Part I: Selective Heck-type reaction of cyclic olefins. Part II: Palladium-catalyzed alkylation of heteroarenes

Wu, Xiaojin

2015

Wu, X. (2015). Part I: Selective Heck-type reaction of cyclic olefins. Part II: Palladium-catalyzed alkylation of heteroarenes. Doctoral thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/62112>

<https://doi.org/10.32657/10356/62112>

Part I Selective Heck-type Reaction of Cyclic Olefins
Part II Palladium-Catalyzed Alkylation of Heteroarenes

WU XIAOJIN
SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES
2014

Part I Selective Heck-type Reaction of Cyclic Olefins
Part II Palladium-Catalyzed Alkylation of Heteroarenes

WU XIAOJIN

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 start by thanking the person who is responsible for instilling me the desire to be a chemist. Some may say that is not a person you thank but you resent. Fortunately, I do not resent my supervisor for help me discover the potentials and perseverance I have. Steve has evolved through my time at NTU. It has been a transformative experience to be member in his group, and it will mark in the rest of my life.

I am honored to be a member in this lab. There are so many fantastic colleagues who will become my friends in the future. When I first joined, I felt like a kid among some of the senior members, such as Dr. Huang Zhiyan, Dr. Wu Wenqiong, Dr. Hu Jian, Dr. Li Xuefeng and Dr. Yang Zhigang. They treated me like a younger brother and taught me experiments step by step. Dr. Huang Zhiyan, who showed how to operate the instruments, is the most serious chemist in the lab. I am sure he will have a lot success as a professor and a father. Other group members such as Yinjun, Junfeng, Liena, Sijia, Chunlin, Kaining, Lihui, Haiyan, Siyu, Lucy, Tracy, Dr, Yang Peng, Dr. Yue Guizou, Dr. Lei Chuanhu and Dr. Chen Zhihua, were always helpful when I encountered problems in the lab.

Support staff here at NTU also deserves my thanks. Ms. Goh Eeling provides NMR support and Ms. Zhu Wenwei provides the MS support.

I also thank my parents for keeping my eyes on the prize and forcing me to study hard when I was a kid. I should have expressed my appreciation to their patience more than I have. They had to make significant sacrifice for me and I can only imagine how tough it is have their son to study in a distant place thousands of miles away.

Finally, I must express my utmost appreciation, love and respect to my wife Qi Congcong. Looking back, this entire Ph.D. experience will become meaningless without her. I also thank my lovely son Wu Sicong. He is my motivation to be a good man and a good father.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

TABLE OF CONTENTS

ABSTRACT

LIST OF ABBREVIATIONS

Chapter 1: Vinylic Selectivity in Mizoroki-Heck Reaction of Cyclic Olefins

1.1 Introduction	1
1.2 Results and discussion	9
Part A: Vinylic selectivity in Mizoroki-Heck reaction of aryl triflates	9
Part B: Vinylic selectivity in Mizoroki-Heck reaction of aryl halides	24
1.3 Conclusion	35
1.4 Experimental section	37
1.5 Reference	100

Chapter 2. An Efficient Method for Heck-Catellani Reaction of Aryl Halides

2.1 Introduction	104
2.2 Results and discussion	110
2.3 Conclusion	119
2.4 Experiment section	120
2.5 Reference	133

Chapter 3. A General Palladium-Catalyzed Method for Alkylation of Heteroarenes Using Alkyl Halides

3.1 Introduction	136
3.2 Results and discussion	152
3.4 Conclusion	167
3.5 Experimental section	169
3.6 Reference	206

Appendix

1. DFT calculations on relative stability of Heck product isomers	211
2. DFT calculations on alkyl radical addition to heterocycles	229

Abstract

Palladium-catalyzed cross-coupling reaction has become an important tool in organic synthesis. The thesis describes three new methods to selectively forming new C-C bonds in the presence of palladium catalysts.

In chapter one, we reported two efficient catalysts for Mizoroki-Heck reaction of cycloolefins with aryl triflates and aryl halides respectively. With our Pd/dppp catalyst, various aryl triflates and cyclic alkenes could selectively generate vinylic products in good to excellent yield. Notably, the isomeric purity of products was >95% in most cases. The Pd/*P*tBu₃ catalyst coupled a wide array of aryl halides. Several cycloolefins, which have poor reactivity in the reaction with aryl triflates, also reacted well. Therefore, two complementary approaches successfully solved the vinylic selectivity in Mizoroki-Heck reaction of cyclic olefins and provided a simple strategy to produce 1-arylcycloolefins.

In chapter two, we developed a general protocol to selectively generate Catellani isomers. By using the bulky *P*tBu₃ ligand, various (hetero)aryl bromides and chlorides bearing no *ortho* substitution can be coupled efficiently with norbornene. Moreover, other bicyclic alkenes besides norbornene can also undergo this type of transformation. Previously, the Catellani isomers were only formed from phenyl bromide and phenyl halides bearing *ortho*-groups.

In chapter three, we explored a general Pd-catalyzed alkylation method for heteroarenes. By the simple Pd/dppp catalyst, topical classes of heteroarenes including azoles, azines, furans, thiophenes, pyrroles, pyridines and even indole derivatives can efficiently be coupled with various unactivated secondary and tertiary alkyl halides in good regioselectivity. Notably, our radical-type alkylation is compatible with sensitive functional groups such as nitriles, aldehydes and ketones. Therefore, our alkylation of heteroarenes is a complementary method to other transition metal-catalyzed alkylation processes, which are based on the initial metalation of C-H bonds.

Chapter 1. Vinylic Selectivity in Mizoroki-Heck Reaction of Cyclic Olefins

1.1 Introduction

1.1.1 General Introduction of Mizoroki-Heck reaction

The palladium-catalyzed arylation and vinylation of alkenes, which is commonly known as Mizoroki-Heck reaction, was discovered independently by Heck and Mizoroki in the early 1970s (Scheme 1.1 and 1.2).^{1a,1b} It has become an indispensable tool for organic synthesis and is commonly used in industry.² For instance, Heck reaction is used in synthesis of a monomer of Dow's CYCLOTENETM (Scheme 1.3).^{1c} The common UV-B sunscreen agent 2-ethylhexyl *p*-methoxy-cinnamate is also produced by Heck reaction of *p*-bromoanisole with an acrylate (Scheme 1.4).^{1c}

Scheme 1 Pioneering works by Mizoroki and Heck and industrial application of olefins.

For acyclic olefins, the regioselectivity of insertion of the aryl group is the key issue (Scheme 2).³ The α/β selectivity is influenced by electronic and steric effects of the olefins, and also by the nature of the palladium catalyst.

Scheme 2 Regioselectivity in Heck reaction of aliphatic olefins.

In the pioneering work by Heck, *trans*-cinnamate was exclusively formed by coupling of phenyl iodide and acrylate via an anionic pathway in the absence of a phosphine ligand (Scheme 3.1).^{1b} The terminal insertion is faster than internal insertion due to trans effect. The former forms a less σ -donating alkyl ligand bearing an α -ester group. Similarly, aryl insertion into styrene is faster at the terminal site than the internal one. The former forms a less donating η -benzyl ligand first. For example, Fu *et al.* used Pd/*t*Bu₃ catalyst in the arylation of styrene using aryl chlorides (Scheme 3.2).⁴ In the case of aliphatic olefins without significant electronic difference between two vinyl sites, it is difficult to control regioselectivity. When aliphatic olefins carry a directing group, β -selectivity is observed. For example, Jiao group reported β -arylation of allylic esters using phenyl iodide (Scheme 3.3).⁵

Scheme 3 Terminal selectivity in Mizoroki-Heck reaction of aliphatic olefins.

Cabri first reported α -selective Mizoroki-Heck reaction between phenyl iodide and *n*-butyl vinyl ether, an electron-rich olefin. A bisphosphine ligand dppp and halide abstractors such as silver or thallium salts were used (Scheme 4.1).⁶ The reaction happened via a cationic pathway. Aryl triflates can also be used without halide abstractors. Recently, Xiao group demonstrated that alkylammonium salts or alcoholic solvents helped halide dissociation via hydrogen bonding.^{7a} Only vinyl ethers and electron-rich styrenes afforded high α -selectivity. In the case of the unactivated olefins, Cabri-type procedures typically gave 3:1 selectivity. Recently, our group successfully achieved high internal regioselectivity.^{7b} As shown in Scheme 4.2, using a ferrocene-based bulky bisphosphine dnpf, *t*-butylphenyl triflate reacted with 1-octene bearing no electronic bias to afford 16:1 intrinsic regioselectivity. Later, our group extended the same Pd/dnpf catalyst to Heck reaction using aryl bromides.^{7c} The bisphosphine dnpf promoted terminal insertion via steric effect. Recently, Jamison group reported a Ni-catalyzed Mizoroki-Heck reaction to afford α -selective products in excellent regioselectivity also using a bulky bisphosphine (Scheme 4.3).^{7d}

Scheme 4 Internal selectivity in Mizoroki-Heck reaction (urotropine: 1,3,5,7-tetraazaadamantane).

1.1.2 Product selectivity in Mizoroki-Heck reaction of cyclic olefins

1.1.2.1 Allylic selectivity in Mizoroki-Heck reaction of cyclic olefins

In Mizoroki-Heck reaction of cyclic olefin, the first Heck product is the allylic isomer, which can undergo olefin isomerization depending on the nature of catalysts and conditions (Figure 1). The isomerization is catalyzed by Pd hydride species that is produced from the catalytic cycle.

Figure 1 Product selectivity in Heck reaction of cyclic olefins.

In 1988, Larock *et al.* reported that 3-arylcylohexene was formed in 16:1 allylic selectivity from aryl iodide and cyclohexene (Scheme 5).⁸ Other olefins such as cyclopentene, cycloheptene and cyclooctene also gave good selectivity. The Pd hydride was quickly removed by the base.

Scheme 5 Allylic selectivity in Mizoroki-Heck reaction of cyclohexene.

Using a chiral phosphinoxazoline as ligand, Pfaltz and coworkers achieved enantioselective Heck reaction of aryl triflates with cyclopentene in 99% ee and 99:1 allylic selectivity (Scheme 6.1).⁹ The Pd hydride species $[(\text{L})\text{PdH}]^+$ was quickly removed by the base since the *P,N*-ligand is less σ -donating than bisphosphines. Allylic selectivity of cyclic olefins is commonly observed in asymmetric Heck reaction using many types of chiral phosphine ligands.¹⁰ For instance, our group

developed a chiral bisphosphine oxide ligand based on a spiro-bisindane backbone for the asymmetric Heck reaction (Scheme 6.2).^{11a,11b} Various aryl triflates and cyclic olefins can be coupled well in excellent ee and allylic selectivity. Later, our group applied the same catalyst to similar Heck reaction using aryl bromides.^{11c}

Scheme 6 Allylic selectivity in Heck reaction of cyclopentene

1.1.2.2 Homoallylic selectivity in Mizoroki-Heck reaction of cyclic olefins

In the pioneering work by Hayashi, homoallylic Heck products were generated in asymmetric Heck reaction of aryl triflates and 2,3-dihydrofuran (Scheme 7.1).^{11d} The formation of homoallylic product was due to Pd hydride-catalyzed isomerization of initial Heck isomers.

In 1999, Beller group reported that Mizoroki-Heck reaction of aryl bromides and cyclohexene produced 4-arylcyclohexene (Scheme 7.2).¹² The homoallylic selectivity was significantly enhanced by DMSO cosolvent. Cyclopentene also reacted well. Nevertheless both reactivity and selectivity were not high enough and the scope was very limited.

In 2003, Santelli group reported some examples of homoallylic selectivity in the Heck reaction of aryl bromide with cyclohexene.¹³ In the presence of *cis, cis, cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane (Tedicyp) ligand, 4-arylcyclohexene was formed in 13:1 selectivity (Scheme 7.3). The tetraphosphines coordinated to Pd as a bidentate chelate and stabilized the Pd catalyst at high temperature.

Scheme 7 Homoallylic selectivity in Mizoroki-Heck reaction of cyclohexene.

1.1.2.3 Vinylic selectivity in Mizoroki-Heck reaction of cyclic olefins

In Mizoroki-Heck reaction of cycloalkenes, it is seemingly simple to form conjugated isomers. However, vinylic selectivity is rather difficult to obtain due to the reaction mechanism. For instance, Trzaciak *et al.* reported Heck reaction of phenyl iodide with cyclohexene to generate a conjugate isomer in less than 1:5 selectivity.¹⁴ In Heck-Matsuda reaction of cyclopentene, vinylic selectivity was obtained in some special cases. Barbero and Fochi used aryldiazonium *o*-benzenedisulfonimides to couple with cyclopentene to produce predominantly 1-arylated cyclopentenenes (Scheme 8.1).¹⁵ It only worked well with cyclopentene and the selectivity strongly depended on the anions of aryldiazonium salts. Recently, Gaunt group isolated a conjugated product as the major isomer from Cu-catalyzed arylation of olefins using Ph_2IOTf as electrophiles (Scheme 8.2). The vinylic selectivity was only 4:1 and only one example was reported.¹⁶

Scheme 8 Vinylic selectivity in arylation of cyclohexene

1.1.3 Conventional approaches to synthesize 1-arylcycloolefins

1-Arylcycloolefins are commonly used as intermediates in the synthesis of natural products.¹⁷ For instance, (-)- γ -lycorane was synthesized via Suzuki coupling as a key step, as shown in Figure 2. In another example, sanggenon is an inhibitor of 5-lipoxygenase containing a 1-arylcyclohexene core.

Figure 2 Examples of 1-arylcycloolefins in total synthesis.

In 2007, Olsson and co-workers reported a two-step protocol to synthesize 1-arylcycloolefins.¹⁸ As shown in Scheme 9.1, the desired 1-arylcyclohexene was formed through an Ir-catalyzed borylation of olefins, followed by Suzuki-Miyaura reaction of an aryl iodide. The method was also applied to cycloheptene and cyclooctene. A few years later, Jamison group reported a similar sequence using a rhodium-catalyzed borylation (Scheme 9.2).¹⁹ However, the substrate scope was still limited to cyclohexene, cycloheptene and cyclooctene.

Scheme 9 Synthesis of 1-arylcyclohexenes via selective borylation of olefins.

Fu group reported an efficient Suzuki coupling of arylboronic acid with vinyl triflates,^{20a} as shown in Scheme 10.1. Vinyl triflates can be easily made from cyclic ketones. Vinyl phosphates, mesylates, tosylates and sulphonates were also applied in this kind of coupling reactions.²⁰ In addition, Barluenga *et al.* developed a Pd-catalyzed coupling of an aryl halide and in situ formed tosylhydrazone to generate arylcyclohexadienes (Scheme 10.2).^{20b}

Scheme 10 Synthesis of 1-arylolefins via coupling reactions.

1.2 Results and discussion

Part A: Vinylic selectivity in Mizoroki-Heck reaction of aryl triflates

1.2.1 Condition optimization

Owing to conjugation effect, 1-arylcycloolefins are considered to be more stable than non-conjugated isomers. However, some controversy regarding relative stability of these isomers was reported.¹² Thus, Dr Yunpeng Lu, in collaboration with us, determined the relative stability of these isomers using DFT calculations. As shown in Figure 3, 1-phenylcyclohexene was calculated to be more stable than non-conjugated

isomers by about 4 kcal/mol. The stability of phenylcyclopentene followed a similar trend. Moreover, when *p*-methoxy or *p*-ester was present on the aryl ring, electronic perturbation had little effect on the relative stability.

Figure 3 Relative stability of isomers of arylcycloolefins based on DFT calculations by B3LYP method with 6-31G(d,p) basis set.

Initially, *p*-*t*-butylphenyl triflate and cyclohexene were chosen as model substrates to search for an efficient palladium catalyst. After extensive research of catalysts and conditions, we found that the desired 1-arylcylohexene was formed in 93% yield and 23:1 vinylic selectivity by using a simple ligand 1,3-bis(diphenylphosphino)propane (dppp). The results are summarized in Table 1. Other common bisphosphines such as 1,2-bis(diphenylphosphino)ethane (dppe), 1,1'-bis(diphenylphosphino)ferrocene (dppf) and dnpf gave poor results. Thus, bisphosphines with the bite angles close to 91° had good reactivity, such as dppp (91°) and BINAP (93°). Other chelating phosphines having larger or smaller bite angles showed much lower catalytic activity.

Table 1 The effect of ligands in model Mizoroki-Heck reaction.

(Ar = *para*-*tert*-butylphenyl)

Entry	Ligand ^a	Bite angle (°) ^b	Conversion (%) ^c	Yield (%) ^d	Selectivity ^c
1	dppbz	83	23	18	3:1
2	dppe	86	16	14	2:1
3	dppp	91	100	93	23:1
4	BINAP	93	48	41	1:24
5	dppb	94	8	0	-

6	dpppent	99	2	0	-
7	dppf	99	19	2	1:6
8	dnpf	103	8	0	-
9	dippf	104	6	0	-
10	DPEphos	104	8	2	1:6
11	Xantphos	108	16	3	1:11

^a dppbz = 1,2-bis(diphenylphosphino)benzene; dppb = 1,4-bis(diphenylphosphino)butane; dpppent = 1,5-bis(diphenylphosphino)pentane; dippf = 1,1'-bis(diisopropylphosphino)ferrocene; DPEphos = bis[(2-diphenylphosphino)phenyl]ether; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

^b Natural bite angle. ^c conversion and selectivity were determined by GC. ^d GC yield.

With regard to the choice of the palladium source, we found that [Pd(hfacac)₂] (hfacac: hexafluoroacetylacetonate) showed exceptionally high activity as compared with other normal palladium source such as [Pd(dba)₂] (dba: dibenzylideneacetone), Pd(OAc)₂ and [Pd(acac)₂] (acac: acetylacetonate). The results are listed in Table 2. We propose that Pd(hfacac)₂ may form the active catalyst (dppp)Pd⁰ faster than other Pd sources.^{21a} In addition, the strong binding of dba to the Pd center reduces the effective concentration of (dppp)Pd⁰ for oxidative addition.^{21b}

Table 2 The effect of palladium sources in model Mizoroki-Heck reaction.

ArOTf + (2 equiv) $\xrightarrow[2 \text{ equiv Li}_2\text{CO}_3, \text{ veratrole, } 120^\circ\text{C}/24 \text{ h}]{4 \text{ mol\% Pd source, } 6 \text{ mol\% dppp}}$ Ar- + isomers

(Ar = *para*-*tert*-butylphenyl)

Entry	Pd catalyst	Conversion(%) ^a	Yield(%) ^b	Selectivity ^a
1	Pd(hfacac) ₂	100	93	23:1
2	Pd(acac) ₂	41	32	10:1
3	Pd(OAc) ₂	26	4	4:1
4	Pd(OCOCF ₃) ₂	78	52	18:1
5	Pd(dba) ₂	60	44	25:1
6	Pd ₂ (dba) ₃	69	36	16:1

^a conversion and selectivity were determined by GC. ^b GC yield.

The choice of the bases has a significant effect on the result of the model reaction. As shown in Table 3, Li_2CO_3 proved to be the optimal base. Notably, the use of *N*-methylmorpholine also led to the desired isomer in more than 20:1 selectivity, but the yield was slightly lower. While other trialkylamines such as Et_3N , *i* Pr_2NEt , and Cy_2NMe were used, the reduction byproduct, *tert*-butylbenzene, was obtained because these amines can donate hydride to arylpalladium centers.^{22a} When 1,4-diazabicyclo-[2.2.2]octane (DABCO) was used as base, no Heck reaction happened. DABCO can strongly coordinate to Pd^{II} centers and inhibited the catalysis.^{22b}

Table 3 The effect of bases in model Mizoroki-Heck reaction.

4 mol% $\text{Pd}(\text{hfacac})_2$
6 mol% dppp
2 equiv base
veratrole, 120 °C/24 h
(Ar = *para*-*tert*-butylphenyl)

Entry	Base	Conversion (%) ^a	Yield (%) ^b	Selectivity ^a
1	Li_2CO_3	100	93	23:1
2	Na_2CO_3	88	69	4:1
3	K_2CO_3	25	13	1:4
4	LiOAc	21	3	1:2
5	K_3PO_4	73	9	1:8
6	Et_3N	100	45	1:1
7	<i>i</i> Pr_2NEt	66	9	1:23
8	Cy_2NMe	53	24	2:1
9	<i>N</i> -Methylmorpholine	100	83	21:1
10	Urotropine	100	47	3:1
11	2,6-lutidine	100	56	8:1
12	Proton sponge	100	73	10:1
13	DABCO	1	0	--

^a conversion and selectivity were determined by GC. ^b GC yield.

The model reaction worked well in veratrole (1,2-dimethoxybenzene), which is aromatic ether. As shown in Table 4, moderate or good selectivity was achieved in

other ethereal solvents such as THF, 2-MeTHF, DME and triglyme in spite of low conversion. In other solvents, poor results were observed in the model reaction.

Table 4 The effect of solvents in model Mizoroki-Heck reaction.

Entry	Solvent	Conversion (%) ^a	Yield (%) ^b	Selectivity ^a
1	Dioxane	23	14	10:1
2	THF	37	31	16:1
3	2-MeTHF	18	17	16:1
4	CPME	27	20	1:1
5	TBME	7	5	12:1
6	DME	39	34	21:1
7	Triglyme	51	43	15:1
8	Diglyme	22	15	4:1
9	Anisole	6	3	3:1
10	Veratrole	100	93	23:1
11	Toluene	6	6	4:1
12	CF ₃ Ph	11	4	11:1
13	NMP	16	7	2:1
14	DMA	11	3	1:2
15	DMSO	12	6	1:5

^a conversion and selectivity were determined by GC. ^b GC yield.

1.2.2 Scope of substrates

Using the optimized condition, we explored the scope of aryl triflates in Mizoroki-Heck reaction of cyclohexene (Figure 4). Both electron-rich and electron-poor aryl triflates yielded the vinylic isomers in more than 20:1 selectivity. Some functional groups such as ketone, aldehyde and free alcohol were well tolerated. When 3-estrone-derived triflate was used as coupling partner, 24:1 selectivity of conjugated product was obtained. Notably, some heteroaryl and vinyl electrophiles also performed well.

Figure 4 The scope of organic triflates in Mizoroki-Heck reaction of cyclohexene. The value of vinylic selectivity versus the sum of all other minor isomers is listed in parentheses.

We also explored other cyclic olefins of different ring size. For cyclopentene, the Pd(dppp) catalyst showed high activity (Figure 5). In all cases, excellent vinylic selectivity was achieved regardless of electronic variation and steric hindrance on aryl rings. Notably, *ortho*-methoxy and nitrile groups on aryl triflates may chelate to the Pd catalyst but did not interfere with the catalysis. Cycloheptene and cyclooctene also coupled with various aryl triflates bearing electronic and steric perturbation in good yield and excellent vinylic selectivity (Figure 6).

Figure 5 Mizoroki-Heck reaction of aryl and vinyl triflates with cyclopentene. The value of vinylic selectivity versus the sum of all other minor isomers is listed in parentheses.

Figure 6 The scope of aryl triflates in Mizoroki-Heck reaction of larger-ring olefins. The value of vinylic selectivity versus the sum of all other minor isomers is listed in parentheses.

1.2.3 Synthetic application

In order to demonstrate synthetic value of our new Heck method, a substituted 1-arylcyclohexene was used in synthesis of a compound for the treatment of hair loss. As shown in Scheme 11, it was synthesized via addition of organolithium reagent to a cyclic ketone, followed by acidic dehydration.^{22c} Using our Heck procedure, the same intermediate can be prepared in 96% yield and 24:1 selectivity. Thus, our Heck method decreased the number of steps and eliminated the harsh basic and acidic conditions.

Scheme 11 Synthesis of a drug candidate.

Some *p*-terphenyls derivatives showed interesting biological activities such as induction of apoptosis of cancer cells²³ and some were used in construction of electronic devices (Scheme 12.1).²⁴ These compounds were synthesized by double cross-coupling reactions of bifunctional coupling reagents (Scheme 12.2).²⁵ Our Heck procedure is a simple and efficient approach to access these compounds. Using our Pd(dppp) catalyst, the symmetrical 1,4-diarylated cyclohexadienes were formed from aryl triflates and 1,3-cyclohexadiene (Scheme 12.3). Notably, no monoarylated product was observed due to fast second arylation. In addition, the unsymmetrical 1,4-diarylated cyclohexadienes could also be produced by the reaction of monoaryl cyclohexadiene, which was synthesized by Barluenga's method (Scheme 12.4).^{20b} Finally, the substituted *p*-terphenyls could be generated in almost quantitative yield via simple oxidations of the above diarylated cyclohexadienes.

Application

Traditional cross-coupling methods

(12.2)

Our Heck methods

(12.3)

Scheme 12 Heck products of cyclic dienes.

1.2.4 Mechanistic study

The Pd(dppp) catalyst showed significantly high vinylic activity when compared with other catalysts such as Pd(dppe) and Pd(dppf). We wondered which step caused the difference among these catalysts.

Initially, we examined the oxidative addition step. As shown in Scheme 13, *p*-*t*-butylphenyl triflate reacted with a Pd⁰ precursor [(tmeda)Pd(Me)₂] (tmeda = *N,N,N',N'*-tetramethylethylenediamine) and a bisphosphine. Unexpectedly, the oxidative addition of Pd(dppp) occurred at 120 °C, while for Pd(dppe) and Pd(dppf) complexes, the oxidative addition happened at 80 °C. All the reactions did not give the oxidative addition complexes and instead, generated an aryl-methyl byproduct in approximately 60% yield. We suppose the byproduct is formed via the methyl exchange between two Pd centers to produce a [(L)Pd(Me)Ph] complex and subsequent reductive elimination leads to the byproduct. A trace amount of biaryl byproduct was also detected by GC.

Scheme 13 Oxidative addition of an aryl triflate

Next, we investigated olefin insertion step of cationic aryl-Pd complexes. As shown in Scheme 14, initially the [(dppp)Pd(Ph)I] complex was reacted with 5 equivalent of cyclohexene in the presence of AgOTf. The desired Heck product was obtained in 78 % yield after 1 h at 120 °C. The vinylic selectivity increased over time and finally reached 42:1 after 12 h (Scheme 14.1). When the [(dppf)Pd(Ph)I] complex was treated under the similar conditions, unexpectedly, about 60% yield of PPh₃ was formed and the desired Heck isomers were obtained in only 8% yield (Scheme 14.2). The faster side reaction, which occurred even at RT, competed against the insertion of cyclohexene to the Pd complex. We propose PPh₃ is generated by reductive elimination of the Pd-phenyl and a ligand PPh₂ group, followed by reinsertion of (L)Pd⁰ into the Fc-(PPh₃)⁺ bond.^{26a} In the reaction of the [(dppe)Pd(Ph)I] complex,

Heck isomers were obtained in only 10% yield with very poor vinylic selectivity (Scheme 14.3). Meanwhile, no PPh_3 was formed and we suspected it was because no reinsertion of $(\text{L})\text{Pd}^0$ into the $\text{C}-(\text{PPh}_3)^+$ bond after fast reductive elimination of the Pd-phenyl and a ligand PPh_2 group. In addition, we also determined the barriers for cyclohexene insertion to the three cationic $(\text{L})\text{Pd}$ -phenyl complexes by DFT calculations. The activation barriers were similar (about 16 kcal/mol).

Therefore, we conclude the poor activity of dppf and dppe catalysts is attributed to the fast side reactions of P-aryl reductive elimination. For the dppp catalyst, the desired olefin insertion is faster than the side reaction.

Scheme 14 Stoichiometric insertion of cyclohexene into $(\text{dppp})\text{Pd}(\text{Ph})\text{I}$ in the presence of AgOTf.

After this, we examined the reason why our $\text{Pd}(\text{dppp})$ catalyst afforded the high vinylic selectivity. As shown in Table 5. We set up a Heck reaction of an electron-poor aryl triflate and cyclohexene and added 3-phenylcyclohexene (1.0 equiv, >99% isomeric purity) into this catalytic process to observe product isomerization. From the Heck reaction, the vinylic isomer became predominant after the first 1.5 hours and the selectivity finally increased to 25:1 after 6 hours. At the same time, the isomerization of the added 3-phenylcyclohexene was fast. After the first 2 hours, the conjugated isomer was dominated with 25:1 selectivity. Besides, 4-phenylcyclohexene was also detected in a trace amount. Based on these results, we propose that the olefin isomerization is a bimolecular process and catalyzed by a hydride catalyst $[(\text{dppp})\text{Pd}(\text{H})]^+$, which could fully dissociate from olefins.

Table 5 Isomerization of added 3-phenylcyclohexene in an active Heck reaction. The selectivities a and b refer to the ratio of the conjugated isomers to the sum of all other isomers.

Entry	Time (h)	Yield (%) ^a	Selectivity (a) ^b	Selectivity (b) ^b
1	0	0	--	<1:100
2	0.5	5	1:7	1:3
3	1	7	1:2	1.4:1
4	1.5	9	5:1	17:1
5	2	22	16:1	25:1
6	6	27	25:1	25:1
7	18	46	26:1	25:1
8	48	89	26:1	25:1

^a GC yield. ^b selectivity was determined by GC.

Therefore, a reaction pathway is proposed in Figure 7. The allylic isomer 3-arylcylohexene is firstly produced due to *syn* β -hydride elimination. After *syn* aryl insertion into the olefin, the benzylic hydrogen is located *anti* to the Pd center in the alkyl-Pd intermediate and 1-arylcylohexene can not directly formed via *syn* elimination. Thus, 1-phenylcylohexene is obtained by the action of the [(dppp)Pd(H)]⁺ catalyst via isomerization of the initially formed 3-arylcylohexene.

Figure 7 An reaction pathway leading to conjugated isomers of Heck reaction.

From the mechanistic understanding, the [(dppp)Pd(H)]⁺ catalyst plays a critical role in achieving the vinylic selectivity. This also helps to explain the beneficial role of veratrole solvent and Li₂CO₃ base. We propose that veratrole can coordinate to [(dppp)Pd(H)]⁺ and shuttle it between isomers of Heck product. Thus, an appreciable concentration of [(dppp)Pd(H)]⁺ is required for fast isomerization of products.^{26b} A strong base will quickly remove the hydride species and prevent product isomerization. In contrast, a relatively weak base such as Li₂CO₃ can establish delicate acid-base equilibrium between the Heck catalyst (dppp)Pd⁰ and the isomerization catalyst [(dppp)Pd(H)]⁺.

1.2.5 Unsuccessful examples in Mizoroki-Heck reaction of cycloolefins

Under our catalytic condition, only cycloolefins of 5-8 membered rings can couple well. Olefins of larger ring size such as cyclododecene, could afford the Heck products in good yield but quite poor selectivity. Indene and 1,4-cyclohexadiene did not react. As shown in Figure 8.1, other cyclic olefins such as cyclopentene or cyclohexene carrying substituents did not couple either, due to steric hindrance. Moreover, common electron-deficient alkenes also showed no reactivity in the reaction of aryl triflates, probably because electron-poor olefins cannot easily coordinate and insert into the cationic aryl palladium complexes. Notably, for the

reaction of electron-rich olefins such as 2,3-dihydrofuran, the major isomer was not the conjugated aryl alkene and 2-aryl-2,3-dihydrofuran was the major isomer due to the product isomerization, as shown in Figure 8.2. A similar observation was made with an *N*-protected 2,3-dihydropyrrole. Other cyclic olefins showed quite poor reactivity and selectivity. In addition, vinyl triflates showed poor results under our conditions, as shown in Figure 8.3.

(a) *unactivated cyclic olefin:*

(b) *electron-deficient cyclic olefin:*

(c) *electron-rich cyclic olefins and related olefins:*

(d) *alkenyl triflates in the reaction of cyclohexene:*

Figure 8 Unsuccessful examples in Mizoroki-Heck reaction of cycloolefins.

Part B: Vinylic selectivity in Mizoroki-Heck reaction of aryl halides

Based on the work in Part A, we have successfully achieved high vinylic selectivity in Mizoroki-Heck reaction of cyclic olefins. Nonetheless, one significant

drawback was the usage of aryl triflates, which are quite expensive to prepare. This limitation would severely hamper synthetic application of our method. Therefore, vinylic selective Mizoroki-Heck reaction of cheaper aryl bromides and chlorides, is described for widening the scope of this Heck reaction.

1.2.6 Condition optimization

In our previous Mizoroki-Heck reaction of aryl triflates that offered excellent vinylic selectivity, a bidentate ligand dppp showed high activity and good selectivity via a cationic pathway. However, for Mizoroki-Heck reaction of aryl halides, a strongly binding monodentate ligand is preferred to create a vacant site on Pd complexes for olefins to bind and insert. We initially explored supporting ligands for the model reaction of *p*-*t*-butylphenyl bromide and cyclohexene. As shown in Table 6, after extensive screening of ligands, we found that a bulky, strongly donating ligand PtBu_3 gave the best results. The desired 1-arylcyclohexene was formed in 94% yield and 33:1 vinylic selectivity. The strongly σ -donating ligand probably stabilizes the active Pd complex at high temperature (120 °C). Another strongly σ -donating ligand $\text{P}(1\text{-adamantyl})_2(n\text{Bu})$ showed moderate reactivity and poor selectivity of the desired isomer. Other common monophosphines such as PPh_3 , PCy_3 and Buchwald's phosphines showed very poor vinylic selectivity. As expected, the bidentate bisphosphines had no catalytic reactivity in the reaction of aryl halides.

Table 6 The effect of supporting ligands in model Mizoroki-Heck reaction.

(5 equiv)
(Ar = *para*-*tert*-butylphenyl)

Entry	Ligand	Conversion (%) ^a	Yield (%) ^b	Selectivity ^a
1	PtBu_3 HBF_4	100	94	33:1
2	PCy_3	72	6	0:1
3	$\text{P}(1\text{-Ad})_2(n\text{Bu})$	100	60	1:4
4	PPh_3	18	5	0:1
5	 $t\text{Bu-DavePhos}$	89	53	1:52

6		100	12	1:43
	RuPhos			
7		100	17	1:21
	XPhos			
8		67	13	0:1
	SPhos			
9	BINAP	8	0	--
10	dppf	7	0	--
11	dppp	8	0	--
12	dppbz	4	0	--
13	dppe	6	0	--

^a conversion and selectivity were determined by GC. ^b GC yield.

The choice of the palladium source was also crucial. The results are listed in Table 7. In our model Mizoroki-Heck reaction, [Pd(hfacac)₂] (hfacac: hexafluoroacetylacetonate) can probably form active catalyst (*t*Bu₃P)Pd⁰ quickly via β -hydride elimination of the trialkylamine base. It showed an exceptionally high activity as compared with other palladium source such as [Pd(dba)₂] (dba: dibenzylideneacetone), Pd(OAc)₂ and [Pd(acac)₂] (acac: acetylacetonate). Poor vinylic selectivity was obtained in the presence of those palladium sources.

Table 7 The effect of palladium sources in model Mizoroki-Heck reaction.

$ \begin{array}{c} \text{ArBr} + \text{Cyclohexene} \xrightarrow[\text{(5 equiv)}]{\begin{array}{l} 4 \text{ mol\% Pd source} \\ 8 \text{ mol\% } t\text{Bu}_3\text{P} \cdot \text{HBF}_4 \\ 1.5 \text{ equiv } i\text{Pr}_2\text{NEt} \\ \text{DMPU, } 120^\circ\text{C}/24 \text{ h} \\ (\text{Ar} = \text{para-tert-butylphenyl}) \end{array}} \text{Ar-Cyclohexene} + \text{isomers} \end{array} $				
Entry	Pd catalyst	Conversion (%) ^a	Yield (%) ^b	Selectivity ^a
1	Pd(hfacac) ₂	100	94	33:1
2	Pd(acac) ₂	100	24	1:2

3	Pd(OAc) ₂	100	38	1:3
4	Pd(OCOCF ₃) ₂	100	4	0:1
5	Pd(dba) ₂	100	62	2:1
6	Pd ₂ (dba) ₃	100	38	0:1

^a conversion and selectivity were determined by GC. ^b GC yield.

With regard to the choice of bases, as shown in Table 8, *i*Pr₂NEt was identified to be the optimal base. When other trialkylamines such as Et₃N, *N*-methylmorpholine, BnNHMe, *n*Bu₂NMe and Cy₂NMe were used, moderate to good yield of the product was achieved, but the vinylic selectivity was quite poor. Notably, Li₂CO₃ also showed good reactivity in the reaction of aryl bromide, but the desired isomer was only generated as a minor isomer.

Table 8 The effect of bases in model Mizoroki-Heck reaction.

(5 equiv) 4 mol% Pd(hfacac)₂
8 mol% P(*t*Bu)₃·HBF₄
1.5 equiv Base
DMPU, 120 °C/24 h
(Ar = *para*-*tert*-butylphenyl)

Entry	Base	Conversion (%) ^a	Yield (%) ^b	Selectivity ^a
1	Et ₃ N	100	81	4:1
2	<i>n</i> Bu ₃ N	82	25	1:2
3	DIPEA	100	94	33:1
4	Cy ₂ NMe	100	76	4:1
5	<i>N</i> -Methyl morpholine	100	73	1:3
6	<i>n</i> Bu ₂ NMe	100	80	3:1
7	BnNHMe	100	95	7:1
8	2,6-lutidine	100	17	1:50
9	DABCO	100	65	0:1
10	Urotropine	100	17	1:13
11	Proton sponge	100	78	1:8
12	Li ₂ CO ₃	100	80	1:10
13	Na ₂ CO ₃	100	58	1:19

14	LiOAc	100	38	1:21
15	NaHCO ₃	100	45	1:45
16	Li ₃ PO ₄	23	11	1:1

^a conversion and selectivity were determined by GC. ^b GC yield.

During the screening of solvents, DMPU (*N, N'*-dimethylpropylene urea) was found to be the best solvent of choice (Table 9). The desired product was obtained in 94% yield and 33:1 selectivity. In addition, in DMA, the model reaction also worked well in 83% yield and 18:1 vinylic selectivity. In other solvents such as DMF, toluene, veratrole and 2-MeTHF, poor vinylic selectivity was seen.

Table 9 The effect of solvents in model Mizoroki-Heck reaction.

Entry	Solvent	Conversion (%) ^a	Yield (%) ^b	Selectivity ^a
1	DMF	100	80	2:1
2	DMA	100	83	18:1
3	NMP	100	82	1:8
4	DMPU	100	94	33:1
5	DME	100	75	1:22
6	Dioxane	95	81	2:1
7	2-MeTHF	100	96	1:1
8	Triglyme	100	75	1:12
9	Veratrole	100	89	6:1
10	Toluene	100	91	2:1

^a conversion and selectivity were determined by GC. ^b GC yield.

1.2.7 Scope of substrates

Using the optimized condition, we explored the substrate scope of aryl halides and cyclic olefins. As shown in Figure 9, both electron-rich and electron-poor aryl bromides formed the vinylic isomers in more than 20:1 selectivity and excellent yield.

Notably, heteroaryl electrophiles of pyridine, quinoline, indole and benzothiazole also coupled well.

Figure 9 The scope of aryl and heteroaryl bromides in Mizoroki-Heck reaction of cyclohexene. The value of vinylic selectivity versus the sum of all other minor isomers is listed in parentheses.

In couplings of cyclopentene (Figure 10), excellent vinylic selectivity was achieved regardless of electronic variation and steric hindrance on aryl rings. Notably, some sensitive functional groups such as aldehydes and free alcohols can also be present. In addition, a wide range of heteroaryl bromides and one vinylic halide also reacted well.

Figure 10 The scope of organic bromides in Mizoroki-Heck reaction of cyclopentene. The value of vinylic selectivity versus the sum of all other minor isomers is listed in parentheses.

The new catalytic process also showed high activity in the reaction of aryl chlorides and cyclopentene. As shown in Figure 11, various aryl chlorides and several heteroaryl chlorides coupled well. In most cases, the conjugated isomers were obtained as the only isomers in excellent yields. However, cycloheptene gave only about 3:1 vinylic selectivity in Mizoroki-Heck reaction of phenyl bromide.

Figure 11 The scope of organic chlorides in Mizoroki-Heck reaction of cyclopentene. The value of vinylic selectivity versus the sum of all other minor isomers is listed in parentheses.

α,β -Unsaturated ketones and lactones, under most of existing Heck conditions, only generated β -arylated products in moderate yields. Moreover, several side reactions such as α' - or γ -arylation were also observed under other reported conditions.²⁷ Our new method can couple with electron-deficient cyclic olefins. The results are summarized in Figure 12, both electron-rich and electron-poor aryl bromides coupled well with α,β -unsaturated ketones and lactones to give the desired products in good to excellent yield. A quick equilibrium between O-bond and C-bond Pd enolates can transport the Pd center *syn* to the β -hydrogen prior to facile β -hydride elimination.

Figure 12 Mizoroki-Heck reaction of α,β -unsaturated ketones and lactones.

Several cyclic olefins such as norbornene are known not to produce Heck-type products via simple *syn* β -hydride elimination. Take norbornene for example, under Catellani's Heck condition, the arylated norbornene was only obtained as a minor product among several products derived from aryl *ortho*-CH activation.²⁸ Surprisingly, our Pd/*Pt*Bu₃ catalyst gave the simple 2-arylated norbornene in excellent yield via *anti*-elimination-type deprotonation (Figure 13.1). The electronic variation on aryl rings had little effect.

For arylation of indene, poor β regioselectivity and multiple arylation were often observed in the previously reported Heck methods.²⁹ Simply changing the solvent and base of our method, the β -arylated indene was successfully produced in excellent yield (Figure 13.2). As far as we know, 1,4-dioxene has not been successfully utilized in Mizoroki-Heck reaction. Herein, the 2-arylated 1,4-dioxenes were formed in good yields (Figure 13.3).

Figure 13 Mizoroki-Heck reaction via direct deprotonation of alkyl-Pd species.

In order to demonstrate the synthetic value of our new Heck procedure, an 1-arylcyclopentene (**A**), which is a key intermediate to access an antipsychotic agent,³⁰ was chosen as the target molecule. The previously reported synthesis involved a Mizoroki-Heck reaction, rhodium-catalyzed double-bond migration and two more steps to introduce the aldehyde group (Figure 14.1). However, under our condition, the desired compound **A** was produced as the only isomer in 93% yield in a single step (Figure 14.2).

Figure 14 The synthetic application of our Mizoroki-Heck reaction.

1.2.8 Mechanistic study

In order to understand the product isomerization process, we set up a Heck reaction of an electron-poor aryl bromide and cyclohexene and added 3-phenylcyclohexene (1.0 equiv, >99% isomeric purity) into this catalytic process to observe product isomerization. As shown in Table 10, from the Heck reaction, the vinylic isomer became predominant after 12 hours and the selectivity finally increased to 25:1 after 3 days. At the same time, the isomerization of the added 3-phenylcyclohexene was also quite slow. After 3 days, the conjugated isomer was the major in 21:1 selectivity. Therefore, the data adequately supported that the conjugate isomer was derived from initial Mizoroki-Heck isomers via Pd hydride-catalyzed double bond isomerization.

Table 10 Isomerization of added 3-phenylcyclohexene in an active Heck reaction.

Entry	Time (h)	Yield (%) ^b	Selectivity (a) ^a	Selectivity (b) ^a
1	0	--	--	<1:200
2	0.5	70	0:1	<1:200
3	1	91	0:1	<1:200
4	1.5	91	0:1	<1:200
5	2	91	1:22	1:20
6	12	91	2:1	4:1
7	24	91	8:1	8:1
8	48	91	17:1	15:1
9	72	91	25:1	21:1

^a selectivity was determined by GC. ^b GC yield.

1.2.9 Unsuccessful examples in Mizoroki-Heck reaction of cycloolefins

In contrast to Mizoroki-Heck reaction of aryl triflates, the reaction of aryl halides showed quite different scope, as shown in Figure 15.1, cycloheptene and cyclooctene could afford the Heck products in good yield but quite poor selectivity. The poor selectivity is probably because the increased steps of olefin isomerization are more difficult to be achieved while the ring size of cycloolefin is increased. Similar limitation with substituted cyclopentenes and cyclohexenes was also observed. Moreover, succinic anhydride and succinimide also gave no product probably because they hydrolyzed under the standard conditions. In addition, many other common vinyl bromides showed no reactivity (Figure 15.2).

Figure 15 Unsuccessful examples in Mizoroki-Heck reaction of aryl halides.

1.3 Conclusion

We have developed two efficient catalysts for Mizoroki-Heck reaction of cycloolefins with aryl triflates and aryl halides respectively. With our Pd/dppp catalyst, various aryl triflates and cyclic alkenes could selectively generate vinylic products in good to excellent yield. Notably, the isomeric purity of products was >95% in most cases. The Pd/*t*Bu₃P catalyst coupled a wide array of aryl halides. Several

cycloolefins, which have poor reactivity in the reaction of aryl triflates, also reacted well. Therefore, two complementary approaches successfully solved the vinylic selectivity in Mizoroki-Heck reaction of cyclic olefins and provided a simple strategy to produce 1-arylcycloolefins.

1.4 Experimental section

1.4.1 General

^1H NMR spectra were acquired on Bruker 400 MHz or 300 MHz spectrometers and chemical shifts were recorded relative to tetramethylsilane (δ 0.00) or residual protiated solvent (CDCl_3 : δ 7.26). 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 at 100 MHz on 400 MHz or 75 MHz on 300 MHz instruments and chemical shifts were recorded relative to solvent resonance (CDCl_3 : δ 77.16). $^{31}\text{P}\{^1\text{H}\}$ NMR spectra were obtained at 121 MHz on 300 MHz instrument or 162 MHz on 400 MHz instrument. Proof of purity of new compounds was demonstrated with copies of ^1H , ^{13}C , ^{31}P and ^{19}F NMR spectra.

Glassware was dried in an oven at 120 °C for at least 2 hours before use. Dry veratrole (Alfa) and DMPU (Aldrich) were degassed by argon bubbling and stored over activated 4 Å molecular sieve beads in an argon-filled glove box before use. Dry hexane, diethyl ether and dichloromethane 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 an argon-filled glove box.

Unless noted otherwise, commercially available chemicals were used without further purification. Dry diisopropylethylamine (DIPEA) and triethylamine were distilled from CaH_2 under argon before use. The GC standard, *n*-dodecane was degassed with argon bubbling and dried over activated 4 Å molecular sieve beads for a few days in the glove box 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 (0.040-0.063 mm).

Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument 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.

1.4.2 Procedure for condition optimization of the Mizoroki-Heck reaction of aryl triflates

Typical Procedure: In an argon-filled glove box, a dry 4-mL reaction tube containing a magnetic stir bar was charged with Pd(hfacac)₂ (4 mol%, 2 mg, 0.004 mmol), dppp (6 mol%, 2.5 mg, 0.006 mmol) and dry veratrole (0.5 mL). After stirring at RT for 10 minutes, *p*-*tert*-butylphenyl triflate (0.10 mmol, 28 mg), Li₂CO₃ (0.20 mmol, 15 mg), cyclohexene (0.20 mmol, 16 mg), and GC standard 1-dodecane (10 µL) were added sequentially via syringe. The tube was capped tightly and the mixture was vigorously stirred in 120 °C oil bath. After 6 hours and 24 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 filtrate was subjected to GC analysis to determine the conversion of aryl triflate, yield and selectivity of the Heck reaction products. The isomers of the Heck products were identified by GCMS. The structure of the major isomer was assigned based on ¹H NMR spectroscopy of the purified sample. Note: ¹H NMR spectroscopy was unsuitable for determination of the ratio of the desired isomers versus minor isomers due to low signal intensity and overlap of signals of the minor isomers.

1.4.3 Procedure for product isolation of Mizoroki-Heck reaction of aryl triflates

The typical procedure using 0.5 mmol of organic triflates was used for all the isolation, unless stated otherwise. In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with Pd(hfacac)₂ (10 mg, 0.02 mmol), dppp (12 mg, 0.03 mmol) and dry veratrole (2.5 mL). After stirring at RT for 10 minutes, aryl triflate (0.5 mmol), cyclic olefin (2 equiv, 1.0 mmol), and Li₂CO₃ (1.0 mmol, 74 mg) were added sequentially. The Schlenk tube was capped tightly and the mixture was heated with vigorous stirring in 120 °C oil bath. After the aryl triflate was fully consumed (monitored by GC), the reaction mixture was passed through a pad of silica gel with diethyl ether washings to remove veratrole, inorganic salts and catalyst first. Then the filtrate was concentrated on a rotary evaporator and the residue was directly subjected to silica gel flash chromatography. The ratio of the conjugated isomer versus all other isomers was determined by GC analysis of unpurified samples. Note: ¹H NMR spectroscopy was unsuitable for determination of the amount of minor isomers due to low signal intensity and overlap of signals. The structure of the desired

isomer was confirmed by ^1H NMR spectroscopy of the purified sample.

The isolation experiments can also be set up using Schlenk manifold that gave similar results. To a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with $\text{Pd}(\text{hfacac})_2$ (10 mg, 0.02 mmol) and dppp (12 mg, 0.03 mmol). The atmosphere was switched from air to argon after three cycles of evacuation and refilling of argon. Dry veratrole (2.5 mL) was added and the mixture was stirred at RT for 10 minutes. Against argon flow, aryl triflate (0.5 mmol), cyclic olefin (2 equiv, 1.0 mmol), and Li_2CO_3 (1.0 mmol, 74 mg) were added sequentially. The Schlenk tube was capped tightly and the mixture was heated with vigorous stirring in 120 °C oil bath until aryl triflate was fully consumed (monitored by GC). Routine workup and flash chromatography was used to isolate the products.

1-Phenylcyclohexene [771-98-2]. In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with $\text{Pd}(\text{hfacac})_2$ (10 mg, 0.02 mmol), dppp (12 mg, 0.03 mmol) and dry veratrole (2.5 mL). After stirring at RT for 10 minutes, phenyl triflate (113 mg, 0.5 mmol), cyclohexene (82 mg, 1.0 mmol) and Li_2CO_3 (74 mg, 1.0 mmol) were added sequentially. The Schlenk tube was capped tightly and the mixture was heated with vigorous stirring in 120 °C oil bath for 48 hours. The product was directly purified by flash chromatography (hexane) as colorless oil (75 mg, 95%). The conjugated selectivity in the reaction mixture was determined to be 20:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.37 (d, $J = 7.6$ Hz, 2H), 7.31-7.27 (m, 2H), 7.22-7.18 (m, 1H), 6.12-6.10 (m, 1H), 2.42-2.39 (m, 2H), 2.23-2.18 (m, 2H), 1.81-1.75 (m, 2H), 1.68-1.62 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 142.7, 136.6, 128.2, 126.5, 124.9, 124.7, 27.4, 25.9, 23.1, 22.2.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{14}$: 158.2. Found: 158.1.

1-(*p-t*-Butylphenyl)cyclohexene [60652-09-7]. The reaction was set up with 2.0

equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 36 hours. The product was purified by flash chromatography (hexane) as colorless oil (96 mg, 91%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 26:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.33 (pseudosinglet, 4H), 6.12-6.09 (m, 1H), 2.43-2.39 (m, 2H), 2.23-2.18 (m, 2H), 1.81-1.75 (m, 2H), 1.69-1.63 (m, 2H), 1.32 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3): δ 149.4, 139.7, 136.2, 125.1, 124.5, 124.0, 34.4, 31.4, 27.3, 25.9, 23.1, 22.2.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{22}$: 214.3. Found: 214.0

1-(*p*-Tolyl)cyclohexene [1821-23-4]. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (hexane) as colorless oil (72 mg, 84%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 23:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.27 (d, J = 7.9 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 6.09-6.06 (m, 1H), 2.41-2.36 (m, 2H), 2.33 (s, 3H), 2.22-2.17 (m, 2H), 1.80-1.74 (m, 2H), 1.68-1.62 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 139.8, 136.4, 136.1, 128.9, 124.8, 123.9, 27.4, 25.8, 23.1, 22.2, 21.0.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{16}$: 172.2. Found: 172.1

1-(*m-t*-Butylphenyl)cyclohexene [93151-02-1]. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (hexane) as colorless oil (95 mg, 90%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 25:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.41 (s, 1H), 7.25-7.21 (m, 2H), 7.20-7.17 (m, 1H), 6.11-6.09 (m, 1H), 2.44-2.41 (m, 2H), 2.23-2.18 (m, 2H), 1.81-1.75 (m, 2H), 1.69-

1.63 (m, 2H), 1.33 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3): δ 150.8, 142.5, 137.1, 127.8, 124.5, 123.6, 122.2, 121.9, 34.7, 31.4, 27.6, 25.9, 23.1, 22.2.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{22}$: 214.1. Found: 214.1

1-(*m*-Xylyl)cyclohexene [107517-89-5]. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 60 hours. The product was purified by flash chromatography (hexane) as colorless oil (81 mg, 87%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 24:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 6.99 (s, 2H), 6.86 (s, 1H), 6.08-6.05 (m, 1H), 2.40-2.36 (m, 2H), 2.30 (s, 6H), 2.21-2.16 (m, 2H), 1.79-1.73 (m, 2H), 1.68-1.62 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 142.8, 137.5, 136.8, 128.2, 124.4, 122.9, 27.6, 25.8, 23.1, 22.2, 21.4.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{18}$: 186.2. Found: 186.1

1-(*m*-Naphthyl)cyclohexene [54607-03-3]. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (91 mg, 88%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 20:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.84-7.78 (m, 4H), 7.64-7.61 (m, 1H), 7.49-7.42 (m, 2H), 6.34-6.31 (m, 1H), 2.59-2.55 (m, 2H), 2.33-2.28 (m, 2H), 1.90-1.84 (m, 2H), 1.77-1.71 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 139.8, 136.3, 133.5, 132.4, 128.0, 127.6, 127.5, 125.9, 125.5, 125.3, 123.8, 123.1, 27.4, 26.0, 23.1, 22.2.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{16}$: 208.2. Found: 208.1

1-(*m*-Anisyl)cyclohexene [1884-41-9]. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 60 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (80 mg, 85%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 20:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.15 (dd, $J = 8.2, 7.8$ Hz, 1H), 6.91 (d, $J = 7.8$ Hz, 1H), 6.85 (t, $J = 2.0$ Hz, 1H), 6.69 (dd, $J = 8.2, 2.1$ Hz, 1H), 6.06-6.04 (m, 1H), 3.74 (s, 3H), 2.34-2.30 (m, 2H), 2.16-2.10 (m, 2H), 1.73-1.67 (m, 2H), 1.61-1.56 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 159.6, 144.3, 136.5, 129.1, 125.1, 117.6, 111.8, 110.9, 55.2, 27.5, 25.9, 23.0, 22.1.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{16}\text{O}$: 188.2. Found: 188.1

1-(*p*-Ethoxycarbonylphenyl)cyclohexene [473596-59-7]. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 70 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (107 mg, 93%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 25:1 by GC. When 2 equiv of Li_2CO_3 was used, the selectivity was lower (6.4:1).

^1H NMR (400 MHz, CDCl_3): δ 7.98-7.96 (m, 2H), 7.44-7.42 (m, 2H), 6.26-6.24 (m, 1H), 4.37 (q, $J = 7.1$ Hz, 2H), 2.43-2.39 (m, 2H), 2.26-2.21 (m, 2H), 1.82-1.76 (m, 2H), 1.70-1.64 (m, 2H), 1.39 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 166.6, 147.0, 135.9, 129.5, 128.4, 127.1, 124.7, 60.8, 27.2, 26.0, 22.9, 22.0, 14.4.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2$: 230.3. Found: 230.1

1-(*p*-Trifluoromethylphenyl)cyclohexene [74975-88-5]. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The

product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (101 mg, 89%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 19:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.55 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 8.4$ Hz, 2H), 6.22-6.20 (m, 1H), 2.43-2.39 (m, 2H), 2.26-2.21 (m, 2H), 1.83-1.77 (m, 2H), 1.71-1.65 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 146.2, 135.7, 128.4 (q, $J_{\text{CF}} = 32$ Hz), 128.1, 127.1, 125.1, 124.4 (q, $J_{\text{CF}} = 270$ Hz), 27.3, 25.9, 22.9, 21.9.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{13}\text{F}_3$: 226.0. Found: 225.9

1-(*p*-Benzophenyl)cyclohexene. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (127 mg, 97%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 23:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.80-7.76 (m, 4H), 7.60-7.56 (m, 1H), 7.50-7.46 (m, 4H), 6.30-6.28 (m, 1H), 2.46-2.43 (m, 2H), 2.27-2.23 (m, 2H), 1.84-1.78 (m, 2H), 1.72-1.66 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 196.2, 146.7, 137.9, 135.8, 135.4, 132.1, 130.1, 129.8, 128.1, 127.3, 124.5, 27.1, 26.0, 22.8, 21.9.

GCMS (EI): Calcd for $\text{C}_{19}\text{H}_{18}\text{O}$: 262.3. Found: 262.1

1-(*p*-Hydroxymethylphenyl)cyclohexene. The reaction was set up with 2 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (84 mg, 89%). The ratio of the desired isomer versus all other isomers in the crude mixture was determined to be 25:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.37 (d, $J = 8.2$ Hz, 2H), 7.28 (d, $J = 8.2$ Hz, 2H), 6.13-6.11 (m, 1H), 4.64 (d, $J = 3.8$ Hz, 2H), 2.41-2.37 (m, 2H), 2.23-2.18 (m, 2H), 1.81-1.75 (m, 3H), 1.69-1.63 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 142.2, 139.1, 136.3, 127.0, 125.1, 124.9, 65.2, 27.4, 25.9, 23.1, 22.2.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{16}\text{O}$: 188.0. Found: 188.0

1-(*m*-Trifluoromethylphenyl)cyclohexene [60652-10-0]. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (109 mg, 96%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 15:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.61 (s, 1H), 7.54 (d, $J = 7.7$ Hz, 1H), 7.45 (d, $J = 7.7$ Hz, 1H), 7.40 (pseudotriplet, $J = 7.7$ Hz, 1H), 6.20-6.17 (pseudotriplet, $J = 7.7$ Hz, 1H), 2.43-2.39 (m, 2H), 2.25-2.20 (m, 2H), 1.83-1.77 (m, 2H), 1.70-1.64 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 143.4, 135.6, 130.5 (q, $J_{\text{CF}} = 32$ Hz), 128.6, 128.2, 126.5, 124.4 (q, $J_{\text{CF}} = 270$ Hz), 123.1 (q, $J_{\text{CF}} = 3.7$ Hz), 121.7 (q, $J_{\text{CF}} = 3.7$ Hz), 27.3, 25.9, 22.9, 22.0.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{13}\text{F}_3$: 226.1. Found: 226.1

1-(*m*-Benzophenyl)cyclohexene. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (82 mg, 89%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 22:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.82-7.80 (m, 3H), 7.63-7.56 (m, 3H), 7.49-7.46 (m, 2H), 7.38 (triplet, $J = 7.7$ Hz, 1H), 6.19-6.16 (m, 1H), 2.43-2.39 (m, 2H), 2.23-2.18 (m, 2H), 1.81-1.75 (m, 2H), 1.69-1.63 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 196.9, 142.8, 137.7, 137.5, 135.8, 132.4, 132.3, 130.0, 128.9, 128.1, 128.0, 126.4, 126.0, 27.3, 25.8, 22.9, 22.0.

GCMS (EI): Calcd for $\text{C}_{19}\text{H}_{18}\text{O}$: 262.3. Found: 262.1

1-(*p*-Anisyl)cyclohexene [20758-60-5]. The reaction was set up with 8 mol% Pd(hfacac)₂, 12 mol% dppp and 2 equiv of Li₂CO₃ and the reaction mixture was stirred at 120 °C for 60 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (76 mg, 81%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 26:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.33-7.30 (m, 2H), 6.86-6.83 (m, 2H), 6.04-6.01 (m, 1H), 3.80 (s, 3H), 2.40-2.35 (m, 2H), 2.21-2.16 (m, 2H), 1.80-1.74 (m, 2H), 1.67-1.62 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 158.4, 135.9, 135.4, 125.9, 123.2, 113.6, 55.3, 27.5, 25.9, 23.2, 22.3.

GCMS (EI): Calcd for C₁₃H₁₆O: 188.1. Found: 188.1

1-(3,4-Dimethoxyphenyl)cyclohexene [27124-93-2]. The reaction was set up with 8 mol% Pd(hfacac)₂, 12 mol% dppp and 2.0 equiv of Li₂CO₃ and the reaction mixture was stirred at 120 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (83 mg, 76%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 24:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 6.94-6.91 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.06-6.03 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 2.41-2.36 (m, 2H), 2.23-2.17 (m, 2H), 1.81-1.75 (m, 2H), 1.68-1.63 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 148.6, 148.0, 136.2, 135.8, 123.6, 117.1, 110.9, 108.4, 55.9, 55.8, 27.6, 25.8, 23.1, 22.2.

GCMS (EI): Calcd for C₁₄H₁₈O₂: 218.2. Found: 218.2

1-(6-Quinoliny)cyclohexene. The reaction was set up with 4 mol% Pd(hfacac)₂, 6

mol% dppp and 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 62 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (95 mg, 91%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 19:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 8.84 (dd, J = 4.2, 1.6 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 8.9 Hz, 1H), 7.83 (dd, J = 8.9, 2.0 Hz, 1H), 7.71 (s, 1H), 7.35 (dd, J = 8.2, 4.2 Hz, 1H), 6.34-6.32 (m, 1H), 2.54-2.51 (m, 2H), 2.30-2.26 (m, 2H), 1.87-1.81 (m, 2H), 1.73-1.67 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 149.8, 147.6, 140.5, 136.1, 135.8, 129.0, 128.3, 127.4, 126.6, 122.7, 121.2, 27.4, 26.1, 23.0, 22.1.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{15}\text{N}$: 209.2. Found: 209.1

1-(2-Quinoxaliny)cyclohexene. The reaction was set up with 4 mol% $\text{Pd}(\text{hfacac})_2$, 6 mol% dppp and 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 62 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (98 mg, 93%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 29:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 9.05 (s, 1H), 8.05-8.02 (m, 2H), 7.74-7.65 (m, 2H), 6.90-6.88 (m, 1H), 2.73-2.68 (m, 2H), 2.39-2.33 (m, 2H), 1.88-1.82 (m, 2H), 1.77-1.71 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 153.5, 142.9, 141.9, 141.1, 136.0, 132.6, 129.8, 129.4, 129.0, 128.8, 26.3, 25.4, 22.6, 21.9.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2$: 210.2. Found: 210.1

Ethyl 2-(1-cyclohexenyl)cyclohex-1-enecarboxylate. The reaction was set up with 8 mol% $\text{Pd}(\text{hfacac})_2$, 12 mol% dppp, 2 equiv of Li_2CO_3 and 5 equiv of cyclohexene.

The reaction mixture was stirred at 120 °C for 62 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (104 mg, 89%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 6:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 5.36-5.34 (m, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.29-2.26 (m, 2H), 2.13-2.11 (m, 2H), 2.08-2.05 (m, 2H), 2.02-1.98 (m, 2H), 1.68-1.54 (m, 8H), 1.25 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): 170.5, 148.3, 140.7, 125.3, 122.0, 59.9, 30.1, 27.3, 26.3, 25.2, 22.8, 22.3, 22.1, 22.0, 14.3.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2$: 234.2. Found: 234.2

3-(1-Cyclohexenyl)estrone. The reaction was set up with $\text{Pd}(\text{hfacac})_2$ (26 mg, 10 mol%), dppp (31 mg, 15 mol%), Li_2CO_3 (111mg, 3 equiv) and cyclohexene (205 mg, 5 equiv) and the reaction mixture was stirred at 120 °C for 78 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (147 mg, 88%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 24:1 by GC. When 2 equiv of Li_2CO_3 was used, 3-estrone triflate cannot be consumed completely even after 4 days at 120 °C (67% yield, 23:1 selectivity).

^1H NMR (400 MHz, CDCl_3): δ 7.23 (d, J = 8.4 Hz, 1H), 7.19-7.16 (m, 1H), 7.12 (s, 1H), 6.09-6.06 (m, 1H), 2.93-2.90 (m, 2H), 2.54-2.36 (m, 4H), 2.32-2.27 (m, 1H), 2.21-2.12 (m, 3H), 2.10-1.92 (m, 3H), 1.80-1.74 (m, 2H), 1.68-1.58 (m, 4H), 1.58-1.44 (m, 4H), 0.90 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 220.9, 140.4, 138.1, 136.3, 136.1, 125.6, 125.2, 124.2, 122.5, 50.5, 48.0, 44.4, 38.3, 35.9, 31.6, 29.6, 27.4, 26.6, 25.9, 25.8, 23.1, 22.2, 21.6, 13.9.

GCMS (EI): Calcd for $\text{C}_{24}\text{H}_{30}\text{O}$: 334.2. Found: 334.2

1-(*p*-Cyano-*m*-trifluoromethylphenyl)cyclohexene. In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with Pd(hfacac)₂ (10 mol%, 0.05 mmol, 26 mg), dppp (15 mol%, 0.075 mmol, 31 mg) and dry veratrole (2.5 mL). After stirring at RT for 10 minutes, *p*-cyano-*m*-trifluoromethylphenyl triflate (160 mg, 0.5 mmol), PhNHMe (1.0 mmol, 107 mg) and cyclohexene (2.5 mmol, 205 mg) were added sequentially. The Schlenk tube was capped tightly and the mixture was heated with vigorous stirring in 120 °C oil bath for 72 hours. The product was directly purified by flash chromatography (1:10 EA/hexane) as colorless oil (121 mg, 96%). The conjugated selectivity in the reaction mixture was determined to be 24:1 by GC. When 4 mol% Pd catalyst and PhNHMe base were used, aryl triflate cannot be fully consumed even after 4 days at 120 °C (63% yield, 19:1 selectivity). Use of 4% Pd catalyst and 2 equiv of Li₂CO₃ led to poor conjugated selectivity.

¹H NMR (400 MHz, CDCl₃): δ 7.75 (m, 2H), 7.64-7.62 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.38-6.35 (m, 1H), 2.43-2.38 (m, 2H), 2.31-2.25 (m, 2H), 1.85-1.79 (m, 2H), 1.72-1.66 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 147.4, 134.7, 134.5, 132.7 (q, *J*_{CF} = 32.3 Hz), 130.4, 128.0, 123.0 (q, *J*_{CF} = 4.7 Hz), 122.6 (q, *J*_{CF} = 273.8 Hz), 115.9, 107.2, 26.9, 26.0, 22.6, 21.6.

¹⁹F NMR (376 MHz, CDCl₃): δ -61.95.

GCMS (EI): Calcd for C₁₄H₁₂F₃N: 251.1. Found: 251.1

1-Phenylcyclopentene [825-54-7]. The reaction was set up with 2.0 equiv of Li₂CO₃ and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (hexane) as colorless oil (68 mg, 95%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.35 (d, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.7 Hz, 2H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.11-6.09 (m, 1H), 2.65-2.60 (m, 2H), 2.47-2.42 (m, 2H), 1.97-

1.89 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 142.4, 136.8, 128.2, 126.8, 126.1, 125.5, 33.3, 33.2, 23.3.

GCMS (EI): Calcd for $\text{C}_{11}\text{H}_{12}$: 144.2. Found: 144.1

1-(*p*-*t*-Butylphenyl)cyclopentene. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (hexane) as colorless oil (95 mg, 95%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.40-7.33 (m, 4H), 6.15-6.13 (m, 1H), 2.72-2.67 (m, 2H), 2.54-2.49 (m, 2H), 2.04-1.97 (m, 2H), 1.32 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3): δ 149.7, 142.2, 134.0, 125.3, 125.2, 125.1, 34.5, 33.3, 33.2, 31.3, 23.4.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{20}$: 200.3. Found: 200.1

1-(*p*-Acetophenyl)cyclopentene [27634-66-8]. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (87 mg, 94%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 198:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.90 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 6.35-6.33 (m, 1H), 2.75-2.69 (m, 2H), 2.58-2.53 (m, 5H), 2.07-2.00 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 197.6, 141.7, 141.3, 135.3, 129.5, 128.5, 125.5, 33.5, 33.0, 26.5, 23.2.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{14}\text{O}$: 186.1. Found: 186.1

1-(*p*-Ethoxycarbonylphenyl)cyclopentene. The reaction was set up with 0.75 equiv

of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (98 mg, 91%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 70:1 by GC. Use of 2 equiv of Li_2CO_3 led to 27:1 selectivity.

^1H NMR (400 MHz, CDCl_3): δ 7.98 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 6.34-6.32 (m, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.75-2.70 (m, 2H), 2.59-2.53 (m, 2H), 2.08-2.00 (m, 2H), 1.39 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): 166.6, 141.9, 141.1, 129.6, 129.2, 128.5, 125.3, 60.8, 33.5, 33.1, 23.3, 14.4.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_2$: 216.1. Found: 216.1

1-(*p*-Formylphenyl)cyclopentene [915016-86-3]. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (81 mg, 94%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 9.97 (s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 6.40-6.38 (m, 1H), 2.76-2.71 (m, 2H), 2.60-2.54 (m, 2H), 2.08-2.01 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 191.7, 142.7, 141.7, 134.7, 130.5, 129.9, 125.9, 33.6, 33.0, 23.2.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{12}\text{O}$: 172.0. Found: 172.0

1-(*p*-Hydroxymethylphenyl)cyclopentene. The reaction was set up with 2 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (81 mg, 93%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.41 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 6.19-6.17 (m, 1H), 4.63 (d, J = 2.4 Hz, 2H), 2.72-2.67 (m, 2H), 2.55-2.50 (m, 2H), 2.05-1.98 (m, 2H), 1.87 (br s, 1H).

^{13}C NMR (100 MHz, CDCl_3): 142.1, 139.4, 136.3, 127.0, 126.3, 125.8, 65.2, 33.4, 33.2, 23.4.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{14}\text{O}$: 174.0. Found: 174.0

1-(*p*-Anisyl)cyclopentene [709-12-6]. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (81 mg, 93%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 200:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.37 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.06-6.04 (m, 1H), 3.81 (s, 3H), 2.70-2.65 (m, 2H), 2.54-2.48 (m, 2H), 2.04-1.97 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 158.6, 141.8, 129.7, 126.7, 123.9, 113.7, 55.3, 33.4, 33.3, 23.4.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{14}\text{O}$: 174.1. Found: 174.1

1-(*m*-Benzophenonyl)cyclopentene. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 52 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (113 mg, 96%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 60:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.35-7.25 (m, 3H), 7.19 (d, J = 7.8 Hz, 1H), 7.12-7.07 (m, 2H), 7.02-7.00 (m, 2H), 6.87-6.84 (m, 1H), 6.18-6.16 (m, 1H), 2.70-2.64 (m, 2H), 2.54-2.49 (m, 2H), 2.04-1.97 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 157.4, 157.0, 141.9, 138.7, 129.7, 129.5, 127.1, 123.0, 120.7, 118.6, 117.4, 116.3, 33.3, 33.2, 23.3.

GCMS (EI): Calcd for $\text{C}_{17}\text{H}_{16}\text{O}$: 236.1. Found: 236.1

1-(*m*-Acetophenyl)cyclopentene. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 54 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (89 mg, 96%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 73:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 8.00 (s, 1H), 7.79 (d, $J = 7.7$ Hz, 1H), 7.62 (d, $J = 7.7$ Hz, 1H), 7.39 (pseudotriplet, $J = 7.7$ Hz, 1H), 6.28-6.26 (m, 1H), 2.76-2.71 (m, 2H), 2.61 (s, 3H), 2.58-2.52 (m, 2H), 2.08-2.00 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 198.3, 141.6, 137.3, 137.1, 130.1, 128.4, 127.6, 126.7, 125.2, 33.4, 33.2, 26.7, 23.3.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{14}\text{O}$: 186.1. Found: 186.1

1-(*m-t*-Butylphenyl)cyclopentene. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (hexane) as colorless oil (94 mg, 94%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 223:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.48 (s, 1H), 7.25 (pseudosinglet, 3H), 6.19-6.17 (m, 1H), 2.75-2.70 (m, 2H), 2.56-2.50 (m, 2H), 2.06-1.98 (m, 2H), 1.33 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3): 150.9, 142.9, 136.5, 128.0, 125.8, 124.0, 122.8, 122.4, 34.7, 33.3 (2 overlapping signals), 31.4, 23.4.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{20}$: 200.1. Found: 200.1

1-(*o*-Cyanophenyl)cyclopentene [100062-80-4]. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 72 hours. The

product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (79 mg, 93%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 24:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.64 (d, $J = 7.7$ Hz, 1H), 7.54-7.50 (pseudotriplet, $J = 7.5$ Hz, 1H), 7.38 (d, $J = 7.9$ Hz, 1H), 7.30-7.26 (pseudotriplet, $J = 7.5$ Hz, 1H), 6.52-6.51 (m, 1H), 2.83-2.77 (m, 2H), 2.63-2.57 (m, 2H), 2.08-2.00 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 141.1, 139.7, 134.0, 133.3, 132.5, 127.9, 126.7, 119.5, 109.6, 35.0, 33.9, 23.4.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{11}\text{N}$: 169.1. Found: 168.1

1-(*o*-Anisyl)cyclopentene [39877-86-6]. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (85 mg, 98%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 40:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.29-7.26 (m, 1H), 7.22-7.17 (m, 1H), 6.95-6.89 (m, 2H), 6.43-6.42 (m, 1H), 3.87 (s, 3H), 2.78-2.73 (m, 2H), 2.58-2.52 (m, 2H), 1.99-1.96 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 157.4, 139.3, 130.4, 128.7, 127.5, 126.2, 120.3, 110.7, 55.1, 35.2, 33.8, 22.9.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{14}\text{O}$: 174.1. Found: 174.1

1-(*o*-Tolyl)cyclopentene [37438-00-9]. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (hexane) as colorless oil (78 mg, 98%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 33:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.21-7.12 (m, 4H), 5.77-5.75 (m, 1H), 2.69-2.64 (m, 2H), 2.56-2.50 (m, 2H), 2.36 (s, 3H), 2.03-1.95 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 143.4, 138.3, 135.5, 130.5, 129.4, 128.1, 126.6, 125.6, 36.8, 33.7, 23.8, 21.3.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{14}$: 158.1. Found: 158.1

1-(6-Quinolinyl)cyclopentene. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (88 mg, 90%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 233:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 8.83 (d, J = 4.2 Hz, 1H), 8.08 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 8.9 Hz, 1H), 7.91 (d, J = 8.9 Hz, 1H), 7.64 (s, 1H), 7.36-7.33 (m, 1H), 6.36-6.35 (m, 1H), 2.83-2.78 (m, 2H), 2.61-2.57 (m, 2H), 2.11-2.03 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 149.8, 147.8, 141.8, 136.0, 134.9, 129.1, 128.4, 128.3, 127.9, 123.6, 121.3, 33.6, 33.2, 23.3.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{13}\text{N}$: 195.1. Found: 194.1

1-(2-Quinoxaliny)cyclopentene. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (87 mg, 89%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 116:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 9.08 (s, 1H), 8.05-8.02 (m, 2H), 7.73-7.64 (m, 2H), 6.85-6.84 (m, 1H), 3.01-2.96 (m, 2H), 2.70-2.65 (m, 2H), 2.13-2.05 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 150.1, 143.8, 142.5, 142.2, 141.0, 135.2, 129.9, 129.4, 129.0, 128.9, 34.2, 32.4, 23.1.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_2$: 196.1. Found: 195.1

Methyl 3-(1-Cyclopentenyl)thiophene-2-carboxylate. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 52 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (94 mg, 90%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 11:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.38 (d, $J = 5.1$ Hz, 1H), 7.01 (q, $J = 5.1$ Hz, 1H), 6.16-6.14 (m, 1H), 3.84 (s, 3H), 2.76-2.71 (m, 2H), 2.55-2.49 (m, 2H), 2.04-1.97 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 162.6, 145.5, 138.1, 132.2, 130.6, 129.7, 126.1, 51.9, 35.8, 33.4, 23.9.

GCMS (EI): Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2\text{S}$: 208.0. Found: 208.0

5-(1-Cyclopentenyl)-2-methylbenzothiazole. The reaction was set up with 2.0 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 42 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (102 mg, 95%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.98 (d, $J = 1.4$ Hz, 1H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.52 (dd, $J = 8.4, 1.4$ Hz, 1H), 6.30-6.27 (m, 1H), 2.84-2.78 (m, 5H), 2.62-2.56 (m, 2H), 2.12-2.04 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 167.2, 153.8, 142.1, 135.2, 133.8, 126.6, 122.7, 120.9, 119.2, 33.5, 33.4, 23.3, 20.2

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{13}\text{NS}$: 215.0. Found: 215.0

4-(1-Cyclopentenyl)-6-phenyl- α , β -unsaturated- δ -lactone. The reaction was set up with 2 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 70 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (110 mg, 92%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.46-7.34 (m, 5H), 6.28 (s, 1H), 5.89 (d, J = 0.7 Hz, 1H), 5.42 (q, J = 4.4 Hz, 1H), 2.88-2.73 (m, 2H), 2.59-2.51 (m, 4H), 2.06-1.95 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 166.1, 150.3, 141.5, 138.9, 137.6, 128.7, 128.6, 126.1, 114.0, 78.9, 33.8, 33.2, 31.5, 22.9.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{16}\text{O}_2$: 240.1. Found: 240.1

Ethyl 2-(1-cyclopentyl)cyclohex-1-enecarboxylate. The reaction was set up with 2 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 51 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (91 mg, 83%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 6:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 5.57 (pseudotriplet, J = 2.1 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.43-2.39 (m, 2H), 2.36-2.30 (m, 4H), 2.21-2.18 (m, 2H), 1.91-1.84 (m, 2H), 1.66-1.62 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): 171.1, 144.7, 139.7, 127.2, 126.7, 60.3, 34.3, 32.8, 29.6, 27.0, 23.9, 22.2, 22.0, 14.1.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2$: 220.1. Found: 220.1

3-(1-Cyclopentyl)-1, 2-dihydronaphthalene. The reaction was set up with 8 mol% Pd(hfacac)₂, 12 mol% dppp, 2.0 equiv of Li₂CO₃ and 5.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 42 hours. The product was purified by flash chromatography (hexane) as colorless oil (90 mg, 92%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.15-7.04 (m, 4H), 6.37 (s, 1H), 5.92 (s, 1H), 2.86-2.82 (m, 2H), 2.63-2.58 (m, 2H), 2.56-2.47 (m, 4H), 2.00-1.93 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 143.7, 135.6, 135.3, 135.0, 127.6, 127.2, 126.5, 126.5, 126.4, 123.4, 33.3, 32.1, 28.1, 25.0, 23.2.

GCMS (EI): Calcd for C₁₅H₁₆: 196.1. Found: 196.1

4-(1-Cyclopentyl)-2H-chromen-2-one. The reaction was set up with 2 equiv of Li₂CO₃ and the reaction mixture was stirred at 120 °C for 42 hours. The product was purified by flash chromatography (1:4 EA/hexane) as colorless oil (103 mg, 97%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.80 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.55-7.50 (m, 1H), 7.35 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.29-7.25 (m, 1H), 6.29-6.27 (m, 2H), 2.77-2.72 (m, 2H), 2.68-2.62 (m, 2H), 2.12-2.04 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 161.3, 154.0, 151.9, 137.9, 136.6, 131.6, 126.4, 124.0, 118.6, 117.4, 112.3, 36.0, 34.3, 23.3.

GCMS (EI): Calcd for C₁₄H₁₂O₂: 212.0. Found: 212.0

1-Phenylcycloheptene [25308-75-2]. The reaction was set up with 2 equiv of Li₂CO₃

and the reaction mixture was stirred at 100 °C for 48 hours. The product was purified by flash chromatography (hexane) as colorless oil (79 mg, 92%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 21:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.32-7.27 (m, 4H), 7.20-7.16 (m, 1H), 6.08 (t, J = 6.8 Hz, 1H), 2.62-2.59 (m, 2H), 2.30-2.26 (m, 2H), 1.86-1.80 (m, 2H), 1.66-1.61 (m, 2H), 1.57-1.52 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 145.0, 144.9, 130.4, 128.1, 126.2, 125.6, 32.8, 32.7, 28.9, 26.9, 26.8.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{16}$: 172.1. Found: 172.1

1-(*p*-Ethoxycarbonylphenyl)cycloheptene [30058-58-3]. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 100 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (107 mg, 88%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 20:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.95 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 6.19 (t, J = 6.8 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.63-2.60 (m, 2H), 2.33-2.29 (m, 2H), 1.88-1.82 (m, 2H), 1.68-1.62 (m, 2H), 1.59-1.54 (m, 2H), 1.39 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 166.6, 149.4, 144.3, 132.5, 129.5, 128.2, 125.5, 60.8, 32.6, 32.5, 29.0, 26.8, 26.6, 14.4.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_2$: 244.1. Found: 244.1

1-(*p*-Anisyl)cycloheptene [32960-45-5]. The reaction was set up with 2 equiv of Li_2CO_3 and the reaction mixture was stirred at 100 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (95 mg, 94%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 26:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.26-7.22 (m, 2H), 6.84-6.80 (m, 2H), 6.01 (t, J = 6.8

Hz, 1H), 3.78 (s, 3H), 2.58-2.56 (m, 2H), 2.28-2.23 (m, 2H), 1.85-1.79 (m, 2H), 1.65-1.59 (m, 2H), 1.56-1.50 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 158.3, 144.4, 137.6, 128.9, 126.7, 113.5, 55.3, 32.9, 32.8, 28.8, 26.9 (2 overlapping signals).

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{18}\text{O}$: 202.1. Found: 202.1

1-(p-Hydroxymethylphenyl)cycloheptene. The reaction was set up with 2 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (93 mg, 92%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 21:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.32-7.25 (m, 4H), 6.09 (t, J = 6.7 Hz, 1H), 4.64 (s, 2H), 2.61-2.59 (m, 2H), 2.31-2.27 (m, 2H), 1.85-1.61 (m, 5H), 1.58-1.53 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 144.6, 144.5, 138.8, 130.5, 126.9, 125.9, 65.2, 32.8, 32.7, 28.9, 26.9, 26.8.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{18}\text{O}$: 202.0. Found: 202.0

1-(p-Formylphenyl)cycloheptene. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (97 mg, 97%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 21:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 9.97 (s, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 6.24 (t, J = 6.8 Hz, 1H), 2.64-2.61 (m, 2H), 2.35-2.30 (m, 2H), 1.88-1.82 (m, 2H), 1.68-1.54 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ 191.8, 151.2, 144.2, 134.5, 133.5, 129.8, 126.1, 32.6, 32.4, 29.0, 26.8, 26.5.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{16}\text{O}$: 200.1. Found: 200.1

1-(*o*-Tolyl)cycloheptene [92377-84-9]. The reaction was set up with 2 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (hexane) as colorless oil (92 mg, 98%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 19:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.13-7.04 (m, 4H), 5.73 (t, J = 6.5 Hz, 1H), 2.42-2.38 (m, 2H), 2.27-2.23 (m, 5H), 1.85-1.79 (m, 2H), 1.66-1.56 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ 146.6, 145.9, 134.6, 131.0, 129.9, 128.3, 126.2, 125.4, 34.8, 32.7, 28.9, 27.2, 27.0, 20.3.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{18}$: 186.1. Found: 186.0

1-(*o*-Anisyl)cycloheptene [92862-65-2]. The reaction was set up with 2 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (88 mg, 87%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 9:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.22-7.18 (m, 1H), 7.10 (dd, J = 7.4, 1.8 Hz, 1H), 6.90-6.83 (m, 2H), 5.87 (t, J = 6.7 Hz, 1H), 3.81 (s, 3H), 2.46-2.43 (m, 2H), 2.28-2.24 (m, 2H), 1.84-1.79 (m, 2H), 1.65-1.62 (m, 2H), 1.61-1.58 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 156.5, 145.1, 135.6, 131.3, 129.4, 127.7, 120.4, 110.5, 55.3, 34.1, 33.0, 29.1, 27.1, 26.9.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{18}\text{O}$: 202.1. Found: 202.0

1-Phenylcyclooctene [137407-47-7]. The reaction was set up with 2 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (hexane) as colorless oil (86 mg, 93%). The ratio of the

desired isomer versus all other isomers in the crude product was determined to be 33:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.32 (d, $J = 7.4$ Hz, 2H), 7.22-7.18 (m, 2H), 7.13-7.09 (m, 1H), 5.92 (t, $J = 8.3$ Hz, 1H), 2.55-2.52 (m, 2H), 2.22-2.17 (m, 2H), 1.55-1.41 (m, 8H).

^{13}C NMR (100 MHz, CDCl_3): δ 143.1, 140.2, 128.2, 127.9, 126.4, 125.7, 30.0, 29.4, 28.4, 27.4, 26.9, 26.1.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{18}$: 186.1. Found: 186.1

1-(*p*-Ethoxycarbonylphenyl)cyclooctene. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 44 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (125 mg, 97%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 28:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.97 (d, $J = 8.6$ Hz, 2H), 7.46 (d, $J = 8.6$ Hz, 2H), 6.14 (t, $J = 8.3$ Hz, 1H), 4.37 (q, $J = 7.1$ Hz, 2H), 2.65-2.62 (m, 2H), 2.34-2.29 (m, 2H), 1.65-1.53 (m, 8H), 1.39 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 166.6, 147.5, 139.5, 130.1, 129.5, 128.3, 125.5, 60.7, 29.8, 29.4, 28.1, 27.5, 26.8, 26.0, 14.3.

GCMS (EI): Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_2$: 258.1. Found: 258.1

1-(*p*-Anisyl)cyclooctene [32960-67-1]. The reaction was set up with 2 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (96 mg, 89%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 37:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.35-7.33 (m, 2H), 6.84-6.82 (m, 2H), 5.93 (t, $J = 8.3$ Hz, 1H), 3.78 (s, 3H), 2.61-2.58 (m, 2H), 2.29-2.24 (m, 2H), 1.62-1.51 (m, 8H).

^{13}C NMR (100 MHz, CDCl_3): δ 158.3, 139.5, 135.6, 126.7, 126.3, 113.5, 55.2, 30.1,

29.3, 28.3, 27.4, 26.9, 26.1.

GCMS (EI): Calcd for C₁₅H₂₀O: 216.1. Found: 216.1

1-(*p*-Hydroxymethylphenyl)cyclooctene. The reaction was set up with 2 equiv of Li₂CO₃ and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (95 mg, 88%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 31:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.41 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 2H), 6.02 (t, *J* = 8.3 Hz, 1H), 4.66-4.65 (m, 2H), 2.64-2.61 (m, 2H), 2.30-2.27 (m, 2H), 1.90 (br s, 1H), 1.64-1.54 (m, 8H).

¹³C NMR (100 MHz, CDCl₃): 142.6, 139.9, 139.0, 128.1, 127.0, 126.0, 65.2, 30.0, 29.4, 28.4, 27.4, 26.9, 26.1.

GCMS (EI): Calcd for C₁₅H₂₀O: 216.1. Found: 216.1

1-(*p*-Formylphenyl)cyclooctene. The reaction was set up with 0.75 equiv of Li₂CO₃ and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (103 mg, 96%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 28:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 9.98 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 6.19 (t, *J* = 8.3 Hz, 1H), 2.67-2.64 (m, 2H), 2.35-2.30 (m, 2H), 1.67-1.53 (m, 8H).

¹³C NMR (100 MHz, CDCl₃): 191.8, 149.3, 139.5, 134.6, 131.3, 129.9, 126.2, 29.8, 29.5, 28.2, 27.6, 26.9, 26.1.

GCMS (EI): Calcd for C₁₅H₁₈O: 214.1. Found: 214.1

1-(*o*-Tolyl)cyclooctene. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (hexane) as colorless oil (94 mg, 94%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 21:1 by GC. ^1H NMR (400 MHz, CDCl_3): δ 7.15-7.04 (m, 4H), 5.50 (t, J = 8.2 Hz, 1H), 2.45-2.42 (m, 2H), 2.29-2.24 (m, 5H), 1.62-1.58 (m, 6H), 1.52-1.49 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 145.0, 141.8, 135.0, 129.9, 128.8, 128.6, 126.4, 125.3, 30.4, 30.0, 28.2, 26.7, 26.6, 26.5, 19.9. GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{20}$: 200.1. Found: 200.0.

1-(*o*-Anisyl)cyclooctene. The reaction was set up with 2 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (103 mg, 95%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 27:1 by GC. ^1H NMR (400 MHz, CDCl_3): δ 7.24-7.20 (m, 1H), 7.10 (dd, J = 7.4, 1.8 Hz, 1H), 6.93-6.82 (m, 2H), 5.65 (t, J = 8.2 Hz, 1H), 3.81 (s, 3H), 2.58-2.55 (m, 2H), 2.30-2.26 (m, 2H), 1.59-1.52 (m, 6H), 1.49-1.45 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 156.6, 140.6, 134.0, 130.5, 129.4, 127.8, 120.4, 110.5, 55.4, 30.0, 29.3, 28.5, 26.9, 26.6, 26.5. GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{20}\text{O}$: 216.1. Found: 216.1

1-(*o*-Cyanophenyl)cyclooctene [23069-13-8]. The reaction was set up with 0.75 equiv of Li_2CO_3 and the reaction mixture was stirred at 120 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (96

mg, 91%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 17:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.64-7.62 (m, 1H), 7.52-7.48 (m, 1H), 7.35-7.27 (m, 2H), 5.93 (pseudotriplet, $J = 8.2$ Hz, 1H), 2.65-2.61 (m, 2H), 2.35-2.30 (m, 2H), 1.63 (pseudosinglet, 6H), 1.56 (pseudosinglet, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 148.7, 138.4, 133.4, 133.1, 132.3, 128.6, 126.7, 119.2, 111.0, 30.2, 29.4, 28.9, 27.3, 26.6, 26.1.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{17}\text{N}$: 211.1. Found: 211.1

1,4-Di(*p*-*tert*-butylphenyl)cyclohexa-1,3-diene. The reaction was set up with 2 equiv of *p*-*tert*-butylphenyl triflate (1.0 mmol, 282 mg), 1,3-cyclohexadiene (0.5 mmol, 40 mg), *n*Bu₂NMe (1.0 mmol, 143 mg) and 2.5 mL of dry veratrole. The reaction mixture was stirred at 120 °C for 43 hours. The product was purified by flash chromatography (hexane) as white solid (149 mg, 87%). When Li_2CO_3 was used as base, no product was detected.

^1H NMR (400 MHz, CDCl_3): δ 7.45 (d, $J = 8.5$ Hz, 4H), 7.38 (d, $J = 8.5$ Hz, 4H), 6.51 (s, 2H), 2.76 (s, 4H), 1.33 (s, 18H).

^{13}C NMR (100 MHz, CDCl_3): δ 150.1, 137.8, 135.4, 125.4, 124.6, 121.1, 34.6, 31.3, 26.1.

GCMS (EI): Calcd for $\text{C}_{26}\text{H}_{32}$: 344.2. Found: 344.2.

1,4-Di(*p*-methoxycarbonylphenyl)cyclohexa-1,3-diene. The reaction was set up with *p*-methoxycarbonylphenyl triflate (1.0 mmol, 284 mg), 1,3-cyclohexadiene (0.5 mmol, 40 mg), *n*Bu₂NMe (1.0 mmol, 143 mg) and 2.5 mL of dry veratrole. The reaction mixture was stirred at 120 °C for 43 hours. The product was purified by flash chromatography (1:4 EA/hexane) as yellow solid (158 mg, 91%).

^1H NMR (400 MHz, CDCl_3): δ 8.02 (d, $J = 8.4$ Hz, 4H), 7.56 (d, $J = 8.4$ Hz, 4H), 6.66 (s, 2H), 3.93 (s, 6H), 2.82 (s, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ 166.9, 144.8, 136.1, 129.8, 128.7, 124.8, 123.4, 52.1, 25.8.

GCMS (EI): Calcd for $C_{22}H_{20}O_4$: 348.1. Found: 348.1

1,4-Di(*p*-anisyl)cyclohexa-1,3-diene. The reaction was set up with *p*-anisyl triflate (1.0 mmol, 256 mg), 1,3-cyclohexadiene (0.5 mmol, 40 mg), *n*Bu₂NMe (1.0 mmol, 143 mg) and 2.5 mL of dry veratrole. The reaction mixture was stirred at 120 °C for 43 hours. The product was purified by flash chromatography (1:4 EA/hexane) as white solid (129 mg, 88%). A small amount of *p*-terphenyl byproduct was detected during chromatography.

¹H NMR (400 MHz, CDCl₃): δ 7.45 (d, *J* = 8.9 Hz, 4H), 6.89 (d, *J* = 8.9 Hz, 4H), 6.43 (s, 2H), 3.83 (s, 6H), 2.74 (s, 4H).

¹³C NMR (100 MHz, CDCl₃): δ 158.8, 134.6, 133.4, 126.0, 120.1, 113.9, 55.3, 26.2.

GCMS (EI): Calcd for $C_{20}H_{20}O_2$: 292.2. Found: 292.2

*Synthesis of 1-arylcyclohexa-1,3-dienes by modifying Barluenga's coupling procedure.*¹ In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with 2-cyclohexenone (53 mg, 0.55 mmol), *p*-tosylhydrazide (119 mg, 0.64 mmol) and dry dioxane (1 mL). After stirring at 70 °C for 2 hours, the mixture was allowed to cool to RT. Then XPhos (10 mol%, 24 mg, 0.50 mmol), Pd₂(dba)₃ (2.5 mol%, 12 mg, 0.013 mmol) and LiOtBu (96 mg, 1.2 mmol) were added sequentially. After stirring at RT for 1 minute, ArBr (0.5 mmol; *m*-OMePhBr, 94 mg or *m*-CNPhBr, 91 mg) and dry dioxane (1 mL) were added. The Schlenk tube was capped tightly and the mixture was heated with vigorous stirring in a 110 °C oil bath for 20 minutes. The reaction mixture was cooled to RT and passed through a pad of Celite. The solvent was evaporated on a rotary evaporator and the product was purified by flash chromatography (1:10 EA/hexane) as yellow oil. 1-(*m*-Anisyl)cyclohexa-1,3-diene, 76 mg, 82%. ¹H NMR (400 MHz, CDCl₃): δ 7.28 (t, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.00-7.03 (m, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.36 (d, *J* = 5.8 Hz, 1H), 6.08-6.14 (m, 1H), 5.90-5.95 (m, 1H), 3.85 (s, 3H), 2.59-2.66 (m, 2H), 2.33-2.39 (m, 2H).

1-(*m*-Cyanophenyl)cyclohexa-1,3-diene, 80 mg, 88%. ¹H NMR (400 MHz, CDCl₃): δ 7.70-7.64 (m, 2H), 7.51-7.48 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 6.36 (d, *J* = 5.6 Hz, 1H), 6.12-6.08 (m, 1H), 5.99-5.95 (m, 1H), 2.57 (t, *J* = 9.8 Hz, 2H), 2.39-2.33 (m, 2H).

1-(*m*-Anisyl)-4-(*p*-*t*-butylphenyl)cyclohexa-1,3-diene. In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with Pd(hfacac)₂ (10 mg, 0.02 mmol), dppp (12 mg, 0.03 mmol) and dry veratrole (2.5 mL). After stirring at RT for 10 minutes, *p*-*tert*-butylphenyl triflate (0.5 mmol, 141 mg), 1-(*m*-anisyl)-cyclohexadiene (0.75 mmol, 140 mg) and *n*Bu₂NMe (1.0 mmol, 143 mg) were added sequentially. The Schlenk tube was capped tightly and the mixture was heated with vigorous stirring in 120 °C oil bath for 36 hours. The product was directly purified by flash chromatography (1:10 EA/hexane) as white solid (143 mg, 90%). The compound was prone to oxidation by air during chromatography.

¹H NMR (400 MHz, CDCl₃): δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.28-7.23 (m, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 6.81-6.78 (m, 1H), 6.53-6.49 (m, 2H), 3.83 (s, 3H), 2.75 (pseudosinglet, 4H), 1.33 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 159.8, 150.3, 142.4, 137.7, 136.1, 135.4, 129.4, 125.4, 124.7, 122.1, 120.9, 117.6, 112.4, 110.6, 55.3, 34.6, 31.3, 26.3, 26.1.

GCMS (EI): Calcd for C₂₃H₂₆O: 318.2. Found: 318.2

1-(*p*-*t*-Butylphenyl)-4-(*m*-cyanophenyl)cyclohexa-1,3-diene. The reaction was set up with *p*-*tert*-butylphenyl triflate (0.50 mmol, 141 mg), 1-(*m*-cyanophenyl)cyclohexa-1,3-diene (0.75 mmol, 136 mg), *n*Bu₂NMe (1.0 mmol, 143 mg) and 2.5 mL of dry veratrole. The reaction mixture was stirred at 120 °C for 41 hours. The product was purified by flash chromatography (1:10 EA/hexane) as yellow solid (130 mg, 83%).

¹H NMR (400 MHz, CDCl₃): δ 7.74-7.68 (m, 2H), 7.52-7.37 (m, 6H), 6.57-6.51 (m, 2H), 2.82-2.70 (m, 4H), 1.34 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 150.8, 142.0, 137.4, 137.2, 133.0, 130.0, 129.2, 128.9, 128.4, 125.5, 124.8, 123.8, 120.4, 119.1, 112.7, 34.6, 31.3, 25.9, 25.8.

GCMS (EI): Calcd for C₂₃H₂₃N: 313.2. Found: 313.2

1,4-Bis(*p*-*t*-butylphenyl)benzene [137062-64-7]. In an argon-filled glove box, to a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with 1,4-di(*p*-*t*-butylphenyl)cyclohexa-1,3-diene (0.5 mmol, 172 mg), CuCl₂ (0.6 mmol, 81 mg) and 2 mL of dry benzene. The reaction mixture was stirred at 100 °C for 2 hours until completion. The product was collected by filtration through silica gel with hexane as eluent as white solid (168 mg, 98%).

¹H NMR (400 MHz, CDCl₃): δ 7.66 (s, 4H), 7.59 (d, *J* = 8.3 Hz, 4H), 7.48 (d, *J* = 8.3 Hz, 4H), 1.38 (s, 18H).

GCMS (EI): Calcd for C₂₆H₃₀: 342.3. Found: 342.3

1,4-Bis(*p*-methoxycarbonylphenyl)benzene [15493-26-2]. Under argon, to a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with 1,4-di(*p*-methoxycarbonylphenyl)cyclohexa-1,3-diene (0.5 mmol, 174 mg), CuCl₂ (1.0 mmol, 134 mg) and 2 mL of dry benzene. The reaction mixture was stirred at 100 °C for 5 hours until completion. The pure product precipitated out as white solid and was collected by filtration (166 mg, 96%).

¹H NMR (400 MHz, CDCl₃): δ 8.14 (d, *J* = 8.4 Hz, 4H), 7.74-7.71 (m, 8H), 3.96 (s, 6H).

GCMS (EI): Calcd for C₂₂H₁₈O₄: 346.1. Found: 346.1

1,4-Bis(*p*-anisyl)benzene [13021-19-7]. In air, to a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with 1,4-di(*p*-anisyl)cyclohexa-1,3-diene (0.50 mmol, 146 mg) and 1 mL of HPLC-grade DCM. The reaction mixture was stirred in air at RT for 16 hours until completion. The solvent was evaporated to give the pure product as white solid (142 mg, 98%).

¹H NMR (400 MHz, CD₂Cl₂): δ 7.62 (s, 4H), 7.59 (d, *J* = 8.7 Hz, 4H), 6.99 (d, *J* = 8.7 Hz, 4H), 3.85 (s, 6H).

GCMS (EI): Calcd for $C_{20}H_{18}O_2$: 290.1. Found: 290.1

1-(*m*-anisyl)-4-(*p*-*t*-Butylphenyl)benzene. Under argon, to a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with 1-(*m*-anisyl)- 4-(*p*-*t*-butylphenyl)-cyclohexa-1,3-diene (0.50 mmol, 159 mg), $CuCl_2$ (1.0 mmol, 134 mg) and dry benzene (2 mL). The reaction mixture was stirred at 100 °C for 5 hours until completion. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (149 mg, 94%).

1H NMR (400 MHz, $CDCl_3$): δ 7.67-7.66 (m, 4H), 7.59 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.37 (pseudotriplet, J = 7.9 Hz, 1H), 7.24-7.22 (m, 1H), 7.17 (pseudotriplet, J = 2.0 Hz, 1H), 6.92-6.89 (m, 1H), 3.88 (s, 3H), 1.38 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 150.4, 142.3, 140.2, 139.7, 137.8, 129.8, 127.5, 127.3, 126.9, 126.7, 125.8, 119.6, 112.8, 55.3, 34.6, 31.4.

GCMS (EI): Calcd for $C_{23}H_{24}O$: 316.2. Found: 316.2.

1.4.4 Procedure for mechanistic study in the Mizoroki-Heck reaction of aryl triflates

Stoichiometric oxidative addition of ArOTf. In an argon-filled glove box, a 4-mL Schlenk tube containing a magnetic stir bar was charged with (TMEDA) $PdMe_2$ (12.6 mg, 0.05 mmol), bisphosphine ligand (1.2 equiv, 0.06 mmol), *p*-*tert*-butylphenyl triflate (0.05 mmol, 14.1 mg), dry veratrole (0.5 mL) and GC standard 1-dodecane (10 μ L) sequentially. The reaction mixture was vigorously stirred at 80 for 5 h and then 120 °C for 5 h. After 5 h at 80 °C and after 5 h at 120 °C, the reaction mixture was cooled to RT and taken into the glove box. An aliquot was removed and passed through a short plug of silica gel with Et_2O washing. The filtrate was subjected to GC analysis to determine the conversion of *p*-*tert*-butylphenyl triflate and amount of organic products. In all three cases, ca. 60% yield of methyl-aryl coupling product was detected after full conversion of ArOTf and <10% yield of aryl-aryl coupling product was also detected by GC.

3-Phenylcyclohexene [15232-96-9]. The compound was made using a reported procedure by Larock. In an argon-filled glove box, a dry 4-mL vial containing a magnetic stir bar was charged with Pd(OAc)₂ (2.5 mol%, 2.8 mg, 0.125 mmol), *n*Bu₄NCl (139 mg, 0.5 mmol) and 1.0 mL of dry DMF. After stirring at room temperature for 10 minutes, phenyl iodide (0.50 mmol, 102 mg), NaOAc (3 equiv, 1.50 mmol, 123 mg), cyclohexene (5 equiv, 2.5 mmol, 205 mg), and GC standard, 1-dodecane (10 μ L) were added sequentially via syringe. The vial was capped tightly and the mixture was vigorously stirred at RT for 5 days (monitored by GC). After removing the solvent, the product was purified by flash chromatography (hexane) as colorless oil (75 mg, 95%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be >200:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.32-7.17 (m, 5H), 5.76 (pseudotriplet, *J* = 13.7 Hz, 2H), 2.83-2.78 (m, 1H), 2.30-2.12 (m, 4H), 1.95-1.92 (m, 1H), 1.81-1.70 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 147.4, 128.4, 127.0, 126.9, 126.8, 126.0, 40.2, 33.5, 29.8, 25.9.

Isomerization of 3-phenylcyclohexene in an active Heck reaction. In an argon-filled glove box, a 4-mL dry reaction tube containing a magnetic stir bar was charged with Pd(hfacac)₂ (4 mol%, 2.0 mg, 0.004 mmol), dppp (6 mol%, 2.5 mg, 0.006 mmol) and 0.5 mL of dry veratrole. After stirring at room temperature for 10 minutes, *p*-ethoxycarbonylphenyl triflate (0.10 mmol, 30 mg), Li₂CO₃ (0.075 mmol, 5.6 mg), cyclohexene (0.5 mmol, 41 mg), 3-phenylcyclohexene (>99% purity, 0.10 mmol, 16 mg) and GC standard 1-dodecane (10 μ L) were added sequentially via syringe. The tube was capped tightly and the mixture was vigorously stirred in a 120 °C oil bath (internal temperature). At intervals, the reaction tube was cooled to RT and taken into the glove box. An aliquot was removed and passed through a short plug of silica gel with Et₂O washing. The filtrate was subjected to GC analysis to determine the yield and conjugated selectivity of the Heck products, as well as the extent of isomerization of added 3-phenylcyclohexene.

Synthesis of (TMEDA)Pd(Ph)I. In an argon-filled glove box, a dry 100-mL Schlenk tube containing a magnetic stir bar was charged with Pd(dba)₂ (1.0 g, 1.75

mmol), dry TMEDA (0.33 mL, 2.25 mmol), phenyl iodide (0.27 mL, 2.5 mmol) and dry benzene (25 mL). The mixture was slowly heated to 50 °C and stirring at 50 °C for 3 hours. The solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ and layered with Et₂O to give the titled compound as yellow powder (694 mg, 93%).

¹H NMR (400 MHz, CDCl₃): δ 7.23 (dd, *J* = 7.9, 1.1 Hz, 2H), 6.90 (t, *J* = 7.4 Hz, 2H), 6.80-6.76 (m, 1H), 2.68 (t, *J* = 5.4 Hz, 2H), 2.64 (s, 6H), 2.52 (t, *J* = 5.4 Hz, 2H), 2.28 (s, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 144.9, 136.5, 126.5, 122.6, 62.1, 58.2, 49.9, 49.7.

Synthesis of (dppp)Pd(Ph)I. In an argon-filled glove box, a dry 20-mL vial containing a magnetic stir bar was charged with (TMEDA)Pd(Ph)I (498 mg, 1.17 mmol), CHCl₃ (5 mL) and dppp (483 mg, 1.17 mmol). The mixture was stirring at rt for 20 min. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography with 1:2 EA/Hexane as eluent. The titled compound was obtained as yellow solid (795 mg, 94%).

¹H NMR (400 MHz, CDCl₃): δ 7.83-7.78 (m, 4H), 7.42-7.40 (m, 6H), 7.30-7.25 (m, 6H), 7.14-7.10 (m, 4H), 6.92-6.88 (m, 2H), 6.55-6.51 (m, 2H), 6.45-6.41 (m, 1H), 2.53-2.48 (m, 2H), 2.41-2.36 (m, 2H), 1.92-1.80 (m, 2H).

³¹P NMR (162 MHz, CDCl₃): δ 11.1 (d, *J* = 42.3 Hz), -10.5 (d, *J* = 52.8 Hz).

Cyclohexene insertion into (dppp)Pd(Ph)I in the presence of AgOTf. In an argon-filled glove box, a 4-mL Schlenk tube containing a magnetic stir bar was charged with (dppp)Pd(Ph)I (72.3 mg, 0.10 mmol) and dry veratrole (0.5 mL). After stirring at rt for 5 min, cyclohexene (2 equiv, 16 mg, 0.2 mmol), Li₂CO₃ (15 mg, 0.2 mmol), AgOTf (26 mg, 0.1 mmol) and 1-dodecane (10 uL) were sequentially added. The reaction mixture was vigorously stirred at 120 °C. At intervals, the reaction mixture was cooled to rt and taken into the glove box. 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 hour were determined to be 78%, 78% and 78%, respectively. The ratio of the desired conjugated isomer versus the sum of other isomers was determined to 10:1, 20:1 and 42:1, respectively. The isomers of the Heck product were confirmed by GCMS.

Synthesis of trans-(PPh₃)₂Pd(Ph)I. Under argon, to a solution of Pd(PPh₃)₄ (2.32 g, 2.0 mmol) in 15 mL of benzene was added PhI (224 μ L, 2.0 mmol) at room temperature. After stirring for 10 hours, the white precipitate was collected, washed with hexane and dried under vacuum. Crystallization from 2:1 dichloromethane/hexane gave pale yellow crystals of *trans*-(PPh₃)₂Pd(Ph)I (1.42 g, 85 % yield).

¹H NMR (400 MHz, CDCl₃): δ 7.52-7.48 (m, 12H), 7.33-7.29 (m, 6H), 7.25-7.21 (m, 12H), 6.61-6.59 (m, 2H), 6.34-6.31 (m, 1H), 6.23-6.19 (m, 2H).

³¹P NMR (162 MHz, CDCl₃): δ 22.9.

Synthesis of (dppf)Pd(Ph)I. Under argon, *trans*-(PPh₃)₂Pd(Ph)I (302 mg, 0.36 mmol) was suspended in 4 mL of freshly distilled THF. Solid dppf (221 mg, 0.40 mmol) was added to the stirred suspension. The reaction was stirred at room temperature for 30 minutes. The product was precipitated by the addition of 15 mL of pentane. The product (250 mg, 80%) was collected as yellow powder.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.05-8.01 (m, 3H), 7.52-7.13 (m, 17H), 6.92-6.89 (m, 2H), 6.52-6.41 (m, 3H), 4.64 (s, 2H), 4.48 (s, 2H), 4.15 (s, 2H), 3.72 (s, 2H).

³¹P NMR (162 MHz, CDCl₃): δ 26.3 (d, J = 34 Hz), 7.9 (d, J = 34 Hz).

Cyclohexene insertion into (dppf)Pd(Ph)I in the presence of AgOTf. In an argon-filled glove box, a 4-mL Schlenk tube containing a magnetic stir bar was charged with (dppf)Pd(Ph)I (87 mg, 0.10 mmol) and dry veratrole (0.5 mL). After stirring at rt for 5 min, cyclohexene (2 equiv, 16 mg, 0.20 mmol), Li₂CO₃ (15 mg, 0.20 mmol), AgOTf (26 mg, 0.10 mmol) and 1-dodecane (10 μ L) were sequentially added. The reaction mixture was vigorously stirred at RT. At intervals (1, 2 and 24 h), the reaction mixture was cooled to RT and taken into the glove box. An aliquot was removed and passed through a short plug of silica gel. The filtrate was subjected to GC analysis. The GC yield of the Heck products (3 isomers in ~1:1:1 ratio) after 1 h was determined to be 8%. The byproduct PPh₃ was detected in 60% yield. The reactions at RT in longer times or at 120 °C did not give difference.

Synthesis of (dppe)Pd(Ph)I. Under argon, a mixture of Pd(PPh₃)₄ (0.50 g, 0.43 mmol) and dppe (175 mg, 0.44 mmol) in 12 mL of benzene was stirred for 1 h. Then PhI (56 μ L, 0.50 mmol) was added to the mixture at room temperature. After stirring at RT for 10 minutes, the resulting solution was allowed to stand overnight without stirring. Yellow crystals were formed and they were collected by filtration, washed with diethyl ether and dried under vacuum. Yield: 0.24 g, 80 %.

¹H NMR (400 MHz, CDCl₃): δ 7.94-7.87 (m, 4H), 7.47-7.40 (m, 6H), 7.37-7.28 (m, 10H), 7.10-7.04 (m, 2H), 6.75-6.61 (m, 3H), 2.46-2.13 (m, 4H).

³¹P NMR (162 MHz, CDCl₃): δ 49.5, 34.6.

Cyclohexene insertion into (dppe)Pd(Ph)I in the presence of AgOTf. In an argon-filled glove box, a 4-mL Schlenk tube containing a magnetic stir bar was charged with (dppe)Pd(Ph)I (72 mg, 0.10 mmol) and dry veratrole (0.50 mL). After stirring at RT for 5 minutes, cyclohexene (2 equiv, 16 mg, 0.20 mmol), Li₂CO₃ (15 mg, 0.20 mmol), AgOTf (26 mg, 0.10 mmol) and 1-dodecane (10 μ L) were sequentially added. The reaction mixture was vigorously stirred at 120 °C. At intervals (1, 2 and 24 h), the reaction mixture was cooled to RT and taken into the glove box. An aliquot was removed and passed through a short plug of silica gel. The filtrate was subjected to GC analysis. The GC yield of the Heck products (3 isomers in ~1:1:1 ratio) after 1 h at 120 °C was determined to be 10%. No PPh₃ was detected. The reactions at longer times did not make changes. When the reaction was conducted at RT, no product was detected.

1.4.5 Procedure for condition optimization of the Mizoroki-Heck reaction of aryl halides

Typical Procedure: In an argon-filled glove box, a dry 4-mL reaction tube containing a magnetic stir bar was charged with Pd(hfacac)₂ (4 mol%, 2 mg, 0.004 mmol), PtBu₃ HBF₄ (8 mol%, 2 mg, 0.008 mmol) and 0.5 mL of dry DMPU. After stirring at room temperature for 10 minutes, *p*-tert-butylphenyl bromide (0.10 mmol, 21 mg), DIPEA (1.5 equiv, 0.15 mmol, 19 mg, distilled over CaH₂), cyclohexene (5 equiv, 0.50 mmol, 41 mg, 52 μ L), and 1-dodecane (10 μ L; GC standard) were added sequentially via syringe. The tube was capped tightly and the mixture was vigorously stirred in a 120 °C oil bath (internal temperature). After 6 hours and 24 hours, aliquots

were taken from the reaction mixture in the glove box and passed through a short plug of silica gel with diethyl ether washing. The filtrate was subjected to GC analysis to determine the conversion of ArBr, yield and selectivity of the Heck reaction products. The isomers of the products were identified by GCMS and the structure of the major isomer was assigned based on ^1H NMR spectroscopy of the purified sample. *^1H NMR spectroscopy was unsuitable for determination of the ratio of the desired isomer versus minor isomers due to low signal intensity and overlap of signals of the minor isomers.*

1.4.6 Procedure for product isolation of Mizoroki-Heck reaction of aryl halides

The typical procedure with 0.5 mmol of ArX was used for all the isolation, unless stated otherwise. In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with $\text{Pd}(\text{hfacac})_2$ (10 mg, 0.02 mmol), $t\text{Bu}_3\text{P HBF}_4$ (12 mg, 0.04 mmol) and 2.5 mL of dry DMPU. After stirring at room temperature for 10 minutes, aryl halide (0.50 mmol), cyclic olefin (2 or 5 equiv, 1.0 or 2.5 mmol), and DIPEA (0.75 mmol, 97 mg) were added sequentially via syringe. The Schlenk tube was capped tightly and the mixture was heated with vigorous stirring in a 120 °C oil bath (external temperature). After the aryl bromide was fully consumed (monitored by GC), the reaction mixture was passed through a pad of silica gel with diethyl ether washings to remove DMPU, inorganic salts and catalyst first. Then the filtrate was concentrated on a rotary evaporator and the residue was directly subjected to silica gel flash chromatography. The ratio of the conjugated isomer versus all other isomers was determined by GC analysis of unpurified samples. ^1H NMR spectroscopy was unsuitable for determination of selectivity.

The experiments can also be set up using Schlenk line that gave similar results. In air, to a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with $\text{Pd}(\text{hfacac})_2$ (10 mg, 0.02 mmol) and $t\text{Bu}_3\text{P HBF}_4$ (12 mg, 0.04 mmol). The atmosphere was switched from air to argon after three cycles of evacuation and refilling of argon. Dry DMPU (2.5 mL) was added via a syringe and the mixture was stirred at RT for 10 minutes. Against argon flow, aryl bromide (0.50 mmol), cyclic olefin (2 or 5 equiv, 1.0 or 2.5 mmol), and DIPEA (0.75 mmol, 97 mg) were added sequentially. The Schlenk tube was capped tightly and the mixture was heated with

vigorous stirring in 120 °C oil bath until aryl halide was fully consumed (monitored by GC). Routine workup and flash chromatography was used to isolate the products.

1-(*p*-*t*-Butylphenyl)cyclohexene [60652-09-7]. The reaction was set up with 5.0 equiv of cyclohexene and the reaction mixture was stirred at 120 °C for 29 hours. The product was purified by flash chromatography (hexane) as colorless oil (103 mg, 94%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 33:1 by GC. When 2 equiv of cyclohexene was used, the reaction gave 58% yield and 20:1 selectivity.

¹H NMR (400 MHz, CDCl₃): δ 7.33 (pseudosinglet, 4H), 6.12-6.09 (m, 1H), 2.43-2.39 (m, 2H), 2.23-2.18 (m, 2H), 1.81-1.75 (m, 2H), 1.69-1.63 (m, 2H), 1.32 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 149.4, 139.7, 136.2, 125.1, 124.5, 124.0, 34.4, 31.4, 27.3, 25.9, 23.1, 22.2.

GCMS (EI): Calcd for C₁₆H₂₂: 214.3. Found: 214.0

1-(*p*-Anisyl)cyclohexene [20758-60-5]. The reaction was set up with 5.0 equiv of cyclohexene and the reaction mixture was stirred at 120 °C for 29 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (86 mg, 91%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 33:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.33-7.30 (m, 2H), 6.86-6.83 (m, 2H), 6.04-6.01 (m, 1H), 3.80 (s, 3H), 2.40-2.35 (m, 2H), 2.21-2.16 (m, 2H), 1.80-1.74 (m, 2H), 1.67-1.62 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 158.4, 135.9, 135.4, 125.9, 123.2, 113.6, 55.3, 27.5, 25.9, 23.2, 22.3.

GCMS (EI): Calcd for C₁₃H₁₆O: 188.1. Found: 188.1

1-(*p*-Methoxycarbonylphenyl)cyclohexene [406232-72-2]. The reaction was set up with 5.0 equiv of cyclohexene and the reaction mixture was stirred at 120 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (101 mg, 93%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 31:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.97 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 6.27-6.24 (m, 1H), 3.90 (s, 3H), 2.44-2.39 (m, 2H), 2.26-2.21 (m, 2H), 1.82-1.76 (m, 2H), 1.70-1.64 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 167.1, 147.1, 135.9, 129.6, 128.0, 127.2, 124.7, 52.0, 27.2, 26.0, 22.9, 22.0.

GCMS (EI): Calcd for C₁₄H₁₆O₂: 216.1. Found: 216.1

1-(2-Naphthyl)cyclohexene [54607-03-3]. The reaction was set up with 5.0 equiv of cyclohexene and the reaction mixture was stirred at 120 °C for 29 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (100 mg, 96%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 28:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.84-7.78 (m, 4H), 7.64-7.61 (m, 1H), 7.49-7.42 (m, 2H), 6.34-6.31 (m, 1H), 2.59-2.55 (m, 2H), 2.33-2.28 (m, 2H), 1.90-1.84 (m, 2H), 1.77-1.71 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 139.8, 136.3, 133.5, 132.4, 128.0, 127.6, 127.5, 125.9, 125.5, 125.3, 123.8, 123.1, 27.4, 26.0, 23.1, 22.2.

GCMS (EI): Calcd for C₁₆H₁₆: 208.2. Found: 208.1

1-(1-Naphthyl)cyclohexene [40358-51-8]. The reaction was set up with 5.0 equiv of cyclohexene and the reaction mixture was stirred at 120 °C for 60 hours. The product was purified by flash chromatography (hexane) as colorless oil (93 mg, 89%). The

ratio of the desired isomer versus all other isomers in the crude product was determined to be 17:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 8.00-7.99 (m, 1H), 7.84-7.80 (m, 1H), 7.71 (d, $J = 8.2$ Hz, 1H), 7.46-7.38 (m, 3H), 7.25 (dd, $J = 7.0, 1.2$ Hz, 1H), 5.77-5.74 (m, 1H), 2.39-2.34 (m, 2H), 2.28-2.23 (m, 2H), 1.87-1.74 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ 143.2, 137.7, 133.8, 131.5, 128.3, 127.3, 126.7, 125.9, 125.6, 125.5, 125.4, 124.9, 31.1, 25.6, 23.3, 22.4.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{16}$: 208.1. Found: 208.1

1-(3-Thienyl)cyclohexene [76441-42-4]. The reaction was set up with 5.0 equiv of cyclohexene and the reaction mixture was stirred at 120 °C for 29 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (73 mg, 89%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 30:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.25-7.22 (m, 2H), 7.08-7.07 (m, 1H), 6.19-6.16 (m, 1H), 2.41-2.37 (m, 2H), 2.22-2.16 (m, 2H), 1.79-1.73 (m, 2H), 1.67-1.62 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 144.1, 131.9, 125.2, 124.7, 123.9, 117.8, 27.3, 25.6, 22.9, 22.3.

GCMS (EI): Calcd for $\text{C}_{10}\text{H}_{12}\text{S}$: 164.0. Found: 164.0

3-(1-Cyclohexenyl)quinoline [33063-43-3]. The reaction was set up with 5.0 equiv of cyclohexene and the reaction mixture was stirred at 120 °C for 29 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (94 mg, 90%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 27:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 9.03 (d, $J = 2.2$ Hz, 1H), 8.06 (d, $J = 8.4$ Hz, 1H), 7.98 (d, $J = 2.0$ Hz, 1H), 7.77 (d, $J = 8.1$ Hz, 1H), 7.66-7.62 (m, 1H), 7.52-7.49 (m,

1H), 6.37-6.35 (m, 1H), 2.52-2.48 (m, 2H), 2.31-2.26 (m, 2H), 1.88-1.82 (m, 2H), 1.74-1.68 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 148.9, 147.0, 134.9, 133.9, 130.3, 129.1, 128.6, 128.0, 127.8, 127.2, 126.6, 27.1, 26.0, 22.9, 22.0.

GCMS (EI): Calcd for C₁₅H₁₅N: 209.1. Found: 209.1

3-(1-Cyclohexenyl)pyridine [19100-10-8]. The reaction was set up with 5.0 equiv of cyclohexene and the reaction mixture was stirred at 120 °C for 29 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (75 mg, 94%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 23:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 8.64 (d, *J* = 2.1 Hz, 1H), 8.44 (d, *J* = 4.8 Hz, 1H), 7.65-7.62 (m, 1H), 7.23-7.20 (m, 1H), 6.18-6.15 (m, 1H), 2.41-2.37 (m, 2H), 2.25-2.20 (m, 2H), 1.83-1.77 (m, 2H), 1.70-1.64 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 147.7, 146.7, 137.9, 133.9, 132.1, 126.6, 123.0, 27.1, 25.8, 22.8, 21.9.

GCMS (EI): Calcd for C₁₁H₁₃N: 159.1. Found: 159.1

5-(1-Cyclohexenyl)-2-methylbenzothiazole. The reaction was set up with 5.0 equiv of cyclohexene and the reaction mixture was stirred at 120 °C for 36 hours. The product was purified by flash chromatography (1:4 EA/hexane) as white solid (103 mg, 90%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 22:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.93 (d, *J* = 1.6 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.41 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.22-6.19 (m, 1H), 2.82 (s, 3H), 2.50-2.45 (m, 2H), 2.27-2.21 (m, 2H), 1.84-1.78 (m, 2H), 1.71-1.65 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 167.1, 153.9, 141.1, 136.2, 133.6, 125.4, 122.2, 120.8, 118.5, 27.6, 26.0, 23.1, 22.1, 20.2.

GCMS (EI): Calcd for C₁₄H₁₅NS: 229.0. Found: 229.0

6-(1-Cyclohexenyl)quinoline. The reaction was set up with 5.0 equiv of cyclohexene and the reaction mixture was stirred at 120 °C for 36 hours. The product was purified by flash chromatography (1:4 EA/hexane) as white solid (90 mg, 86%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 29:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 8.84 (d, *J* = 3.0 Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 8.02 (d, *J* = 8.9 Hz, 1H), 7.83 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.70 (s, 1H), 7.35 (dd, *J* = 8.2, 4.0 Hz, 1H), 6.33-6.31 (m, 1H), 2.53-2.50 (m, 2H), 2.30-2.24 (m, 2H), 1.86-1.80 (m, 2H), 1.73-1.67 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 149.7, 147.6, 140.5, 136.1, 135.7, 129.0, 128.3, 127.4, 126.6, 122.7, 121.2, 27.3, 26.0, 23.0, 22.1.

GCMS (EI): Calcd for C₁₅H₁₅N: 209.1. Found: 209.0

5-(1-Cyclohexenyl)indole. The reaction was set up with 1 equiv of *N*-Boc-5-bromoindole and 5 equiv of cyclohexene. The reaction mixture was stirred at 120 °C for 36 hours. The Boc-deprotected product was isolated by flash chromatography (1:4 EA/hexane) as colorless oil (92 mg, 93%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 33:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 8.02 (br s, 1H), 7.63 (s, 1H), 7.31-7.26 (m, 2H), 7.15-7.14 (m, 1H), 6.52-6.51 (m, 1H), 6.10-6.07 (m, 1H), 2.51-2.47 (m, 2H), 2.25-2.19 (m, 2H), 1.83-1.77 (m, 2H), 1.71-1.65 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 137.4, 135.1, 134.9, 127.9, 124.4, 123.1, 120.1, 116.9, 110.6, 102.9, 28.1, 26.0, 23.3, 22.4.

GCMS (EI): Calcd for C₁₄H₁₅N: 197.1. Found: 197.1

4-(1-Cyclohexenyl)isoquinoline. The reaction was set up with 5.0 equiv of cyclohexene and the reaction mixture was stirred at 120 °C for 60 hours. The product was purified by flash chromatography (1:4 EA/hexane) as colorless oil (95 mg, 91%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 23:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 9.14 (s, 1H), 8.33 (s, 1H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.68 (pseudotriplet, *J* = 7.4 Hz, 1H), 7.58 (pseudotriplet, *J* = 7.4 Hz, 1H), 5.85-5.83 (m, 1H), 2.40-2.36 (m, 2H), 2.31-2.27 (m, 2H), 1.89-1.76 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ 151.2, 141.5, 135.8, 134.4, 134.2, 130.0, 129.0, 128.4, 127.8, 126.8, 124.7, 30.9, 25.6, 23.1, 22.1.

GCMS (EI): Calcd for C₁₅H₁₅N: 209.1. Found: 209.1

1-(*p*-*t*-Butylphenyl)cyclopentene. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (hexane) as colorless oil (94 mg, 94%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.40-7.33 (m, 4H), 6.15-6.13 (m, 1H), 2.72-2.67 (m, 2H), 2.54-2.49 (m, 2H), 2.04-1.97 (m, 2H), 1.32 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 149.7, 142.2, 134.0, 125.3, 125.2, 125.1, 34.5, 33.3, 33.2, 31.3, 23.4.

GCMS (EI): Calcd for C₁₅H₂₀: 200.3. Found: 200.1

1-(*p*-Anisyl)cyclopentene [709-12-6]. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (79 mg, 91%).

The ratio of the desired isomer versus all other isomers in the crude product was determined to be 91:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.37 (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 6.06-6.04 (m, 1H), 3.81 (s, 3H), 2.70-2.65 (m, 2H), 2.54-2.48 (m, 2H), 2.04-1.97 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 158.6, 141.8, 129.7, 126.7, 123.9, 113.7, 55.3, 33.4, 33.3, 23.4.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{14}\text{O}$: 174.1. Found: 174.1

1-(*p*-Methoxycarbonylphenyl)cyclopentene [579472-58-5]. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (95 mg, 94%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 54:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.97 (d, $J = 8.6$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 6.34-6.32 (m, 1H), 3.91 (s, 3H), 2.75-2.70 (m, 2H), 2.58-2.53 (m, 2H), 2.08-2.00 (m, 2H).

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2$: 202.0. Found: 202.0

1-(9-Phenanthrecenyl)cyclopentene [6569-76-8]. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (hexane) as colorless oil (109 mg, 89%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 44:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 8.69 (d, $J = 8.1$ Hz, 1H), 8.63 (d, $J = 7.9$ Hz, 1H), 8.17 (d, $J = 7.8$ Hz, 1H), 7.81 (d, $J = 7.5$ Hz, 1H), 7.65-7.20 (m, 5H), 5.98-5.96 (m, 1H), 2.87-2.82 (m, 2H), 2.67-2.62 (m, 2H), 2.16-2.09 (m, 2H).

GCMS (EI): Calcd for $\text{C}_{19}\text{H}_{16}$: 244.1. Found: 244.1

1-(2-Mesityl)cyclopentene [335233-28-8]. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (hexane) as colorless oil (88 mg, 95%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 204:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 6.85 (s, 2H), 5.49-5.47 (m, 1H), 2.54-2.43 (m, 4H), 2.26 (s, 3H), 2.18 (s, 6H), 2.05-1.97 (m, 2H).

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{18}$: 186.1. Found: 186.1

1-(2,6-Dimethoxyphenyl)cyclopentene [64343-06-2]. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (94 mg, 92%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 47:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.16 (t, J = 8.3 Hz, 1H), 6.57 (d, J = 8.3 Hz, 2H), 5.78-5.76 (m, 1H), 3.78 (s, 6H), 2.67-2.61 (m, 2H), 2.56-2.50 (m, 2H), 2.05-1.95 (m, 2H).

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$: 204.1. Found: 204.1

2-(1-Cyclopentenyl)-4, 5-difluorophenol. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (89 mg, 91%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 6.97-6.92 (m, 1H), 6.75-6.70 (m, 1H), 6.10 (m, 1H), 5.50 (s, 1H), 2.69-2.57 (m, 4H), 2.05-1.97 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 149.2 (d, $J_{\text{CF}} = 11.5$ Hz), 149.1 (dd, $J_{\text{CF}} = 248.0$, 14 Hz), 144.4 (dd, $J_{\text{CF}} = 239.0$, 13 Hz), 138.6, 129.9 (d, $J_{\text{CF}} = 1.1$ Hz), 119.9 (d, $J_{\text{CF}} = 5.6$ Hz), 115.5 (dd, $J_{\text{CF}} = 18.5$, 1.2 Hz), 104.8 (d, $J_{\text{CF}} = 20.3$ Hz), 36.2, 34.0, 22.8.

^{19}F NMR (376 MHz, CDCl_3): δ -137.4 (d, $J_{\text{FF}} = 21.8$ Hz), -148.9 (d, $J_{\text{FF}} = 21.8$ Hz).

GCMS (EI): Calcd for $\text{C}_{11}\text{H}_{10}\text{F}_2\text{O}$: 196.0. Found: 196.0

1-(p-Formylphenyl)cyclopentene [915016-86-3]. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (80 mg, 93%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 9.97 (s, 1H), 7.81 (d, $J = 8.2$ Hz, 2H), 7.56 (d, $J = 8.2$ Hz, 2H), 6.40-6.38 (m, 1H), 2.76-2.71 (m, 2H), 2.60-2.54 (m, 2H), 2.08-2.01 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 191.7, 142.7, 141.7, 134.7, 130.5, 129.9, 125.9, 33.6, 33.0, 23.2.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{12}\text{O}$: 172.0. Found: 172.0

1-(4-Hydroxymethylphenyl)cyclopentene. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (78 mg, 90%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.41 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 6.19-6.17 (m, 1H), 4.63 (d, J = 2.4 Hz, 2H), 2.72-2.67 (m, 2H), 2.55-2.50 (m, 2H), 2.05-1.98 (m, 2H), 1.87 (br s, 1H).

^{13}C NMR (100 MHz, CDCl_3): 142.1, 139.4, 136.3, 127.0, 126.3, 125.8, 65.2, 33.4, 33.2, 23.4.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{14}\text{O}$: 174.0. Found: 174.0

5-(1-Cyclopentenyl)pyrimidine [1352124-38-9]. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (65 mg, 89%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 9.05 (s, 1H), 8.77 (s, 2H), 6.40-6.38 (m, 1H), 2.75-2.70 (m, 2H), 2.61-2.56 (m, 2H), 2.11-2.04 (m, 2H).

GCMS (EI): Calcd for $\text{C}_9\text{H}_{10}\text{N}_2$: 146.2. Found: 146.2

5-(1-Cyclopentenyl)indole. The reaction was set up with 1 equiv of 5-bromoindole and 2 equiv of cyclopentene. The reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (85 mg, 93%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.97 (s, 1H), 7.64 (s, 1H), 7.40 (dd, J = 8.6, 1.6 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 7.11 (t, J = 2.8 Hz, 1H), 6.52-6.51 (m, 1H), 6.13-6.11 (m, 1H), 2.81-2.76 (m, 2H), 2.57-2.51 (m, 2H), 2.07-1.99 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 143.3, 135.0, 129.2, 127.9, 124.4, 123.6, 120.5, 117.8, 110.9, 103.0, 33.7, 33.4, 23.5.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{13}\text{N}$: 183.2. Found: 183.2

***N,N*-Dimethyl-*p*-(1-cyclopentenyl)aniline.** The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (84 mg, 90%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.34 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 5.98-5.96 (m, 1H), 2.94 (s, 6H), 2.70-2.64 (m, 2H), 2.53-2.47 (m, 2H), 2.02-1.95 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 149.6, 142.2, 126.5, 125.7, 122.0, 112.4, 40.6, 33.3 (2 overlapping signals), 23.4.

GCMS (EI): Calcd for C₁₃H₁₇N: 187.2. Found: 187.2

1-(3-Thienyl)cyclopentene [115754-84-2]. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (74 mg, 98%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.25 (s, 2H), 7.07 (pseudotriplet, *J* = 1.9 Hz, 1H), 6.02-6.00 (m, 1H), 2.70-2.65 (m, 2H), 2.53-2.48 (m, 2H), 2.03-1.96 (m, 2H).

GCMS (EI): Calcd for C₉H₁₀S: 150.0. Found: 150.0

1-(3-Pyridyl)cyclopentene [62113-25-1]. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (70 mg, 96%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 8.69 (d, $J = 2.0$ Hz, 1H), 8.44 (dd, $J = 4.8, 1.4$ Hz, 1H), 7.70-7.67 (m, 1H), 7.24-7.20 (m, 1H), 6.28-6.26 (m, 1H), 2.74-2.69 (m, 2H), 2.58-2.52 (m, 2H), 2.08-2.00 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 147.9, 147.2, 139.5, 132.5, 132.3, 128.2, 123.2, 33.4, 32.9, 23.2.

GCMS (EI): Calcd for $\text{C}_{10}\text{H}_{11}\text{N}$: 145.0. Found: 145.0

3-(1-Cyclopentenyl)quinoline [1352124-42-5]. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (90 mg, 92%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 9.13 (d, $J = 2.1$ Hz, 1H), 8.06 (d, $J = 8.4$ Hz, 1H), 7.92 (s, 1H), 7.77 (d, $J = 8.1$ Hz, 1H), 7.66-7.62 (m, 1H), 7.50 (pseudotriplet, $J = 7.5$ Hz, 1H), 6.44-6.43 (m, 1H), 2.83-2.78 (m, 2H), 2.63-2.59 (m, 2H), 2.11-2.04 (m, 2H).

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{13}\text{N}$: 195.1. Found: 195.1

5-(1-Cyclopentenyl)-2-methylbenzothiazole. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (97 mg, 90%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 130:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.98 (d, $J = 1.4$ Hz, 1H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.52 (dd, $J = 8.4, 1.4$ Hz, 1H), 6.30-6.27 (m, 1H), 2.84-2.78 (m, 5H), 2.62-2.56 (m, 2H), 2.12-2.04 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 167.2, 153.8, 142.1, 135.2, 133.8, 126.6, 122.7, 120.9, 119.2, 33.5, 33.4, 23.3, 20.2

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{13}\text{NS}$: 215.0. Found: 215.0

4-(1-Cyclopentenyl)-1,3,5-trimethyl-1H-pyrazole. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (1:4 EA/hexane) as colorless oil (79 mg, 90%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

¹H NMR (400 MHz, CDCl₃): δ 5.60-5.58 (m, 1H), 3.71 (s, 3H), 2.64-2.59 (m, 2H), 2.49-2.44 (m, 2H), 2.24 (pseudosinglet, 6H), 1.99-1.91 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 145.2, 136.1, 135.9, 126.4, 115.3, 35.9, 35.8, 32.8, 23.7, 13.7, 10.9.

GCMS (EI): Calcd for C₁₁H₁₆N₂: 176.1. Found: 176.2

N-Acetyl-*p*-(1-cyclopentenyl)aniline. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product was purified by flash chromatography (1:4 EA/hexane) as colorless oil (75 mg, 94%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.45-7.36 (m, 5H), 6.12-6.11 (m, 1H), 2.70-2.65 (m, 2H), 2.54-2.49 (m, 2H), 2.16 (s, 3H), 2.04-1.97 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 168.3, 141.8, 136.6, 133.0, 126.1, 125.4, 119.7, 33.3, 33.2, 24.6, 23.3.

GCMS (EI): Calcd for C₁₃H₁₅NO: 201.2. Found: 201.2

2-Acetyl-5-(1-cyclopentenyl)thiophene. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 30 hours. The product

was purified by flash chromatography (1:10 EA/hexane) as colorless oil (73 mg, 76%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.56 (d, $J = 3.9$ Hz, 1H), 6.94 (d, $J = 3.9$ Hz, 1H), 6.26-6.24 (m, 1H), 2.73-2.67 (m, 2H), 2.57-2.53 (m, 5H), 2.08-2.00 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 190.6, 149.5, 141.8, 136.5, 133.1, 130.3, 124.1, 33.9, 33.6, 26.5, 23.4.

GCMS (EI): Calcd for $\text{C}_{11}\text{H}_{12}\text{OS}$: 192.0. Found: 192.1

1-(*m*-Formylphenyl)cyclopentene [680203-54-7]. The reaction was set up with 2.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 41 hours. The product was purified by flash chromatography (1:10 EA/hexane) as yellow oil (80 mg, 93%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 10.02 (s, 1H), 7.91 (s, 1H), 7.73-7.69 (m, 2H), 7.47 (t, $J = 7.6$ Hz, 1H), 6.31-6.29 (m, 1H), 2.77-2.72 (m, 2H), 2.59-2.54 (m, 2H), 2.09-2.02 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 192.6, 141.3, 137.8, 136.5, 131.5, 128.9, 128.2, 128.1, 126.6, 33.5, 33.2, 23.3.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{12}\text{O}$: 172.1. Found: 172.1

1-Styrylcyclopentene [109432-85-1]. The reaction was set up with 5.0 equiv of cyclopentene and the reaction mixture was stirred at 120 °C for 36 hours. The product was purified by flash chromatography (hexane) as white oil (63 mg, 74%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.40 (d, $J = 7.5$ Hz, 2H), 7.30 (t, $J = 7.6$ Hz, 2H), 7.19 (t, $J = 7.3$ Hz, 1H), 7.01 (d, $J = 16.0$ Hz, 1H), 6.41 (d, $J = 16.0$ Hz, 1H), 5.85 (s, 1H), 2.57-2.53 (m, 2H), 2.49-2.45 (m, 2H), 2.01-1.93 (m, 2H).

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{14}$: 170.1. Found: 170.1

3-(*p*-*t*-Butylphenyl)cyclopent-2-enone [115614-45-4]. The reaction was set up with 2% $\text{Pd}(\text{hfacac})_2$, 3% $t\text{Bu}_3\text{P}$ HBF_4 and 1.5 equiv of Li_2CO_3 . The reaction mixture was stirred at 120 °C for 36 hours. The product was purified by flash chromatography (1:4 EA/hexane) as white solid (100 mg, 93%). When $i\text{Pr}_2\text{NEt}$ was used as base, the yield was 80% due to partial reduction of ArBr to ArH.

^1H NMR (400 MHz, CDCl_3): δ 7.61 (d, $J = 8.5$ Hz, 2H), 7.48 (d, $J = 8.5$ Hz, 2H), 6.55 (t, $J = 1.6$ Hz, 1H), 3.06-3.03 (m, 2H), 2.59-2.57 (m, 2H), 1.35 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3): δ 209.4, 173.9, 155.0, 131.4, 126.8, 126.7, 125.9, 35.3, 35.0, 31.1, 28.6.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{18}\text{O}$: 214.1. Found: 214.1

3-(*p*-Anisyl)cyclopent-2-enone [2108-53-4]. The reaction was set up with 2% $\text{Pd}(\text{hfacac})_2$, 3% $t\text{Bu}_3\text{P}$ HBF_4 and 1.5 equiv of Li_2CO_3 . The reaction mixture was stirred at 120 °C for 42 hours. The product was purified by flash chromatography (1:4 EA/hexane) as white solid (92 mg, 97%).

^1H NMR (400 MHz, CDCl_3): δ 7.62 (d, $J = 8.9$ Hz, 2H), 6.96 (d, $J = 8.9$ Hz, 2H), 6.47 (t, $J = 1.6$ Hz, 1H), 3.87 (s, 3H), 3.03-3.00 (m, 2H), 2.57-2.55 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 209.3, 173.6, 162.1, 128.6, 126.7, 125.5, 114.3, 55.4, 35.2, 28.6.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{12}\text{O}_2$: 188.0. Found: 188.0

3-(*p*-Methoxycarbonylphenyl)cyclopent-2-enone [1107640-98-1]. The reaction was set up with 2% Pd(hfacac)₂, 3% *t*Bu₃P HBF₄ and 1.5 equiv of Li₂CO₃. The reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:4 EA/hexane) as white solid (61 mg, 56%), the conjugate addition byproduct was also isolated in 42% yield.

¹H NMR (400 MHz, CDCl₃): δ 8.11 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 1.4 Hz, 1H), 3.95 (s, 3H), 3.09-3.06 (m, 2H), 2.63-2.61 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 208.9, 172.2, 166.3, 138.1, 132.2, 130.1, 129.3, 126.7, 52.4, 35.3, 28.7.

GCMS (EI): Calcd for C₁₃H₁₂O₃: 216.0. Found: 216.0

3-*p*-(*t*-Butylphenyl)cyclohex-2-enone. The reaction was set up with 2% Pd(hfacac)₂, 3% *t*Bu₃P HBF₄ and 1.5 equiv of Li₂CO₃. The reaction mixture was stirred at 120 °C for 36 hours. The product was purified by flash chromatography (1:4 EA/hexane) as yellow oil (103 mg, 90%).

¹H NMR (400 MHz, CDCl₃): δ 7.50 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 6.43 (t, *J* = 1.3 Hz, 1H), 2.79-2.75 (m, 2H), 2.50-2.46 (m, 2H), 2.18-2.11 (m, 2H), 1.34 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 199.9, 159.6, 153.6, 135.8, 125.9, 125.7, 124.8, 37.3, 34.8, 31.2, 28.0, 22.8.

GCMS (EI): Calcd for C₁₆H₂₀O: 228.1. Found: 228.1

3-*p*-Anisylcyclohex-2-enone [17159-98-7]. The reaction was set up with 2% Pd(hfacac)₂, 3% *t*Bu₃P HBF₄ and 1.5 equiv of Li₂CO₃. The reaction mixture was stirred at 120 °C for 42 hours. The product was purified by flash chromatography (1:4 EA/hexane) as white solid (95 mg, 94%).

^1H NMR (400 MHz, CDCl_3): δ 7.52 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 6.39 (s, 1H), 3.84 (s, 3H), 2.76-2.73 (m, 2H), 2.46 (t, J = 6.8 Hz, 2H), 2.16-2.11 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 199.9, 161.2, 159.1, 130.8, 127.6, 123.7, 114.1, 55.4, 37.2, 27.8, 22.8.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2$: 202.0. Found: 202.0

3-*p*-(*t*-Butylphenyl)cyclohex-2-enone. The reaction was set up with 4% $\text{Pd}(\text{hfacac})_2$, 8% $t\text{Bu}_3\text{P}$ HBF_4 and 1.5 equiv of DIPEA. The reaction mixture was stirred at 120 °C for 36 hours. The product was purified by flash chromatography (1:4 EA/hexane) as white solid (101 mg, 88%).

^1H NMR (400 MHz, CDCl_3): δ 7.51-7.45 (m, 4H), 6.37 (s, 1H), 4.52 (t, J = 6.2 Hz, 2H), 2.88-2.84 (m, 2H), 1.34 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3): δ 165.2, 155.1, 154.4, 133.0, 126.0, 125.8, 114.2, 66.0, 34.9, 31.1, 26.2.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2$: 230.1. Found: 230.1

3-*p*-Anisyl)cyclohex-2-enone. The reaction was set up with 4% $\text{Pd}(\text{hfacac})_2$, 8% $t\text{Bu}_3\text{P}$ HBF_4 , and 1.5 equiv of DIPEA. The reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:2 EA/hexane) as white solid (78 mg, 76%).

^1H NMR (400 MHz, CDCl_3): δ 7.52 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.30 (d, J = 1.1 Hz, 1H), 4.51 (t, J = 6.2 Hz, 2H), 3.86 (s, 3H), 2.84 (t, J = 6.2, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 165.4, 161.7, 154.7, 128.1, 127.6, 114.4, 112.8, 65.9, 55.5, 26.2.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{12}\text{O}_3$: 204.1. Found: 204.1

2-(*p*-*t*-Butylphenyl)-1, 4-dioxene. The reaction was set up with 4% Pd(hfacac)₂, 8% *t*Bu₃P HBF₄, 1.5 equiv of DIPEA and 5 equiv of 1, 4-dioxene. The reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (hexane) as colorless oil (93 mg, 85%).

¹H NMR (400 MHz, CDCl₃): δ 7.33 (ψs, 4H), 6.60 (s, 1H), 4.25-4.23 (m, 2H), 4.13-4.11 (m, 2H), 1.31 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 150.1, 136.5, 131.1, 125.2, 123.8, 122.7, 64.7, 64.4, 34.5, 31.3.

GCMS (EI): Calcd for C₁₄H₁₈O₂: 218.1. Found: 218.1

2-(*p*-Anisyl)-1,4-dioxene. The reaction was set up with 4% Pd(hfacac)₂, 8% *t*Bu₃P HBF₄, 1.5 equiv of DIPEA and 5 equiv of 1, 4-dioxene. The reaction mixture was stirred at 120 °C for 42 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (71 mg, 74%).

¹H NMR (400 MHz, CDCl₃): δ 7.32 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.51 (s, 1H), 4.26-4.24 (m, 2H), 4.12-4.10 (m, 2H), 3.80 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 158.9, 136.4, 126.7, 124.4, 123.0, 113.8, 64.8, 64.3, 55.3.

GCMS (EI): Calcd for C₁₁H₁₂O₃: 192.1. Found: 192.1

2-(*p*-*t*-Butylphenyl)norborn-2-ene. The reaction was set up with 4% Pd(hfacac)₂, 8% *t*Bu₃P HBF₄, 2.0 equiv of NaOPh, 2 equiv of norbornene and 1mL of dry PhCF₃. The reaction mixture was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (hexane) as colorless oil (99 mg, 90%). When *i*Pr₂NEt and DMPU were used under standard conditions, no reaction occurred at 120 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.39-7.32 (m, 4H), 6.25 (d, $J = 3.1$ Hz, 1H), 3.31 (s, 1H), 2.97 (d, $J = 1.4$ Hz, 1H), 1.81-1.73 (m, 2H), 1.53-1.50 (m, 1H), 1.31 (s, 9H), 1.24 (d, $J = 8.1$ Hz, 1H), 1.14 (dd, $J = 7.4, 2.4$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 149.7, 147.6, 133.0, 128.9, 125.3, 124.6, 47.9, 43.4, 43.1, 34.5, 31.3, 26.9, 24.8.

GCMS (EI): Calcd for $\text{C}_{17}\text{H}_{22}$: 226.2. Found: 226.2

2-(*p*-Anisyl)norborn-2-ene [24920-37-4]. The reaction was set up with 4% $\text{Pd}(\text{hfacac})_2$, 8% $t\text{Bu}_3\text{P}$ HBF_4 , 2.0 equiv of NaOPh , 2 equiv of norbornene and 1mL of dry PhCF_3 . The reaction mixture was stirred at 120 $^\circ\text{C}$ for 72 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (63 mg, 63%).

^1H NMR (400 MHz, CDCl_3): δ 7.35 (d, $J = 8.9$ Hz, 2H), 6.85 (d, $J = 8.9$ Hz, 2H), 6.15 (d, $J = 3.1$ Hz, 1H), 3.81 (s, 3H), 3.28 (s, 1H), 2.97-2.96 (m, 1H), 1.81-1.71 (m, 2H), 1.54-1.50 (m, 1H), 1.25-1.24 (m, 1H), 1.22-1.08 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 158.6, 147.2, 128.6, 127.4, 126.1, 113.9, 55.3, 47.9, 43.4, 43.0, 27.0, 24.8.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{16}\text{O}$: 200.0. Found: 200.0

2-(*p*-Methoxycarbonylphenyl)norborn-2-ene. The reaction was set up with 4% $\text{Pd}(\text{hfacac})_2$, 8% $t\text{Bu}_3\text{P}$ HBF_4 , 2.0 equiv of NaOPh , 2 equiv of norbornene and 1mL of dry PhCF_3 . The reaction mixture was stirred at 120 $^\circ\text{C}$ for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (95 mg, 83%).

^1H NMR (400 MHz, CDCl_3): δ 7.96 (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 8.4$ Hz, 2H), 6.44 (d, $J = 3.1$ Hz, 1H), 3.90 (s, 3H), 3.34 (s, 1H), 3.03 (s, 1H), 1.85-1.76 (m, 2H), 1.56-1.53 (m, 1H), 1.28 (d, $J = 8.3$ Hz, 1H), 1.19-1.10 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 167.0, 147.2, 140.3, 132.8, 129.8, 128.0, 124.6, 52.0, 47.9, 43.4, 43.3, 26.6, 24.8.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_2$: 228.0. Found: 228.0

2-Phenyl-1H-indene [4505-48-0]. The reaction was set up with 4% $\text{Pd}(\text{dba})_2$ (12 mg, 0.02 mmol), 8% $t\text{Bu}_3\text{P HBF}_4$ (12 mg, 0.04 mmol), 1.5 equiv of BnNHMe (102 mg, 0.75 mmol), 2 equiv of indene (116 mg, 1.0 mmol) and 2.5 mL of dry DMPU. The reaction mixture was stirred at 120 °C for 46 hours. The product was purified by flash chromatography (Hexane) as white solid (90 mg, 94%). When the standard condition was used including $\text{Pd}(\text{hfacac})_2$, $t\text{Bu}_3\text{P HBF}_4$, $i\text{Pr}_2\text{NEt}$ and DMPU, β/α selectivity of arylated product was 4:1.

^1H NMR (400 MHz, CDCl_3): δ 7.65-7.63 (m, 2H), 7.47 (d, $J = 7.2$ Hz, 1H), 7.41-7.37 (m, 3H), 7.29-7.24 (m, 3H), 7.21-7.17 (m, 1H), 3.80 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 146.4, 145.4, 143.2, 136.0, 128.7, 127.5, 126.6, 126.5, 126.7, 124.8, 123.7, 121.0, 39.0.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{12}$: 192.2. Found: 192.2

2-(p-Acetophenyl)-1H-indene [79449-08-4]. The reaction was set up with 4% $\text{Pd}(\text{dba})_2$ (12 mg, 0.02 mmol), 8% $t\text{Bu}_3\text{P HBF}_4$ (12 mg, 0.04 mmol), 1.5 equiv of BnNHMe (102 mg, 0.75 mmol), 1 equiv of ArBr , 2 equiv of indene (116 mg, 1.0 mmol) and 2.5 mL of dry DMPU. The reaction mixture was stirred at 120 °C for 40 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (108 mg, 92%).

^1H NMR (400 MHz, CDCl_3): δ 7.96 (d, $J = 8.4$ Hz, 2H), 7.69 (d, $J = 8.4$ Hz, 2H), 7.49 (d, $J = 7.6$ Hz, 1H), 7.44 (d, $J = 7.2$ Hz, 1H), 7.37 (s, 1H), 7.30 (ψt, $J = 7.4$ Hz, 1H), 7.23(ψt, $J = 7.4$ Hz, 1H), 3.81 (s, 2H), 2.61 (s, 3H).

GCMS (EI): Calcd for $\text{C}_{17}\text{H}_{14}\text{O}$: 234.1. Found: 234.1

2-(*p*-Anisyl)-1*H*-indene [54288-29-8]. The reaction was set up with 4% Pd(dba)₂ (12 mg, 0.02 mmol), 8% *t*Bu₃P HBF₄ (12 mg, 0.04 mmol), 1.5 equiv of BnNHMe (102 mg, 0.75 mmol), 1 equiv of ArBr, 2 equiv of indene (116 mg, 1.0 mmol) and 2.5 mL of dry DMPU. The reaction mixture was stirred at 120 °C for 40 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (102 mg, 92%).

¹H NMR (400 MHz, CDCl₃): δ 7.57 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.25 (ψt, *J* = 7.4 Hz, 1H), 7.15 (ψt, *J* = 7.4 Hz, 1H), 7.09 (s, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 2H).

GCMS (EI): Calcd for C₁₆H₁₄O: 222.1. Found: 222.1

Heck reactions of aryl and heteroaryl chlorides using 0.5 mmol of organic chlorides. In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with Pd(hfacac)₂ (10 mg, 0.02 mmol), *t*Bu₃P HBF₄ (12 mg, 0.04 mmol) and 2.5 mL of dry DMPU. After stirring at room temperature for 10 minutes, aryl chloride (0.50 mmol), cyclic olefin (5 equiv, 2.5 mmol), and DIPEA (0.75 mmol, 97 mg) were added sequentially via syringe. The Schlenk tube was capped tightly and the mixture was heated with vigorous stirring in a 120 °C oil bath (external temperature). After the aryl chloride was fully consumed (monitored by GC), the reaction mixture was passed through a pad of silica gel with diethyl ether washings to remove DMPU, inorganic salts and catalyst first. Then the filtrate was concentrated on a rotary evaporator and the residue was directly subjected to silica gel flash chromatography. The ratio of the conjugated isomer versus all other isomers was determined by GC analysis of unpurified samples.

Note: ¹H NMR spectroscopy was unsuitable for determination of the amount of minor isomers due to low signal intensity and overlap of signals. The structure of the desired isomer was confirmed by ¹H NMR spectroscopy of the purified sample.

1-Phenylcyclopentene [825-54-7]. The reaction was stirred at 120 °C for 27 hours. The product was purified by flash chromatography (hexane) as colorless oil (69 mg,

96%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.35 (d, $J = 7.7$ Hz, 2H), 7.22 (t, $J = 7.7$ Hz, 2H), 7.12 (t, $J = 7.7$ Hz, 1H), 6.11-6.09 (m, 1H), 2.65-2.60 (m, 2H), 2.47-2.42 (m, 2H), 1.97-1.89 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 142.4, 136.8, 128.2, 126.8, 126.1, 125.5, 33.3, 33.2, 23.3.

GCMS (EI): Calcd for $\text{C}_{11}\text{H}_{12}$: 144.2. Found: 144.1

1-(*p*-Anisyl)cyclopentene [709-12-6]. The reaction was stirred at 120 °C for 66 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (80 mg, 92%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 147:1 by GC.

1-(*p*-Cyanophenyl)cyclopentene. The reaction was stirred at 120 °C for 52 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (82 mg, 97%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 174:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.59 (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 8.4$ Hz, 2H), 6.38-6.36 (m, 1H), 2.74-2.69 (m, 2H), 2.61-2.56 (m, 2H), 2.10-2.03 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 141.2, 141.1, 132.1, 130.7, 126.0, 119.2, 109.9, 33.6, 32.9, 23.2.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{11}\text{N}$: 169.1. Found: 169.1

1-(*p*-Acetophenyl)cyclopentene. The reaction was stirred at 120 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (91 mg, 98%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.90 (d, $J = 8.3$ Hz, 2H), 7.49 (d, $J = 8.3$ Hz, 2H), 6.35-6.34 (m, 1H), 2.74-2.70 (m, 2H), 2.58-2.53 (m, 5H), 2.08-2.00 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 197.6, 141.8, 141.4, 135.4, 129.6, 128.5, 125.6, 33.6, 33.1, 26.5, 23.3.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{14}\text{O}$: 186.1. Found: 186.1

1-(6-Quinolinyl)cyclopentene. The reaction was stirred at 120 °C for 27 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (89 mg, 91%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

^1H NMR (400 MHz, CDCl_3): δ 8.83 (d, $J = 4.2$ Hz, 1H), 8.08 (d, $J = 8.3$ Hz, 1H), 8.01 (d, $J = 8.9$ Hz, 1H), 7.91 (d, $J = 8.9$ Hz, 1H), 7.64 (s, 1H), 7.36-7.33 (m, 1H), 6.36-6.35 (m, 1H), 2.83-2.78 (m, 2H), 2.61-2.57 (m, 2H), 2.11-2.03 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): 149.8, 147.8, 141.8, 136.0, 134.9, 129.1, 128.4, 128.3, 127.9, 123.6, 121.3, 33.6, 33.2, 23.3.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{13}\text{N}$: 195.1. Found: 195.1

5-(1-Cyclopentenyl)-2-methylindole. The reaction was stirred at 120 °C for 46 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (95 mg, 97%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 118:1 by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.68 (s, 1H), 7.52 (s, 1H), 7.30 (dd, $J = 8.4, 1.5$ Hz, 1H), 7.15 (d, $J = 8.4$ Hz, 1H), 6.17-6.16 (m, 1H), 6.10 (d, $J = 1.9$ Hz, 1H), 2.79-2.75 (m, 2H), 2.55-2.51 (m, 2H), 2.38 (s, 3H), 2.06-1.98 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 143.4, 135.4, 135.3, 129.1, 128.9, 123.1, 119.3, 116.8, 110.0, 100.7, 33.7, 33.4, 23.5, 13.7.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{15}\text{N}$: 197.1. Found: 197.1

4-(1-Cyclopentenyl)-2,6-dimethoxypyrimidine. The reaction was stirred at 120 °C for 52 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (93 mg, 90%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 61:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 6.87-6.85 (m, 1H), 6.27 (s, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 2.70-2.64 (m, 2H), 2.59-2.53 (m, 2H), 2.07-2.00 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 172.4, 165.0, 163.3, 141.7, 135.7, 97.3, 54.5, 53.7, 33.4, 31.8, 23.2.

GCMS (EI): Calcd for C₁₁H₁₄N₂O₂: 206.1. Found: 206.1

5-(1-Cyclopentenyl)-2-methylbenzothiazole. The reaction was stirred at 120 °C for 66 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (98 mg, 91%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 105:1 by GC.

1-(3-Pyridyl)cyclopentene [62113-25-1]. The reaction was stirred at 120 °C for 27 hours. The product was purified by flash chromatography (1:10 EA/hexane) as colorless oil (68 mg, 94%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

5-(1-Cyclopentenyl)furan-2-carbaldehyde. The reaction was stirred at 120 °C for 27 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (72 mg, 89%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

¹H NMR (400 MHz, CDCl₃): δ 9.57 (s, 1H), 7.22 (d, *J* = 3.7 Hz, 1H), 6.48 (pseudosinglet, 1H), 6.37 (d, *J* = 3.7 Hz, 1H), 2.70-2.65 (m, 2H), 2.59-2.54 (m, 2H), 2.07-1.99 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 177.1, 157.8, 151.6, 132.3, 132.1, 123.5, 108.6, 33.6, 32.1, 23.2.

GCMS (EI): Calcd for C₁₀H₁₀O₂: 162.1. Found: 162.1

5-(1-Cyclopentenyl)-2-(*p*-ethoxycarbonylphenyl)indole. The reaction was stirred at 120 °C for 46 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (125 mg, 98%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 127:1 by GC.

¹H NMR (400 MHz, CDCl₃): δ 8.92 (s, 1H), 7.64 (s, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.20 (s, 1H), 6.15 (pseudosinglet, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.80-2.76 (m, 2H), 2.57-2.53 (m, 2H), 2.08-2.01 (m, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 161.9, 142.7, 136.0, 130.1, 127.7, 127.6, 124.5, 124.0, 119.1, 111.6, 109.0, 61.0, 33.5, 33.4, 23.4, 14.4.

GCMS (EI): Calcd for C₁₆H₁₇NO₂: 255.1. Found: 255.1

2-Acetyl-5-(1-cyclopentenyl)thiophene. The reaction was stirred at 120 °C for 27 hours. The product was purified by flash chromatography (1:10 EA/hexane) as white solid (85 mg, 88%). The ratio of the desired isomer versus all other isomers in the crude product was determined to be 100:0 by GC.

1.4.7 Procedure for mechanistic study of Mizoroki-Heck reaction of aryl halides

Isomerization of 3-phenylcyclohexene in an active Heck reaction of ArBr and cyclohexene. In an argon-filled glove box, a dry 4-mL reaction tube containing a magnetic stir bar was charged with Pd(hfacac)₂ (4 mol%, 2 mg, 0.004 mmol), *t*Bu₃P HBF₄ (8 mol%, 2 mg, 0.008 mmol) and 0.5 mL of dry DMPU. After prestirring at room temperature for 10 minutes, *p*-methoxycarbonylphenyl bromide (0.10 mmol, 22 mg), DIPEA (1.5 equiv, 19 mg), cyclohexene (5 equiv, 0.50 mmol, 41 mg, 52 μ L), 3-phenylcyclohexene (>99% purity, 1 equiv, 0.10 mmol, 16 mg) and GC standard 1-dodecane (10 μ L) were added sequentially via syringe. The tube was capped tightly and the mixture was vigorously stirred in a 120 °C oil bath. At intervals, the reaction tube was cooled to RT and taken into the glove box. An aliquot was removed and passed through a short plug of silica gel with Et₂O washing. The filtrate was subjected to GC analysis to determine the yield and conjugated selectivity of the Heck products, as well as the extent of the isomerization of 3-phenylcyclohexene.

1.5 Reference

- (1) (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320. (c) De Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086.
- (2) (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (d) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146.
- (3) (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481. (b) Vallin, K. S. A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 4340. (c) Andersson, C. M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757.
- (4) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989
- (5) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4729.
- (6) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *Tetrahedron Lett.* **1991**, *32*, 1753.
- (7) (a) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2004**, *127*, 751. (b) Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5915. (c) Qin, L.; Hirao, H.; Zhou, J. *Chem. Commun.* **2013**, *49*, 10236. (d) Tasker, S. Z.; Gutierrez, A. C.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 1858.
- (8) Larock, R. C.; Baker, B. E. *Tetrahedron Lett.* **1988**, *29*, 905.
- (9) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, *1997*, 1338.
- (10) (a) Mc Cartney, D.; Guiry, P. J. *Chem. Soc. Rev.* **2011**, *40*, 5122. (b) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453.
- (11) (a) Hu, J.; Lu, Y.; Li, Y.; Zhou, J. *Chem. Commun.* **2013**, *49*, 9425. (b) Hu, J.; Hirao, H.; Li, Y.; Zhou, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 8676. (c) Wu, C.; Zhou, J. *J. Am. Chem. Soc.* **2014**, *136*, 650. (d) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417.
- (12) Hartung, C. G.; Köhler, K.; Beller, M. *Org. Lett.* **1999**, *1*, 709.

- (13) Berthiol, F.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2003**, *44*, 1221.
- (14) Mieczyska, E.; Trzeciak, A. M. *Molecules* **2010**, *15*, 2166.
- (15) Artuso, E.; Barbero, M.; Degani, I.; Dughera, S.; Fochi, R. *Tetrahedron* **2006**, *62*, 3146.
- (16) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773.
- (17) (a) White, L. V.; Schwartz, B. D.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2011**, *76*, 6250. (b) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. R.; Wu, A. W. *J. Org. Chem.* **2000**, *65*, 4241. (c) Nishimata, T.; Sato, Y.; Mori, M. *J. Org. Chem.* **2004**, *69*, 1837. (d) Tanimoto, H.; Saito, R.; Chida, N. *Tetrahedron Lett.* **2008**, *49*, 358.
- (18) Olsson, V. J.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6891.
- (19) Kondoh, A.; Jamison, T. F. *Chem. Commun.* **2010**, *46*, 907.
- (20) (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (b) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Adv. Synth. Catal.* **2010**, *352*, 3235.
- (21) (a) Siedle, A. R.; Newmark, R. A.; Pignolet, L. H. *Inorg. Chem.* **1983**, *22*, 2281. (b) Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178–180, Part 1*, 511.
- (22) (a) Cabri, W.; Candiani, I.; DeBernardinis, S.; Francalanci, F.; Penco, S.; Santo, R. *J. Org. Chem.* **1991**, *56*, 5796. (b) Li, J.; Liu, W. *Org. Lett.* **2004**, *6*, 2809. (c) Li, J. J.; Iula, D. M.; Nguyen, M. N.; Hu, L.-Y.; Dettling, D.; Johnson, T. R.; Du, D. Y.; Shanmugasundaram, V.; Van Camp, J. A.; Wang, Z.; Harter, W. G.; Yue, W.-S.; Boys, M. L.; Wade, K. J.; Drummond, E. M.; Samas, B. M.; Lefker, B. A.; Hoge, G. S.; Lovdahl, M. J.; Asbill, J.; Carroll, M.; Meade, M. A.; Ciotti, S. M.; Krieger-Burke, T. *J. Med. Chem.* **2008**, *51*, 7010.
- (23) (a) Simoni, D.; Giannini, G.; Roberti, M.; Rondanin, R.; Baruchello, R.; Rossi, M.; Grisolia, G.; Invidiata, F. P.; Aiello, S.; Marino, S.; Cavallini, S.; Siniscalchi, A.; Gebbia, N.; Crosta, L.; Grimaudo, S.; Abbadessa, V.; Di Cristina, A.; Tolomeo, M. *J. Med. Chem.* **2005**, *48*, 4293. (b) Roberti, M.; Pizzirani, D.; Recanatini, M.; Simoni, D.; Grimaudo, S.; Di, C.; Abbadessa, V.; Gebbia, N.; Tolomeo, M. *J. Med. Chem.* **2006**, *49*, 3012.

- (24) (a) Modjewski, M.; Lindeman, S. V.; Rathore, R. *Org. Lett.* **2009**, *11*, 4656. (b) Maya, F.; Tour, J. M. *Tetrahedron* **2004**, *60*, 81.
- (25) Antelo Miguez, J. M.; Adrio, L. A.; Sousa-Pedrares, A.; Vila, J. M.; Hii, K. K. *J. Org. Chem.* **2007**, *72*, 7771.
- (26) (a) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441. (b) Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T. *J. Am. Chem. Soc.* **2010**, *132*, 7998.
- (27) (a) Gottumukkala, A. L.; de Vries, J. G.; Minnaard, A. J. *Chem. Eur. J.* **2011**, *17*, 3091. (b) Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, *6*, 433. (c) Froemming, M. K.; Sames, D. *J. Am. Chem. Soc.* **2007**, *129*, 14518.
- (28) (a) Reiser, O.; Weber, M.; de Meijere, A. *Angew. Chem., Int. Ed.* **1989**, *28*, 1037. (b) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1985**, *286*, c13. (c) Catellani, M.; Chiusoli, G. P.; Ricotti, S. *J. Organomet. Chem.* **1985**, *296*, c11.
- (29) (a) Dyker, G.; Heiermann, J.; Miura, M.; Inoh, J.-I.; Pivsa-Art, S.; Satoh, T.; Nomura, M. *Chem. Eur. J.* **2000**, *6*, 3426. (b) Nifant'ev, I. E.; Sitnikov, A. A.; Andriukhova, N. V.; Laishevstev, I. P.; Luzikov, Y. N. *Tetrahedron Lett.* **2002**, *43*, 3213. (c) Maeda, K.; Farrington, E. J.; Galardon, E.; John, B. D.; Brown, J. M. *Adv. Synth. Catal.* **2002**, *344*, 104.
- (30) Cuisiat, S.; Bourdiol, N.; Lacharme, V.; Newman-Tancredi, A.; Colpaert, F.; Vacher, B. *J. Med. Chem.* **2007**, *50*, 865.
- (31) Gaussian 09, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S.

Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2010**.

(32) (a) Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B.* **1988**, 37, 785. (c) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, 58, 1200. (c) Hehre, W. R.; Schleyer, P. v. R.; Pople, J. *Ab Initio Molecular Orbital Theory*, John Wiley & Sons, New York, **1986**. (d) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, 4, 294. (e) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta.* **1973**, 28, 213.

Chapter 2. An Efficient Method for Heck-Catellani Reaction of Aryl Halides

2.1 Introduction

In Mizoroki-Heck reaction, arylated olefins were obtained after olefin insertion into the aryl-Pd bond. The Heck method has become an indispensable tool in synthesis.¹ However, when a special cyclic olefin norbornene is used, no *syn* β -hydride is available for elimination after norbornene insertion. Catellani initially studied such a special case in 1984. In Pd-catalyzed reaction of 1-bromo-4-fluorobenzene and norbornene, two benzocyclobutene-containing compounds were formed in 5% and 19% yield, respectively (Scheme 1).² A possible reaction pathway involving ortho C-H activation is shown in Scheme 1. A norbornene-derived palladacycle is the key intermediate.³ The postulated palladacycle has been isolated which was chelated by a phenanthroline ligand.⁴ The pioneering work set the stage for further development of novel transformations.

Scheme 1 An early example of Heck-Catellani reaction.

In 1985, Catellani reported an improved procedure to produce the Catellani isomers (Scheme 2).⁵ Only phenyl bromide and aryl bromides bearing *ortho* groups formed Catellani isomer as major isomers. Aromatic bromides bearing substituents on other positions gave low yield and poor selectivity. Notably, the base PhOK also

played a special role. Other weaker or stronger bases such as KOAc or *t*BuOK led to multiple insertion of norbornene or multiple arylation.

Scheme 2 An improved condition for Heck-Catellani reaction.

In 1996, Catellani reported that using Pd(PPh₃)₄ catalyst and K₂CO₃ base, various aryl bromides or iodides reacted with norbornene in moderate to good yields.⁶ However, the reactivity and selectivity were still limited to aryl rings bearing *ortho* groups (Scheme 3.1). Without *ortho* groups, complex products were formed. Notably, two other bicyclic olefins can also couple (Scheme 3.2 and 3.3).

Scheme 3 The scope of olefins in Heck-Catellani reaction.

In 2011, Lautens group reported a modified procedure.⁷ Several strained olefins including norbornene, norbornadiene and benzonorbornadiene reacted well (Scheme 4.1). For aryl iodides without ortho groups, however, the reaction still showed poor selectivity (Scheme 4.2). Their mechanistic studies confirmed the key steps toward the formation of Catellani isomers (Scheme 4.1).

Scheme 4 Lautens's procedure for Heck-Catellani reaction.

The pioneering works provided a foundation for recent development of norbornene-mediated *ortho* C-H functionalization in the presence of Pd catalysts.⁸ In 1997, Catellani reported a multi-component coupling between an aryl iodide, a primary alkyl iodide and a terminal olefin such as acrylate (Scheme 5).⁹ The key step in the catalytic cycle involved S_N2-type oxidative addition of a primary alkyl halide on the Pd(II) center of the palladacycle to produce an alkylpalladium(IV) species. The involvement of Pd(IV) intermediates has gained some support from mechanistic studies.¹⁰

Scheme 5 Initial investigations on Catellani reaction.

By introducing different termination steps, Catellani, Lautens and others devised a wide array of synthetic methods.¹¹ A brief summary is listed in Scheme 6. For example, termination using insertion into acrylates and styrenes introduced olefins into products (Scheme 6.1).¹² Lautens group also developed an intramolecular variant of this sequence (Scheme 6.2).¹³ Catellani used arylboronic acids to install aryl rings as the last step (Scheme 6.3).¹⁴ Alkynes can also be used, similar to Cassar-Sonogashira reaction (Scheme 6.4).¹⁵ Intramolecular C-N bond formation can also be used for termination (Scheme 6.5).¹⁶ The last step can be aryl-CN coupling on the Pd center, as reported by Lautens *et al.* (Scheme 6.6).¹⁷ The termination step can also be C-H activation/C-C coupling of pedant indole rings to form annulated indole products in moderate yield (Scheme 6.7).¹⁸ Recently Dong group reported an *ortho*-amination of aryl iodides using benzoyloxyamine followed by a C-H bond formation using isopropanol as hydride source (Scheme 6.8).¹⁹

Scheme 6 Synthetic application of Catellani Reaction.

Although Catellani reaction has been well developed, the foundational Heck-Catellani reaction itself has not been well investigated. Up to now, only aryl halides bearing *ortho*-group showed good reactivity and selectivity. Therefore, the

development of more efficient, general method for Heck-Catellani reaction is highly desired.

2.2 Results and discussion

2.2.1 Condition optimization

Initially, we chose *p-t*-butyl phenyl bromide and norbornene as the model substrates and tried three conditions previously reported by Catellani⁵ and Lautens⁶ (Figure 1). Under the Catellani's conditions, both Catellani and Heck isomers were formed in about 1:1 ratio. Under Lautens's condition, only Catellani isomer was formed, but the yield was quite low.

a) 10 mol% Pd(PPh₃)₄, KOPh, anisole, 105 °C, 24 h (by Catellani *et al.*): 42% A and 42% B

b) Same as a) except 2,6-*t*Bu₂-4-MePhONa as base (by Catellani *et al.*): 49% A and 31% B

c) 10 mol% Pd(OAc)₂, 22% PPh₃, *n*Bu₄NOH, 1:1 toluene/water, 80 °C, 24 h (Lautens *et al.*): 31% A and 0% B

Figure 1 Comparison of three conditions applied in the model reaction.

Since the existing conditions were unsatisfactory for the model reaction, we made efforts to explore other ligands and conditions. After extensive research of catalysts and conditions, we were glad to find that the desired benzocyclobutane product was generated in 95% yield by using a simple Pd(dba)₂/*Pt*Bu₃ catalyst (entry 1). The results of ligand optimization are summarized in Table 1. Other commonly used bulky, electron-rich monophosphines such as P(1-Ad)₂*n*Bu, *Pt*Bu₂Me and PCy₃ also worked well. However, the less electron-donating monophosphines only showed poor activity. Moreover, in the presence of the diphosphines and *N*-heterocyclic carbenes such as IPr and IMes, almost no desired product was formed and the reduction of *p-t*-butyl phenyl bromide was the major side reaction. Notably, when we tried a palladium complex Pd(*t*Bu₃P)₂ as catalyst, the reaction also performed well.

Table 1 The effect of ligands in model Heck-Catellani reaction.

Entry	Ligand	Conv (%) ^a	Catellani isomer (%) ^b	Heck isomer (%) ^b	Reductive byproduct (%) ^b
1	<i>t</i>Bu₃P•HBF₄	100	95	1	1
2	P(Ad) ₂ <i>n</i> Bu	100	94	1	3
3	P(Ad) ₂ Bn	62	24	12	6
4	<i>Pt</i> Bu ₂ Me	100	90	5	3
5	PCy ₃	100	81	5	12
6	PPh ₃	100	25	6	4
7	P(<i>o</i> -Tol) ₃	100	5	3	2
8	P(2-furyl) ₃	89	4	1	2
9	DavePhos	100	32	1	30
10	<i>t</i> Bu-XPhos	92	12	3	25
11	XPhos	100	36	1	4
12	SPhos	100	46	1	8
13	QPhos	100	60	0	3
14	P(NMe ₂) ₃	87	23	1	35
15	P(OEt) ₃	86	0	0	52
16	Dppp (8%)	54	0	0	37
17	Dppf (8%)	100	10	2	30
18	Dppe (8%)	10	0	0	0
19	SIPr•HCl	100	0	0	54
20	IMes•HCl	100	0	0	62
21	Pd(<i>Pt</i> Bu ₃) ₂	100	95	1	2

^a conversion was determined by GC. ^b GC yield.

The choice of base also had a significant effect on the reactivity. As shown in Table 2, among several common bases, NaOPh was the best and offered the desired product in 95% yield (entry 6). Other inorganic bases such as K₃PO₄, KOPh, LiO*t*Bu and CsF afforded moderate yield (entries 5, 7, 8, 11). When other inorganic bases and alkylamines were used as bases, almost no desired Catellani isomer was observed (entries 1-4, 9-10 and 12-17).

Table 2 The effect of bases in model Heck-Catellani reaction.

Entry	Base	Conv (%) ^a	Catellani isomer (%) ^b	Heck isomer (%) ^b	Reductive byproduct (%) ^b
1	Li ₂ CO ₃	10	0	0	0
2	Na ₂ CO ₃	10	0	0	0
3	K ₂ CO ₃	49	27	1	1
4	Cs ₂ CO ₃	73	23	1	19
5	K ₃ PO ₄	100	80	15	1
6	NaOPh	100	95	1	1
7	KOPh	100	74	11	2
8	LiOtBu	100	70	1	4
9	KOtBu	100	5	0	21
10	NaOH	96	23	2	11
11	CsF	85	63	5	1
12	Et ₃ N	21	1	1	5
13	DIPEA	10	0	0	0
14	<i>n</i> Bu ₂ NMe	54	2	1	48
15	BnNHMe	10	0	0	0
16	Urotropine	10	0	0	0
17	Proton sponge	35	0	0	20

^a conversion was determined by GC. ^b GC yield.

When we investigated the effect of solvents, the reaction in many amide and ethereal solvents generated the product in moderate to excellent yield (entries 1-6, Table 3). DMF was the best solvent (entry 2). However, in various aromatic solvents such as veratrole, anisole, toluene and PhCF₃, the Catellani isomer was only a minor isomer and the major byproduct was the Heck isomer (entries 7-10). The Heck isomer is probably formed via external base-assisted deprotonation of the benzylic C-H bond of the Pd-alkyl intermediate.

Table 3 The effect of solvents in model Heck-Catellani reaction.

Entry	Solvent	Conv (%) ^a	Catellani isomer (%) ^b	Heck isomer (%) ^b	Reductive byproduct (%) ^b
1	DMA	100	76	1	8
2	DMF	100	95	1	1
3	DMPU	100	54	1	3
4	NMP	100	50	1	43
5	1,4-Dioxane	100	72	7	20
6	2-MeTHF	100	83	7	6
7	1,2-(MeO) ₂ C ₆ H ₄	100	37	21	3
8	PhOMe	100	4	92	2
9	Toluene	100	13	79	2
10	PhCF ₃	100	6	78	2

^a conversion was determined by GC. ^b GC yield.

With regard to the choice of palladium source, several Pd(0) and Pd(II) precursors were screened. The results are listed in Table 4. All the palladium sources showed good catalytic activities. Therefore we used common Pd(dba)₂ in further studies.

Table 4 The effect of Palladium sources in model Heck-Catellani reaction.

Entry	Pd source	Conversion ^a	Catellani isomer (%) ^b	Heck isomer (%) ^b	Reductive byproduct (%) ^b
1	Pd ₂ (dba) ₃	100	93	1	2
2	Pd(dba)₂	100	95	1	1
3	Pd(OAc) ₂	100	93	1	2
4	Pd(OCOCF ₃) ₂	100	87	1	2
5	Pd(hfacac) ₂	100	93	1	1
6	Pd(acac) ₂	100	93	1	2
7	PdCl ₂	100	92	1	2

^a conversion was determined by GC. ^b GC yield.

2.2.2 Scope of substrates

Using the optimized conditions, we next tested structurally diverse aromatic halides. Aryl bromides bearing electron-donating and electron-withdrawing groups at the *para* position afforded the corresponding adducts in excellent yields (Figure 2.1). Notably, in the case of the methyl *para*-bromobenzoate, the yield of desired product was increased from less than 10% to 93% by changing the solvent and base to 1,2-dimethoxybenzene and Cs₂CO₃. As expected, aromatic bromides carrying *ortho* substitutions performed well under our catalytic condition (Figure 2.2). In the reaction of 1-naphthyl bromide, the CH activation occurred selectively at the C2 position (Figure 2.3). In the case of 2-naphthyl bromide, the CH bond cleavage happened at the less hindered C3 position, instead of the more hindered C1 site (Figure 2.4). Moreover, our approach can be applied to the heteroaryl bromides. 5-Bromoindole gave the corresponding benzocyclobutene in 76% yield (Figure 2.6). Gratifyingly, the new procedure also performed well with several aryl iodides and chlorides (Figure 2.7 and 2.8).

Figure 2 The scope of (hetero)aryl halides in Heck-Catellani reaction.

Next, we paid our effort to explore other strained bicyclic olefins. As shown in

Figure 3, two oxa-substituted norbornene derivatives reacted well with *p*-*t*-butyl phenyl bromide in good yield (Figure 3.1). Moreover, two benzonorbornadiene derivatives also coupled well (Figure 3.2). In the reaction of the norbornadiene, by simply changing the solvent and base to prevent the formation of Heck isomers, the corresponding Catellani isomer was generated in 88% yield (Figure 3.3). Notably, we also applied the cyclopentadiene dimer in the coupling with *p*-*t*-butyl phenyl bromide and the desired compounds were formed in 1:1 diastereoselectivity (Figure 3.4).

Figure 3 The scope of strained olefins in Heck-Catellani reaction.

Interestingly, in the coupling between 1,4-dibromobenzene and excess norbornene, the doubly cyclized products were formed in a 2:1 diastereoselectivity due to relative orientation of two bridging methylene units in two norbornanes (Figure 4.1). In order to obtain the high yield, LiOtBu base and tetrahydropyran solvent were used. Similarly, the reaction of 1,3-dibromobenzene also generated two isomers in 2:1 selectivity (Figure 4.2). However, 1,2-dibromobenzene gave the same product as phenyl bromide due to the reduction of the second C-Br bond. In addition, 4,4'-dibromo-1,1'-biphenyl also worked well to afford the dicyclobutane adduct in excellent yield (Figure 4.3). Notably, the MOM-protected (S)-6,6'-dibromo-BINOL

also successfully produced the dicyclobutane derivative in 94% yield and 1:1 selectivity (Figure 4.4). After acidic hydrolysis, the (*S*)-BINOL derivative was generated in excellent yield, which provided an opportunity for ligand modification of BINOL.

Figure 4 Double CH activation/cyclization using aryl dibromides.

2.2.3 Mechanistic study

In order to understand the beneficial role of the bulky ligand *Pt*Bu₃, we conducted some mechanistic studies. Initially, the norbornene-derived palladacycle was prepared in 88% yield from the reaction of Pd(PPh₃)₄, PhI and norbornene (Figure 5.1). Next, the palladacycle was heated in DMF at 80 °C with or without additional ligands. As shown in Figure 5.2, we found added PPh₃ slowed down the reductive elimination process. Thus, the palladacycle first dissociates one PPh₃ ligand to form the three-coordinated complex, which is the active species for reductive elimination. However, by adding a bulky ligand *t*Bu₃P, the C-C reductive elimination was accelerated significantly via a T-shaped palladacycle bearing one *t*Bu₃P ligand.²⁰ Besides, a similar observation was made in the presence of another bulky ligand PCy₃. So the bulky ligand *Pt*Bu₃ promoted the reductive elimination and therefore out-competed other side reactions such as multiple arylation or multiple norbornene insertion.

added ligand	0.5 h	1 h
none	28	34
PPh ₃ (5 equiv)	20	25
PtBu ₃ (2 equiv)	78	84
PCy ₃ (2 equiv)	67	73

Figure 5 Stoichiometric reductive elimination.

2.2.4 Unsuccessful examples in the Heck-Catellani reaction

In the reaction with norbornene, several heteroaryl bromides such as 2-bromothiophene, 2- or 3-bromopyridine and 3-bromobenzothiophene, showed no reactivity. The same situation also happened to some *di*- or *tri*-bromo(hetero)arenes which included 2,6-dibromopyridine, 3,4-dibromothiophene, 1,3-dibromoazulene and 1,3,5-tribromobenzene (Figure 6.1). Other strained alkenes did not give desired products due to basic hydrolysis or N-N bond cleavage (Figure 6.2). In the case of aryl iodides, *p*-*t*-butylphenyl iodide and *p*-methoxyphenyl iodide only generated the corresponding product in about 10 to 20% yield (Figure 6.3). The major side reaction is the fast reductive reaction of aryl iodide to form the corresponding arene. 2,3-Dihydro-1,4-dioxine, in the reaction of ethyl 3-bromobenzoate, only gave a trace amount of product (Figure 6.4).

No reactivity in the reaction with norbornene

Figure 6 Unsuccessful examples in Heck-Catellani reaction.

2.3 Conclusion

In summary, we have developed a general protocol to selectively generate Catellani isomers from aryl bromides and norbornene and related bicyclic olefins. Using the bulky $PtBu_3$ ligand, various (hetero)aryl bromides and chlorides bearing no *ortho* substitution can be coupled efficiently with norbornene. Moreover, other bicyclic alkenes can also undergo this type of transformation to form strained rings. Previously, the Catellani isomers were only formed from phenyl bromide and phenyl halides bearing *ortho*-groups.

2.4 Experiment section

2.4.1 General

^1H NMR spectra were acquired on Bruker 400 MHz or 300 MHz spectrometers and chemical shifts were recorded relative to tetramethylsilane (δ 0.00) or residual protiated solvent (CDCl_3 : δ 7.26). 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 at 100 MHz on 400 MHz or 75 MHz on 300 MHz instruments and chemical shifts were recorded relative to solvent resonance (CDCl_3 : δ 77.16). Proof of purity of new compounds was demonstrated with copies of ^1H , ^{13}C , ^{31}P and ^{19}F NMR spectra.

Glassware was dried in an oven at 120 °C for at least 2 hours before use. Dry veratrole (Alfa) was degassed by argon bubbling and stored over activated 4 Å molecular sieve beads in an argon-filled glove box before use. Dry hexane, diethyl ether and dichloromethane 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 an argon-filled glove box.

Unless noted otherwise, commercially available chemicals were used without further purification. Dry diisopropylethylamine (DIPEA) and triethylamine were distilled from CaH_2 under argon before use. The GC standard, *n*-dodecane was degassed with argon bubbling and dried over activated 4 Å molecular sieve beads for a few days in the glove box 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 (0.040-0.063 mm).

Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument 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.

2.4.2 Procedure for condition optimization

Typical procedure for optimization: In an argon-filled glove box, a dry 4-mL reaction tube containing a magnetic stirbar was charged with $\text{Pd}(\text{dba})_2$ (4 mol%, 2.3 mg, 0.004 mmol), $\text{PtBu}_3 \text{HBF}_4$ (8 mol%, 2.3 mg, 0.008 mmol) and dry DMF (0.2 mL). After stirring at RT for 10 minutes, *p*-*t*-butylphenyl bromide (0.10 mmol, 21 mg), NaOPh (0.20 mmol, 23 mg), norbornene (2 equiv, 0.20 mmol, 19 mg), and GC standard 1-dodecane (10 μL) were added sequentially via syringe. The tube was capped tightly and the mixture was vigorously stirred in pre-warmed 120 °C oil bath. After 6 hours and 24 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 filtrate was subjected to GC analysis to determine the conversion of aryl bromide and yield of the products.

2.4.3 Procedure for Product isolation of Heck-Catellani Reaction of aryl halides.

Typical procedure for isolation: In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stirbar was charged with Pd(dba)₂ (11.5 mg, 0.02 mmol), PtBu₃·HBF₄ (11.5 mg, 0.03 mmol) and dry DMF (1.0 mL). After stirring at RT for 10 minutes, aryl bromide (0.5 mmol), norbornene (2 equiv, 1.0 mmol), and NaOPh (1.0 mmol, 116 mg) were added sequentially. The Schlenk tube was capped tightly and the mixture was heated with vigorous stirring in 120 °C oil bath. After the aryl bromide was fully consumed (monitored by GC), the reaction mixture was passed through a pad of silica gel with diethyl ether washings to remove DMF, inorganic salts and Pd catalyst first. Then the filtrate was concentrated on a rotary evaporator and the resulting residue was directly subjected to silica gel flash chromatography. The structure of the desired product was confirmed by ¹H NMR spectroscopy of the purified sample. The typical procedure using 0.5 mmol of organic bromides was used for all the isolation, unless stated otherwise. Similar results were obtained when Schlenk tubes and a vacuum manifold were used instead to set up the experiments.

exo-6-(*t*-Butyl)-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (hexanes) as colorless oil (106 mg, 94%).

¹H NMR (400 MHz, CDCl₃): δ 7.23 (d, *J* = 7.7 Hz, 1H), 7.04 (s, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 3.13-3.12 (m, 2H), 2.25-2.24 (m, 2H), 1.58 (ψd, *J* = 8.3 Hz, 2H), 1.30 (s, 9H), 1.17-1.15 (m, 2H), 0.94 (d, *J* = 10.1 Hz, 1H), 0.86 (d, *J* = 10.1 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 150.4, 146.2, 143.4, 124.2, 121.3, 118.8, 50.3, 50.0, 36.7, 36.6, 35.0, 32.1, 31.8, 27.9 (2 overlapping signals).

GCMS (EI): Calcd for C₁₇H₂₂: 226.1. Found: 226.1.

***exo*-6-Methoxy-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene [104030-40-2].** The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as colorless oil (94 mg, 94%).

¹H NMR (400 MHz, CDCl₃): δ 6.89 (d, *J* = 8.0 Hz, 1H), 6.74 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.60 (d, *J* = 2.1 Hz, 1H), 3.77 (s, 3H), 3.11-3.09 (m, 2H), 2.23-2.22 (m, 2H), 1.58 (d, *J* = 6.9 Hz, 2H), 1.17-1.15 (m, 2H), 0.95 (d, *J* = 10.1 Hz, 1H), 0.86 (d, *J* = 10.1 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 159.6, 147.3, 138.3, 122.9, 113.6, 107.7, 55.4, 49.7, 49.5, 36.8, 36.5, 31.9, 27.9, 27.8.

GCMS (EI): Calcd for C₁₄H₁₆O: 200.0. Found: 200.0.

***exo*-6-Methoxycarbonyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene.** The reaction was set up with 2.0 equiv of Cs₂CO₃ and 2.5 mL of dry veratrole. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow solid (106 mg, 93%). When NaOPh and dry DMF were used instead, only 6% yield of desired product was obtained.

¹H NMR (400 MHz, CDCl₃): δ 7.94 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.66 (dd, *J* = 1.4, 0.8 Hz, 1H), 7.04 (dd, *J* = 7.7, 0.8 Hz, 1H), 3.88 (s, 3H), 3.20 (ψs, 2H), 2.29 (ψs, 2H), 1.62-1.58 (m, 2H), 1.22-1.16 (m, 2H), 0.97 (d, *J* = 10.4 Hz, 1H), 0.81 (d, *J* = 10.4 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 167.7, 152.3, 146.5, 129.4, 129.3, 123.1, 121.8, 51.9, 50.6, 50.1, 36.6 (2 overlapping signals), 31.9, 27.8, 27.7.

GCMS (EI): Calcd for C₁₅H₁₆O₂: 228.1. Found: 228.1.

***exo*-1,2,3,4,4a,8b-Hexahydro-1,4-methanobiphenylene [100568-89-6].** The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (hexanes) as colorless oil (77 mg, 90%), which contained about 5% of a byproduct derived from insertion of two nbe molecules (by GC and GCMS).

¹H NMR (400 MHz, CDCl₃): δ 7.20-7.16 (m, 2H), 7.02-6.96 (m, 2H), 3.18 (s, 2H), 2.26 (s, 2H), 1.63-1.55 (m, 2H), 1.21-1.14 (m, 2H), 0.96 (d, *J* = 10.2 Hz, 1H), 0.85 (d, *J* = 10.2 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 146.6, 127.1, 121.9, 50.5, 36.6, 31.9, 27.8.

GCMS (EI): Calcd for C₁₃H₁₄: 170.1. Found: 170.1.

exo-6b,7,8,9,10,10a-Hexahydro-7,10-methanobenzo[a]biphenylene [105381-78-0]. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (hexanes) as colorless oil (96 mg, 88%), which contained about 5% of impurity derived from the coupling of ArBr and two nbe molecules (by GC).

¹H NMR (400 MHz, CDCl₃): δ 7.83 (d, *J* = 8.1 Hz, 1H), 7.73-7.70 (m, 2H), 7.47-7.37 (m, 2H), 7.18 (d, *J* = 8.1 Hz, 1H), 3.42 (d, *J* = 3.4 Hz, 1H), 3.27 (d, *J* = 3.5 Hz, 1H), 2.42-2.41 (m, 1H), 2.29-2.28 (m, 1H), 1.69-1.60 (m, 2H), 1.30-1.22 (m, 2H), 0.93 (d, *J* = 10.3 Hz, 1H), 0.74 (d, *J* = 10.3 Hz, 1H).

GCMS (EI): Calcd for C₁₇H₁₆: 220.1. Found: 220.1.

exo-1,2,3,4,4a,10b-Hexahydro-1,4-methanobenzo[b]biphenylene [69583-85-3]. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (hexanes) as white solid (100 mg, 91%).

¹H NMR (400 MHz, CDCl₃): δ 7.79-7.77 (m, 2H), 7.40-7.36 (m, 4H), 3.35 (s, 2H), 2.39 (s, 2H), 1.65-1.60 (m, 2H), 1.28-1.19 (m, 2H), 1.01-0.94 (m, 2H).

GCMS (EI): Calcd for C₁₇H₁₆: 220.1. Found: 220.1.

exo-8c,9,10,11,12,12a-Hexahydro-9,12-methanobenzo[3,4]cyclobuta[1,2]phenathrene [105381-81-5]. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (hexanes) as white solid (120 mg, 89%). The reaction also gave about 10% of the Heck isomer.

^1H NMR (400 MHz, CDCl_3): δ 8.75-8.71 (m, 2H), 7.81-7.78 (m, 2H), 7.62-7.57 (m, 4H), 3.48 (s, 2H), 2.44 (s, 2H), 1.73-1.68 (m, 2H), 1.37-1.31 (m, 2H), 0.98 (d, $J = 10.4$ Hz, 1H), 0.84 (d, $J = 10.4$ Hz, 1H).

GCMS (EI): Calcd for $\text{C}_{21}\text{H}_{18}$: 270.1. Found: 270.1.

***exo*-5-Methyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene** [231609-44-2]. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (hexanes) as colorless oil (84 mg, 92%).

^1H NMR (400 MHz, CDCl_3): δ 7.09 (ψt , $J = 7.5$ Hz, 1H), 6.96 (d, $J = 7.8$ Hz, 1H), 6.80 (d, $J = 7.2$ Hz, 1H), 3.13 (ψq , $J = 3.8$ Hz, 2H), 2.28-2.25 (m, 2H), 2.17 (s, 3H), 1.61-1.56 (m, 2H), 1.18-1.16 (m, 2H), 0.95 (d, $J = 10.1$ Hz, 1H), 0.84 (d, $J = 10.1$ Hz, 1H).

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{16}$: 184.1. Found: 184.1.

***exo*-5-Methoxy-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene**[104030-39-9]. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as colorless oil (82 mg, 82%).

^1H NMR (400 MHz, CDCl_3): δ 7.12 (ψt , $J = 7.5$ Hz, 1H), 6.67 (d, $J = 8.4$ Hz, 1H), 6.60 (d, $J = 7.1$ Hz, 1H), 3.88 (s, 3H), 3.30 (d, $J = 3.8$ Hz, 1H), 3.15 (d, $J = 3.8$ Hz, 1H), 2.31 (s, 1H), 2.26 (s, 1H), 1.62-1.59 (m, 2H), 1.26-1.16 (m, 2H), 1.00 (ψs , 2H).

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{16}\text{O}$: 200.1. Found: 200.1.

5-Fluoro-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene [180347-57-3]. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as colorless oil (68 mg, 73%).

^1H NMR (400 MHz, CDCl_3): δ 7.20-7.15 (m, 1H), 6.86-6.78 (m, 2H), 3.25 (s, 1H), 3.19-3.18 (m, 1H), 2.38 (s, 1H), 2.27 (s, 1H), 1.62-1.58 (m, 2H), 1.20-1.18 (m, 2H), 1.01 (d, $J = 10.4$ Hz, 1H), 0.89 (d, $J = 10.4$ Hz, 1H).

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{13}\text{F}$: 188.1. Found: 188.1.

1-Methyl-4b,5,6,7,8,8a-hexahydro-1H-5,8-methanobenzo[3,4]cyclobuta[1,2-f]indole. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as colorless oil (85 mg, 76%). The reaction also gave about 10% of the Heck isomer.

^1H NMR (400 MHz, CDCl_3): δ 7.21 (d, $J = 1.2$ Hz, 1H), 6.97-6.94 (m, 2H), 6.44-6.43 (m, 1H), 3.75 (s, 3H), 3.20 (vs, 2H), 2.29-2.28 (m, 2H), 1.62-1.57 (m, 2H), 1.23-1.18 (m, 2H), 0.90 (vs, $J = 10.4$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 140.7, 137.8, 136.7, 128.2, 127.1, 113.7, 102.7, 101.0, 49.2, 49.1, 37.5, 37.4, 33.0, 32.1, 28.0, 27.9.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{17}\text{N}$: 223.1. Found: 223.1.

exo,exo-1,2,3,4,4a,5b,6,7,8,9,9a,10b-Dodecahydro-1,4,6,9-dimethanobenzo[3,4]cyclobuta[1,2-b]biphenylene. The reaction was set up with 1.0 equiv of 1,4-dibromobenzene, 6.0 equiv of norbornene, 4.0 equiv of LiOtBu and 2.5 mL of dry THP. The reaction mixture was stirred at 100 °C for 24 hours. The product was purified by flash chromatography (hexanes) as white solid (125 mg, 95%, *dr* 2:1). When NaOPh and dry DMF were used instead, only 16% yield of the desired product was obtained.

^1H NMR of two isomers (400 MHz, CDCl_3): δ 6.64 (s, 1H), 6.63 (s, 0.5H), 3.07 (vs, 4H), 2.22-2.20 (m, 4H), 1.59-1.53 (m, 4H), 1.17-1.12 (m, 4H), 0.93-0.78 (m, 4H).

^{13}C NMR of two isomers (100 MHz, CDCl_3): δ 145.0, 144.9, 116.0, 115.8, 50.1, 50.0, 36.9, 36.8, 31.8, 27.9, 27.8.

GCMS (EI): Calcd for $\text{C}_{20}\text{H}_{22}$: 262.1. Found: 262.1.

***exo, exo*-1,2,3,4,4a,5b,6,7,8,9,9a,10b-Dodecahydro-1,4,6,9-dimethanobenzo[3,4]cyclobuta [1,2-*b*]biphenylene.** The reaction was set up with 1.0 equiv of 1,3-dibromobenzene, 6.0 equiv of norbornene, 4.0 equiv of LiOtBu and 2.5 mL of dry THP. The reaction mixture was stirred at 100 °C for 24 hours. The product was purified by flash chromatography (hexanes) as white solid (122 mg, 93%, *dr* 2:1). When NaOPh and dry DMF were used, only 14% yield of desired product was obtained.

***exo, exo*-2,2',3,3',4,4',5,5',12,12',13,13'-Dodecahydro-1H,1'H-8,8'-bi(1,4-methanobiphenylene).** The reaction was set up with 1.0 equiv of 4,4'-dibromo-1,1'-biphenyl, 6.0 equiv of norbornene, 4.0 equiv of *t*BuOLi and 2.5 mL of dry THP. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (hexanes) as white solid (162 mg, 96%, *dr* ~1:1). When NaOPh and dry DMF were used instead, only 27% yield of desired product was obtained.

¹H NMR of two isomers (400 MHz, CDCl₃): δ 7.37 (d, *J* = 7.6 Hz, 2H), 7.16 (s, 2H), 7.02 (d, *J* = 7.6 Hz, 2H), 3.20 (s, 4H), 2.28 (s, 4H), 1.62-1.58 (m, 4H), 1.22-1.28 (m, 4H), 0.99-0.92 (m, 4H).

¹³C NMR of two isomers (100 MHz, CDCl₃): δ 146.9, 145.2, 141.9, 141.8, 126.7, 126.6, 122.0, 121.0, 50.2, 50.1, 36.7, 36.6, 32.0, 27.9.

GCMS (EI): Calcd for C₂₆H₂₆: 338.2. Found: 338.2.

8-(*tert*-Butyl)-3,3-dimethyl-1,5,5a,6,6a,10b,11,11a-octahydro-6,11-methanobiphenylene [2,3-*e*][1,3]dioxepine. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as colorless oil (130 mg, 80%).

¹H NMR (400 MHz, CDCl₃): δ 7.25-7.23 (m, 1H), 7.00 (s, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 4.09-4.04 (m, 2H), 3.79-3.75 (m, 2H), 3.54 (s, 2H), 2.43 (d, *J* = 4.6 Hz, 2H), 2.31 (s, 2H), 1.45 (s, 3H), 1.40 (s, 3H), 1.29 (s, 9H), 1.17 (d, *J* = 10.4 Hz, 1H), 1.05 (d, *J* = 10.4 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 150.8, 145.2, 142.4, 124.4, 121.1, 118.6, 101.1, 62.2, 44.3, 44.0, 42.9, 42.8, 40.8, 40.7, 35.0, 34.9, 31.7.

GCMS (EI): Calcd for C₂₂H₃₀O₂: 326.2. Found: 326.2.

8-(*tert*-Butyl)-3,3-dimethyl-1,5,5a,6,6a,10b,11,11a-octahydro-6,11-epoxybiphenyleno[2,3-e][1,3]dioxepine. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (1:8 EA/hexanes) as white solid (144 mg, 88%).

^1H NMR (400 MHz, CDCl_3): δ 7.27 (dd, $J = 1.6, 7.8$ Hz, 1H), 7.07 (s, 1H), 6.95 (d, $J = 7.8$ Hz, 1H), 4.12 (ψ d, $J = 7.0$ Hz, 2H), 3.93-3.80 (m, 4H), 3.49-3.47 (m, 2H), 2.27-2.21 (m, 2H), 1.40 (s, 3H), 1.37 (s, 3H), 1.28 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3): δ 151.1, 143.7, 140.9, 125.1, 121.4, 118.8, 101.3, 78.8, 78.7, 64.0, 50.8, 50.5, 47.8, 47.7, 35.1, 31.6, 28.5, 20.6.

GCMS (EI): Calcd for $\text{C}_{21}\text{H}_{28}\text{O}_3$: 328.2. Found: 328.2.

2-(*tert*-Butyl)-4b,5,10,10a-tetrahydro-5,10-epoxybenzo[*b*]biphenylene. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (108 mg, 78%).

^1H NMR (400 MHz, CDCl_3): δ 7.35-7.33 (m, 3H), 7.24-7.19 (m, 3H), 7.13-7.11 (m, 1H), 5.28 (ψ d, $J = 3.0$ Hz, 2H), 3.47-3.44 (m, 2H), 1.33 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3): δ 151.2, 145.0, 143.1, 140.3, 126.7, 125.2, 121.5, 119.8, 119.7, 119.1, 78.6 (2 overlapping signals), 49.5, 49.2, 35.2, 31.7.

GCMS (EI): Calcd for $\text{C}_{20}\text{H}_{20}\text{O}$: 276.1. Found: 276.1.

2-(*tert*-Butyl)-4b,5,10,10a-tetrahydro-5,10-methanobenzo[*b*]biphenylene. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (hexanes) as yellow oil (125 mg, 91%).

^1H NMR (400 MHz, CDCl_3): δ 7.30 (dd, $J = 1.5, 7.8$ Hz, 1H), 7.27-7.24 (m, 2H), 7.17 (s, 1H), 7.12-7.09 (m, 2H), 7.05 (d, $J = 7.8$ Hz, 1H), 3.30-3.25 (m, 4H), 1.65 (d, $J = 9.6$ Hz, 1H), 1.33 (s, 9H), 1.29 (d, $J = 9.6$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 151.0, 147.9, 147.8, 144.7, 142.0, 125.6, 124.6, 121.5, 121.4, 119.0, 49.2, 49.0, 43.8, 43.7, 42.4, 35.1, 31.7.

GCMS (EI): Calcd for $\text{C}_{21}\text{H}_{22}$: 274.1. Found: 274.1.

3a,4,4a,8b,9,9a-Hexahydro-1H-4,9-methanocyclopenta[b]biphenylene [105381-84-8]. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (hexanes) as colorless oil (96 mg, 92%), which contained about 5% of an inseparable impurity (by GC).

^1H NMR (400 MHz, CDCl_3): δ 7.19-7.13 (m, 2H), 6.97-6.91 (m, 2H), 5.69-5.60 (m, 2H), 3.32 (d, J = 3.8 Hz, 1H), 3.22-3.13 (m, 2H), 2.71-2.62 (m, 1H), 2.39-2.23 (m, 4H), 1.19 (d, J = 10.1 Hz, 1H), 1.00 (d, J = 10.1 Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 146.9, 146.2, 131.3, 131.1, 127.1 (2 overlapping signals), 121.8, 121.6, 52.2, 46.9, 44.0, 41.3, 40.8, 38.9, 35.5, 31.4.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{16}$: 208.1. Found: 208.1

7-(tert-Butyl)-3a,4,4a,8b,9,9a-Hexahydro-1H-4,9-methanocyclopenta[b]biphenylene.

The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (hexanes) as colorless oil (124 mg, 94%) as a 1:1 mixture of two isomers depending on the relative positioning of the olefin and *t*-butyl group.

^1H NMR of two isomers (400 MHz, CDCl_3): δ 7.21 (dd, J = 1.2, 7.7 Hz, 1H), 6.99 (s, 1H), 6.87 (d, J = 7.7 Hz, 1H), 5.67-5.65 (m, 1H), 5.61-5.60 (m, 1H), 3.29-3.26 (m, 1H), 3.19-3.13 (m, 2H), 2.70-2.62 (m, 1H), 2.38-2.35 (m, 1H), 2.32-2.27 (m, 2H), 2.23-2.21 (m, 1H), 1.29 (s, 9H), 1.18 (d, J = 10.1 Hz, 1H), 1.00 (d, J = 10.1 Hz, 1H).

^{13}C NMR of two isomers (100 MHz, CDCl_3): δ 150.3, 146.4, 145.8, 143.7, 143.0, 131.4, 131.3, 131.1, 131.0, 124.1, 121.3, 121.0, 118.8, 118.5, 52.3, 52.2, 46.6, 46.3, 43.8, 43.4, 41.3, 40.9, 40.8, 39.0, 38.9, 35.6, 35.0, 31.8, 31.5. Some overlapped signals are not indicated.

GCMS (EI): Calcd for $\text{C}_{20}\text{H}_{24}$: 264.2. Found: 264.2

6-(*t*-Butyl)-1,4,4a,8b-tetrahydro-1,4-methanobiphenylene. The reaction was set up with 4.0 equiv of norbornadiene, 2.0 equiv of Cs₂CO₃ and 1.0 mL of dry DMPU. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (hexanes) as colorless oil (99 mg, 88%). When NaOPh and dry DMF were used, a 1:2 mixture of both Catellani and Heck isomers was obtained in 82% combined yield.

¹H NMR (400 MHz, CDCl₃): δ 7.24 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.12 (s, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.21 (ψt, *J* = 1.6 Hz, 2H), 3.12-3.09 (m, 2H), 2.78-2.76 (m, 2H), 1.31 (s, 9H), 1.27 (d, *J* = 9.0 Hz, 1H), 0.88 (d, *J* = 9.0 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 150.4, 145.7, 142.9, 136.7, 136.6, 124.0, 121.2, 118.8, 47.3, 47.0, 41.6, 41.5, 41.4, 35.0, 31.7.

GCMS (EI): Calcd for C₁₇H₂₀: 224.1. Found: 224.1

(1*R*,1'*R*,4*S*,4'*S*,5*R*,5'*R*,9'*S*,16*S*,16'*S*)-10,10'-Bis(methoxymethoxy)-2,2',3,3',4,4',5,5',16,16',

17,17'-dodecahydro-1*H*,1'*H*-9,9'-bi(1,4-methanobenzo[*b*]biphenylene). The reaction was set up with 4 equiv of nornornene, 4.0 equiv of LiOtBu and 2.5 mL of dry THP. The reaction mixture was stirred at 120 °C for 24 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as white solid (262 mg, 94%). Chiral HPLC analysis (Chiralpak IC column; 5% *i*PrOH in hexanes; flow rate 0.5 mL) of the purified sample showed a 1:1 mixture of 2 isomers.

¹H NMR of two isomers (400 MHz, CDCl₃): δ 7.88-7.85 (m, 2H), 7.46-7.40 (m, 4H), 6.80-6.68 (m, 2H), 5.16-5.13 (m, 1H), 5.03-4.98 (m, 1H), 4.93-4.87 (m, 2H), 3.30-3.27 (m, 2H), 3.17-3.10 (m, 8H), 2.35 (s, 2H), 2.13 (s, 2H), 1.60-1.46 (m, 4H), 1.21-1.10 (m, 4H), 0.90 (s, 4H).

¹³C NMR of two isomers (100 MHz, CDCl₃): δ 151.8, 151.6, 151.4, 151.3, 146.2, 146.1, 146.0, 143.7, 143.6, 134.7, 130.6, 130.5, 130.4, 130.3, 129.2, 122.8, 122.5, 122.3, 121.9, 119.7, 119.5, 117.9, 117.7, 117.6, 117.5, 116.1, 115.3, 114.9, 95.6, 95.4, 94.8, 94.5, 55.8, 55.79, 55.76, 55.72, 50.5, 50.4, 50.3, 50.2, 50.1, 37.7, 37.5, 37.4, 37.3, 32.4, 32.3, 27.9, 27.8, 27.7. Overlapping signals are not indicated.

(1R,1'R,4S,4'S,5R,5'R,9'S,16S,16'S)-2,2',3,3',4,4',5,5',16,16',17,17'-dodecahydro-1H,1'H-[9,9'-bi(1,4-methanobenzo[b]biphenylene)]-10,10'-diol. Under argon, to a solution of the MOM-protected BINOL derivative (167 mg, 0.3 mmol) in methanol (15 mL) and THF (15 mL) was added conc. HCl (2 mL). After stirring at RT for 4 h, saturated aqueous NaHCO₃ (8 mL) was added to quench the reaction. The organic phase was separated and the aqueous phase was further extracted with EA (50 mL). The combined organic phases were washed with water (50 mL) and brine and then dried over Na₂SO₄. After evaporation under partial vacuum, the residue was purified by column chromatography on silica gel using EA/Hexane (1:10) as the eluent to give the desired product as white solid (130 mg, 92%). Chiral HPLC analysis of the purified sample (Chiralpak IC column; 5% *i*PrOH in hexanes; flow rate 0.5 mL) showed a 1:1 mixture of two isomers.

¹H NMR of 2 isomers (400 MHz, CDCl₃): δ 7.88-7.85 (m, 2H), 7.44-7.42 (m, 2H), 7.27-7.24 (m, 2H), 6.74 (d, *J* = 28.7 Hz, 1H), 6.64 (s, 1H), 4.98 (s, 1H), 4.89 (d, *J* = 35.8 Hz, 1H), 3.29-3.26 (m, 2H), 3.18-3.10 (m, 2H), 2.36-2.35 (m, 2H), 2.25-2.15 (m, 2H), 1.61-1.49 (m, 4H), 1.21-1.08 (m, 4H), 0.97-0.90 (m, 4H).

¹³C NMR of 2 isomers (100 MHz, CDCl₃): δ 151.8, 151.7, 151.6, 147.6, 147.5, 143.7, 134.2, 134.0, 133.9, 131.4, 131.3, 129.9, 120.4, 120.3, 116.5, 116.3, 116.1, 115.9, 112.0, 111.9, 50.5, 50.3, 50.2, 50.1, 37.6, 37.5, 37.4, 37.3, 32.4, 32.3, 27.8, 27.7, overlapping signals are not indicated.

Typical procedure for isolation: In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with Pd(dba)₂ (11.5 mg, 0.02 mmol), PtBu₃·HBF₄ (11.5 mg, 0.03 mmol) and dry DMF (1.0 mL). After stirring at RT for 10 minutes, aryl chloride or iodide (0.5 mmol), norbornene (2 equiv, 1.0 mmol, 95 mg), and NaOPh (1.0 mmol, 116 mg) were added sequentially. The Schlenk tube was capped tightly and the mixture was heated with vigorous stirring in a 120 °C oil bath. After aryl halide was fully consumed (monitored by GC), the reaction mixture was passed through a pad of silica gel with diethyl ether washings to remove DMF, inorganic salts and Pd catalyst. Then the filtrate was concentrated on a rotary evaporator and the resulting residue was directly subjected to silica gel flash chromatography. The structure of the desired product was confirmed by ¹H NMR

spectroscopy of the purified sample. The typical procedure using 0.5 mmol of ArX was used for all the isolation, unless stated otherwise.

1,2,3,4,4a,8b-Hexahydro-1,4-methanobiphenylene[100568-89-6]. The reaction was set up with 1.0 equiv of PhCl and stirred at 120 °C for 24 hours. The product was purified by flash chromatography (hexanes) as colorless oil (68 mg, 80%).

6-Methoxy-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene [104030-40-2]. The reaction was set up with 1.0 equiv of *p*-MeOPhCl and stirred at 120 °C for 24 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as colorless oil (83 mg, 83%).

6b,7,8,9,10,10a-Hexahydro-7,10-methanobenzo[a]biphenylene [105381-78-0]. The reaction mixture was set up with 1.0 equiv of 1-iodonaphthalene and stirred at 120 °C for 24 hours. The product was purified by flash chromatography (hexanes) as colorless oil (103 mg, 94%).

2.4.4 Procedure for mechanistic studies of Heck-Catellani reaction of aryl bromides

Synthesis of the norbornene-derived palladacycle, $(C_6H_4)(C_6H_{10})Pd(PPh_3)_2$. In an argon-filled glove box, a dry 8-mL reaction tube containing a magnetic stir bar was charged with $Pd(PPh_3)_4$ (231 mg, 0.2 mmol), PhI (204 mg, 1.0 mmol), norbornene (94 mg, 1.0 mmol), KOPh (53 mg, 0.4 mmol) and 5 mL of dry DCM. The tube was capped tightly and the mixture was vigorously stirred in a 50 °C oil bath for 12 h. After cooled to room temperature, the solid was filtered away via Celite in the glove box and the filtrate was concentrated to dryness. The residue was dissolved in dry diethyl ether (7 mL) at room temperature in the glove box and the pure complex slowly precipitated out as white solid, upon standing at room

temperature (140 mg, 88% yield). We noticed the complex was prone to hydrolysis in methanol or water via protonation of the Pd-C bond.

^1H NMR (400 MHz, CD_2Cl_2): δ 7.53 (t, $J = 8.5$ Hz, 6H), 7.35-7.25 (m, 9H), 7.17-7.15 (m, 9H), 7.04 (m, 6H), 6.91 (d, $J = 5.8$ Hz, 1H), 6.65-6.61 (m, 2H), 6.13-6.11 (m, 1H), 2.98 (s, 1H), 2.73-2.70 (m, 1H), 2.23 (s, 1H), 2.08-2.05 (m, 2H), 1.28-1.27 (m, 1H), 0.94-0.88 (m, 3H), -0.17 (s, 1H).

^{31}P NMR (162 MHz, CD_2Cl_2): δ 27.2 (d, $J = 17.8$ Hz), 22.3 (d, $J = 17.8$ Hz).

Reductive elimination of norbornene-derived palladacycle. In an argon-filled glove box, a 4-mL dry reaction tube containing a magnetic stir bar was charged with the palladacycle $(\text{C}_6\text{H}_4)(\text{C}_6\text{H}_{10})\text{Pd}(\text{PPh}_3)_2$ (16.0 mg, 0.02 mmol), added ligand (0.04 mmol, 2 equiv), 0.5 mL of dry DMF and GC standard, 1-dodecane (5 μL). The reaction was stirring at 80 $^\circ\text{C}$. After 0.5, 1, 2, 5 and 24 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 filtrate was subjected to GC analysis to determine the yield of the reductive elimination product.

2.5 Reference

- (1) (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (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.
- (2) Bocelli, G.; Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1985**, 279, 225.
- (3) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1985**, 286, c13.
- (4) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1988**, 346, C27.
- (5) Catellani, M.; Chiusoli, G. P.; Ricotti, S. *J. Organomet. Chem.* **1985**, 296, c11.
- (6) Catellani, M.; Ferioli, L. *Synthesis* **1996**, 1996, 769.
- (7) Chai, D. I.; Thansandote, P.; Lautens, M. *Chem. Eur. J.* **2011**, *17*, 8175.
- (8) (a) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512. (b) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563. (c) Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372. (d) Weinstabl, H.; Suhartono, M.; Qureshi, Z.; Lautens, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 5305.
- (9) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 119.
- (10) (a) Bocelli, G.; Catellani, M.; Ghelli, S. *J. Organomet. Chem.* **1993**, 458, C12. (b) Cárdenas, D. J.; Martín-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 5033. (c) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1992**, 425, 151. (d) Catellani, M.; Paolo Chiusoli, G.; Castagnoli, C. *J. Organomet. Chem.* **1991**, 407, C30. (e) Sicher, J. *Angew. Chem., Int. Ed.* **1972**, *11*, 200.
- (11) Martins, A.; Mariampillai, B.; Lautens, M. In *C-H Activation*; Yu, J.-Q., Shi, Z., Eds.; Springer Berlin Heidelberg: 2010; Vol. 292, p 1.

- (12) (a) Mitsudo, K.; Thansandote, P.; Wilhelm, T.; Mariampillai, B.; Lautens, M. *Org. Lett.* **2006**, *8*, 3939. (b) Motti, E.; Faccini, F.; Ferrari, I.; Catellani, M.; Ferraccioli, R. *Org. Lett.* **2006**, *8*, 3967. (c) Pache, S.; Lautens, M. *Org. Lett.* **2003**, *5*, 4827.
- (13) (a) Lautens, M.; Paquin, J.-F.; Piguel, S. *J. Org. Chem.* **2002**, *67*, 3972. (b) Lautens, M.; Paquin, J.-F.; Piguel, S.; Dahlmann, M. *J. Org. Chem.* **2001**, *66*, 8127. (c) Lautens, M.; Piguel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045. (d) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485.
- (14) Catellani, M.; Motti, E.; Minari, M. *Chem. Commun.* **2000**, 157.
- (15) Motti, E.; Rossetti, M.; Bocelli, G.; Catellani, M. *J. Organomet. Chem.* **2004**, *689*, 3741.
- (16) (a) Ferraccioli, R.; Carenzi, D.; Rombolà, O.; Catellani, M. *Org. Lett.* **2004**, *6*, 4759. (b) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255.
- (17) Mariampillai, B.; Alberico, D.; Bidau, V.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 14436.
- (18) (a) Blaszykowski, C.; Aktoudianakis, E.; Alberico, D.; Bressy, C.; Hulcoop, D. G.; Jafarpour, F.; Joushaghani, A.; Laleu, B.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 1888. (b) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148.
- (19) (a) Dong, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, *135*, 18350. (b) Martins, A.; Lautens, M. *Org. Lett.* **2008**, *10*, 5095. (c) Wilhelm, T.; Lautens, M. *Org. Lett.* **2005**, *7*, 4053.
- (20) Yamashita, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5344.

Chapter 3. A General Palladium-Catalyzed Method for Alkylation of Heteroarenes Using Alkyl Halides

3.1 General Introduction

Alkylated heteroarenes are widely used in pharmaceuticals and advanced material.¹ As shown in Figure 1. Lipitor is a blockbuster drug for lowering of blood cholesterol. Voriconazole is an important antifungal agent for the treatment of invasive aspergillosis. Nexium is a proton pump inhibitor, which is used in the treatment of heartburn and esophagitis. Alkylated polythiophenes (PTs) are common electron conducting materials.

Figure 1 Industrial applications of alkyl heteroarenes.

3.1.1 Friedel-Crafts alkylation of heteroarenes

In 1877, Charles Friedel and James Mason Crafts reported alkylation of benzene using amyl chloride in the presence of AlCl_3 .² Since then, it has become an important method for alkylation of aromatic compounds. The classical Friedel-Crafts alkylation methods need stoichiometric amounts of Lewis acids or Brønsted acids and easily

lead to regioisomers and overalkylation.^{3a} More importantly, the scope of heteroarenes is limited to electron-rich 5-membered rings such as indole, pyrrole, thiophene and furan. The reaction is not applicable to electron-poor heteroarenes such as pyridine, quinoline and azoles. Secondary and tertiary halides are commonly used to form stable carbocations.³ For instance, in alkylation of thiophene using isopropylchloride, both monoalkylation and dialkylation occurred in poor yield and poor regioselectivity of monoalkylation (Scheme 1.1).^{3b} Primary aliphatic halides tend to isomerize to branched alkyl groups. In 2005, Beller group found that $\text{H}_2[\text{PtCl}_6]$ efficiently catalyzed the benzylation of furan and thiophene using 1-phenylethyl acetate.⁴ One year later, they found HAuCl_4 showed similar catalytic activity. In the reaction of 1-phenylethylacetate and 3-methylthiophene, three regioisomers were obtained (Scheme 1.2).⁴

In 2006, Rueping group discovered an efficient $\text{Bi}(\text{OTf})_3$ -catalyzed benzylation of heteroarenes such as furan, thiophene and indole using free benzyl alcohol (Scheme 1.3).⁵ The low catalyst loading is remarkable.

Scheme 1 Friedel-Crafts alkylation via electrophilic aromatic substitution.

In 2006, Beller group successfully employed FeCl_3 as a cheap catalyst for alkylation using styrene (Scheme 2.1).⁶ However, only two thiophenes worked well and led to regioisomers too. Probably, FeCl_3 was hydrolyzed under reaction conditions to generate a trace amount of HCl , which was the actual acid catalyst.^{6b,6c} Similarly, $\text{Bi}(\text{OTf})_3$ catalyst was also used in alkylation using styrene.⁷

In 2008, Che group used $(\text{PPh}_3)\text{AuCl}$ catalyst for alkylation of indoles using olefins such as 1,1-diphenylethylene and cyclohexene (Scheme 2.2 and 2.3).^{8a} Only indoles were suitable nucleophiles.

In 2006, Widenhoefer group used a platinum catalyst for hydroheteroarylation of indoles using 1-propene (Scheme 2.4).^{8b} A mixture of alkylated indoles were formed in 88% yield and 6:1 regioselectivity.

Scheme 2 Friedel-Crafts alkylation via hydroheteroarylation of olefins.

In 2002, Cozzi group described InBr_3 -catalyzed ring opening of optically pure aryl epoxides by indoles. Complete stereoinversion of configuration occurred on the epoxide. Thus, an $\text{S}_{\text{N}}2$ pathway was probably operative (Scheme 3.1).⁹ In 2001, Jorgensen *et al.* reported a copper-catalyzed enantioselective Friedel-Crafts alkylation (Scheme 3.2).¹⁰ In the presence of *t*-Bu-Box ligand, the optically active alkylated indole was formed from indoles and alkylidene malonates in good ee. Recently, Hartwig group disclosed Ir-catalyzed asymmetric hydroheteroarylation of bicyclic

olefins (Scheme 3.3).^{10b} Several furans, thiophenes, unprotected pyrroles and indoles reacted well. However, the scope of olefins was limited to norbornene-type strain bicycloalkenes.

Scheme 3 Asymmetric Friedel-Crafts alkylation of heteroarenes.

3.1.2 Minisci-type alkylation of heteroarenes

In 1971, Minisci group reported nucleophilic radical addition to protonated heteroaromatic compounds to afford new selectivity (Scheme 4.1).¹¹ Mechanistically, silver(II) nitrate induced oxidative decarboxylation of aliphatic acids and the resulting nucleophilic radicals added to protonated pyridines (Scheme 4.2). The regioselectivity and scope of heteroarenes are distinct from those in Friedel-Crafts alkylation. In general, Minisci reaction suffers from low yields, poor regioselectivity for many azines and competing dialkylation.¹² For example, 4-cyanopyridine was cyclohexylated at the C2 position in 68% yield along with 32% yield of a dialkylation product (Scheme 4.3).¹² However, for quinoline, the alkylation occurred at both the C2 and C4 positions and 29% yield of dialkylated quinoline was also formed (Scheme 4.4).

Scheme 4 Minisci-type alkylation of pyridine and quinoline.

In 1994, Yokoyama group realized Minisci-type radical addition to protonated azacycles using various alkyl bromides and iodides.¹³ In the presence of tetrakis(trimethylsilyl)silane, primary, secondary and tertiary alkyl bromides reacted with protonated heteroarenes such as lepidine, pyridine and benzothiophene under photochemical conditions (Scheme 5.1). The methyl group was necessary to prevent alkylation at the C4 position.¹⁴

In 2009, Duncanson group reported alkylation using unactivated alkyl iodides under Fenton conditions.¹⁵ As demonstrated in Scheme 5.2, 4-methyl-2-(oxetan-3-yl)quinoline was formed from 3-iodo-oxetane and lepidine in about 40% yield. The scope and limitation are similar to typical Minisci procedure.

In 2011, Molander group used alkyltrifluoroborates in Minisci-type reaction.¹⁶ In the presence of a strong oxidant $\text{Mn}(\text{OAc})_3$, cyclobutylation of benzothiazole with cyclobutyltrifluoroborate occurred at 50 °C in rather low yield (Scheme 5.3).

Baran *et al.* found that zinc sulfinate salts could act as efficient radical precursors.¹⁷ 2-Isopropylpyrrole was obtained as the only isomer in 17% yield (Scheme 5.4). Later, Baran group extended this method to other heteroarenes (Scheme 5.5).¹⁸ The regioselectivity was still poor in many cases.

Scheme 5 Minisci-type alkylation using different types of radical precursors.

3.1.3 Transition metal-catalyzed hydroheteroarylation of olefins

In 2001, Bergman and Ellman reported pioneering work of Rh-catalyzed intramolecular hydroheteroarylation of benzimidazole using $[\text{RhCl}(\text{coe})_2]_2/\text{PCy}_3$ (coe: cyclooctene) catalyst (Scheme 6.1).¹⁹

Later, the same group realized the intermolecular alkylation of *N*-methylbenzimidazole using *n*-hexene in 67% yield (Scheme 6.2).²⁰ The Rh catalysis was expanded to several azoles. However, only linear products were formed from terminal aliphatic olefins.

In 2007, the same group expanded the Rh catalysts to quinolines and pyridines using *n*-hexene.¹⁸ A mixture of linear and branched isomers was formed in 6:1 selectivity (Scheme 6.4). A plausible mechanism was proposed (Scheme 6.3).²¹ First, selective C-H activation of benzimidazole led to an Rh carbene complex. It then underwent oxidative addition of HCl to produce hydride species. Regioselective olefin insertion led to a primary alkyl-Rh complex. Finally, reductive elimination of heteroaryl-alkyl led to the alkylation product.

Scheme 6 Rhodium-catalyzed hydroheteroarylation of olefins.

In 2009, Nakao group reported nickel-catalyzed direct alkylation of pyridone derivatives.²² In the presence of $\text{Ni}(\text{cod})_2$ and 1,3-dimesitylimidazol-2-ylidene (IMes), the pyridones were alkylated at the C6 position by 2-vinylnaphthalene, in the presence of a Lewis acid AlMe_3 (Scheme 7.1). However, the yield was only moderate and scope of heteroarenes was very limited. Upon activation by Lewis acid AlMe_3 , the C-H bond on C6 position of pyridones was cleaved by oxidative addition of $(\text{L})\text{Ni}^0$ to generate a nickel hydride. Subsequently regioselective insertion of vinyl arene forms an η^1 - or η^3 benzyl complexes. Finally, reductive elimination gives the product.

The nickel-catalyzed hydroheteroarylation was expanded to other azacycles such as indoles in good yields (Scheme 7.2).²³ Branched products were obtained from the reaction of *N*-methyldindole and styrene. With the aid of a bulky Lewis acid 2,6-*t*-Bu₂-

4-Me-C₆H₂O)₂AlMe (MAD), pyridines were alkylated by aliphatic olefins with good linear selectivity by Ni/IPr [IPr: 1,3-(2,6-diisopropylphenyl)imidazol-2-ylidene] catalyst (Scheme 7.3).²⁴

Scheme 7 Nickel-catalyzed hydroheteroarylation of olefins.

In 2013, Kanai group developed a simple cobalt catalyst for C4-selective benzylation of pyridine with 2-vinylnaphthalene in 60% yield and 7:1 branched regioselectivity (Scheme 8.1).²⁵ Notably, primary alkylation could be achieved by this procedure. For an aliphatic olefin, the linear isomer was the major product (Scheme 8.2). The reaction was only applicable to pyridines.

In 2011, Hou *et al.* reported two half-sandwich rare-earth catalysts of Sc and Y for alkylation of pyridines.^{26a} 2-Ethylpyridine coupled with 1-hexene smoothly at C6 position in the presence of B(C₆F₅)₃ to give a branched product (Scheme 8.3).

Scheme 8 Other transition metal-catalyzed hydroheteroarylation of olefins.

3.1.4 Transition metal-catalyzed alkylation of heteroarenes using alkyl halides

In 2010, Hu *et al.* reported pioneering work on nickel-catalyzed coupling of azole using unactivated alkyl halides bearing β -hydrogens.²⁷ In the presence of nickel and copper catalysts, *n*-butylation of 1,3-benzoxazole occurred in 78% yield (Scheme 9.1). Various primary alkyl iodides, bromides and chlorides showed high activity. Nevertheless, they failed to couple secondary alkyl halides. A possible pathway involved metalation of azole as first step, transmetalation to the Ni catalyst and radical-type oxidative addition of alkyl halides. Finally the product was generated via reductive elimination.

In 2011, Ackermann group reported a simple nickel catalyst for alkylation of azoles.²⁸ As shown in Scheme 9.2, in the presence of (diglyme)NiBr₂ and CuI, primary alkyl bromides and chlorides directly coupled with 1,3-benzoxazole in moderate to good yields. The substrates were limited to primary halides and azoles.

Recently, Ackermann group reported alkylation of indoles with unactivated secondary alkyl halides.²⁹ With the assistance of an amidoquinoline directing group, the C-H bond in the C2 position of indole was cleaved, and subsequent coupling with bromocyclohexane afforded the desired product in 87% yield (Scheme 9.3). However, for heteroarenes, only indole derivative was employed.

Scheme 9 Nickel-catalyzed alkylation of heteroarenes with alkyl halides.

In the past decades, several palladium catalysts have been developed for benzylation of azoles³⁰ with benzyl precursors such as benzyl halides, phosphate³¹ and carbonates.³² In 2009, Hoarau and coworkers disclosed that an oxazole reacted with 1-bromobutane to afford the alkylated product in 60% yield using $\text{Pd}(\text{OAc})_2$ /2-(dicyclohexylphosphino)biphenyl (JohnPhos) (Scheme 10.1).³³ Although only one example was reported, it was the first Pd-catalyzed alkylation of heterocycles using unactivated alkyl halides.

Soon after, Miura group reported detailed studies on Pd-catalyzed alkylation of azoles.³⁴ In the presence of a $\text{Pd}/\text{P}n\text{Bu}_3$ catalyst, unactivated primary alkyl bromides and chlorides coupled well with oxazoles (Scheme 10.2). Notably, the procedure worked well with various primary halides. However, neither secondary nor tertiary alkyl halides could be used. Moreover, the scope of heterocycles was limited to

oxazoles. A large amount (30%) of $PnBu_3$ ligand was needed to ensure reasonable yields of products. The mechanism of Pd-catalyzed couplings was briefly studied (Scheme 10.2). The desired product was formed by S_N2 -type oxidative addition of alkyl halide to L_2Pd^0 , followed by transmetalation of heteroaryllithium and subsequently reductive elimination. 6-Bromohexene did not give a ring-closed product.

Bach group recently reported alkylation of indoles under Pd and norbornene dual catalysis.³⁵ Free indole was C2-alkylated by 1-bromobutane to form the 2-butyldindole in 67% yield (Scheme 10.3). A dialkylated product was also detected in about 10% yield. No examples of secondary and tertiary alkyl halides were reported. Later, the dual catalysis was extended to electron-poor pyrroles.³⁵

Very recently, Fu group in china realized alkylation of electron-poor pyridine *N*-oxides using unactivated secondary and tertiary alkyl bromides.¹⁹ As shown in Scheme 10.4, in the presence of a $Pd(OAc)_2(dppf)$ catalyst, coupling between cyclohexyl bromide and 2-methylpyridine *N*-oxide afforded the C6-alkylated product in 88% yield. However, only pyridine *N*-oxides bearing C2-substituents showed good reactivity. The alkyl groups were introduced as alkyl radicals onto the electron-poor azines with low-lying LUMOs.

group such as ester and ketones can be present due to the use of a strong base TMPMgCl.

Hu group recently realized alkylation of azoles using secondary alkyl iodides and bromides by developing an elaborate copper catalyst. 1,3-Benzoxazole was coupled with various secondary alkyl iodides and bromides (Scheme 11.2).³⁸ Notably, this is the first time that secondary alkyl halides were coupled with azoles. Nevertheless, the method was limited to oxazoles.

Recently, Ackermann and coworkers applied cobalt catalysis to the functionalization of indoles bearing *N*-directing groups.³⁹ In the presence of Co(acac)₂/IPr (*N,N*-bis(2,6-diisopropylphenyl)imidazole) catalyst, the alkylation of *N*-pyrimidylindole with 1-octyl chloride afforded the C2-alkylated adduct in 71% yield (Scheme 11.3). Only two examples of indoles carrying *N*-directing groups were reported and free indoles cannot react. Secondary alkylation of *N*-pyridylindole gave very low yield.

Similarly, Yoshikai group reported one example of C2-selective alkylation of indole using a CoBr₂ and *N*-heterocyclic carbene catalyst via directed metalation of indole (Scheme 11.4).⁴⁰ Another example for directed alkylation of thiophene was also reported. Later, the same group extended the cobalt catalyst to intramolecular alkylation of indole bearing pendant olefins.⁴¹

Scheme 11 Other transition metal-catalyzed direct alkylation of heteroarenes with alkyl halides.

3.1.4 Transition metal-catalyzed alkylation using *N*-tosylhydrazones

N-Tosylhydrazones, which can be easily made from ketones, serve as secondary alkyl groups donors via metal carbene intermediates. Wang *et al.* initially explored the *N*-tosylhydrazone as secondary benzyl precursors.⁴² In the presence of a CuI catalyst, 1,3-benzoxazole was benzylated in 80% yield using *N*-tosylhydrazone (Scheme 12.1). The method was limited to azoles. Although the detailed mechanism is still unclear, a plausible pathway involves metalation of 1,3-benzoxazole by base, followed by dediazotization of in situ formed diazo compounds to afford copper carbene species. Finally, the product was generated via α -migratory insertion.

In addition, Miura group has also chosen *N*-tosylhydrazones as more efficient alkyl sources for the alkylation of heteroarenes.⁴³ Under $\text{NiBr}_2/1,10\text{-phenanthroline}$ (phen)

catalyst, an oxazole directly reacted with *N*-tosylhydrazone to generate the alkylation product in 59% yield (Scheme 12.2). However, only azoles can be used.

Scheme 12 The direct coupling between heteroarenes and *N*-tosylhydrazones.

Overall, although many methods have been developed for the alkylation of heteroarenes, no single method can tolerate many types of heteroarenes and introduce of structurally diverse alkyl groups. Therefore, a general, transition metal-catalyzed alkylation with a broad scope is highly desired.

3.2 Results and discussion

3.2.1 Condition optimization

Initially, we used highly reactive 1,3-benzoxazole and cyclohexyl iodide as the model substrates. Two catalytic systems, which were developed by Miura³⁴ and Fu *et al.*³⁶, were examined. As shown in Scheme 13, the alkylation product was obtained in only 5% and 30% yield, respectively.

Scheme 13 Attempt to use reported catalyst in the model reaction.

Since the existing conditions were unsatisfactory, we made extensive efforts to explore other ligands and conditions. Eventually, we were glad to find that the desired product, 2-cyclohexyl-1,3-benzoxazole was formed in 88% yield by using a simple $\text{Pd}(\text{PPh}_3)_4$ and 1,3-bis(diphenylphosphino)propane (dppp) catalyst (entry 2). The results of ligand optimization are summarized in Table 1. Other common bisphosphines such as 1,2-bis(diphenylphosphino)ethane (dppe), 1,1'-bis(diphenylphosphino)ferrocene (dppf) and BINAP showed lower activity (entries 1-10). In addition, several monophosphines and one *N*-heterocyclic carbene (IMes) showed low activities (entries 11-19). When no ligand was added, the reaction afforded the desired adduct in only 32% yield (entry 20). Furthermore, we used ferrocene-derived di-, tri-, and tetraphosphines, which were developed by Hierso *et al.*. Unfortunately, no improvement was achieved (Table 2).

Table 1 The effect of ligands in the model alkylation reaction.

Reaction scheme: 1,3-benzoxazole + cyclohexyl iodide (2 equiv) $\xrightarrow[110\text{ }^\circ\text{C}/24\text{h}]{5\text{ mol\% Pd(PPh}_3)_4, 7\text{ mol\% Ligand, Cs}_2\text{CO}_3, \text{PhCF}_3}$ 2-cyclohexyl-1,3-benzoxazole

Entry	Ligand	Conversion (%) ^a	Yield (%) ^b
1	DPPE	97	63
2	DPPP	97	88
3	DPPB	93	70
4	DPPPent	97	58
5	DPPBz	79	37
6	XantPhos	76	57
7	DPEPhos	90	68
8	DPPF	79	56
9	DiPPF	94	56
10	BINAP	76	70
11	PCy ₃ (10%)	51	21
12	<i>t</i> Bu ₃ P•HBF ₄ (10%)	63	33
13	P(<i>o</i> -Tol) ₃ (10%)	68	47
14	P(<i>p</i> -OMe-Ph) ₃ (10%)	70	68
15	P <i>t</i> Bu ₂ Me (10%)	82	52
16	JohnPhos (10%)	89	65
17	P(1-Ada) ₂ Bn (10%)	95	58
18	SPhos (10%)	53	36
19	IMes (10%)	76	57

20	No added ligand	58	32
----	-----------------	----	----

^a conversion was determined by GC. ^b GC yield.

Table 2 The effect of ferrocene-derived ligands developed by Hierso *et al.* in the model alkylation.

Entry	Ligand	Conversion (%) ^a	Yield (%) ^b
1		86	38
2		87	42
3		96	69
4		87	36
5		70	20
6		82	50
7		38	14
8		87	55
9		63	55

(10%)

^a conversion was determined by GC. ^b GC yield.

With regard to the choice of the palladium source, several Pd(0) and Pd(II) precursors were screened. The results are listed in Table 3. We found that Pd(PPh₃)₄ showed exceptionally high activity as compared with common palladium source such as [Pd(dba)₂] (dba: dibenzylideneacetone), Pd(OAc)₂, [Pd(acac)₂] (acac: acetylacetonate) and [Pd(hfacac)₂] (hfacac: hexafluoroacetylacetonate). Pd(PPh₃)₄ probably formed quickly the active catalyst (dppp)Pd⁰.

Table 3 The effect of palladium source in the model alkylation.

2 equiv

Entry	Pd source	Conversion (%) ^a	Yield (%) ^b
1	Pd ₂ (dba) ₃	39	18
2	Pd(dba) ₂	53	29
3	Pd(OAc) ₂	68	26
4	Pd(OCOCF ₃) ₂	68	40
5	Pd(hfacac) ₂	76	37
6	Pd(acac) ₂	50	8
7	PdI ₂	46	36
8	Pd(PPh₃)₄	97	88

^a conversion was determined by GC. ^b GC yield.

The choice of the bases also had a significant effect. As shown in Table 4, both Cs₂CO₃ and K₃PO₄ showed good activity (entries 4 and 5). However, other inorganic bases only afforded very poor yields (entries 1-3 and 6-10). Several common alkylamines such as Et₃N, *i*Pr₂NEt and Cy₂NMe gave almost no desired alkylated product (entries 11-17). In addition, in the absence of the base, the reaction only afforded the adduct in a trace amount (entry 18).

Table 4 The effect of bases in the model alkylation reaction.

2 equiv

Entry	Base	Conversion (%) ^a	Yield (%) ^b
1	Li ₂ CO ₃	24	7

^a conversion was determined by GC. ^b GC yield.

2	Na ₂ CO ₃	4	2
3	K ₂ CO ₃	74	67
4	Cs₂CO₃	97	88
5	K₃PO₄	89	85
6	K ₃ PO ₄ •H ₂ O	73	53
7	KOH	77	14
8	KOtBu	54	12
9	CsF	57	44
10	CsOPiv	72	23
11	Et ₃ N	13	4
12	<i>n</i> Bu ₃ N	9	3
13	DIPEA	22	4
14	Cy ₂ NMe	5	4
17	Proton sponge	11	3
18	No added base	15	6

^a conversion was determined by GC. ^b GC yield.

In the screening of solvents, the reaction can be conducted in both aromatic and ethereal solvents. As shown in Table 5, PhCF₃ was the best solvent. In other aromatic and ethereal solvents such as *n*Bu₂O, THP and anisole, the reaction gave moderate yields. In 1,2-dichloroethane, alcohols and amide solvents (DMF and NMP), the alkylation took place sluggishly (entries 13-16).

Table 5 The effect of solvents in the model alkylation reaction.

Entry	Solvent	Conversion (%) ^a	Yield (%) ^b
1	Triglyme	78	44
2	1,4-Dioxane	52	14
3	DME	62	30
4	2-MeTHF	61	43
5	<i>c</i> -CypOMe	52	10
6	<i>n</i> Bu ₂ O	79	63
7	<i>t</i> BuOMe	21	10
8	THP	86	54
9	<i>o</i> -(MeO) ₂ benzene	53	17
10	PhOMe	86	69

11	Toluene	64	53
12	PhCF₃	97	88
13	DCE	11	9
14	<i>n</i> BuOH	62	18
15	DMF	36	4
16	NMP	41	2

^a conversion was determined by GC. ^b GC yield.

Another critical parameter was the molar ratio of two substrates. As shown in Table 6. When we used CyI in two equivalents, the yield was 88%. when we used 1,3-benzoxazole in excess, the yield of the desired product dropped significantly to 60%.

Table 6 The effect of molar ratio of SM in the model alkylation reaction.

Entry	Ratio of reactants	Conversion of benzoxazole (%) ^a	Yield (%) ^b
1	2:1	54	60
2	1:1	66	45
3	1:1.5	74	56
4	1:2	97	88

^a conversion was determined by GC. ^b GC yield.

3.2.2 Scope of substrates

After we optimized the catalyst and conditions, we tried to determine the substrate scope. Initially, several secondary alkyl iodides were examined for the coupling with 1,3-benzoxazole (Figure 2.1). To our satisfaction, both cyclic and acyclic alkyl iodides reacted well. Especially, when 4-*t*-butylcyclohexyl iodide as a 2:1 molar mixture of *trans*- and *cis*-isomers was tested, the *cis*-isomer was predominantly consumed and the adduct was generated in a *tran/cis* ratio of 8:1. Gratifyingly, challenging tertiary alkyl iodides reacted well and both *t*-butyl and 1-adamantyl iodides gave the desired products in good yield. Furthermore, the model reaction of 1,3-benzoxazole and cyclohexyl iodide was scaled up to 10 mmol using the standard condition (Figure 2.2). The product, 2-cyclohexyl-1,3-benzoxazole, was obtained in 72% yield. At 2 mol% of Pd catalyst, the yield dropped. We then applied our method

to a more complex molecule. 3 β -Iodo-5-androsten-17-one was chosen as the alkyl halide, which was derived from 3 β -hydroxy-5-androsten-17-one. As shown in Scheme Figure 2.3, it reacted well with 1,3-benzoxazole and the product was formed in 61% yield and 4:1 diastereoselectivity. Notably, the major isomer also had β configuration.

Figure 2 The scope of alkyl iodides in the alkylation of 1,3-benzoxazole (isolated yield of major isomers).

Next, we tried to explore secondary and tertiary bromides. As shown in Figure 3, many alkyl bromides coupled successfully in the presence of two equivalent of NaI. Without NaI, the yield was less than 10% in the reaction of cyclohexyl bromide and 1,3-benzoxazole. During the reaction, a small amount of alkyl iodides were detected, which suggested that alkyl iodides might be the actual reactants. In the case of *exo*-2-bromonorbornane, the alkylation product was formed in a 10:1 mixture of *exo* and *endo* isomers. In the reaction of 4-bromo-2-pentyltetrahydropyran, which was a 2:1

mixture of *cis*- and *trans*-isomers, the product was obtained in a *cis/trans* ratio of 17:1. Notably, several tertiary bromides also reacted well.

Figure 3 The scope of alkyl bromides in the alkylation of 1,3-benzoxazole (isolated yield of major isomers).

To our joy, various heteroarenes reacted under our conditions. Initially, several azoles were tested in the reaction of cyclohexyl iodide. As shown in Figure 4, not only oxazoles and thiazoles but also *N*-protected imidazoles reacted in good yields. Notably, various 6-membered-ring azines including quinazoline, 1,3,5-triazine and pyridine *N*-oxide could also couple with cyclohexyl iodide efficiently in good regioselectivity. Interesting, pyridines bearing electron-withdrawing groups such as aldehydes, ketones and nitriles showed good reactivity and afforded the alkylation products in good regioselectivity.

Figure 4 Alkylation of 1,3-azoles and azines with CyI (isolated yield of major isomers).

Furans, thiophenes, pyrroles and their benzofused derivatives such as indoles are another class of common heteroarenes, which have been rarely investigated in metal-catalyzed alkylations. As shown in Figure 5, with the activation of electron-withdrawing group such as aldehydes, ketones and nitriles, various furan, thiophene and pyrrole derivatives gave the product in good yields and good selectivities. For pyrrole derivatives, the choice of *N*-protecting group was also critical for the reactivity. An *N*-ethoxycarbonyl group significantly enhanced the reactivity as compared to an *N*-methyl group. Notably, both electron-rich and electron-neutral indoles bearing *N*-carbamate groups afforded the desired adducts in good yield and high C2-regioselectivity.

Figure 5 Alkylation of furans, thiophenes, pyrroles and their benzoid derivatives with CyI (isolated yield of major isomers).

We also examined the alkylation using tertiary alkyl iodides. By choosing 1-adamantyl iodide as the model halide, a series of azoles, azines, electron-poor furans, thiophenes and pyrroles derivatives were tested. As shown in Figure 6, many families of heteroarenes were suitable. Once again, both the electron-rich and electron-neutral indoles bearing the *N*-ethoxycarbonyl group were successfully alkylated.

Figure 6 Coupling of 1-adamantyl iodide with various heteroarenes (isolated yield of major isomers).

Generally, primary alkyl iodides bearing linear chains showed poor reactivity due to palladium-catalyzed elimination to olefins. However, some branched primary alkyl iodides performed well with selected heteroarenes. As shown in Figure 7, when 2-fluoro-4-cyanopyridine and 3-formylfuran were treated with (iodomethyl)cyclohexane or 1-iodo-3-methylbutane, the corresponding adducts were produced in moderate to good yields.

Figure 7 Pd-catalyzed alkylation using primary alkyl halides.

3.2.3 Mechanistic study

In the alkylation of pyridine *N*-oxide which was reported by Fu group recently,³⁶ a radical addition pathway was proposed in the presence of the palladium catalyst. In addition, in palladium-catalyzed Heck-type reactions, alkyl radicals were also detected.⁴⁴ Our diastereoselective reactions in Figures 2-3 also led us to suspect that our reaction also involve a radical pathway. Two sets of radical trapping experiments were conducted. In the presence of TEMPO, several conditions were tested between 1,3-benzoxazole and cyclohexyl iodide (Table 7). All the reactions afforded a large amount of *N*-cyclohexyl-TEMPO, which indicated the presence of cyclohexyl radical during the reaction. At the same time, the desired alkylation product was formed albeit in lower yield. A significant trend of ligand dependence was observed. Dppp and dppf gave 40-50% yield of the coupling product in the presence of TEMPO (entries 6 and 7).

Table 7 Trapping experiment using TEMPO.

Entry	Pd Catalyst	Conv. HetAr (%) ^a	Product (%) ^b	TEMPO-Cy (%) ^b
1	0% Pd(PPh ₃) ₄ /DPPP	4	0	0
2	0% Pd(PPh ₃) ₄ /DPPP, no base	7	0	0
3	10% Pd(PPh ₃) ₄	15	0	56
4	10% Pd(PPh ₃) ₄ , 14% DPPE	35	19	59

5	10% Pd(PPh ₃) ₄ , 14% DPEPhos	23	16	61
6	10% Pd(PPh ₃) ₄ , 14% DPPF	48	42	50
7	10% Pd(PPh ₃) ₄ , 14% DPPP	50	46	62
8	10% Pd(dba) ₂ , 14% DPPP	4	0	50
9	10% Pd(OAc) ₂ , 14% DPPP	39	0	35
10	10% PdI ₂ , 14% DPPP	8	0	33

^a conversion was determined by GC. ^b GC yield.

Another radical trapping experiment was performed in tertiary alkylation of indole. As shown in Table 8, a hydrogen atom donor, 1,4-cyclohexadiene was introduced to trap the adamantyl radical to form adamantane. Without added 1,4-cyclohexadiene, the desired product was formed in a reasonable yield and only a trace amount of adamantane was observed (4%). In the presence of 3 equivalents of 1,4-cyclohexadiene, adamantane was formed in 80% yield while the alkylated indole was detected in only 14% yield. Therefore, alkyl radicals are present under our reaction conditions.

Table 8 Trapping experiment using 1,4-cyclohexadiene.

Entry	1,4-cyclohexadiene	Conv. indole (%) ^a	Conv. RI (%) ^a	Product (%) ^b	Adamantane (%) ^b
1	0 equiv	93	100	64	4
2	3 equiv	22	100	14	80
3	5 equiv	12	100	7	89

^a conversion was determined by GC. ^b GC yield.

Next, we sought support for the radical addition mechanism from density functional theory (DFT) calculations. Hajime Hirao group optimized transition states for the reactions between heteroarenes and a cyclohexyl radical, using Gaussian 09.⁴⁶ The B3LYP functional was used in conjunction with a 6-31+G* basis set in vacuum.⁴⁷ As shown in Table 9, the experimental values of regioselectivity corroborated well with the calculated enthalpy gap between two transition states of cyclohexyl radical addition to the major and minor sites of various heteroarenes. The

equatorial radical orbital was formed to add to heteroarene faster than the axial one in the cyclohexene ring.

Table 9 Transition state energies for cyclohexyl radical addition obtained at the B3LYP/6-31+G* level.

Heterocycle	Minor site and TS energy (hartrees)	Major site and TS energy (hartrees)	TS energy difference (kcal/mol)	Expt. selectivity ^a
C2 -653.193888	C4 -653.195275	-0.9	10:1
C3 -596.832066	C5 -596.832669	-0.4	4:1
C4 -596.831788	C6 -596.833362	-1.0	7:1
C2 -596.827898	C3 -596.828942	-0.7	7:1
C4 -880.459696	C2 -880.468598	-5.6	32:1
C3 -598.032678	C5 -598.034793	-1.3	7:1
C3 -866.244809	C2 -866.247653	-1.8	28:1

^a selectivity was determined by GC.

Putting together all the evidences, we propose a possible catalytic cycle for our reaction. As shown in Figure 8, initially the single electron transfer from (dppp)Pd⁰ to an alkyl halide produced an alkyl radical and (dppp)Pd^IX.⁴⁵ Next, radical adds to

heteroarene, followed by back electron transfer to $(\text{dppp})\text{Pd}^{\text{I}}\text{X}$ and deprotonation which furnishes the alkylated heteroarene and regenerates the active Pd^0 catalyst. Different from many Minisci-type processes, the heteroarenes herein do not need to be activated by protonation. Moreover, based on the radical addition mechanism, the limited success of primary alkyl halides can be explained by the relatively low nucleophilicity of primary alkyl radicals.

Figure 8 A proposed catalytic cycle for the alkylation of heteroarenes.

3.3 Unsuccessful examples in the alkylation of heteroarenes

When we tried the coupling between primary alkyl iodides such as 1-iododecane and 1,3-benzoxazole, as shown in Scheme 14.1, only a trace amount of the product was observed. The major side reaction was Pd-catalyzed β -hydride elimination to olefins (decene in 78% yield).

In reactions of secondary alkyl chlorides and 1,3-benzoxazole, almost no conversion of the starting materials was observed and no product was detected, even when various additives were introduced (Scheme 14.2).

Scheme 14 Primary alkyl iodide and secondary alkyl chloride in alkylation of 1,3-benzoxazole.

Several cyclic alkyl halides bearing substituents were attempted but they failed to afford the alkylation products (Figure 9). Only a large amount of reductive byproducts of alkyl halides were observed. With regard to heteroarenes, several quinoline and isoquinoline derivatives were tried. The alkylation products were formed in reasonable yields but the regioselectivity was very low (about 1:1 ratio) and sometimes more than two isomers were detected (Figure 9).

Figure 9 Other examples that fail to couple in alkylation.

3.4 Conclusion

In conclusion, we have developed a general Pd-catalyzed alkylation method for heteroarenes. Simple Pd/dppp catalyst allowed coupling of most of typical classes of heteroarenes including azoles, azines, furans, thiophenes, pyrroles, pyridines and even indole derivatives, with various unactivated secondary and tertiary alkyl halides in good regioselectivity. Notably, our radical-type alkylation is compatible with sensitive functional groups such as nitriles, aldehydes and ketones. Therefore, it is a

complementary to other transition metal-catalyzed alkylation processes which rely on initial metalation of CH bonds.

3.5 Experimental section

3.5.1 General

^1H NMR spectra were acquired on Bruker 400 MHz or 300 MHz spectrometers and chemical shifts were recorded relative to tetramethylsilane (δ 0.00) or residual protiated solvent (CDCl_3 : δ 7.26). 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 at 100 MHz on 400 MHz or 75 MHz on 300 MHz instruments and chemical shifts were recorded relative to solvent resonance (CDCl_3 : δ 77.16). Proof of purity of new compounds was demonstrated with copies of ^1H , ^{13}C , ^{31}P and ^{19}F NMR spectra.

Glassware was dried in an oven at 120 °C for at least 2 hours before use. Dry PhCF_3 (Sigma Aldrich) was degassed by argon bubbling and stored over activated 4 Å molecular sieve beads in an argon-filled glove box before use. Dry hexane, diethyl ether and dichloromethane 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 an argon-filled glove box.

Unless noted otherwise, commercially available chemicals were used without further purification. Dry diisopropylethylamine (DIPEA) and triethylamine were distilled from CaH_2 under argon before use. The GC standard, *n*-dodecane was degassed with argon bubbling and dried over activated 4 Å molecular sieve beads for a few days in the glove box 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 (0.040-0.063 mm).

Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with Agilent J & W GC column DB-5MS-UI. GCMS 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.

3.5.2 Procedure for condition optimization of Pd-catalyzed alkylation of heteroarenes

Typical procedure for condition optimization: In an argon-filled glove box, a dry 4-mL reaction tube containing a magnetic stirbar was charged with $\text{Pd}(\text{PPh}_3)_4$ (5 mol%, 5.8 mg, 0.005 mmol), DPPP (7 mol%, 2.8 mg, 0.007 mmol) and dry PhCF_3 (0.6 mL). After stirring at room temperature for 10 minutes, 1,3-benzoxazole (1 equiv, 0.10 mmol, 12 mg), Cs_2CO_3 (2 equiv, 0.20 mmol, 65 mg), iodocyclohexane (2 equiv, 0.20 mmol, 42 mg) and GC standard, 1-dodecane (10 μL) were added sequentially. The tube was capped tightly and the mixture

was vigorously stirred in a pre-warmed 110 °C oil bath. After 24 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 filtrate was subjected to GC analysis to determine the conversion of 1,3-benzoxazole and calibrated GC yield of the product.

3.5.3 Procedure for product isolation of Pd-catalyzed alkylation of heteroarenes

Typical procedure for alkylation of 1,3-benzoxazole with alkyl iodides: In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stirbar was charged with Pd(PPh₃)₄ (5 mol%, 29 mg, 0.025 mmol), DPPP (7 mol%, 14 mg, 0.035 mmol) and dry PhCF₃ (3.0 mL). After stirring at room temperature for 10 minutes, 1,3-benzoxazole (1 equiv, 0.5 mmol, 60 mg), Cs₂CO₃ (2 equiv, 1.0 mmol, 326 mg) and alkyl iodides (2 equiv, 1.0 mmol) were added sequentially. The tube was capped tightly and the mixture was vigorously stirred in a pre-warmed 110 °C oil bath. After 1,3-benzoxazole was almost fully consumed (monitored by GC), the reaction mixture was concentrated on a rotary evaporator and the resulting residue was directly subjected to silica gel flash chromatography. The structure of the desired product was confirmed by ¹H NMR spectroscopy of the purified sample. The typical procedure using 0.5 mmol of 1,3-benzoxazole was used for all the isolation, unless stated otherwise.

2-Cyclohexyl-1,3-benzoxazole [104462-82-0]. The reaction mixture was stirred at 110 °C for 24 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (87 mg, 86%).

¹H NMR (400 MHz, CDCl₃): δ 7.70-7.66 (m, 1H), 7.48-7.45 (m, 1H), 7.33-7.26 (m, 2H), 2.99-2.91 (m, 1H), 2.19-2.15 (m, 2H), 1.89-1.84 (m, 2H), 1.76-1.66 (m, 2H), 1.48-1.27 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ 170.4, 150.6, 141.3, 124.3, 124.0, 119.6, 110.3, 38.0, 30.5, 25.8, 25.6.

GCMS (EI): Calcd for C₁₃H₁₅NO: 201.1. Found: 201.1.

Gram-scale alkylation of 1,3-benzoxazole and CyI using a Schlenk manifold: To a dry 100-mL Schlenk tube containing a magnetic stirbar was charged with Pd(PPh₃)₄ (5 mol%, 580 mg, 0.5 mmol) and DPPP (7 mol%, 280 mg, 0.7 mmol). The tube was connected to the Schlenk line and evacuated and refilled with argon for three cycles and dry PhCF₃ (60 mL) was added via a syringe under the protection of argon. After stirring at room temperature for 10 minutes,

1,3-benzoxazole (1 equiv, 10 mmol, 1.19 g), Cs_2CO_3 (2 equiv, 20 mmol, 6.52 g) and cyclohexyl iodide (2 equiv, 20 mmol, 4.20 g) were added sequentially under the flow of argon. The tube was capped tightly and the mixture was vigorously stirred in a pre-warmed 110 °C oil bath for 56 hours. The reaction mixture was concentrated on a rotary evaporator and the resulting residue was directly subjected to silica gel flash chromatography (1:10 EA/hexanes) and the desired product was obtained as yellow oil (1.45 g, 72%).

2-Isopropylbenzoxazole [6797-15-5]. The reaction mixture was stirred at 110 °C for 44 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (68 mg, 85%).

^1H NMR (400 MHz, CDCl_3): δ 7.71-7.66 (m, 1H), 7.50-7.46 (m, 1H), 7.32-7.27 (m, 2H), 3.30-3.20 (heptet, $J = 7.0$ Hz, 1H), 1.47 (d, $J = 7.0$ Hz, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 171.3, 150.7, 141.3, 124.4, 124.0, 119.6, 110.3, 28.9, 20.3.

GCMS (EI): Calcd for $\text{C}_{10}\text{H}_{11}\text{ON}$: 161.0. Found: 161.0.

2-(2-Octyl)-1,3-benzoxazole. The reaction mixture was stirred at 110 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (103 mg, 89%).

^1H NMR (400 MHz, CDCl_3): δ 7.71-7.66 (m, 1H), 7.50-7.46 (m, 1H), 7.32-7.27 (m, 2H), 3.17-3.08 (m, 1H), 1.97-1.88 (m, 1H), 1.74-1.65 (m, 1H), 1.43 (d, $J = 6.8$ Hz, 3H), 1.33-1.25 (m, 8H), 0.86 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 170.9, 150.7, 141.3, 124.3, 124.0, 119.6, 110.3, 35.1, 34.3, 31.7, 29.1, 27.2, 22.6, 18.4, 14.0.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}$: 231.1. Found: 231.1.

2-(1-Methyl-3-phenyl-1-propyl)-1,3-benzoxazole [1365572-69-5]. The reaction mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (103 mg, 83%).

^1H NMR (400 MHz, CDCl_3): δ 7.71-7.68 (m, 1H), 7.50-7.47 (m, 1H), 7.32-7.25 (m, 4H), 7.19-7.15 (m, 3H), 3.21-3.12 (m, 1H), 2.74-2.63 (m, 2H), 2.34-2.24 (m, 1H), 2.06-1.97 (m, 1H), 1.47 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 170.4, 150.7, 141.5, 141.3, 128.5, 128.4, 126.0, 124.5, 124.1, 119.7, 110.4, 36.6, 33.7, 33.4, 18.5.

GCMS (EI): Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}$: 251.1. Found: 251.0.

2-(3-Octyl)-1,3-benzoxazole. The reaction mixture was stirred at 110 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (97 mg, 84%).

^1H NMR (400 MHz, CDCl_3): δ 7.71-7.67 (m, 1H), 7.50-7.47 (m, 1H), 7.32-7.27 (m, 2H), 2.98-2.91 (m, 1H), 1.92-1.71 (m, 4H), 1.37-1.16 (m, 6H), 0.91 (t, J = 7.4 Hz, 3H), 0.86-0.83 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 170.1, 150.7, 141.3, 124.3, 124.0, 119.6, 110.3, 41.9, 33.2, 31.7, 27.0, 26.7, 22.5, 14.0, 11.8.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}$: 231.1. Found: 231.1.

2-Cyclopentyl-1,3-benzoxazole [175611-05-9]. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (61 mg, 65%).

¹H NMR (400 MHz, CDCl₃): δ 7.69-7.65 (m, 1H), 7.49-7.45 (m, 1H), 7.31-7.27 (m, 2H), 3.42-3.34 (m, 1H), 2.21-2.13 (m, 2H), 2.09-2.00 (m, 2H), 1.91-1.78 (m, 2H), 1.78-1.67 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 170.6, 150.8, 141.4, 124.3, 124.0, 119.5, 110.2, 38.9, 31.4, 25.7.

GCMS (EI): Calcd for C₁₂H₁₃NO: 187.1. Found: 187.1.

trans-1-(1,3-benzoxazol-2-yl)-4-t-butylcyclohexane [1361973-87-6]. The reaction mixture was stirred at 110 °C for 36 hours, using 1-*t*-butyl-4-iodocyclohexane (1.0 mmol, 266 mg, *trans/cis* 2.3:1). The product was purified by flash chromatography (1:10 EA/hexanes) as yellow solid (101 mg, 79%). The *trans/cis* ratio in the crude mixture was determined to be 8:1 by GC. The *trans* configuration of the major isomer was determined by comparison with reported NMR data, particularly on the benzylic type proton (*cf.* T. Yao, K. Hirano, T. Satoh and M. Miura, *Angew. Chem. Int. Ed.*, **2012**, 51, 775).

¹H NMR (400 MHz, CDCl₃): δ 7.70-7.65 (m, 1H), 7.50-7.45 (m, 1H), 7.31-7.28 (m, 2H), 2.85 (tt, *J* = 12.2, 3.6 Hz, 1H), 2.31-2.27 (m, 2H), 1.97-1.94 (m, 2H), 1.71-1.61 (m, 2H), 1.22-1.08 (m, 3H), 0.90 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 170.5, 150.6, 141.3, 124.3, 124.0, 119.6, 110.3, 47.5, 38.2, 32.5, 31.0, 27.5, 26.8.

GCMS (EI): Calcd for C₁₇H₂₃NO: 257.1. Found: 257.1.

N-Benzoxycarbonyl-4-(1,3-benzoxazol-2-yl)piperidine. The reaction mixture was stirred at 110 °C for 48 hours. The product was purified by flash chromatography (1:6 EA/hexanes) as yellow solid (114 mg, 68%).

¹H NMR (400 MHz, CDCl₃): δ 7.70-7.68 (m, 1H), 7.50-7.48 (m, 1H), 7.38-7.29 (m, 7H), 5.16 (s, 2H), 4.21 (s, 2H), 3.19-3.06 (m, 3H), 2.18-2.16 (m, 2H), 1.99-1.89 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 168.2, 155.2, 150.7, 141.1, 136.8, 128.5, 128.0, 127.9, 124.8, 124.3, 119.8, 110.4, 67.2, 43.3, 35.9, 29.2.

GCMS (EI): Calcd for C₂₀H₂₀N₂O₃: 336.1. Found: 336.0.

2-Cycloheptyl-1,3-benzoxazole [175611-08-2]. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (72 mg, 67%).

^1H NMR (400 MHz, CDCl_3): δ 7.69-7.66 (m, 1H), 7.48-7.46 (m, 1H), 7.31-7.26 (m, 2H), 3.19-3.12 (m, 1H), 2.23-2.16 (m, 2H), 2.00-1.90 (m, 2H), 1.87-1.80 (m, 2H), 1.70-1.57 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 171.4, 150.7, 141.3, 124.3, 123.9, 119.6, 110.2, 39.8, 32.3, 28.3, 26.3.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}$: 215.1. Found: 215.1.

2-Cyclooctyl-1,3-benzoxazole [175611-03-7]. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (64 mg, 56%).

^1H NMR (400 MHz, CDCl_3): δ 7.70-7.66 (m, 1H), 7.48-7.46 (m, 1H), 7.31-7.27 (m, 2H), 3.25-3.18 (m, 1H), 2.19-2.11 (m, 2H), 2.05-1.96 (m, 2H), 1.84-1.77 (m, 2H), 1.66-1.62 (m, 8H).

^{13}C NMR (100 MHz, CDCl_3): δ 171.6, 150.7, 141.3, 124.3, 123.9, 119.6, 110.2, 38.3, 29.9, 27.0, 26.1, 25.2.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}$: 229.1. Found: 229.1.

2-(1-Adamantyl)-1,3-benzoxazole [52725-81-2]. The reaction was set up with 1-iodoadamantane (2 equiv, 262 mg, 1.0 mmol). The mixture was stirred at 110 °C for 44 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as white solid (121 mg, 96%).

^1H NMR (400 MHz, CDCl_3): δ 7.72-7.67 (m, 1H), 7.51-7.46 (m, 1H), 7.31-7.26 (m, 2H), 2.17-2.13 (m, 9H), 1.85-1.79 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 173.0, 150.5, 141.3, 124.3, 123.9, 119.7, 110.3, 40.3, 36.5, 36.1, 28.0.

GCMS (EI): Calcd for $\text{C}_{17}\text{H}_{19}\text{NO}$: 253.1. Found: 253.1.

2-*t*-Butyl-1,3-benzoxazole [54696-03-6]. The reaction was set up with Pd(PPh₃)₄ (10 mol%, 58 mg, 0.05 mmol), DPPP (14 mol%, 28 mg, 0.07 mmol), *tert*-butyl iodide (4 equiv, 368 mg, 2.0 mmol) and dry *n*Bu₂O (3.0 mL). The mixture was stirred at 110 °C for 67 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (67 mg, 77%).
¹H NMR (400 MHz, CDCl₃): δ 7.72-7.67 (m, 1H), 7.52-7.46 (m, 1H), 7.31-7.27 (m, 2H), 1.50 (s, 9H).
¹³C NMR (100 MHz, CDCl₃): δ 173.5, 150.8, 141.3, 124.4, 124.0, 119.7, 110.3, 34.2, 28.5.
 GCMS (EI): Calcd for C₁₁H₁₃NO: 175.1. Found: 175.1.

Typical procedure for alkylation of 1,3-benzoxazole with alkyl bromides: In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stirbar was charged with Pd(PPh₃)₄ (10 mol%, 58 mg, 0.05 mmol), DPPP (14 mol%, 28 mg, 0.07 mmol) and dry PhCF₃ (3.0 mL). After stirring at room temperature for 10 minutes, 1,3-benzoxazole (1 equiv, 0.5 mmol, 60 mg), Cs₂CO₃ (2 equiv, 1.0 mmol, 326 mg), alkyl bromides (2 equiv, 1.0 mmol) and NaI (2 equiv, 1.0 mmol, 150 mg) were added sequentially. The tube was capped tightly and the mixture was vigorously stirred in a pre-warmed 110 °C oil bath. After 1,3-benzoxazole was almost fully consumed (monitored by GC), the reaction mixture was concentrated on a rotary evaporator and the resulting residue was directly subjected to silica gel flash chromatography. The structure of the desired product was confirmed by ¹H NMR spectroscopy of the purified sample. The typical procedure using 0.5 mmol of 1,3-benzoxazole was used for all the isolation, unless stated otherwise.

2-Isopropyl-1,3-benzoxazole [6797-15-5]. The reaction mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (55 mg, 68%).

2-(3-Pentyl)-1,3-benzoxazole [73713-91-4]. The reaction mixture was stirred at 110 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (52 mg, 54%).

¹H NMR (400 MHz, CDCl₃): δ 7.71-7.67 (m, 1H), 7.50-7.47 (m, 1H), 7.32-7.27 (m, 2H), 2.91-2.84 (m, 1H), 1.95-1.76 (m, 4H), 0.92 (t, *J* = 7.4 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 169.9, 150.7, 141.3, 124.3, 124.0, 119.6, 110.3, 43.4, 26.2, 11.8.

GCMS (EI): Calcd for C₁₂H₁₅NO: 189.1. Found: 189.1.

2-(4-Phenyl-2-butyl)-1,3-benzoxazole [1365572-69-5]. The reaction mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (63 mg, 50%).

2-Cyclohexyl-1,3-benzoxazole [104462-82-0]. The reaction mixture was stirred at 110 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (73 mg, 73%).

2-(4-Tetrahydropyranyl)-1,3-benzoxazole [1361973-82-1]. The reaction mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as white solid (64 mg, 63%).

¹H NMR (400 MHz, CDCl₃): δ 7.72-7.68 (m, 1H), 7.52-7.47 (m, 1H), 7.33-7.29 (m, 2H), 4.08 (dt, *J* = 11.6, 3.6 Hz, 2H), 3.58 (td, *J* = 11.0, 3.6 Hz, 2H), 3.25-3.18 (m, 1H), 2.14-2.01 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ 168.5, 150.7, 141.1, 124.7, 124.2, 119.8, 110.4, 67.1, 35.1, 30.0.

GCMS (EI): Calcd for C₁₂H₁₃NO₂: 203.1. Found: 203.1.

N-Benzoxycarbonyl-4-(1,3-benzoxazol-2-yl)piperidine. The reaction mixture was stirred at 110 °C for 60 hours. The product was purified by flash chromatography (1:6 EA/hexanes) as yellow solid (104 mg, 62%).

cis-4-(1,3-Benzoxazol-2-yl)-2-pentyltetrahydropyran. 4-Bromo-2-pentyl tetrahydropyran (1.0 mmol, 235 mg, *cis/trans* 2:1) were used. The reaction mixture was stirred at 110 °C for 60 hours. The *cis:trans* ratio in the unreacted alkyl bromide was determined to be 6:1 by GC. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (93 mg, 68%). The *cis:trans* ratio in the crude mixture was determined to be 17:1 by GC and GCMS. The *cis* configuration of the major isomer was assigned with large coupling constants at 4.16 and 3.59 ppm, which correspond to two axial hydrogens in a cyclohexane chair system.

¹H NMR (400 MHz, CDCl₃): δ 7.72-7.67 (m, 1H), 7.50-7.47 (m, 1H), 7.33-7.29 (m, 2H), 4.16 (ddd, *J* = 11.6, 4.4, 1.2 Hz, 1H), 3.59 (ψtd, *J* = 12.0, 2.4 Hz, 1H), 3.45-3.39 (m, 1H), 3.20 (ψtt, *J* = 12.2, 4.0 Hz, 1H), 2.19-2.07 (m, 2H), 2.01-1.91 (m, 1H), 1.72-1.56 (m, 2H), 1.52-1.29 (m, 7H), 0.92-0.88 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 168.7, 150.6, 141.1, 124.6, 124.2, 119.8, 110.4, 67.3, 36.3, 35.8, 35.4, 31.9, 30.0, 25.1, 22.6, 14.0.

GCMS (EI): Calcd for C₁₇H₂₃NO₂: 273.1. Found: 273.1.

exo-2-(2-Norbornyl)-1,3-benzoxazole. *exo*-2-Bromonorbornane (1.0 mmol, 175 mg) was used. The reaction mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (73 mg, 68%). The *exo:endo* ratio of 10:1 was determined by GC.

¹H NMR (400 MHz, CDCl₃): δ 7.70-7.64 (m, 1H), 7.48-7.44 (m, 1H), 7.31-7.25 (m, 2H), 3.01-2.97 (dd, *J* = 9.2, 5.2 Hz, 1H), 2.68 (d, *J* = 3.2 Hz, 1H), 2.43 (s, 1H), 2.21-2.15 (m, 1H), 1.79-1.73 (m, 1H), 1.71-1.56 (m, 3H), 1.48-1.37 (m, 1H), 1.34-1.25 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 170.5, 150.9, 141.3, 124.3, 123.9, 119.6, 110.2, 42.1, 41.6, 36.4, 36.3, 35.4, 29.6, 28.8.

GCMS (EI): Calcd for C₁₄H₁₅NO: 213.1. Found: 213.1.

2-(1-Adamantyl)-1,3-benzoxazole [52725-81-2]. The reaction was set up with 1-bromoadamantane (4 equiv, 430 mg, 2.0 mmol). The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as white solid (104 mg, 82%).

5-(1,3-Benzoxazol-2-yl)adamantan-2-one. The reaction was set up with 5-bromoadamantan-2-one (4 equiv, 458 mg, 2.0 mmol). The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow solid (107 mg, 80%).

¹H NMR (400 MHz, CDCl₃): δ 7.72-7.68 (m, 1H), 7.52-7.48 (m, 1H), 7.34-7.30 (m, 2H), 2.72 (s, 2H), 2.51-2.47 (m, 4H), 2.39 (s, 2H), 2.32-2.31 (m, 1H), 2.19-2.04 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ 216.2, 170.4, 150.6, 141.0, 124.8, 124.3, 119.9, 110.5, 45.9, 41.4, 39.3, 38.4, 35.8, 27.4.

GCMS (EI): Calcd for C₁₇H₁₇NO₂: 267.1. Found: 267.0.

2-*t*-Butyl-1,3-benzoxazole [54696-03-6]. The reaction was set up with *tert*-butyl bromide (4 equiv, 274 mg, 2.0 mmol) and dry CPME (3.0 mL). The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (51 mg, 58%).

A typical procedure for alkylation of various heterocycles using cyclohexyl iodide: In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stirbar was charged with Pd(PPh₃)₄ (5 mol%, 29 mg, 0.025 mmol), DPPP (7 mol%, 14 mg, 0.035 mmol) and dry PhCF₃ (3.0 mL). After stirring at room temperature for 10 minutes, heteroarene (2 equiv, 1.0 mmol), Cs₂CO₃ (2 equiv, 1.0 mmol, 326 mg) and cyclohexyl iodide (1 equiv, 105 mg, 0.5 mmol) were added sequentially. The tube was capped tightly and the mixture was vigorously

stirred in a pre-warmed 110 °C oil bath. After cyclohexyl iodide was almost fully consumed (monitored by GC), the reaction mixture was cooled and concentrated on a rotary evaporator and the resulting residue was directly subjected to silica gel flash chromatography. The structure of the (major) product was assigned with ¹H NMR spectroscopy of the purified sample. The reaction scale of 0.5 mmol of cyclohexyl iodide was used for all the isolation, unless stated otherwise. When the molar ratio of heterarene to CyI was 1:2, the yield was much lower.

2-Cyclohexyl-5-methyl-1,3-benzoxazole [404584-29-8]. The reaction was conducted with 5 mol% Pd catalyst, 5-methyl-1,3-benzoxazole (1 equiv, 67 mg, 0.5 mmol) and cyclohexyl iodide (4 equiv, 420 mg, 2.0 mmol). The mixture was stirred at 110 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (74 mg, 68%). ¹H NMR (400 MHz, CDCl₃): δ 7.46 (s, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 2.93 (tt, *J* = 11.3, 3.6 Hz, 1H), 2.45 (s, 3H), 2.18-2.14 (m, 2H), 1.88-1.84 (m, 2H), 1.75-1.65 (m, 3H), 1.48-1.22 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 170.5, 148.8, 141.5, 133.7, 125.3, 119.6, 109.6, 38.0, 30.5, 25.8, 25.6, 21.4.

GCMS (EI): Calcd for C₁₄H₁₇NO: 215.1. Found: 215.1.

2-Cyclohexyl-4-ethoxycarbonyl-4-methyl-1,3-oxazole [933782-12-8]. The reaction was conducted with Pd(PPh₃)₄ (10 mol%, 58 mg, 0.05 mmol), DPPP (14 mol%, 28 mg, 0.07 mmol), ethyl 4-methyl-1,3-oxazole-5-carboxylate (1 equiv, 78 mg, 0.5 mmol) and cyclohexyl iodide (2 equiv, 210 mg, 1.0 mmol). The mixture was stirred at 110 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (86 mg, 72%). When 5 mol% of Pd catalyst was used, the yield was only about 25%.

¹H NMR (400 MHz, CDCl₃): δ 4.36 (q, *J* = 7.1 Hz, 2H), 2.81 (tt, *J* = 11.5, 3.6 Hz, 1H), 2.44 (s, 3H), 2.10-2.04 (m, 2H), 1.85-1.81 (m, 2H), 1.72-1.70 (m, 1H), 1.65-1.58 (m, 2H), 1.41-1.25 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 169.7, 159.0, 145.7, 136.9, 60.9, 37.7, 30.4, 25.6, 25.5, 14.4, 13.4.

GCMS (EI): Calcd for C₁₃H₁₉NO₃: 237.1. Found: 237.1.

2-Cyclohexyl-4-methyl-1,3-thiazole [25039-87-6]. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (60 mg, 66%). Only one isomer was detected by GCMS.

¹H NMR (400 MHz, CDCl₃): δ 6.70 (d, *J* = 0.8 Hz, 1H), 2.96 (tt, *J* = 11.4, 3.6 Hz, 1H), 2.41 (d, *J* = 0.8 Hz, 3H), 2.14-2.10 (m, 2H), 1.84 (dt, *J* = 12.6, 3.3 Hz, 2H), 1.76-1.71 (m, 1H), 1.56-1.44 (m, 2H), 1.42-1.34 (m, 2H), 1.32-1.21 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 176.5, 151.9, 111.6, 42.7, 33.8, 26.1, 25.8, 17.1.

GCMS (EI): Calcd for C₁₀H₁₅NS: 181.0. Found: 181.0.

2-Cyclohexyl-4,5-dimethyl-1,3-thiazole [25039-88-7]. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (62 mg, 63%).

¹H NMR (400 MHz, CDCl₃): δ 2.87 (tt, *J* = 11.4, 3.4 Hz, 1H), 2.30 (s, 3H), 2.28 (s, 3H), 2.10-2.06 (m, 2H), 1.84-1.80 (m, 2H), 1.74-1.70 (m, 1H), 1.51-1.35 (m, 4H), 1.34-1.21 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 172.5, 146.9, 124.2, 42.6, 33.9, 26.2, 25.8, 14.6, 11.3.

GCMS (EI): Calcd for C₁₁H₁₇NS: 195.1. Found: 195.1.

N-Ethoxycarbonyl-2-cyclohexylbenzimidazole. The reaction was conducted with Pd(PPh₃)₄ (10 mol%, 58 mg, 0.05 mmol), DPPP (14 mol%, 28 mg, 0.07 mmol), ethyl benzoimidazole-1-carboxylate (1 equiv, 95 mg, 0.5 mmol), K₂CO₃ (2 equiv, 138 mg, 1.0 mmol) and cyclohexyl iodide (4 equiv, 420 mg, 2.0 mmol). The mixture was stirred at 110 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (87 mg, 64%). When 5 mol% of Pd catalyst was used, the yield was only 22%.

¹H NMR (400 MHz, CDCl₃): δ 7.94-7.89 (m, 1H), 7.74-7.70 (m, 1H), 7.33-7.27 (m, 2H), 4.56 (q, *J* = 7.2 Hz, 2H), 3.55 (tt, *J* = 11.6, 3.2 Hz, 1H), 2.12 (d, *J* = 11.6 Hz, 2H), 1.92-1.88 (m, 2H), 1.79-1.67 (m, 3H), 1.53 (t, *J* = 7.2 Hz, 3H), 1.50-1.31 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 160.8, 150.5, 142.4, 132.9, 124.3, 124.2, 119.7, 115.0, 63.9, 38.8, 31.9, 26.4, 26.0, 14.2.

GCMS (EI): Calcd for C₁₆H₂₀N₂O₂: 272.1. Found: 272.1.

8-Cyclohexyl-1,3,7-trimethylpurine-2,6-dione [110166-60-4]. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:4 EA/hexanes) as white solid (105 mg, 76%).

^1H NMR (400 MHz, CDCl_3): δ 3.93 (s, 3H), 3.57 (s, 3H), 3.39 (s, 3H), 2.72 (tt, $J = 11.8, 3.4$ Hz, 1H), 1.93-1.85 (m, 4H), 1.78-1.64 (m, 3H), 1.44-1.29 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 158.0, 155.4, 151.8, 148.1, 107.0, 35.8, 31.4, 30.9, 29.7, 27.8, 26.0, 25.5.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_2$: 276.1. Found: 276.1.

4-Cyclohexylquinazoline [1466541-55-8]. The reaction mixture was stirred at 110 °C for 36 hours. The regioselectivity of C4 and C2 alkylation was determined to be 10:1 by GC and GCMS. The product was purified by flash chromatography (1:10 EA/hexanes) as colorless oil (76 mg, 72%). (cf: A. Antonchick and L. Burgmann, *Angew. Chem. Int. Ed.*, **2013**, 52, 3267).

^1H NMR (400 MHz, CDCl_3): δ 9.25 (s, 1H), 8.19 (d, $J = 8.4$ Hz, 1H), 8.04 (d, $J = 8.4$ Hz, 1H), 7.87 (ψt, $J = 7.6$ Hz, 1H), 7.63 (ψt, $J = 7.6$ Hz, 1H), 3.59-3.53 (m, 1H), 1.98-1.94 (m, 4H), 1.87-1.77 (m, 3H), 1.59-1.48 (m, 2H), 1.44-1.34 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 175.1, 154.8, 150.1, 133.2, 129.4, 127.3, 124.2, 123.3, 41.3, 32.0, 26.5, 26.0.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2$: 212.1. Found: 212.1

2-Cyclohexyl-1,3,5-triazine [27431-29-4]. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as colorless oil (65 mg, 80%). Double alkylation was not detected by GCMS.

^1H NMR (400 MHz, CDCl_3): δ 9.09 (s, 2H), 2.82 (tt, $J = 11.7, 3.4$ Hz, 1H), 2.03-2.00 (m, 2H), 1.89-1.85 (m, 2H), 1.81-1.74 (m, 1H), 1.62 (ψqd , $J = 12.4, 2.9$ Hz, 2H), 1.47-1.24 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 182.7, 165.8, 46.9, 31.1, 25.9, 25.8.

GCMS (EI): Calcd for $\text{C}_9\text{H}_{13}\text{N}_3$: 163.1. Found: 163.1

2-Cyclohexylpyrazine *N*-oxide [1417437-49-0]. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (EA) as yellow solid (67 mg, 75%). The reaction also generated a trace amount of two dialkylation products as observed by GC and GCMS and the ratio of mono- versus dialkylation was estimated to 10:1.

^1H NMR (400 MHz, CDCl_3): δ 8.42 (s, 1H), 8.29 (d, $J = 4.0$ Hz, 1H), 8.10 (d, $J = 4.0$ Hz, 1H), 3.36 (tt, $J = 11.9, 3.2$ Hz, 1H), 2.07-2.05 (m, 2H), 1.91-1.86 (m, 2H), 1.84-1.79 (m, 1H), 1.55-1.44 (m, 2H), 1.42-1.24 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 151.4, 145.7, 144.6, 133.7, 35.6, 30.1, 26.2, 26.0.

GCMS (EI): Calcd for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}$: 178.1. Found: 178.1.

2-Cyclohexyl-6-methylpyridine *N*-oxide [1126110-20-0]. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (EA) as yellow oil (67 mg, 70%). only one monoalkylation isomer was detected by GC.

^1H NMR (400 MHz, CDCl_3): δ 7.15-7.08 (m, 3H), 3.58 (tt, $J = 11.9, 2.9$ Hz, 1H), 2.53 (s, 3H), 2.06 (d, $J = 12.5$ Hz, 2H), 1.88-1.78 (m, 3H), 1.58-1.47 (m, 2H), 1.32-1.22 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 156.6, 149.0, 124.7, 123.4, 120.5, 37.5, 31.0, 26.4, 26.3, 18.5.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}$: 191.1. Found: 191.1.

5-Cyclohexylpicolinonitrile. The reaction was conducted with $\text{Pd}(\text{PPh}_3)_4$ (5 mol%, 29 mg, 0.025 mmol), DPPP (7 mol%, 14 mg, 0.035 mmol), picolinonitrile (2 equiv, 104 mg, 1.0

mmol), CsF (2 equiv, 152 mg, 1.0 mmol) and cyclohexyl iodide (1 equiv, 110 mg, 0.5 mmol). The mixture was stirred at 110 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as colorless oil (57 mg, 61%).

The regioselectivity in the crude mixture was determined to be 12:1 by GC and GCMS. When 1:2 molar ratio of picolinonitrile and cyclohexyl iodide was used in the presence of Cs₂CO₃ as base, the yield was only about 20%.

¹H NMR (400 MHz, CDCl₃): δ 8.57 (s, 1H), 7.65-7.61 (m, 2H), 2.64-2.60 (m, 1H), 1.89 (d, *J* = 8.9 Hz, 4H), 1.79 (d, *J* = 12.8 Hz, 1H), 1.48-1.36 (m, 4H), 1.32-1.25 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 150.6, 147.1, 134.8, 131.4, 128.3, 117.5, 42.2, 33.7, 26.4, 25.7.

GCMS (EI): Calcd for C₁₂H₁₄N₂: 186.1. Found: 186.1.

5-Cyclohexylpicolinaldehyde. The reaction mixture was stirred at 110 °C for 36 hours. About 53% of picolinaldehyde and 100% of cyclohexyl iodide were consumed as judged by GC. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (43 mg, 45%). The regioselectivity in the crude mixture was determined to be 4:1 by GC and GCMS.

¹H NMR (400 MHz, CDCl₃): δ 10.06 (d, *J* = 0.6 Hz, 1H), 8.64 (d, *J* = 2.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.69 (dd, *J* = 8.0, 2.0 Hz, 1H), 2.68-2.61 (m, 1H), 1.92-1.88 (m, 4H), 1.82-1.78 (m, 1H), 1.52-1.37 (m, 4H), 1.34-1.26 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 193.2, 151.1, 149.5, 148.1, 135.0, 121.7, 42.3, 33.8, 26.5, 25.8.

GCMS (EI): Calcd for C₁₂H₁₅NO: 189.1. Found: 189.1.

6-Cyclohexylnicotinaldehyde. The reaction mixture was stirred at 110 °C for 36 hours. About 61% of nicotinaldehyde and 100% of cyclohexyl iodide were consumed as judged by GC. The product was purified by flash chromatography (1:10 EA/hexanes) as colorless oil (52 mg, 55%). The C6/C4 selectivity in the mixture was determined to be 7:1 by GC and GCMS.

^1H NMR (400 MHz, CDCl_3): δ 10.07 (s, 1H), 8.98 (d, $J = 2.0$ Hz, 1H), 8.09 (dd, $J = 8.1, 2.0$ Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 1H), 2.81 (tt, $J = 11.7, 3.3$ Hz, 1H), 1.98-1.86 (m, 4H), 1.79-1.76 (m, 1H), 1.56 (ψqd , $J = 12.5, 2.8$ Hz, 2H), 1.43 (ψqt , $J = 12.6, 3.0$ Hz, 2H), 1.35-1.24 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 190.6, 172.8, 152.0, 136.1, 129.5, 121.6, 47.0, 32.6, 26.4, 25.9.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}$: 189.1. Found: 189.1.

4-Cyclohexylnicotinaldehyde (minor isomer). ^1H NMR (400 MHz, CDCl_3): δ 10.43 (s, 1H), 8.74 (dd, $J = 4.7, 1.9$ Hz, 1H), 8.10 (dd, $J = 7.8, 1.9$ Hz, 1H), 7.30-7.26 (m, 1H), 3.58-3.50 (m, 1H), 1.92-1.74 (m, 7H), 1.52-1.28 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 191.0, 168.1, 153.5, 137.5, 128.4, 121.4, 41.1, 32.6, 26.5, 25.9.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}$: 189.1. Found: 189.1.

3-Acetyl-6-cyclohexylpyridine. The reaction mixture was stirred at 110 °C for 36 hours. About 66% of nicotinaldehyde and 100% of cyclohexyl iodide were consumed as judged by GC. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (59 mg, 58%). The C6/C2 selectivity in the mixture was determined to be 9:1 by GC and GCMS.

^1H NMR (400 MHz, CDCl_3): δ 9.08 (d, $J = 1.8$ Hz, 1H), 8.15 (dd, $J = 8.2, 1.8$ Hz, 1H), 7.26 (d, $J = 8.2$ Hz, 1H), 2.78 (tt, $J = 11.7, 3.3$ Hz, 1H), 2.61 (s, 3H), 1.97-1.85 (m, 4H), 1.80-1.75 (m, 1H), 1.55 (ψqd , $J = 12.5, 3.0$ Hz, 2H), 1.42 (ψqt , $J = 12.5, 3.0$ Hz, 2H), 1.35-1.24 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 196.6, 171.3, 149.6, 135.9, 130.2, 121.0, 46.8, 32.6, 26.6, 26.4, 25.9.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}$: 203.1. Found: 203.1.

3-Acetyl-2-cyclohexylpyridine (minor isomer). ^1H NMR (400 MHz, CDCl_3): δ 8.64 (dd, $J = 4.8, 1.7$ Hz, 1H), 7.77 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.16 (dd, $J = 7.8, 4.8$ Hz, 1H), 3.13 (tt, $J = 11.6, 3.5$ Hz, 1H), 2.58 (s, 3H), 1.86-1.79 (m, 4H), 1.75-1.65 (m, 3H), 1.45-1.24 (m, 3H).

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}$: 203.1. Found: 203.1.

3-Cyclohexyl-4-formylpyridine. The reaction was conducted with Pd(PPh₃)₄ (5 mol%, 29 mg, 0.025 mmol), DPPP (7 mol%, 14 mg, 0.035 mmol), isonicotinaldehyde (2 equiv, 107 mg, 1.0 mmol), CsF (2 equiv, 152 mg, 1.0 mmol) and cyclohexyl iodide (1 equiv, 110 mg, 0.5 mmol). The mixture was stirred at 110 °C for 60 hours. About 57% of nicotinaldehyde and 100% of cyclohexyl iodide were consumed as judged by GC. The product was purified by flash chromatography (1:2 EA/hexanes) as yellow oil (38 mg, 40%). The regioselectivity in the mixture was determined to be 7:1 by GC and GCMS. When Cs₂CO₃ was used as base, the yield was only about 20%.

¹H NMR (400 MHz, CDCl₃): δ 10.44 (s, 1H), 8.80 (s, 1H), 8.68 (d, *J* = 4.9 Hz, 1H), 7.59 (d, *J* = 4.9 Hz, 1H), 3.46-3.40 (m, 1H), 1.93-1.80 (m, 5H), 1.65-1.56 (m, 2H), 1.53-1.43 (m, 2H), 1.37-1.26 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 191.6, 149.9, 148.3, 142.4, 138.2, 122.2, 37.2, 34.2, 25.9, 25.5.

GCMS (EI): Calcd for C₁₂H₁₅NO: 189.1. Found: 189.1.

4-Cyano-3-cyclohexyl-2-fluoropyridine. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow solid (76 mg, 74%). The regioselectivity in the mixture was determined to be 17:1 by GC and GCMS.

¹H NMR (400 MHz, CDCl₃): δ 8.19 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.39 (dd, *J* = 5.0, 1.0 Hz, 1H), 3.06 (tt, *J* = 11.7, 3.4 Hz, 1H), 1.96-1.87 (m, 4H), 1.80-1.76 (m, 3H), 1.48-1.26 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 161.9 (d, *J*_{C-F} = 242.6 Hz), 145.6 (d, *J*_{C-F} = 16.2 Hz), 132.2 (d, *J*_{C-F} = 31.8 Hz), 124.3 (d, *J*_{C-F} = 5.3 Hz), 123.5 (d, *J*_{C-F} = 8.5 Hz), 115.3 (d, *J*_{C-F} = 5.5 Hz), 40.7 (d, *J*_{C-F} = 4.2 Hz), 30.5 (d, *J*_{C-F} = 3.0 Hz), 26.4, 25.4.

¹⁹F NMR (376 MHz, CDCl₃): δ -63.44.

GCMS (EI): Calcd for C₁₂H₁₃FN₂: 204.1. Found: 204.1.

3-Cyano-2-cyclohexylthiophene. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (88 mg, 92%). The regioselectivity in the mixture was determined to be 32:1 by GC and GCMS.

^1H NMR (400 MHz, CDCl_3): δ 7.15 (d, $J = 5.3$ Hz, 1H), 7.10 (d, $J = 5.3$ Hz, 1H), 3.20-3.12 (m, 1H), 2.07-2.05 (m, 2H), 1.86-1.84 (m, 2H), 1.79-1.75 (m, 1H), 1.50-1.37 (m, 4H), 1.32-1.22 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 164.0, 128.1, 123.4, 115.3, 106.4, 39.6, 35.2, 26.3, 25.6.

GCMS (EI): Calcd for $\text{C}_{11}\text{H}_{13}\text{NS}$: 191.1. Found: 191.1.

3-Acetyl-2-cyclohexylthiophene. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (95 mg, 91%). The regioselectivity in the mixture was determined to be 36:1 by GC and GCMS.

^1H NMR (400 MHz, CDCl_3): δ 7.33 (d, $J = 5.4$ Hz, 1H), 7.06 (d, $J = 5.4$ Hz, 1H), 3.77 (tt, $J = 11.7, 3.4$ Hz, 1H), 2.51 (s, 3H), 2.05-2.01 (m, 2H), 1.83-1.72 (m, 3H), 1.52-1.40 (m, 2H), 1.39-1.19 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 194.0, 162.4, 134.5, 128.9, 121.2, 38.8, 35.5, 30.3, 26.6, 26.0.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{16}\text{OS}$: 208.1. Found: 208.1.

2-Cyclohexyl-3-formylthiophene. The reaction mixture was set up with $\text{Pd}(\text{PPh}_3)_4$ (10 mol%, 58 mg, 0.05 mmol) and DPPP (14 mol%, 28 mg, 0.07 mmol) then stirred at 110 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (63 mg, 65%). The regioselectivity in the mixture was determined to be >50:1 by GC and GCMS.

^1H NMR (400 MHz, CDCl_3): δ 10.07 (s, 1H), 7.37 (d, $J = 5.3$ Hz, 1H), 7.08 (d, $J = 5.3$ Hz, 1H), 3.59-3.53 (m, 1H), 2.06-2.01 (m, 2H), 1.91-1.85 (m, 2H), 1.80-1.76 (m, 1H), 1.54-1.39 (m, 4H), 1.33-1.24 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 184.3, 165.1, 135.8, 127.2, 122.4, 38.0, 36.2, 26.5, 25.7.

GCMS (EI): Calcd for $\text{C}_{11}\text{H}_{14}\text{OS}$: 194.0. Found: 194.0.

5-Cyclohexyl-2-formylthiophene. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (65 mg, 67%). The C5:C3 regioselectivity in the mixture was determined to be 3:1 by GC and GCMS. ¹H NMR (400 MHz, CDCl₃): δ 9.82 (s, 1H), 7.61 (d, *J* = 3.8 Hz, 1H), 6.92 (dd, *J* = 3.8, 0.4 Hz, 1H), 2.88-2.82 (m, 1H), 2.07-2.05 (m, 2H), 1.90-1.83 (m, 2H), 1.77-1.73 (m, 1H), 1.50-1.35 (m, 4H), 1.31-1.21 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 182.8, 164.0, 140.9, 136.8, 123.8, 40.2, 35.0, 26.2, 25.7.

GCMS (EI): Calcd for C₁₁H₁₄OS: 194.0. Found: 194.0.

3-Cyclohexyl-2-formylthiophene (minor isomer). ¹H NMR (400 MHz, CDCl₃): δ 10.10 (d, *J* = 1.0 Hz, 1H), 7.63 (dd, *J* = 5.0, 0.6 Hz, 1H), 7.09 (d, *J* = 5.0 Hz, 1H), 3.27 (tt, *J* = 11.4, 3.1 Hz, 1H), 1.93-1.84 (m, 4H), 1.82-1.76 (m, 1H), 1.56-1.37 (m, 4H), 1.33-1.22 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 182.2, 158.2, 137.0, 134.6, 128.2, 38.1, 34.6, 26.5, 25.8.

GCMS (EI): Calcd for C₁₁H₁₄OS: 194.0. Found: 194.0.

3-Cyclohexyl-2-formyl-5-methylthiophene. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (70 mg, 67%). Only one isomer was detected by GC and GCMS.

¹H NMR (400 MHz, CDCl₃): δ 9.98 (s, 1H), 6.77 (s, 1H), 3.21-3.15 (m, 1H), 2.50 (s, 3H), 1.90-1.83 (m, 4H), 1.79-1.76 (m, 1H), 1.52-1.35 (m, 4H), 1.31-1.21 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 181.5, 159.1, 150.8, 135.2, 127.2, 38.2, 34.6, 26.5, 25.9, 16.3.

GCMS (EI): Calcd for C₁₂H₁₆OS: 208.0. Found: 208.0.

2-Cyclohexyl-3-formylbenzothiophene [6774-26-1]. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow solid (120 mg, 98%). Only one isomer was detected by GCMS.

¹H NMR (400 MHz, CDCl₃): δ 10.40 (s, 1H), 8.60 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.46-7.42 (m, 1H), 7.37-7.33 (m, 1H), 3.67 (tt, *J* = 11.5, 3.4 Hz, 1H), 2.11-2.08 (m, 2H),

1.93-1.88 (m, 2H), 1.84-1.79 (m, 1H), 1.60 (ψ qd, $J = 12.4, 2.8$ Hz, 2H), 1.48 (ψ qt, $J = 12.4, 2.8$ Hz, 2H), 1.38-1.25 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 184.1, 170.6, 137.3, 136.9, 128.6, 125.8, 125.0, 124.1, 121.8, 38.4, 36.1, 26.5, 25.6.

GCMS (EI): Calcd for $\text{C}_{15}\text{H}_{16}\text{OS}$: 244.1. Found: 244.0.

2-Acetyl-3-Cyclohexylbenzothiophene. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (118 mg, 92%). Only one isomer was detected by GC and GCMS.

^1H NMR (400 MHz, CDCl_3): δ 8.20 (d, $J = 8.1$ Hz, 1H), 7.82 (d, $J = 7.3$ Hz, 1H), 7.45-7.35 (m, 2H), 4.04 (tt, $J = 12.5, 3.6$ Hz, 1H), 2.63 (s, 3H), 2.16-2.04 (m, 2H), 1.90-1.76 (m, 5H), 1.53-1.37 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 193.8, 148.3, 140.4, 139.2, 134.9, 126.7, 126.3, 124.1, 123.0, 38.8, 31.4, 31.0, 27.0, 26.2.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{18}\text{OS}$: 258.1. Found: 258.1.

5-Cyclohexyl-2-formylfuran. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (72 mg, 80%). The regioselectivity in the mixture was determined to be 17:1 by GC and GCMS.

^1H NMR (400 MHz, CDCl_3): δ 9.52 (s, 1H), 7.17 (d, $J = 3.6$ Hz, 1H), 6.21 (d, $J = 3.6$ Hz, 1H), 2.76-2.69 (m, 1H), 2.08-2.05 (m, 2H), 1.83-1.79 (m, 2H), 1.74-1.71 (m, 1H), 1.50-1.21 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ 177.0, 168.1, 151.5, 123.3, 106.7, 37.6, 31.1, 25.8, 25.7.

GCMS (EI): Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_2$: 178.0. Found: 178.0.

2-Acetyl-5-cyclohexylfuran. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (72 mg, 75%). The regioselectivity in the mixture was determined to be 24:1 by GC and GCMS.

¹H NMR (400 MHz, CDCl₃): δ 7.10 (d, *J* = 3.5 Hz, 1H), 6.12 (d, *J* = 3.5 Hz, 1H), 2.73-2.67 (m, 1H), 2.42 (s, 3H), 2.07-2.04 (m, 2H), 1.83-1.80 (m, 2H), 1.74-1.70 (m, 1H), 1.48-1.30 (m, 4H), 1.28-1.21 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 186.1, 166.2, 151.2, 118.9, 106.1, 37.5, 31.2, 25.9, 25.8, 25.7.

GCMS (EI): Calcd for C₁₂H₁₆O₂: 192.1. Found: 192.1.

2-Cyclohexyl-3-formylfuran. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (87 mg, 98%). The regioselectivity in the mixture was determined to be 17:1 by GC and GCMS.

¹H NMR (400 MHz, CDCl₃): δ 10.0 (s, 1H), 7.29 (d, *J* = 1.9 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 3.16 (tt, *J* = 11.8, 3.3 Hz, 1H), 1.90-1.85 (m, 4H), 1.78-1.62 (m, 3H), 1.46-1.24 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 184.6, 169.8, 141.7, 121.1, 107.8, 36.9, 31.5, 26.1, 25.6.

GCMS (EI): Calcd for C₁₁H₁₄O₂: 178.0. Found: 178.0.

2-Acetyl-3-cyclohexylbenzofurane. The reaction mixture was stirred at 110 °C for 48 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (74 mg, 61%). The regioselectivity in the mixture was determined to be 12:1 by GC and GCMS.

¹H NMR (400 MHz, CDCl₃): δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.46-7.42 (m, 1H), 7.27-7.23 (m, 1H), 3.84-3.76 (m, 1H), 2.62 (s, 3H), 1.95-1.80 (m, 7H), 1.54-1.24 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 191.7, 154.4, 147.0, 133.3, 127.7, 127.6, 123.8, 122.8, 112.4, 35.2, 31.9, 28.3, 26.7, 26.2.

GCMS (EI): Calcd for C₁₆H₁₈O₂: 242.1. Found: 242.1.

***N*-Methyl-2-cyclohexyl-5-formylpyrrole.** The reaction mixture was stirred at 110 °C for 60 hours. About 54% of *N*-methyl-2-formylpyrrole and 100% of cyclohexyl iodide were consumed as judged by GC. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (42 mg, 44%). The regioselectivity in the mixture was determined to be 7:1 by GC and GCMS.

¹H NMR (400 MHz, CDCl₃): δ 9.43 (s, 1H), 6.85 (d, *J* = 4.1 Hz, 1H), 6.04 (d, *J* = 4.1 Hz, 1H), 3.91 (s, 3H), 2.60-2.54 (m, 1H), 1.93-1.84 (m, 4H), 1.81-1.75 (m, 1H), 1.45-1.38 (m, 4H), 1.36-1.22 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 178.9, 150.0, 131.6, 124.8, 106.5, 35.3, 32.5, 32.2, 26.4, 25.9.

GCMS (EI): Calcd for C₁₂H₁₇NO: 191.1. Found: 191.1.

***N*-Ethoxycarbonyl-2-cyclohexyl-5-formylpyrrole.** The reaction was conducted with Pd(PPh₃)₄ (5 mol%, 29 mg, 0.025 mmol), DPPP (7 mol%, 14 mg, 0.035 mmol), *N*-ethoxycarbonyl-2-formylpyrrole (2 equiv, 167 mg, 1.0 mmol), CsF (2 equiv, 152 mg, 1.0 mmol), cyclohexyl iodide (1 equiv, 110 mg, 0.5 mmol) and PhCF₃ (3 mL). The mixture was stirred at 110 °C for 44 hours. The product was purified by flash chromatography (1:8 EA/hexanes) as yellow oil (85 mg, 68%). The regioselectivity in the mixture was determined to be 3:1 by GC and GCMS. When Cs₂CO₃ was used as base, no desired product was detected.

¹H NMR (400 MHz, CDCl₃): δ 9.79 (s, 1H), 7.04 (d, *J* = 3.8 Hz, 1H), 6.11 (d, *J* = 3.8 Hz, 1H), 4.48 (q, *J* = 7.2 Hz, 2H), 3.05-2.99 (m, 1H), 2.00-1.98 (m, 2H), 1.84-1.81 (m, 2H), 1.77-1.73 (m, 1H), 1.45-1.32 (m, 7H), 1.29-1.22 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 179.7, 151.0, 149.8, 134.1, 122.8, 108.9, 64.7, 36.7, 33.3, 26.4, 26.0, 13.9.

GCMS (EI): Calcd for C₁₄H₁₉NO₃: 249.1. Found: 249.1.

***N*-Methyl-3-acetyl-2-cyclohexylpyrrole.** The reaction mixture was stirred at 110 °C for 60 hours. About 50% of *N*-methyl-3-acetylpyrrole and 100% of cyclohexyl iodide were consumed as judged by GC. The product was purified by flash chromatography (1:10 EA/hexanes) as white solid (43 mg, 42%).

¹H NMR (400 MHz, CDCl₃): δ 6.46 (d, *J* = 3.0 Hz, 1H), 6.37 (d, *J* = 3.0 Hz, 1H), 3.65 (s, 3H), 3.43-3.40 (m, 1H), 2.40 (s, 3H), 2.05-1.96 (m, 2H), 1.83-1.81 (m, 2H), 1.73-1.70 (m, 1H), 1.67-1.61 (m, 2H), 1.43-1.31 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 194.6, 143.3, 121.3, 120.9, 110.7, 36.4, 35.7, 29.3, 29.1, 27.0, 25.8.

GCMS (EI): Calcd for C₁₃H₁₉NO: 205.1. Found: 205.1.

***N*-Ethoxycarbonyl-2-acetyl-5-cyclohexylpyrrole.** The reaction was conducted with Pd(PPh₃)₄ (5 mol%, 29 mg, 0.025 mmol), DPPP (7 mol%, 14 mg, 0.035 mmol), *N*-ethoxycarbonyl-2-acetylpyrrole (2 equiv, 182 mg, 1.0 mmol), CsF (2 equiv, 152 mg, 1.0 mmol), cyclohexyl iodide (1 equiv, 110 mg, 0.5 mmol) and PhCF₃ (3 mL). The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:8 EA/hexanes) as yellow oil (86 mg, 65%). The regioselectivity in the mixture was determined to be 14:1 by GC and GCMS. When Cs₂CO₃ was used as base, no desired product was detected.

¹H NMR (400 MHz, CDCl₃): δ 6.85 (d, *J* = 3.8 Hz, 1H), 5.99 (d, *J* = 3.8 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 2.75-2.69 (m, 1H), 2.39 (s, 3H), 2.00-1.92 (m, 2H), 1.82-1.71 (m, 3H), 1.41-1.29 (m, 7H), 1.27-1.20 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 186.4, 152.6, 148.0, 132.2, 119.8, 106.5, 65.0, 35.8, 33.2, 26.3, 25.9, 25.8, 13.7.

GCMS (EI): Calcd for C₁₅H₂₁NO₃: 263.1. Found: 263.1.

***N*-Ethoxycarbonyl-2-cyclohexylindole.** The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as colorless oil (75 mg, 55%). The regioselectivity in the mixture was determined to be 28:1 by GC and GCMS. (*cf.* A. Yasuhara, Y. Takeda, N. Suzuki and T. Sakamoto, *Chem. Pharm. Bull.* **2002**, *50*, 235).

¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J* = 8.1 Hz, 1H), 7.47-7.45 (d, *J* = 8.1 Hz, 1H), 7.25-7.17 (m, 2H), 6.39 (s, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 3.37 (tt, *J* = 11.1, 3.0 Hz, 1H), 2.11 (d, *J*

= 13.2 Hz, 2H), 1.87-1.83 (m, 2H), 1.79-1.76 (m, 1H), 1.50 (t, $J = 7.1$ Hz, 3H), 1.47-1.21 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ 152.0, 148.1, 136.5, 129.6, 123.4, 122.8, 119.9, 115.7, 105.4, 62.9, 37.6, 33.7, 26.7, 26.4, 14.3.

GCMS (EI): Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_2$: 271.1. Found: 271.1.

***N*-Ethoxycarbonyl-5-ethoxycarbonyl-2-cyclohexylindole.** The reaction was conducted with $\text{Pd}(\text{PPh}_3)_4$ (10 mol%, 58 mg, 0.05 mmol), DPPP (14 mol%, 28 mg, 0.07 mmol), *N*-ethoxycarbonyl-5-ethoxycarbonylindole (2 equiv, 247 mg, 1.0 mmol), K_3PO_4 (2 equiv, 213 mg, 1.0 mmol), cyclohexyl iodide (1 equiv, 110 mg, 0.5 mmol) and PhCF_3 (3 mL). The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as white solid (109 mg, 66%). The regioselectivity in the mixture was determined to be 23:1 by GC and GCMS. When Cs_2CO_3 was used as base, the yield was only about 15% and the regioselectivity was 20:1.

^1H NMR (400 MHz, CDCl_3): δ 8.17 (d, $J = 1.5$ Hz, 1H), 8.11 (d, $J = 8.8$ Hz, 1H), 7.93 (dd, $J = 8.8, 1.5$ Hz, 1H), 6.44 (s, 1H), 4.52 (q, $J = 7.1$ Hz, 2H), 3.93 (s, 3H), 3.37-3.31 (m, 1H), 2.10 (d, $J = 11.9$ Hz, 2H), 1.87-1.84 (m, 2H), 1.78 (d, $J = 12.8$ Hz, 1H), 1.51 (t, $J = 7.1$ Hz, 3H), 1.47-1.25 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ 167.6, 151.7, 149.4, 139.3, 129.4, 124.8, 124.7, 122.1, 115.3, 105.6, 63.4, 52.0, 37.7, 33.6, 26.6, 26.3, 14.3.

GCMS (EI): Calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_4$: 329.1. Found: 329.1.

***N*-Ethoxycarbonyl-5-methoxy-2-cyclohexylindole.** The reaction was conducted with $\text{Pd}(\text{PPh}_3)_4$ (10 mol%, 58 mg, 0.05 mmol), DPPP (14 mol%, 28 mg, 0.07 mmol), *N*-ethoxycarbonyl-5-methoxyindole (2 equiv, 219 mg, 1.0 mmol), K_3PO_4 (2 equiv, 213 mg, 1.0 mmol), cyclohexyl iodide (1 equiv, 110 mg, 0.5 mmol) and PhCF_3 (3 mL). The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as colorless oil (95 mg, 63%). The regioselectivity in the mixture was determined to be 10:1 by GC and GCMS. When Cs_2CO_3 was used as base, the yield was only about 15% with 7:1 regioselectivity.

^1H NMR (400 MHz, CDCl_3): δ 7.97 (d, J = 9.1 Hz, 1H), 6.94 (d, J = 2.6 Hz, 1H), 6.84 (dd, J = 9.1, 2.6 Hz, 1H), 6.32 (s, 1H), 4.48 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.34 (tt, J = 11.4, 3.0 Hz, 1H), 2.10 (d, J = 12.5 Hz, 2H), 1.87-1.82 (m, 2H), 1.79-1.75 (m, 1H), 1.51-1.38 (m, 5H), 1.36-1.25 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 155.9, 151.9, 148.9, 131.2, 130.5, 116.5, 111.7, 105.3, 102.7, 62.8, 55.7, 37.7, 33.7, 26.7, 26.4, 14.4.

GCMS (EI): Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_3$: 301.1. Found: 301.1.

3-Acetyl-2-cyclohexylindole. The reaction was set up with $\text{Pd}(\text{PPh}_3)_4$ (5 mol%, 29 mg, 0.025 mmol), DPPP (7 mol%, 14 mg, 0.035 mmol), *N*-ethoxycarbonyl-3-acetylindole (2 equiv, 231 mg, 1.0 mmol), Cs_2CO_3 (2 equiv, 326 mg, 1.0 mmol), cyclohexyl iodide (1 equiv, 110 mg, 0.5 mmol) and PhCF_3 (3 mL). The mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:4 EA/hexanes) as white solid (84 mg, 70%). The *N*-carbamate group was completely hydrolyzed by the base during the reaction. When 3-acetylindole was used as the substrate, the yield was only about 5%.

^1H NMR (400 MHz, CDCl_3): δ 9.09 (s, 1H), 7.96 (d, J = 7.7 Hz, 1H), 7.39 (dd, J = 7.2, 1.1 Hz, 1H), 7.27-7.19 (m, 2H), 3.83-3.77 (m, 1H), 2.71 (s, 3H), 2.12-2.05 (m, 2H), 1.87-1.76 (m, 3H), 1.54-1.40 (m, 4H), 1.29-1.19 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 195.0, 153.0, 134.7, 126.9, 122.2, 121.9, 120.8, 113.0, 111.3, 36.8, 32.3, 31.7, 26.5, 26.1.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}$: 241.1. Found: 241.1.

2-Cyclohexyl-3-formylindole. The reaction was set up with $\text{Pd}(\text{PPh}_3)_4$ (5 mol%, 29 mg, 0.025 mmol), DPPP (7 mol%, 14 mg, 0.035 mmol), *N*-ethoxycarbonyl-3-formylindole (2 equiv, 217 mg, 1.0 mmol), K_2CO_3 (2 equiv, 138 mg, 1.0 mmol), cyclohexyl iodide (1 equiv, 110 mg, 0.5 mmol) and PhCF_3 (3 mL). The mixture was stirred at 110 °C for 36 hours. After the mixture was cooled to room temperature, KOH (2 equiv, 56 mg, 1.0 mmol) was added to completely remove the carbamate group. The mixture was stirred at 110 °C for 24 hours. The product was purified by flash chromatography (1:4 EA/hexanes) as yellow solid (100 mg,

88%). If Cs₂CO₃ was used as base during coupling, the yield was only about 3%. When 3-formylindole was used in the presence of K₂CO₃, the yield was only about 19%.

¹H NMR (400 MHz, CDCl₃): δ 10.27 (s, 1H), 9.31 (s, 1H), 8.30-8.28 (m, 1H), 7.40-7.37 (m, 1H), 7.28-7.22 (m, 2H), 3.41 (tt, *J* = 12.0, 3.3 Hz, 1H), 2.09-2.05 (m, 2H), 1.91 (ψdt, *J* = 6.7, 3.1 Hz, 2H), 1.84-1.77 (m, 1H), 1.62 (ψqd, *J* = 12.6, 3.1 Hz, 2H), 1.48 (ψqt, *J* = 12.8, 3.1 Hz, 2H), 1.34-1.22 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 184.4, 156.3, 135.1, 126.1, 123.4, 122.8, 121.2, 113.1, 111.1, 36.0, 33.3, 26.3, 25.8.

GCMS (EI): Calcd for C₁₅H₁₇NO: 227.1. Found: 227.1.

***N*-Methyl-2-Cyclohexyl-3-formylindole.** The reaction was conducted with Pd(PPh₃)₄ (10 mol%, 58 mg, 0.05 mmol), DPPP (14 mol%, 28 mg, 0.07 mmol), *N*-methyl-3-formylindole (2 equiv, 159 mg, 1.0 mmol), Cs₂CO₃ (2 equiv, 1.0 mmol, 326 mg), cyclohexyl iodide (1 equiv, 110 mg, 0.5 mmol) and PhCF₃ (3 mL). The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:8 EA/hexanes) as yellow oil (96 mg, 80%).

¹H NMR (400 MHz, CDCl₃): δ 10.44 (s, 1H), 8.39-8.35 (m, 1H), 7.31-7.26 (m, 3H), 3.80 (s, 3H), 3.23 (t, *J* = 11.7 Hz, 1H), 2.00-1.84 (m, 7H), 1.51-1.35 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 184.8, 155.2, 137.0, 126.2, 123.2, 123.0, 121.7, 114.0, 109.4, 37.4, 32.9, 31.0, 27.0, 25.8.

GCMS (EI): Calcd for C₁₆H₁₉NO: 241.1. Found: 241.1.

Typical procedure for alkylation of heterocycles using 1-adamantyl iodide: In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stirbar was charged with Pd(PPh₃)₄ (10 mol%, 58 mg, 0.05 mmol), DPPP (14 mol%, 28 mg, 0.07 mmol) and dry PhCF₃ (3.0 mL). After stirring at room temperature for 10 minutes, heteroarene (2 equiv, 1.0 mmol), Cs₂CO₃ (2 equiv, 1.0 mmol, 326 mg) and 1-adamantyl iodide (1 equiv, 131 mg, 0.5 mmol) were added sequentially. The tube was capped tightly and the mixture was vigorously stirred in a pre-warmed 110 °C oil bath. After alkyl iodide was almost fully consumed (monitored by GC), the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator. The resulting residue was directly subjected to silica gel flash chromatography. The structure of the purified product was assigned by ¹H NMR spectroscopy. The typical procedure on a 0.5 mmol of 1-adamantyl iodide was used for all the isolation, unless stated otherwise.

2-(1-Adamantyl)-1,3-benzothiazole. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:20 EA/hexanes) as white solid (108 mg, 80%).

^1H NMR (400 MHz, CDCl_3): δ 7.99 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.45-7.41 (m, 1H), 7.34-7.30 (m, 1H), 2.15 (ψ s, 9H), 1.82 (ψ s, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 182.2, 153.2, 134.4, 125.7, 124.4, 122.7, 121.6, 43.0, 40.2, 36.6, 28.6.

GCMS (EI): Calcd for $\text{C}_{17}\text{H}_{19}\text{NS}$: 269.1. Found: 269.1.

2-(1-Adamantyl)-4-methyl-1,3-thiazole. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as colorless oil (79 mg, 68%).

^1H NMR (400 MHz, CDCl_3): δ 6.71 (d, J = 0.9 Hz, 1H), 2.43 (d, J = 0.9 Hz, 3H), 2.10-2.01 (m, 9H), 1.79-1.75 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 181.2, 151.9, 111.4, 43.2, 39.2, 36.5, 28.6, 17.3.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{19}\text{NS}$: 233.1. Found: 233.1.

2-(1-Adamantyl)-5-(2-hydroxyethyl)-4-methyl-1,3-thiazole. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:4 EA/hexanes) as yellow solid (100 mg, 72%).

^1H NMR (400 MHz, CDCl_3): δ 3.81 (ψ s, 2H), 2.96 (t, J = 6.4 Hz, 2H), 2.34 (s, 3H), 2.08 (ψ s, 3H), 2.02 (ψ d, J = 2.8 Hz, 6H), 1.84-1.74 (m, 7H).

^{13}C NMR (100 MHz, CDCl_3): δ 178.3, 148.1, 125.3, 63.2, 43.1, 39.2, 36.5, 29.9, 28.6, 15.1.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{23}\text{NOS}$: 277.1. Found: 277.1.

2-(1-Adamantyl)-4-ethoxycarbonyl-5-methyl-1,3-oxazole. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as white solid (72 mg, 50%).

¹H NMR (400 MHz, CDCl₃): δ 4.36 (q, *J* = 7.1 Hz, 2H), 2.45 (s, 3H), 2.09-2.06 (m, 9H), 1.81-1.74 (m, 6H), 1.38 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 172.2, 159.0, 145.6, 136.8, 60.8, 40.1, 36.3, 35.9, 27.9, 14.4, 13.4.

GCMS (EI): Calcd for C₁₇H₂₃NO₃: 289.1. Found: 289.1.

8-(1-Adamantyl)-1,3,7-trimethylpurine-2,6-dione. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:4 EA/hexanes) as white solid (148 mg, 90%).

¹H NMR (400 MHz, CDCl₃): δ 4.17 (s, 3H), 3.56 (s, 3H), 3.39 (s, 3H), 2.15-2.12 (m, 9H), 1.84-1.77 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 159.5, 155.7, 151.8, 147.1, 108.1, 39.9, 36.7, 36.4, 34.4, 29.5, 28.2, 27.8.

GCMS (EI): Calcd for C₁₈H₂₄N₄O₂: 328.2. Found: 328.2.

2-(1-Adamantyl)-1,3,5-triazine. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:20 EA/hexanes) as white solid (69 mg, 64%).

¹H NMR (400 MHz, CDCl₃): δ 9.11 (s, 2H), 2.13 (s, 3H), 2.95-2.04 (m, 6H), 1.83-1.76 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 184.7, 165.8, 41.1, 40.4, 36.5, 28.3.

GCMS (EI): Calcd for C₁₃H₁₇N₃: 215.1. Found: 215.1.

2-(1-Adamantyl)pyrimidine. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:6 EA/hexanes) as yellow solid (67 mg, 63%). The regioselectivity in the mixture was determined to be 5:1 by GC and GCMS.

^1H NMR (400 MHz, CDCl_3): δ 8.70 (d, $J = 4.8$ Hz, 2H), 7.08 (t, $J = 4.8$ Hz, 1H), 2.12-2.07 (m, 9H), 1.81-1.79 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 176.8, 156.7, 118.1, 41.2, 41.0, 36.8, 28.7.

GCMS (EI): Calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2$: 214.1. Found: 214.1.

5-(1-Adamantyl)-2-cyanopyridine. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as white solid (74 mg, 62%).

^1H NMR (400 MHz, CDCl_3): δ 8.73 (dd, $J = 2.4, 0.8$ Hz, 1H), 7.76 (dd, $J = 8.2, 2.4$ Hz, 1H), 7.64 (dd, $J = 8.2, 0.8$ Hz, 1H), 2.15 (s, 3H), 1.93 (m, 6H), 1.85-1.75 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 150.1, 149.1, 133.4, 130.9, 128.0, 117.5, 42.4, 36.3, 35.9, 28.5.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2$: 238.1. Found: 238.1.

6-(1-Adamantyl)-5-formylpyridine. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as white solid (104 mg, 86%).

^1H NMR (400 MHz, CDCl_3): δ 10.07 (s, 1H), 9.01 (d, $J = 2.2$ Hz, 1H), 8.11 (dd, $J = 8.2, 2.2$ Hz, 1H), 7.45 (d, $J = 8.2$ Hz, 1H), 2.14 (s, 3H), 2.02 (ψ d, $J = 2.8$ Hz, 6H), 1.84-1.77 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 190.7, 175.3, 151.6, 136.0, 129.1, 119.4, 41.6, 39.9, 36.6, 28.6.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}$: 241.1. Found: 241.1.

4-Acetyl-2-(1-adamantyl)pyridine. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as orange solid (87 mg, 68%). The regioselectivity in the mixture was determined to be 62:1 by GC and GCMS.

^1H NMR (400 MHz, CDCl_3): δ 9.12 (d, $J = 2.4$ Hz, 1H), 8.17 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 1H), 2.61 (s, 3H), 2.13 (s, 3H), 2.01 (ψ d, $J = 2.6$ Hz, 6H), 1.84-1.76 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 196.7, 173.8, 149.3, 135.8, 129.8, 118.9, 41.7, 39.6, 36.7, 28.6, 26.6.

GCMS (EI): Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}$: 255.2. Found: 255.2.

4-(1-Adamantyl)-3-cyanopyridine. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:6 EA/hexanes) as yellow solid (106 mg, 89%). The regioselectivity in the mixture was determined to be 12:1 by GC and GCMS.

^1H NMR (400 MHz, CDCl_3): δ 8.81 (s, 1H), 8.69 (d, $J = 5.4$ Hz, 1H), 7.33 (d, $J = 5.4$ Hz, 1H), 2.18-2.15 (m, 9H), 1.82 (ψ s, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 162.0, 155.3, 153.1, 120.8, 118.2, 108.1, 40.4, 37.6, 36.2, 28.5.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2$: 238.1. Found: 238.1.

1-Acetyl-5-(1-adamantyl)furan. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (100 mg, 82%). The regioselectivity in the mixture was determined to be 23:1 by GC and GCMS.

^1H NMR (400 MHz, CDCl_3): δ 7.10 (d, $J = 3.5$ Hz, 1H), 6.10 (d, $J = 3.5$ Hz, 1H), 2.43 (s, 3H), 2.07 (s, 3H), 1.96 (ψ d, $J = 2.8$ Hz, 6H), 1.81-1.74 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 186.3, 169.5, 151.1, 118.8, 104.9, 40.8, 36.5, 35.1, 28.1, 25.8.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_2$: 244.1. Found: 244.1.

2-(1-Adamantyl)-3-formylfuran. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow solid (94 mg, 82%). No isomer was detected by GC and GCMS.

^1H NMR (400 MHz, CDCl_3): δ 10.31 (s, 1H), 7.25 (d, $J = 1.2$ Hz, 1H), 6.74 (d, $J = 1.2$ Hz, 1H), 2.12 (ψ s, 9H), 1.80 (ψ s, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 185.8, 170.9, 140.6, 122.4, 108.8, 41.8, 38.0, 36.5, 28.2.

GCMS (EI): Calcd for C₁₅H₁₈O₂: 230.1. Found: 230.1.

2-(1-Adamantyl)-5-formylthiophene. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as white solid (106 mg, 86%). No isomer was detected by GC and GCMS.

¹H NMR (400 MHz, CDCl₃): δ 9.83 (s, 1H), 7.62 (d, *J* = 3.9 Hz, 1H), 6.95 (d, *J* = 3.9 Hz, 1H), 2.10 (s, 3H), 1.98-1.95 (m, 6H), 1.82-1.74 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 182.9, 169.7, 140.5, 136.8, 122.2, 44.5, 37.2, 36.4, 28.7.

GCMS (EI): Calcd for C₁₅H₁₈OS: 246.1. Found: 246.1.

2-(1-Adamantyl)-3-cyanothiophene. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:20 EA/hexanes) as yellow solid (105 mg, 86%). The regioselectivity in the mixture was determined to be 34:1 by GC and GCMS.

¹H NMR (400 MHz, CDCl₃): δ 7.17 (d, *J* = 5.3 Hz, 1H), 7.11 (d, *J* = 5.3 Hz, 1H), 2.17-2.12 (m, 9H), 1.80-1.78 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 167.5, 130.5, 122.3, 116.4, 104.3, 42.7, 37.6, 36.2, 28.6.

GCMS (EI): Calcd for C₁₅H₁₇NS: 243.1. Found: 243.1.

2-(1-Adamantyl)-3-formylthiophene. The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow solid (108 mg, 88%). The regioselectivity in the mixture was determined to be >50:1 by GC and GCMS.

¹H NMR (400 MHz, CDCl₃): δ 10.48 (s, 1H), 7.51 (d, *J* = 5.4 Hz, 1H), 7.03 (d, *J* = 5.4 Hz, 1H), 2.19-2.13 (m, 9H), 1.81-1.80 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 185.1, 168.0, 136.6, 129.0, 121.3, 44.8, 38.4, 36.3, 28.9.

GCMS (EI): Calcd for C₁₅H₁₈OS: 246.1. Found: 246.1.

***N*-Methyl-2-(1-adamantyl)-5-formylpyrrole.** The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as white solid (80 mg, 66%). The regioselectivity in the mixture was determined to be 4:1 by GC and GCMS.

^1H NMR (400 MHz, CDCl_3): δ 9.43 (s, 1H), 6.82 (d, $J = 4.2$ Hz, 1H), 6.06 (d, $J = 4.2$ Hz, 1H), 4.14 (s, 3H), 2.10-2.03 (m, 9H), 1.82-1.74 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 179.2, 152.3, 133.0, 124.8, 107.9, 40.7, 36.6, 35.6, 35.0, 28.4.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}$: 243.1. Found: 243.1.

***N*-Methyl-3-(1-adamantyl)-2-formylpyrrole (minor isomer).** ^1H NMR (400 MHz, CDCl_3): δ 10.20 (s, 1H), 6.71 (d, $J = 2.5$ Hz, 1H), 6.04 (d, $J = 2.5$ Hz, 1H), 3.91 (s, 3H), 2.07-2.03 (m, 9H), 1.81-1.74 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 179.8, 149.2, 130.4, 127.6, 107.0, 45.1, 38.2, 36.7, 34.7, 29.0.

GCMS (EI): Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}$: 243.1. Found: 243.1.

***N*-Ethoxycarbonyl-2-acetyl-5-(1-adamantyl)pyrrole.** The reaction was conducted with CsF (2 equiv, 152 mg, 1.0 mmol) as base. The mixture was stirred at 110 °C for 53 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow solid (100 mg, 64%). The regioselectivity in the mixture was determined to be >50:1 by GC and GCMS. When Cs_2CO_3 was used as base, no desired product was detected.

^1H NMR (400 MHz, CDCl_3): δ 6.84 (d, $J = 4.0$ Hz, 1H), 6.04 (d, $J = 4.0$ Hz, 1H), 4.45 (q, $J = 7.2$ Hz, 2H), 2.37 (s, 3H), 2.04-2.01 (m, 9H), 1.77-1.70 (m, 6H), 1.39 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 186.5, 154.5, 150.4, 132.6, 118.6, 107.3, 65.2, 41.2, 36.5, 35.4, 28.4, 25.6, 13.5,

GCMS (EI): Calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_3$: 315.1. Found: 315.1.

***N*-Ethoxycarbonyl-2-(1-adamantyl)indole.** The mixture was stirred at 110 °C for 72 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as white solid (105 mg, 65%). The regioselectivity in the mixture was determined to be 32:1 by GC and GCMS.

¹H NMR (400 MHz, CDCl₃): δ 7.88 (d, *J* = 8.3 Hz, 1H), 7.48-7.45 (m, 1H), 7.23-7.15 (m, 2H), 6.49 (s, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 2.21-2.20 (m, 6H), 2.08 (s, 3H), 1.81-1.74 (m, 6H), 1.52 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 152.7, 151.1, 137.4, 128.9, 123.4, 122.4, 120.1, 115.0, 107.2, 63.4, 41.1, 36.8, 36.4, 28.8, 14.4.

GCMS (EI): Calcd for C₂₁H₂₅NO₂: 323.2. Found: 323.2.

***N*-Ethoxycarbonyl-2-(1-adamantyl)-5-methoxyindole.** The reaction was conducted with K₃PO₄ (2 equiv, 213 mg, 1.0 mmol) as base. The mixture was stirred at 110 °C for 53 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as white solid (113 mg, 64%). The regioselectivity in the mixture was determined to be 20:1 by GC and GCMS. If Cs₂CO₃ was used as base, the yield was only about 24%.

¹H NMR (400 MHz, CDCl₃): δ 7.80 (d, *J* = 9.1 Hz, 1H), 6.93 (d, *J* = 2.6 Hz, 1H), 6.83 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.42 (s, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 2.19 (ψd, *J* = 2.6 Hz, 6H), 2.07 (s, 3H), 1.81-1.73 (m, 6H), 1.50 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 155.7, 152.5, 152.0, 132.1, 129.7, 116.2, 112.1, 107.3, 102.6, 63.2, 55.7, 41.0, 36.8, 36.5, 28.8, 14.4.

GCMS (EI): Calcd for C₂₂H₂₇NO₃: 353.1. Found: 353.1.

***N*-Methyl-2-(1-adamantyl)-3-formylindole.** The mixture was stirred at 110 °C for 53 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow solid (88 mg, 60%).

¹H NMR (400 MHz, CDCl₃): δ 10.72 (s, 1H), 8.55-8.52 (m, 1H), 7.27-7.24 (m, 3H), 4.01 (s, 3H), 2.35 (ψd, *J* = 2.9 Hz, 6H), 2.18 (s, 3H), 1.84 (ψs, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 188.8, 155.7, 138.0, 126.6, 123.4, 122.9, 122.8, 116.2, 108.9, 42.4, 39.3, 36.4, 34.7, 28.5.

GCMS (EI): Calcd for C₂₀H₂₃NO: 293.1. Found: 293.1.

3β-Iodo-5-androsten-17-one. The new compound was prepared using a reported procedure (*cf.* J. Yi, X. Lu, Y. Sun, B. Xiao, L. Liu, *Angew. Chem. Int. Ed.*, **2013**, 52, 12409). Under argon, a dry 100-mL Schlenk tube containing a magnetic stirbar was charged with imidazole (1.4 equiv, 17.5 mmol, 1.19 g), PPh₃ (1.4 equiv, 17.5 mmol, 4.59 g) and dry DCM (20 mL). The resulting solution was cooled to 0 °C and I₂ (1.4 equiv, 17.5 mmol, 4.45 g) was added in one portion. 3β-Hydroxy-5-androsten-17-one (1.0 equiv, 12.5 mmol, 3.61 g from Aldrich) was dissolved in dry DCM (10 mL) and then added dropwise to the mixture maintained at 0 °C. The reaction mixture was allowed to warm up to r.t. overnight with stirring. Et₂O (40 mL) was added and the solid was filtrated off. The filtrate was concentrated and the resulting residue was purified by flash chromatography (1:10 EA/hexanes) to give desired product as white solid (3.58 g, 72%). The assignment of β configuration at C3 carbon was based on the large coupling constant at 4.03 ppm, which was typical of an axial proton in a cyclohexane chair system.

¹H NMR (400 MHz, CDCl₃): δ 5.38-5.36 (m, 1H), 4.03 (ψtt, *J* = 12.4, 4.2 Hz, 1H), 2.97-2.90 (m, 1H), 2.70 (ddd, *J* = 13.6, 4.4, 2.0 Hz, 1H), 2.50-2.43 (m, 1H), 2.33-2.19 (m, 2H), 2.16-2.04 (m, 2H), 1.98-1.93 (m, 1H), 1.87-1.82 (m, 1H), 1.75 (ψdt, *J* = 13.6, 3.4 Hz, 1H), 1.66-1.58 (m, 3H), 1.57-1.41 (m, 2H), 1.31-1.13 (m, 3H), 1.07 (s, 3H), 1.04-0.97 (m, 1H), 0.92-0.88 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 143.0, 120.9, 51.7, 50.5, 47.5, 46.3, 41.8, 36.6, 36.5, 35.8, 31.4, 31.3, 30.6, 29.8, 21.9, 20.1, 19.3, 13.5.

3β-(1,3-Benzoxazol-2-yl)-5-androsten-17-one. In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stirbar was charged with Pd(PPh₃)₄ (10 mol%, 58 mg, 0.05 mmol), DPPP (14 mol%, 28 mg, 0.07 mmol) and dry PhCF₃ (3.0 mL). After stirring at room temperature for 10 minutes, 1,3-benzoxazole (1 equiv, 0.5 mmol, 60 mg), Cs₂CO₃ (2

equiv, 1.0 mmol, 326 mg) and 3 β -iodo-5-androsten-17-one (4 equiv, 2.0 mmol, 797 mg) were added sequentially. The tube was capped tightly and the mixture was vigorously stirred in a pre-warmed 110 °C oil bath for 72 hours. The reaction mixture was concentrated on a rotary evaporator and the resulting residue was directly subjected to silica gel flash chromatography (1:10 EA/hexanes). The conversion of benzoxazole was 65% judged by GC and the desired product was obtained as white solid (118 mg, 61%). The *dr* was determined to be 4:1 by GC and GCMS. The assignment of 3 β configuration in the major isomer was based on the large coupling constant at 2.94 ppm, typical of an axial proton in a cyclohexane chair system.

¹H NMR (400 MHz, CDCl₃): δ 7.71-7.67 (m, 1H), 7.50-7.47 (m, 1H), 7.33-7.28 (m, 2H), 5.48 (d, *J* = 5.2 Hz, 1H), 2.94 (m, *J* = 12.6, 3.9 Hz, 1H), 2.74-2.67 (m, 1H), 2.57-2.44 (m, 2H), 2.19-2.11 (m, 3H), 2.08-1.94 (m, 3H), 1.90-1.86 (m, 1H), 1.75-1.70 (m, 3H), 1.60-1.50 (m, 2H), 1.36-1.24 (m, 3H), 1.16-1.09 (m, 4H), 0.91 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 221.0, 169.7, 150.6, 141.2, 141.1, 124.5, 124.1, 120.8, 119.7, 110.3, 51.8, 50.4, 47.5, 39.3, 38.8, 37.2, 36.4, 35.9, 31.5, 30.8, 26.7, 21.9, 20.2, 19.4, 13.6.

GCMS (EI): Calcd for C₂₆H₃₁NO₂: 389.2. Found: 389.2.

A typical procedure for alkylation of heterocycles using primary alkyl halides: In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stirbar was charged with Pd(PPh₃)₄ (10 mol%, 58 mg, 0.05 mmol), DPPP (14 mol%, 28 mg, 0.07 mmol) and dry PhCF₃ (3.0 mL). After stirring at room temperature for 10 minutes, heteroarene (1 equiv, 0.5 mmol), Cs₂CO₃ (2 equiv, 1.0 mmol, 326 mg) and primary alkyl iodide (2 equiv, 1.0 mmol) were added sequentially. The tube was capped tightly and the mixture was vigorously stirred in a pre-warmed 110 °C oil bath. After heteroarene was almost fully consumed (monitored by GC), the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator. The resulting residue was directly subjected to silica gel flash chromatography. The structure and regioselectivity of the purified product was assigned by ¹H NMR spectroscopy. The typical procedure on 0.5 mmol of the heteroarene was used for all the isolation, unless stated otherwise.

4-Cyano-3-cyclohexylmethyl-2-fluoropyridine. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (56 mg, 51%).

^1H NMR (400 MHz, CDCl_3): δ 8.20 (d, $J = 5.0$ Hz, 1H), 7.39 (d, $J = 5.0$ Hz, 1H), 2.76 (d, $J = 7.0$ Hz, 2H), 1.73-1.64 (m, 6H), 1.26-1.06 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ 162.2 (d, $J_{\text{C-F}} = 240.5$ Hz), 145.8 (d, $J_{\text{C-F}} = 15.5$ Hz), 127.3 (d, $J_{\text{C-F}} = 35.2$ Hz), 125.0 (d, $J_{\text{C-F}} = 7.1$ Hz), 123.6 (d, $J_{\text{C-F}} = 5.0$ Hz), 115.2 (d, $J_{\text{C-F}} = 5.5$ Hz), 38.7, 35.6 (d, $J_{\text{C-F}} = 2.5$ Hz), 32.9, 26.1, 26.0.

^{19}F NMR (376 MHz, CDCl_3): δ -66.9.

GCMS (EI): Calcd for $\text{C}_{13}\text{H}_{15}\text{FN}_2$: 218.1. Found: 218.1.

4-Cyano-2-fluoro-3-isopentylpyridine. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (46 mg, 48%).

^1H NMR (400 MHz, CDCl_3): δ 8.20 (d, $J = 5.0$ Hz, 1H), 7.38 (d, $J = 5.0$ Hz, 1H), 2.88-2.84 (m, 2H), 1.72-1.62 (m, 1H), 1.58-1.50 (m, 2H), 0.99 (d, $J = 6.6$ Hz, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 162.0 (d, $J_{\text{C-F}} = 241.0$ Hz), 145.8 (d, $J_{\text{C-F}} = 15.6$ Hz), 128.8 (d, $J_{\text{C-F}} = 34.8$ Hz), 124.3 (d, $J_{\text{C-F}} = 7.5$ Hz), 123.6 (d, $J_{\text{C-F}} = 5.3$ Hz), 114.8 (d, $J_{\text{C-F}} = 5.6$ Hz), 38.6, 28.1, 26.1 (d, $J_{\text{C-F}} = 1.4$ Hz), 22.2.

^{19}F NMR (376 MHz, CDCl_3): δ -68.5.

GCMS (EI): Calcd for $\text{C}_{11}\text{H}_{13}\text{FN}_2$: 193.1. Found: 193.1.

2-Cyclohexylmethyl-3-formylfuran. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (79 mg, 82%).

^1H NMR (400 MHz, CDCl_3): δ 9.92 (s, 1H), 7.31 (d, $J = 2.0$ Hz, 1H), 6.69 (d, $J = 2.0$ Hz, 1H), 2.83 (d, $J = 7.0$ Hz, 2H), 1.77-1.63 (m, 6H), 1.29-1.12 (m, 3H), 1.05-0.95 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 184.8, 165.3, 142.1, 123.3, 107.8, 37.6, 34.4, 33.0, 26.1, 26.0.

GCMS (EI): Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2$: 192.1. Found: 192.1.

2-Isopentyl-3-formylfuran. The reaction mixture was stirred at 110 °C for 36 hours. The product was purified by flash chromatography (1:10 EA/hexanes) as yellow oil (61 mg, 74%).
¹H NMR (400 MHz, CDCl₃): δ 9.96 (s, 1H), 7.31 (d, *J* = 2.0 Hz, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 2.96 (m, 2H), 1.65-1.56 (m, 3H), 0.94 (d, *J* = 6.3 Hz, 6H).
¹³C NMR (100 MHz, CDCl₃): δ 184.7, 166.3, 142.0, 122.2, 108.0, 37.3, 27.6, 24.9, 22.2.
 GCMS (EI): Calcd for C₁₀H₁₄O₂: 167.1. Found: 167.1.

3.5.4 Procedure for mechanistic study on Pd-catalyzed alkylation of heteroarenes

(a) Trapping of alkyl radicals using TEMPO

Typical procedure: In an argon-filled glove box, a dry 4-mL reaction tube containing a magnetic stirbar was charged with Pd(PPh₃)₄ (10 mol%, 5.8 mg, 0.005 mmol), DPPP (14 mol%, 2.8 mg, 0.007 mmol) and dry PhCF₃ (0.3 mL). After stirring at room temperature for 10 minutes, 1,3-benzoxazole (1 equiv, 0.05 mmol, 6 mg), Cs₂CO₃ (2 equiv, 0.10 mmol, 32.6 mg), iodocyclohexane (2 equiv, 0.10 mmol, 21 mg), TEMPO (1 equiv, 0.05 mmol, 7.8 mg) and GC standard, 1-dodecane (10 μL) were added sequentially. The tube was capped tightly and the mixture was vigorously stirred in a pre-warmed 110 °C oil bath. After 24 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 filtrate was subjected to GC analysis to determine the conversion of 1,3-benzoxazole and calibrated GC yield of the coupling product and TEMPO-Cy.

(b) Trapping of alkyl radicals using 1,4-cyclohexadiene

Typical procedure: In an argon-filled glove box, a dry 4-mL reaction tube containing a magnetic stirbar was charged with Pd(PPh₃)₄ (10 mol%, 5.8 mg, 0.005 mmol), DPPP (14 mol%, 2.8 mg, 0.007 mmol) and dry PhCF₃ (0.3 mL). After stirring at room temperature for 10 minutes, *N*-ethoxycarbonylindole (2 equiv, 0.1 mmol, 19 mg), Cs₂CO₃ (2 equiv, 0.10 mmol, 32.6 mg), 1-iodoadamantane (1 equiv, 13.1 mg, 0.05 mmol), hydrogen atom donor 1,4-cyclohexadiene (3 equiv, 0.15 mmol, 12 mg or 5 equiv, 0.25 mmol, 20 mg) and GC standard, 1-dodecane (10 μL) were added sequentially. The tube was capped tightly and the mixture was vigorously stirred in a pre-warmed 110 °C oil bath. After 24 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 filtrate was subjected to GC analysis to determine the conversion of *N*-ethoxycarbonylindole, 1-iodoadamantane and calibrated GC yield of the coupling product and reductive byproduct adamantane.

3.6 Reference

- (1) (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2009**, *110*, 624. (c) Kraft, A.; Grimsdale, A. C.; Holmes, A. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 402. (d) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245.
- (2) Friedel, C. C., J. M. *J. Chem. Soc.* **1877**, *32*, 67.
- (3) (a) Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2010**, *6*, 6. (b) Belen'kii, L. I.; Yakubov, A. P.; Zelinsky, N. D. *Tetrahedron* **1986**, *42*, 759.
- (4) (a) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913. (b) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 238. (c) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 691.
- (5) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, *348*, 1033.
- (6) (a) Kischel, J.; Iovel, I.; Mertins, K.; Zapf, A.; Beller, M. *Org. Lett.* **2005**, *8*, 19. (b) Rozenman, M. M.; Kanan, M. W.; Liu, D. R. *J. Am. Chem. Soc.* **2007**, *129*, 14933. (c) Shirakawa, S.; Kobayashi, S. *Org. Lett.* **2006**, *9*, 311.
- (7) Rueping, M.; Nachtsheim, B. J.; Scheidt, T. *Org. Lett.* **2006**, *8*, 3717.
- (8) (a) Wang, M.-Z.; Wong, M.-K.; Che, C.-M. *Chem. Eur. J.* **2008**, *14*, 8353. (b) Zhang, Z.; Wang, X.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 3717.
- (9) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 5386.
- (10) (a) Zhuang, W.; Hansen, T.; Jorgensen, K. A. *Chem. Commun.* **2001**, 347. (b) Sevov, C. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2116.

- (11) Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinnunmo, M. *Tetrahedron* **1971**, *27*, 3575.
- (12) (a) Fontana, F.; Minisci, F.; Nogueira Barbosa, M. C.; Vismara, E. *Tetrahedron* **1990**, *46*, 2525. (b) Francesco Minisci, E. V., and Francesca Fontana *Heterocycles* **1989**, *28*. (c) Minisci, F. *Synthesis* **1973**, *1973*, 1. (d) Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res.* **1983**, *16*, 27.
- (13) (a) Togo, H.; Hayashi, K.; Yokoyama, M. *Chem. Lett.* **1991**, *20*, 2063. (b) Togo, H.; Hayashi, K.; Yokoyama, M. *Chem. Lett.* **1993**, *22*, 641. (c) Togo, H.; Hayashi, K.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2522.
- (14) Cowden, C. J. *Org. Lett.* **2003**, *5*, 4497.
- (15) Duncton, M. A. J.; Estiarte, M. A.; Johnson, R. J.; Cox, M.; O'Mahony, D. J. R.; Edwards, W. T.; Kelly, M. G. *J. Org. Chem.* **2009**, *74*, 6354.
- (16) Molander, G. A.; Colombel, V.; Braz, V. A. *Org. Lett.* **2011**, *13*, 1852.
- (17) Fujiwara, Y.; Fionn O'Hara, J. A. D.; Erik, D. F.; Darryl, D. D.; Rodriguez, R. A.; Ryan, D. B.; Bart Herlé N. S.; Michael, R. C.; Yoshihiro, I.; Baran, P. S. *Nature* **2012**, *492*, 5.
- (18) O'Hara, F.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2013**, *135*, 12122.
- (19) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013.
- (20) (a) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964. (b) Tan, K. L.; Park, S.; Ellman, J. A.; Bergman, R. G. *J. Org. Chem.* **2004**, *69*, 7329.

- (21) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332.
- (22) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 15996.
- (23) Nakao, Y.; Kashiwara, N.; Kanyiva, K. S.; Hiyama, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 4451.
- (24) Nakao, Y.; Yamada, Y.; Kashiwara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666.
- (25) Andou, T.; Saga, Y.; Komai, H.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 3213.
- (26) Guan, B.-T.; Hou, Z. *J. Am. Chem. Soc.* **2011**, *133*, 18086.
- (27) (a) Hu, X. *Chemical Science* **2011**, *2*, 1867. (b) Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061.
- (28) Ackermann, L.; Punji, B.; Song, W. *Adv. Synth. Catal.* **2011**, *353*, 3325.
- (29) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 2477.
- (30) (a) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158. (b) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160. (c) Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 33.
- (31) Ackermann, L.; Barfusser, S.; Pospech, J. *Org. Lett.* **2010**, *12*, 724.
- (32) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 1360.
- (33) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647.

- (34) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 12307.
- (35) Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990.
- (36) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616.
- (37) Tran, L. D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 4277.
- (38) Ren, P.; Salihu, I.; Scopelliti, R.; Hu, X. *Org. Lett.* **2012**, *14*, 1748.
- (39) Punji, B.; Song, W.; Shevchenko, G. A.; Ackermann, L. *Chem. Eur. J.* **2013**, *19*, 10605.
- (40) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 9279.
- (41) Ding, Z.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 8574.
- (42) Zhao, X.; Wu, G.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 3296.
- (43) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 775.
- (44) (a) Bloome, K. S.; McMahan, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146. (b) McMahan, C. M.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5974. (c) Ryu, I.; Kreimerman, S.; Araki, F.; Nishitani, S.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2002**, *124*, 3812. (d) Zou, Y.; Zhou, J. *Chem. Commun.* **2014**, *50*, 3725.
- (45) Kramer, A. V.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7832.
- (46) Gaussian 09, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J.

Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2010**.

(47) (a) Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B.* **1988**, 37, 785. (c) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, 58, 1200. (d) Hehre, W. R.; Schleyer, P. v. R.; Pople, J. *Ab Initio Molecular Orbital Theory*, John Wiley & Sons, New York, **1986**. (e) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, 4, 294. (f) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta.* **1973**, 28, 213.

Appendix

1. DFT calculation on relative stability of Heck product isomers

Computational Details

DFT calculations were carried out with the Gaussian 09 package.³¹ Both olefin isomers are fully optimized by B3LYP³² method with 6-31G(d,p) basis set. Harmonic frequency calculations are carried out to validate whether an optimized geometry is local or global minimum and to work out zero-point energy corrections.

Computational Results and coordinates of optimized conformations

The energies refer to the sum of electronic energy and vibrational energy and are corrected by zero-point energy at 0 K. For each compound, only the energy of the most stable conformer is listed in each table. The relative energy of isomers in each series is reported with respect to the most stable isomer.

The dihedral angles in tables are the angles formed by the aryl ring and double bond in the partially saturated ring if they are in conjugation. If they are not in conjugation, dihedral angles refer to the angles formed between the aryl ring and the benzylic single bond in the partially saturated rings that is closer to double bonds.

1. Isomers of arylcyclohexene

Table 1 Isomers of phenylcyclohexene

Compounds	Energy (a.u.)	Relative Energy (kcal/mol)	Dihedral angle (degree)
1-phenylcyclohexene	- 465.4986	0	32
3-phenylcyclohexene	- 465.4919	4.2	45

4-phenylcyclohexene

- 4.3 64
465.4918

1-phenylcyclohexene	H	1.114774	2.057223	0.696577
C -3.484372 -0.091175 -0.325135	C	3.711212	-0.013870	-0.023865
C -2.801329 -1.036422 0.668005	H	3.505459	-2.057958	-0.675554
C -1.328283 -1.250388 0.294056	H	3.577406	2.028925	0.653881
C -0.603423 0.051429 -0.012134	H	4.797089	-0.031164	-0.029090
C -1.291293 1.173692 -0.292116	3-phenylcyclohexene			
C -2.794609 1.279759 -0.321228	C	1.324021	-0.976514	-0.773370
H -0.806711 -1.776420 1.102927	C	2.844942	-1.033200	-0.587929
H -2.860229 -0.605865 1.676540	C	3.419975	0.367111	-0.326541
H -3.319694 -2.001279 0.706434	C	2.579305	1.144478	0.655453
H -3.425128 -0.524963 -1.332194	C	1.346734	0.784551	1.027337
H -4.549249 0.018955 -0.091047	C	0.619676	-0.434630	0.493463
H -0.742833 2.082809 -0.530422	H	4.449681	0.292443	0.047137
H -3.129578 1.865487 0.549767	H	3.080707	-1.685226	0.263571
H -3.103367 1.865069 -1.197464	H	3.320627	-1.481104	-1.467879
H -1.268857 -1.917330 -0.579285	H	1.083561	-0.318505	-1.618512
C 0.883554 0.031414 -0.007128	H	0.921359	-1.964941	-1.021441
C 1.591497 -1.128965 -0.368243	H	3.020966	2.043619	1.082625
C 1.632927 1.162008 0.367187	H	0.809620	1.385309	1.759176
C 2.985798 -1.149969 -0.382393	H	0.670312	-1.218702	1.265352
H 1.047934 -2.022575 -0.658036	H	3.492545	0.929478	-1.270316
C 3.025484 1.142335 0.354156				

C	-0.856878	-0.166691	0.234201	H	1.270433	0.085151	1.760229
C	-1.829595	-1.098061	0.617907	H	0.860219	-1.591040	1.417904
C	-1.275129	0.998351	-0.424586	H	0.845565	-1.038099	-1.043654
C	-3.181668	-0.877498	0.350519	H	4.601155	0.056902	-0.110222
H	-1.523812	-2.005090	1.134438	H	3.373765	1.722723	-1.345917
C	-2.625040	1.223816	-0.692897	H	0.974457	1.901110	-0.233420
H	-0.533347	1.735044	-0.721740	H	0.990569	1.228574	-1.844913
C	-3.584239	0.285620	-0.306485	H	2.966953	-1.985046	0.278946
H	-3.919855	-1.612283	0.659715	C	-0.840898	-0.118765	-0.135909
H	-2.928937	2.134365	-1.201925	C	-1.711615	-0.900474	-0.905989
H	-4.636041	0.461586	-0.512627	C	-1.401736	0.784078	0.780629
				C	-3.096449	-0.788564	-0.769627
4-phenylcyclohexene				H	-1.297619	-1.606494	-1.622009
C	0.663684	-0.256894	-0.292735	C	-2.784209	0.899907	0.921410
C	1.363251	-0.708536	1.007903	H	-0.752207	1.403625	1.393295
C	2.850947	-1.004382	0.765808	C	-3.638307	0.113240	0.145862
C	3.512873	0.055688	-0.077907	H	-3.750200	-1.406338	-1.379035
C	2.832187	0.973294	-0.770873	H	-3.195618	1.605276	1.638125
C	1.325750	1.037180	-0.817093	H	-4.715186	0.203167	0.255075
H	3.374845	-1.094137	1.726719				

Table 2 Isomers of *o*-tolylcyclohexene

Compounds	Energy (a.u.)	Relative Energy (kcal/mol)	Dihedral angle (degree)
1- <i>o</i> -tolylcyclohexene	-504.7871	0.0	64
3- <i>o</i> -tolylcyclohexene	-504.7793	4.9	58

4-o-tolylcyclohexene

-504.7774 6.1 75

1-o-tolylcyclohexene

C 3.552985 0.176566 -0.161860
C 2.880435 0.246855 1.213362
C 1.397703 0.623680 1.078239
C 0.690300 -0.171394 -0.009443
C 1.379032 -0.862226 -0.932571
C 2.883494 -0.895440 -1.033265
H 0.877873 0.463402 2.031264
H 2.963167 -0.731584 1.705226
H 3.391796 0.968721 1.860443
H 3.463510 1.153662 -0.655153
H 4.624653 -0.029792 -0.062632
H 0.825959 -1.441639 -1.670317
H 3.241562 -1.895091 -0.740728
H 3.184129 -0.776608 -2.082707
H 1.308618 1.699365 0.872752
C -0.804770 -0.222502 0.018455
C -1.607033 0.917036 -0.220509
C -1.430997 -1.448152 0.293532

C -2.999918 0.782699 -0.168143
C -2.819478 -1.563531 0.344595
H -0.807514 -2.318620 0.475833
C -3.609522 -0.438785 0.116300
H -3.617659 1.655486 -0.366299
H -3.277454 -2.524379 0.561297
H -4.692911 -0.510040 0.150669
C -1.003320 2.261197 -0.560793
H -0.685634 2.805258 0.337044
H -0.124378 2.153101 -1.203305
H -1.729183 2.892733 -1.080778

3-o-tolylcyclohexene

C 1.413194 -0.622729 -1.128748
C 2.920771 -0.832496 -0.934204
C 3.521174 0.247481 -0.020626
C 2.654378 0.511381 1.185687
C 1.387251 0.097510 1.291981
C 0.663957 -0.700917 0.221166

H	4.527700	-0.047309	0.303905	C	-2.957538	-0.075872	-1.246578
H	3.091366	-1.819647	-0.484493	C	-3.592534	-0.228560	0.113409
H	3.433120	-0.836838	-1.903033	C	-2.891377	-0.288075	1.249648
H	1.243008	0.355119	-1.593210	C	-1.384312	-0.253273	1.306923
H	1.002102	-1.371600	-1.814826	H	-3.530607	0.645467	-1.843950
H	3.101823	1.070797	2.005929	H	-1.470619	1.435310	-0.883413
H	0.825324	0.307375	2.200541	H	-0.996226	0.276522	-2.120732
H	0.713617	-1.752601	0.543872	H	-0.940073	-1.508140	-0.347457
H	3.658767	1.184802	-0.581806	H	-4.679035	-0.288503	0.150602
C	-0.828876	-0.385826	0.113385	H	-3.416130	-0.378235	2.199597
C	-1.727334	-1.448754	0.291248	H	-1.052468	0.693178	1.756060
C	-1.352807	0.900856	-0.156525	H	-1.021191	-1.034432	1.987772
C	-3.107771	-1.277594	0.210834	H	-3.026441	-1.028581	-1.794194
H	-1.327741	-2.438022	0.502028	C	0.777874	-0.318934	-0.070030
C	-2.744602	1.058203	-0.224851	C	1.523968	-1.504434	-0.166636
C	-3.621940	-0.009506	-0.047804	C	1.481421	0.903122	0.061989
H	-3.771050	-2.125391	0.355996	C	2.916858	-1.517584	-0.137081
H	-3.145026	2.049692	-0.422948	H	0.989775	-2.446211	-0.267373
H	-4.694550	0.151347	-0.107394	C	2.883365	0.872759	0.092740
C	-0.487481	2.119178	-0.399404	C	3.605044	-0.314755	-0.005761
H	0.398239	2.136184	0.238869	H	3.454083	-2.458363	-0.215333
H	-0.138327	2.160571	-1.438621	H	3.419454	1.813012	0.197619
H	-1.057845	3.034808	-0.217641	H	4.690698	-0.296655	0.022462
4- <i>o</i> -tolylcyclohexene				C	0.812439	2.260410	0.146441
C	-0.742711	-0.459569	-0.086091	H	0.468993	2.602625	-0.836459
C	-1.491456	0.374071	-1.148047	H	-0.055353	2.269722	0.810219
				H	1.518898	3.007441	0.519032

Table 3 Isomers of *p*-anisylcyclohexene

Compounds	Energy (a.u.)	Relative Energy (kcal/mol)	Dihedral angle (degree)
1-(<i>p</i> -anisyl)cyclohexene	-579.9909	0	32

3-(*p*-anisyl)cyclohexene

-579.9840 4.3

46

4-(*p*-anisyl)cyclohexene

-579.9840 4.3

64

1-(*p*-anisyl)cyclohexene

C 4.370745 -0.043323 -0.286153
C 3.719568 0.915652 0.715214
C 2.265831 1.212108 0.322715
C 1.480013 -0.043821 -0.023777
C 2.115501 -1.192968 -0.319055
C 3.611796 -1.376934 -0.321296
H 1.758297 1.747064 1.134700
H 3.739137 0.462099 1.715231
H 4.285875 1.851647 0.782657
H 4.350055 0.412655 -1.284906
H 5.424667 -0.212059 -0.037461
H 1.525639 -2.066791 -0.589036
H 3.901012 -1.994223 0.544454
H 3.908284 -1.960678 -1.202908
H 2.255163 1.899666 -0.536693
C -0.002501 0.054068 -0.033733

C -0.653328 1.257379 -0.371631
C -0.818548 -1.036511 0.302156
C -2.037742 1.355311 -0.400528
H -0.066682 2.132211 -0.633505
C -2.211282 -0.956462 0.279587
H -0.357278 -1.968437 0.614205
C -2.830998 0.246340 -0.077752
H -2.530050 2.283421 -0.672178
H -2.795928 -1.825643 0.556963
O -4.182394 0.443123 -0.130067
C -5.030425 -0.647857 0.188320
H -4.881917 -0.990399 1.220671
H -6.051303 -0.279098 0.077631
H -4.877592 -1.494327 -0.493697

3-(*p*-anisyl)cyclohexene

C -2.174891 0.941970 -0.831826

C	-3.700948	1.000612	-0.695503	C	1.530423	-0.340531	-0.193370
C	-4.278449	-0.386745	-0.376319	C	2.240318	-0.362012	1.177514
C	-3.464397	-1.105561	0.670644	C	3.721098	-0.745678	1.034571
C	-2.245489	-0.718330	1.059901	C	4.388446	-0.028588	-0.111864
C	-1.505368	0.472762	0.481771	C	3.713033	0.627495	-1.059917
H	-5.319111	-0.297593	-0.037623	C	2.207381	0.700944	-1.112970
H	-3.964421	1.695672	0.112809	H	4.255500	-0.528678	1.969089
H	-4.152193	1.398576	-1.611652	H	2.166862	0.632713	1.635851
H	-1.906819	0.241071	-1.633190	H	1.729330	-1.057089	1.852652
H	-1.768453	1.917665	-1.121032	H	1.689881	-1.326171	-0.652655
H	-3.914885	-1.983300	1.131862	H	5.476170	-0.058297	-0.150506
H	-1.728193	-1.275812	1.838839	H	4.258961	1.139855	-1.850650
H	-1.580951	1.297082	1.208682	H	1.877386	1.713922	-0.837618
H	-4.321120	-0.999258	-1.290282	H	1.861410	0.556669	-2.144938
C	-0.021533	0.195000	0.285443	H	3.817440	-1.833208	0.891317
C	0.944260	1.128343	0.665576	C	0.030757	-0.130299	-0.082043
C	0.423886	-0.993879	-0.316991	C	-0.866533	-1.093580	-0.547868
C	2.309574	0.906661	0.457654	C	-0.512715	1.032300	0.493061
H	0.631900	2.056393	1.139112	C	-2.252171	-0.926529	-0.454703
C	1.774181	-1.234656	-0.531272	H	-0.480732	-2.005055	-0.998481
H	-0.304214	-1.743537	-0.615404	C	-1.884538	1.218998	0.595958
C	2.729333	-0.282575	-0.145751	H	0.147911	1.808666	0.869840
H	3.024494	1.658154	0.771297	C	-2.767374	0.238072	0.121031
H	2.117621	-2.154352	-0.993795	H	-2.907842	-1.702826	-0.830815
O	4.032300	-0.612380	-0.398610	H	-2.299712	2.117483	1.040946
C	5.038823	0.317246	-0.034879	O	-4.098567	0.515197	0.267050
H	5.987939	-0.135238	-0.326348	C	-5.034236	-0.445100	-0.193708
H	4.918812	1.272881	-0.561736	H	-4.927136	-1.402300	0.333101
H	5.047291	0.505537	1.046664	H	-6.021346	-0.030037	0.015597
				H	-4.938880	-0.620178	-1.273294

4-(*p*-anisyl)cyclohexene

Table 4 Isomers of (*p*-methoxycarbonyl)phenylcyclohexene

Compounds	Energy (a.u.)	Relative Energy (kcal/mol)	Dihedral angle (degree)
1-(<i>p</i> -methoxycarbonyl)phenylcyclohexene	-693.3389	0	31
3-(<i>p</i> -methoxycarbonyl)phenylcyclohexene	-693.3320	4.3	43
4-(<i>p</i> -methoxycarbonyl)phenylcyclohexene	-693.3319	4.4	65

1-(<i>p</i> -methoxycarbonyl)phenylcyclohexene	H	-2.435369	2.025048	-0.658954			
	H	-4.826226	1.755174	0.384842			
C	-5.066300	-0.272265	-0.360196	H	-4.763726	1.638625	-1.357206
C	-4.354414	-1.114385	0.702864	H	-2.759808	-1.991659	-0.466625
C	-2.866610	-1.277748	0.363838	C	-0.719189	0.099123	0.015501
C	-2.202681	0.038631	-0.010862	C	0.054602	-1.050718	-0.231330
C	-2.940754	1.104850	-0.373382	C	-0.034124	1.297771	0.297529
C	-4.445739	1.129308	-0.438062	C	1.445011	-1.003539	-0.227488
H	-2.334656	-1.727115	1.211151	H	-0.436526	-1.993836	-0.446440
H	-4.451575	-0.622556	1.679830	C	1.352604	1.350721	0.304129
H	-4.824173	-2.099825	0.797722	H	-0.600685	2.190838	0.540060
H	-4.969523	-0.767753	-1.335290	C	2.108967	0.200577	0.038337
H	-6.138841	-0.200218	-0.148213	H	2.021475	-1.898489	-0.431500

H 1.875387 2.274659 0.527191
 C 3.590949 0.314819 0.062879
 O 4.202290 1.339612 0.299046
 O 4.206954 -0.861036 -0.211862
 C 5.641000 -0.812842 -0.205871
 H 6.013169 -0.508492 0.775560
 H 5.970638 -1.824232 -0.443332
 H 6.006566 -0.104589 -0.953591

3-(*p*-methoxycarbonyl)phenylcyclohexene

C -2.861238 -0.846391 0.937200
 C -4.392253 -0.877467 0.863687
 C -4.949753 0.483391 0.420343
 C -4.162083 1.066276 -0.726183
 C -2.967837 0.610380 -1.117065
 C -2.236678 -0.535714 -0.445374
 H -6.004597 0.387358 0.131810
 H -4.703584 -1.647411 0.145486
 H -4.814192 -1.163158 1.833789
 H -2.544924 -0.072594 1.648487
 H -2.466744 -1.797395 1.312067
 H -4.611213 1.901271 -1.261710
 H -2.470429 1.068946 -1.969789
 H -2.359716 -1.429784 -1.076505
 H -4.941533 1.190171 1.264321
 C -0.740952 -0.285880 -0.322239
 C 0.175911 -1.316240 -0.570899
 C -0.245305 0.963420 0.082496
 C 1.545350 -1.115786 -0.417931
 H -0.190180 -2.288895 -0.890238
 C 1.120283 1.173519 0.236577
 H -0.941560 1.775650 0.271673
 C 2.028111 0.134937 -0.011460

H 2.243408 -1.921124 -0.615205
 H 1.508417 2.137492 0.547745
 C 3.477938 0.416146 0.169617
 O 3.936337 1.487554 0.517581
 O 4.253356 -0.663171 -0.095530
 C 5.664030 -0.453472 0.064411
 H 5.897143 -0.165313 1.092459
 H 6.133028 -1.405945 -0.182025
 H 6.015999 0.332957 -0.607851

4-(*p*-methoxycarbonyl)phenylcyclohexene

C -2.250652 -0.412393 0.049132
 C -2.946882 0.107103 -1.227944
 C -4.436979 -0.266615 -1.236609
 C -5.095315 -0.018904 0.097026
 C -4.411981 0.213981 1.221293
 C -2.905593 0.225189 1.296031
 H -4.958088 0.301120 -2.018673
 H -2.847322 1.198924 -1.273803
 H -2.448152 -0.292418 -2.117613
 H -2.439811 -1.493189 0.102778
 H -6.183498 -0.034415 0.123836
 H -4.950553 0.403242 2.148322
 H -2.548387 1.258243 1.420400
 H -2.571456 -0.306289 2.196610
 H -4.559420 -1.324710 -1.514957
 C -0.746424 -0.213323 0.024920
 C 0.119640 -1.311767 0.116334
 C -0.178901 1.067022 -0.087699
 C 1.502752 -1.148468 0.097709
 H -0.298356 -2.311321 0.204001
 C 1.199848 1.240913 -0.107516
 H -0.822960 1.938725 -0.161102

C 2.054212 0.133704 -0.014457
H 2.157758 -2.008988 0.170214
H 1.639440 2.228802 -0.194054
C 3.521557 0.379406 -0.037587
O 4.037140 1.477173 -0.127665
O 4.241075 -0.765109 0.054173

C 5.665653 -0.591464 0.040567
H 5.987544 0.021795 0.885962
H 6.085204 -1.594701 0.113993
H 5.986722 -0.107637 -0.885169

2. Isomers of arylcyclopentene

Table 5 Isomers of phenylcyclopentene

Compounds	Energy (a.u.)	Relative Energy (kcal/mol)	Dihedral angle (degree)
1-phenylcyclopentene
-426.2075	0.0	17
3-phenylcyclopentene
-426.1986	5.6	43
4-phenylcyclopentene
-426.1974	6.4	61
1-phenylcyclopentene	C 3.188141 -0.655657 0.331340		

C 3.173353 0.787484 -0.230561
 C 1.707524 1.138329 -0.218985
 C 0.914384 0.067363 -0.032305
 C 1.757536 -1.194413 0.094408
 H 3.387545 -0.621646 1.407699
 H 3.571227 0.829876 -1.256267
 H 3.786001 1.478297 0.361682
 H 1.354108 2.148141 -0.403721
 H 1.697346 -1.785421 -0.831421
 H 1.418491 -1.851253 0.903742
 H 3.960015 -1.283573 -0.122488
 C -0.558309 0.042839 -0.008864
 C -1.256308 -1.169586 -0.150695
 C -1.315071 1.218875 0.158705
 C -2.650751 -1.204667 -0.144228
 H -0.703361 -2.094806 -0.277602
 C -2.705578 1.184389 0.165560
 H -0.804806 2.166329 0.301666
 C -3.383048 -0.028675 0.011903
 H -3.164239 -2.154876 -0.261072
 H -3.264889 2.106111 0.299346
 H -4.468674 -0.054861 0.020768

3-phenylcyclopentene

C 1.738961 -0.665804 0.999575
 C 3.164672 -0.146555 0.688615
 C 2.954893 0.683958 -0.556495
 C 1.763012 0.457905 -1.113825
 C 0.949456 -0.569069 -0.345143
 H 1.261898 -0.005641 1.731156
 H 3.863347 -0.971695 0.485324
 H 3.596399 0.422865 1.520438
 H 3.716927 1.343607 -0.961409
 H 1.012171 -1.532218 -0.874821

H 1.726802 -1.676700 1.416640
 H 1.403148 0.905195 -2.035575
 C -0.523109 -0.239972 -0.175353
 C -1.503450 -1.222938 -0.356465
 C -0.934865 1.050145 0.190391
 C -2.856400 -0.932476 -0.171948
 H -1.202573 -2.227395 -0.645234
 C -2.285036 1.345721 0.373710
 H -0.186793 1.827015 0.326378
 C -3.252015 0.354058 0.194362
 H -3.600285 -1.710855 -0.317530
 H -2.583654 2.352091 0.654196
 H -4.304104 0.583891 0.335885

4-phenylcyclopentene

C -0.968623 -0.589984 -0.001399
 C -1.770655 -0.067323 -1.234679
 C -3.142470 0.209736 -0.666761
 C -3.142226 0.206902 0.668226
 C -1.770200 -0.072632 1.234447
 H -1.775852 -0.798025 -2.052234
 H -1.327186 0.849811 -1.648199
 H -4.003991 0.427162 -1.291427
 H -1.775086 -0.806895 2.048818
 H -1.062201 -1.681957 -0.003713
 H -4.003501 0.421694 1.294137
 H -1.326531 0.842700 1.651673
 C 0.509052 -0.254003 -0.000741
 C 1.471738 -1.271007 -0.001791
 C 0.956196 1.076793 0.001088
 C 2.836578 -0.975652 -0.001047
 H 1.146652 -2.308749 -0.003228
 C 2.317206 1.377602 0.001825
 H 0.231976 1.887714 0.001936

C	3.264683	0.351169	0.000762	H	2.639767	2.415133	0.003225
H	3.563032	-1.783518	-0.001906	H	4.325244	0.585325	0.001328

Table 6 Isomers of *o*-tolylcyclopentene

Compounds	Energy (a.u.)	Relative Energy (kcal/mol)	Dihedral angle (degree)
1-(<i>o</i> -tolyl)cyclopentene	-465.4948	0	48
3-(<i>o</i> -tolyl)cyclopentene	-465.4886	3.9	35
4-(<i>o</i> -tolyl)cyclopentene	-465.4868	5.0	61

1-(<i>o</i> -tolyl)cyclopentene				H	-1.377953	-0.181946	1.754926
C	-3.253851	0.176460	0.688273	H	-3.900300	0.997096	0.527880
C	-3.235456	-0.694716	-0.591890	H	-3.737853	-0.431105	1.538871
C	-1.763263	-0.959883	-0.788174	H	-3.922801	-1.293494	-0.961640
C	-0.983811	-0.146766	-0.054823	H	-1.035222	1.368261	-0.825428
C	-1.845983	0.815768	0.757736	H	-1.723702	1.525412	1.478939
H	-3.401680	-0.469683	1.560391	H	-1.580090	-1.011289	-2.023460
H	-3.654591	-0.158981	-1.457393	C	0.425592	-0.035846	-0.141613
H	-3.826124	-1.612686	-0.486072	C	1.484319	0.898191	-0.124474
H	-1.384784	-1.703085	-1.483901	C	0.718109	-1.395141	0.033181
H	-1.847668	1.817232	0.308821	C	2.792431	0.432412	0.062248
H	-1.485192	0.935959	1.785757	C	2.024737	-1.843947	0.218968
H	-4.057961	0.918143	0.691763	H	-0.100073	-2.110543	0.020540
C	0.497046	-0.211990	-0.000916	C	3.070594	-0.923197	0.232229
C	1.331651	0.922782	-0.143531	H	3.608025	1.151442	0.074235
C	1.095097	-1.468903	0.197234	H	2.222117	-2.904103	0.350120
C	2.719313	0.750230	-0.077135	H	4.095419	-1.254264	0.373867
C	2.478355	-1.621238	0.258291	C	1.246070	2.382247	-0.301483
H	0.449657	-2.332980	0.322189	H	0.826020	2.615854	-1.287191
C	3.297810	-0.502383	0.124825	H	0.549573	2.779949	0.444891
H	3.359282	1.620985	-0.197338	H	2.183071	2.937295	-0.206066
H	2.909547	-2.605560	0.416333				
H	4.378456	-0.600445	0.173641	4-(<i>o</i> -tolyl)cyclopentene			
C	0.774771	2.304022	-0.404990	C	-1.041273	0.429161	0.000192
H	0.013604	2.288917	-1.191763	C	-1.875615	-0.037414	1.236347
H	0.308643	2.735298	0.488158	C	-3.259571	-0.241040	0.667310
H	1.568743	2.986590	-0.719991	C	-3.259489	-0.240463	-0.667622
				C	-1.875368	-0.036701	-1.236182
3-(<i>o</i> -tolyl)cyclopentene				H	-1.844117	0.701326	2.046434
C	-1.804990	0.527256	1.038739	H	-1.486377	-0.972833	1.662214
C	-3.264342	0.119451	0.717133	H	-4.132004	-0.410125	1.291907
C	-3.113971	-0.701937	-0.542627	H	-1.843670	0.702261	-2.046065
C	-1.906822	-0.556058	-1.093216	H	-1.078673	1.520887	0.000677
C	-1.022765	0.398475	-0.309164	H	-4.131882	-0.408893	-1.292446

H	-1.486086	-0.971945	-1.662414	H	3.614226	1.142017	0.000171
C	0.411842	-0.014555	-0.000092	H	2.221436	-2.919574	-0.000251
C	1.478379	0.910659	-0.000059	H	4.106172	-1.280648	-0.000028
C	0.711152	-1.385271	-0.000138	C	1.247758	2.407070	0.000235
C	2.794654	0.427551	0.000048	H	0.685447	2.737839	-0.880504
C	2.023771	-1.851455	-0.000179	H	0.686754	2.737694	0.881845
H	-0.104412	-2.104274	-0.000089	H	2.200879	2.942515	-0.000424
C	3.075812	-0.936916	-0.000032				

Table 7 Isomers of *p*-anisylcyclopentene

Compounds	Energy (a.u.)	Relative Energy (kcal/mol)	Dihedral angle (degree)
1-(<i>p</i> -anisyl)cyclopentene
-540.7000	0	17
3-(<i>p</i> -anisyl)cyclopentene
-540.6907	5.8	44
4-(<i>p</i> -anisyl)cyclopentene
-540.6896	6.5	61
1-(<i>p</i> -anisyl)cyclopentene	C 4.029089	-0.923507	-0.214339
C 4.113880	0.510578	0.364774	C 2.545772
			-1.193090
			-0.228893

C 1.808991 -0.082732 -0.038879
 C 2.718469 1.129119 0.115327
 H 4.925239 1.100684 -0.070871
 H 4.593942 -1.652080 0.380527
 H 4.442724 -0.976693 -1.233441
 H 2.140446 -2.179793 -0.431946
 H 2.404569 1.793602 0.928718
 H 2.703929 1.734358 -0.803287
 H 4.295990 0.453816 1.443279
 C 0.341564 0.026913 -0.027460
 C -0.292217 1.278509 -0.158995
 C -0.488269 -1.096575 0.118393
 C -1.675280 1.398476 -0.163268
 H 0.308975 2.175241 -0.270133
 C -1.877777 -0.994442 0.116991
 H -0.041067 -2.076749 0.252823
 C -2.481985 0.261501 -0.027002
 H -2.155833 2.365443 -0.270241
 H -2.475024 -1.890587 0.237141
 O -3.830202 0.480198 -0.039308
 C -4.691884 -0.637663 0.100689
 H -4.540537 -1.149337 1.059930
 H -5.707875 -0.241960 0.062468
 H -4.555976 -1.360060 -0.714542

3-(*p*-anisyl)cyclopentene

C -2.611526 0.613324 1.050623
 C -4.039340 0.096161 0.747392
 C -3.850457 -0.671648 -0.540839
 C -2.674388 -0.405011 -1.113796
 C -1.852547 0.592169 -0.314649
 H -2.111633 -0.078303 1.736624
 H -4.749305 0.923509 0.599199
 H -4.447830 -0.516498 1.560069

H -4.614893 -1.320128 -0.959135
 H -1.939873 1.579307 -0.794929
 H -2.597920 1.601892 1.518362
 H -2.331392 -0.803711 -2.063920
 C -0.372789 0.275156 -0.200941
 C 0.595173 1.265876 -0.372529
 C 0.071830 -1.022879 0.104568
 C 1.961424 0.996361 -0.241368
 H 0.283181 2.279220 -0.614805
 C 1.422800 -1.312563 0.236755
 H -0.657947 -1.817882 0.234605
 C 2.380195 -0.301375 0.066233
 H 2.677700 1.796857 -0.383547
 H 1.765386 -2.315709 0.469361
 O 3.683837 -0.686197 0.217174
 C 4.692508 0.297543 0.060363
 H 4.588658 1.106919 0.794832
 H 5.642117 -0.214329 0.223853
 H 4.685752 0.729747 -0.948823

4-(*p*-anisyl)cyclopentene

C -1.863348 0.593656 -0.000050
 C -2.662076 0.067173 1.233637
 C -4.034163 -0.212707 0.667612
 C -4.034165 -0.212833 -0.667542
 C -2.662110 0.067037 -1.233647
 H -2.667309 0.795723 2.053191
 H -2.215402 -0.849974 1.644078
 H -4.895397 -0.430162 1.292780
 H -2.667387 0.795496 -2.053291
 H -1.968328 1.684848 -0.000107
 H -4.895408 -0.430389 -1.292660
 H -2.215442 -0.850143 -1.644011

C	-0.382704	0.274854	-0.000042	H	2.648811	1.849209	-0.000047
C	0.572731	1.292785	-0.000053	H	1.803308	-2.364395	0.000080
C	0.087279	-1.051001	0.000020	O	3.698598	-0.688904	0.000025
C	1.945942	1.024518	-0.000023	C	4.693126	0.321446	-0.000007
H	0.244066	2.329446	-0.000095	H	5.652389	-0.198419	0.000007
C	1.444511	-1.340218	0.000045	H	4.627943	0.956217	-0.893361
H	-0.622495	-1.874517	0.000053	H	4.627946	0.956267	0.893309
C	2.387297	-0.301039	0.000028				

Table 8 Isomers of (*p*-methoxycarbonyl)phenylcyclopentene

Compounds	Energy (a.u.)	Relative Energy (kcal/mol)	Dihedral angle (degree)
1-(<i>p</i> -methoxycarbonyl)phenylcyclopentene
-654.0479	0.0	16
3-(<i>p</i> -methoxycarbonyl)phenylcyclopentene
-654.0387	5.8	42
4-(<i>p</i> -methoxycarbonyl)phenylcyclopentene
-654.0371	6.8	59

1-(*p*-
methoxycarbonyl)phenylcyclopentene

C 4.768809 -0.823723 0.336283
C 4.837929 0.604807 -0.258053
C 3.397390 1.045240 -0.248622
C 2.541311 0.028832 -0.032801
C 3.305546 -1.279333 0.121715
H 4.979487 -0.778616 1.409925
H 5.230445 0.601447 -1.286526
H 5.493713 1.271529 0.314972
H 3.106056 2.070362 -0.455331
H 3.201845 -1.889204 -0.787671
H 2.933006 -1.892020 0.950492
H 5.496288 -1.507587 -0.109434
C 1.072309 0.099825 -0.006781
C 0.298034 -1.071517 -0.103542
C 0.390804 1.328209 0.118089
C -1.092574 -1.022794 -0.095262
H 0.790971 -2.033419 -0.197060
C -0.994329 1.381994 0.126990
H 0.958011 2.247072 0.225142
C -1.753028 0.206411 0.018205
H -1.671219 -1.935642 -0.176770
H -1.516657 2.327587 0.224924
C -3.234816 0.325678 0.034619
O -3.843101 1.374306 0.134867
O -3.853365 -0.875067 -0.077243
C -5.287479 -0.824365 -0.071078
H -5.656054 -0.223947 -0.906552
H -5.618968 -1.858193 -0.167275
H -5.654627 -0.388855 0.861590

3-(*p*-
methoxycarbonyl)phenylcyclopentene

C 3.312925 -0.536683 1.100155
C 4.725961 0.023215 0.803268
C 4.540587 0.714581 -0.527356
C 3.390819 0.373373 -1.113737
C 2.591418 -0.616877 -0.284037
H 2.768762 0.167805 1.737374
H 5.472531 -0.779916 0.716346
H 5.086347 0.693935 1.592197
H 5.289886 1.369999 -0.961543
H 2.727632 -1.623147 -0.709128
H 3.326506 -1.500254 1.616833
H 3.058115 0.707623 -2.091788
C 1.099189 -0.353771 -0.212503
C 0.180347 -1.406917 -0.312342
C 0.604131 0.946065 -0.020399
C -1.190404 -1.179823 -0.217531
H 0.545798 -2.419085 -0.466683
C -0.762139 1.183058 0.072423
H 1.302645 1.775212 0.051038
C -1.672254 0.121088 -0.024036
H -1.890034 -2.003932 -0.295829
H -1.149617 2.185782 0.217771
C -3.123270 0.432669 0.082294
O -3.581039 1.547422 0.246068
O -3.900627 -0.672460 -0.022700
C -5.312639 -0.435029 0.073538
H -5.646535 0.234946 -0.722687
H -5.783186 -1.413022 -0.026702
H -5.563548 0.014664 1.037435

4-(*p*-
methoxycarbonyl)phenylcyclopentene

C -2.635092 0.855874 -0.000015
C -3.386560 0.266491 1.245986

C	-4.314927	-0.770984	0.667214
C	-4.315039	-0.770981	-0.667005
C	-3.386762	0.266460	-1.245892
H	-3.947542	1.046590	1.778695
H	-2.686867	-0.158191	1.976033
H	-4.921836	-1.420834	1.290976
H	-3.947846	1.046614	-1.778420
H	-2.727965	1.945456	-0.000031
H	-4.922029	-1.420865	-1.290657
H	-2.687205	-0.158111	-1.976103
C	-1.155562	0.522616	-0.000023
C	-0.190862	1.538478	-0.000104
C	-0.714277	-0.812214	-0.000102
C	1.170948	1.243063	-0.000101
H	-0.512175	2.576965	-0.000200
C	0.641260	-1.116079	-0.000086
H	-1.444810	-1.616612	-0.000171
C	1.597536	-0.090293	-0.000051
H	1.905086	2.040490	-0.000128
H	0.985277	-2.144868	-0.000118
C	3.034755	-0.474091	-0.000011
O	3.445152	-1.618965	-0.000090
O	3.859385	0.601521	0.000090
C	5.261055	0.294059	0.000137
H	5.773547	1.256000	0.000328
H	5.529565	-0.283889	0.887962
H	5.529680	-0.283590	-0.887848

2. DFT calculations on alkyl radical addition to heterocycles

Method

Density functional theory (DFT) calculations were performed to optimize the transition states for the reactions between aromatic molecules and a cyclohexyl radical, using the Gaussian 09 program.⁴⁶ The B3LYP DFT functional was used in conjunction with the 6-31+G* basis set in vacuum.⁴⁷

XYZ coordinates of TSs

* Examples of TS structures

=== #1 (2) ===

N	0.734393	0.743903	-0.023104
C	1.927496	1.357743	0.084153
N	2.160957	2.712203	-0.132180
C	1.104622	3.469651	-0.259273
C	-1.385057	3.774082	-0.349302
C	-2.640835	3.193027	-0.367832
C	-2.770783	1.784193	-0.278331
C	-1.660065	0.971317	-0.165226
C	-0.233652	2.965410	-0.231582
C	-0.357955	1.543422	-0.128956
H	-1.271429	4.853747	-0.427612
H	1.272464	4.537661	-0.414917
H	2.799649	0.725156	-0.064405
H	-1.747074	-0.109290	-0.098897
H	-3.763021	1.340218	-0.300756
H	-3.529377	3.811976	-0.457202
C	2.741657	-0.410369	4.061331
C	2.278787	-0.210440	2.593878
C	2.370704	1.245288	2.223637
C	3.723747	1.873191	2.419596
C	4.187828	1.673981	3.886726
C	4.135882	0.193160	4.294630
H	1.517463	1.860982	2.516113
H	2.939654	-0.802282	1.941236
H	1.262934	-0.591716	2.449222
H	2.017780	0.067284	4.737830
H	2.739107	-1.481901	4.302909
H	4.457867	1.389877	1.756007
H	3.709837	2.935799	2.158545
H	5.204643	2.071899	4.006226
H	3.539047	2.260084	4.554139
H	4.876943	-0.370074	3.706955
H	4.423215	0.081549	5.348712

=== #1 (4) ===

N	0.803234	0.443459	-0.091912
C	1.999248	0.971901	-0.314957
N	2.325966	2.272139	-0.442537
C	1.329085	3.161798	-0.236299
C	-1.157287	3.595174	-0.191889
C	-2.440917	3.085842	-0.088646
C	-2.644087	1.692933	0.056091
C	-1.570634	0.822306	0.075243
C	-0.044129	2.727087	-0.160001
C	-0.248686	1.320829	-0.046728
H	-0.996523	4.665071	-0.305698
H	1.537778	4.190780	-0.528630
H	2.823305	0.268208	-0.422359
H	-1.705980	-0.251448	0.166413
H	-3.656611	1.306408	0.141018
H	-3.296722	3.755042	-0.120825
C	3.663964	4.766945	3.185475
C	3.236024	4.227772	1.794510
C	1.803647	3.772717	1.851307
C	0.820637	4.816079	2.303759
C	1.244372	5.357790	3.696967
C	2.698808	5.852878	3.685801
H	1.643190	2.770528	2.252410
H	3.340676	5.043095	1.061660
H	3.894658	3.417428	1.469095
H	3.685747	3.935286	3.904603
H	4.688231	5.158256	3.125014
H	0.814721	5.660419	1.596206
H	-0.198781	4.418465	2.347842
H	0.561910	6.164319	3.996862
H	1.134387	4.556645	4.441813
H	2.776149	6.735942	3.033164

H 2.990198 6.182465 4.691864

=== #2 (3) ===

N	0.010935	-0.056550	0.027785
C	1.337844	0.110715	-0.121360
C	1.981255	1.383880	-0.047654
C	1.126012	2.520758	-0.121476
C	-0.237854	2.344139	0.013007
C	-0.750951	1.032417	0.131609
C	2.105045	-1.119647	-0.390101
O	3.311645	-1.152700	-0.596363
H	3.014732	1.445022	-0.373940
H	-1.818674	0.865701	0.259166
H	-0.918797	3.191141	0.004357
H	1.548925	3.514893	-0.239254
H	1.488253	-2.039295	-0.412387
C	4.007580	0.416236	3.864760
C	3.358938	0.258838	2.462973
C	2.712744	1.556242	2.060144
C	3.633480	2.747890	2.058209
C	4.292617	2.908786	3.454058
C	4.977840	1.607508	3.899808
H	1.721622	1.733070	2.481946
H	4.140129	-0.015182	1.741209
H	2.632099	-0.561415	2.477572
H	3.218400	0.563583	4.616491
H	4.528080	-0.513451	4.130067
H	4.433454	2.601138	1.315887
H	3.101439	3.668278	1.788309
H	5.014377	3.736160	3.424444
H	3.521385	3.187378	4.186872
H	5.829889	1.400126	3.235023
H	5.391198	1.727969	4.909880

=== #2 (5) ===

N	0.366142	-0.047300	0.227214
C	1.661660	0.005114	-0.172950
C	2.268028	1.190527	-0.636925
C	1.537796	2.364179	-0.626680
C	0.230496	2.358870	-0.063387
C	-0.326329	1.078888	0.239048
C	2.392981	-1.276957	-0.149219
O	3.565223	-1.410137	-0.471757
H	3.285189	1.146052	-1.014665
H	-1.370156	1.001717	0.539390
H	-0.443329	3.190353	-0.251911
H	1.965012	3.287601	-1.008250
H	1.785714	-2.137284	0.194981
C	1.299803	5.297966	3.141626
C	1.215609	4.535708	1.792922
C	0.505460	3.222866	1.987278
C	-0.864908	3.328199	2.602169
C	-0.785568	4.091586	3.951037
C	-0.087556	5.450257	3.784347
H	1.124919	2.401672	2.350028
H	0.657477	5.162789	1.078897
H	2.220860	4.388943	1.381617
H	1.962392	4.747498	3.824699
H	1.760324	6.281438	2.978079
H	-1.535700	3.888717	1.931062
H	-1.311243	2.339342	2.757193
H	-1.797713	4.223581	4.356181
H	-0.231018	3.480513	4.677346
H	-0.710105	6.103479	3.153863
H	0.001227	5.949300	4.758100

=== #3 (4) ===

N	0.549700	-0.113424	-0.657039
C	1.820388	0.198148	-0.384029
C	2.246552	1.429563	0.133692
C	1.256029	2.394263	0.499477
C	-0.070872	2.112993	0.070401
C	-0.365493	0.863969	-0.452616
C	3.679292	1.709655	0.243068
O	4.161015	2.768768	0.627835
H	2.559065	-0.570218	-0.615863
H	-1.384516	0.618618	-0.745941
H	-0.859545	2.850543	0.188622
H	1.579322	3.416919	0.670994
H	4.345593	0.879080	-0.073234
C	2.201820	2.112731	4.884594
C	2.362958	2.095048	3.339853
C	1.007637	2.210767	2.697514
C	0.216972	3.425956	3.104636
C	0.058160	3.455518	4.648642
C	1.420808	3.351080	5.350476
H	0.438546	1.281095	2.645623
H	2.999076	2.938455	3.041017
H	2.874974	1.177740	3.028432
H	1.674156	1.203249	5.206788
H	3.195387	2.084525	5.350870
H	0.748304	4.339267	2.795876
H	-0.770184	3.442613	2.628035
H	-0.461209	4.377148	4.943152
H	-0.581661	2.617556	4.960864
H	2.010608	4.254522	5.134511
H	1.281104	3.321179	6.439069

=== #3 (6) ===

N	-0.028245	0.514702	-0.465144
C	1.273913	0.327818	-0.297120
C	2.205770	1.354857	-0.036135
C	1.725124	2.683576	0.004644
C	0.374263	2.905004	-0.156610
C	-0.502490	1.787160	-0.296762
C	3.627292	1.036465	0.130269
O	4.507251	1.857830	0.352616
H	1.626480	-0.700137	-0.397193
H	-1.515358	1.951745	-0.658126
H	-0.035934	3.910986	-0.150584
H	2.430866	3.498254	0.141577
H	3.881570	-0.041653	0.042798
C	-2.856183	2.832979	3.381142
C	-2.039869	2.954526	2.065636
C	-1.427287	1.624024	1.723007
C	-2.398251	0.481561	1.611550
C	-3.208406	0.355310	2.929222
C	-3.877512	1.687518	3.303004
H	-0.480401	1.396979	2.215081
H	-2.726605	3.269548	1.263668
H	-1.276327	3.734187	2.168159
H	-2.164748	2.651795	4.216494
H	-3.358688	3.787336	3.587884
H	-3.105935	0.671753	0.789420
H	-1.881709	-0.454547	1.379183
H	-3.960412	-0.437503	2.820359
H	-2.534812	0.042673	3.740207
H	-4.641883	1.933101	2.549993
H	-4.404363	1.589464	4.261278

=== #4 (2) ===

N	0.045097	0.402704	0.114223
C	1.409415	0.452283	0.226124
C	2.135101	1.629642	-0.122125
C	1.441644	2.809804	-0.346360
C	0.030441	2.787500	-0.297084
C	-0.597774	1.554175	-0.092692
C	2.190634	4.052368	-0.654423
O	1.680282	5.141457	-0.842343
H	1.911609	-0.511135	0.161937
H	3.221482	1.604395	-0.174112
H	-0.538332	3.695162	-0.469639
H	-1.684492	1.487747	-0.128977
H	3.294655	3.932457	-0.703637
C	1.236783	-1.180830	4.317888
C	0.992625	-0.919650	2.808951
C	1.699312	0.341744	2.388559
C	3.177575	0.366831	2.676072
C	3.430473	0.097215	4.183199
C	2.738340	-1.194670	4.645593
H	1.165576	1.269836	2.601738
H	1.390683	-1.776591	2.242901
H	-0.078038	-0.862359	2.589761
H	0.739705	-0.396537	4.907146
H	0.770775	-2.133194	4.604128
H	3.685685	-0.420093	2.095355
H	3.626720	1.324950	2.388777
H	4.511566	0.045375	4.369948
H	3.048575	0.946414	4.768047
H	3.209366	-2.056489	4.148426
H	2.888964	-1.335741	5.723972

=== #4 (3) ===

N	-0.153184	0.313709	0.128988
C	1.157854	0.283746	-0.024427
C	1.977716	1.450976	-0.121910
C	1.300851	2.686862	-0.337042
C	-0.089503	2.717507	-0.141522
C	-0.762304	1.530072	0.116296
C	2.041445	3.889242	-0.746810
O	1.549154	5.000899	-0.887602
H	1.622055	-0.701197	-0.032338
H	3.008985	1.341524	-0.450988
H	-0.625330	3.657257	-0.238786
H	-1.838990	1.518803	0.265963
H	3.123208	3.731207	-0.944694
C	4.224846	0.347170	3.605169
C	3.545224	0.281709	2.210904
C	2.710479	1.515293	1.989401
C	3.452676	2.815532	2.132779
C	4.123494	2.886116	3.530388
C	5.008200	1.656272	3.786662
H	1.714664	1.495033	2.434575
H	4.335853	0.219071	1.445950
H	2.943113	-0.630658	2.133348
H	3.452450	0.270757	4.383790
H	4.886266	-0.520519	3.729811
H	4.244203	2.884983	1.369944
H	2.788383	3.675575	1.992507
H	4.712443	3.809716	3.605523
H	3.342315	2.944902	4.301691
H	5.860364	1.670221	3.089937
H	5.432579	1.702710	4.798071

=== #5 (2) ===

S	0.158712	0.523181	-0.133770
C	1.882694	0.827221	-0.136130
C	2.145947	2.091073	-0.693557
C	0.957367	2.854366	-0.926866
C	-0.184068	2.148539	-0.663261
C	3.455511	2.562353	-0.978153
N	4.527186	2.953686	-1.223388
H	2.565365	-0.012234	-0.148664
H	0.968574	3.878959	-1.281692
H	-1.208618	2.486969	-0.744900
C	2.624483	-0.481624	4.194954
C	2.143328	-0.401599	2.720341
C	2.385116	0.977755	2.173914
C	3.800248	1.470124	2.273112
C	4.283282	1.395403	3.747323
C	4.081797	-0.012234	4.329922
H	1.599420	1.713807	2.347244
H	2.716503	-1.142929	2.138833
H	1.085235	-0.682068	2.651592
H	1.975824	0.150125	4.818658
H	2.513165	-1.510829	4.562277
H	4.465295	0.836027	1.665463
H	3.901427	2.492482	1.894579
H	5.340301	1.687702	3.801311
H	3.721092	2.124719	4.348369
H	4.740675	-0.719955	3.803827
H	4.384823	-0.030294	5.385155

=== #5 (4) ===

S	-0.638771	0.824576	-0.624591
C	0.889551	0.013778	-0.573638
C	1.899222	0.841185	-0.153309
C	1.433968	2.174680	0.239753
C	0.085441	2.322675	-0.119724
C	3.258061	0.417025	-0.084654
N	4.372216	0.078158	-0.038488
H	0.974476	-1.026546	-0.859329
H	2.111072	3.023807	0.244342
H	-0.522902	3.212698	-0.037252
C	3.151116	2.539283	4.320021
C	3.008442	2.360847	2.786274
C	1.561216	2.144146	2.415955
C	0.625262	3.220494	2.906291
C	0.762252	3.400641	4.438537
C	2.224254	3.647128	4.843832
H	1.196451	1.123936	2.554380
H	3.385283	3.275674	2.299966
H	3.641084	1.534669	2.445286
H	2.904656	1.589879	4.817177
H	4.197648	2.762276	4.567394
H	0.875219	4.179433	2.422939
H	-0.414344	2.989876	2.644623
H	0.124758	4.231037	4.771868
H	0.390984	2.495846	4.941684
H	2.553856	4.616614	4.439483
H	2.304922	3.721916	5.936380

=== #7 (3) ===

N	0.134521	0.027257	0.038403
---	----------	----------	----------

C	1.519393	0.081360	-0.079990
C	1.916411	1.433688	0.139352
C	0.704282	2.198808	0.221227
C	-0.341614	1.303110	0.203819
C	2.359900	-1.033572	-0.407232
O	1.993076	-2.201245	-0.588652
C	-0.699391	-1.166180	-0.059085
H	-0.593927	-1.631464	-1.042225
H	-0.409148	-1.900804	0.695499
H	-1.738850	-0.867403	0.099226
H	2.877684	1.819888	-0.179162
H	0.618393	3.270425	0.337829
H	-1.406048	1.475938	0.299258
H	3.432335	-0.766983	-0.503230
C	4.515767	0.712281	3.743348
C	3.808601	0.554964	2.372272
C	2.679496	1.541991	2.250797
C	3.073762	2.979586	2.466226
C	3.782811	3.147130	3.835429
C	4.957188	2.165843	3.979160
H	1.738881	1.239045	2.713051
H	4.554372	0.738359	1.581199
H	3.454274	-0.474669	2.246201
H	3.825088	0.405748	4.542331
H	5.379047	0.034742	3.794479
H	3.775454	3.297312	1.677166
H	2.203091	3.644022	2.409096
H	4.130544	4.183270	3.948667
H	3.055678	2.967391	4.640732
H	5.740063	2.428997	3.251073
H	5.411609	2.265405	4.973886

=== #7 (5) ===

N	0.413546	0.061864	0.030113
C	1.599226	-0.142453	-0.662856
C	1.981923	1.097255	-1.218776
C	1.040373	2.048483	-0.847067
C	0.105066	1.407690	0.013157
C	2.293946	-1.396893	-0.779910
O	1.958617	-2.470129	-0.270015
C	-0.392162	-0.969949	0.672970
H	-0.612901	-1.771283	-0.035536
H	0.134086	-1.409766	1.524363
H	-1.323854	-0.512868	1.014260
H	2.866532	1.251618	-1.824578
H	1.031353	3.099124	-1.103341
H	-0.915968	1.712114	0.212691
H	3.211113	-1.336296	-1.401864
C	0.703209	4.428239	3.300892
C	0.539562	3.745672	1.918695
C	0.663899	2.248731	2.040402
C	-0.254058	1.620665	3.058139
C	-0.086022	2.300154	4.442563
C	-0.254632	3.823791	4.339272
H	1.679663	1.852142	2.009780
H	-0.457883	4.007619	1.526112
H	1.276458	4.146868	1.213339
H	1.740339	4.300954	3.643537
H	0.532584	5.509154	3.202673
H	-1.305004	1.746050	2.746750
H	-0.071822	0.543965	3.149690
H	-0.811814	1.878708	5.151582
H	0.913769	2.068515	4.837147
H	-1.292560	4.054890	4.053258
H	-0.090943	4.289138	5.320274

=== #8 (2) ===

N	-0.078162	0.426064	-0.029849
C	1.341830	0.430342	0.065331
C	1.792752	1.672599	-0.372133
C	0.510475	3.873921	-0.913231
C	-0.770325	4.407403	-1.030322
C	-1.907852	3.610588	-0.803932
C	-1.796126	2.260125	-0.456587
C	-0.510513	1.731499	-0.345463
C	0.654814	2.517762	-0.566285
C	-0.901139	-0.685240	0.053093
O	-0.176354	-1.822375	0.141745
O	-2.117866	-0.644324	0.031834
C	-0.945073	-3.046753	0.254034
C	0.037619	-4.202358	0.273927
H	-2.669288	1.644150	-0.284559
H	-2.897194	4.049951	-0.899968
H	-0.895191	5.453513	-1.298207
H	1.388144	4.491383	-1.087721
H	2.832078	1.958646	-0.464893
H	1.859071	-0.516387	0.025555
H	-1.542706	-2.998755	1.170106
H	-1.631844	-3.105510	-0.595447
H	0.720984	-4.128186	1.126683
H	-0.512358	-5.146989	0.356866
H	0.631286	-4.230643	-0.646120
C	1.431062	-0.696661	4.502496
C	1.060710	-0.666529	2.996049
C	1.704359	0.518926	2.325593
C	3.199189	0.599206	2.492695
C	3.582622	0.562955	3.994435
C	2.954666	-0.648741	4.701751
H	1.167500	1.463191	2.430372
H	1.418618	-1.600140	2.535421
H	-0.029892	-0.647830	2.882186
H	0.968704	0.165359	5.004941
H	1.010634	-1.598069	4.969961
H	3.678427	-0.261603	1.996342
H	3.602308	1.505044	2.023951
H	4.676323	0.545039	4.099385
H	3.233221	1.487965	4.475720
H	3.401035	-1.572440	4.301536
H	3.194751	-0.625989	5.773148

=== #8 (3) ===			
N	-0.132303	0.115252	-0.133309
C	1.272173	0.069606	-0.218883
C	1.789368	1.361115	-0.149976
C	0.518560	3.650431	-0.334372
C	-0.754042	4.225260	-0.353005
C	-1.903045	3.423516	-0.263355
C	-1.814876	2.031529	-0.171158
C	-0.536688	1.470556	-0.167946
C	0.634505	2.260219	-0.232139
C	-0.985369	-0.975325	-0.074461
O	-0.285269	-2.131869	-0.076901
O	-2.200811	-0.901887	-0.028669
C	-1.078216	-3.344814	-0.030715
C	-0.115837	-4.517374	-0.050892
H	-2.697346	1.407564	-0.115470
H	-2.884844	3.889610	-0.275145
H	-0.856614	5.304036	-0.437747
H	1.406284	4.273118	-0.406128
H	2.782212	1.614990	-0.503584
H	1.773143	-0.883722	-0.248301
H	-1.687501	-3.327508	0.878219
H	-1.753603	-3.351744	-0.891752
H	0.557356	-4.490696	0.812751
H	-0.682172	-5.455309	-0.016131
H	0.489386	-4.515505	-0.963834
C	4.140010	0.690627	3.583251
C	3.397291	0.491383	2.238661
C	2.535253	1.686824	1.923148
C	3.266921	3.004492	1.928190
C	4.013760	3.212132	3.271157
C	4.921078	2.014780	3.595863
H	1.556813	1.696480	2.406863
H	4.153107	0.357717	1.446175
H	2.800740	-0.428750	2.268020
H	3.406655	0.692046	4.402957
H	4.816882	-0.155818	3.765526
H	4.015684	3.019781	1.117906
H	2.580225	3.839910	1.748378
H	4.601651	4.139743	3.230251
H	3.275940	3.340661	4.076520
H	5.731521	1.962498	2.852159
H	5.403055	2.160132	4.571897