Heck products was determined to be 49:1 by GC. The ratio was 18:1 after 12 h at 110 ^oC. The alternative

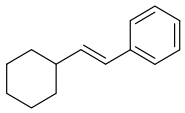
procedure using iodocyclopentane: colorless oil (67 mg, 78% yield) and 20:1 *trans/cis* selectivity.

General procedure using bromocyclopentane (75 mg, 0.5 mmol): colorless oil (40 mg, 47% yield) and 23:1 *trans/cis* selectivity. The alternative procedure using bromocyclopentane: colorless oil (65 mg, 76%) and 13:1 *trans/cis* selectivity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.32 (ψt, *J* = 7.5 Hz, 2H), 7.23-7.19 (m, 1H), 6.41 (d, *J* = 15.9 Hz, 1H), 6.24 (dd, *J* = 15.9, 7.7 Hz, 1H), 2.68-2.58 (m, 1H), 1.93-1.86 (m, 2H), 1.79-1.64 (m, 4H), 1.48-1.39 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 135.8, 128.6, 128.0, 126.9, 126.1, 44.0, 33.4, 25.4.

GCMS (EI): calcd for $C_{13}H_{16}$ M: 172.13. Found: 172.18.



(*E*)-*β*-Cyclohexylstyrene [18869-27-7]. General procedure using cyclohexyl iodide (105 mg, 0.5 mmol): the titled compound was obtained as colorless oil (73 mg, 78% yield) after flash chromatography using hexanes as eluent. The *trans/cis* selectivity of the isolated Heck products was determined to be 40:1 by GC. The ratio after 12 h at 110 ^{o}C was 14:1.

General procedure using cyclohexyl bromide (82 mg, 0.5 mmol): colorless oil (39 mg, 42% yield) and 32:1 *trans*/*cis* selectivity. The alternative procedure using cyclohexyl bromide: colorless oil (71 mg, 76% yield) and 21:1 olefinic selectivity.

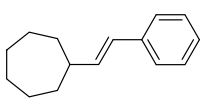
Gram-scale Heck procedure using 2 mol% Pd catalyst and a vacuum

manifold. In air, dppf (124 mg, 0.224 mmol) and $Pd(PPh_3)_4$ (185 mg, 0.160 mmol) were quickly added into a 100-mL dry reaction tube containing a magnetic stir bar. After three cycles of evacuation and backfilling with argon, 32 mL of degassed, dry $PhCF_3$ was added under argon and the mixture was stirred at room temperature for 10 minutes. Then degassed cyclohexyl iodide (1.68 g, 8.0 mmol), styrene (1.66 g, 16.0 mmol) and Cy_2NMe (2.34 g, 12.0 mmol) were added via syringes under argon. The reaction tube was capped tightly and the mixture was heated with vigorous stirring in a pre-heated 110 ^oC oil bath for 36 hours. After it was cooled down to room temperature, the mixture was diluted with 30 mL of hexane and passed through a short pad of silica gel to remove insoluble salts with diethyl ether washings. The filtrate was concentrated on a rotary evaporator under reduce pressure and the resulting residue was directly subjected to silica gel flash chromatography using hexanes as eluent. The title compound was obtained as colorless oil (1.12 g, 75% yield, >96% purity by GC). The *trans/cis* selectivity of the isolated Heck products was determined to be 38:1 by GC.

^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.35 (m, 2H), 7.31-7.28 (m, 2H), 7.22-7.17 (m, 1H), 6.36 (d, J = 16.0 Hz, 1H), 6.19 (dd, J = 16.0, 6.9 Hz, 1H), 2.19-2.10 (m, 1H), 1.84-1.67 (m, 5H), 1.40-1.14 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 137.0, 128.6, 127.4, 126.9, 126.1, 41.3, 33.1, 26.4, 26.2.

GCMS (EI): calcd for $C_{14}H_{18}$ M: 186.14. Found: 186.07.



(*E*)-*β*-Cycloheptylstyrene [592510-48-0]. General procedure using iodocyclo-heptane (112 mg, 0.5 mmol): the titled compound was obtained as

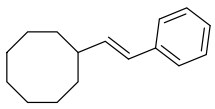
colorless oil (68 mg, 68% yield) after flash chromatography using hexanes as eluent. The *trans/cis* selectivity of the isolated Heck products was determined to be 41:1 by GC. The ratio was 13:1 after 12 h at 110 ^{o}C.

General procedure using cyclohexyl bromide (89 mg, 0.5 mmol): colorless oil (63 mg, 63% yield) and 26:1 *trans*/*cis* selectivity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.8 Hz, 2H), 7.32 (ψt, *J* = 7.8 Hz, 2H), 7.23-7.20 (m, 1H), 6.36 (d, *J* = 15.9Hz, 1H), 6.26 (dd, *J* = 15.9, 7.4 Hz, 1H), 2.38-2.36 (m, 1H), 1.87-1.43 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 137.8, 128.6, 126.84, 126.81, 126.1, 43.4, 34.9, 28.6, 26.4.

GCMS (EI): calcd for $C_{15}H_{20}$ M: 200.16. Found: 200.10.

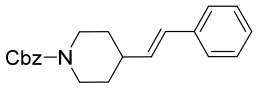


(*E*)-*β*-Cyclooctylstyrene [592510-49-1]. General procedure using iodocyclooctane (119 mg, 0.5 mmol): the titled compound was obtained as colorless oil (50 mg, 48% yield) after flash chromatography using hexanes as eluent. The olefinic selectivity of the isolated Heck products was determined to be 5:1 by GC. The ratio was 3:1 after 12 h at 110 ^{o}C. The alternative procedure using iodocyclooctane: colorless oil (76 mg, 71%) and 12:1olefinic selectivity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.7 Hz, 2H), 7.31 (ψt, *J* = 7.7 Hz, 2H), 7.23-7.19 (m, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 6.25 (dd, *J* = 16.0, 7.2 Hz, 1H), 2.42 (m, 1H), 1.84-1.56 (m, 14H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 138.0, 128.6, 127.0, 126.8, 126.1, 41.5, 32.0, 27.6, 26.2, 25.2.

GCMS (EI): calcd for $C_{16}H_{22}$ M: 214.17. Found: 214.12.

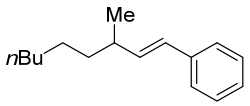


(*E*)-*N*-Cbz-4-(*β*-styryl)piperidine. General procedure using *N*-Cbz-4-iodo-piperidine (173 mg, 0.5 mmol): the titled compound was obtained as brown oil (120 mg, 86% yield) after flash chromatography using EA/hexanes (1:10) as eluent. The *trans/cis* selectivity of the isolated Heck products was determined to be 10:1 by ^{1}H NMR spectroscopy.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.18 (m, 10H), 6.38 (d, *J* = 16.0 Hz, 1H),6.13 (dd, *J* = 16.0, 6.9 Hz, 1H), 5.14 (s, 2H), 4.21 (br s, 2H), 2.89-2.83 (m, 2H), 2.35-2.26 (m, 1H), 1.79-1.71 (m, 2H), 1.44-1.39 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 137.5, 137.1, 134.2, 128.8, 128.7, 128.6, 128.1, 128.0, 127.3, 126.2, 67.1, 44.0, 39.4, 31.9.

GCMS (EI): calcd for $C_{21}H_{23}NO_2$ M: 321.17. Found: 321.10.

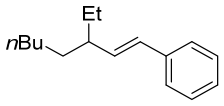


(*E*)-*β*-(2-Octyl)styrene [441287-15-6]. General procedure using 2-iodooctane (120 mg, 0.5 mmol): the titled compound was obtained as colorless oil (74 mg, 69% yield) after flash chromatography using hexanes as eluent. The olefinic selectivity of the isolated Heck products was determined to be 24:1 by GC. The ratio was 13:1 after 12 h at 110 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.6 Hz, 2H), 7.33 (ψt, *J* = 7.6 Hz, 2H), 7.24-7.22 (m, 1H), 6.38 (d, *J* = 15.9 Hz, 1H), 6.14 (dd, *J* = 15.9, 7.7 Hz, 1H), 2.36-2.27 (m, 1H), 1.41-1.33 (m, 10H), 1.12 (d, *J* = 6.7 Hz, 3H), 0.93 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 137.2, 128.6, 128.1, 126.9, 126.1, 37.5, 37.3, 32.1, 29.6, 27.6, 22.9, 20.8, 14.3.

GCMS (EI): calcd for $C_{16}H_{24}$ M: 216.19. Found: 216.14.

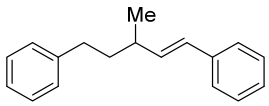


(*E*)-*β*-(3-Octyl)styrene. General procedure using 3-iodooctane (120 mg, 0.5 mmol): the titled compound was obtained as colorless oil (72 mg, 67% yield) after flash chromatography using hexane as eluent. The olefinic selectivity of the isolated Heck products was determined to be 15:1 by GC. The ratio was 7:1 after 12 h at 110 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.6 Hz, 2H), 7.33 (ψt, *J* = 7.6 Hz, 2H), 7.24-7.21 (m, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.00 (dd, *J* = 15.9, 9.0 Hz, 1H), 2.08-2.06 (m, 1H), 1.57-1.32 (m, 10H), 0.95-0.91 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 135.8, 129.8, 128.6, 126.9, 126.1, 45.3, 35.3, 32.2, 28.4, 27.2, 22.8, 14.3, 12.0.

GCMS (EI): calcd for $C_{16}H_{24}$ M: 216.19. Found: 216.13.



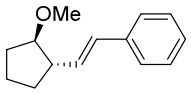
(*E*)-*β*-(2-(4-phenyl)butyl)styrene [685535-68-6]. General procedure using2-iodo-4-phenylbutane (130 mg, 0.5 mmol): the titled compound was obtained as colorless oil (84 mg, 71% yield) after flash chromatography using hexanes. The selectivity of the isolated Heck products was determined to be 12:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.37 (m, 2H), 7.32-7.25 (m, 4H), 7.22-7.15 (m, 4H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.12 (dd, *J* = 15.8, 8.0 Hz, 1H), 2.71-2.58 (m, 2H), 2.39-2.29 (m, 1H), 1.75-1.69 (m, 2H), 1.12 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 138.0, 136.6, 128.8, 128.7, 128.6,

128.5, 127.0, 126.2, 125.8, 38.9, 37.1, 33.9, 20.9.

GCMS (EI): calcd for $C_{18}H_{20}$ M: 236.16. Found: 236.08.

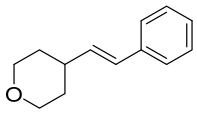


(*E*)-(*trans*-1-Methoxy-2-(*β*-styryl)cyclopentane. General procedure using *trans*-1-iodo-2-methoxycyclopentane (113 mg, 0.5 mmol): the titled compound was obtained as colorless oil (56 mg, 55% yield) after preparative TLC using hexanes as eluent. The *trans/cis* selectivity of the isolated Heck products was determined to be 57:1 by GC. The *trans* configuration was assigned by comparison to reported NMR data of a related compound.[57]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.35 (m, 2H), 7.32-7.27 (m, 2H), 7.22-7.18 (m, 1H), 6.45 (d, *J* = 15.9 Hz, 1H), 6.21 (dd, *J* = 15.9, 8.0 Hz, 1H), 3.62-3.58 (m, 1H), 3.35 (s, 3H), 2.70-2.63 (m, 1H), 1.99-1.92 (m, 2H), 1.79-1.65 (m, 3H), 1.55-1.48 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 133.3, 129.6, 128.6, 127.1, 126.2, 88.0, 57.3, 49.5, 31.3, 31.0, 22.6.

GCMS (EI): calcd for $C_{14}H_{18}O$ M: 202.14. Found: 202.07.

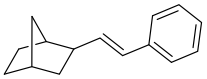


(*E*)-*β*-(Tetrahydro-4-pyranyl)styrene [592510-37-7]. General procedure using 4-bromo-tetrahydropyran (83 mg, 0.5 mmol): the titled compound was obtained as colorless oil (60 mg, 64% yield) after flash chromatography using hexanes. The *trans/cis* selectivity of the isolated Heck products was determined to be 82:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.5 Hz, 2H), 7.31 (dd, *J* = 7.9, 7.5 Hz, 2H), 7.21 (t, *J* = 7.9 Hz, 1H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.17 (dd, *J* = 16.0, 6.8 Hz, 1H), 4.01 (dd, *J* = 11.6, 2.8 Hz, 2H), 3.47 (dt, *J* = 11.6, 1.9 Hz, 2H), 2.44-2.34 (m, 1H), 1.72 (d, *J* = 12.9 Hz, 2H), 1.63-1.52 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 134.8, 128.7, 128.4, 127.2, 126.2, 67.9, 38.5, 32.8.

GCMS (EI): calcd for $C_{13}H_{16}O$ M: 188.12. Found: 188.07.

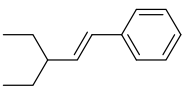


(*E*)-*β*-(*exo*-2-Norbonyl)styrene [76217-04-4]. General procedure using *exo*-2-bromonorbornane (88 mg, 0.5 mmol): the titled compound was obtained as colorless oil (71 mg, 72% yield) after flash chromatography using hexanes as eluent. The *trans/cis* selectivity of the isolated Heck products was determined to be 24:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.5 Hz, 2H), 7.31 (ψt, *J* = 7.5 Hz, 2H), 7.23-7.19 (m, 1H), 6.34 (d, *J* = 15.8 Hz, 1H), 6.16 (dd, *J* = 15.8, 8.0 Hz, 1H), 2.32-2.28 (m, 2H), 2.18 (s, 1H), 1.63-1.19 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 136.6, 128.6, 127.4, 126.8, 126.1, 45.6, 42.9, 38.1, 36.8, 36.0, 29.9, 29.2.

GCMS (EI): calcd for $C_{15}H_{18}$ M: 198.14. Found: 198.09.



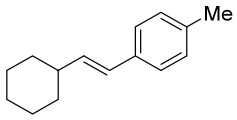
(*E*)-*β*-(3-Pentyl)styrene [40132-62-5]. General procedure using 3-bromopentane (76 mg, 0.5 mmol): the titled compound was obtained as colorless oil (40 mg, 46% yield) after flash chromatography using hexanes. The selectivity of the isolated Heck products was determined to be 24:1 by GC. The

alternative procedure using 3-bromopentane: colorless oil (70 mg, 80%) and 38:1 olefinic selectivity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (m, 2H), 7.33-7.29 (m, 2H), 7.23-7.19 (m, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 5.98 (dd, *J* = 15.8, 8.9 Hz, 1H), 2.01-1.92 (m, 1H), 1.58-1.48 (m, 2H), 1.42-1.29 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 135.4, 130.0, 128.6, 126.9, 126.1, 47.0, 28.0, 12.0.

GCMS (EI): calcd for $C_{13}H_{18}$ M: 174.14. Found: 174.11.

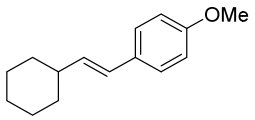


(*E*)-*β*-Cyclohexyl-4-methylstyrene [61153-38-6]. General procedure using cyclo-hexyl iodide (105 mg, 0.5 mmol): the titled compound was obtained as colorless oil (80 mg, 80% yield) after flash chromatography using hexanes and the contaminant of 4-methylstyrene after purification was removed under vacuum. The *trans/cis* selectivity of the isolated Heck products was determined to be 32:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 7.7 Hz, 2H), 7.08 (d, *J* = 7.7 Hz, 2H), 6.30 (d, *J* = 15.9 Hz, 1H), 6.11 (dd, *J* = 15.9, 6.9 Hz, 1H), 2.31 (s, 3H), 2.11-2.09 (m, 1H), 1.81-1.66 (m, 5H), 1.35-1.12 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5, 136.0, 135.4, 129.3, 127.2, 126.0, 41.3, 33.2, 26.4, 26.2, 21.3.

GCMS (EI): calcd for $C_{15}H_{20}$ M: 200.16. Found: 200.08.

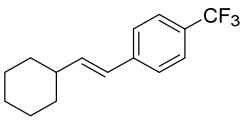


(*E*)-*β*-Cyclohexyl-4-methoxystyrene [104151-26-0]. General procedure using cyclohexyl iodide (105 mg, 0.5 mmol) and $Pd(dba)_2$ (0.025 mmol, 14.4 mg) instead of $Pd(PPh_3)_4$: the titled compound was obtained as colorless oil (82 mg, 76% yield) after flash chromatography using hexanes and the contaminant of 4-methoxystyrene after purification was removed under vacuum. The *trans/cis* selectivity of the isolated Heck products was determined to be 53:1 by GC. The ratio was 23:1 after 12 h at 110 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-1.25 (m, 2H), 6.84-6.81 (m, 2H), 6.28 (d, *J* = 16.0 Hz, 1H), 6.03 (dd, *J* = 16.0, 6.9 Hz, 1H), 3.79 (s, 3H), 2.13-2.06 (m, 1H), 1.81-1.65 (m, 5H), 1.37-1.11 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 134.9, 131.1, 127.1, 126.7, 114.1, 55.4, 41.3, 33.3, 26.4, 26.2.

GCMS (EI): calcd for $C_{15}H_{20}O$ M: 216.15. Found: 216.10



(*E*)-*β*-Cyclohexyl-4-trifluoromethylstyrene. General procedure using cyclohexyl iodide (105 mg, 0.5 mmol): the titled compound was obtained as white solid (96 mg, 76% yield) after flash chromatography using hexanes as eluent and the contaminant of 4-trifluoromethylstyrene after purification was removed under vacuum.The *trans/cis* selectivity of the isolated Heck products was determined to be 40:1 by GC. The *trans* ratio was 38:1 after 12 h at 110 ^{o}C.

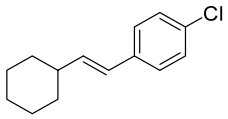
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 6.36 (d, *J* = 16.0 Hz, 1H), 6.27 (dd, *J* = 16.0, 6.6 Hz, 1H), 2.15-2.11 (m, 1H), 1.82-1.67 (m, 5H), 1.37-1.14 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 139.4, 128.7 (q, *J* = 32.5 Hz), 126.3,

126.2, 125.5 (q, J = 3.9 Hz), 124.5 (q, J = 271.8 Hz), 41.4, 32.9, 26.3, 26.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ -62.8.

GCMS (EI): calcd for $C_{15}H_{17}F_3$ M: 254.13. Found: 254.06.

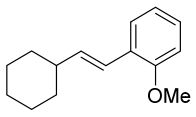


(*E*)-β-Cyclohexyl-4-chlorostyrene. General procedure using cyclohexyl iodide (105 mg, 0.5 mmol): the titled compound was obtained as white solid (90 mg, 82% yield) after flash chromatography using hexanes and the contaminant of 4-chlorostyrene after purification was removed under vacuum. The *trans/cis* selectivity of the isolated Heck products was determined to be 38:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.17 (m, 4H), 6.27 (d, J = 16.0 Hz, 1H), 6.13 (dd, J = 16.0, 6.8 Hz, 1H), 2.11-2.08 (m, 1H), 1.80-1.66 (m, 5H), 1.35-1.11 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 136.7, 132.4, 128.7, 127.3, 126.3, 41.3, 33.0, 26.3, 26.2.

GCMS (EI): calcd for $C_{14}H_{17}Cl$ M: 220.10. Found: 220.05.

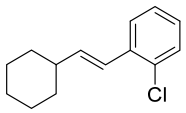


(*E*)-β-Cyclohexyl-2-methoxystyrene. General procedure using cyclohexyl iodide (105 mg, 0.5 mmol): the titled compound was obtained as colorless oil (70 mg, 65% yield) after flash chromatography using hexanes and then the contaminant of 2-vinylanisole after purification was removed under vacuum. The *trans/cis* selectivity of the isolated Heck products was determined to be 49:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.4 Hz, 1H), 7.20 (dd, *J* = 8.0, 7.4 Hz, 1H), 6.93 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 16.1 Hz, 1H), 6.19 (dd, *J* = 16.1, 7.0 Hz, 1H), 3.86 (s, 3H), 2.19-2.17 (m, 1H), 1.87-1.70 (m, 5H), 1.40-1.18 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 137.6, 127.9, 127.2, 126.3, 121.9, 120.7, 110.9, 55.6, 41.7, 33.2, 26.4, 26.2.

GCMS (EI): calcd for $C_{15}H_{20}O$ M: 216.15. Found: 216.09.

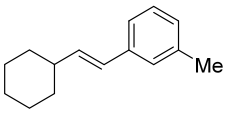


(*E*)-β-Cyclohexyl-2-chlorostyrene [441287-17-8]. General procedure using cyclohexyl iodide (105 mg, 0.5 mmol): the reaction was heated for 96 h to improve the *E*/*Z* selectivity. The titled compound was obtained as colorless oil (65 mg, 59% yield) after flash chromatography using hexanes and subsequent removal of some contaminant of 2-chlorostyrene under vacuum. The selectivity of the isolated Heck products was determined to be 16:1 by ^{1}H NMR spectroscopy. The selectivity in the reaction mixture after 12 h was determined to be 2:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.32 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.21-7.17 (m, 1H), 7.14-7.10 (m, 1H), 6.73 (d, *J* = 15.9 Hz, 1H), 6.16 (dd, *J* = 15.9, 7.0 Hz, 1H), 2.22-2.15 (m, 1H), 1.85-1.67 (m, 5H), 1.38-1.25 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 136.3, 132.8, 129.7, 127.9, 126.8, 126.7, 123.8, 41.5, 33.0, 26.3, 26.2.

GCMS (EI): calcd for $C_{14}H_{17}Cl$ M: 220.10. Found: 220.07.

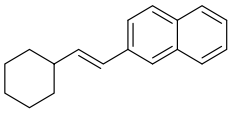


(*E*)-*β*-Cyclohexyl-3-methylstyrene. General procedure using cyclohexyl iodide (105 mg, 0.5 mmol): the titled compound was obtained as colorless oil (70 mg, 70% yield) after flash chromatography using hexanes and subsequent removal of some of 3-methylstyrene as contaminant under vacuum. The *trans/cis* selectivity of the isolated Heck products was determined to be 30:1 by GC. The ratio was 29:1 after 12 h at 110 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.16 (m, 3H), 7.17 (d, *J* = 6.7 Hz, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.19 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.16-2.14 (m, 1H), 1.85-1.70 (m, 5H), 1.40-1.17 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 138.1, 136.8, 128.5, 127.7, 127.4, 126.8, 123.3, 41.3, 33.1, 26.4, 26.2, 21.6.

GCMS (EI): calcd for $C_{15}H_{20}$ M: 200.16. Found: 200.04.

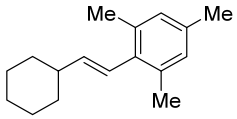


(*E*)-2-(2-Cyclohexylvinyl)naphthalene [592510-43-5]. General procedure using cyclohexyl iodide (105 mg, 0.5 mmol) and 2-vinylnaphthalene (84.8 mg, 0.55 mmol): the titled compound was obtained as white solid (76 mg, 64% yield) after flash chromatography using hexanes as eluent and subsequent removal of 2-vinylnaphthalene contaminant under vacuum. The *trans/cis* selectivity of the isolated Heck products was determined to be 14:1 by GC. The ratio was 4:1 after 12 h at 110 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79-7.75 (m, 3H), 7.68 (s, 1H), 7.59 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.46-7.38 (m, 2H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.31 (dd, *J* = 16.0, 7.0 Hz, 1H), 2.23-2.15 (m, 1H), 1.87-1.68 (m, 5H), 1.41-1.18 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 135.7, 133.9, 132.8, 128.2, 128.0, 127.8, 127.5, 126.2, 125.52, 125.50, 123.8, 41.5, 33.2, 26.4, 26.2.

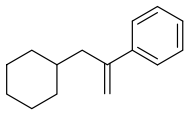
GCMS (EI): calcd for $C_{18}H_{20}$ M: 236.16. Found: 236.10.



(*E*)-*β*-Cyclohexyl-2,4,6-trimethylstyrene. General procedure using cyclohexyl iodide (105 mg, 0.5 mmol): the titled compound was obtained as colorless oil (54 mg, 47% yield) after flash chromatography using hexanes as eluent and subsequent removal of some contaminant of 2,4,6-trimethylstyrene under vacuum. The selectivity of the isolated Heck products was determined to be 3:1 after 36 h by ^{1}H NMR. The selectivity after 12 h was determined to be 1:1 by GC.

^{1}H NMR of major isomer (400 MHz, $CDCl_3$): δ 6.86 (s, 2H), 6.24 (d, *J* = 16.2 Hz, 1H), 5.59 (dd, *J* = 16.2, 7.1 Hz, 1H), 2.27 (s, 3H), 2.26 (s, 6H), 1.86-1.56 (m, 11H).

GCMS (EI): calcd for $C_{17}H_{24}$ M: 228.19. Found: 228.14.



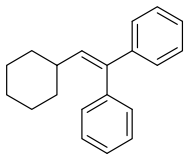
***α*-(Cyclohexylmethyl)styrene [136490-39-6].** General procedure using cyclo-hexyl iodide (105 mg, 0.5 mmol): the reaction was heated for 8 h. The titled compound was obtained as colorless oil (74 mg, 74% yield) after flash chromatography using hexanes and subsequent removal of some contaminant of

α-methylstyrene under vacuum. The selectivity of the isolated Heck products was determined to be 12:1 by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.37 (m, 2H), 7.34-7.29 (m, 2H), 7.28-7.23 (m, 1H), 5.26 (d, *J* = 1.8 Hz, 1H), 5.00 (d, *J* = 1.8 Hz, 1H), 2.39 (dd, *J* = 7.1, 0.8 Hz, 2H), 1.71-1.59 (m, 5H), 1.38-1.28 (m, 1H), 1.15-1.06 (m, 3H), 0.93-0.90 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 141.7, 128.4, 127.3, 126.4, 113.6, 43.8, 35.9, 33.4, 26.7, 26.4.

GCMS (EI): calcd for $C_{15}H_{20}$ M: 200.16. Found: 200.10.

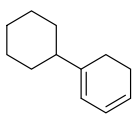


1-Cyclohexyl-2,2'-diphenylethene [91083-83-9]. General procedure using cyclo-hexyl iodide (105 mg, 0.5 mmol): the reaction was heated for 96 h. The titled compound was obtained as colorless oil (99 mg, 76% yield) after flash chromatography using hexanes and subsequent removal of some contaminant of 1,1-diphenylethene under vacuum.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.16 (m, 10H), 5.90 (d, *J* = 10.1 Hz, 1H), 2.17-2.08 (m, 1H), 1.68-1.59 (m, 5H), 1.25-1.16 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 140.8, 139.8, 136.1, 129.9, 128.3, 128.2, 127.4, 126.92, 126.85, 38.46, 33.49, 26.15, 25.75.

GCMS (EI): calcd for $C_{20}H_{22}$ M: 262.17. Found: 262.11.



1-Cyclohexyl-1,3-cyclohexadiene [65181-98-8]. General procedure using cyclo-hexyl iodide (105 mg, 0.5 mmol) and 1,3-cyclohexadiene (200 mg, 2.5

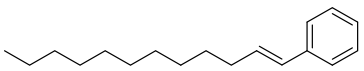
mmol): the titled compound was obtained as colorless oil (50 mg, 62% yield) after flash chromatography using hexanes. The isomeric ratio of the isolated Heck products was determined to be 3:1 by GC. The NMR spectroscopy of the major isomer was identified by comparison with reported NMR data.[58]

GCMS (EI): calcd for $C_{12}H_{18}$ M: 162.14. Found: 162.11.

General procedure for Heck reaction of primary alkyl halides using 1:2 RX and styrene: In an argon-filled glove box, a dry 10-mL reaction tube containing a magnetic stir bar was charged sequentially with $Pd(dba)_2$ (14.4 mg, 0.025 mmol, 5 mol%), dppf (19.4 mg, 0.035 mmol, 7 mol%) and 2.0 mL of dry $PhCF_3$. After stirring at room temperature for 30 minutes, alkyl halide (0.50 mmol, 1.0 equiv), styrene (104 mg, 1.0 mmol, 2.0 equiv), *n*-dodecane (GC standard, 20 μL), Cy_2NMe (146 mg, 0.75 mmol, 1.5 equiv) and LiI (134 mg, 1.0 mmol, 2.0 equiv) were added sequentially. The reaction tube was capped tightly and the mixture was heated with vigorous stirring in a 110 ^oC oil bath for 36 h, unless stated otherwise. At the end of the reaction, the mixture was cooled to room temperature. It was diluted with diethyl ether and then passed through a short pad of silica gel to remove insoluble salts with diethyl ether washings. The filtrate was concentrated under reduced pressure and the residue was directly subjected to silica gel flash chromatography for isolation. The ratio of the amount of (*E*)-isomer to other isomers was determined by GC in both the crude mixtures and isolated samples. In most cases, the ratio did not change after flash chromatography.

An alternative procedure using 3:1 RX and styrene: In an argon-filled glove box, a dry 10-mL reaction tube containing a magnetic stir bar was charged sequentially with $Pd(dba)_2$ (28.8 mg, 0.050 mmol, 10 mol%), dppf

(38.8 mg, 0.070 mmol, 14 mol%) and 2.0 mL of dry $PhCF_3$. After stirring at room temperature for 30 minutes, alkyl halide (1.50 mmol, 3.0 equiv), styrene (52 mg, 0.5 mmol, 1.0 equiv), *n*-dodecane (GC standard, 20 μL) and Cy_2NMe (390 mg, 2.0 mmol, 4.0 equiv) and LiI (201 mg, 1.5 mmol, 3.0 equiv) were added sequentially. The reaction tube was capped tightly and the mixture was heated with vigorous stirring in a 110 ^oC oil bath for 48 h, unless stated otherwise. At the end of the reaction, the mixture was cooled down to room temperature. It was passed through a short pad of silica gel to remove insoluble salts with diethyl ether washings. The filtrate was concentrated under reduced pressure and the residue was directly subjected to silica gel flash chromatography for isolation.



(*E*)-*β*-(1-Decyl)styrene [117780-29-7]. General procedure using *n*-decyl iodide (134 mg, 0.5 mmol): the titled compound was obtained as colorless oil (76 mg, 62% yield) after flash chromatography using hexanes as eluent and the olefinic selectivity was determined to be 9:1. The alternative procedure using *n*-decyl iodide: colorless oil (90 mg, 74% yield) and 8:1 olefinic selectivity.

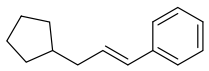
General procedure using *n*-decyl bromide (111 mg, 0.5 mmol): colorless oil (74 mg, 61%) and 8:1 olefinic selectivity. The alternative procedure using *n*-decyl bromide: colorless oil (90 mg, 74%) and 4:1 olefinic selectivity.

^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 7.7 Hz, 2H), 7.31 (ψt, J = 7.7 Hz, 2H), 7.22-7.19 (m, 1H), 6.40 (d, J = 15.9 Hz, 1H), 6.26 (dt, J = 15.9, 6.8 Hz, 1H), 2.26-2.20 (m, 2H), 1.51-1.46 (m, 2H), 1.34-1.30 (m, 14H), 0.92 (t, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 131.4, 129.9, 128.6, 126.9, 126.1,

33.2, 32.1, 29.8 (2 overlapping signals), 29.7, 29.6, 29.5, 29.4, 22.9, 14.3.

GCMS (EI): calcd for $C_{18}H_{28}$ M: 244.22. Found: 244.10.



(*E*)-*β*-(Cyclopentylmethyl)styrene [91083-79-3]. General procedure using cyclo-pentylmethyl iodide (105 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (0.025 mmol, 28.9 mg): the titled compound was obtained as colorless oil (51 mg, 55% yield) after flash chromatography using hexanes as eluent. The olefinic selectivity of the isolated Heck products was determined to be 13:1 by GC. The alternative procedure using cyclopentylmethyl iodide and $Pd(PPh_3)_4$ (0.050 mmol, 57.8 mg): colorless oil (70 mg, 75%) and 10:1 olefinic selectivity.

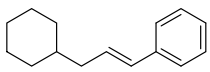
General procedure using cyclopentylmethyl bromide (82 mg, 0.5 mmol): colorless oil (54 mg, 58% yield) and 12:1 olefinic selectivity.

General procedure using 6-iodo-1-hexene (105 mg, 0.5 mmol): colorless oil (48 mg, 52% yield) and 3:1 olefinic selectivity. <5% of the noncyclized isomer carrying a terminal vinyl group was detected by ^{1}H NMR spectroscopy.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.3 Hz, 2H), 7.31 (ψt, *J* = 7.3 Hz, 2H), 7.22-7.17 (m, 1H), 6.38 (d, *J* = 15.8 Hz, 1H), 6.24 (dt, *J* = 15.8, 7.1 Hz, 1H), 2.22 (t, *J* = 7.1 Hz, 2H), 2.02-1.90 (m, 1H), 1.83-1.75 (m, 2H), 1.68-1.49 (m, 4H), 1.27-1.16 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 130.7, 130.3, 128.6, 126.9, 126.1, 40.2, 39.6, 32.5, 25.3.

GCMS (EI): calcd for $C_{14}H_{18}$ M: 186.14. Found: 186.08.



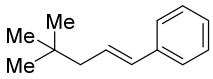
(*E*)-*β*-(Cyclohexylmethyl)styrene [182320-85-0]. General procedure using cyclo-hexylmethyl iodide (114 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (0.025 mmol, 28.9 mg) instead of $Pd(dba)_2$: the titled compound was obtained as colorless oil (60 mg, 60% yield) after flash chromatography using hexanes as eluent. The olefinic selectivity of the isolated Heck products was determined to be 15:1 by GC. The alternative procedure using cyclohexylmethyl iodide and $Pd(PPh_3)_4$ (0.050 mmol, 57.8 mg): colorless oil (78 mg, 78%) and 12:1 olefinic selectivity.

General procedure using cyclohexylmethyl bromide (89 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (0.025 mmol, 28.9 mg) instead of $Pd(dba)_2$: colorless oil (55 mg, 55% yield) and 16:1 olefinic selectivity. The alternative procedure using cyclohexylmethyl bromide and $Pd(PPh_3)_4$ (0.050 mmol, 57.8 mg): colorless oil (75 mg, 75%) and 13:1 olefinic selectivity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.34 (m, 2H), 7.31-7.27 (m, 2H), 7.20-7.17 (m, 1H), 6.36 (d, J = 15.8 Hz, 1H), 6.23 (dt, J = 15.8, 7.2 Hz, 1H), 2.11 (t, J = 7.0 Hz, 2H), 1.78-1.64 (m, 5H), 1.46-1.35 (m, 1H), 1.29-1.10 (m, 3H), 1.00-0.92 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 130.9, 129.9, 128.6, 126.9, 126.1, 41.2, 38.4, 33.4, 26.7, 26.5.

GCMS (EI): calcd for $C_{15}H_{20}$ M: 200.16. Found: 200.11.



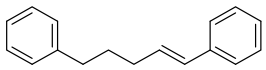
(*E*)-*β*-Neopentylstyrene [40132-64-7]. General procedure using neopentyl iodide (99 mg, 0.5 mmol): the reaction completed after 96 h. The titled compound was obtained as colorless oil (50 mg, 57% yield) after flash chromatography using hexanes as eluent. The *trans/cis* selectivity of the isolated Heck products was determined to be 15:1 by GC. The alternative

procedure using neopentyl iodide: colorless oil (64 mg, 74%) and 6:1 *trans/cis* selectivity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.6 Hz, 2H), 7.29 (ψt, *J* = 7.6 Hz, 2H), 7.20-7.16 (m, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 6.26 (dt, *J* = 15.8, 7.3 Hz, 1H), 2.09 (d, *J* = 7.3 Hz, 2H), 0.94 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 132.0, 128.6, 128.4, 127.0, 126.2, 47.8, 31.6, 29.6.

GCMS (EI): calcd for $C_{13}H_{18}$ M: 174.14. Found: 174.19.

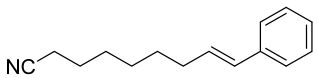


(*E*)-*β*-(3-Phenyl-1-propyl)styrene [7433-54-7]. General procedure using 1-bromo-3-phenylpropane (100 mg, 0.5 mmol): the titled compound was obtained as colorless oil (74 mg, 63% yield) after flash chromatography using hexanes as eluent. The olefinic selectivity of the isolated Heck products was determined to be 12:1 by GC. The alternative procedure using 1-bromo-3-phenylpropane: colorless oil (83 mg, 75%) and 4:1 olefinic selectivity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.13 (m, 10H), 6.39 (d, *J* = 15.9 Hz, 1H), 6.22 (dt, *J* = 15.9, 6.8 Hz, 1H), 2.66 (t, *J* = 7.6 Hz, 2H), 2.24 (tt, *J* = 7.2, 7.2 Hz), 1.80 (dt, *J* = 7.6, 7.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.5, 138.0, 130.7, 130.4, 128.6 (2 overlapping signals), 128.5, 127.0, 126.1, 125.9, 35.5, 32.7, 31.2.

GCMS (EI): calcd for $C_{17}H_{18}$ M: 222.14. Found: 222.08.



(*E*)-*β*-(7-Cyanoheptyl)styrene. General procedure using 7-Bromoheptanenitrile (95 mg, 0.5 mmol): the titled compound was obtained as

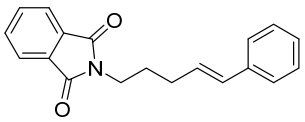
colorless oil (63 mg, 59% yield) after flash chromatography using EA/hexanes (1:30) as eluent. The olefinic selectivity of the isolated Heck products was determined to be 21:1 by GC. The sample for NMR spectroscopy was obtained after preparative TLC. The alternative procedure using 7-bromoheptanenitrile: colorless oil (81 mg, 76%) and 9:1 olefinic selectivity.

General procedure using 7-chloroheptanenitrile: colorless oil (55 mg, 50% yield) and 20:1 olefinic selectivity. The alternative procedure using 7-chloroheptanenitrile: colorless oil (69 mg, 64%) and 7:1 olefinic selectivity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 4H), 7.22-7.17 (m, 1H), 6.38 (d, *J* = 15.8 Hz, 1H), 6.20 (dt, *J* = 15.8, 6.9 Hz, 1H), 2.34 (t, *J* = 7.1 Hz, 2H), 2.25-2.19 (m, 2H), 1.71-1.64 (m, 2H), 1.52-1.36 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 130.7, 130.2, 128.6, 127.0, 126.1, 119.9, 33.0, 29.1, 28.7, 28.4, 25.5, 17.3.

GCMS (EI): calcd for $C_{15}H_{19}N$ M: 213.15. Found: 213.13.

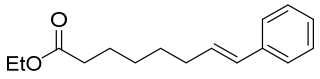


(*E*)-*β*-(Phthalimidopropyl)styrene. General procedure using *N*-(3-bromopropyl)-phthalimide (134 mg, 0.5 mmol): the titled compound was obtained as white solid (82 mg, 56% yield) after flash chromatography using EA/hexanes (1:30) as eluent. The selectivity of the isolated Heck products was determined to be 13:1 by GC. The pure sample for NMR spectroscopy was obtained after preparative TLC. The alternative procedure using *N*-(3-bromopropyl)phthalimide: white solid (110 mg, 76%) and 17:1 olefinic selectivity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85-7.80 (m, 2H), 7.72-7.66 (m, 2H), 7.31-7.24 (m, 4H), 7.19-7.15 (m, 1H), 6.41 (d, *J* = 15.9 Hz, 1H), 6.20 (dt, *J* = 15.9, 6.8 Hz, 1H), 3.75 (t, *J* = 7.2 Hz, 2H), 2.32-2.26 (m, 2H), 1.92-1.85 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 137.7, 134.0, 132.4, 130.9, 129.3, 128.6, 127.1, 126.1, 123.3, 37.8, 30.5, 28.2.

GCMS (EI): calcd for $C_{19}H_{17}NO_2$ M: 291.13. Found: 291.07.

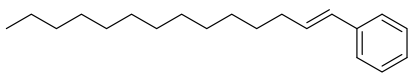


Ethyl 6-(*E*)-*β*-styrylhexanoate. General procedure usingethyl 6-bromohexanoate (112 mg, 0.5 mmol): the titled compound was obtained as colorless oil (40 mg, 37% yield) after flash chromatography using EA/hexanes (1:30) as eluent. Theselectivity of the isolated Heck products was determined to be 2:1 by GC. The sample for NMR spectroscopy was obtained after preparative TLC. The alternative procedure using 6-bromohexanoate: light yellow oil (90 mg, 73%) and 2:1 olefinic selectivity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.27 (m, 4H), 7.21-7.19 (m, 1H), 6.38 (d, *J* = 15.8 Hz, 1H), 6.21 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.47-2.19 (m, 2H), 1.70-1.63 (m, 2H), 1.54-1.46 (m, 2H), 1.42-1.35 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 138.0, 130.9, 130.1, 128.6, 127.0, 126.1, 60.3, 34.5, 32.9, 29.1, 28.8, 25.0, 14.4.

GCMS (EI): calcd for $C_{16}H_{22}O$ M: 246.16. Found: 246.12.



(*E*)-*β*-(1-Dodecyl)styrene [99464-24-1]. General procedure using 1-chloro-dodecane (102 mg, 0.5 mmol): the titled compound was obtained as colorless

oil (70 mg, 51% yield) after flash chromatography using hexanes as eluent. The olefinic selectivity of the isolated Heck products was determined to be 9:1 by GC. The alternative procedure using 1-chlorododecane: colorless oil (100 mg, 74%) and 4:1 olefinic selectivity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.35 (m, 2H), 7.32-7.28 (m, 2H), 7.22-7.18 (m, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 6.26 (dt, *J* = 15.8, 6.8 Hz, 1H), 2.25-2.19 (m, 2H), 1.52-1.28 (m, 20H), 0.92-0.88 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 131.4, 129.9, 128.6, 126.9, 126.1, 33.2, 32.1, 29.86 (2 overlapping signals), 29.82, 29.80, 29.7, 29.6, 29.5, 29.4, 22.9, 14.3.

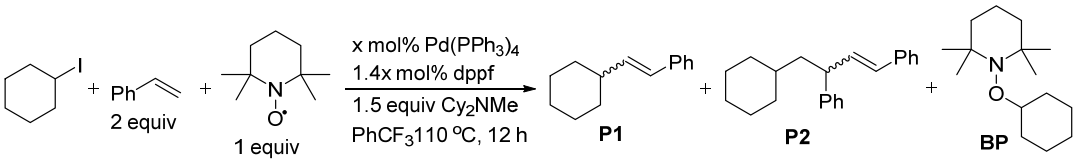
GCMS (EI): calcd for $C_{20}H_{32}$ M: 272.25. Found: 272.22.

2.4.3 Mechanistic study

Typical procedure: In an argon-filled glove box, a dry 8.0-mL reaction tube containing a magnetic stir bar was charged with $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol), dppf (3.9 mg, 0.007 mmol) and 0.40 mL of dry $PhCF_3$. After stirring at room temperature for 30 minutes, cyclohexyl iodide (21.0 mg, 0.10 mmol), styrene (20.8 mg, 0.20 mmol), GC standard *n*-dodecane (10 μL), Cy_2NMe (29.3 mg, 0.15 mmol) and TEMPO (15.6 mg, 0.1 mmol) were added sequentially. The tube was capped tightly and the reaction mixture was heated with stirring in an aluminum-heating block maintained at 110 ^{o}C. After 12 hours, aliquots were taken from the reaction mixture in the glove box and passed through a short plug of silica gel with diethyl ether washings. The filtrates were subjected to GC analysis to determine the conversion of cyclohexyl iodide, the yield and isomeric selectivity of the Heck products and yield of a byproduct derived from double styrene insertion. The structures of the major isomer, (*E*)-*β*-

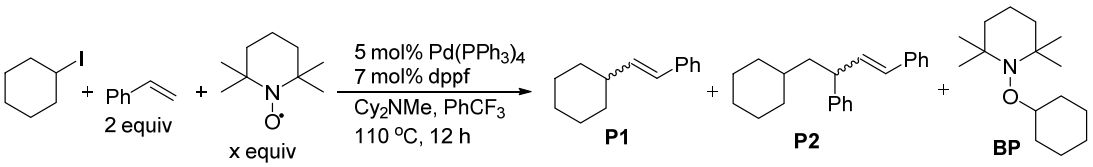
cyclohexylstyrene and its minor (*Z*)-isomer in the crude mixture were assigned by ^{1}H NMR spectroscopy and confirmed by GCMS. The ratio of the two isomers was determined by GC analysis.

Table 2.4.1. Trapping experiment using 1 equiv of TEMPO



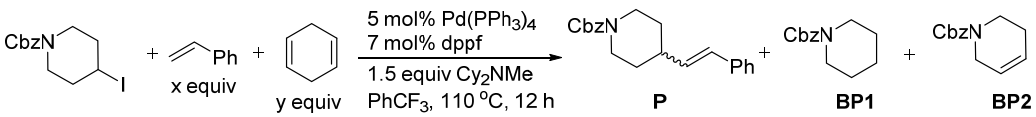
Entry	x mol% Pd	Conv. CyI(%)	**BP**(%)
1	0	0	0
2	5	19	10
3	10	23	20
4	20	44	41
5	50	100	100

Table 2.4.2. Trapping experiment using TEMPO



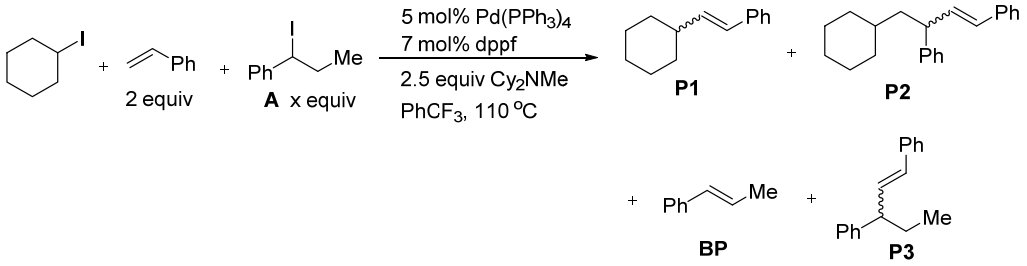
Entry	TEMPO (x equiv)	Conv. CyI (%)	**P1** (%), *E/Z*		**P2** (%), *E/Z*		**BP** (%)
1	0	100	79	19	11	8	0
2	0.1	20	0	-	0	-	8
3	0.5	24	0	-	0	-	10
4	1.0	25	0	-	0	-	11

Table 2.4.3. Trapping experiment using 1,4-cyclohexadiene



Entry	Styrene (x equiv)	1,4-Cyclohexadiene (y equiv)	Conv. (%)	**P** (%) *E/Z*		**BP1** (%)	**BP2** (%)
1		0	100	91	10	1	7
2	2.0	1	100	81	10	9	7
3		5	100	46	10	26	13
4		0	100	0	-	9	65
5	0	1	100	0	-	35	40
6		5	100	0	-	68	15

Table 2.4.4. Elimination of 1-iodo-1-phenylpropane A in model Heck reaction



Entry	**A** (x equiv)	Time	Conv. of Cy-I (%)	Conv. of **A** (%)	**P1** (%)	**P2** (%)	**P3** (%)	**BP** (%)
1	1.0	5 h	24	100	0	0	< 5	43
		12 h	75	100	13	4	< 5	41
2	0	5 h	98	-	73	9	-	-
		12 h	100	-	76	10	-	-

2.5 References

(1) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.

(2) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

(3) (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (d) Bräse, S.; Meijere, A. D. In *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH Verlag GmbH: 2008, p 217. (e) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062.

(4) (a) Schils, D. P. R.; Willems, J. J. M.; Medaer, P. A. M.; Pasquier, E. T. J.; Janssen, P. A. J.; Heeres, J.; Leenders, R. G. G.; Google Patents: 2004. (b) Schils, D.; Stappers, F.; Solberghe, G.; van Heck, R.; Coppens, M.; Van den Heuvel, D.; Van der Donck, P.; Callewaert, T.; Meeussen, F.; Bie, E. D.; Eersels, K.; Schouteden, E. *Org. Process Res. Dev.* **2008**, *12*, 530. (c) Janssen, P. A. J.; Lewi, P. J.; Arnold, E.; Daeyaert, F.; de Jonge, M.; Heeres, J.; Koymans, L.; Vinkers, M.; Guillemont, J.; Pasquier, E.; Kukla, M.; Ludovici, D.; Andries, K.; de Béthune, M.-P.; Pauwels, R.; Das, K.; Clark, A. D.; Frenkel, Y. V.; Hughes, S. H.; Medaer, B.; De Knaep, F.; Bohets, H.; De Clerck, F.; Lampo, A.; Williams, P.; Stoffels, P. *J. Med. Chem.* **2004**, *48*, 1901.

(5) (a) Larock, R. C.; Leung, W.-Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629. (b) Kjell, D. P.; Slattery, B. J.; Semo, M. J. *J. Org. Chem.* **1999**, *64*, 5722. (c) Kjell, D. P.; Hallberg, D. W.; Kalbfleisch, J. M.; McCurry, C. K.; Semo, M. J.; Sheldon, E. M.; Spitler, J. T.; Wang, M. *Org. Process Res. Dev.* **2005**, *9*, 738.

(6) Fortineau, A. D.; WO2008053148 (A1): 2008.

(7) The Nobel Prize in Chemistry 2010,

http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/.

(8) (a) Baumann, M.; Baxendale, I. R. *Beilstein Journal of Organic Chemistry* **2013**, *9*, 2265. (b) Law, V.; Knox, C.; Djoumbou, Y.; Jewison, T.; Guo, A. C.; Liu, Y.; Maciejewski, A.; Arndt, D.; Wilson, M.; Neveu, V.; Tang, A.; Gabriel, G.; Ly, C.; Adamjee, S.; Dame, Z. T.; Han, B.; Zhou, Y.; Wishart, D. S. *Nucleic Acids Res.* **2014**, *42*, D1091.

(9) WHO Model Lists of Essential Medicines 18th ed. http://apps.who.int/iris/bitstream/10665/93142/1/EML_18_eng.pdf?ua=1.

(10) (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (b) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656.

(11) (a) McCrindle, R.; Ferguson, G.; Arsenault, G. J.; McAlees, A. J. *J. Chem. Soc., Chem. Commun.* **1983**, 571. (b) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, *21*, 2177.

(12) Wu, G. Z.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2507.

(13) (a) Yi, P.; Zhuangyu, Z.; Hongwen, H. *Synth. Commun.* **1992**, *22*, 2019. (b) Pan, Y.; Zhang, Z.; Hu, H. *Synthesis* **1995**, *1995*, 245.

(14) Kumar, P. *Org. Prep. Proced. Int.* **1997**, *29*, 477.

(15) Higuchi, K.; Sawada, K.; Nambu, H.; Shogaki, T.; Kita, Y. *Org. Lett.* **2003**, *5*, 3703.

(16) Narahashi, H.; Yamamoto, A.; Shimizu, I. *Chem. Lett.* **2004**, *33*, 348.

(17) Yang, Z.; Zhou, J. *J. Am. Chem. Soc.* **2012**, *134*, 11833.

(18) Narahashi, H.; Shimizu, I.; Yamamoto, A. *J. Organomet. Chem.* **2008**, *693*, 283.

(19) Mori, M.; Oda, I.; Ban, Y. *Tetrahedron Lett.* **1982**, *23*, 5315.

(20) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1990**, *31*, 933.

(21) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477.

(22) Liu, H.; Qiao, Z.; Jiang, X. *Org. Biomol. Chem.* **2012**, *10*, 7274.

(23) Glorius, F. *Tetrahedron Lett.* **2003**, *44*, 5751.

(24) Bräse, S.; Waegell, B.; de Meijere, A. *Synthesis* **1998**, *1998*, 148.

(25) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340.

(26) Zhou, W.; An, G.; Zhang, G.; Han, J.; Pan, Y. *Org. Biomol. Chem.* **2011**, *9*, 5833.

(27) Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146.

(28) McMahon, C. M.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5974.

(29) Lebedev, S. A.; Lopatina, V. S.; Petrov, E. S.; Beletskaya, I. P. *J. Organomet. Chem.* **1988**, *344*, 253.

(30) Lebedev, S. A.; Lopatina, V. S.; Lukyanova, T. V.; Berestova, S. S.; Shifrina, R. R.; Shapetko, N. N.; Petrov, E. S.; Beletskaya, I. P. *Zh. Org. Khim.* **1985**, *21*, 721.

(31) Redkina, L. I.; Makovets.Kl; Tinyakov.Ei; Dolgoplo.Ba *Doklady Akademii Nauk Sssr* **1969**, *186*, 397.

(32) (a) Matsubara, R.; Gutierrez, A. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2011**, *133*, 19020. (b) Standley, E. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2013**, *135*, 1585.

(33) (a) Liu, C.; Tang, S.; Liu, D.; Yuan, J.; Zheng, L.; Meng, L.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3638. (b) Tang, S.; Liu, C.; Lei, A. *Chem. Commun.* **2013**, *49*, 2442.

(34) Nishikata, T.; Noda, Y.; Fujimoto, R.; Sakashita, T. *J. Am. Chem. Soc.* **2013**, *135*, 16372.

(35) (a) Taylor, M. J. W.; Eckenhoff, W. T.; Pintauer, T. *Dalton Trans.* **2010**, *39*, 11475. (b) Eckenhoff, W. T.; Pintauer, T. *Dalton Trans.* **2011**, *40*, 4909.

(36) Branchaud, B. P.; Detlefsen, W. D. *Tetrahedron Lett.* **1991**, *32*, 6273.

(37) Giese, B.; Erdmann, P.; Göbel, T.; Springer, R. *Tetrahedron Lett.* **1992**, *33*, 4545.

(38) Weiss, M. E.; Kreis, L. M.; Lauber, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11125.

(39) Kreis, L. M.; Krautwald, S.; Pfeiffer, N.; Martin, R. E.; Carreira, E. M. *Org. Lett.* **2013**, *15*, 1634.

(40) (a) Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514. (b) Affo, W.; Ohmiya, H.; Fujioka, T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068.

(41) (a) Terao, J.; Kambe, N. *J. Synth. Org. Chem Jpn.* **2001**, *59*, 1044. (b) Terao, J.; Watabe, H.; Miyamoto, M.; Kambe, N. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2209.

(42) (a) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158. (b) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393. (c) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866.

(43) Maerckar, A. *Org. React.* **1965**, *14*, 270.

(44) (a) Gu, Y.; Tian, S.-K. *Top. Curr. Chem.* **2012**, *327*, 197. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (c) Dong, D.-J.; Li, H.-H.; Tian, S.-K. *J. Am. Chem. Soc.* **2010**, *132*, 5018. (d) Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; de Vicente, J. *J. Am. Chem. Soc.* **2003**, *125*, 6034. (e) Schlosser, M.;

Christmann, K. F. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 126.

(45) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(46) (a) Gürtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

(47) Lu, X. *Top. Catal.* **2005**, *35*, 73.

(48) Bissember, A. C.; Levina, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 14232.

(49) (a) Eckenhoff, W. T.; Pintauera, T. *Catal. Rev.* **2010**, *52*, 1. (b) Pintauer, T.; Matyjaszewski, K. *Chem. Soc. Rev.* **2008**, *37*, 1087.

(50) Giese, B.; Meister, J. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 178.

(51) Ren, P.; Vechorkin, O.; Allmen, K. v.; Scopelliti, R.; Hu, X. *J. Am. Chem. Soc.* **2011**, *133*, 7084.

(52) Allen, J.; Horne, D. B.; Hu, E.; Kaller, M. R.; Monenschein, H.; Nguyen, T. T.; Reichelt, A.; Rzasa, R. M.; WO Patent App. PCT/US2011/036,342: 2011.

(53) Jereb, M.; Zupan, M.; Stavber, S. *Green Chem.* **2005**, *7*, 100.

(54) Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5915.

(55) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618.

(56) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176.

(57) Affo, W.; Ohmiya, H.; Fujioka, T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068.

(58) Hirano, F.; Kamezawa, M.; Kamei, H. *Bull. Okayama Coll. Sci.* **1976**, *12*, 105.

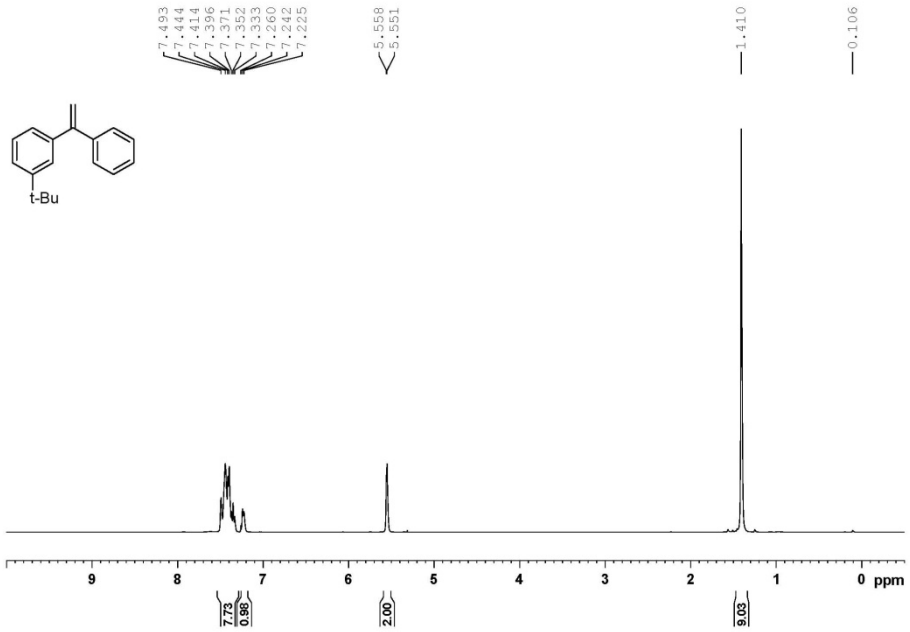
Appendix: List of publication**s**

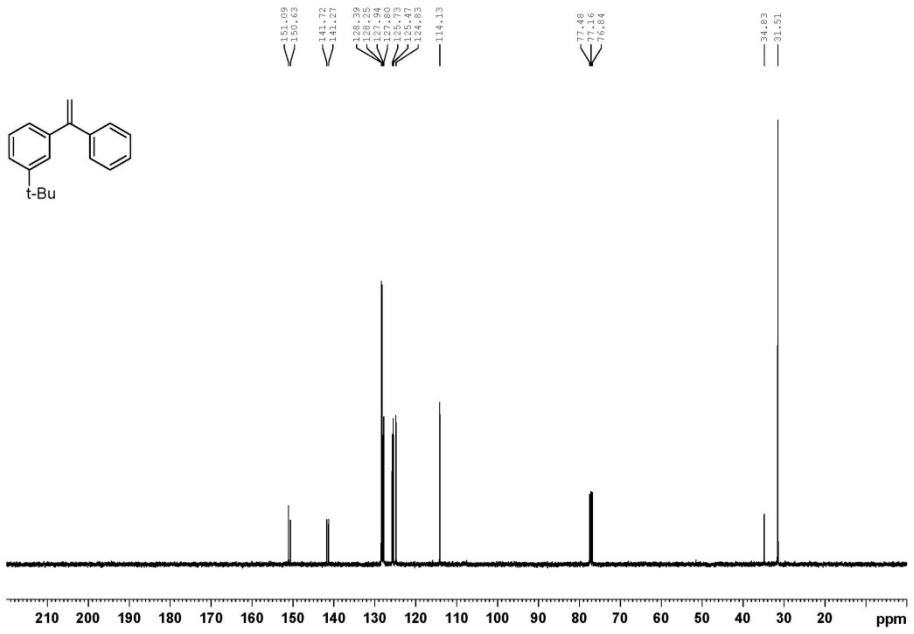
Zou, Y., Qin, L., Ren, X., Lu, Y., Li, Y. and Zhou, J. "Selective Arylation and Vinylation at the α Position of Vinylarenes" *Chem. Eur. J.*, **2013**, 19, 3504.

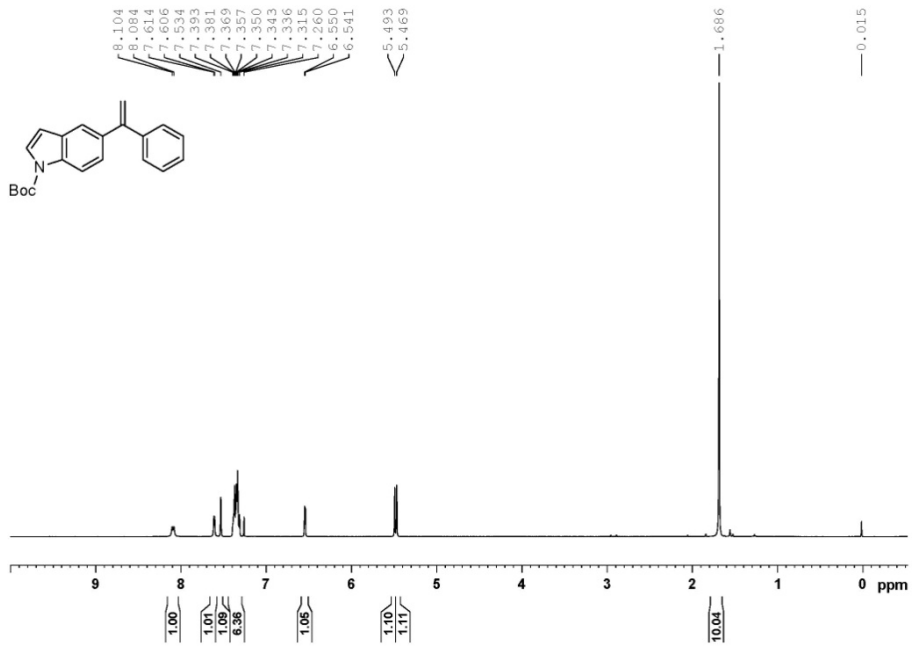
Zou, Y. and Zhou, J. "Palladium-Catalyzed Intermolecular Heck Reaction of Alkyl Halides" *Chem. Commun.*, **2014**, 50, 3725.

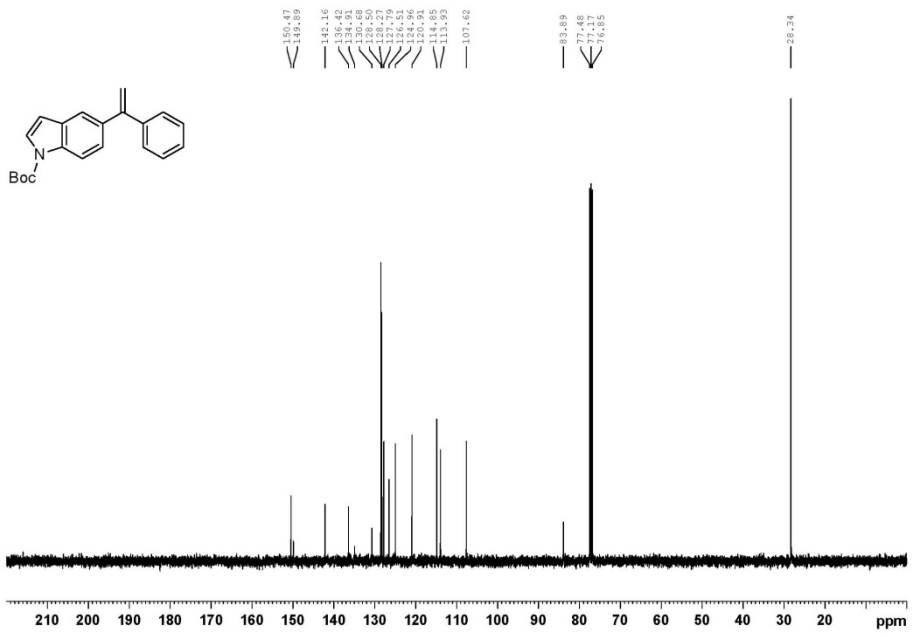
Zou, Y., Yue, G., Xu, J. and Zhou J. "Versatile Suzuki Coupling of Heteroaryl Bromides Using Tri-*t*-butylphosphine as Supporting Ligand" *Submitted.*

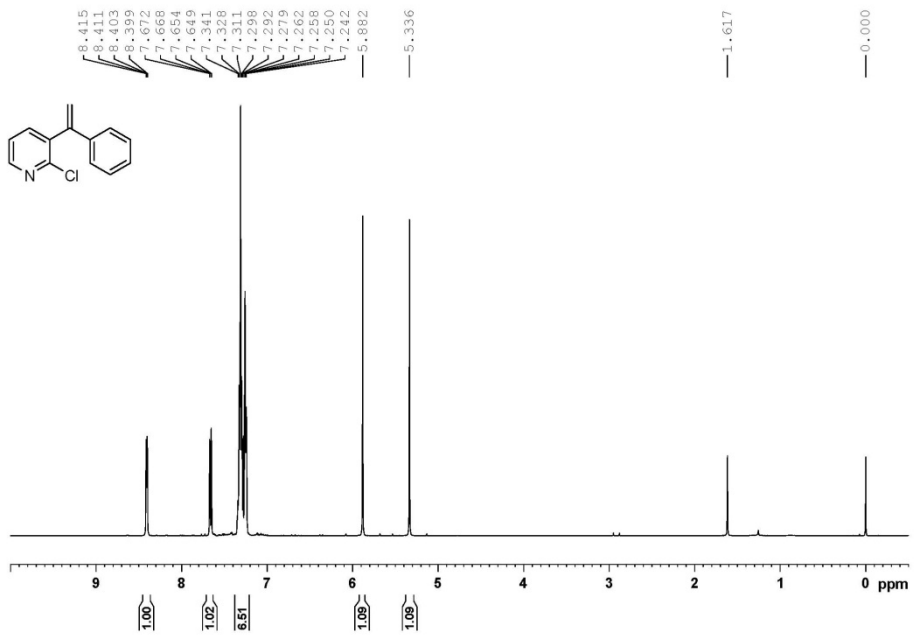
Appendix: Selected NMR spectra

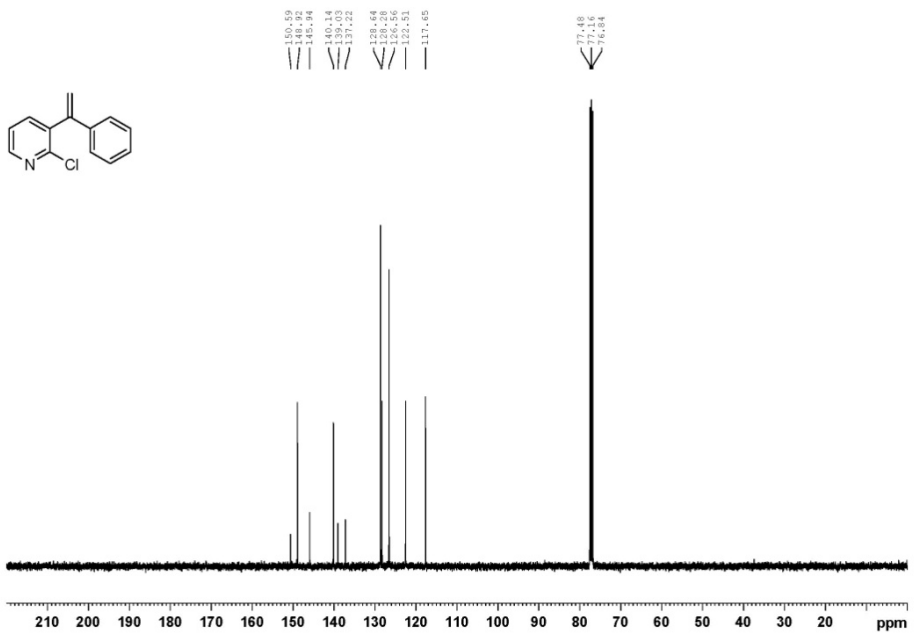


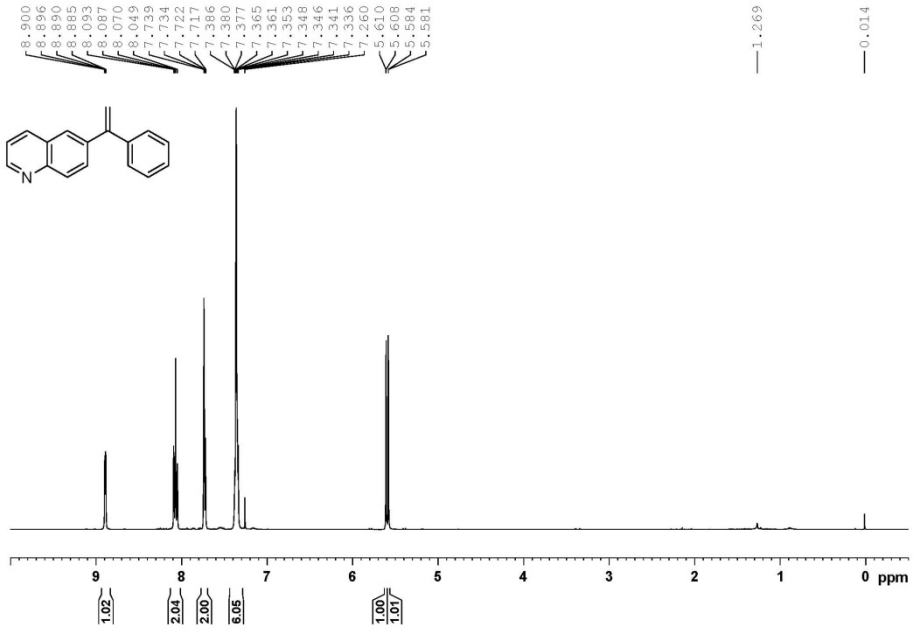


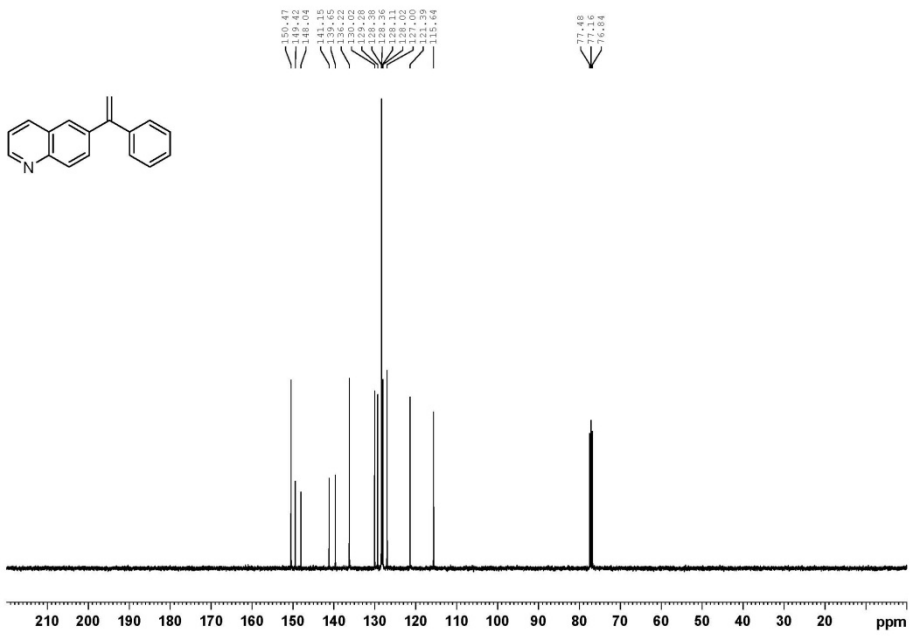

8.104
8.084
7.614
7.606
7.534
7.393
7.381
7.369
7.357
7.350
7.343
7.336
7.315
7.260
6.550
6.541
5.493
5.469
1.686
0.015
Boc
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.01
1.09
8.36
1.05
1.10
1.11
10.04

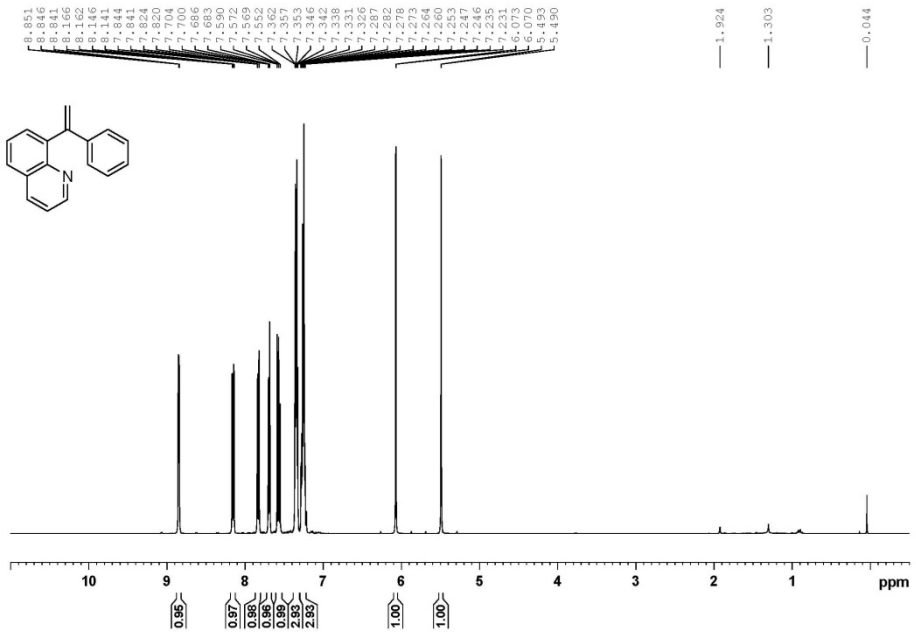

150.47
149.89
142.16
136.42
134.91
130.68
128.50
128.27
127.79
127.21
124.96
120.91
114.85
113.93
107.62
83.89
77.48
77.17
76.85
28.34
Boc
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

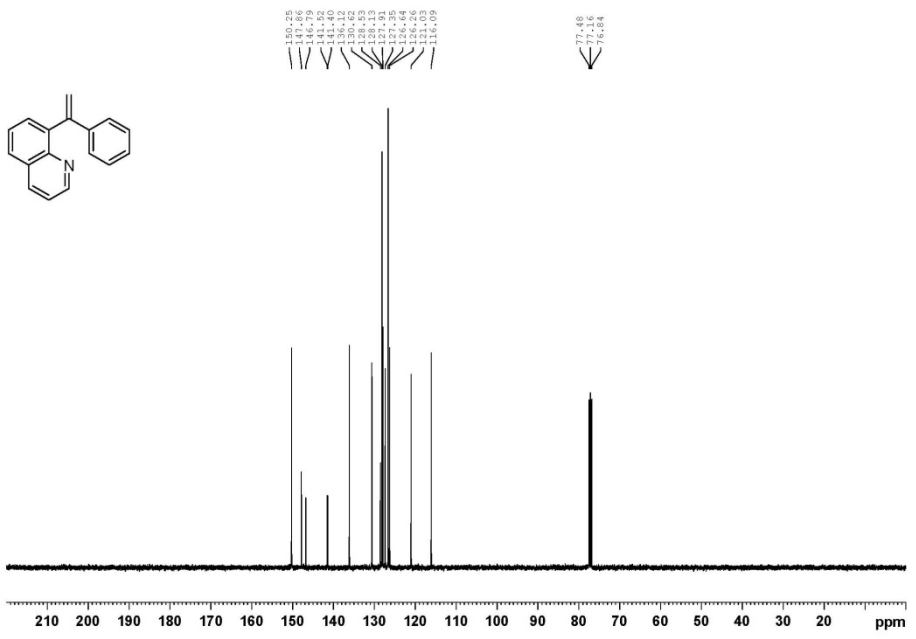

8.415
8.411
8.403
8.399
7.672
7.668
7.654
7.649
7.341
7.328
7.311
7.298
7.292
7.279
7.262
7.258
7.250
7.242
5.882
5.336
1.617
0.000
N
Cl
9
8
7
6
5
4
3
2
1
0 ppm
1.00
1.02
6.51
1.09
1.09

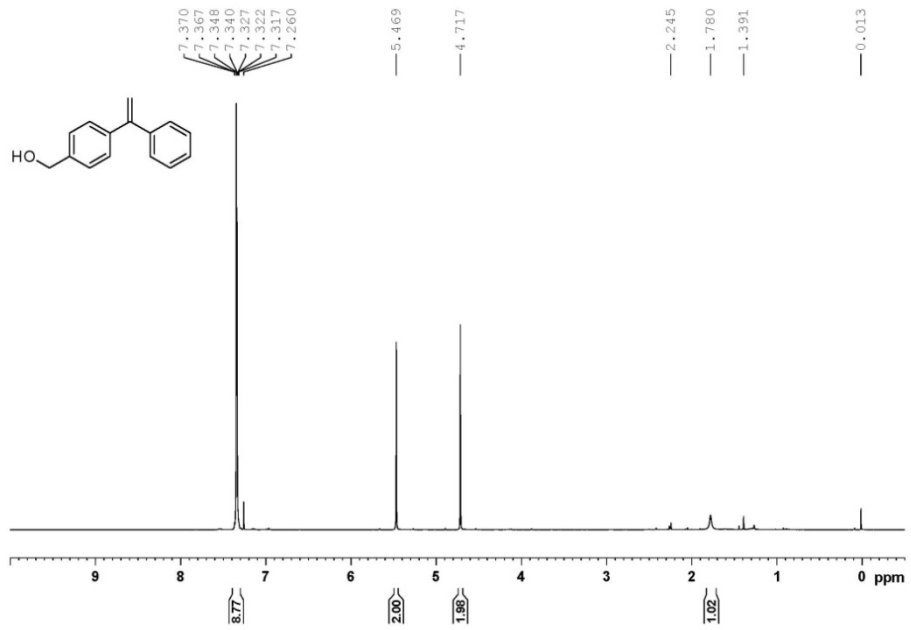

150.59
148.92
145.94
140.14
139.03
137.22
128.64
128.28
126.56
122.51
117.65
77.48
77.16
76.84
N
Cl
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

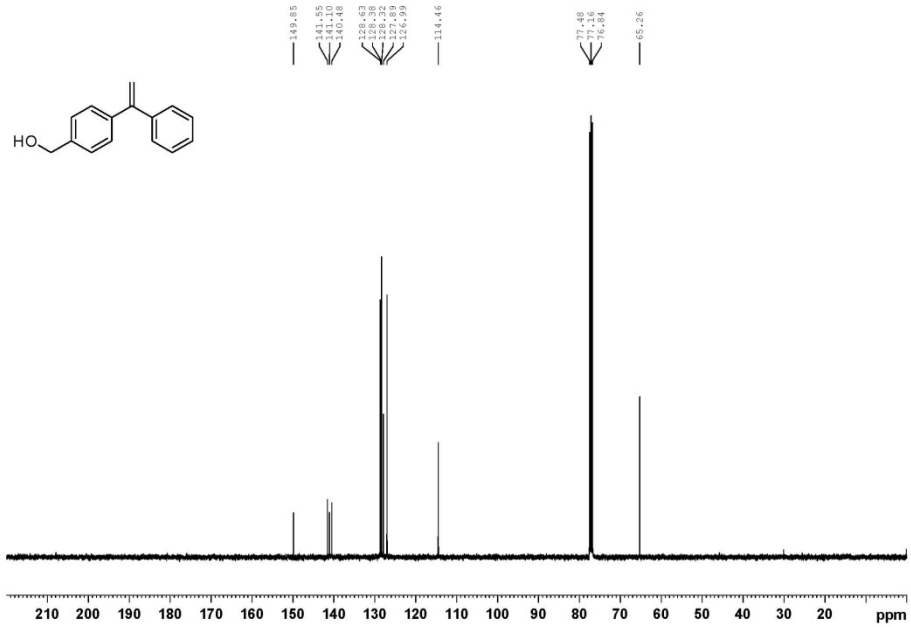

8.900
8.896
8.890
8.885
8.093
8.087
8.070
8.049
7.739
7.734
7.722
7.717
7.386
7.380
7.377
7.365
7.361
7.353
7.348
7.346
7.341
7.336
7.260
5.610
5.608
5.584
5.581
1.269
0.014
N
9
8
7
6
5
4
3
2
1
0 ppm
1.02
2.04
2.00
6.05
1.00
1.01

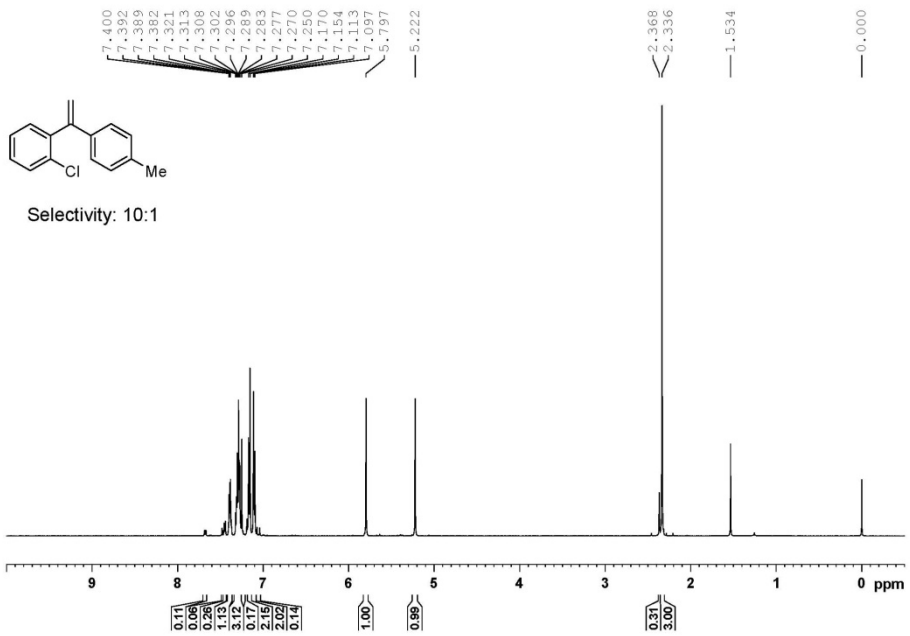

150.47
149.42
148.04
141.15
139.55
136.22
130.02
128.38
128.38
128.36
128.11
126.02
121.00
121.39
115.64
77.48
77.16
76.84
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

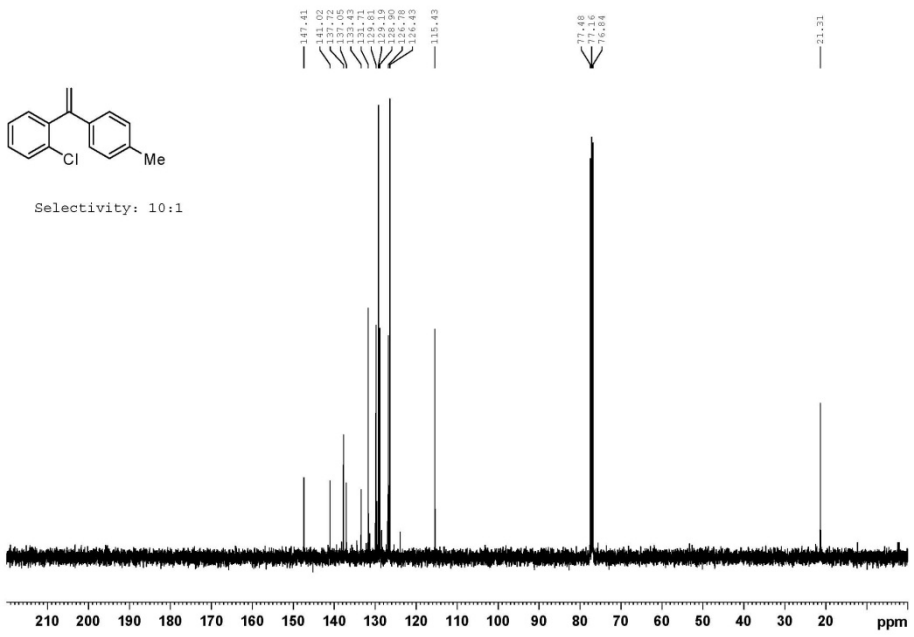

8.851
8.846
8.841
8.166
8.162
8.146
8.141
7.844
7.841
7.824
7.820
7.704
7.700
7.686
7.683
7.590
7.572
7.569
7.552
7.362
7.357
7.353
7.346
7.342
7.338
7.331
7.326
7.287
7.282
7.278
7.273
7.264
7.260
7.253
7.247
7.246
7.235
7.231
6.073
6.070
5.493
5.490
1.924
1.303
0.044
10
9
8
7
6
5
4
3
2
1
ppm
0.95
0.97
0.88
0.96
0.98
2.93
2.93
1.00
1.00

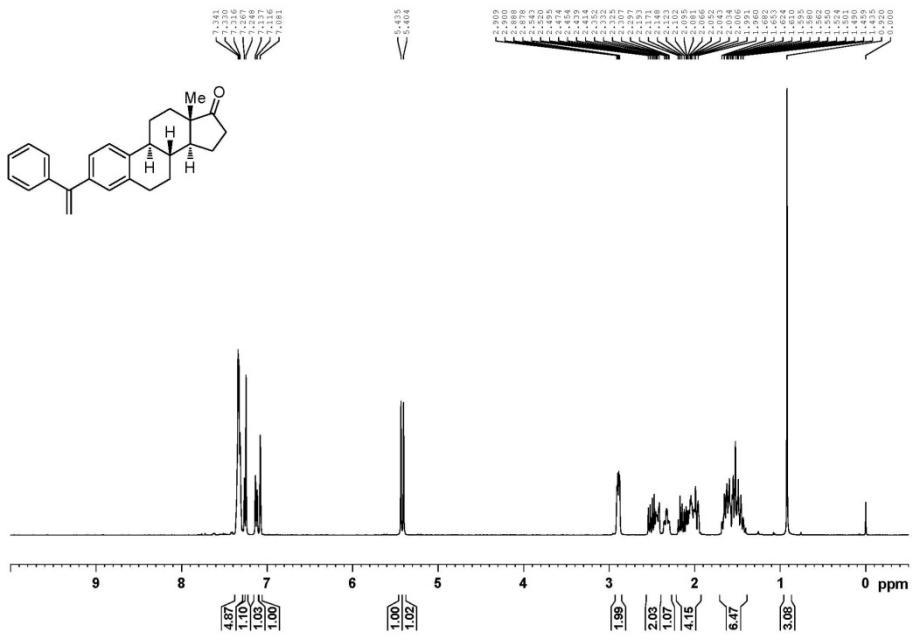

150.25
147.86
146.79
141.82
141.40
136.12
130.62
130.33
128.13
127.91
127.35
126.64
126.26
121.03
116.09
77.48
77.16
76.84
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

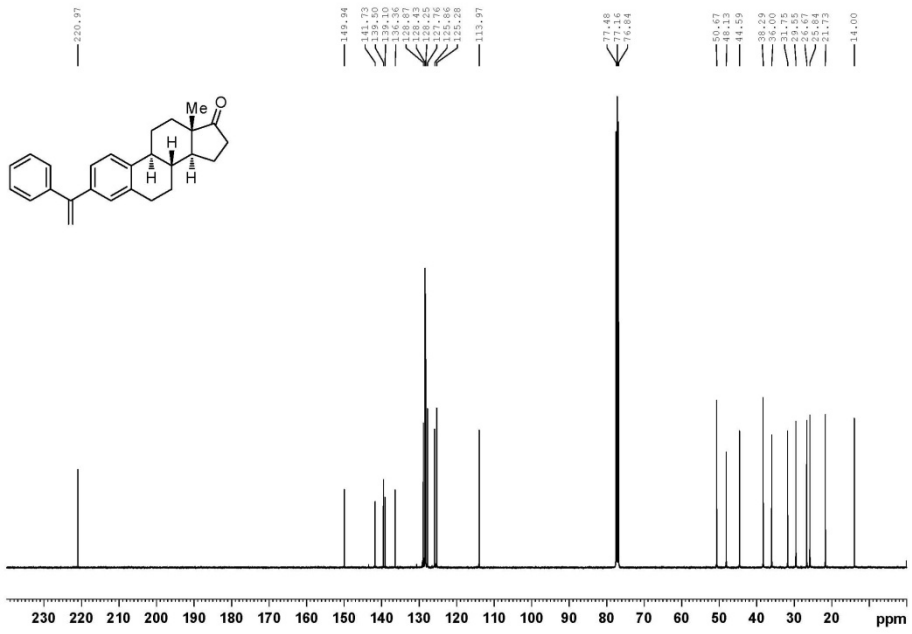

7.370
7.367
7.348
7.340
7.327
7.322
7.317
7.260
5.469
4.717
2.245
1.780
1.391
0.013
HO
9
8
7
6
5
4
3
2
1
0 ppm
8.77
2.00
1.98
1.02

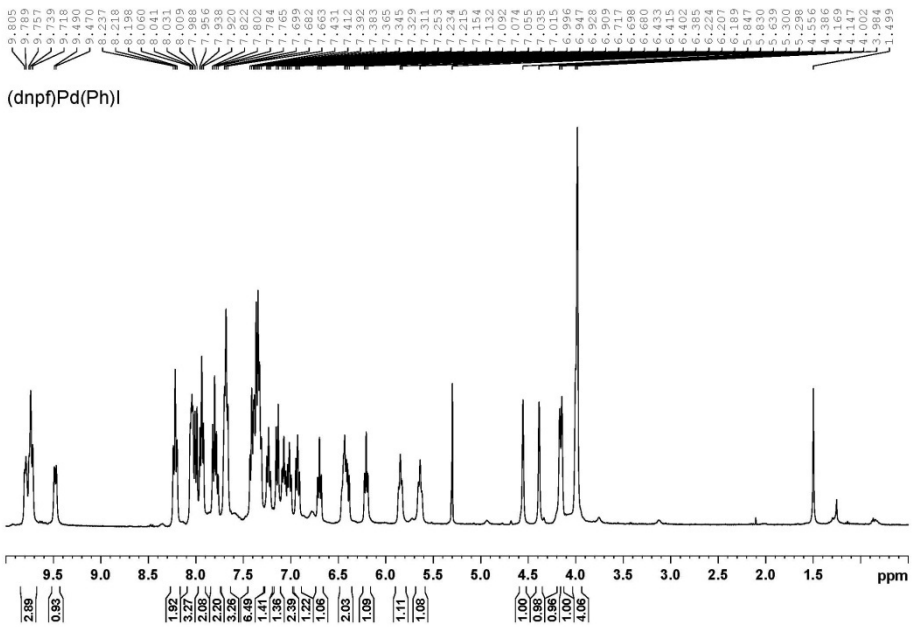

149.85
141.55
141.10
140.48
128.63
128.38
128.32
127.89
126.99
114.46
77.48
77.16
76.84
65.26
HO
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

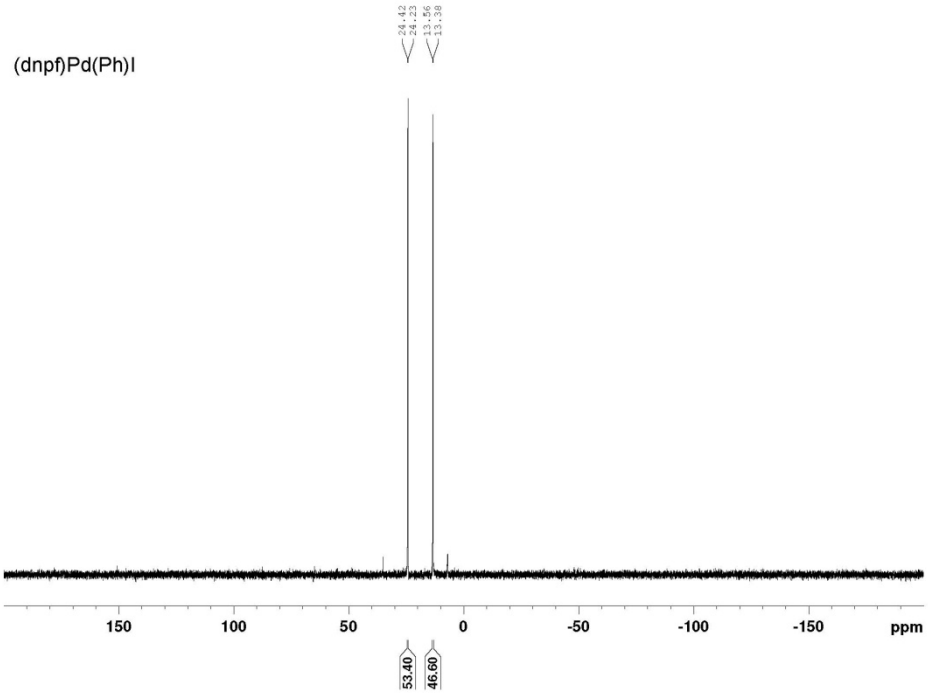

7.400
7.392
7.389
7.382
7.321
7.313
7.308
7.302
7.286
7.283
7.277
7.270
7.250
7.170
7.154
7.113
7.097
5.797
5.222
2.368
2.336
1.534
0.000
Cl
Me
Selectivity: 10:1
9
8
7
6
5
4
3
2
1
0 ppm
0.11
0.06
0.26
1.13
3.12
0.17
2.15
2.02
0.14
1.00
0.99
0.31
3.00

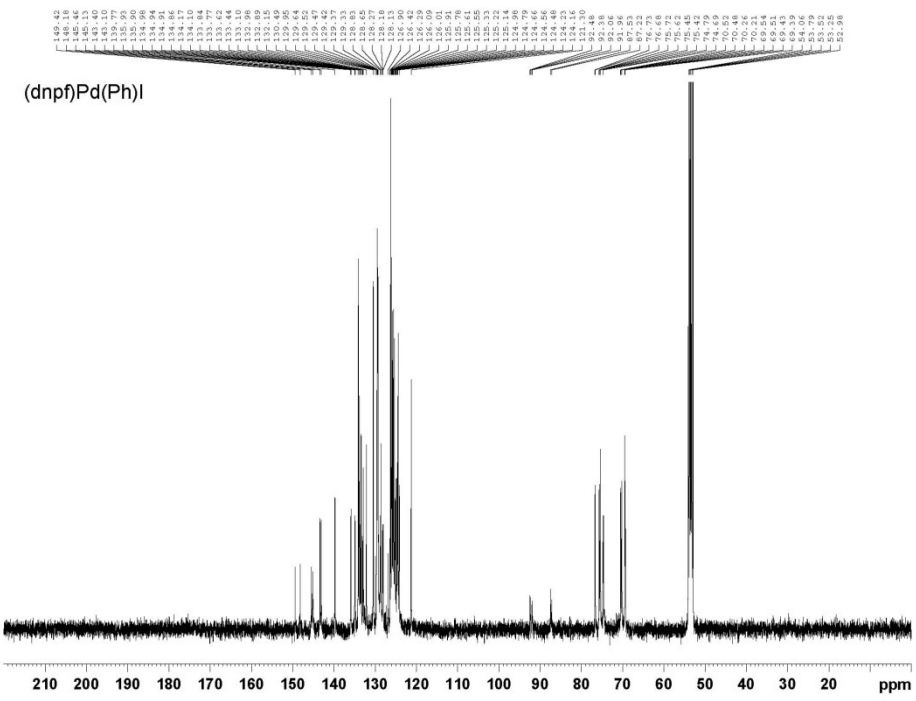

147.41
141.02
131.72
137.05
133.43
131.71
129.61
129.19
128.90
126.68
126.43
115.43
77.48
77.16
76.84
21.31
Cl
Me
Selectivity: 10:1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

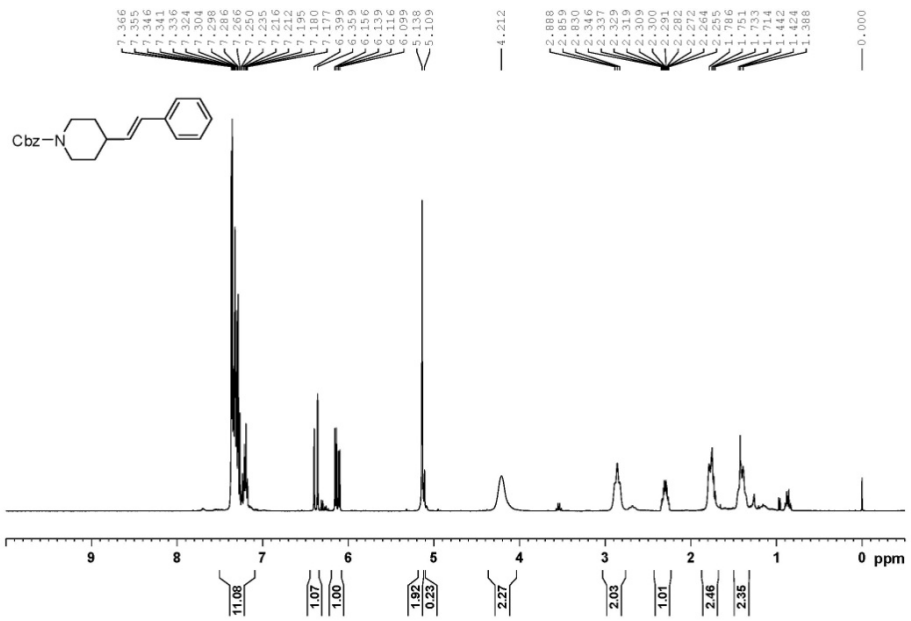

Me
O
H
H
H
9
8
7
6
5
4
3
2
1
0 ppm

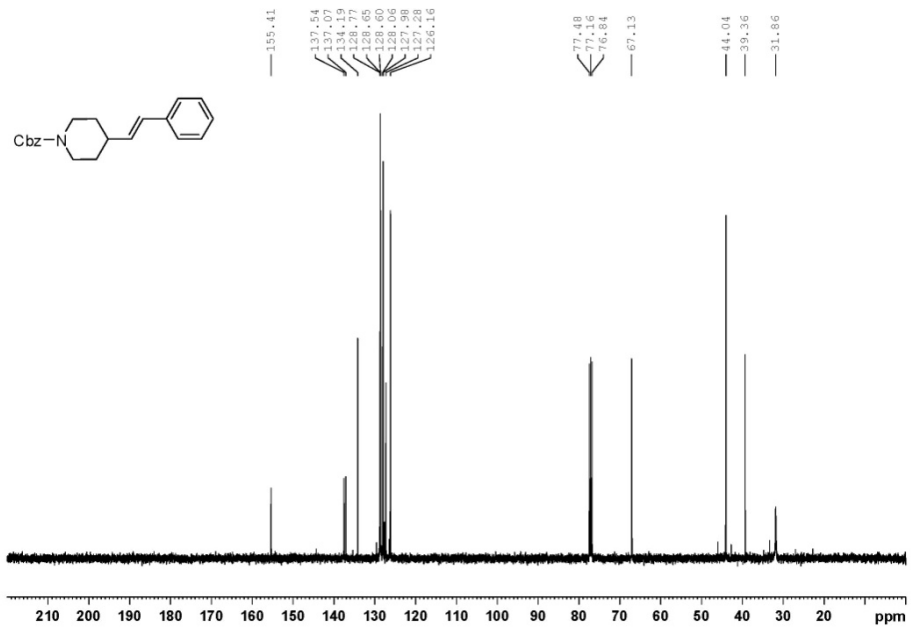

Me
O
H
H
H
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

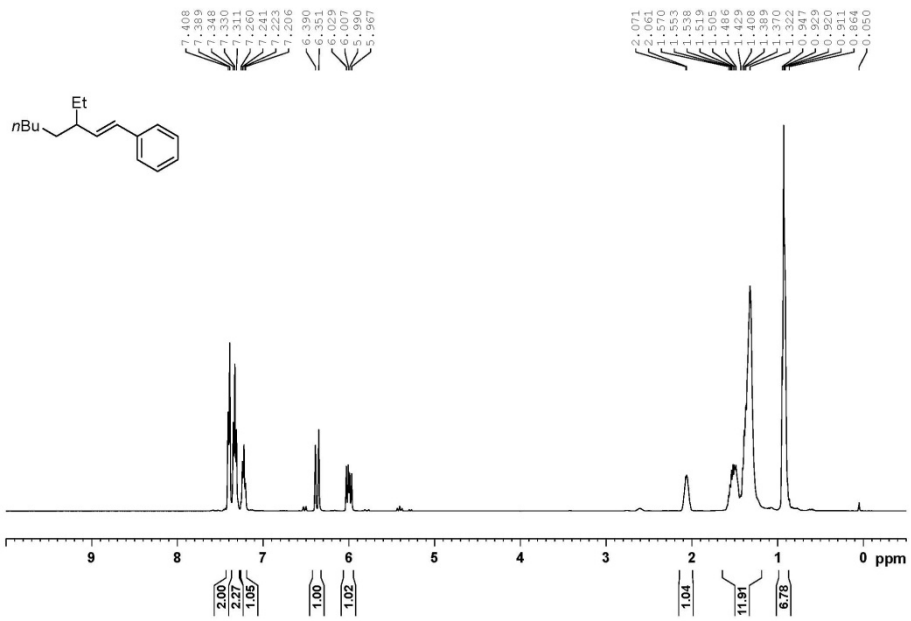

(dnpf)Pd(Ph)I
9.805
9.789
9.757
9.739
9.718
9.490
9.470
8.237
8.218
8.198
8.060
8.041
8.031
8.009
7.988
7.956
7.938
7.920
7.822
7.802
7.784
7.765
7.699
7.682
7.663
7.431
7.412
7.392
7.383
7.365
7.345
7.329
7.311
7.253
7.234
7.215
7.154
7.132
7.092
7.074
7.055
7.035
7.015
6.996
6.947
6.928
6.909
6.717
6.698
6.680
6.433
6.415
6.402
6.385
6.224
6.207
6.189
5.847
5.830
5.639
5.300
5.298
4.556
4.386
4.169
4.147
4.002
3.984
1.499
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
2.89
0.93
1.92
3.27
2.08
2.20
3.28
6.49
1.41
1.36
2.39
1.22
1.06
2.03
1.09
1.11
1.08
1.00
0.98
0.96
1.00
4.06

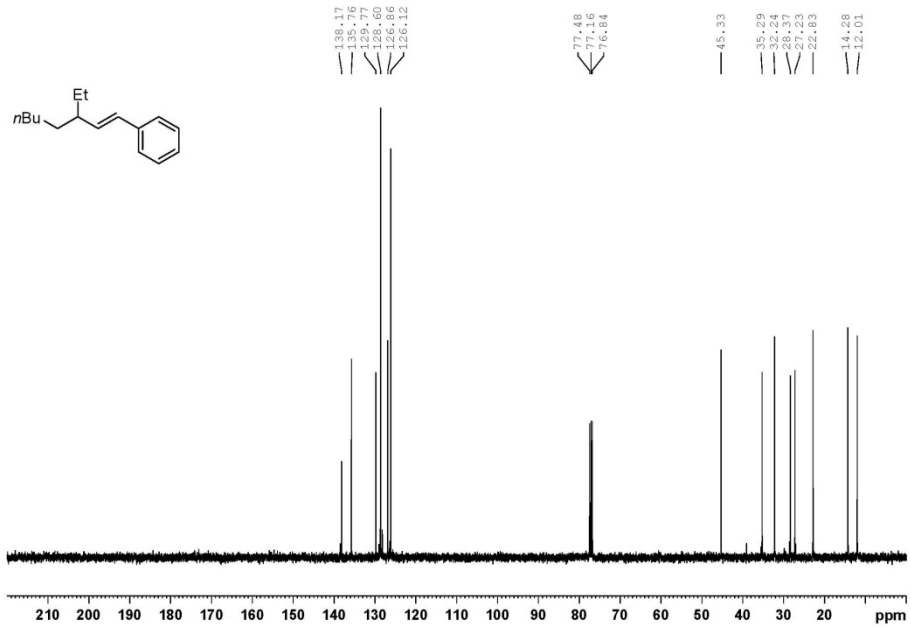

(dnpf)Pd(Ph)I
24.42
24.23
13.56
13.38
150 100 50 0 -50 -100 -150 ppm
53.40
46.60

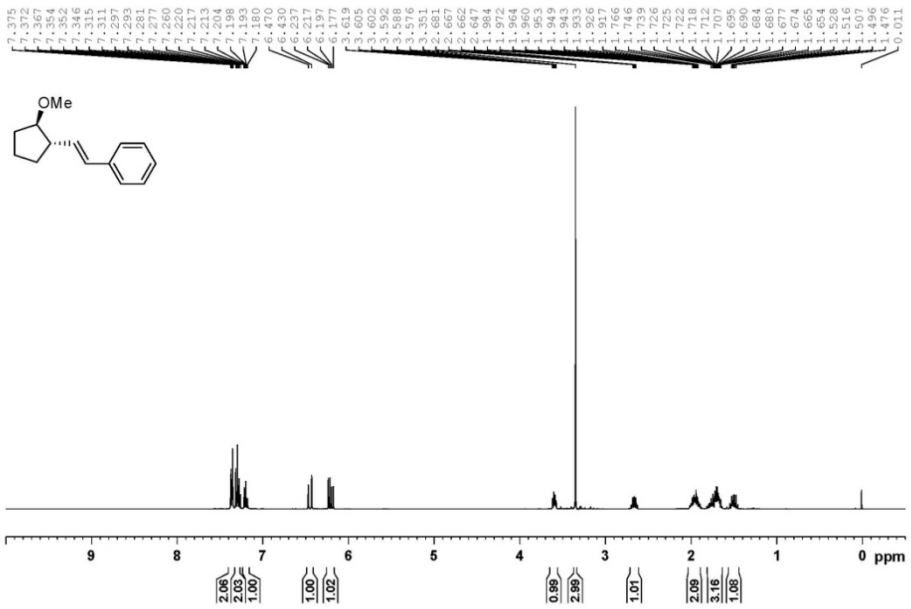

(dnpf)Pd(Ph)I
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

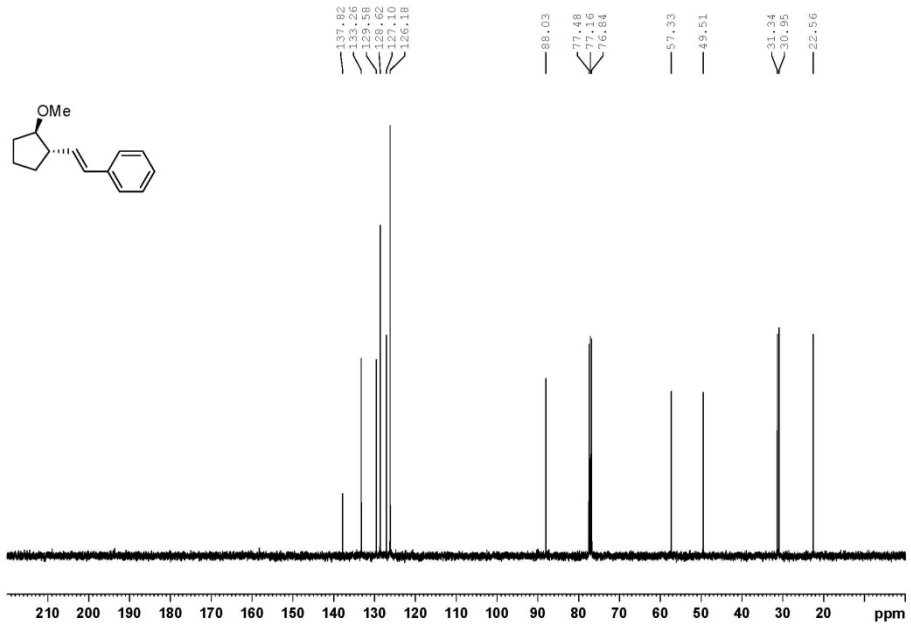

7.366
7.355
7.346
7.341
7.336
7.324
7.304
7.298
7.286
7.266
7.250
7.235
7.216
7.212
7.195
7.180
7.177
6.399
6.359
6.156
6.139
6.116
6.099
6.038
5.109
4.212
2.888
2.859
2.830
2.346
2.337
2.329
2.319
2.309
2.300
2.291
2.282
2.272
2.264
2.255
1.786
1.751
1.733
1.714
1.442
1.424
1.388
0.000
Cbz–N
9
8
7
6
5
4
3
2
1
0 ppm
11.08
1.07
1.00
1.92
0.23
2.27
2.03
1.01
2.46
2.35

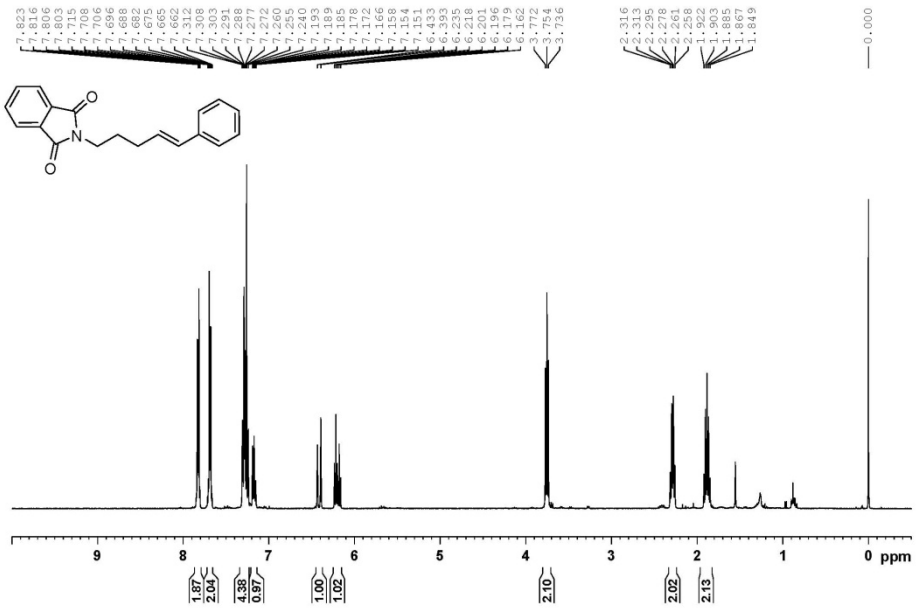

155.41
137.54
137.07
134.19
128.77
128.65
128.60
128.06
127.98
127.28
126.16
77.48
77.16
76.84
67.13
44.04
39.36
31.86
Cbz–N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

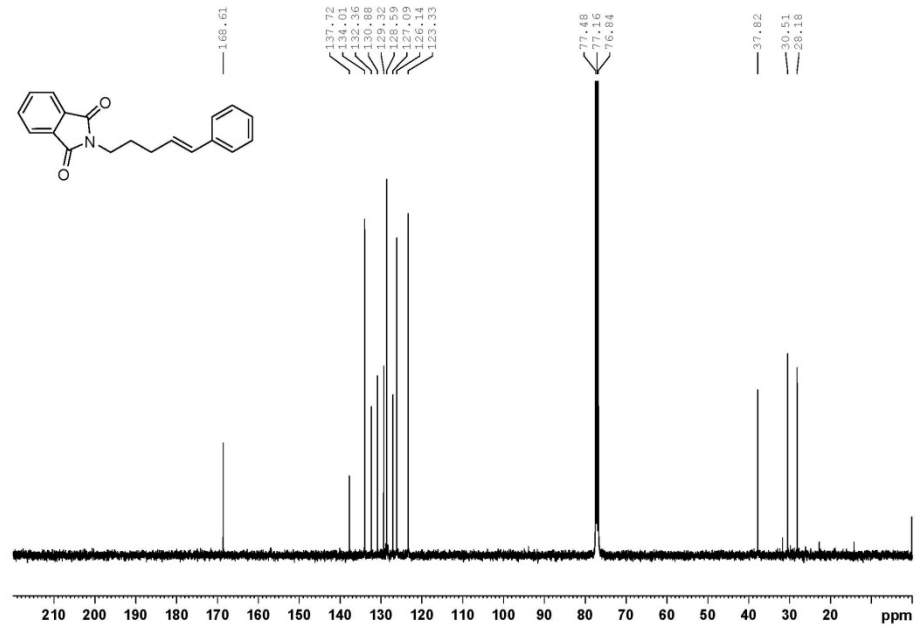

7.408
7.389
7.348
7.330
7.311
7.260
7.241
7.223
7.206
6.390
6.351
6.029
6.007
5.990
5.967
2.071
2.061
1.570
1.553
1.538
1.519
1.505
1.486
1.428
1.408
1.389
1.370
1.322
0.947
0.929
0.920
0.911
0.864
0.050
Et
nBu
9
8
7
6
5
4
3
2
1
0 ppm
2.00
2.27
1.05
1.00
1.02
1.04
11.91
6.78

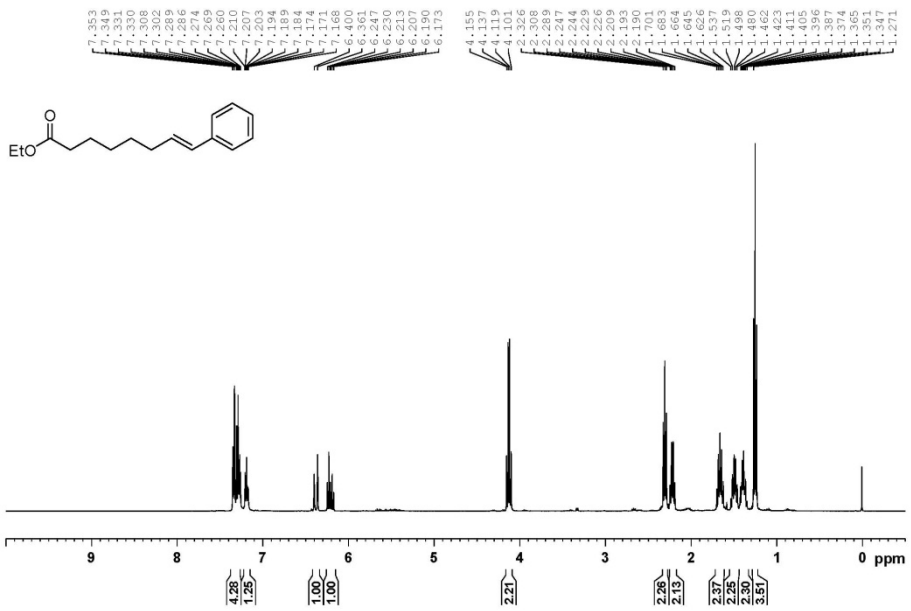

138.17
135.76
129.77
128.60
126.86
126.12
77.48
77.16
76.84
45.33
35.29
32.24
28.37
27.23
22.83
14.28
12.01
Et
nBu
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

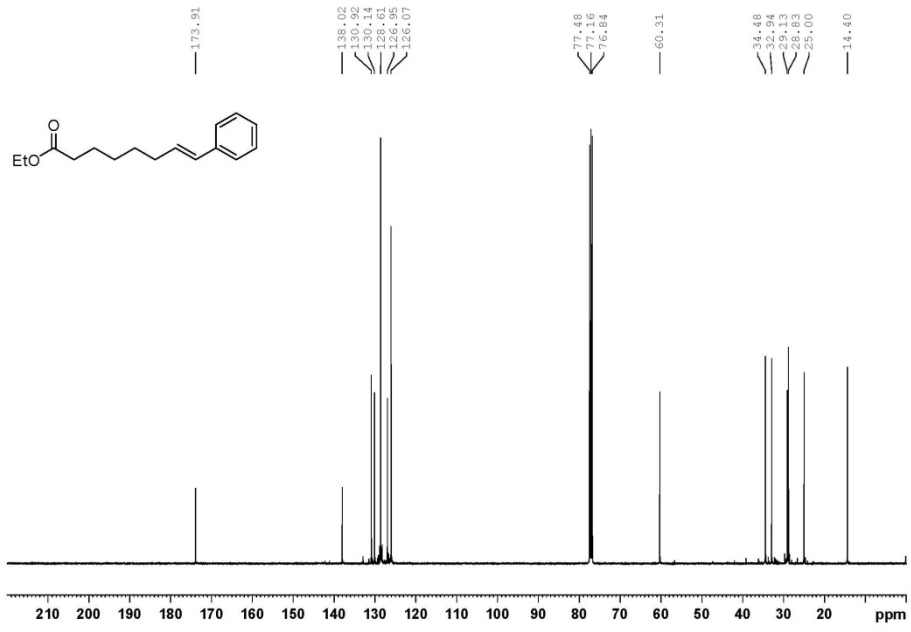

OMe
9
8
7
6
5
4
3
2
1
0 ppm

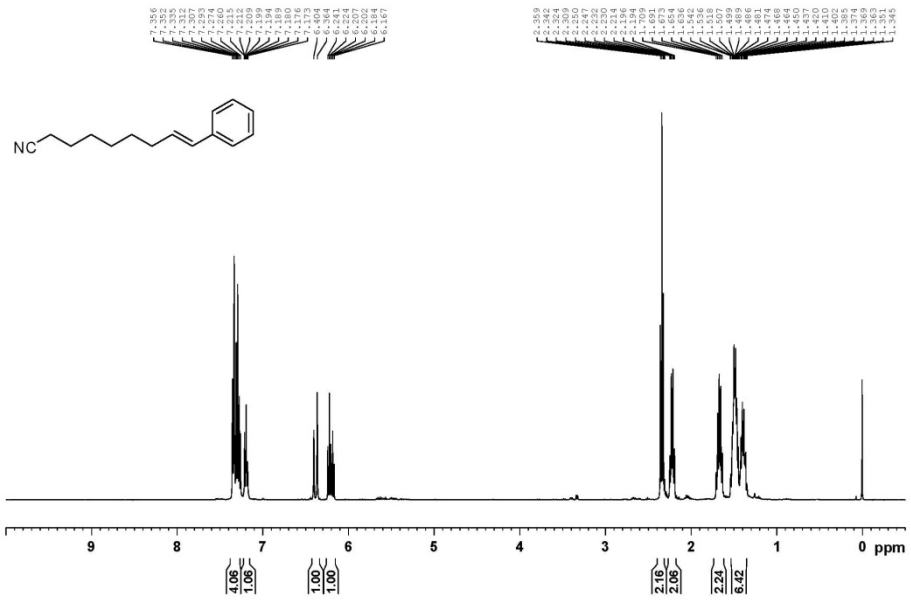

OMe
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

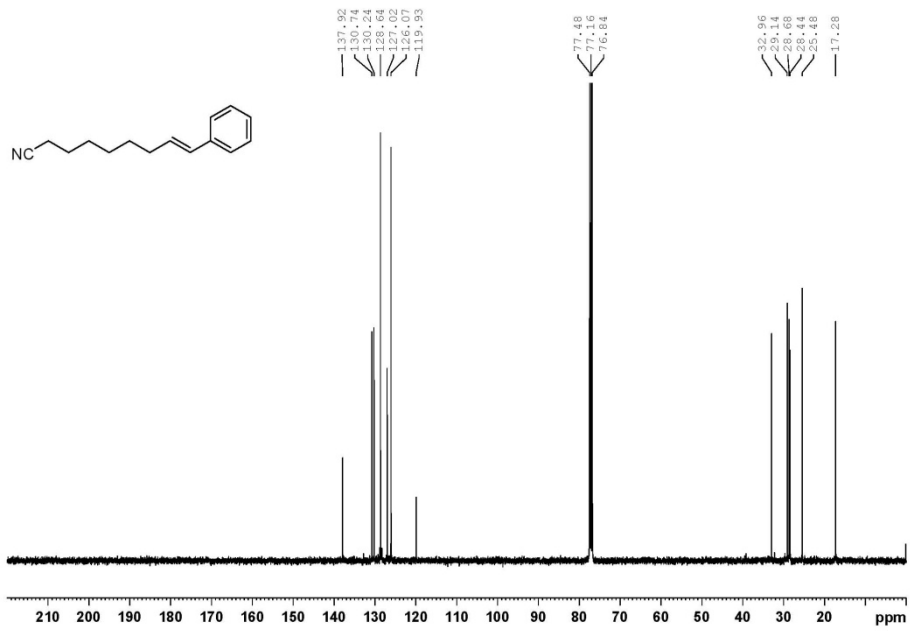

7.823
7.816
7.806
7.803
7.715
7.708
7.706
7.696
7.688
7.682
7.675
7.665
7.662
7.312
7.308
7.303
7.291
7.288
7.277
7.272
7.260
7.255
7.240
7.193
7.189
7.185
7.178
7.172
7.166
7.158
7.154
7.151
6.433
6.393
6.235
6.218
6.201
6.196
6.179
6.162
3.772
3.754
3.736
2.316
2.313
2.295
2.278
2.261
2.258
1.922
1.903
1.885
1.867
1.849
0.000
9
8
7
6
5
4
3
2
1
0 ppm
1.87
2.04
4.38
0.97
1.00
1.02
2.10
2.02
2.13

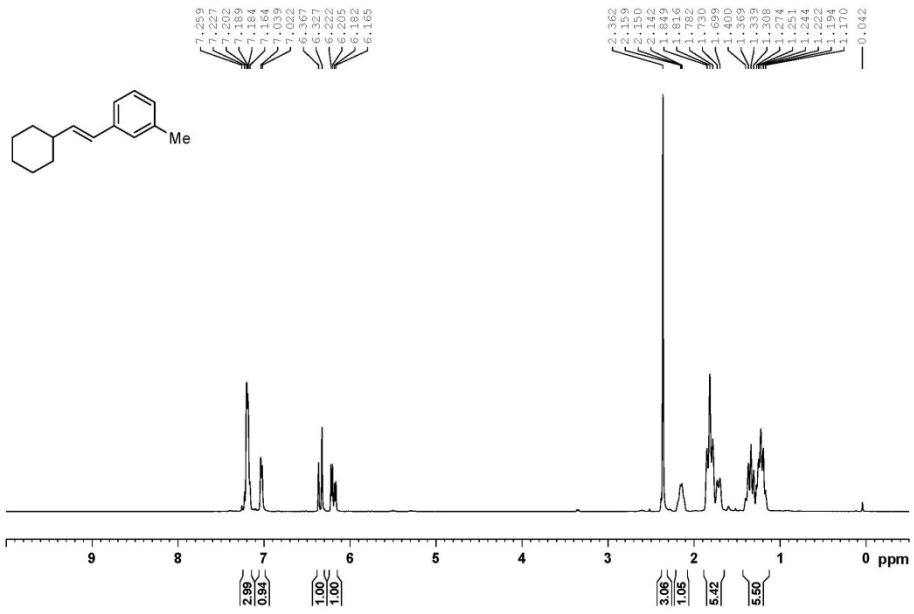

168.61
137.72
134.01
132.36
130.88
128.32
128.59
127.09
126.14
123.33
77.48
77.16
76.84
37.82
30.51
28.18
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

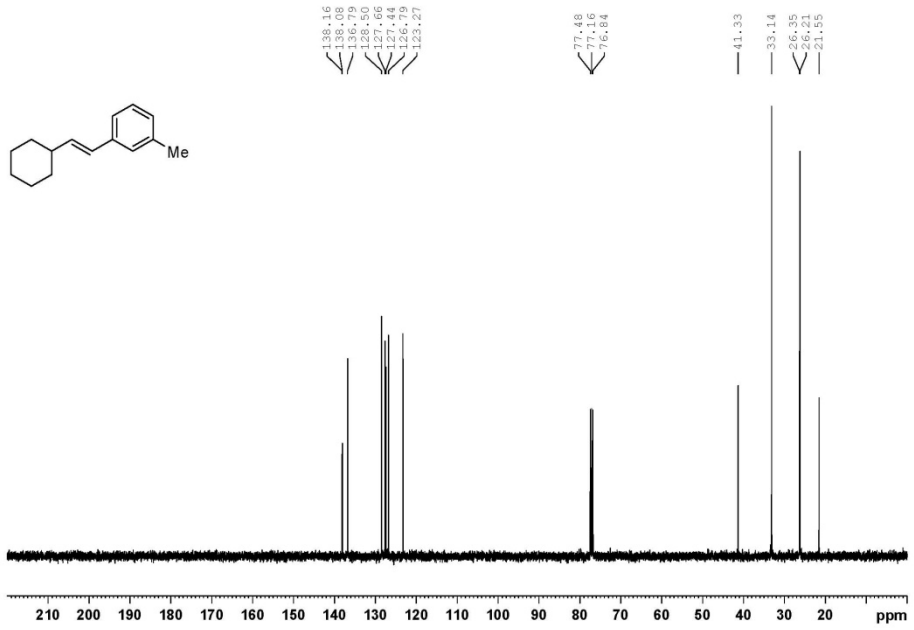

7.353
7.349
7.331
7.330
7.308
7.302
7.289
7.286
7.274
7.269
7.260
7.210
7.207
7.203
7.194
7.189
7.184
7.174
7.171
7.168
6.400
6.361
6.247
6.230
6.213
6.207
6.190
6.173
4.155
4.137
4.119
4.101
2.326
2.308
2.289
2.247
2.244
2.229
2.226
2.209
2.193
2.190
1.701
1.683
1.664
1.645
1.626
1.537
1.519
1.498
1.480
1.462
1.423
1.411
1.405
1.396
1.387
1.374
1.365
1.351
1.347
1.271
EtO
9
8
7
6
5
4
3
2
1
0 ppm
4.28
1.25
1.00
1.00
2.21
2.26
2.13
2.37
2.25
2.30
3.51

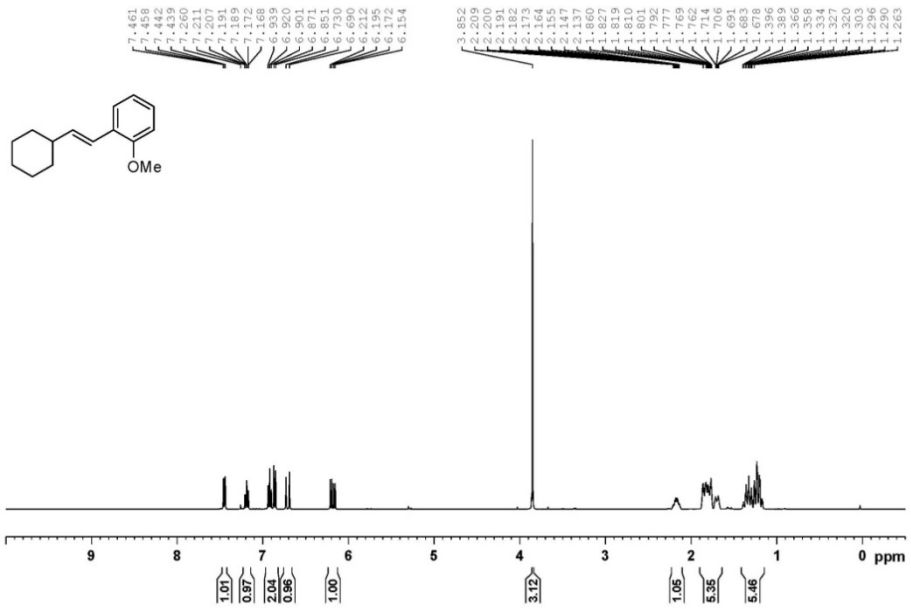

173.91
138.02
130.92
130.14
128.61
126.95
126.07
77.48
77.16
76.84
60.31
34.48
32.94
29.13
28.83
25.00
14.40
EtO
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

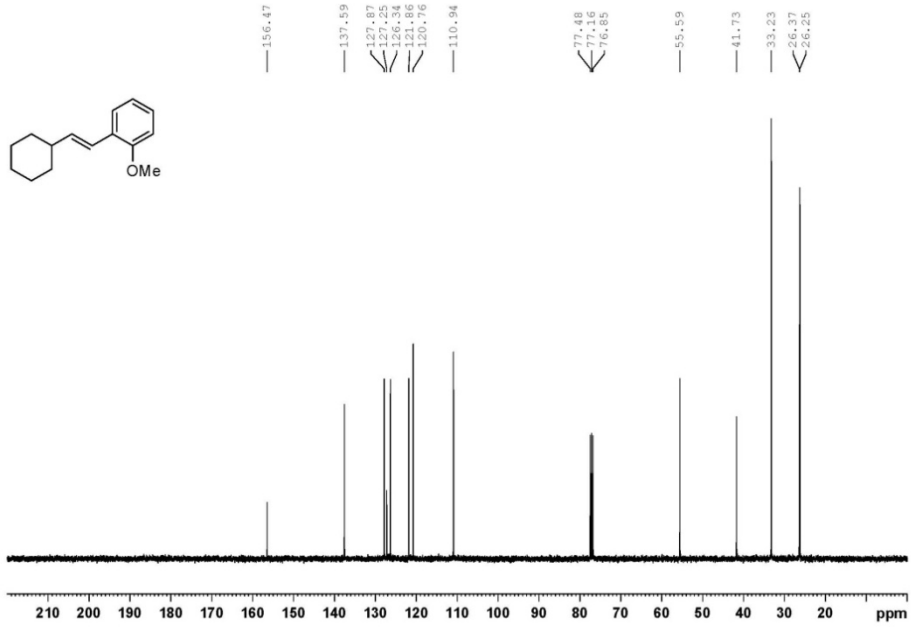

NC
9
8
7
6
5
4
3
2
1
0 ppm
4.06
1.06
1.00
1.00
2.16
2.06
2.24
6.42

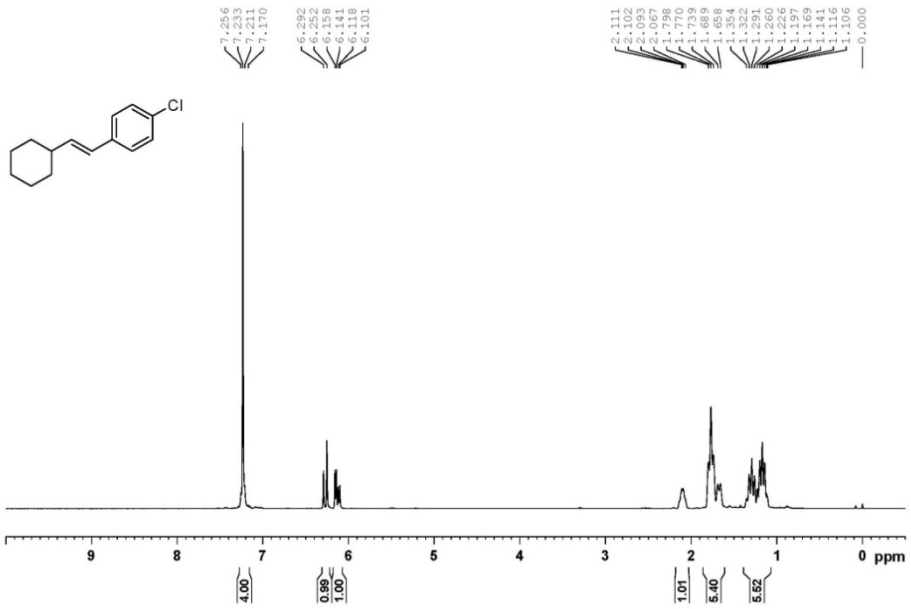

NC
137.92
130.74
130.24
128.64
127.02
126.07
119.93
77.48
77.16
76.84
32.96
29.14
28.68
28.44
25.48
17.28
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

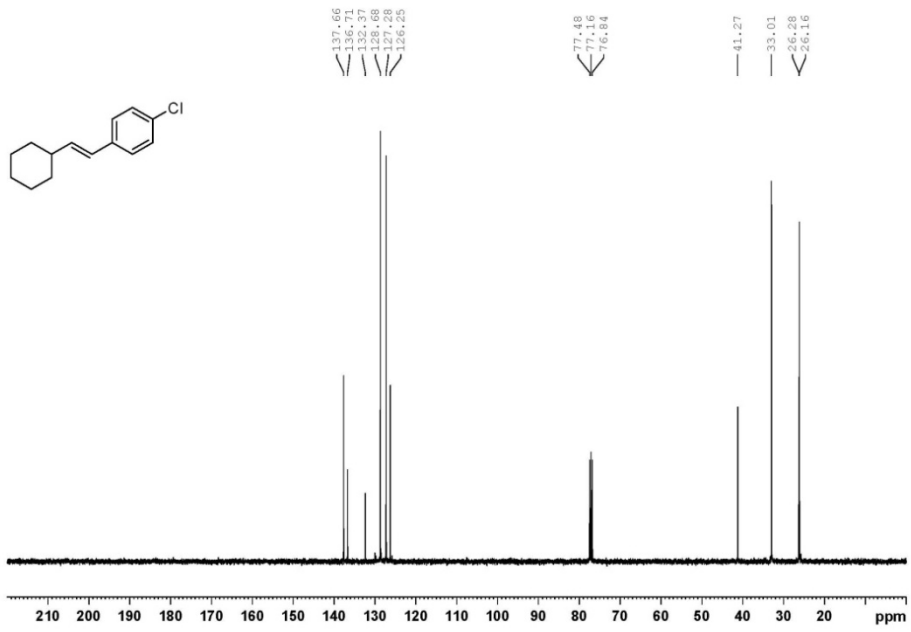

7.259
7.227
7.202
7.189
7.184
7.164
7.039
7.022
6.367
6.327
6.222
6.205
6.182
6.165
2.362
2.159
2.150
2.142
1.849
1.816
1.782
1.730
1.699
1.400
1.369
1.339
1.308
1.274
1.251
1.244
1.222
1.194
1.170
0.042
Me
9
8
7
6
5
4
3
2
1
0 ppm
2.99
0.94
1.00
1.00
3.06
1.05
5.42
5.50

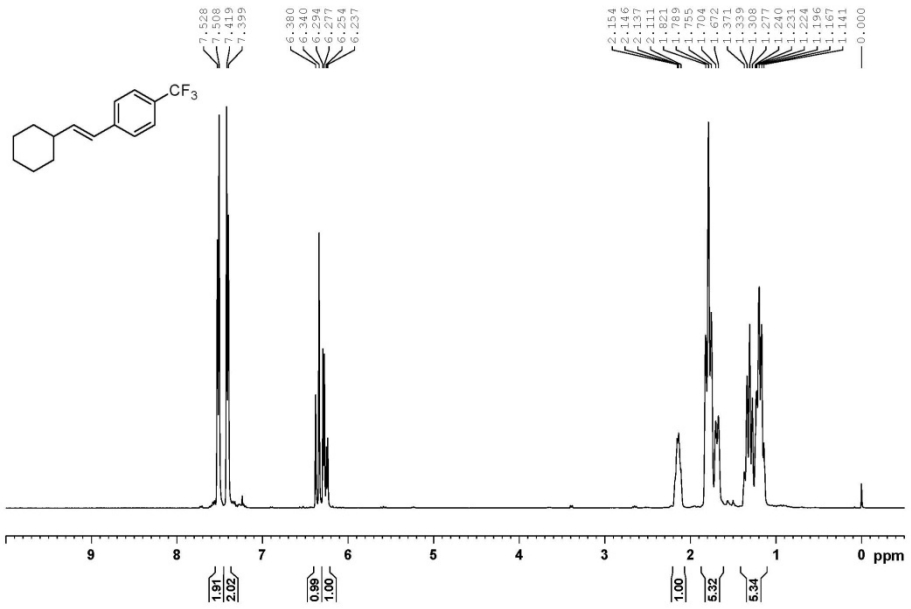

138.16
138.08
136.79
128.50
127.66
127.44
126.79
123.27
77.48
77.16
76.84
41.33
33.14
26.35
26.21
21.55
Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

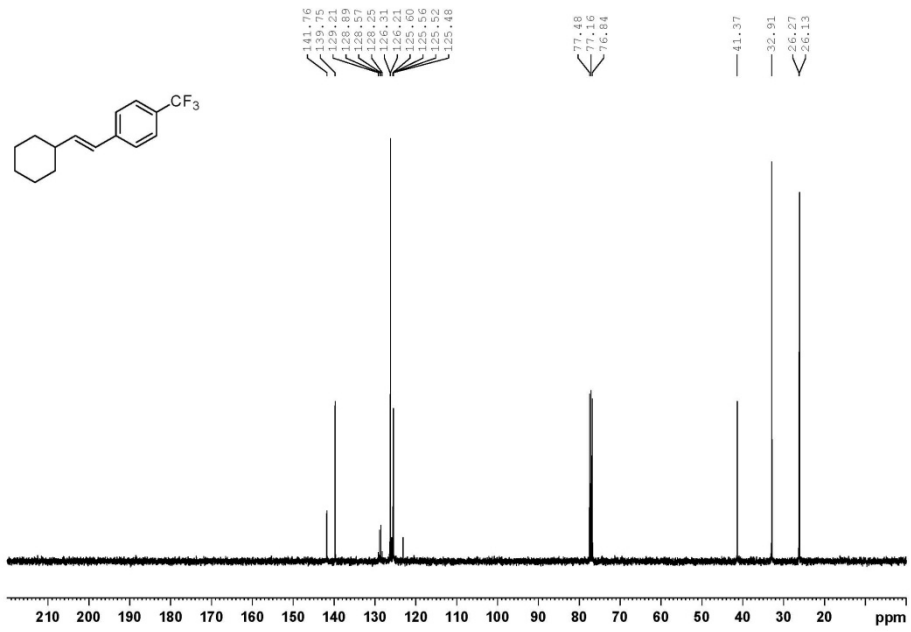

7.461
7.458
7.442
7.439
7.260
7.211
7.207
7.191
7.189
7.173
7.168
6.939
6.920
6.901
6.871
6.851
6.730
6.690
6.212
6.195
6.172
6.154
3.852
2.209
2.200
2.191
2.182
2.173
2.164
2.155
2.147
2.137
1.860
1.827
1.819
1.810
1.801
1.792
1.777
1.769
1.762
1.714
1.706
1.691
1.683
1.678
1.396
1.389
1.366
1.358
1.334
1.327
1.320
1.303
1.296
1.290
1.263
OMe
9
8
7
6
5
4
3
2
1
0 ppm
1.01
0.97
2.04
0.96
1.00
3.12
1.06
5.35
5.46

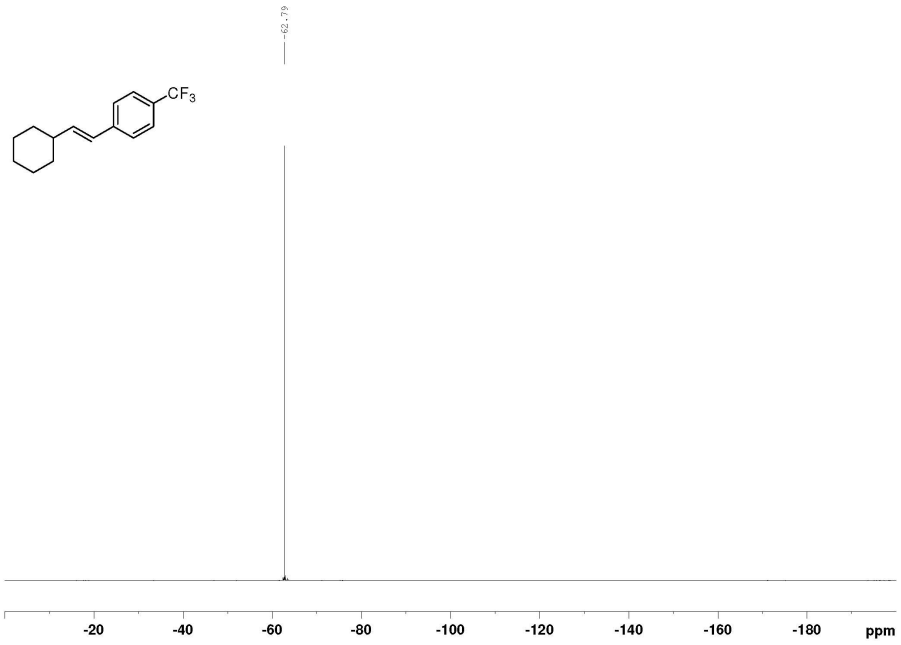

156.47
137.59
127.87
127.25
126.34
121.86
120.76
110.94
77.48
77.16
76.85
55.59
41.73
33.23
26.37
26.25
OMe
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

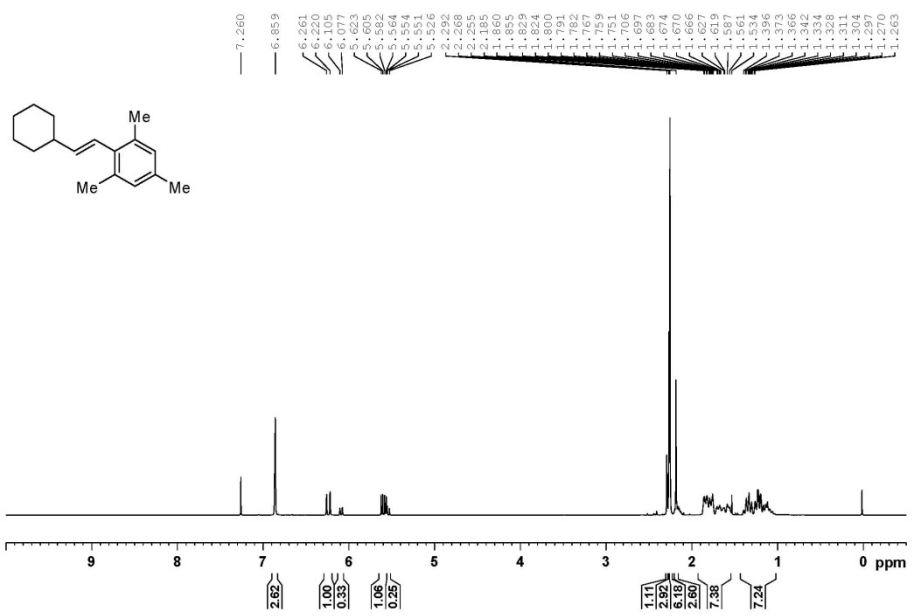

7.256
7.233
7.211
7.170
6.292
6.252
6.158
6.141
6.118
6.101
2.111
2.102
2.093
2.067
1.798
1.770
1.739
1.689
1.658
1.354
1.322
1.291
1.260
1.226
1.197
1.169
1.141
1.116
1.106
0.000
Cl
9
8
7
6
5
4
3
2
1
0 ppm
4.00
0.99
1.00
1.01
5.40
5.62


137.66
136.71
132.37
128.68
127.28
126.25
77.48
77.16
76.84
41.27
33.01
26.28
26.16
Cl
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


7.528
7.508
7.419
7.399
6.380
6.340
6.294
6.277
6.254
6.237
2.154
2.146
2.137
2.111
1.821
1.789
1.755
1.704
1.672
1.371
1.339
1.308
1.277
1.240
1.231
1.224
1.196
1.167
1.141
0.000
CF3
9
8
7
6
5
4
3
2
1
0 ppm
1.91
2.02
0.99
1.00
1.00
5.32
5.34


141.76
139.75
129.21
128.89
128.57
128.25
126.31
126.21
125.60
125.56
125.52
125.48
77.48
77.16
76.84
41.37
32.91
26.27
26.13
CF3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


CF3
-62.79
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm


Me
Me
Me
7.260
6.859
9
8
7
6
5
4
3
2
1
0 ppm
2.62
1.00
0.33
1.06
0.25
1.11
2.92
6.18
2.60
7.38
7.24