Method Development for the Palladium-Catalyzed Synthesis of Nitrogen Heterocycles and Mechanistic Analysis of Migratory Alkene Insertion into Pd–N Bonds

by

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DEDICATION

To family and friends who have supported me along the way.

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9-BBN……..……..…….…….....…9-borabicyclo(3.3.1)nonane

acetic acid-d_4……..……..……...…perdeuterated acetic acid

AcOH……..……..…….……..…acetic acid

ACS……..American Chemical Society

Anal……..……..…….....…analytical

app……..……..……..…….....…apparent

Ar……..……..……..……..……..…aryl

ArBr……..……..……..……..…aryl bromide

atm……..……..atmosphere

ATP……..……..……..……..…adenosine triphosphate

BINAP……..……..……2,2’-bis(diphenylphosphino)-1,1’-binaphthyl

Bn……..……..……..……..……..…benzyl

Boc……..……..……..……....…*tert*-butyloxycarbonyl

br……..……..……..……..……..……..…broad

Br……..bromine

brine……..……..….....saturated aqueous sodium chloride

ca……..……..……..……..…crude approximation

CaH_2……..……..……..……..…calcium hydride

calcd……..……..…….....…calculated

$CaSO_4$……..……..……..……...…calcium sulfate

cat……....catalytic

CD_2Cl_2……..……..……..…perdeuterated dichloromethane

$CDCl_3$……..……..……..……...…deuterated chloroform

CH_2Cl_2……..……..……..……...……dichloromethane

cm^{-1}……wavenumbers

COSY……correlation spectroscopy

Cp……cyclopentadienyl

Cs_2CO_3……cesium carbonate

d……doublet

DCE……1,2-dichloroethane

dd……doublet of doublets

ddd……doublet of doublets of doublets

ddm……doublet of doublet of multiplets

°C……degrees Celsius

δ……chemical shift

$\Delta H^{\neq}$……enthalpy of activation

$\Delta S^{\neq}$……entropy of activation

DIC……diisopropylcarbodiimide

dm……doublet of multiplets

DMAD……dimethylacetylenedicarboxylate

DMAP……*N*,*N*-dimethylpyridine-4-amine

DMF……dimethylformamide

DMSO……dimethylsulfoxide

DPE-Phos……bis(2-diphenylphosphino)phenyl ether

dpp-Benzene……1,2-bis(diphenylphosphino)benzene

dppe……1,2-bis(diphenylphosphino)ethane

dppf……1,1'-bis(diphenylphosphino)ferrocene

dppf-*p*-CF_3……1,2-bis(bis(4-trifluoromethyl)phenyl)phosphino)ferrocene

dppf-*p*-OMe……1,2-bis(bis(4-methoxyphenyl)phosphino)ferrocene

dppp……1,2-bis(diphenylphosphino)propane

dq……doublet of quartets

dr……diastereomeric ratio

dt……doublet of triplets

EI……electron impact mass spectrometry

equiv……equivalents

ESI……electrospray injection mass spectrometry

Et……ethyl

Et_3N……triethylamine

Et_2O……diethyl ether

EtOAc……ethyl acetate

EtOH……ethanol

eu……entropy units

g……grams

GC……gas chromatography

GC/MS……gas chromatography/mass spectrometry

h……hours

H^+……proton

HCl……hydrochloric acid

H_2O……water

HOBT……*N*-hydroxybenzotriazole

H_3PO_4……phosphoric acid

HRMS……high resolution mass spectrometry

HSQC……heteronuclear single quantum correlation

Hz……hertz

i-Pr……isopropyl

i-Pr_2NEt……diisopropylethylamine

Ir……iridium

IR……infrared spectroscopy

J……coupling constant value

kcal……kilocalorie

KHMDS…… potassium bis(trimethylsilyl)amide

KOH……potassium hydroxide

LDA……lithium diisopropylamide

$LiAlH_4$……lithium aluminum hydride

LiHMDS……..……..……..…… lithium bis(trimethylsilyl)amide

L–L……..……..…….....…generic bidentate ligand

L_n…….……..……..……..…generic ligand

m……..……..……..……..……..…multiplet

Me……..……..……..……...….methyl

MeMgBr……..…….....…methyl magnesium bromide

Me_4NOAc…….……tetramethylammonium acetate

mg……..……..……..……...…milligrams

MHz……..……..……..……...…megahertz

µL……..……..……..……..microliters

µmol…….……..…….....…micromole

min……..……..……..……..…minutes

mL……..……..……..……...…milliliters

mM……..……..…….....…millimolar

mmol……..……..……..……..…millimoles

mol……..……..…….....…mole

m.p……..……..……..……melting point

MS……..……..……..……..…mass spectrometry

N-Me-Nixantphos……..…4,6-bis(diphenylphosphino)-10-methyl-10*H*-phenoxazine

Na……..……..……..……...…sodium

Na^+……..……..……..……..…sodium ion

Na_2CO_3……..……..……...…sodium carbonate

NaOH……..……..……..……..…sodium hydroxide

NaO*t*-Bu……..……..……..…sodium *tert*-butoxide

Na_2SO_4……..……..…….....…sodium sulfate

NIH……..…..…National Institutes of Health

nixantphos……..……...……4,6-bis(diphenylphosphino)phenoxazine

NMR……..……..……..……nuclear magnetic resonance

nOe……..……..……..……...…nuclear Overhauser effect

NSF……..National Science Foundation

O_2……....dioxygen

obsd……..……..…….....…observed

$P(2\text{-fur})_3$……..……..……..……..……tri-2-furylphosphine

$P(4\text{-F-}C_6H_4)_3$……..……..…tris(4-fluorophenyl)phosphine

PCy_2Ph……..……..……..……dicyclohexylphenylphosphine

Pd……..……..……..……..…palladium

$PdCl_2(MeCN)_2$…...……..……..……dichlorobis(acetonitrile)palladium(II)

$Pd(dba)_2$……..……..bis(dibenzylideneacetone)palladium(0)

$Pd_2(dba)_3$…...……..……tris(dibenzylideneacetone)dipalladium(0)

$Pd(OAc)_2$…...……..……..……..……..…palladium(II) acetate

PG……..……..……..……..……..…generic protecting group

Ph……..……..……..……..……..…phenyl

PhCHO……..……..……..……..……...…benzaldehyde

$PhI(OAc)_2$……iodobenzenediacetate

phth……phthalimidyl

PMP……..……..……..……..……..…*para*-methoxyphenyl

P–P……..……..……..…generic bidentate phosphine ligand

PPh_2Cy……..……..……..…cyclohexyldiphenylphosphine

ppm……..……..……..……parts per million

p-tol……..……..……..*para*-tolyl

py……pyridine

q……..……..……..……..……..…quartet

qdd……..……..……...…quartet of doublet of doublets

quint……..……..……..……quintet

quintd……..……..……..quintet of doublets

R……..……..……..……generic alkyl group

rac……..……..……..……racemic

rt……..……..……..……..…room temperature

s……..……..……..……..……...…singlet

sec……..……..……..……..……..…seconds

S-Phos……...……2-dicyclohexylphosphino-2’,6’-di-isopropoxy-1,1’-biphenyl

t……..……..……..……..……..……..……triplet

t-Bu……..……..……..……..……..……*tert*-butyl

tdd……..……..……..……..……triplet of doublets of doublets

TFA……..……..……..……..……trifluoroacetic acid

THF……..……..……..……..……tetrahydrofuran

THF-d_8……..……..……..……..……perdeuterated tetrahydrofuran

TLC……..……..……..……..……...….thin layer chromatography

TMS……..……..……..……..……..…tetramethylsilane

Toluene-d_8……..……..……..……..…perdeuterated toluene

Ts……..……4-methylbenzene-1-sulfonyl

TsCl……..……..……..……..……4-methylbenzene-1-sulfonyl chloride

tt……..……..……..……..……..……triplet of triplets

xantphos……..……..……..……9,9-dimethyl-4,5-bis-(diphenylphosphino)xanthene

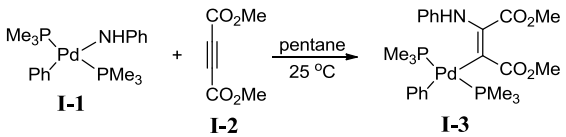
X-Phos……2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

CHAPTER I

Introduction

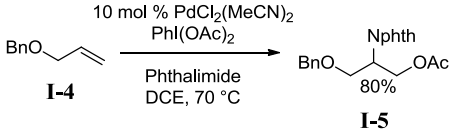
Along with the venerable Wacker oxidation reaction[1] thought to proceed historically via *anti*-oxypalladtion of alkenes,[2] *anti*-aminopalladation reactions have similarly become highly developed over the past 35 years.[3,4,5] In contrast, Pd-mediated *syn*-aminopalladations of alkenes have been discovered only in relatively recent times. In 1992, Boncella and co-workers provided direct evidence for intramolecular *syn*-insertion of DMAD (**I-2**) into Pd-amido complex **I-1** to form vinyl Pd-complex **I-3** (Scheme I.1),[6] but the analogous alkene insertion had not been demonstrated with a Pd-catalyst. S*yn*-aminopalladation was a topic of research in the late 1980s to the mid-1990s mainly using transition metals other than Pd. Casalnuovo and co-workers reported Ir(I)-catalyzed addition of aniline to norbornylene in 1988.[7] Around the same time, Trogler and Cowan reported insertion of acrylonitrile into a Pt-amido complex, which was conceptually challenging because late-metal-amido complexes had been thought to be thermodynamically unstable complexes.[8,9,10]

Scheme I.1 *Syn*-Insertion of DMAD into Pd-Amido Complex **I-1**

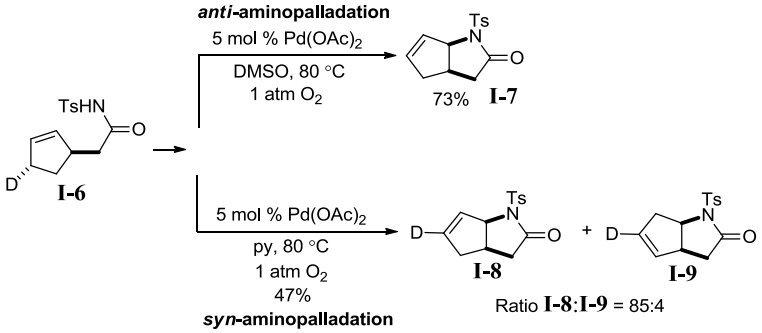


Despite being a more recent phenomenon, mechanistic and synthetic work has begun to reveal intermolecular *syn*-aminopalladation of alkenes as an expedient method for the preparation of linear, functionalized amines such as **I-5** (Scheme I.2).[11] Recent direct evidence for intermolecular Pd-mediated *syn*-aminopalladations of ethylene and 1-octene has been put forth by Hartwig and co-workers.[12] Stahl and Liu have also shown that oxidative, intramolecular *anti*- or *syn*-aminopalladations are both possible depending on the nature of the catalyst employed.[13] For example, a catalyst composed of $Pd(OAc)_2$/DMSO/O_2 yields only *anti*-aminopalladation product **I-7** whereas a $Pd(OAc)_2$/pyridine/O_2 catalyst system affords *syn*-aminopalladation products **I-8** and **I-9** (Scheme I.3).

Scheme I.2 Aminoacetoxylation of Terminal Alkenes with Phthalimide and Acetate



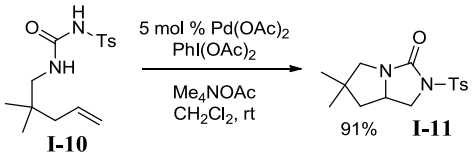
Scheme I.3 *Syn*- and *Anti*-Aminopalladation Dependent on Reaction Conditions



In addition, intramolecular aminopalladation processes have been demonstrated as a preferred route for the synthesis of valuable nitrogen heterocycles. For example, intramolecular alkene diamination (Scheme I.4, **I-10→I-11**),[14] chloroamination,[15] and

hetero-Heck-type transformations[16] have appeared in the literature for the synthesis of a plethora of valuable nitrogen-containing structures.

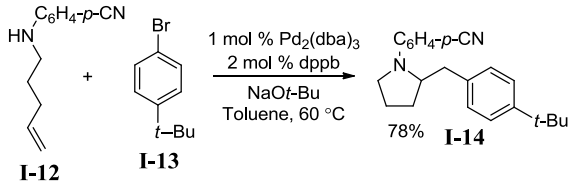
Scheme I.4 Alkene Diamination with a Urea Substrate



I-10 **I-11**

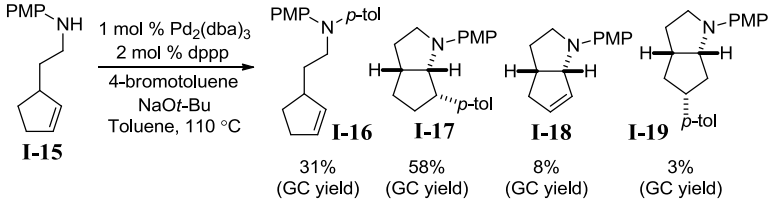
Pd-catalyzed carboamination of alkenes has also become a useful method for the synthesis of a broad array of nitrogen-containing heterocycles.[17,18] In 2004, Wolfe and Ney reported the Pd-catalyzed coupling of γ-aminoalkenes such as **I-12** with aryl bromides to yield 2-benzylpyrrolidines such as **I-14** (Scheme I.5).[19] In addition to pyrrolidines being an interesting class of medicinally-relevant compounds,[20] this carboamination method was demonstrated to involve a novel, intramolecular *syn*-aminopalladation step. In 2005, Wolfe and Ney illustrated that carboamination of γ-*N*-arylaminoalkene substrate **I-15** gave products **I-17** and **I-19** derived from *syn*-addition of the nitrogen and aryl group across the pendant alkene (Scheme I.6).[21]

Scheme I.5 Pd-Catalyzed Carboamination Reactions to Afford 2-Benzylpyrrolidines



I-12 **I-13** **I-14**

Scheme I.6 Regioselectivity and Stereochemical Evidence for *Syn*-Insertion

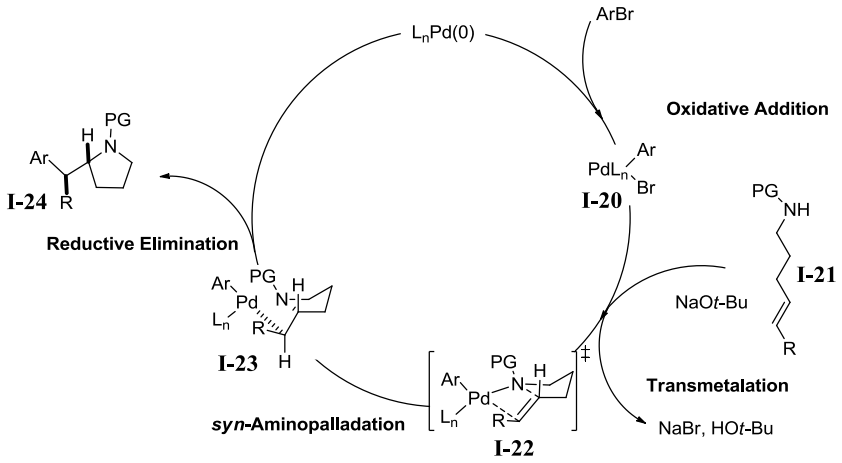


I-15 **I-16** **I-17** **I-18** **I-19**

31% (GC yield) 58% (GC yield) 8% (GC yield) 3% (GC yield)

From this initial work, a catalytic cycle was postulated involving: (1) oxidative addition of the ArBr to a Pd(0) complex to afford **I-20**; (2) transmetalation of the deprotonated amine substrate **I-21** with complex **I-20** to give a Pd-amido complex; (3) *syn*-aminopalladation from the Pd-amido complex through transition state **I-22** to give Pd-complex **I-23**; and (4) reductive elimination to liberate pyrrolidine **I-24** and regenerate the Pd(0) species (Scheme I.7).

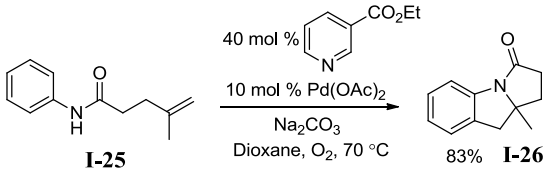
Scheme I.7 Generic Catalytic Cycle for Wolfe Group Carboamination Reactions



Since this seminal work, several syntheses of other important nitrogen-containing heterocycles have been undertaken by the Wolfe Group, including more easily cleavable *N*-Boc pyrrolidines,[22,23,24] imidazolidin-2-ones,[25] pyrazolidines,[26] piperazines,[27] isoxazolidines,[28] morpholines,[29] as well as polycyclic nitrogen-containing heterocycles.[30,31] In another recent development, an enantioselective synthesis of *N*-Boc pyrrolidines has been communicated.[32] Moreover, advances such as the general use of aryl chlorides as coupling partners[33] and a synthetic route to *trans*-2,5-disubstituted pyrrolidines[34] have both been recently published.

In addition to Wolfe Group *syn*-aminopalladation reactions, other researchers have been active in this field. Earlier this year, Yang and Yip demonstrated a tandem *syn*-amidopalladation sequence using a $Pd(OAc)_2$ pre-catalyst with an ethyl nicotinate ligand for the synthesis of polycyclic nitrogen-containing heterocycle **I-26** from **I-25** (Scheme I.8).[35] In 2009 Michael and co-workers demonstrated the synthesis of 2-benzylpyrrolidines via a Pd(II)/Pd(IV) sequence involving tandem intramolecular alkene aminopalladation and C–H activation of solvent arene molecules.[36] Additionally, in 2009 Oshima demonstrated Pd-catalyzed carboamination to be a convenient method for accessing aziridine products.[37] Metal-catalyzed carboamination reactions for the synthesis of nitrogen-containing heterocycles employing other metals such as Cu and Au have also been disclosed by Chemler[38] and Zhang[39] respectively.

Scheme I.8 Intramolecular *Syn*-Amidopalladation and C–H Activation Sequence



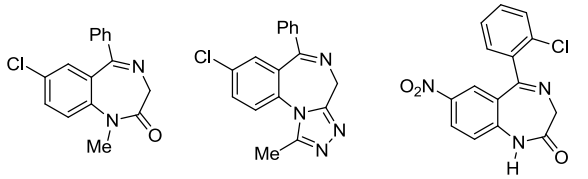
I-25 **I-26**

A large body of literature has been amassed since 2004 by the Wolfe Group for the Pd-catalyzed synthesis of nitrogen-containing heterocycles. However, little was known about the key intramolecular *syn*-aminopalladation step in the catalytic cycle until work described in Chapters III and IV of this dissertation. In addition, Wolfe Group methodology had not yet been expanded to the synthesis of 7-membered ring heterocycles until the studies described in Chapter II of this dissertation.

Specifically, 7-membered ring benzodiazepine heterocycles have captured the imagination of medicinal and organic chemists for the past 50 years. As a metric of how

important benzodiazepines have been in the treatment of anxiety etc. in humans, the common benzodiazepine drug diazepam (**I-27**) has been cited in > 30,000 journal articles according to SciFinder Scholar as of 04/26/2011. Related benzodiazepine alprazolam (**I-28**) had been cited 2,831 times whereas clonazepam (**I-29**) had been cited 4,999 times in journal articles according to SciFinder Scholar as of 04/26/2011 (Figure I.1).

Figure I.1 Structures of Commonly Prescribed Anti-Anxiety Benzodiazepines



A key feature of most biologically active benzodiazepines to date is various degrees of unsaturation such as a double bond in the 7-membered ring or a carbonyl moiety. Despite intense interest in and many methods for convenient syntheses of new and potentially therapeutic benzodiazepines, most recent methods are not suited for expeditious synthesis of fully saturated benzodiazepine variants. Literature methods for ring closure of the 7-membered benzodiazepine ring include intramolecular *N*-arylation,[40] *anti*-aminopalladation/*β*-hydride elimination,[41] ring-expansion of anhydrides with amines,[42] Mitsunobu reactions,[43] 1,3-dipolar cycloaddition,[44] electrophilic aromatic substitution,[45] and multicomponent reactions[46] especially those using amino acids.[47,48,49] In Chapter II, we illustrate a new method utilizing *syn*-aminopalladation of alkenes to yield fully saturated 1,4-benzodiazepine and 1,4-benzodiazepin-5-one products.

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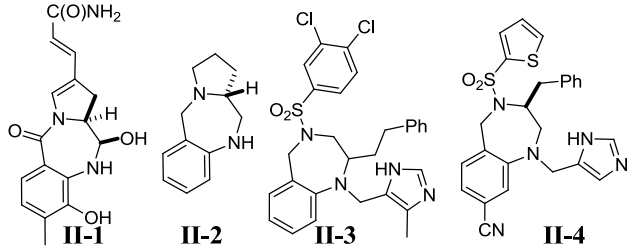
CHAPTER II

Synthesis of Saturated 1,4-Benzodiazepines via Pd-Catalyzed Carboamination Reactions

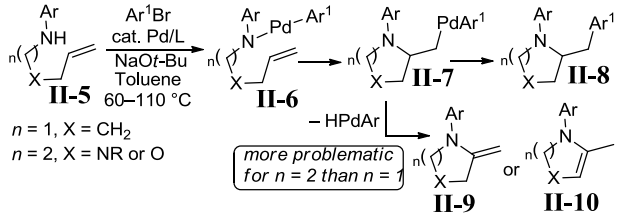
The benzodiazepine moiety is considered a privileged scaffold in medicinal chemistry, and many biologically active compounds bear this core.[50] Although much effort has been directed towards the construction of unsaturated 1,4-benzodiazepines,[51] fewer methods for the synthesis of saturated derivatives have been developed.[52] This remains an important goal, as saturated 1,4-benzodiazepines are displayed in both natural products and pharmaceutical leads (Figure II.1). For example, anthramycin (**II-1**) is a naturally occurring antitumor antibiotic,[53] and analogs such as **II-2** display antileishmanial activity.[54] Benzodiazepine **II-3** is an inhibitor of mitochondrial F_1F_0 ATP hydrolase, and has been examined as a potential candidate for treatment of cardiac ischemic conditions.[55] In addition, benzodiazepine **II-4** exhibits potent antitumor activity.[56]

Figure II.1 Biologically Active Saturated 1,4-Benzodiazepines



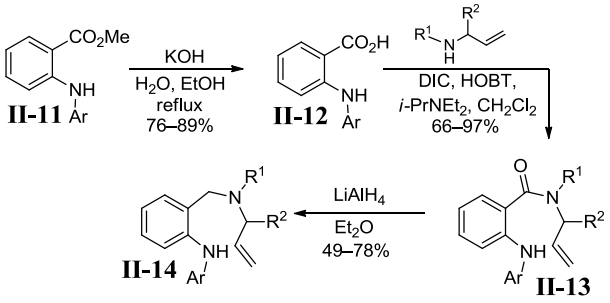
Our group has demonstrated that Pd-catalyzed carboamination reactions between aryl or alkenyl halides and amines bearing pendant alkenes are effective for the synthesis of a broad array of five-[57] and six-membered[58] nitrogen heterocycles.[59,60] However, our prior studies suggested that generation of seven-membered heterocycles via this strategy would be quite challenging, as both yields and reaction rates diminish with increasing ring size. This appears to be due to two main problems related to the mechanism of these transformations: as ring size increases, (a) *Syn*-aminopalladation of the alkene (Scheme II.1), **II-6**→**II-7**, becomes more difficult due to entropic and stereoelectronic effects; and (b) competing formation of enamine side products **II-9** or **II-10**, via *β*-hydride elimination from intermediate **II-7**, becomes more problematic.[29] The application of this methodology to the construction of seven-membered rings has not previously been demonstrated, and the formation of seven-membered nitrogen heterocycles via other metal-catalyzed alkene difunctionalization reactions is very rare.[61] For example, Michael has described a conceptually related Pd(II)-catalyzed C–H activation/carboamination of a *N*-allyl-2-(aminomethyl)aniline derivative that afforded a 3-substituted 1,4-benzodiazepine. However, only a single example was reported, and the yield was modest (53%).[36]

Scheme II.1 Mechanism and Competing Pathways



To determine the feasibility of forming seven-membered nitrogen heterocycles via Pd-catalyzed carboamination reactions, we elected to examine the synthesis of saturated 1,4-benzodiazepines. The substrates **II-14** for these studies were prepared in three steps from readily available diarylamines **II-11** (Scheme II.2), which can be generated via Pd-catalyzed *N*-arylation of methyl-2-aminobenzoate.[62] Saponification of the ester followed by coupling of the resulting acid **II-12** with an allylic amine provided amides **II-13**. Reduction of the amides with $LiAlH_4$ then afforded **II-14** in moderate to good yield.

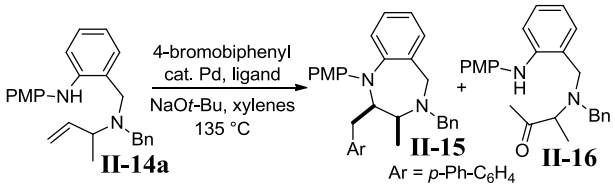
Scheme II.2 Synthesis of Substrates



In our preliminary experiments we examined the Pd-catalyzed coupling of **II-14a** with 4-bromobiphenyl (Table II.1). Our previous studies indicated that use of $P(2\text{-fur})_3$ as a ligand gave satisfactory results in six-membered ring forming reactions.[27] However, use of this ligand in a reaction of **II-14a** provided desired product **II-15** in a modest 58% NMR yield, along with 13% of ketone **II-16**. This side product presumably results from hydrolysis of an enamine (**II-9**, n = 3), which is generated via a competing β-hydride elimination pathway (Scheme II.1). In order to minimize this side reaction, several other monodentate ligands were examined. Use of S-Phos failed to afford the desired product. Instead, competing *N*-arylation of the starting material was observed. However, after

additional experimentation we discovered that a catalyst composed of $PdCl_2(MeCN)_2$ and PPh_2Cy provided acceptable results (79% NMR yield), and upon isolation the desired product **II-15** was obtained in 65% yield.

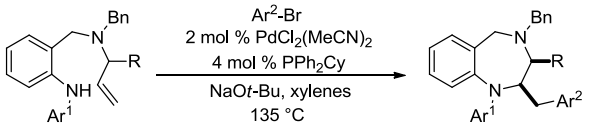
Table II.1 Optimization of Reaction Conditions

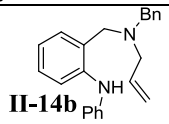
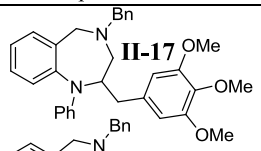
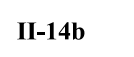
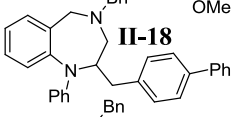
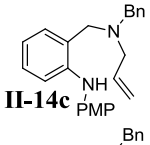
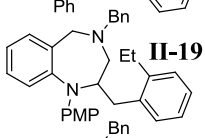
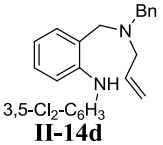
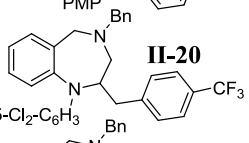
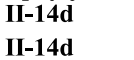
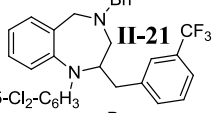
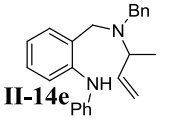
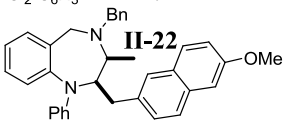
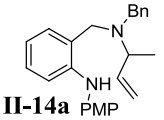
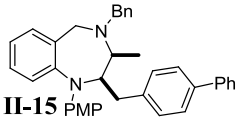
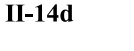
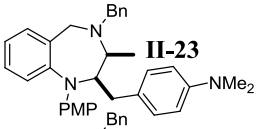
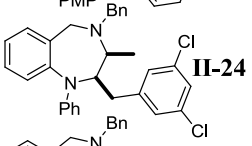
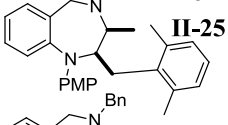
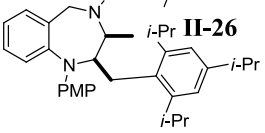


Pd-source	ligand	conversion (%)	yield **II-15** (%)[a]	yield **II-16** (%)[a]
$Pd_2(dba)_3$	$P(2\text{-fur})_3$	91	58	13
$Pd_2(dba)_3$	S-Phos	100	0	0[b]
$Pd_2(dba)_3$	PCy_2Ph	100	46	8
$Pd_2(dba)_3$	PPh_2Cy	100	79	6
$PdCl_2(MeCN)_2$	**PPh_2Cy**	**100**	**79 (65)[c]**	**4**

Conditions: 1.0 equiv **II-14a**, 2.0 equiv 4-bromobiphenyl, 2.0 equiv NaO*t*-Bu, 2 mol % [Pd], 4 mol % ligand. Product **II-15** was formed with >20:1 dr. [a] Yields were determined by ^{1}H NMR analysis of crude reaction mixtures using phenanthrene as an internal standard. [b] The major product resulted from *N*-arylation of the starting material. [c] Isolated yield (average of two experiments).

Table II.2 Synthesis of Saturated 1,4-Benzodiazepines



entry	substrate	product	yield (%)[a]
1			78
2			84
3			94
4			71
5			74
6			82[b]
7			65
8			81[b]
9			62
10			84
11			60

Conditions: Reactions were conducted on a 0.15 mmol scale using 1.0 equiv substrate, 2.0 equiv ArBr, 2.0 equiv NaO*t*-Bu, 2 mol % $PdCl_2(MeCN)_2$, 4 mol % PPh_2Cy, xylenes (0.2 M), 135 °C, 18–24 h reaction time. [a] Isolated yield (average of two experiments). In all cases, 2,3-disubstituted products were obtained with >20:1 dr. [b] This product contained ca. 8% of ketone side product **II-16**.

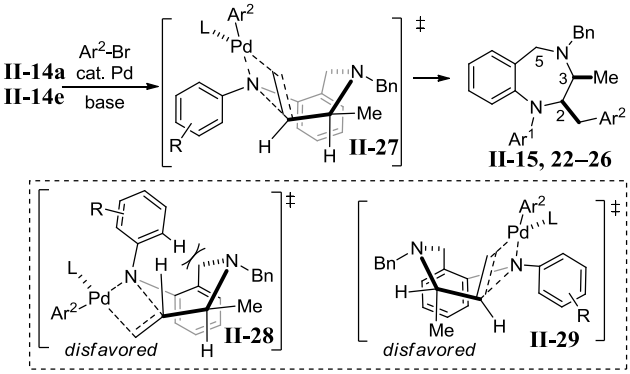
As shown in Table II.2, the transformations were effective for a number of different substrate combinations. Aryl bromides bearing electron-donating or electron-withdrawing groups were coupled in good yields. However, *N*-arylation of the substrate was observed with highly electron-poor aryl bromides such as 4-bromo-2-fluorobenzonitrile. In most cases reactions were also effective for aryl bromides bearing *o*-alkyl substituents (Table II.2, entries 3, 10–11) including the very hindered 2,4,6-triisopropylbromobenzene (Table II.2, entry 11). However, no reaction was observed in the attempted coupling of 1-bromo-2-chlorobenzene with **II-14a**, and no desired product was obtained in a reaction between 1-bromopentamethylbenzene and **II-14d**; competing Heck arylation of the starting material was observed. Efforts to employ alkenyl bromides have thus far been unsuccessful.

Although sterically bulky aryl bromides were reasonably well-tolerated, transformations of hindered diamine substrates proved to be more challenging. For example, substrates that contained an allylic-methyl group were stereoselectively transformed to *cis*-2,3-disubstituted products with >20:1 dr (Table II.2, entries 6–11). However, substrates bearing either larger substituents at the allylic position, or 1,1-disubstituted alkenes, failed to react. The electronic properties of the *N*-aryl group on the cyclizing nitrogen atom did not have a large influence on chemical yield, as substrates bearing *N*-phenyl-, *N*-PMP-, and *N*-(3,5-dichlorophenyl)-groups were all effectively converted to products in moderate to good yield. However, attempts to employ substrates with a benzyl group on the cyclizing nitrogen atom were unsuccessful.

The stereochemical outcome of transformations involving substrates **II-14a** and **II-14e** is likely determined during C–N bond-forming alkene aminopalladation of an

intermediate palladium(aryl)(amido) complex.[63] Our prior studies have indicated that alkene aminopalladations proceed via organized transition states in which the alkene is eclipsed with the Pd–N bond. This suggests reactions of substrates **II-14a** and **II-14e**, which afford *cis*-2,3-disubstituted products, most likely occur via boat-like transition state **II-27** (Scheme II.3).[64] Pathways leading to the *trans*-disubstituted products appear to be high in energy. Chair-like transition state **II-28** suffers from unfavorable steric interactions between the *N*-aryl group and the C5 methylene unit, and boat-like transition state **II-29** is presumably disfavored due to the axial orientation of the C3 methyl group.

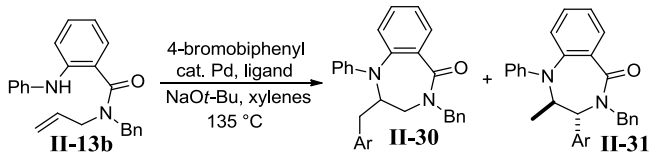
Scheme II.3 Origin of Observed Diastereoselectivity



In order to further explore the scope of benzodiazepine-forming reactions, we examined the use of amides **II-13** as substrates for the carboamination reactions. As shown in Scheme II.4, the conditions that were optimized for transformations of diamine substrates provided good yields of **II-30** in the coupling of **II-13b** with 4-bromobiphenyl, although small amounts of regioisomer **II-31** were also obtained.[65] After some additional optimization we found that use of P(4-F-C_6H_4)$_3$ as ligand provided slightly improved selectivities. The regioisomer was separable by chromatography, and **II-30** was obtained in 79% isolated yield. These modified conditions proved to be useful for the coupling of

amides **II-13b**, **II-13d**, and **II-13f** with a number of different aryl bromides (Table II.3). However, efforts to employ an amide substrate bearing an allylic methyl group were unsuccessful; complex mixtures of regioisomers were obtained.

Scheme II.4 Subtle Differences in Regioselectivity



Ar = *p*-Ph-C_6H_4

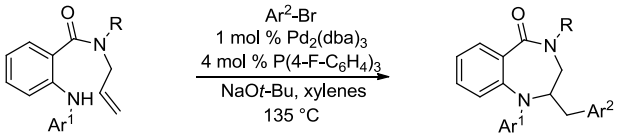
ligand = PPh_2Cy: 90% NMR Yield, 10:1 regioselectivity

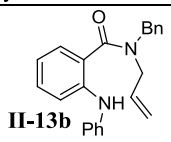
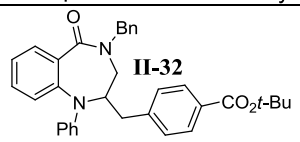
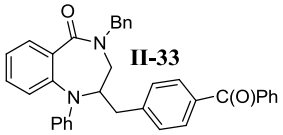
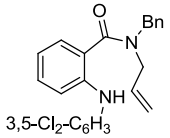
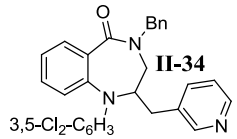
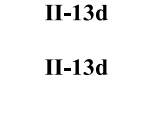
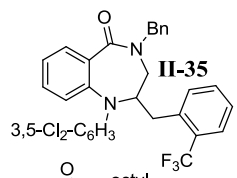
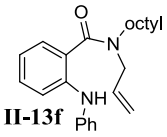
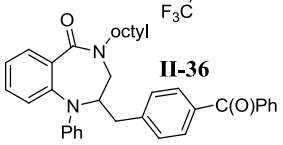
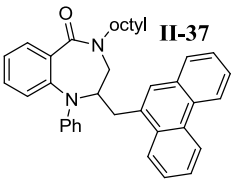
ligand = $P(4\text{-F-}C_6H_4)_3$: 87% NMR Yield, **13:1 regioselectivity**

79% Isolated Yield **II-30**

In conclusion we have developed an efficient entry into saturated 1,4-benzodiazepines and 1,4-benzodiazepin-5-ones via Pd-catalyzed alkene carboamination reactions. The method is effective for a variety of different aryl bromide coupling partners, and *cis*-2,3-disubstituted 1,4-benzodiazepines are formed with >20:1 dr. These transformations are rare examples of 7-membered ring-forming alkene difunctionalization reactions. Further studies toward enantioselective synthesis of 1,4-benzodiazepines and application of this strategy to biologically active targets are currently in progress.

Table II.3 Synthesis of 1,4-Benzodiazepin-5-one Products



entry	substrate	product	yield (%)[a]
1			67
2			62
3			74
4			48
5			70
6			77

Conditions: Reactions were conducted on a 0.15 mmol scale using 1.0 equiv substrate, 2.0 equiv ArBr, 2.0 equiv NaO*t*-Bu, 1 mol % $Pd_2(dba)_3$, 4 mol % $P(4\text{-F-}C_6H_4)_3$, xylenes (0.2 M), 135 °C, 18–24 h reaction time. [a] Isolated yield (average of two experiments).

Experimental

All reactions were carried out under a dry nitrogen atmosphere in flame-dried glassware using standard Schlenk techniques. All reagents were obtained from commercial sources and used without further purification. Toluene, THF, diethyl ether, and dichloromethane were purified using a GlassContour solvent purification system.

Xylenes and diisopropylethylamine were distilled over CaH_2 before use. Methyl 2-(phenylamino)benzoate,[66] methyl 2-(3,5-dichlorophenylamino)benzoate,[66] methyl 2-(4-methoxyphenylamino)benzoate,[67] *N*-benzylbut-3-enyl-2-amine,[68] *N*-allyloctan-1-amine,[69] *N*-benzylprop-2-en-1-amine,[69] and *tert*-butyl 4-bromobenzoate[70] were prepared according to literature procedures. (*E*)-but-2-enyl acetate was prepared by treatment of crotyl alcohol with acetic anhydride, triethylamine and DMAP at rt in dichloromethane. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted. The product yields reported in the experimental section are the result of a single experiment whereas the yields in Chapter II are an average of two experiments.

General Procedure 1: Saponifcation of Benzoate Substrates. A flask equipped with a magnetic stirbar was charged with the benzoate substrate (1.0 equiv) and a 1:1 mixture of water:EtOH (7.5 mL/mmol substrate). Finely ground KOH (2.5 equiv) was added, and the resulting mixture was heated to reflux for 3 h. The mixture was then cooled to rt and concentrated to remove all of the EtOH. Additional water (15 mL) was added, the mixture was acidified to pH ~ 2 with HCl (1 M), and a precipitate formed. The precipitate was collected by filtration and the crude product was purified by flash column chromatography on silica gel to furnish the pure carboxylic acid product.

General Procedure 2: Peptide Coupling of Acid Substrates with Allylic Amines. A flame-dried flask equipped with a magnetic stirbar was charged with the appropriate carboxylic acid substrate (1.0 equiv) and *N*-hydroxybenzotriazole, (1.2 equiv). The flask

was purged with nitrogen for 5 min, then the appropriate allylic amine substrate (1.0 equiv), diisopropylethylamine (3.0 equiv), and dichloromethane (3 mL/mmol substrate) were added. The resulting clear solution was stirred for ca. 2 min, then diisopropylcarbodiimide (1.05 equiv) was added. The reaction mixture was stirred for 12–24 h and then concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel to afford the pure benzamide product.

General Procedure 3: Reduction of Amides to Amine Substrates. A flame-dried flask equipped with a magnetic stirbar was charged with the appropriate benzamide substrate (1.0 equiv) and purged with nitrogen for 5 min. THF (1 mL/mmol substrate) was added, the resulting solution was cooled to 0 °C, and a 1 M solution of $LiAlH_4$ in diethyl ether (1.0 equiv) was added slowly over 5 min. The reaction mixture was stirred at 0 °C for 15 min then warmed to rt and stirred until TLC analysis indicated complete consumption of starting material. The reaction mixture was cooled to 0 °C, then water (0.05 mL/mmol substrate), 6 M NaOH (0.05 mL/mmol substrate) and additional water (0.15 mL/mmol substrate) were sequentially added. The resulting white suspension was stirred vigorously for 30 min, then filtered and the white precipitate was washed with diethyl ether (3 × 30 mL). The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting product was purified by flash column chromatography on silica gel.

***N*-Allyl-*N*-benzyl-2-(phenylamino)benzamide (II-13b).** 2-(Phenylamino)benzoic acid (1.02 g, 4.8 mmol) was coupled with *N*-benzylprop-2-en-1-amine (680 mg, 4.6 mmol) for

24 h using General Procedure 2. Flash chromatography on silica gel (90:10 hexanes:ethyl acetate) afforded 1.40 g (89%) of the title compound as a white solid, m.p. 73–75 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.33 (d, *J* = 8.0 Hz, 1 H), 7.29–7.18 (m, 8 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 6.97–6.89 (m, 2 H), 6.83 (t, *J* = 8.0 Hz, 1 H), 5.81–5.69 (m, 1 H), 5.20–5.08 (m, 2 H), 4.67 (s, 2 H), 4.04–3.90 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, 60°C) δ 171.4, 142.6, 142.2, 136.9, 133.0, 130.2, 129.3, 128.7, 127.7, 127.49, 127.47, 124.7, 121.5, 119.8, 118.9, 117.9, 117.7, 49.4, one aliphatic carbon signal is incidentally equivalent; IR (film) 3332, 1627 cm^{-1}. MS (ESI) 343.1801 (343.1805 calcd for $C_{23}H_{22}N_2O$, $[M + H]^+$).

***N*-Allyl-*N*-benzyl-2-(3,5-dichlorophenylamino)benzamide (II-13d).** Methyl 2-(3,5-dichlorophenylamino)benzoate (2.50 g, 8.4 mmol) was saponified according to General Procedure 1. Purification via flash chromatography on silica gel using 50:50 hexanes:ethyl acetate → 100% ethyl acetate as the eluent to afforded 1.81 g (76%) of 2-(3,5-dichlorophenylamino)benzoic acid as a fluffy white solid, m.p. 245–246 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.1 (s, br, 1 H), 9.54 (s, br, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.52–7.44 (m, 1 H), 7.35 (d, *J* = 8.4 Hz, 1 H), 7.22 (d, *J* = 2.0 Hz, 2 H), 7.11 (s, 1 H), 6.95 (t, *J* = 7.2 Hz, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.3, 144.3, 144.2, 134.7, 134.1, 131.9, 120.7, 120.0, 117.3, 116.6, 115.9.

The above 2-(3,5-dichlorophenylamino)benzoic acid (998 mg, 3.5 mmol) was coupled with *N*-benzylprop-2-en-1-amine (556 mg, 3.8 mmol) for 15 h using General Procedure 2. Flash chromatography on silica gel (85:15 hexanes:ethyl acetate) afforded 1.24 g (85%) of the title compound as a white solid, m.p. 131–132 °C. ^{1}H NMR (400

MHz, $CDCl_3$, 62 °C) δ 7.38–7.21 (m, 7 H), 7.17 (s, br, 1 H), 7.07–7.00 (m, 1 H), 6.97 (dt, *J* = 0.8, 7.6 Hz, 1 H), 6.88–6.83 (m, 3 H), 5.81–5.66 (m, 1 H), 5.22–5.07 (m, 2 H), 4.65 (s, 2 H), 4.04–3.83 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, 62 °C) δ 170.8, 145.2, 139.9, 136.7, 135.7, 130.6, 128.9, 128.6, 127.7, 127.5, 121.9, 121.8, 120.5, 120.4, 118.1, 115.3, 115.2, 49.1, two aliphatic carbon signals are incidentally equivalent; IR (film) 3298, 1621 cm^{-1}. MS (ESI) 433.0850 (433.0845 calcd for $C_{23}H_{20}Cl_2N_2O$, $[M + Na]^+$).

***N*-Allyl-*N*-octyl-2-(phenylamino)benzamide (II-13f).** Methyl 2-(phenylamino)benzoate (2.76 g, 12.1 mmol) was saponified according to General Procedure 1. Purification via flash chromatography on silica gel using 70:30 hexanes:ethyl acetate as the eluent to afforded 1.96 g (76%) of 2-(phenylamino)benzoic acid as a white solid, m.p. 185–187 °C. ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 10.8 (s, br, 1 H), 9.32 (s, br, 1 H), 8.04 (dd, *J* = 0.8, 6.4 Hz, 1 H), 7.40–7.32 (m, 3 H), 7.30–7.20 (m, 3 H), 7.13 (t, *J* = 5.6 Hz, 1 H), 6.76 (t, *J* = 6.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 173.7, 148.9, 140.3, 135.2, 132.6, 129.4, 124.1, 123.2, 117.2, 114.0, 110.4; IR (film) 3339, 1658 cm^{-1}.

The above 2-(phenylamino)benzoic acid (1.0 g, 4.7 mmol) was coupled with *N*-allyloctan-1-amine (790 mg, 4.7 mmol) for 24 h using General Procedure 2. Flash chromatography on silica gel (90:10 hexanes:ethyl acetate) afforded 1.55 g (91%) of the title compound as a viscous, colorless oil. ^1H NMR (400 MHz, $CDCl_3$, 60°C) δ 7.33 (d, *J* = 8 Hz, 1 H), 7.29–7.15 (m, 4 H), 7.05 (d, *J* = 7.6 Hz, 2 H), 6.92 (t, *J* = 7.2 Hz, 1 H), 6.88–6.81 (m, 2 H), 5.87–5.71 (m, 1 H), 5.23–5.12 (m, 2 H), 4.10–3.96 (m, 2 H), 3.46–3.31 (m, 2 H), 1.61–1.48 (m, 2 H), 1.31–1.15 (m, 10 H), 0.86 (t, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 60°C) δ 171.0, 142.6, 141.9, 129.4, 129.2, 127.6, 127.4, 125.1,

121.4, 119.6, 119.0, 118.8, 117.4, 46.8, 31.8, 29.2, 29.1, 27.9, 26.9, 22.6, 13.9, one aliphatic carbon signal is incidentally equivalent; IR (film) 3311, 1622 cm^{-1}. MS (ESI) 365.2589 (365.2587 calcd for $C_{24}H_{32}N_2O$, $[M + H]^+$).

2-{[Allyl(benzyl)amino]methyl}-*N*-phenylaniline (II-14b). *N*-Allyl-*N*-benzyl-2-(phenylamino)benzamide (4.95 g, 14.5 mmol) was reduced according General Procedure 3. Flash chromatography on silica gel (98:2 hexanes:ethyl acetate) afforded 3.19 g (67%) of the title compound as a white solid, m.p. 70–71 °C . ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, br, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.32–7.15 (m, 11 H), 6.89 (t, *J* = 7.2 Hz, 1 H), 6.78 (t, *J* = 7.2 Hz, 1 H), 5.96–5.84 (m, 1 H), 5.18 (dd, *J* = 2.4, 14.4 Hz, 2 H), 3.66 (s, 2 H), 3.54 (s, 2 H), 3.06 (d, *J* = 6.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 143.0, 138.6, 134.4, 131.1, 129.3, 129.2, 128.4, 128.1, 127.1, 125.2, 120.2, 119.2, 118.8, 117.7, 114.9, 57.9, 57.7, 55.8; IR (film) 3255, 1593 cm^{-1}. MS (ESI) 329.2017 (329.2018 calcd for $C_{23}H_{24}N_2$, $[M + H]^+$).

2-{[Allyl(benzyl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (II-14c). Methyl 2-(4-methoxyphenylamino)benzoate (6.12 g, 23.8 mmol) was saponified according to General Procedure 1. Purification via flash chromatography on silica gel using 50:50 hexanes:ethyl acetate → 100% ethyl acetate as the eluent to afforded 5.20 g (89%) of 2-(4-methoxyphenylamino)benzoic acid as a light yellow solid, m.p. 185–186 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.7 (s, br, 1 H), 9.14 (s, br, 1 H), 8.02 (dd, *J* = 1.5, 8.0 Hz, 1 H), 7.33–7.27 (m, 1 H), 7.24–7.16 (m, 2 H), 6.97–6.90 (m, 3 H), 6.69 (dt, *J* = 1, 7.5 Hz, 1 H)

3.83 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 157.0, 150.5, 135.2, 132.9, 132.5, 126.4, 116.3, 114.7, 113.4, 109.4, 55.5; IR (film) 3323, 1664 cm^{-1}.

The above 2-(4-methoxyphenylamino)benzoic acid (2.0 g, 8.2 mmol) was coupled with *N*-benzylprop-2-en-1-amine (1.2 g, 8.2 mmol) for 18 h using General Procedure 2. Flash chromatography on silica gel (80:20 hexanes:ethyl acetate) afforded 2.96 g (97%) of *N*-allyl-*N*-benzyl-2-(4-methoxyphenylamino)benzamide as a viscous, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.40–7.02 (m, 10 H), 6.89–6.83 (m, 2 H), 6.79–6.71 (m, 1 H), 5.84–5.75 (m, 1 H), 5.22–5.11 (m, 2 H), 4.69 (s, 2 H), 3.98 (d, *J* = 4.4 Hz, 2 H), 3.79 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 171.7, 155.8, 144.2, 137.1, 135.4, 133.1, 130.4, 128.8, 127.8, 127.52, 127.51, 123.0, 122.6, 118.4, 117.9, 115.6, 115.0, 55.7, 49.6, 2 aliphatic carbon signals are incidentally equivalent; IR (film) 3351, 1626 cm^{-1}. MS (ESI) 373.1911 (373.1911 calcd for $C_{24}H_{24}N_2O_2$, $[M + H]^+$).

N-Allyl-*N*-benzyl-2-(4-methoxyphenylamino)benzamide (2.96 g, 8.0 mmol) was reduced according General Procedure 3. Flash chromatography on silica gel (95:5 hexanes:ethyl acetate) afforded 1.68 g (59%) of the title compound as an off-white, solid, m.p. 59–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, br, 1 H), 7.29 (d, *J* = 4.4 Hz, 4 H), 7.26–7.19 (m, 1 H), 7.16–7.02 (m, 5 H), 6.89–6.83 (m, 2 H), 6.72 (dt, *J* = 1.6, 6.8 Hz, 1 H), 5.97–5.85 (m, 1 H), 5.22–5.15 (m, 2 H), 3.80 (s, 3 H), 3.66 (s, 2 H), 3.55 (s, 2 H), 3.06 (d, *J* = 6.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 145.1, 138.7, 136.1, 134.5, 131.0, 129.2, 128.3, 128.2, 127.1, 123.8, 121.3, 118.7, 118.1, 114.6, 113.0, 58.0, 57.6, 55.8, 55.6; IR (film) 3240, 1599 cm^{-1}. MS (ESI) 359.2120 (359.2133 calcd for $C_{24}H_{26}N_2O$, $[M + H]^+$).

***N*-{2-[(Allyl<benzyl>amino)methyl]phenyl}-3,5-dichloroaniline (II-14d).** *N*-Allyl-*N*-benzyl-2-(3,5-dichlorophenylamino)benzamide (950 mg, 2.3 mmol) was reduced according General Procedure 3. Flash chromatography on silica gel (98:2 hexanes:ethyl acetate) afforded 712 mg (78%) of the title compound as a viscous, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, br, 1 H), 7.35–7.17 (m, 7 H), 7.15 (dd, *J* = 1.0, 7.5 Hz, 1 H), 6.89 (dt, *J* = 1.0, 7.5 Hz, 1 H), 6.86–6.76 (m, 3 H), 5.93–5.82 (m, 1 H), 5.24–5.15 (m, 2 H), 3.61 (s, 2 H), 3.52 (s, 2 H), 3.04 (d, *J* = 7.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 141.6, 138.3, 135.3, 134.2, 131.3, 129.3, 128.5, 128.3, 127.4, 126.7, 121.2, 119.23, 119.17, 117.1, 114.4, 57.9, 57.5, 56.0; IR (film) 3238, 1594 cm^{-1}. MS (ESI) 397.1234 (397.1233 calcd for $C_{23}H_{22}Cl_2N_2$, $[M + H]^+$).

2-{[Benzyl(but-3-en-2-yl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (II-14a). 2-(4-Methoxyphenylamino)benzoic acid (494 mg, 1.8 mmol) was coupled with *N*-benzylbut-3-enyl-2-amine (314 mg, 1.9 mmol) for 22 h using General Procedure 2. Flash chromatography on silica gel (80:20 hexanes:ethyl acetate) afforded 499 mg (66%) of *N*-benzyl-*N*-(but-3-en-2-yl)-2-(4-methoxyphenylamino)benzamide as a viscous, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.37–7.10 (m, 6 H), 7.07–6.97 (m, 3 H), 6.88–6.83 (m, 2 H), 6.76 (dt, *J* = 1.0, 7.5 Hz, 1 H), 6.69–6.63 (m, 1 H), 5.95–5.84 (m, 1 H), 5.19–5.08 (m, 2 H), 4.88–4.80 (m, 1 H), 4.77 (d, *J* = 15.5 Hz, 1 H), 4.44 (d, *J* = 16.0 Hz, 1 H), 3.79 (s, 3 H), 1.24 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 172.1, 155.8, 144.0, 138.6, 135.4, 130.2, 128.4, 127.30, 127.26, 126.9, 123.6, 122.4, 118.6, 116.3, 115.8, 115.0, 114.9, 55.7, 49.7, 18.0, one aliphatic carbon signal is incidentally

equivalent; IR (film) 3354, 1626 cm^{-1}. MS (ESI) 387.2067 (387.2067 calcd for $C_{25}H_{26}N_2O_2$, $[M + H]^+$).

The above *N*-benzyl-*N*-(but-3-en-2-yl)-2-(4-methoxyphenylamino)benzamide (1.49 g, 2.0 mmol) was reduced according General Procedure 3. Flash chromatography on silica gel (95:5 hexanes:ethyl acetate) afforded 701 mg (49%) of the title compound as a viscous, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, br, 1 H), 7.35–7.05 (m, 8 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 6.69 (dt, *J* = 2.0, 7.2 Hz, 1 H), 6.03–5.91 (m, 1 H), 5.23 (d, *J* = 10.4 Hz, 1 H), 5.11 (d, *J* = 17.2 Hz, 1 H), 3.80 (s, 3 H), 3.74 (d, *J* = 12.8 Hz, 1 H), 3.65–3.55 (m, 2 H), 3.53–3.46 (m, 1 H), 3.38 (quint, *J* = 6.4 Hz, 1 H), 1.22 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 145.2, 139.6, 138.4, 136.0, 131.1, 129.1, 128.3, 128.1, 127.0, 123.7, 121.3, 118.0, 116.9, 114.5, 112.9, 55.6, 55.1, 53.61, 53.57, 14.5; IR (film) 3240, 1599 cm^{-1}. MS (ESI) 373.2276 (373.2274 calcd for $C_{25}H_{28}N_2O$, $[M + H]^+$).

2-{[Benzyl(but-3-en-2-yl)amino]methyl}-*N*-phenylaniline (II-14e).

2-(Phenylamino)benzoic acid (995 mg, 4.7 mmol) was coupled with *N*-benzylbut-3-enyl-2-amine (748 mg, 4.6 mmol) for 22 h using General Procedure 2. Flash chromatography on silica gel (80:20 hexanes:ethyl acetate) afforded 1.52 g (92%) of *N*-benzyl-*N*-(but-3-en-2-yl)-2-(phenylamino)benzamide as a viscous, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.31 (d, *J* = 8.0 Hz, 1 H), 7.28–7.13 (m, 8 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 6.93 (t, *J* = 7.6 Hz, 1 H), 6.88–6.79 (m, 2 H), 5.91–5.78 (m, 1 H), 5.15–5.04 (m, 2 H), 4.85–4.72 (m, 2 H), 4.41 (d, *J* = 15.6 Hz, 1 H), 1.20 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 171.7, 142.6, 141.8, 138.8, 138.4, 130.0, 129.3, 128.4, 127.2,

126.9, 126.6, 125.6, 121.4, 120.0, 118.8, 117.8, 116.3, 55.6, 46.7, 17.9; IR (film) 3377, 1624 cm^{-1}. MS (ESI) 357.1962 (357.1961 calcd for $C_{24}H_{24}N_2O$, $[M + H]^+$).

The above *N*-benzyl-*N*-(but-3-en-2-yl)-2-(phenylamino)benzamide (5.34 g, 15 mmol) was reduced according General Procedure 3. Flash chromatography on silica gel (98:2 hexanes:ethyl acetate) afforded 3.17 g (62%) of the title compound as a viscous, light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, br, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.33–7.01 (m, 9 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 6.88 (dt, *J* = 0.8, 7.6 Hz, 1 H), 6.77 (t, *J* = 7.2 Hz, 1 H), 6.03–5.91 (m, 1 H), 5.22 (d, *J* = 10.4 Hz, 1 H), 5.11 (d, *J* = 17.2 Hz, 1 H), 3.76 (d, *J* = 13.2 Hz, 1 H), 3.65–3.54 (m, 2 H), 3.49 (d, *J* = 13.2 Hz, 1 H), 3.37 (quint, *J* = 6.8 Hz, 1 H), 1.22 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 142.9, 139.5, 138.3, 131.2, 129.2, 129.1, 128.4, 128.0, 127.0, 125.0, 120.2, 119.2, 117.8, 117.0, 114.6, 55.2, 53.7, 53.5, 14.5; IR (film) 3253, 1593 cm^{-1}. MS (ESI) 343.2171 (343.2169 calcd for $C_{24}H_{26}N_2$, $[M + H]^+$).

General Procedure 4: Pd-Catalyzed Synthesis of 1,4-Benzodiazepines. A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $PdCl_2(MeCN)_2$ (2 mol %), PPh_2Cy (4 mol %), NaO*t*-Bu (2.0 equiv), and ArBr (2.0 equiv). The tube was purged with nitrogen and a solution of the amine substrate (1.0 equiv) in xylenes (5 mL/mmol amine) was added. The mixture was heated to 135 °C with stirring until the starting material had been consumed as judged by TLC analysis (18–24 h; the reaction times were not minimized). The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (2 mL) and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 5

mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

4-Benzyl-1-phenyl-2-(3,4,5-trimethoxybenzyl)methyl]-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (II-17). General Procedure 4 was used for the coupling of 2-{[allyl(benzyl)amino]methyl}-*N*-phenylaniline (50 mg, 0.15 mmol) with 5-bromo-1,2,3-trimethoxybenzene (75 mg, 0.30 mmol) to afford 60 mg (79%) of the title compound as a foamy, white solid with a wide m.p. range 51–64 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.36 (m, 2 H), 7.33 (t, *J* = 8.0 Hz, 2 H), 7.29–7.21 (m, 2 H), 7.18–7.12 (m, 4 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.77–6.71 (m, 3 H), 6.40 (s, 2 H), 4.49 (m, 1 H), 3.81 (s, 3 H), 3.73 (s, 6 H), 3.72–3.63 (m, 2 H), 3.60 (d, *J* = 14.0 Hz, 1 H), 3.41 (d, *J* = 13.0 Hz, 1 H), 2.81–2.67 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 148.5, 143.7, 139.3, 137.1, 136.3, 135.5, 130.4, 129.7, 129.1, 128.4, 128.3, 127.8, 127.0, 125.6, 118.2, 115.4, 106.1, 62.6, 60.8, 58.9, 57.9, 57.7, 56.0, 39.0; IR (film) 1591 cm^{-1}. MS (ESI) 495.2637 (495.2648 calcd for $C_{32}H_{34}N_2O_3$, $[M + H]^+$).

4-Benzyl-2-(biphenyl-4-ylmethyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (II-18). General Procedure 4 was used for the coupling of 2-{[allyl(benzyl)amino]methyl}-*N*-phenylaniline (51 mg, 0.15 mmol) with 4-bromobiphenyl (71 mg, 0.30 mmol) to afford 65 mg (88%) of the title compound as a foamy, white solid with a wide m.p. range 50–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.53 (m, 2 H), 7.47–7.13 (m, 17 H), 7.06 (d, *J* = 7.6 Hz, 1 H), 6.79–6.72 (m, 3 H),

4.55–4.47 (m, 1 H), 3.67–3.59 (m, 3 H), 3.44 (d, *J* = 12.8 Hz, 1 H), 2.90–2.71 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 143.8, 141.0, 139.3, 139.0, 138.9, 137.0, 130.4, 129.6, 129.5, 129.2, 128.9, 128.7, 128.3, 128.0, 127.04, 127.03, 126.9, 125.6, 118.2, 115.5, 62.7, 59.0, 58.0, 56.8, 37.3, one aromatic carbon signal is incidentally equivalent; IR (film) 1593 cm^{-1}. MS (ESI) 481.2645 (481.2638 calcd for $C_{35}H_{32}N_2$, $[M + H]^+$).

4-Benzyl-2-(2-ethylbenzyl)-1-(4-methoxyphenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (II-19). General Procedure 4 was used for the coupling of 2-{[allyl(benzyl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (49 mg, 0.14 mmol) with 1-bromo-2-ethylbenzene (39 μL, 0.28 mmol) to afford 60 mg (94%) of the title compound as a viscous, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2 H), 7.34 (t, *J* = 7.5 Hz, 2 H), 7.31–7.26 (m, 1 H), 7.20–7.01 (m, 7 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 6.77–6.73 (m, 2 H), 6.72–6.67 (m, 2 H), 4.36–4.30 (m, 1 H), 3.75 (s, 3 H), 3.68 (d, *J* = 14.0 Hz, 2 H), 3.59 (d, *J* = 13.5 Hz, 1 H), 3.40 (d, *J* = 13.0 Hz, 1 H), 2.83 (d, *J* = 7.0 H, 2 H), 2.77–2.55 (m, 4 H), 1.15 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 145.4, 143.0, 142.3, 139.3, 137.6, 136.0, 130.2, 130.1, 128.8, 128.30, 128.27, 127.8, 127.0, 126.3, 125.7, 124.3, 118.8, 114.6, 62.7, 59.2, 59.1, 57.6, 55.6, 34.5, 25.4, 15.3, one aromatic carbon signal is incidentally equivalent; IR (film) 1507 cm^{-1}. MS (ESI) 463.2735 (463.2749 calcd for $C_{32}H_{34}N_2O$, $[M + H]^+$).

4-Benzyl-1-(3,5-dichlorophenyl)-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (II-20). General Procedure 4 was used for the coupling of *N*-{2-[(allyl<benzyl>amino)methyl]phenyl}-3,5-dichloroaniline (53 mg, 0.13 mmol) with

1-bromo-4-(trifluoromethyl)benzene (38 μL, 0.27 mmol) to afford 53 mg (74%) of the title compound as a viscous, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2 H), 7.38–7.24 (m, 7 H), 7.21 (d, *J* = 6.5 Hz, 1 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 6.97 (d, *J* = 7.0 Hz, 1 H), 6.69 (t, *J* = 2.0 Hz, 1 H), 6.48 (d, *J* = 1.0 Hz, 2 H), 4.45–4.35 (m, 1 H), 3.67 (d, *J* = 13.0 Hz, 1 H), 3.60 (d, *J* = 13.0 Hz, 2 H), 3.38 (d, *J* = 13 Hz, 1 H), 2.85–2.65 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 143.1, 141.2, 138.8, 135.6, 130.8, 130.0, 129.4, 128.9, 128.5, 128.43, 128.40, 127.4, 127.3, 125.33, 125.29, 124.2 (q, *J* = 272 Hz), 117.5, 112.2, 62.9, 59.2, 57.2, 37.6, 29.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.4 (m); IR (film) 1580 cm^{-1}. MS (ESI) 541.1432 (541.1425 calcd for $C_{30}H_{25}Cl_2F_3N_2$, $[M + H]^+$).

4-Benzyl-1-(3,5-dichlorophenyl)-2-[3-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (II-21). General Procedure 4 was used for the coupling of *N*-{2-[(allyl<benzyl>amino)methyl]phenyl}-3,5-dichloroaniline (53 mg, 0.13 mmol) with 1-bromo-3-(trifluoromethyl)benzene (38 μL, 0.27 mmol) to afford 56 mg (78%) of the title compound as a viscous, colorless film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.2 Hz, 1 H), 7.38–7.22 (m, 10 H), 7.19 (d, *J* = 6.8 Hz, 1 H), 6.92 (d, *J* = 6.8 Hz, 1 H), 6.63 (t, *J* = 1.6 Hz, 1 H), 6.47 (d, *J* = 1.2 Hz, 2 H), 4.41 (m, 1 H), 3.64 (s, 2 H), 3.60 (d, *J* = 13.2 Hz, 1 H), 3.36 (d, *J* = 13.2 Hz, 1 H), 2.85–2.67 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 141.2, 139.8, 138.7, 137.5, 135.6, 132.3, 130.8, 130.5, 130.1, 128.8, 128.4, 127.33, 127.26, 126.20, 126.16, 124.1 (q, *J* = 272 Hz), 123.3, 123.2, 117.5, 112.3, 62.9, 58.9, 57.4, 37.5, 29.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.6 (m); IR (film) 1580 cm^{-1}. MS (ESI) 541.1429 (541.1425 calcd for $C_{30}H_{25}Cl_2F_3N_2$, $[M + H]^+$).

(±)-(2*R*,3*S*)-4-Benzyl-2-(biphenyl-4-methyl)-1-(4-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (II-15). General Procedure 4 was used for the coupling of 2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (52 mg, 0.14 mmol) with 4-bromobiphenyl (64 mg, 0.28 mmol) to afford 48 mg (65%) of the title compound as a viscous, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.5 Hz, 2 H), 7.52 (d, *J* = 7.5 Hz, 2 H), 7.48–7.18 (m, 11 H), 7.12–7.04 (m, 2 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 6.63 (d, *J* = 9.0 Hz, 2 H), 6.47 (d, *J* = 9.0 Hz, 2 H), 4.41 (td, *J* = 2.3, 11.0 Hz, 1 H), 3.85–3.65 (m, 7 H), 3.48 (dq, *J* = 2.0, 6.8 Hz, 1 H), 2.97 (d, *J* = 13.5 Hz, 1 H), 2.50 (dd, *J* = 10.5, 14.0 Hz, 1 H), 1.42 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 145.0, 143.4, 141.0, 140.8, 140.0, 138.8, 137.0, 130.8, 129.7, 129.5, 128.7, 128.5, 128.3, 127.9, 127.0, 126.98, 126.95, 126.8, 124.3, 119.0, 114.4, 67.5, 61.2, 57.1, 55.6, 52.4, 33.8, 19.2; IR (film) 1504 cm^{-1}. MS (ESI) 525.2909 (525.2900 calcd for $C_{37}H_{36}N_2O$, $[M + H]^+$).

(±)-3-{benzyl[2-(phenylamino)benzyl]amino}butan-2-one (II-16). General Procedure 4 was used for the coupling of 2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-phenylaniline (49 mg, 0.14 mmol) with 1-bromo-3,5-dichlorobenzene (66 mg, 0.29 mmol) to afford 8.7 mg (12%) of the title compound as a viscous, colorless film. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, br, 1 H), 7.37–7.31 (m, 3 H), 7.30–7.11 (m, 7 H), 7.09–7.04 (m, 2 H), 6.90 (tt, *J* = 1.0, 7.5 Hz, 1 H), 6.77 (td, *J* = 7.5, 1.5 Hz, 1 H), 3.89 (d, *J* = 13.0 Hz, 1 H), 3.72 (d, *J* = 13.0 Hz, 1 H), 3.53 (d, *J* = 13.0 Hz, 1 H), 3.44 (q, *J* = 7.0 Hz, 1 H), 3.42 (d, *J* = 13.5 Hz, 1 H), 2.15 (s, 3 H), 1.28 (d, *J* = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 143.3, 142.6, 138.7, 131.5, 129.13, 129.11, 128.6, 128.5, 127.5, 124.3, 120.7, 119.2, 118.3,

115.0, 62.8, 54.6, 53.9, 27.9, 8.1; IR (film) 1714, 1593 cm^{-1}. MS (ESI) 359.2117 (359.2118 calcd for $C_{24}H_{26}N_2O$, $[M + H]^+$).

(±)-(2*R*,3*S*)-4-Benzyl-2-[(6-methoxynaphthalen-2-yl)methyl]-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (II-22). General Procedure 4 was used for the coupling of 2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-phenylaniline (50 mg, 0.15 mmol) with 2-bromo-6-methoxynaphthalene (70 mg, 0.28 mmol) to afford 59 mg (81%) of the title compound as a foamy, light yellow solid with a wide m.p. range 51–69 °C. This material contained ca. 8% of ketone **II-16**, which could not be separated by chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 1 H), 7.61 (d, *J* = 9.6 Hz, 1 H), 7.43–7.15 (m, 9 H), 7.12–7.07 (m, 3 H), 7.06–7.00 (m, 2 H), 6.86 (dd, *J* = 2.0, 7.2 Hz, 1 H), 6.63 (t, *J* = 7.2 Hz, 1 H), 6.54 (d, *J* = 8.0 Hz, 2 H), 4.68 (dt, *J* = 2.0, 10.8 Hz, 1 H), 3.90 (s, 3 H), 3.80 (d, *J* = 14.0 Hz, 1 H), 3.73–3.63 (m, 3 H), 3.58 (dd, *J* = 2.4, 6.8 Hz, 1 H), 3.07 (dd, *J* = 2.0, 15.2 Hz, 1 H), 2.54 (dd, *J* = 10.8, 15.2 Hz, 1 H), 1.46 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 148.8, 143.4, 140.8, 138.4, 135.2, 133.1, 131.1, 130.9, 129.0, 128.9, 128.4, 128.3, 127.8, 127.7, 127.3, 126.8, 126.7, 125.6, 118.6, 117.7, 115.3, 110.0, 105.6, 64.6, 60.8, 56.8, 55.3, 52.1, 33.6, 19.1; IR (film) 1605, 1592 cm^{-1}. MS (ESI) 499.2741 (499.2749 calcd for $C_{35}H_{34}N_2O$, $[M + H]^+$).

(±)-4-[(2*R*,3*S*)-4-Benzyl-1-(4-methoxyphenyl)-3-methyl(-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-2-yl)methyl]-*N*,*N*-dimethylaniline (II-23). General Procedure 4 was used for the coupling of 2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (52 mg, 0.14 mmol) with 4-bromo-*N*,*N*-dimethylaniline (56 mg,

0.28 mmol) to afford 55 mg (81%) of the title compound as a viscous, colorless film. This material contained ca. 8% of ketone **II-16**, which could not be separated by chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.16 (m, 6 H), 7.11–6.99 (m, 4 H), 6.90 (d, *J* = 7.6 Hz, 1 H), 6.69 (d, *J* = 8.4 Hz, 2 H), 6.63 (d, *J* = 9.2 Hz, 2 H), 6.47 (d, *J* = 9.2 Hz, 2 H), 4.32 (td, *J* = 2.0, 10.4 Hz, 1 H), 3.81–3.67 (m, 6 H), 3.64 (d, *J* = 14.0 Hz, 1 H), 3.51–3.41 (m, 1 H), 2.91 (s, 6 H), 2.83 (dd, *J* = 2.0, 14.8 Hz, 1 H), 2.33 (dd, *J* = 10.8, 14.8 Hz, 1 H), 1.38 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 149.1, 145.3, 143.6, 140.9, 136.9, 130.8, 129.7, 129.6, 128.8, 128.5, 128.2, 127.8, 126.7, 124.0, 119.1, 114.4, 113.0, 67.7, 61.2, 57.0, 55.6, 52.1, 40.9, 33.1, 19.1; IR (film) 1506 cm^{-1}. MS (ESI) 492.3014 (492.3009 calcd for $C_{33}H_{37}N_3O$, $[M + H]^+$).

(±)-(2*R*,3*S*)-4-benzyl-2-(3,5-dichlorobenzyl)-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (II-24). General Procedure 4 was used for the coupling of 2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-phenylaniline (49 mg, 0.14 mmol) with 1-bromo-3,5-dichlorobenzene (66 mg, 0.29 mmol) to afford 44 mg (63%) of the title compound as a viscous, colorless film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 4 H), 7.32–7.22 (m, 2 H), 7.21–7.03 (m, 5 H), 7.01–6.97 (m, 2 H), 6.85 (dd, *J* = 1.2, 7.6 Hz, 1 H), 6.70 (t, *J* = 7.2 Hz, 1 H), 6.55 (d, *J* = 8.0 Hz, 2 H), 4.52 (td, *J* = 2.4, 11.6 Hz, 1 H), 3.69 (s, 2 H), 3.63–3.57 (m, 2 H), 3.50 (dq, *J* = 2.4, 6.8 Hz, 1 H), 2.90 (dd, *J* = 2.4, 15.2 Hz, 1 H), 2.41 (dd, *J* = 11.2, 15.2 Hz, 1 H), 1.41 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 143.7, 142.9, 140.5, 138.3, 134.5, 131.0, 130.8, 129.2, 128.33, 128.30, 127.5, 126.9, 126.3, 125.9, 118.2, 115.4, 64.5, 60.6, 57.0, 52.7, 33.2, 19.1; IR (film) 1592 cm^{-1}. MS (ESI) 487.1698 (487.1708 calcd for $C_{30}H_{28}Cl_2N_2$, $[M + H]^+$).

(±)-(2*R*,3*S*)-4-Benzyl-2-(2,6-dimethylbenzyl)-1-(4-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (II-25). General Procedure 4 was used for the coupling of 2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (52 mg, 0.14 mmol) with 2-bromo-*meta*-xylene (37 μL, 0.28 mmol) to afford 58 mg (87%) of the title compound as a viscous, colorless film. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.32 (m, 4 H), 7.29–7.25 (m, 1 H), 7.08–7.03 (m, 1 H), 7.02–6.89 (m, 5 H), 6.69–6.65 (m, 2 H), 6.63–6.56 (m, 3 H), 4.48–4.42 (m, 1 H), 3.99 (d, *J* = 14.5 Hz, 1 H), 3.88 (d, *J* = 14.0 Hz, 1 H), 3.72 (s, 3 H), 3.57 (d, *J* = 14.0 Hz, 1 H), 3.53 (d, *J* = 14.5 Hz, 1 H), 3.24 (dq, *J* = 2.5, 7.0 Hz, 1 H), 3.02 (dq, *J* = 8.0, 14.5 Hz, 2 H), 2.16 (s, 6 H), 1.23 (d, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 146.7, 146.0, 142.9, 140.7, 137.2, 137.1, 132.8, 130.6, 128.6, 128.3, 127.8, 126.7, 126.5, 125.8, 122.5, 122.0, 114.4, 65.3, 60.9, 56.1, 55.5, 55.3, 29.9, 20.7, 19.2; IR (film) 1506 cm^{-1}. MS (ESI) 477.2905 (477.2900 calcd for $C_{33}H_{36}N_2O$, $[M + H]^+$).

(±)-(2*R*,3*S*)-4-Benzyl-1-(4-methoxyphenyl)-3-methyl-2-(2,4,6-triisopropylbenzyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (II-26). General Procedure 4 was used for the coupling of 2-{[benzyl(but-3-en-2-yl)amino]methyl}-*N*-(4-methoxyphenyl)aniline (52 mg, 0.14 mmol) with 2-bromo-1,3,5-triisopropylbenzene (71 μL, 0.28 mmol) to afford 51 mg (64%) of the title compound as a viscous, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5 H), 7.12 (td, *J* = 1.5, 8.0 Hz, 1 H), 7.05–7.01 (dd, *J* = 1.5, 7.5 Hz, 1 H), 6.95 (td, *J* = 1.0, 7.0 Hz, 1 H), 6.90 (s, 2 H), 6.78 (d, *J* = 7.5 Hz, 1 H), 6.73–6.68 (m, 2 H), 6.67–6.61 (m, 2 H), 4.16 (t, *J* = 5.0 Hz, 1 H), 4.03 (d, *J* = 14.0 Hz, 1 H),

3.78–3.70 (m, 4 H), 3.54 (dd, *J* = 10.5, 14.0 Hz, 2 H), 3.22–3.10 (m, 4 H), 2.90 (dd, *J* = 5.5, 15.0 Hz, 1 H), 2.89–2.81 (m, 1 H), 1.24 (d, *J* = 7.0 Hz, 6 H), 1.13 (d, *J* = 7.0 Hz, 3 H), 1.11 (d, *J* = 6.5 Hz, 6 H), 1.03 (d, *J* = 7.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 147.4, 147.2, 146.5, 142.9, 140.5, 132.7, 132.2, 130.6, 128.6, 128.2, 127.8, 126.7, 126.1, 122.6, 122.4, 120.8, 114.4, 67.5, 60.1, 56.0, 55.9, 55.5, 34.1, 29.2, 29.0, 24.6, 24.1, 23.8, 18.8; IR (film) 1507 cm^{-1}. MS (ESI) 575.4002 (575.3996 calcd for $C_{40}H_{50}N_2O$, $[M + H]^+$).

General Procedure 5: Pd-Catalyzed Synthesis of 1,4-Benzodiazepin-5-ones. A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd) or $Pd(dba)_2$ (2 mol %), P(4-F-C_6H_4)$_3$ (4 mol %), NaO*t*-Bu (2.0 equiv), and ArBr (2.0 equiv). The tube was purged with nitrogen and a solution of the amine substrate (1.0 equiv) in xylenes (5 mL/mmol amine) was added. The mixture was heated to 135 °C with stirring until the starting material had been consumed as judged by TLC analysis (18–24 h; the reaction times were not minimized). The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (2 mL) and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

2-([1,1'-Biphenyl]-4-ylmethyl)-4-benzyl-1-phenyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (II-30). General Procedure 5 was used for the

coupling of *N*-allyl-*N*-benzyl-2-(phenylamino)benzamide (40 mg, 0.12 mmol) with 4-bromobiphenyl (52 mg, 0.22 mmol) to afford 44 mg (76%) of the title compound as a white solid with a wide m.p. range 67–85 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.62–7.58 (m, 2 H), 7.55–7.40 (m, 6 H), 7.39–7.34 (m, 1 H), 7.32–7.20 (m, 3 H), 7.19–7.01 (m, 7 H), 6.77 (t, *J* = 7.5 Hz, 1 H), 6.52 (d, *J* = 8 Hz, 2 H), 5.10 (d, *J* = 14.5 Hz, 1 H), 4.15 (d, *J* = 14.5 Hz, 1 H), 3.99–3.89 (m, 1 H), 3.27 (dd, *J* = 11.5, 15.5 Hz, 1 H), 3.22–3.09 (m, 2 H), 2.44 (dd, *J* = 10.0, 14.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 148.3, 140.6, 139.8, 139.6, 137.0, 136.4, 136.2, 132.3, 130.4, 130.3, 129.03, 129.02, 128.8, 128.6, 128.4, 127.5, 127.4, 127.3, 127.1, 127.0, 118.3, 113.7, 62.9, 51.3, 50.1, 36.4; IR (film) 1648 cm^{-1}. MS (ESI) 495.2423 (495.2431 calcd for $C_{35}H_{30}N_2O$, $[M + H]^+$).

***tert*-Butyl-4-[(4-benzyl-5-oxo-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-2-yl)methyl]benzoate (II-32).** General Procedure 5 was used for the coupling of *N*-allyl-*N*-benzyl-2-(phenylamino)benzamide (36 mg, 0.10 mmol) with *tert*-butyl 4-bromobenzoate (40 μL, 0.20 mmol) to afford 39 mg (72%) of the title compound as a foamy white solid with a wide m.p. range 68–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.86 (m, 3 H), 7.52 (dt, *J* = 2.0, 7.6 Hz, 1 H), 7.42 (dt, *J* = 1.2, 7.6 Hz, 1 H), 7.29–7.20 (m, 2 H), 7.17–7.08 (m, 4 H), 7.07–6.98 (m, 4 H), 6.77 (t, *J* = 7.2 Hz, 1 H), 6.47 (d, *J* = 8.0 Hz, 2 H), 5.14 (d, *J* = 14.4 Hz, 1 H), 4.06 (d, *J* = 14.4 Hz, 1 H), 3.94–3.82 (m, 1 H), 3.30–3.10 (m, 2 H), 3.04 (dd, *J* = 5.2, 15.2 Hz, 1 H), 2.44 (dd, *J* = 6.0, 14.0 Hz, 1 H), 1.61 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.5, 148.2, 142.1, 139.6, 136.9, 136.2, 132.3, 130.5, 130.4, 130.3, 129.9, 129.1, 128.7, 128.5, 128.4, 127.5, 127.2, 118.4,

113.6, 81.1, 62.7, 51.3, 50.2, 36.8, 28.2; IR (film) 1711, 1649 cm^{-1}. MS (ESI) 541.2465 (541.2462 calcd for $C_{34}H_{34}N_2O_3$, $[M + Na]^+$).

2-(4-Benzoylbenzyl)-4-benzyl-1-phenyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (II-33). General Procedure 5 was used for the coupling of *N*-allyl-*N*-benzyl-2-(phenylamino)benzamide (34 mg, 0.10 mmol) with 4-bromobenzophenone (52 mg, 0.20 mmol) to afford 33 mg (64%) of the title compound as a viscous, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.81–7.76 (m, 2 H), 7.72 (d, *J* = 8 Hz, 2 H), 7.64–7.59 (m, 1 H), 7.56–7.48 (m, 3 H), 7.47–7.41 (m, 2 H), 7.28–7.21 (m, 1 H), 7.16–7.10 (m, 6 H), 7.04 (d, *J* = 7.5 Hz, 2 H), 6.78 (t, *J* = 7.5 Hz, 1 H), 6.48 (d, *J* = 7.5 Hz, 2 H), 5.15 (d, *J* = 14.5 Hz, 1 H), 4.13 (d, *J* = 14.5 Hz, 1 H), 3.98–3.90 (m, 1 H), 3.27 (dd, *J* = 11.5, 15.5 Hz, 1 H), 3.19 (dd, *J* = 4.5, 14.0 Hz, 1 H), 3.09 (dd, *J* = 5.0, 15.0 Hz, 1 H), 2.50 (dd, *J* = 9.5, 14.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 169.5, 148.2, 142.3, 139.5, 137.5, 136.8, 136.2, 136.1, 132.5, 132.4, 130.6, 130.4, 130.3, 130.0, 129.1, 128.7, 128.6, 128.4, 128.3, 127.6, 127.2, 118.4, 113.6, 62.7, 51.3, 50.2, 36.9; IR (film) 1649, 1603 cm^{-1}. MS (ESI) 523.2377 (523.2380 calcd for $C_{36}H_{30}N_2O_2$, $[M + H]^+$).

(±)-(2*R*,3*R*)-3-(4-benzoylphenyl)-4-benzyl-2-methyl-1-phenyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (II-S1). General Procedure 5 was used for the coupling of *N*-allyl-*N*-benzyl-2-(phenylamino)benzamide (34 mg, 0.10 mmol) with 4-bromobenzophenone (52 mg, 0.20 mmol) to afford 5 mg (9%) of the title compound as an off-white film in ca. 80% purity. The structure and relative stereochemistry of II-**31** was assigned based on analogy to **II-S1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 1.6,

8.0 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 2 H), 7.84–7.79 (m, 2 H), 7.64–7.58 (m, 1 H), 7.54–7.43 (m, 3 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.29–7.21 (m, 1 H), 7.16–7.09 (m, 3 H), 7.00–6.94 (m, 2 H), 6.85 (t, *J* = 7.6 Hz, 2 H), 6.79 (d, *J* = 7.6 Hz, 2 H), 6.63 (d, *J* = 7.2 Hz, 2 H), 5.21 (d, *J* = 15.2 Hz, 1 H), 4.79 (d, *J* = 10.4 Hz, 1 H), 3.40–3.31 (m, 1 H), 2.45 (d, *J* = 14.8 Hz, 1 H), 1.46 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 161.7, 147.8, 146.7, 142.4, 137.5, 136.6, 135.6, 132.9, 132.5, 130.7, 130.0, 129.2, 128.7, 128.4, 128.3, 128.1, 127.8, 127.1, 124.1, 123.4, 123.3, 122.9, 121.3, 79.8, 48.9, 43.8, 18.2; IR (film) 1653, 1603 cm^{-1}. MS (ESI) 523.2371 (523.2380 calcd for $C_{36}H_{30}N_2O_2$, $[M + H]^+$).

4-Benzyl-1-(3,5-dichlorophenyl)-2-(pyridine-3-ylmethyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (II-34). General Procedure 5 was used for the coupling of *N*-allyl-*N*-benzyl-2-(3,5-dichlorophenylamino)benzamide (35 mg, 0.09 mmol) with 3-bromopyridine (17 μL, 0.17 mmol) to afford 32 mg (78%) of the title compound as a white solid, m.p. 153–155 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 1.5, 4.5 Hz, 1 H), 8.30 (d, *J* = 2.0 Hz, 1 H), 7.90 (dd, *J* = 2.0, 8.0 Hz, 1 H), 7.58 (dt, *J* = 1.5, 7.5 Hz, 1 H), 7.51 (dt, *J* = 1.5, 7.5 Hz, 1 H), 7.34–7.27 (m, 2 H), 7.26–7.21 (m, 1 H), 7.20–7.15 (m, 3 H), 7.05–7.01 (m, 2 H), 6.72 (t, *J* = 1.5 Hz, 1 H), 6.10 (s, 2 H), 5.33 (d, *J* = 14.5 Hz, 1 H), 3.93 (d, *J* = 14.5 Hz, 1 H), 3.62–3.54 (m, 1 H), 3.25 (dd, *J* = 11.5, 15.0 Hz, 1 H), 3.09 (dd, *J* = 5.5, 15.5 Hz, 1 H), 2.89 (dd, *J* = 5.0, 14.0 Hz, 1 H), 2.42 (dd, *J* = 9.0, 14.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 150.0, 149.8, 148.6, 137.4, 136.9, 136.0, 135.4, 132.8, 132.2, 130.8, 130.1, 128.9, 128.5, 128.4, 128.0, 123.6, 118.1, 111.4, 62.9, 51.0, 50.1, 34.1; IR (film) 1643 cm^{-1}. MS (ESI) 488.1292 (488.1291 calcd for $C_{28}H_{23}Cl_2N_3O$, $[M + H]^+$).

4-Benzyl-1-(3,5-dichlorophenyl)-2-[2-(trifluoromethyl)benzyl]-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (II-35). General Procedure 5 was used for the coupling of *N*-allyl-*N*-benzyl-2-(3,5-dichlorophenylamino)benzamide (36 mg, 0.09 mmol) with 1-bromo-2-(trifluoromethyl)benzene (23 μL, 0.17 mmol) to afford 25 mg (50%) of the title compound as a white solid, m.p. 235–237 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.69–7.60 (m, 2 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 7.38 (quint, *J* = 7.6 Hz, 2 H), 7.32–7.23 (m, 2 H), 7.19–7.09 (m, 3 H), 7.08–7.02 (m, 2 H), 6.62 (t, *J* = 1.6 Hz, 1 H), 5.81 (d, *J* = 2.0 Hz, 2 H), 5.39 (d, *J* = 14.4 Hz, 1 H), 3.90 (d, *J* = 14.0 Hz, 1 H), 3.83–3.73 (m, 1 H), 3.28 (dd, *J* = 11.6, 15.2 Hz, 1 H), 3.09 (dd, *J* = 4.8, 14.8 Hz, 1 H), 2.85 (dd, *J* = 7.2, 14.4 Hz, 1 H), 2.75–2.64 (m, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –59.0 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 150.5, 137.3, 136.9, 136.5, 135.6, 135.1, 132.9, 132.1, 131.6, 130.9, 130.5, 128.8, 128.6, 128.5, 127.9, 127.2, 126.6, 126.5, 124.3 (q, *J* = 275 Hz), 117.8, 111.4, 63.4, 51.5, 50.3, 33.6; IR (film) 1646 cm^{-1}. MS (ESI) 577.1023 (577.1032 calcd for $C_{30}H_{23}Cl_2F_3N_2O$, $[M + Na]^+$).

2-(4-Benzoylbenzyl)-4-octyl-1-phenyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (II-36). General Procedure 5 was used for the coupling of *N*-allyl-*N*-octyl-2-(phenylamino)benzamide (35 mg, 0.10 mmol) with 4-bromobenzophenone (52 mg, 0.20 mmol) to afford 36 mg (69%) of the title compound as a viscous, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.78 (m, 4 H), 7.61 (dt, *J* = 1.5, 7 Hz, 1 H), 7.55–7.47 (m, 3 H), 7.44–7.38 (m, 3 H), 7.28–7.24 (m, 2 H), 7.19–7.12 (m, 2 H), 6.77 (t, *J* = 7.0 Hz, 1 H), 6.65 (d, *J* = 8.0 Hz, 2 H), 4.54–4.40 (m, 1 H), 3.62–3.53 (m, 1 H), 3.43–3.20 (m, 3 H), 3.15 (dd, *J* = 5.5, 15.5 Hz, 1 H), 2.66 (dd, *J* = 9.0, 13.5 Hz, 1 H), 1.50–1.00 (m, 12 H),

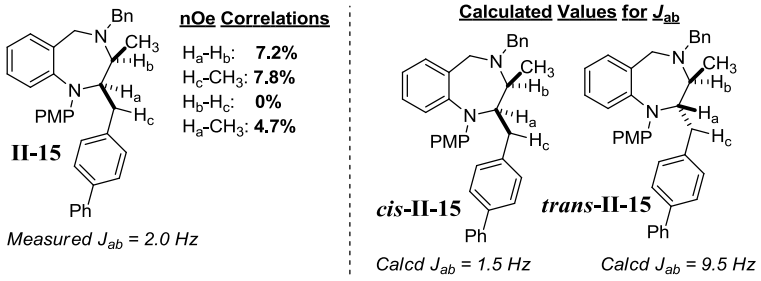
0.83 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 169.3, 148.3, 142.5, 139.5, 137.5, 136.6, 136.3, 132.5, 132.1, 130.8, 130.4, 130.01, 129.98, 129.1, 128.9, 128.3, 127.1, 118.6, 113.7, 63.5, 52.1, 47.1, 37.2, 31.7, 29.4, 29.1, 28.7, 26.6, 22.6, 14.1; IR (film) 1649, 1602 cm^{-1}. MS (ESI) 545.3166 (545.3163 calcd for $C_{37}H_{40}N_2O_2$, [M + H]$^+$).

4-Octyl-2-(phenanthren-9-ylmethyl)-1-phenyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one (II-37). General Procedure 5 was used for the coupling of *N*-allyl-*N*-octyl-2-(phenylamino)benzamide (38 mg, 0.10 mmol) with 9-bromophenanthrene (50 mg, 0.19 mmol) to afford 41 mg (74%) of the title compound as a viscous, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85–8.76 (m, 1 H), 8.69 (d, J = 8.4 Hz, 1 H), 8.22–8.16 (m, 1 H), 7.87–7.80 (m, 3 H), 7.77–7.79 (m, 2 H), 7.69–7.55 (m, 4 H), 7.46 (dt, J = 1.2, 7.6 Hz, 1 H), 7.37 (dd, J = 0.8, 8 Hz, 1 H), 7.15–7.07 (m, 2 H), 6.73 (t, J = 7.6 Hz, 1 H), 6.66 (d, J = 8.4 Hz, 1 H), 4.87–4.77 (m, 1 H), 3.72 (dd, J = 5.2, 14.8 Hz, 1 H), 3.58–3.46 (m, 1 H), 3.40 (dd, J = 11.6, 14.8 Hz, 1 H), 3.20–2.97 (m, 3 H), 1.42–0.95 (m, 12 H), 0.82 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 148.8, 139.6, 137.1, 132.2, 131.8, 131.5, 131.1, 130.9, 130.6, 130.4, 129.9, 129.2, 128.2, 127.8, 127.3, 127.0, 126.9, 126.7, 126.6, 123.9, 123.6, 122.5, 118.3, 113.6, 62.4, 52.6, 47.0, 34.5, 31.7, 29.3, 29.0, 28.6, 26.5, 22.6, 14.1; IR (film) 1646 cm^{-1}. MS (ESI) 541.3217 (541.3213 calcd for $C_{38}H_{40}N_2O$, [M + H]$^+$).

Assignment of Stereochemistry

The stereochemistry of **II-15** was assigned on the basis of nOe correlations as shown below. In addition, the measured value of J_{ab} = 2.0 Hz correlates well with the calculated value of 1.5 Hz for a *cis*-arrangement of these protons. The stereochemistry of other disubstituted products was assigned based on analogy to **II-15**.

Figure II.2 Assignment of Stereochemistry



The *trans*-stereochemistry of **II-S1** was assigned on the basis of the measured value of J_{ab} = 10.4 Hz. The stereochemistry of **II-31** was assigned based on analogy to **II-S1**.

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([64]) The major stereoisomers could also arise from chairlike transition states in which the methyl groups are oriented in axial positions. However, these transitions states appear to be higher in energy than **II-27** due to 1,3-diaxial interactions and unfavorable steric interactions between the *N*-aryl group and the C5 methylene similar to those illustrated in **II-28**.

([65]) This regioisomer likely originates from competing β-hydride elimination processes similar to those illustrated in Scheme II.1. For further discussion, see reference 21.

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CHAPTER III

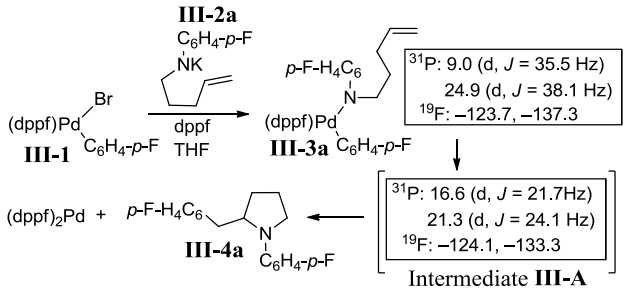
Intramolecular Alkene Aminopalladation Reactions of (dppf)Pd(Ar)[N(Ar^1)(CH_2)$_3$CH=CH_2] Complexes. Insertion of Unactivated Alkenes into Pd–N Bonds

The prospect of effecting *syn*-migratory insertion of alkenes into palladium-nitrogen bonds has been of longstanding interest in organometallic chemistry. Studies on the viability of this transformation were a focal point of early work towards the development of late-metal catalyzed hydroamination reactions.[71,72] However, a number of experiments suggested that aminopalladation reactions of alkenes generally proceed through outer-sphere *anti*-addition pathways.[73] More recently, the *syn*-insertion of alkenes into Pd–N bonds has been implicated as a key step in many useful Pd-catalyzed reactions including alkene carboaminations,[74] diaminations,[75] oxidative aminations,[76] chloroaminations,[77] aminoacetoxylations,[78] and hetero-Heck transformations.[79,80] However, despite the considerable interest in these processes, the *syn*-migratory insertion of an alkene into the Pd–N bond of a well-characterized palladium amido complex has yet to be observed.[81,82]

In this Chapter we describe the synthesis of (dppf)Pd(C_6H_4-*p*-F)[N(Ar^1)(CH_2)$_3$CH=CH_2] complexes **III-3**, which are thought to be intermediates in Pd-catalyzed alkene carboamination reactions. We illustrate that these complexes are transformed to 2-benzylpyrrolidines via migratory insertion of the alkene into the Pd–N bond, followed by reductive elimination of the resulting

(dppf)palladium(aryl)(pyrrolidin-2-ylmethyl) complexes. These are the first examples of insertions of alkenes into Pd–N bonds of well-defined complexes.

Scheme III.1 Overall Reaction Sequence

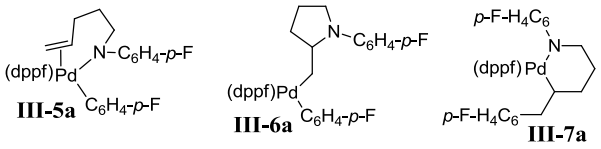


Prior studies on the synthesis of $L_nPd(Ar)(NRR')$ complexes suggested that the high reactivity of these species would preclude their isolation in most cases.[83] As such, the isolable (dppf)Pd(C_6H_4-*p*-F)(Br) complex **III-1** was prepared using previously described routes[83,84] and the potassium anilide salt of *N*-(C_6H_4-*p*-F)-pent-4-enylamine (**III-2a**) was synthesized via deprotonation of the corresponding amine with KHMDS.[83] As shown in Scheme III.1, a solution of **III-1** in THF or THF-d_8 was treated with **III-2a** (1.05 equiv) in the presence of 2-fluorotoluene as internal standard and dppf (2 equiv) as a trap for Pd(0). The conversion of **III-1** to **III-3a** was complete upon mixing, and the formation of amido complex **III-3a** was evident by the presence of a pair of doublets at 24.9 ppm (J_{PP} = 38.1 Hz) and 9.0 ppm (J_{PP} = 35.5 Hz) in the ^{31}P NMR spectrum, which are comparable to data previously reported for (dppf)Pd(Ar)[N(Ar^1)(R)] complexes.[83,85] New signals at –123.7 and –137.3 ppm were also observed in the ^{19}F NMR spectrum of **III-3a**.

Shortly after forming,[86] amido complex **III-3a** underwent reaction to generate a new intermediate complex (**III-A**), which exhibited ^{19}F NMR resonances at –124.1 and –

133.3 ppm, and ^{31}P NMR signals at 21.3 ppm (J_{PP} = 24.1 Hz) and 16.6 ppm (J_{PP} = 21.7 Hz). This intermediate was transformed to pyrrolidine **III-4a** and $(dppf)_2Pd$ at a rate that appeared to be roughly comparable to that of its formation from **III-3a**. Overall, the conversion of **III-3a** to **III-4a** proceeded in 86% NMR yield in 45 min at 24 °C. No additional intermediates on the pathway from **III-3a** to **III-4a** were detected, and no side products resulting from β-hydride elimination were observed.

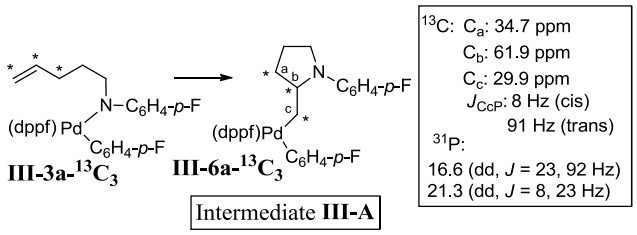
Figure III.1 Possible Structures of Intermediate **III-A**



As shown in Figure III.1, it seemed most likely that intermediate **III-A** was either a 5-coordinate alkene complex (**III-5a**), or an aryl(alkyl) palladium complex (**III-6a**). In addition, although Pd-catalyzed carboamination reactions have been shown to proceed through aminopalladation rather than carbopalladation pathways, we sought to exclude the possible intermediacy of **III-7a** in the stoichiometric transformation. However, the data obtained in our initial experiments could not be used to assign the structure of **III-A**. For example, the ^{1}H NMR alkene signals of **III-3a** decreased as the reaction proceeded, but this region of the spectrum was sufficiently complicated that the presence of a new alkene containing intermediate (**III-5a**) could not be definitively confirmed or refuted. Similarly, the complicated ^{1}H NMR data also did not allow for differentiation of **III-6a** vs. **III-7a**. We observed that (dppf)Pd(C_6H_4-*p*-F)[CH_2(cyclopentyl)] (**III-8**) generated *in situ* from **III-1** and (cyclopentyl)CH_2MgBr underwent C–C bond-forming reductive elimination in < 5 min at rt,[87] which seemed to argue against the intermediacy of **III-6a**.

However, the reductive elimination of **III-6a** could be significantly slowed relative to **III-8** due to the inductive electron-withdrawing effect of the nitrogen atom in **III-6a**.[88] Thus, the identity of intermediate **III-A** could not be ascertained without additional experimentation.

Scheme III.2 ^{13}C–Labeling Experiment to Ascertain the Structure of Intermediate **III-A**



In order to elucidate the structure of **III-A** we prepared and examined the reactivity of ^{13}C labeled amido complex **III-3a-^{13}C$_3$** (Scheme III.2). Analysis of the reaction by ^{13}C and ^{31}P NMR indicated that intermediate **III-A** is the aryl(alkyl)palladium complex **III-6a**. The chemical shifts of the labeled carbon atoms in **III-A** were not consistent with an alkene, and the chemical shift of C_b indicated it was located adjacent to a heteroatom. Thus, this data ruled out the possible intermediacy of **III-5a** and **III-7a**. Moreover, the ^{31}P chemical shifts, coupling constants, and J_{CP} correlate well with data reported by Brown for (dppf)Pd(Ph)(Me).[89]

Having ascertained the structure of intermediate **III-A**, kinetic data were measured at 24 °C for the transformation of amido complex **III-3a** to pyrrolidine **III-4a** by way of intermediate **III-6a** (Scheme III.3 and Figure III.2). Rate constants were extracted for the consecutive first-order reactions (**III-3a** to **III-6a**, $k_1 = 1.74 \times 10^{-3}s^{-1}$; **III-6a** to **III-4a**, $k_2 = 1.36 \times 10^{-3}s^{-1}$), which occur with rates within one order of

magnitude from each other.[90] The activation parameters for the conversion of related amido complex **III-3b** to **III-4b** were determined by Eyring plot analysis (25–60 °C),[91] and are similar for both steps of the transformation. For the conversion of **III-3b** to **III-6b** $\Delta H^{\ddagger}$ = 24.8 ± 0.6 kcal/mol, $\Delta S^{\ddagger}$ = 4.6 ± 1.8 eu. For the reductive elimination of **III-4b** from **III-6b** $\Delta H^{\ddagger}$ = 23.3 ± 0.8 kcal/mol, $\Delta S^{\ddagger}$ = 4.6 ± 2.5 eu. The reaction enthalpies are comparable to those observed for insertion of alkenes into late-metal–carbon bonds,[92a–c] and for C–C bond-forming reductive elimination processes.[92d] The small entropy values are consistent with unimolecular transformations.[92]

Scheme III.3 Reaction Scheme with Different *N*-Aryl Groups

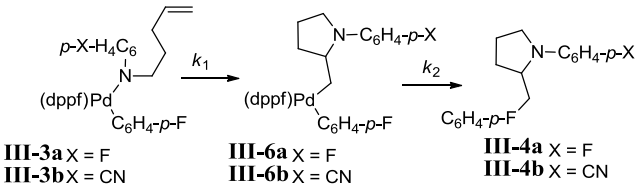
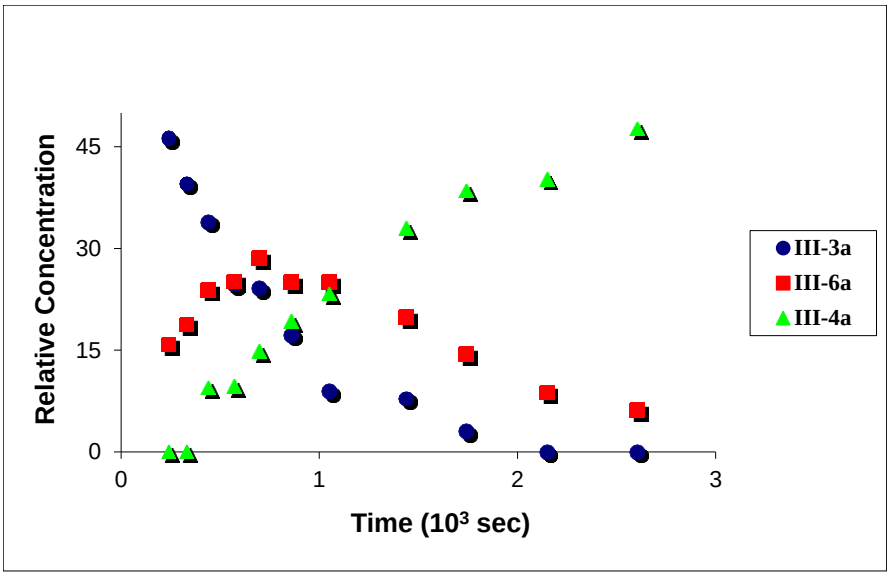
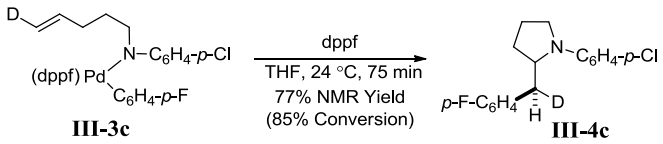


Figure III.2 Representative Plot of Raw Kinetic Data



The stereochemistry of the aminopalladation reaction was determined through reaction of deuterated amido complex **III-3c**. As shown in Scheme III.4, this complex was cleanly transformed to pyrrolidine **III-4c** with net *syn*-addition of the aryl group and the N-atom across the C–C double bond. This supports a mechanism involving *syn*-migratory insertion of the alkene into the Pd–N bond, rather than amide dissociation, alkene coordination, and outer-sphere attack of the pendant nucleophile. This result is also consistent with the stereochemical outcome of Pd-catalyzed carboamination reactions between γ–aminoalkene derivatives and aryl bromides.[24]

Scheme III.4 Deuterium Labeling Study to Establish *Syn*-Insertion



In conclusion, we have described the first examples of intramolecular *syn*-migratory insertion reactions of alkenes into well-defined palladium(aryl)(amido) complexes. These reactions proceed with complete chemoselectivity for insertion into the Pd–N bond vs. the Pd–C bond, and provide observable (dppf)palladium(aryl)(pyrroldin-2-ylmethyl) complexes. These results provide further support for postulated *syn*-aminopalladation mechanistic pathways in palladium-catalyzed alkene difunctionalization reactions.

Experimental

All reactions were carried out under a dry nitrogen atmosphere in flame-dried glassware using standard Schlenk techniques or in a nitrogen-filled glovebox. All reagents were obtained from commercial sources and used without further purification. $Cp_2Zr(D)Cl$,[93] and 4-(pent-4-enylamino)benzonitrile[19] were prepared according to literature procedures. $\{[(o\text{-tol})_3P]Pd(C_6H_4\text{-}p\text{-}F)(Br)\}_2$[94] and $(dppf)Pd(C_6H_4\text{-}p\text{-}F)(Br)$[95] were prepared using methods analogous to those previously described by Buchwald.[95] Pent-4-ynyl-4-methylbenzenesulfonate was prepared by treatment of 4-pentyn-1-ol with 1.2 equiv TsCl, 2 equiv Et_3N, and 0.1 equiv DMAP at 0 °C in dichloromethane. Toluene, THF, diethyl ether, and dichloromethane solvents used in the synthesis of organic substrates or air-stable Pd-complexes were purified using a GlassContour solvent purification system. THF and THF-d_8 solvents used for preparation of Pd-amido complexes and kinetics experiments were dried over sodium/benzophenone overnight under vacuum and then vacuum transferred before use. 2-Fluorotoluene and 4-fluorotoluene were purified by distillation from CaH_2 under nitrogen. Benzaldehyde was purified by distillation from $CaSO_4$ under nitrogen. CD_2Cl_2, acetic acid-d_4, and propargyl alcohol-$^{13}C_3$ were obtained anhydrous from Cambridge Isotope Laboratories and used as received. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^1H NMR analysis unless otherwise noted. The yields reported in the experimental section describe the result of a single experiment, whereas all kinetic data have been averaged over duplicate experiments. All kinetic experiments were set up in a glovebox under nitrogen atmosphere. All glassware and microsyringes associated with kinetic experiments were oven dried at 120 °C overnight before use. ^{31}P NMR shifts are

given relative to an 85% H_3PO_4 external standard. ^{1}H NMR shifts for the experimental section are reported downfield of TMS in $CDCl_3$ or referenced to residual protia in THF-d_8. ^{19}F NMR shifts are referenced to 2-fluorotoluene (–117.2 ppm) or 4-fluorotoluene (–117.9 ppm) in THF-d_8.

Preparation and Characterization of Potassium Amide Substrates

General Procedure 6: Conversion of *N*-aryl-pent-4-enamides to *N*-aryl-pent-4-enylamines. A flame-dried flask equipped with a magnetic stirbar was charged with the appropriate *N*-aryl-pent-4-enamide (1.0 equiv) and purged with nitrogen for 5 min. THF (4 mL/mmol substrate) was added and the resulting solution was cooled to 0 °C. To this solution, a 1 M solution of $LiAlH_4$ in diethyl ether (1.2 equiv) was added slowly over 10 min. The reaction mixture was stirred at 0 °C for 15 min then warmed to rt and stirred overnight (ca. 16 h). The reaction mixture was cooled to 0 °C, then water (0.05 mL/mmol substrate), 6 M NaOH (0.05 mL/mmol substrate) and additional water (0.15 mL/mmol substrate) were sequentially added. The resulting white suspension was stirred vigorously for 30 min, then filtered through glass wool and the white precipitate was washed with diethyl ether (3 × 30 mL). The filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting product was purified by flash chromatography on silica gel.

General Procedure 7: Conversion of *N*-aryl-pent-4-enylamines to Potassium *N*-aryl-pent-4-enyl Amides. A flame-dried flask equipped with a magnetic stirbar was charged with the appropriate *N*-aryl-pent-4-enylamine (1.3 equiv) and purged with nitrogen for 5

min. In the glovebox, a separate flame-dried Schlenk flask equipped with a magnetic stirbar was charged with solid KHMDS (1.0 equiv), capped with a septum, removed from the glovebox, and connected to a vacuum/nitrogen manifold. Toluene (5 mL/mmol KHMDS) was added to each flask to afford clear solutions. Subsequently the amine solution was added dropwise to the KHMDS solution at rt to afford a bright yellow solution. The solution was stirred for 1.5 h at rt, over which time the solution became progressively more cloudy. The solvent was removed under high vacuum to afford a crude solid, which was taken into the glovebox under vacuum. The crude solid was purified on a medium glass frit via rinsing/trituration with pentane (4 × 10 mL) The resulting potassium *N*-aryl-pent-4-enyl amides were determined to contain ca. 1.6–1.8% KHMDS as judged by ^{1}H NMR analysis. This material was used without further purification.

Potassium (4-fluorophenyl)(pent-4-enyl)amide (III-2a). A flame-dried flask equipped with a magnetic stirbar was charged with 4-pentenoic acid (2.0 mL, 19.6 mmol) and purged with nitrogen for 5 min. Dichloromethane (35 mL) and DMF (50 μL) were subsequently added and the resulting solution was cooled to 0 °C. To this solution oxalyl chloride (19.8 mmol) was added dropwise over 5 min. The resulting solution was stirred for 15 min at 0 °C and then allowed to warm to rt over 3 h. The solution was then cooled to 0 °C and added dropwise to a solution of 4-fluoroaniline (3.8 mL, 40 mmol) in dichloromethane (20 mL). The reaction mixture was warmed to rt and stirred overnight (ca. 16 h). Water (50 mL) was added and the resulting biphasic mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted

with diethyl ether (3 × 40 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL) then were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting product was purified by flash chromatography on silica gel. This procedure afforded 3.28 g (81%) of *N*-(4-fluorophenyl)pent-4-enamide as a white solid, m.p. 75–78.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, br, 1 H), 7.49–7.41 (m, 2 H), 7.02–6.93 (m, 2 H), 5.93–5.80 (m, 1 H), 5.11 (dd, *J* = 1.6, 17.2 Hz, 1 H), 5.05 (d, *J* = 10.8 Hz, 1 H), 2.51–2.40 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 159.5 (d, *J* = 244 Hz), 137.0, 134.0, 122.0 (d, *J* = 7.6 Hz), 116.2, 115.8 (d, *J* = 23.0 Hz), 36.8, 29.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –118.0 (m).

N-(4-Fluorophenyl)pent-4-enamide (1.50 g, 7.8 mmol) was reduced using a solution $LiAlH_4$ in diethyl ether (9.36 mL, 9.36 mmol) according to General Procedure 6. This procedure afforded 1.20 g (86%) of 4-fluoro-*N*-(pent-4-enyl)aniline as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94–6.84 (m, 2 H), 6.58–6.49 (m, 2 H), 5.90–5.77 (m, 1 H), 5.10–4.97 (m, 2 H), 3.49 (s, br, 1 H), 3.08 (t, *J* = 7.2 Hz, 2 H), 2.22–2.13 (m, 2 H), 1.70 (quint, *J* = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9 (d, *J* = 235 Hz), 145.0 (d, *J* = 2.3 Hz), 138.2, 115.8 (d, *J* = 22.2 Hz), 115.4, 113.7 (d, *J* = 7.6 Hz), 44.3, 31.5, 28.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ –128.5 (m); IR (film) 3414, 1221 cm^{-1}. MS (EI) 179.1109 (179.1110 calcd for $C_{11}H_{14}FN$).

General Procedure 7 was used for the conversion of 4-fluoro-*N*-(pent-4-enyl)aniline (266 mg, 1.5 mmol) to the title compound. This procedure afforded 189 mg (69%) of the title compound as a tan powder that contained ca. 1.8% KHMDS as judged by ^{1}H NMR analysis. This material was used without further purification. ^{1}H NMR (400 MHz, THF-d_8) δ 6.49 (t, *J* = 8.8 Hz, 2 H), 6.00–5.85 (m, 3 H), 5.03 (d, *J* = 17.2 Hz, 1 H),

4.91 (d, J = 10.0 Hz, 1 H), 2.87–2.78 (m, 2 H), 2.24–2.15 (m, 2 H), 1.80–1.68 (m, 2 H, partially obscured by THF signal); ^{13}C NMR (100 MHz, THF-d_8) δ 159.0, 150.4 (d, J = 219 Hz), 141.0, 116.2 (d, J = 20.0 Hz), 114.0, 109.5 (br), 52.7, 34.1, 33.9; ^{19}F NMR (376 MHz, THF-d_8) δ –143.9 (s, br).

Potassium (4-cyanophenyl)(pent-4-enyl)amide (III-2b). General Procedure 7 was used for the conversion of 4-(pent-4-enylamino)benzonitrile[19] (400 mg, 2.1 mmol) to the title compound. This procedure afforded 309 mg (80%) of the title compound as a peach-colored powder that contained ca. 1.8% KHMDS as judged by ^{1}H NMR analysis. This material was used without further purification. ^{1}H NMR (400 MHz, THF-d_8) δ 6.77 (d, J = 8.4 Hz, 2 H), 6.05–5.80 (m, 3 H), 4.97 (d, J = 16.8 Hz, 1 H), 4.86 (d, J = 9.6 Hz, 1 H), 2.94–2.86 (m, 2 H), 2.18–2.08 (m, 2 H), 1.69–1.58 (m, 2 H, partially obscured by THF signal); ^{13}C NMR (100 MHz, THF-d_8) δ 161.8, 140.8, 133.0, 126.0, 114.1, 113.3 (br), 82.1, 50.2, 33.6, 32.6.

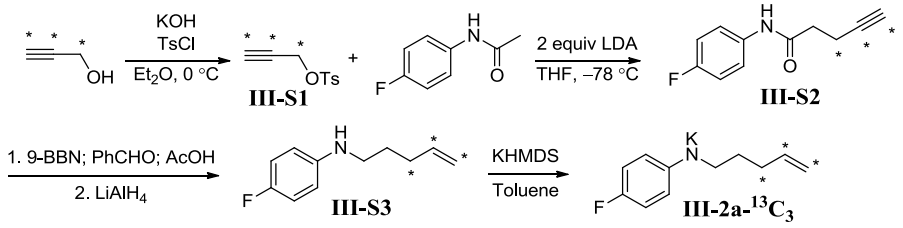
Potassium (*E*)-(4-chlorophenyl)(5-deuteriopent-4-enyl)amide (III-2c). A flame-dried flask equipped with a magnetic stirbar was charged with pent-4-ynyl-4-methylbenzenesulfonate (708 mg, 3.0 mmol) and purged with nitrogen for 5 min. THF (10 mL) was added followed by a solution of 9-BBN in THF (12 mL, 6 mmol, 0.5 M) at rt. The reaction mixture was stirred for 6 h at rt then PhCHO (300 µL, 2.9 mmol) was added. The resulting solution was stirred for an additional 3.5 h at rt and then was cooled to 0 °C. Acetic acid-d_4 (200 µL, 3.6 mmol) was added and the solution was warmed to rt and stirred for 45 min. Saturated aqueous Na_2CO_3 (15 mL) and EtOAc (10 mL) were

sequentially added, and the resulting mixture was transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with diethyl ether (1 × 20 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford (*E*)-(5-deuteriopent-4-enyl)-4-methylbenzenesulfonate as a colorless oil that was used in the next step without further purification.

A flame-dried flask equipped with a magnetic stirbar was charged with 4-chloroaniline (540 mg, 4.2 mmol) and purged with nitrogen for 5 min. THF (4 mL) was added followed by a solution of LiHMDS in THF (2.5 mL, 2.5 mmol, 1.0 M) to afford a dark green solution. This solution was added to a solution of the crude (*E*)-(5-deuteriopent-4-enyl)-4-methylbenzenesulfonate from the previous reaction in THF (4 mL). The resulting mixture was heated to 50 °C for 2 h then cooled to rt. Water (20 mL) and EtOAc (10 mL) were added, the mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting product was purified by flash chromatography on silica gel to afford 271 mg (51%) of (*E*)-4-chloro-*N*-(5-deuteriopent-4-enyl)aniline as a pale yellow oil with ~87% deuterium incorporation as judged by GC/MS and ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.08 (m, 2 H), 6.55–6.48 (m, 2 H), 5.90–5.77 (m, 1 H), 5.04 (td, J = 1.2, 17.2 Hz, 1 H), 3.63 (s, br, 1 H), 3.10 (t, J = 7.2 Hz, 2 H), 2.16 (qd, J = 1.2, 6.8 Hz, 2 H), 1.71 (quint, J = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 138.0, 129.2, 121.9, 115.2 (t, J_{CD} = 24.1 Hz), 113.9, 43.7, 31.4, 28.7; IR (film) 3416 cm^{-1}. MS (EI) 196.0883 (196.0878 calcd for $C_{11}H_{13}DClN$).

General Procedure 7 was used for the conversion of (*E*)-4-chloro-*N*-(5-deuteriopent-4-enyl)aniline (201 mg, 1.0 mmol) to the title compound. This procedure afforded 105 mg (55%) of the title compound as a yellow powder that contained ca. 1.6% KHMDS as judged by ^{1}H NMR analysis. This material was used without further purification. ^{1}H NMR (400 MHz, THF-d_8) δ 6.61 (d, J = 8.8 Hz, 2 H), 6.00–5.85 (m, 3 H), 5.00 (d, J = 16.8 Hz, 0.88 H), 4.90 (d, J = 15.2 Hz, 0.12 H), 2.87–2.77 (m, 2 H), 2.18 (q, J = 6.8 Hz, 2 H), 1.75–1.65 (m, 2 H, partially obscured by THF signal); ^{13}C NMR (100 MHz, THF-d_8) δ 160.1, 140.8, 129.6, 114.1 (t, J_{CD} = 26.1 Hz), 112.0 (br), 108.2, 51.9, 33.9, 33.6.

Scheme III.5 Synthesis of ^{13}C–Labeled Substrate



3,4,5-^{13}C-Potassium (4-fluorophenyl)(pent-4-enyl)amide (III-2a-$^{13}C_3$). Labeled potassium amide **III-2a-$^{13}C_3$** was synthesized in 5 linear steps in 10% overall yield, starting from propargyl alcohol-$^{13}C_3$, as shown in Scheme III.5. A round-bottomed flask equipped with a stirbar was charged with powdered KOH (2.37 g, 42.3 mmol), TsCl (1.99 g, 10.4 mmol), and dry Et_2O (20 mL). The resulting suspension was cooled to 0 °C and propargyl alcohol-$^{13}C_3$ (500 mg, 8.46 mmol) was added. The mixture was stirred for 2.5 h and allowed to warm gradually from 0 °C to room temperature over that time. Water (25 mL) and Et_2O (25 mL) were then added to the reaction mixture and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 25 mL), and the

combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford propargyl tosylate-$^{13}C_3$ (**III-S1**) as a colorless oil (1.74 g, 97%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82 (d, J = 8.0 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 2 H), 4.71 (dm, J = 154 Hz, 2 H), 2.47 (ddm, J = 72.5, 232 Hz, 1 H), 2.46 (s, 3 H).

A solution of *N*-(4-fluorophenyl)acetamide[96] (3.75g, 24.5 mmol) in 30 mL dry THF was added slowly to a solution of freshly prepared LDA (49.0 mmol) in THF and hexanes at –78 °C, and allowed to stir for 1 h. A solution of propargyl tosylate-$^{13}C_3$ (**III-S1**) (1.74 g, 8.17 mmol) in 60 mL dry THF was then added slowly via addition funnel over the course of 1 h while maintaining a reaction temperature of –78 °C. The resulting solution was stirred for 3 h at –78 °C and warmed slowly to rt over the course of 2 h before being quenched with aqueous NH_4Cl solution (40 mL). Water (120 mL) and Et_2O (120 mL) were added, the layers were separated, and the aqueous layer was extracted with ether (2 × 120 mL). The combined organic layers were washed with brine (120 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to afford labeled amide **III-S2** as pale orange solid (1.04 g, 66%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52–7.41 (m, 3 H), 7.04–6.98 (m, 2 H), 2.66 (dm, J_{CH} = 135 Hz, 2 H), 2.58 (quint, J = 6.2 Hz, 2 H), 2.07 (qdd, J = 2.6, 51, 249 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz, labeled carbons only) δ 83.0 (dd, J = 67, 171 Hz), 69.9 (dd, J = 11.2, 171 Hz), 15.0 (dd, J = 11.2, 67 Hz).

Reduction of the alkyne was accomplished using the method of Soderquist,[97] and reduction of the amide was conducted without isolating the resulting alkene. An oven-dried round-bottomed flask was charged with amide **III-S2** (1.01 g, 5.20 mmol) and

purged with nitrogen. Anhydrous THF (20 mL) and a solution of 9-BBN in THF (0.5 M, 42 mL, 21 mmol) were added, and the resulting solution was stirred at rt for 12 h. PhCHO (690 μL, 6.67 mmol) was added, and the resulting solution was stirred at rt for 7 h. Acetic acid (650 μL, 10.6 mmol) was added, and the solution was stirred at rt for 45 min. Water (25 mL) and ether (25 mL) were then added and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 40 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated, and purified by flash chromatograpy on silica gel. This procedure afforded an oil, which was dissolved in 20 mL dry THF under nitrogen, and cooled to 0 °C. A solution of $LiAlH_4$ (1.0 M in ether, 8.5 mL, 8.5 mmol) was added slowly via syringe, and the resulting mixture was stirred at 0 °C for 4 h. Aqueous workup and filtration were conducted according to General Procedure 6. The resulting crude product was purified by flash chromatography on silica gel to afford *p*-fluoro-N-(3,4,5-$^{13}C_3$-pent-4-enyl)aniline **III-S3** as a colorless oil (260 mg, 28% from **III-S2**). HRMS detected only triply ^{13}C-labeled compound (M–1 not observed, M+1 intensity was as predicted by natural abundance of isotopes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.91–6.85 (m, 2 H), 6.56–6.51 (m, 2 H), 5.83 (dm, J_{CH} = 152 Hz, 1 H), 5.05 (dm, J_{CH} = 153 Hz, 1 H), 5.01 (dm, J_{CH} = 158 Hz, 1 H), 3.48 (s, br, 1 H), 3.11–3.07 (m, 2 H), 2.17 (dm, J_{CH} = 126 Hz, 2 H), 1.75–1.67 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz, labeled carbons only) δ 137.9 (dd, *J* = 41.6, 68.7 Hz), 115.1 (d, *J* = 69.1 Hz), 31.3 (d, *J* = 41.5 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ –128.5 (m). MS (EI) 182.1215 (182.1211 calcd for $^{12}C_8{}^{13}C_3H_4FN$).

General Procedure 7 was used for the conversion of labeled amine **III-S3** (250 mg, 1.37 mmol) to the title compound. This procedure yielded 185 mg (0.841 mmol,

77%) of a bright yellow powder which was stored in a –20 °C freezer in the glovebox. ^{1}H NMR (THF-d_8, 400 MHz) δ 6.50 (t, J = 8.8 Hz, 2 H), 5.92 (m, 2 H), 5.89 (dm, J_{CH} = 150 Hz, 1 H), 5.00 (dm, J_{CH} = 153 Hz, 1 H), 4.89 (dm, J_{CH} = 158 Hz, 1 H), 2.86–2.81 (m, 2 H), 2.18 (dm, J_{CH} = 118 Hz, 2 H), 1.73–1.65 (m, partially obscured by THF signal); ^{13}C NMR (THF-d_8, 100 MHz, labeled carbons only) δ 140.9 (dd, J = 42.2, 69.4 Hz), 114.0 (d, J = 69.4 Hz), 33.8 (d, J = 41.8 Hz); ^{19}F NMR (THF-d_8, 376 MHz) δ –143.8 (s, br).

Synthesis of Authentic Samples of Pyrrolidine Products Formed in Kinetic Runs

General Procedure 8: Pd-Catalyzed Carboamination of γ-(*N*-arylamino)alkenes with Aryl Bromides.[98] An oven or flame-dried Schlenk tube was cooled under a stream of argon or nitrogen and charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), dppf (2 mol %), NaO*t*-Bu (1.0 equiv), and the ArBr (1.5 equiv). The tube was purged with argon or nitrogen and a solution of the amine substrate (1.0 equiv) in toluene (4 mL/mmol aryl bromide) was added. The mixture was heated to 60–110 °C with stirring until the starting material had been consumed as judged by GC or ^{1}H NMR analysis. The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (2 mL) and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

1-(4-Fluorophenyl)-2-(4-fluorobenzyl)pyrrolidine (III-4a). General Procedure 8 was used for the coupling of 4-fluoro-*N*-(pent-4-enyl)aniline (51 mg, 0.28 mmol) with 1-

bromo-4-fluorobenzene (47 μL, 0.42 mmol) to afford 53 mg (68%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.11 (m, 2 H), 7.03–6.93 (m, 4 H), 6.60–6.53 (m, 2 H), 3.94–3.85 (m, 1 H), 3.42–3.32 (m, 1 H), 3.19–3.08 (m, 1 H), 2.94 (dd, *J* = 3.2, 13.6 Hz, 1 H), 2.58 (dd, *J* = 8.8, 13.6 Hz, 1 H), 1.95–1.74 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, *J* = 245 Hz), 155.0 (d, *J* = 234 Hz), 143.9 (d, *J* = 1.6 Hz), 135.1 (d, *J* = 3.1 Hz), 130.9 (d, *J* = 7.6 Hz), 115.9 (d, *J* = 22.2 Hz), 115.4 (d, *J* = 20.7 Hz), 112.4 (d, *J* = 6.9 Hz), 60.2, 49.2, 38.0, 29.9, 23.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –117.0 (m), –130.7 (m); IR (film) 1225 cm^{-1}. MS (ESI) 274.1413 (274.1407 calcd for $C_{17}H_{17}F_2N$, M + H^+).

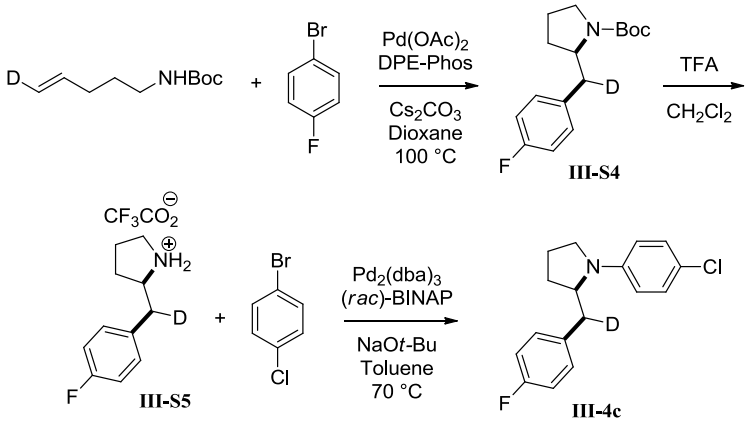
4-[2-(4-Fluorobenzyl)pyrrolidin-1-yl]benzonitrile (III-4b). General Procedure 8 was used for the coupling of 4-(pent-4-enylamino)benzonitrile (34 mg, 0.18 mmol) with 1-bromo-4-fluorobenzene (40 μL, 0.37 mmol) to afford 41 mg (79%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.45 (m, 2 H), 7.17–7.09 (m, 2 H), 7.04–6.96 (m, 2 H), 6.64–6.57 (m, 2 H), 4.06–3.97 (m, 1 H), 3.45–3.35 (m, 1 H), 3.28–3.16 (m, 1 H), 2.93 (dd, *J* = 3.2, 14.0 Hz, 1 H), 2.62 (dd, *J* = 8.8, 13.6 Hz, 1 H), 2.02–1.80 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7 (d, *J* = 245 Hz), 149.2, 134.0, 133.6, 130.6 (d, *J* = 7.6 Hz), 120.8, 115.3 (d, *J* = 21.1 Hz), 111.8, 97.0, 59.6, 48.2, 37.1, 29.3, 22.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –116.4 (m); IR (film) 2211, 1222 cm^{-1}. MS (ESI) 281.1462 (281.1454 calcd for $C_{18}H_{17}FN_2$, M + H^+).

(±)-(2*R,1'*S**)-*N*-(4-Chlorophenyl)-2-(1'-deuterio-*p*-fluorobenzyl)pyrrolidine (III-4c).** General Procedure 8 was used for the coupling of (*E*)-4-chloro-*N*-(5-deuteriopent-4-

enyl)aniline (27 mg, 0.14 mmol) with 1-bromo-4-fluorobenzene (24 μL, 0.22 mmol) to afford 31 mg (78%) of the title compound as a colorless oil. This material was judged to contain ~87% deuterium incorporation by GC/MS and ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.10 (m, 4 H), 7.02–6.95 (m, 2 H), 6.59–6.53 (m, 2 H), 3.94–3.86 (m, 1 H), 3.38–3.31 (m, 1 H), 3.18–3.08 (m, 1 H), 2.90 (s, 0.85 H), 2.59 (dd, J = 8.8, 14.0 Hz, 0.13 H), 1.95–1.70 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, J = 245 Hz), 145.7, 134.9 (d, J = 3.1 Hz), 130.9 (d, J = 7.6 Hz), 129.3, 120.5, 115.4 (d, J = 21.4 Hz), 113.1, 59.9, 48.8, 37.4 (t, J_{CD} = 19.6 Hz), 29.7, 23.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –116.9 (m); IR (film) 1222 cm^{-1}. MS (ESI) 291.1185 (291.1175 calcd for $C_{17}H_{16}DClFN$, $M + H^+$).

The stereochemistry of **III-4c** was assigned by carboamination of the analogous *N*-Boc-substituted substrate with 1-bromo-4-fluorobenzene. We have previously demonstrated that reactions of this substrate proceed with *syn*-addition of the nitrogen atom and the aryl group across the alkene.[24] Cleavage of the Boc-group followed by Pd-catalyzed *N*-arylation of the resulting pyrrolidine with 1-bromo-4-chlorobenzene afforded **III-4c** as depicted in Scheme III.6 below. The *N*-arylation has been previously demonstrated to occur with no scrambling of stereochemistry using the conditions illustrated below.[99]

Scheme III.6 Synthesis of Stereochemistry Comparison Substrate



Proof of Stereochemistry of III-4c via Alternative Synthesis.

A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (4.8 mg, 0.021 mmol), DPE-Phos (23.7 mg, 0.044 mmol), and Cs_2CO_3 (807 mg, 2.5 mmol). The tube was purged with nitrogen for 5 min and a solution of (*E*)-*tert*-Butyl-5-*d*-pent-4-enylcarbamate[24] (203 mg, 1.1 mmol) and 1-bromo-4-fluorobenzene (150 μL, 1.4 mmol) in 1,4-dioxane (5 mL) was added. The mixture was heated to 100 °C with stirring for 38 h upon which time the reaction mixture was quenched as in General Procedure 8. The crude product was then purified by flash chromatography on silica gel to afford 187 mg (61%) of pyrrolidine **III-S4** as a colorless oil. ^{1}H NMR (400 MHz, toluene-d_8, 100 °C) δ 6.95–6.88 (m, 2 H), 6.75 (t, J = 8.8 Hz, 2 H), 3.92–3.81 (m, 1 H), 3.32–3.20 (m, 1 H), 3.15–3.04 (m, 1 H), 2.98–2.90 (m, 1 H), 1.46 (s, 9 H), 1.40–1.28 (m, 4 H); ^{13}C NMR (100 MHz, toluene-d_8, 100 °C) δ 162.4 (d, J = 245 Hz), 154.4, 135.6, 131.2 (d, J = 7.9 Hz), 115.4 (d, J = 20.9 Hz), 78.9, 59.1, 47.0, 39.6 (t, J_{CD} = 19.1 Hz), 30.0, 28.9, 23.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –116.5 (m); IR (film) 1693, 1222 cm^{-1}. MS (ESI) 303.1595 (303.1595 calcd for $C_{16}H_{21}DFNO_2$, M + Na^+).

A flame-dried flask was charged with pyrrolidine **III-S4** (153 mg, 0.55 mmol) and CH_2Cl_2 (3 mL). Trifluoroacetic acid (1 mL) was added and the mixture was allowed to stir at rt for 4 h. The reaction mixture was then concentrated *in vacuo*. Residual trifluoracetic acid was removed by addition of benzene (4 mL) followed by concentration *in vacuo* (repeated three times). This procedure afforded 160 mg (100 %) of pyrrolidinium trifluoroacetate salt **III-S5** as a viscous brown oil that was used without further purification.

Crude pyrrolidinium trifluoroacetate **III-S5** was *N*-arylated with 1-bromo-4-chlorobenzene using conditions developed by Buchwald for *N*-arylation of amines bearing stereocenters adjacent to the nitrogen atom.[99] A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (6.3 mg, 0.007 mmol), (*rac*)-BINAP (8.8 mg, 0.014 mmol), NaO*t*-Bu (82.1 mg, 0.85 mmol), and 1-bromo-4-chlorobenzene (78.1 mg, 0.41 mmol). The tube was purged with nitrogen for 5 min and a solution of **III-S5** (100 mg, 0.34 mmol) in toluene (1.1 mL) was added. The mixture was heated to 70 °C with stirring for 6 h upon which time the reaction mixture was quenched as in General Procedure 8. The crude product was purified by flash chromatography on silica gel to afford 47 mg (48%) of pyrrolidine **III-4c** as a colorless oil that was spectroscopically identical to the material prepared directly from **III-3c**, thus establishing the *syn*-addition stereochemistry illustrated above.

Preparation and Characterization of (dppf)Pd(C_6H_4-*p*-F)(Br) (III-1).

A flame-dried flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (497 mg, 0.54 mmol), and P(*o*-tol)$_3$ (412 mg, 1.4

mmol). The flask was purged with nitrogen for 5 min, toluene (20 mL) and 1-bromo-4-fluorobenzene (300 μL, 2.8 mmol) were added, and the resulting dark purple-brown solution was stirred at 25 °C for 2.5 h. At this time the solution had changed to a dark purple-yellowish color and was subsequently filtered through celite eluting with diethyl ether (ca. 100 mL) to obtain a yellow-orange filtrate. The filtrate was concentrated *in vacuo* to ca. 15 mL, layered with 60 mL pentane and transferred to an Erlenmeyer flask. The stoppered, layered solution was then allowed to settle at rt for 2 h upon which time significant formation of a yellow precipitate had occurred. The mixture was filtered to isolate 322 mg of dimeric [(*o*-tol)$_3$P]Pd(C$_6$H$_4$-*p*-F)(Br) as a fluffy yellow powder that was subsequently used without further purification.

A flame-dried flask equipped with magnetic stir bar was charged with 121 mg (0.1 mmol) of the dimeric [(*o*-tol)$_3$P]Pd(C$_6$H$_4$-*p*-F)(Br) complex and dppf (115 mg, 0.21 mmol). The flask was purged with nitrogen for 5 min and CH_2Cl_2 (6 mL) was added. The resulting orange solution was stirred for 1 h at rt and then concentrated *in vacuo* to ca. 0.5 mL. Et_2O (7 mL) was added, the resulting slurry was stirred for 1 min and then allowed to settle for 1 h at rt. The mixture was then filtered to yield 114 mg (33% over 2 steps) of an orange solid that was washed with Et_2O (3 × 8 mL) and pentane (3 × 8 mL) to afford the title complex. m.p. 185 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.00 (m, 4 H), 7.50–7.10 (m, 16 H), 6.91–6.81 (m, 2 H), 6.41–6.31 (m, 2 H), 4.71–4.65 (m, 2 H), 4.52–4.47 (m, 2 H), 4.18–4.12 (m, 2 H), 3.66–3.60 (m, 2 H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 160.7 (d, *J* = 239 Hz), 152.0 (s), 150.7 (s), 136.2 (m), 135.9 (d, *J* = 11.7 Hz), 134.6 (d, *J* = 12.5 Hz), 133.9 (d, *J* = 13.3 Hz), 133.4 (d, *J* = 33.4 Hz), 130.9 (dd, *J* = 2.0, 9.7 Hz), 128.6 (d, *J* = 9.4 Hz), 128.5 (d, *J* = 10.9 Hz), 114.4 (m), 77.1 (dd *J* = 7.4, 51.0

Hz), 76.7 (d, J = 11.7 Hz), 75.4 (dd, J = 2.7, 38.5 Hz), 74.9 (d, J = 8.6 Hz), 74.1 (d, J = 7.8 Hz), 72.9 (d, J = 4.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –124.6 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.9 (dd, J = 2.3, 32.0 Hz), 9.9 (dd, J = 1.9, 32.0 Hz); IR (film) 1474, 1435, 1211 cm^{-1}. Anal calcd for $C_{40}H_{32}BrFFeP_2Pd$: C, 57.48; H, 3.86. Found: C, 57.42; H, 3.80.

Representative Procedure for *In Situ* Formation of Pd-Amido Complexes III-3 and Conversion to III-6.

In a glovebox under nitrogen atmosphere, (dppf)Pd(C_6H_4-*p*-F)(Br) (**III-1**) (6.3 mg, 0.0075 mmol) and dppf (4.7 mg, 0.0085 mmol) were placed into a small vial. THF-d_8 (550 μL) was added and the resulting orange solution was transferred to an NMR tube. 4-Fluorotoluene (0.3 μL, 0.0027 mmol) was added as an internal ^{19}F standard, and the tube was sealed with a septum. The tube was cooled to –60 °C in the probe of an NMR spectrometer and ^{1}H, ^{19}F, and ^{31}P spectra were obtained. A solution of potassium (4-fluorophenyl)(pent-4-enyl)amide (**III-2a**) (2.7 mg, 0.012 mmol) in 200 μL THF-d_8 was prepared in the glovebox and 121 μL (1 equiv) of that solution was loaded into a gas tight syringe and injected into the NMR tube containing the Pd complex. The tube was inverted several times to ensure complete mixing, and a rapid color change from orange to red was observed. The tube was returned to the cold NMR probe and allowed to re-equilibrate at –60 °C and a ^{19}F spectrum was obtained. The solution was then warmed to –20 °C and ^{1}H, ^{19}F, and ^{31}P spectra were obtained. Experiments in which the ratio of Pd-complex **III-1** to dppf were varied over a range of 0.75 to 2 equivalents dppf:Pd had no effect on the identity of the species formed in these reactions.

(dppf)Pd(C_6H_4-*p*-F)[N(C_6H_4-*p*-F)($CH_2CH_2CH_2CH{=}CH_2$)] (III-3a): ^{1}H NMR (400 MHz, THF-d_8) δ 7.95–7.87 (m), 7.76 (t, *J* = 8.6 Hz) 7.59–7.40 (m), 7.20–7.12 (m), 7.06–7.01 (m), 6.60 (q, *J* = 7.4 Hz), 6.36 (t, *J* = 8.4 Hz), 6.09 (t, *J* = 8.6 Hz), 5.62 (tdd, *J* = 6.8, 10.0, 16.8 Hz, 1 H), 4.88–4.81 (m, 2 H), 2.57–2.51 (m, 1 H), 2.22–2.14 (m, 1 H), 1.70 (m, obscured by THF), 1.42–1.30 (m, 1 H), 1.20–1.08 (m, 1H) (due to overlap and spectral crowding, accurate integration values for aryl protons could not be determined and are not reported); ^{19}F NMR (376 MHz, THF-d_8) δ –123.7 (m, Pd-C_6H_4F), –137.3 (s, N-C_6H_4F); ^{31}P NMR (162 MHz, THF-d_8) δ 24.9 (d, *J* = 38.1 Hz), 9.0 (d, *J* = 35.5 Hz).

The solution of the palladium-amido complex **III-3a** was warmed to 15 °C, monitoring at 2 min intervals by ^{19}F NMR for appearance of peaks at –124.1 and –133.3 ppm (attributed to **III-6a**), along with diminishment of the peaks at –123.7 and –137.3 ppm. When the new peaks were near their maximum, the solution was cooled to –20 °C and ^{1}H, ^{19}F, and ^{31}P spectra were obtained. ^{19}F and ^{31}P data are reported; the ^{1}H spectrum for this and related compounds could not be extracted from the combined spectra of the species present in the reaction mixture. This general protocol was also followed for the reactions of **III-3a-$^{13}C_3$**, **III-3b**, and **III-3c**. Data for these amido complexes and intermediates **III-6a-$^{13}C_3$**, **III-6b**, and **III-6c** are provided below.

(dppf)Pd(C_6H_4-*p*-F){CH_2[$\overline{CHCH_2CH_2CH_2N}$($C_6H_4$-*p*-F)]} (III-6a): ^{19}F NMR (376.9 MHz, THF-d_8) δ –124.1 (s), –133.3 (s); ^{31}P NMR (162 MHz, THF-d_8) δ 21.3 (d, *J* = 24.1 Hz), 16.6 (d, *J* = 21.7 Hz).

(dppf)Pd(C_6H_4-*p*-F)[N(C_6H_4-*p*-F)($CH_2CH_2{}^{13}CH_2{}^{13}CH={}^{13}CH_2$)] (III-3a-$^{13}C_3$): ^{19}F NMR (376 MHz, THF-d_8) δ –123.7 (m, Pd-C_6H_4F), –137.3 (s, N-C_6H_4F); ^{31}P NMR (162 MHz, THF-d_8) δ 24.9 (d, J = 38.1 Hz), 9.0 (d, J = 35.5 Hz); ^{13}C NMR (100 MHz, THF-d_8) δ 140.3 (dd, J_{CC} = 42.0, 69.3 Hz), 114.0 (d, J_{CC} = 69.3 Hz), 33.2 (d, J_{CC} = 42.0 Hz) (data are provided only for ^{13}C labeled carbon atoms).

(dppf)Pd(C_6H_4-*p*-F){$^{13}CH_2$[$^{13}\overline{CH^{13}CH_2CH_2CH_2N}$($C_6H_4$-*p*-F)]} **(III-6a-$^{13}C_3$):** ^{19}F NMR (376 MHz, THF-d_8) δ –124.1 (m), –133.3 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 21.3 (dd, J_{PC} = 7.6 Hz, J_{PP} = 22.5 Hz); 16.6 (dd, J_{PP} = 22.5 Hz, J_{PC} = 91.5 Hz); ^{13}C NMR (100 MHz, THF-d_8) δ 62.0 (t, J_{CC} = 37.4 Hz), 34.8 (d, J_{CC} = 36.3 Hz), 30.0 (ddd, J_{CP} = 8.2, 91.1 Hz, J_{CC} = 38.1 Hz) (data are provided only for ^{13}C labeled carbon atoms).

(dppf)Pd(C_6H_4-*p*-F)[N(C_6H_4-*p*-CN)($CH_2CH_2CH_2CH=CH_2$)] (III-3b): ^{1}H NMR (400 MHz, THF-d_8) δ 7.87–7.78 (m), 7.64–7.35 (m), 7.21–7.13 (m), 6.99–6.90 (m), 6.80–6.70 (m), 6.22–6.12 (m), 5.64 (tdd, J = 6.8, 10.0, 16.8 Hz, 1 H), 5.57 (dd, J = 2.0, 8.8 Hz, 1 H), 4.89-4.85 (m, 2H), 4.49 (br, 3 H), 4.40 (s, 1 H), 4.38 (s, 1 H), 4.33 (s, 2 H), 4.21 (s, 1 H), 2.57–2.37 (m, 2 H), 1.76–1.62 (m, partially obscured by THF, ~2 H), 1.49–1.37 (m, 1 H), 1.07–0.94 (m, 1 H); ^{19}F NMR (376 MHz, THF-d_8) δ –122.7 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 23.4 (dd, J = 2.6, 30.5 Hz), 13.7 (dd, J = 2.6, 30.5 Hz).

(dppf)Pd(C_6H_4-*p*-F){CH_2[$\overline{CHCH_2CH_2CH_2N}$($C_6H_4$-*p*-CN)]} **(III-6b):** ^{19}F NMR (376 MHz, THF-d_8) δ –123.8 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 21.2 (d, J = 25.4 Hz), 17.2 (dd, J = 2.4, 24.1 Hz).

(dppf)Pd(C_6H_4-*p*-F)[N(C_6H_4-*p*-Cl)(*E*-$CH_2CH_2CH_2CH$=CHD)] (III-3c): ^{1}H NMR (400 MHz, THF-d_8) δ 7.90–7.71 (m), 7.58–7.38 (m), 7.36–7.09 (m, partially obscured), 7.09–6.95 (m), 6.67 (q, *J* = 7.4 Hz), 6.56–6.45 (m), 6.12 (t, *J* = 8.4 Hz), 5.63 (td, *J* = 6.6, 17.2 Hz, 1 H), 4.85 (d, *J* = 17.2 Hz, 1 H), 4.49 (s, 2 H), 4.46 (s, 1 H), 4.41 (s, 1 H), 4.39 (s, 1 H), 4.34 (s, 1 H) (remaining Cp protons obscured), 2.53–2.43 (m, 1 H), 2.26–2.13 (m, 1 H), 1.73–1.62 (m, partially obscured), 1.50–1.39 (m, 1 H), 1.18–1.05 (m, 1 H); ^{19}F NMR (376 MHz, THF-d_8) δ –123.4 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 24.3 (d, *J* = 35.3 Hz), 10.8 (d, *J* = 34.2 Hz).

(dppf)Pd(C_6H_4-*p*-F){CHD[$\overline{CHCH_2CH_2CH_2N}$($C_6H_4$-*p*-Cl)]} (III-6c): ^{19}F NMR (376 MHz, THF-d_8) δ –124.0 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 21.3 (d, *J* = 24.1 Hz), 16.8 (dd, *J* = 2.6, 23.0 Hz).

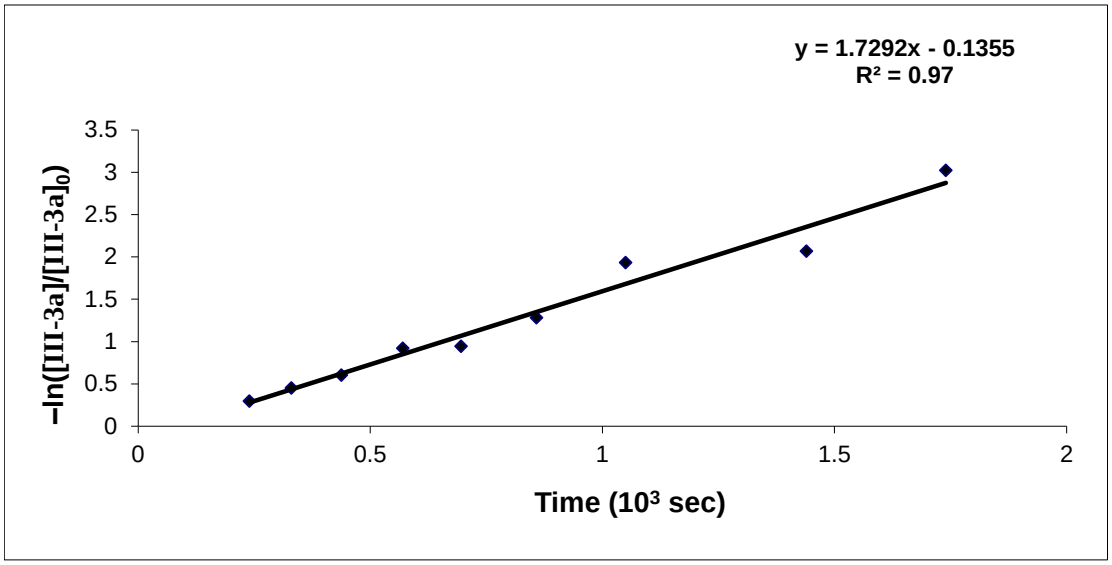
Representative Protocol for Measurements of Reaction Kinetics

In the glovebox, (dppf)Pd(C_6H_4-*p*-F)(Br) (**III-1**) (4.0 mg, 0.0048 mmol) and dppf (5.3 mg, 0.0096 mmol) were accurately weighed into a small vial and THF (660 μL) was added to give a homogeneous orange solution. The entire solution was transferred to a sealable screw-top NMR tube with Teflon septum and tightly sealed. Into a separate small vial, potassium (4-fluorophenyl)(pent-4-enyl)amide (**III-2a**) (3.5 mg, 0.015 mmol) was accurately weighed and 2 μL of 2-fluorotoluene (internal standard) was added. THF (300 μL) was added to dissolve and the vial was sealed tightly via screw-cap with Teflon septum. Both glass vessels were taken out of the glovebox and transported to the NMR

instrument where 100 μL (0.005 mmol) of the solution of **III-2a** was added to the contents of the sealed NMR tube via gastight microsyringe. Upon addition, the solution was inverted once to homogenize the color and then quickly placed in the NMR probe pre-adjusted to the appropriate temperature. Periodic monitoring by ^{19}F NMR spectroscopy of the disappearance of Pd-amido complex **III-3a**, intermediate **III-6a** and appearance of pyrrolidine product **III-4a** afforded kinetic data over approximately 3 half-lives. The NMR yield of the transformation was determined based on comparison of the ^{19}F NMR integrations to 2-fluorotoluene (internal standard).

The consumption of Pd-amido complex **III-3a** as it undergoes alkene insertion, is modeled by the first order kinetic equation given in Figure III.3.

Figure III.3 First Order Consumption of Pd-Amido Complex **III-3a** at 24 °C



Kinetic Model of Reaction System/Rate Constants

Kinetic data indicates the reaction system follows a consecutive irreversible reaction scheme as described by Swain.[100] As shown in Scheme 3, Pd-amido complex **III-3a** is transformed to **III-6a**, which then undergoes carbon-carbon bond-forming reductive elimination to afford pyrrolidine **III-4a** and $(dppf)_2Pd$.

For this reaction system, the consumption of **III-3a** obeys first-order kinetics and:

$$d[\textbf{III-3a}]/dt = -k_1[\textbf{III-3a}] \qquad (1)$$

Integrating gives:

$$[\textbf{III-3a}] = [\textbf{III-3a}]_0 e^{-k_1 t} \qquad (2)$$

From which the first-order relationship between [**III-3a**] and reaction time gives k_1 (Figure III.3). Additionally, because **III-6a** is both produced by **III-3a** and depleted in production of **III-4a**, [**III-6a**] is governed by the relationship:

$$d[\textbf{III-6a}]/dt = k_1[\textbf{III-3a}] - k_2[\textbf{III-4a}] \qquad (3)$$

Integrating gives the single transcendental equation:

$$[\textbf{III-6a}] = \{([\textbf{III-3a}]_0 k_1)/(k_2 - k_1)\}(e^{-k_1 t} - e^{-k_2 t}) \qquad (4)$$

Equation 4 cannot be solved exactly but can be accurately approximated via the mathematical treatment of Emanuel.[101] Thus after some manipulations:

$$\beta_{max} = \kappa^{[\kappa/(1-\kappa)]} \qquad (5)$$

where β_{max} = ([**III-6a**]$_{max}$/[**III-3a**]$_0$) and $\kappa = k_2/k_1$

The value of β_{max} can be calculated graphically directly from Figure III.2 and κ can be calculated iteratively so that equation 5 is satisfied. The value of k_2 is calculated from the product of κ and k_1.

Figure III.4 Eyring Plot for k_1 in the Conversion of **III-3b** to **III-6b** from 25–60 °C

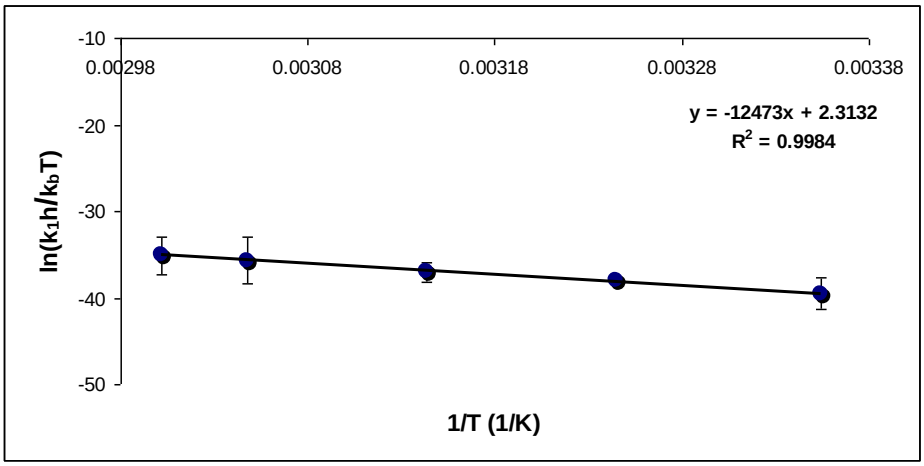


Figure III.5 Eyring Plot for k_2 in the Conversion of **III-6b** to **III-4b** from 25–60 °C

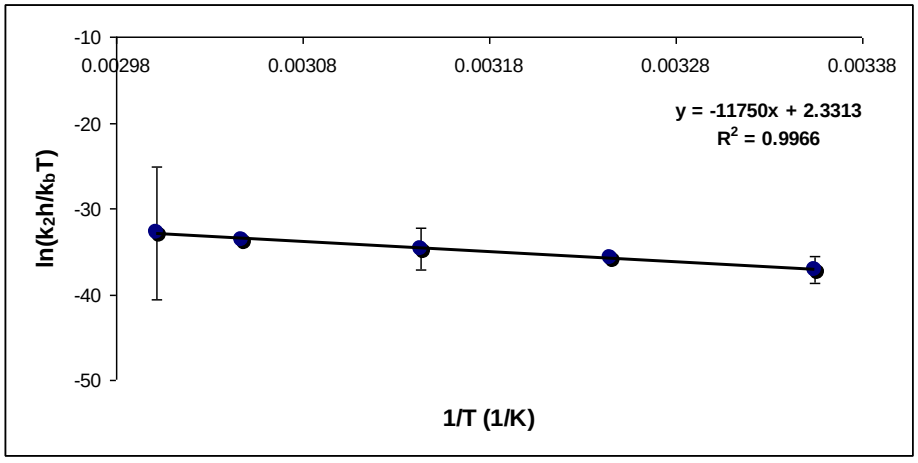


Table III.1 Average Rate Constant Data for Eyring Plots

Transformation	Temperature (K)	k_1 (sec^{-1})	k_2 (sec^{-1})
III-3a→III-6a→III-4a	297	$1.74 \pm 0.02 \times 10^{-3}$	$1.36 \pm 0.41 \times 10^{-3}$
III-3b→III-6b→III-4b	298	$4.16 \pm 0.19 \times 10^{-5}$	$4.78 \pm 0.20 \times 10^{-4}$
III-3b→III-6b→III-4b	308	$1.88 \pm 0.01 \times 10^{-4}$	$1.96 \pm 0.03 \times 10^{-4}$
III-3b→III-6b→III-4b	318	$5.71 \pm 0.17 \times 10^{-4}$	$6.05 \pm 0.43 \times 10^{-3}$
III-3b→III-6b→III-4b	328	$2.15 \pm 0.16 \times 10^{-3}$	$1.72 \pm 0.02 \times 10^{-2}$
III-3b→III-6b→III-4b	333	$3.98 \pm 0.24 \times 10^{-3}$	$3.85 \pm 0.91 \times 10^{-2}$

Description of Structural Assignment for III-6a

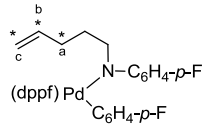
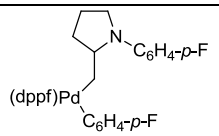
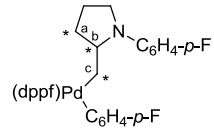
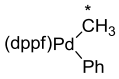
The structure of **III-6a** was assigned through comparison of ^{13}C chemical shifts of **III-6a-$^{13}C_3$** with pyrrolidine product **III-4a**, amido complex **III-3a-$^{13}C_3$**, and through comparison of ^{31}P NMR chemical shifts and P–C coupling constants with the known complex (dppf)Pd(Ph)($^{13}CH_3$).[87]

The assignment of the chemical shifts shown below to C_a, C_b, and C_c in pyrrolidine product **III-4a** was established through COSY and HSQC experiments. The signal attributed to C_a in **III-3a-$^{13}C_3$** was assigned on the basis of chemical shift (the only labeled carbon in the aliphatic region of the spectrum). Signals assigned to C_b and C_c appear in the alkene region of the ^{13}C NMR spectrum. The signal at δ 114.0 is coupled to only one other labeled carbon atom, whereas the signal at δ 140.3 is coupled to two labeled carbon atoms. This indicates that the signal at δ 140.3 corresponds to C_b (the internal alkene carbon), whereas the signal at δ 114.0 is attributed to C_c. The observation that the chemical shifts of the alkene carbon atoms in **III-3a-$^{13}C_3$** are nearly identical to those of the corresponding potassium arylamide **III-2a-$^{13}C_3$** and the parent aniline **III-S3**

is consistent with the assignment of **III-3a-$^{13}C_3$** as the four-coordinate, alkene unbound species illustrated below.

A listing of key NMR data is provided below in Table III.2 Analysis of this data is provided below.

Table III.2 Key Spectroscopic Data for the Reaction Mixture

Molecule	δC_a	δC_b	δC_c	δP_1	δP_2
 **III-3a-$^{13}C_3$**	33.2 (d J = 42.0 Hz)	140.3 (dd, J = 42.0, 69.3 Hz)	114.0 (d, J = 69.3 Hz)	24.9 (d, J = 38.1 Hz)	9.0 (d, J = 35.5 Hz)
 **III-4a**	30.0 (d, J = 35.6 Hz)	61.3 (app t, J = 35.2 Hz)	38.3 (d, J = 35.5 Hz)	–	–
Data for Intermediate **III-A**, which has been assigned the structure shown below  **III-6a-$^{13}C_3$**	34.8 (d, J = 36.0 Hz)	62.0 (app t, J = 37.1 Hz)	30.0 (ddd, J = 8.1, 38.2, 91.1 Hz)	21.3 (dd, J_{PP} = 23 Hz, J_{PC} = 8 Hz)	16.6 (dd, J_{PP} = 23 Hz, J_{PC} = 92 Hz)
	–	–	δCH_3 = 7.8	21.3 (dd, J_{PP} = 23 Hz, J_{PC} = 8 Hz)	17.8 (dd, J_{PP} = 23 Hz, J_{PC} = 92 Hz)

Several aspects of the data shown in row 3 for intermediate **III-A** are consistent with the illustrated structure **III-6a-$^{13}C_3$**, and are inconsistent with other reasonable possible alternative structures for intermediate **III-A**.

Evidence that Supports the Assignment of III-A as Structure III-6a

The chemical shift, splitting pattern, and coupling constant of C_b (62.0 ppm, app t, J = 37.1 Hz) is nearly identical to those of C_b in the pyrrolidine product **III-4a** (61.3 ppm, app t, J = 35.2 Hz).

The assignment of the peak at 62.0 ppm in the carbon spectrum of intermediate **III-A** as C_b is supported by the observation that C_b is an apparent triplet, indicating coupling to both C_a and C_c. In contrast, the signal for C_a is a doublet, indicating that C_a is coupled with only a single adjacent labeled carbon atom. The signal for C_c is a doublet of doublet of doublets (ddd), which results from coupling with a single additional labeled carbon and the two phosphorus atoms (noted below).

Carbon C_c is coupled to the phosphorus atoms of the dppf ligand, which is consistent with a C_c–Pd bond. In addition, the C_c–P^1 and C_c–P^2 coupling constants (8.1 Hz and 92 Hz, respectively) are identical to those reported for the known complex (dppf)Pd(Ph)($^{13}CH_3$) (8 Hz and 92 Hz).

Carbon C_c is shifted upfield in intermediate **III-A** (30.0 ppm) relative to C_c in the pyrrolidine product **III-4a** (38.3 ppm). This is also consistent with the presence of a C_c–Pd bond in intermediate **III-A**.

The chemical shifts of P^1 and P^2 in intermediate **III-A** (21.3 and 16.6 ppm) are very close to the chemical shifts of P^1 and P^2 in the (dppf)Pd(Ph)($^{13}CH_3$) complex (21.3 and 17.8 ppm).

Evidence that Rules out Assignment of III-A as Structure III-5a

The chemical shift of all three labeled carbon atoms present in intermediate **III-A** are upfield of 65 ppm, and are inconsistent with the presence of alkene functionality.

The chemical shift of P^2 in intermediate **III-A** (16.6 ppm) is significantly different from the chemical shift of P^2 in amido complex **III-3a**, suggesting that P^2 in intermediate **III-A** is not *trans* to an electronegative atom.

Evidence that Rules out Assignment of III-A as Structure III-7a

The chemical shift of C_b in intermediate **III-A** appears at 62 ppm, which is inconsistent with a metal-bound carbon atom that is not adjacent to a heteroatom. The chemical shift of C_b in **III-7a** should be well upfield of 62 ppm, as C_b in this structure is not adjacent to an electronegative heteroatom.

Carbon C_b in the spectrum of intermediate **III-A** does not show evidence for coupling with either of the phosphorous atoms. However, the C_b atom that would correspond to **III-7a** should show strong coupling to P^1 and P^2.

Carbon C_c in the spectrum of intermediate **III-A** shows characteristic two-bond P–C coupling. However, the C_c atom that would correspond to **III-7a** should not show significant P–C coupling.

The chemical shift of P^2 in intermediate **III-A** (16.6 ppm) is significantly different from the chemical shift of P^2 in amido complex **III-3a**, suggesting that P^2 in intermediate **III-A** is not *trans* to an electronegative atom.

Analysis of ^{13}C NMR Data for 6a-$^{13}C_3$

^{13}C NMR spectra were taken during the course of the conversion of **III-3a-$^{13}C_3$** to **III-4a-$^{13}C_3$** in the presence of 1.1 equiv of dppf. The observable species present in these spectra are: **III-3a-$^{13}C_3$, III-4a-$^{13}C_3$**, **III-6a-$^{13}C_3$**, dppf, and a small amount of free *N*-(*p*-fluorophenyl)pent-4-enylamine (bearing ^{13}C labeled allylic and alkenyl carbon atoms).

Two signals (one due to **III-6a-$^{13}C_3$**, and one due to **III-4a-$^{13}C_3$**) appear at ca. 30 ppm. There is a ddd centered at 30 ppm (J = 8.1, 38.2, 91.1 Hz) that is attributed to C_c in the labeled intermediate **III-6a-$^{13}C_3$**. In addition, a second signal is also centered at 30 ppm (d, J = 35.6 Hz) that is attributed to C_a in the labeled pyrrolidine product **III-4a-$^{13}C_3$**. The signal attributed to pyrrolidine was assigned on the basis of COSY and HSQC spectra from the isolated pyrrolidine **III-4a**. The signal attributed to **III-6a-$^{13}C_3$** was assigned on the basis of C–P coupling through the metal. The coupling constants of 8.1 and 91.1 Hz are very close to C–P coupling constants reported in the literature for (dppf)Pd(Ph)($^{13}CH_3$).

There are two signals (one due to **III-6a-$^{13}C_3$**, and one due to **III-4a-$^{13}C_3$**) that appear close to each other near 60 ppm. The signal centered at 61.3 ppm (app t) has been assigned as C_b (the carbon adjacent to the nitrogen atom) in the pyrrolidine product **III-4a-$^{13}C_3$**. This assignment was corroborated by HSQC NMR data for **III-4a**. A second signal is centered at 62.0 ppm (app t) and has been assigned as C_b (the carbon adjacent to the nitrogen atom) in intermediate **III-6a-$^{13}C_3$**. This assignment was made on the basis of chemical shift and the splitting pattern that indicates it is coupled to two other ^{13}C labeled atoms. Although these signals for C_b in both **III-4a-$^{13}C_3$** and **III-6a-$^{13}C_3$** should, in

principle, appear as dd, the coupling constants are sufficiently similar to give rise to the apparent triplets.

The third labeled carbon signal for **III-6a-$^{13}C_3$** appears at 34.8 ppm (d, J = 36.0 Hz). This signal has been assigned as C_a on the basis of chemical shift and its coupling to a single labeled carbon atom.

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CHAPTER IV

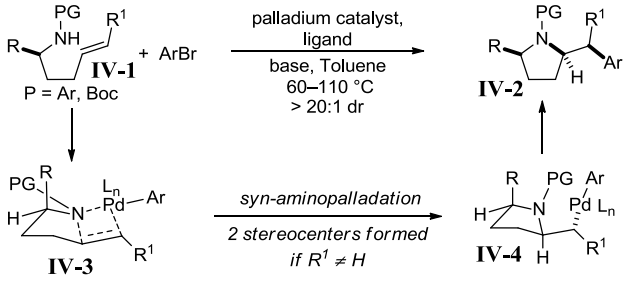
Intramolecular Insertion of Alkenes into Pd–N Bonds. Effects of Substrate and Ligand Structure on the Reactivity of (P–P)Pd(Ar)[N(Ar^1)(CH_2)$_3$CR=CHR'] Complexes

Studies on the synthesis and reactivity of a series of (P–P)Pd(Ar)[N(Ar^1)(CH_2)$_3$CR=CHR'] complexes **IV-3** are described. These complexes are transformed to observable (P–P)Pd(Ar)[pyrrolidin-2-ylmethyl] complexes **IV-4** via *syn*-insertion of the pendant alkene into the Pd–N bond. Complexes **IV-4** then undergo C–C bond-forming reductive elimination to yield *N*-aryl-2-benzylpyrrolidine derivatives **IV-2**. Kinetic studies indicate the rates of conversion of **IV-3** to **IV-4** and **IV-4** to **IV-2** are within one order of magnitude. The effects of phosphine ligand structure, alkene substitution, and the electronic properties of the Ar and Ar^1 groups on reaction rates are reported, as are the results of deuterium isotope effect studies. The mechanism of the aminopalladation step is discussed in detail, and the results of the experiments described in this paper are most consistent with conversion of **IV-3** to **IV-4** via rate-determining ligand displacement followed by fast aminopalladation. These transformations represent rare examples of *syn*-migratory insertion of unactivated alkenes into Pd–N bonds.

The *syn*-insertion of alkenes into Pd–N bonds has been implicated as a key step in many useful Pd-catalyzed reactions. For example, Pd-catalyzed alkene carboaminations between γ-aminoalkene derivatives **IV-1** and aryl bromides are believed to involve *syn*-aminopalladation of intermediate palladium(aryl)amido complexes (e.g., **IV-3**), followed

by reductive elimination of the resulting palladium(aryl)(pyrroldin-2-ylmethyl) complexes (e.g, **IV-4**) to yield substituted pyrrolidine products **IV-2** (Scheme IV.1).[102] The *syn*-aminopalladation step leads to formation of a C–N bond, and also leads to generation of two stereocenters, which are retained in the pyrrolidine products. This mechanistic pathway is also believed to occur in Pd-catalyzed diaminations,[103] oxidative aminations,[104] chloroaminations,[105] aminoacetoxylations,[106] and hetero-Heck transformations.[107,108]

Scheme IV.1 Pd-Catalyzed Alkene Carboamination



Despite the significance of *syn*-aminopalladation processes, and the influence of this pathway on the stereochemical outcome of synthetically useful reactions, documented unambiguous examples of *syn*-insertions of olefins into late transition metal-nitrogen bonds are very rare,[109] and cases involving palladium complexes have only recently been described by our group and Hartwig's group. As such, little is known about the effect of palladium amido complex structure on the facility of aminopalladation. However, information on the relationship between structural features and reactivity could potentially be used to improve the efficiency of catalytic processes, or to guide the design of new catalysts for use in challenging reactions or enantioselective transformations.

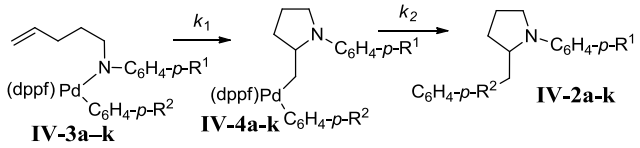
In this Chapter, detailed studies on the synthesis and reactivity of (P–P)Pd(Ar)[N(Ar^1)(CH_2)$_3$CR=CHR'] complexes **IV-3** are described.[110] These complexes undergo *syn*-migratory insertion of the alkene into the Pd–N bond to provide detectable (P–P)Pd(Ar)(pyrrolidin-2-ylmethyl) complexes **IV-4**, which undergo C–C bond forming reductive elimination to yield *N*-aryl-2-benzylpyrrolidine derivatives **IV-2**. The rates of aminopalladation of **IV-3** and reductive elimination of **IV-4** are influenced by several structural parameters, including the electronic properties of the Ar and Ar^1 groups, the degree of alkene substitution, and the nature of the bis-phosphine ligand. Our experiments suggest the alkene aminopalladation occurs from a four-coordinate complex, and illustrate that ligand electronic properties can be tuned to have a positive influence on the rates of both aminopalladation and reductive elimination.

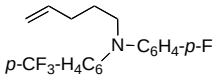
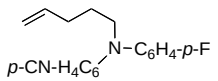
Following our initial experiments on the reactivity of complex **III-3a** (Chapter III), we sought to probe the effects of *N*-aryl group structure, Pd-aryl group structure, and ligand structure on the rate of the alkene aminopalladation process. To this end a series of (bis-phosphine)Pd(Ar)(Br) complexes were prepared using standard routes[111] and were treated with potassium salts of *N*-(aryl)-pent-4-enylamine derivatives in a manner analogous to that described above in Chapter III. In all cases the amido complexes (**IV-3a-k**) were generated in < 2 min at rt, and were characterized by diagnostic ^{31}P NMR signals with chemical shifts close to those observed for **III-3a**. Reactions were allowed to proceed at rt and kinetic data were collected by ^{19}F NMR spectroscopy. Rate constants for k_1 (conversion of **IV-3** to **IV-4**) and for k_2 (conversion of **IV-4** to **IV-2**) were then determined as in Chapter III and are provided in Table IV.1.

Hammett plots were constructed from the data shown in Table IV.1. Clear trends were observed in transformations of complexes **IV-3a**–**3f** bearing various *N*-aryl substituents, and linear plots of $\log(k_R/k_H)$ were obtained for both steps in the conversion of **IV-3a**–**f** to **IV-2a**–**f** (Figures IV.1 and IV.2). Best fits were obtained using the Hammett σ_p parameters which gave $\rho = -2.5 \pm 0.2$ for step 1 (**IV-3** to **IV-4)** and $\rho = -0.92 \pm 0.06$ for step 2 (**IV-4** to **IV-2**). The increased reactivity of complexes bearing electron-rich *N*-aryl groups is consistent with trends previously reported by Hartwig for alkene insertion reactions of cyclometalated [*t*-$Bu_2PCH_2C_6H_4$]Pd(NAr_2)complexes.[12]

A similar analysis of data obtained in reactions of *N*-(*p*-fluorophenyl)pentenylamine derived complexes **IV-3a** and **IV-3g**–**k** bearing various R^2 groups failed to provide clear trends. Hammett plots derived from this series of experiments were nonlinear (Figures IV.3 and IV.4), although all values of k_1 for this series were within a factor of 2.5 of each other, and all values of k_2 for this series were within a factor of 7 of each other. As such, although the precise effect of Pd-aryl substituent on reactivity is unclear, it appears to be relatively small. We were unable to obtain k_1 and k_2 values for reactions of complexes derived from electron-poor aryl bromides (R = CN, CF_3), as these complexes underwent rapid C–N bond-forming reductive elimination (full conversion was observed in < 1 min at rt) to yield *N*-(*p*-fluorophenyl)-*N*-(C_6H_4-*p*-R^2)-pent-4-enylamines, rather than the desired aminopalladation to afford **IV-4**.

Table IV.1 Effect of *N*-Aryl Group and Pd-Aryl Group on Reaction Rates



Starting Complex	Intermediate Complex	Product	R^1	R^2	k_1 ($10^{-3}s^{-1}$)	k_2 ($10^{-3}s^{-1}$)
IV-3b	**IV-4b**	**IV-2b**	*t*-Bu	F	5.59 ± 0.46	2.64 ± 0.45
IV-3c	**IV-4c**	**IV-2c**	OMe	F	4.45 ± 0.70	2.18 ± 0.38
IV-3d	**IV-4d**	**IV-2d**	H	F	2.44 ± 0.12	1.88 ± 0.07
IV-3a	**IV-4a**	**IV-2a**	F	F	1.74 ± 0.02	1.36 ± 0.41
IV-3e	**IV-4e**	**IV-2e**	Cl	F	0.56 ± 0.02	0.90 ± 0.02
IV-3f	**IV-4f**	**IV-2f**	CN	F	0.042 ± 0.006	0.42 ± 0.14
IV-3g	**IV-4g**	**IV-2g**	F	*t*-Bu	3.55 ± 0.08	4.08 ± 0.52
IV-3h	**IV-4h**	**IV-2h**	F	OMe	4.03 ± 1.15	2.64 ± 1.13
IV-3i	**IV-4i**	**IV-2i**	F	H	4.55 ± 0.49	9.00 ± 1.33
IV-3j	–		F	CF_3	–[a]	–[a]
IV-3k	–		F	CN	–[a]	–[a]

Conditions: All reactions were conducted in NMR tubes with [**IV-3**] = 6.26 mM, [dppf] = 12.6 mM, [2-fluorotoluene] = 11.8 mM (internal standard), THF, 24 °C. All values for k_1 and k_2 are the average obtained over duplicate runs. [a] C–N bond-forming reductive elimination from **IV-3** to provide the corresponding *N*-(C_6H_4-*p*-F)-*N*-(C_6H_4-*p*-R^2)-pent-4-enylamine was the predominant reaction pathway observed.

Figure IV.1 Hammett Correlation for the *N*-Aryl Group k_1

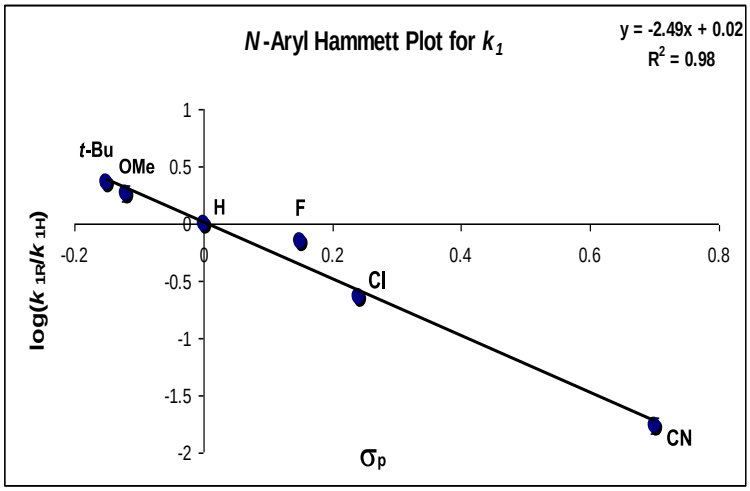


Figure IV.2 Hammett Correlation for the *N*-Aryl Group k_2

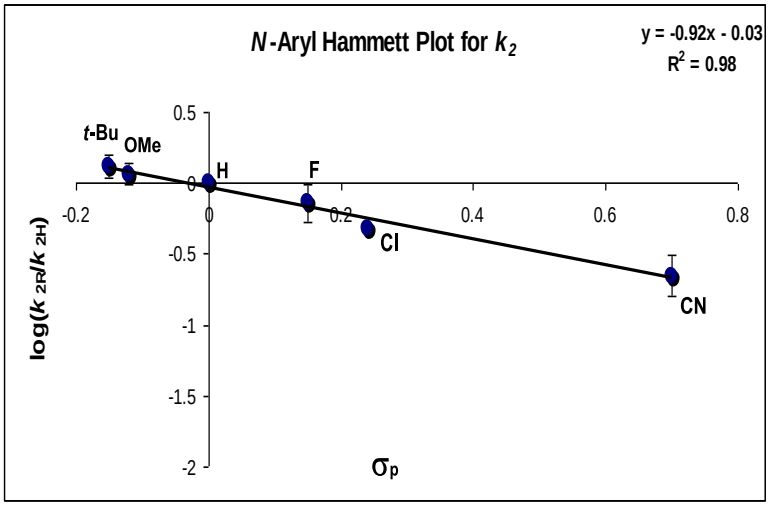


Figure IV.3 Hammett Correlation for the Pd-Aryl Group k_1

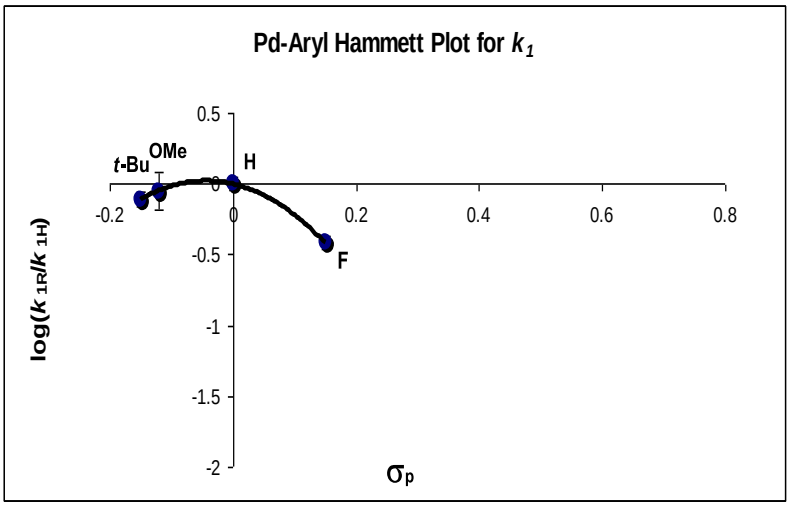
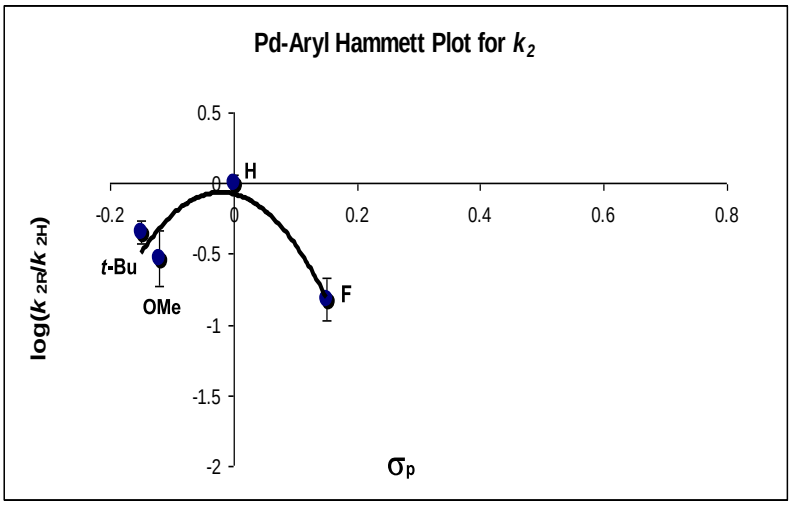


Figure IV.4 Hammett Correlation for the Pd-Aryl Group k_2



The steric and electronic properties of the bis-phosphine ligand also had a significant influence on reactivity in the conversion of **IV-3l-r** to **IV-2e**. As shown in Table IV.2, the fastest transformations were observed with wide bite angle ligands *N*-methyl-nixantphos[112] and xantphos. Amido complexes **IV-3q-r** bearing these ligands were rapidly converted to pyrrolidine **IV-2e** at rt with rates too fast to accurately measure; both reactions proceeded to completion in < 1 min. In contrast, complexes **IV-3l-o** bearing ligands with relatively small bite angles failed to undergo the desired transformation. Complexes **IV-3m** and **IV-3o** did not react at temperatures up to 60 °C, and complexes **IV-3l** and **IV-3n** decomposed to afford complex mixtures of products. The DPE-Phos complex **IV-3p** was transformed to **IV-2e** with an observed rate constant of 0.686×10^{-3} s^{-1}; no intermediate complex **IV-4** was detected during this reaction.

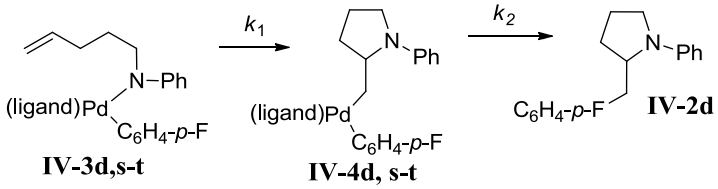
Table IV.2 Effect of Ligand Bite Angle on Reactivity

Starting Complex	Intermediate Complex	Ligand	Bite Angle (°)	Result
IV-3l	Not observed	dppe	86	Decomposition of Complex[a]
IV-3m	Not observed	dpp-Benzene	87	No Reaction[b]
IV-3n	Not observed	dppp	91	Decomposition of Complex[a]
IV-3o	Not observed	(*rac*)-BINAP	93	No Reaction[b]
IV-3e	**IV-4e**	dppf	99	$k_1 = 0.56 \pm 0.02 \times 10^{-3}$ s^{-1} $k_2 = 0.90 \pm 0.02 \times 10^{-3}$ s^{-1}
IV-3p	Not observed	DPE-Phos	104	$k_{obs} = 0.686 \times 10^{-3}$ s^{-1}[c]
IV-3q	Not observed	xantphos	108	Too fast to measure[d]
IV-3r	Not observed	nixantphos-Me	114	Too fast to measure[d]

Conditions: All reactions were conducted in NMR tubes with [**IV-3**] = 6.26 mM, [dppf] = 12.6 mM, [2-fluorotoluene] = 11.8 mM (internal standard), THF, 24 °C. All values for k_1 and k_2 are the average obtained over two or more runs. [a.] Decomposition to afford a complex mixture of products was observed. The expected pyrrolidine **IV-2e** was not detected in significant amounts. [b.] No reaction was observed at temperatures up to 60 °C. [c.] No intermediate was detected in this reaction. [d.] Complete conversion to **IV-2e** was observed within 1 min of mixing **IV-3q-r** and the potassium *N*-arylamide salt.

The effect of ligand electronic properties on reaction rates was examined through comparison of complexes bearing differently substituted dppf-derived ligands. As shown in Table IV.3, the presence of *para*-electron withdrawing trifluoromethyl groups on the P-Ar substituents in complex **IV-3s** led to acceleration of both steps of the transformation to **IV-2d** relative to the analogous reaction of parent dppf complex **IV-3d**. In contrast, decreased rates were observed for both steps in the conversion of complex **IV-3t** bearing *para*-electron donating methoxy groups to **IV-2d**.

Table IV.3 Ligand Electronic Effects



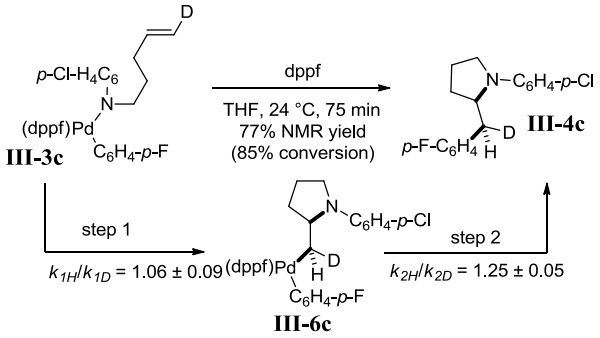
IV-3d,s-t **IV-4d, s-t** **IV-2d**

Starting Complex	Intermediate Complex	Ligand	k_1 ($10^{-3}s^{-1}$)	k_2 ($10^{-3}s^{-1}$)
IV-3s	**IV-4s**	dppf-*p*-CF_3	4.08 ± 0.03	14.6 ± 2.4
IV-3d	**IV-4d**	dppf	2.44 ± 0.12	1.88 ± 0.07
IV-3t	**IV-4t**	dppf-*p*-OMe	0.77 ± 0.01	0.59 ± 0.20

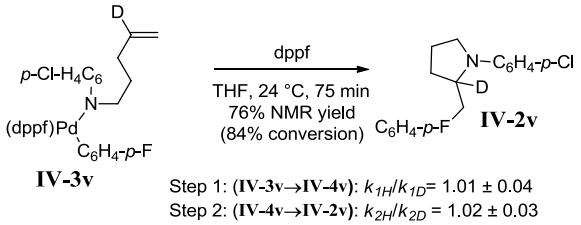
Conditions: All reactions were conducted in NMR tubes with [**IV-3**] = 6.26 mM, [dppf] = 12.6 mM, [2-fluorotoluene] = 11.8 mM (internal standard), THF, 24 °C. All values for k_1 and k_2 are the average obtained over two runs.

The stereochemistry of the aminopalladation reaction was determined through reaction of deuterated amido complex **III-3c**. As shown in Scheme IV.2, this complex was cleanly transformed to pyrrolidine **III-4c** with net *syn*-addition of the aryl group and the N-atom across the C–C double bond. This supports a mechanism involving *syn*-migratory insertion of the alkene into the Pd–N bond, rather than amide dissociation, alkene coordination, and outer-sphere attack of the pendant nucleophile. This result is also consistent with the stereochemical outcome of Pd-catalyzed carboamination reactions between γ–aminoalkene derivatives and aryl bromides.[24,102]

Scheme IV.2 Deuterium Isotope Effect at Terminal Alkene Position



Scheme IV.3 Absence of Deuterium Isotope Effect at Internal Alkene Position



Kinetic measurements were acquired for the two-step conversion of **III-3c** to **III-4c** (k_1 = 0.528 ± 0.041 × $10^{-3}s^{-1}$; k_2 = 0.701 ± 0.023 × $10^{-3}s^{-1}$) and were compared to values obtained for the analogous non-deuterated complex **IV-3e**. This comparison indicated no significant isotope effect for step 1 of the transformation (k_{1H}/k_{1D} = 1.06 ± 0.09), but an isotope effect was observed for the reductive elimination (step 2, k_{2H}/k_{2D} = 1.25 ± 0.05). Related experiments conducted with substrate **IV-3v**, which contains a deuterium atom at the internal alkene carbon, indicated no significant isotope effect for either step (Scheme IV.3).

In order to probe the effect of alkene substitution on reactivity, complexes **IV-3w-y** bearing 1,1- or 1,2-disubstituted alkenes were prepared in an analogous manner to the amido complexes described above. As shown in Table IV.4, complex **IV-3w**, which contains a substituent at the internal alkene carbon, undergoes aminopalladation to give

intermediate **IV-4w** at a rate that is 10-fold slower than for the analogous conversion of unsubstituted derivative **IV-3d** to **IV-4d**. However, the rate of reductive elimination from intermediate **IV-4w** to yield **IV-2w** is comparable to that for the transformation of **IV-4d** to **IV-2d**. Complexes **IV-3x** and **IV-3y** failed to undergo aminopalladation at temperatures up to 60 °C.

Table IV.4 Alkene Substituent Effects

Starting Complex	Intermediate Complex	Product	R	R^1	R^2	k_1 ($10^{-3}s^{-1}$)	k_2 ($10^{-3}s^{-1}$)
IV-3d	**IV-4d**	**IV-2d**	H	H	H	2.44 ± 0.12	1.88 ± 0.07
IV-3w	**IV-4w**	**IV-2w**	H	H	Me	0.25 ± 0.09	1.58 ± 0.16
IV-3x	Not obsd	–	Me	H	H	–[a]	–[a]
IV-3y	Not obsd	–	H	Me	H	–[a]	–[a]

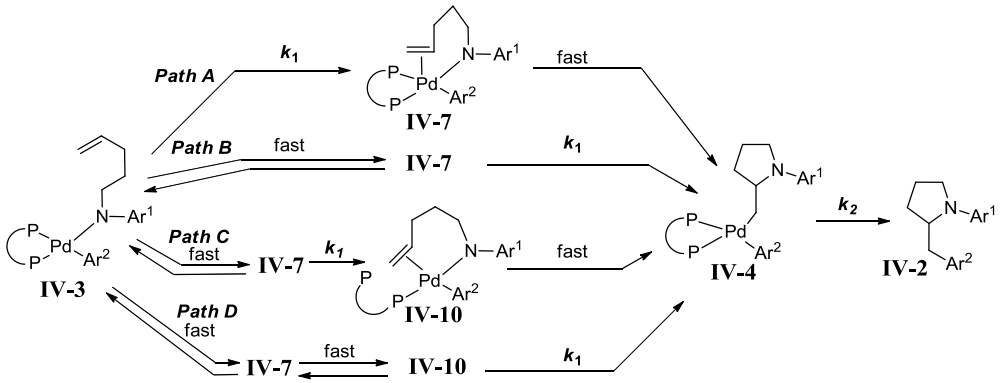
Conditions: All reactions were conducted in NMR tubes with [**IV-3**] = 6.26 mM, [dppf] = 12.6 mM, [2-fluorotoluene] = 11.8 mM (internal standard), THF, 24 °C. All values for k_1 and k_2 are the average obtained over two or more runs. [a] No reaction was observed up to 60 °C.

Plausible Mechanistic Scenarios for the Conversion of Amido Complexes IV-3 to Palladium(aryl)(pyrrolidin-2-ylmethyl) Complexes IV-4

The conversion of (P–P)Pd(Ar)[N(Ar^1)(CH_2)$_3$C(R)=C(R)(R') complexes **IV-3** to (P–P)Pd(Ar)(pyrrolidin-2-ylmethyl) complexes **IV-4** presumably does not occur via a single step, but instead likely involves: (a) intramolecular coordination of the alkene to palladium; and (b) *syn*-aminopalladation. As such, the conversion of **IV-3** to **IV-4** could potentially proceed through four different reasonable pathways (Scheme IV.4). Two scenarios would involve *syn*-aminopalladation from five-coordinate complex **IV-7**. The first would entail rate-limiting alkene coordination of **IV-3** to provide **IV-7**, which could then undergo rapid aminopalladation to afford **IV-4** (Path A). Alternatively, fast and

reversible intramolecular alkene coordination of **IV-3** would yield **IV-7**, which could undergo rate-limiting aminopalladation to **IV-4** (Path B).

Scheme IV.4 Possible Mechanistic Pathways for Conversion of **IV-3** to **IV-4**



Two other possibilities would involve ligand substitution of alkene for one arm of the chelating bis-phosphine ligand to give four-coordinate alkene complex **IV-10** (presumably via an associative mechanism; **IV-7** would be a transient intermediate *en route* to **IV-10**).[113] One of these pathways (Path C) would proceed via rate-limiting associative substitution of **IV-3** to give **IV-10**, followed by fast aminopalladation of **IV-10** to yield **IV-4**. Finally, fast and reversible associative ligand substitution of **IV-3** to **IV-10** followed by rate-limiting aminopalladation from **IV-10** to **IV-4** is also a reasonable possibility (Path D).

As shown in Scheme IV.4, Path B and Path D for the conversion of **IV-3** to **IV-4** both involve rapid formation of an alkene-bound complex (**IV-7** or **IV-10**) followed by rate-limiting aminopalladation (from either **IV-7** or **IV-10**). The fact that neither **IV-7** nor **IV-10** are detectable intermediates argues against Paths B and D, but cannot be used to rule out these pathways as it is possible the equilibrium between **IV-3** and **IV-7** or **IV-3** and **IV-10** is fast but lies far to the left favoring **IV-3**. In contrast, the results obtained in

reactions with deuterated substrates **III-3c** and **IV-3v** provide good evidence that neither Path B nor D are in operation.[114] The transformations of **IV-7** to **IV-4** and **IV-10** to **IV-4** both involve rehybridization of the alkene carbon atoms from sp^2 to sp^3. As such, if this step were rate limiting, a significant deuterium isotope effect should be observed at both alkene carbon atoms. However, the conversions of deuterated complexes **III-3c** and **IV-3v** to **III-4c** and **IV-4v** respectively proceed at the same rate as the transformation of all-protio complex **IV-3e** to **IV-4e**. Finally, the observed effect of ligand bite angle on reaction rate (Table IV.2) provides additional evidence against Path D, as the bite angle should not influence the rate of aminopalldation from **IV-10** to **IV-4** if the ligand is not bound to the metal by both phosphine groups in the rate determining step.[115]

Paths A and C both involve rate-limiting alkene coordination to the metal center, but differ in the nature of the intermediate complex that undergoes aminopalladation. In Path A, aminopalladation would occur directly from the five-coordinate intermediate **IV-7**, whereas Path C involves substitution of alkene for phosphine followed by insertion from four-coordinate complex **IV-10**. Several pieces of evidence indicate the mechanism of conversion of **IV-3** to **IV-4** does not proceed via Path A. First of all, the positive entropy values measured for the conversion of **IV-3f** to **IV-4f** suggest that Path A is not operating, as the conversion of **IV-3** to **IV-7** should have a fairly large negative entropy of activation due to the increase in organization in the transition state between complex **IV-3** with a single chelate (P–P) and **IV-7**, which contains two chelates (P–P and alkene–N). In contrast, the measured entropy of +4.6 eu is consistent with the conversion of **IV-3** to **IV-10** via intermediate **IV-7** (Path C), as mono-chelated complex **IV-10** is less ordered than doubly-chelated complex **IV-7**.

The effect of ligand and amine properties on reaction rate can also be used to differentiate between Paths A and C. If transformations proceed via Path C the reaction rate should be strongly influenced by factors that favor phosphine displacement.[116] In contrast, the rate of reactions that proceed by way of Path A should be insensitive to factors that favor ligand substitution, and instead should only be affected by parameters that influence initial alkene binding to the metal. The effect of phosphine ligand properties on reaction rate is most consistent with reaction via Path C. As illustrated in Scheme IV.3, complex **IV-3s**, which contains electron-withdrawing *p*-CF_3-C_6H_4 groups on the phosphines, reacts ca. five times faster than the related complex **IV-3t** that bears *p*-MeO-C_6H_4 phosphine substituents. The displacement of one arm of the electron-poor *p*-CF_3-dppf ligand should be more facile than for the relatively electron rich *p*-MeO-dppf ligand. In addition, although we were unable to obtain quantitative rate data for ligands with very large or very small bite angles, qualitatively it is clear that the transformation is facilitated by wide bite angle ligands and impeded by ligands with small bite angles. This effect is also consistent with rate-limiting associative ligand substitution (Path C).[117]

The reactions of complexes bearing electron-rich *N*-aryl groups are considerably faster than those bearing electron-poor *N*-aryl groups. For example, the conversion of complexes **IV-3b** and **IV-3c**, which contain electron-donating *p*-*t*-Bu and *p*-OMe groups on the *N*-aryl moiety, to **IV-4b** and **IV-4c** are two orders of magnitude faster than the conversion of **IV-3f** to **IV-4f** (*N*-aryl = *p*-CN-C_6H_4). This electronic effect also suggests the conversion of **IV-3** to **IV-4** proceeds via Path C rather than Path A. The electron-rich amido groups should increase the electron density of the metal center, which should in turn increase the ease of phosphine displacement. In contrast, if Path A were operating,

coordination of the relatively electron-rich alkene should be facilitated by a less electron-rich, more Lewis acidic metal center,[118,119] and rates should be faster with relatively electron-poor *N*-aryl groups.

No clear trend was observed for the influence of Pd-aryl group electronics on the rate of conversion of **IV-3** to **IV-4**. As such this data cannot be used to refute any of the possible mechanistic pathways. The origin of these electronic effects is unclear, but the differences in relative rates of aminopalladation for complexes **IV-3a**, and **IV-3g-i** are small (within a factor of ca. 2). However, our data do indicate that the rate of C–N bond-forming reductive elimination dramatically increases relative to the rate of aminopalladation in complexes **IV-3j-k**, which contain strong electron-withdrawing substituents on the Pd-Ar group.

Influence of Structural Features on Carbon–Carbon Bond-Forming Reductive Elimination of IV-4 to Afford IV-2

The rate of C–C bond-forming reductive elimination from (dppf)Pd(Ar)(pyrrolidin-2-ylmethyl) complexes **IV-4** is also affected by structural features of the complexes. For example, the electronic properties of the *N*-aryl group have a significant influence on this transformation, as complexes **IV-4** bearing electron-rich *N*-aryl groups undergo reductive elimination five times faster than electron-poor derivatives. In addition, the rate of reductive elimination of the (dppf)Pd(Ar)(pyrrolidin-2-ylmethyl) complexes **IV-4** is considerably slower than the analogous reaction of the (dppf)Pd(Ar)(alkyl) derivative (dppf)Pd(C_6H_4-*p*-F)[CH_2(cyclopentyl)] (**III-8**). These trends are likely due to inductive effects that slow the relative rate of reductive elimination as the electron-withdrawing power of the nitrogen atom increases in

derivatives of **IV-4**. The possibility that the rate of reductive elimination is slowed by binding of the nitrogen atom in **IV-4** to the metal center appears less likely given the fact that electron-poor *N*-aryl groups should disfavor *N*-coordination, but rates are slowest with these groups.

The effect of ligand electronic properties and bite angle on the rate of reductive elimination from **IV-4** to **IV-2** is also consistent with prior observations on rates of C–C bond formation from Pd(II) complexes.[120,121] In our system complex **IV-4s**, which bears a relatively electron-poor ligand, undergoes reductive elimination twenty-five times faster than the related complex **IV-4t**, which is ligated by a more electron-rich phosphine. This is likely due to the destabilizing effect of the electron-poor phosphine on the Pd(II) oxidation state.[120] The reductive elimination processes also appear to be most facile with wide-bite angle ligands, which both destabilize the ground state of (P–P)Pd(Ar)(R) complexes and also stabilize the transition state for C–C bond formation.[121] The observed deuterium isotope effect at the carbon undergoing bond-formation is consistent with rate-limiting C–C bond formation in the conversion of **IV-4** to **IV-2**, rather than rate limiting phosphine dissociation.

In conclusion, our experiments on the conversion of (P–P)Pd(Ar)[N(Ar^1)(CH_2)$_3$CR=CHR'] complexes **IV-3** to *N*-aryl-2-benzylpyrrolidine derivatives **IV-2** indicate that the transformations proceed via *syn*-insertion of the alkene into the Pd–N bond. This alkene *syn*-aminopalladation pathway has rarely been observed in well-characterized palladium complexes, but plays a key role in catalytic reactions. These studies illustrate that ligand structure and heteroatom basicity/nucleophilicity have a large impact on the rate of aminopalladation, and the observed trends could potentially

be used in the design of new catalysts for reactions involving aminopalladation. Finally, our data suggest that insertion occurs from a four-coordinate alkene complex, rather than a five-coordinate species. This mechanistic information provides insight into previously observed trends in asymmetric Pd-catalyzed alkene carboamination reactions. Use of chiral bis-phosphine ligands provides poor enantioselectivity in these transformations,[32] which is likely due to dissociation of one arm of the bis-phosphine ligand prior to aminopalladation.

Experimental

All reactions were carried out under a dry nitrogen atmosphere in flame-dried glassware using standard Schlenk techniques or in a nitrogen-filled glovebox. All reagents were obtained from commercial sources and used without further purification. Crude palladium dimers[122] and pure bisphosphine-ligated Pd-complexes[123] were prepared analogous to the methods of Buchwald. Toluene, THF, diethyl ether, and dichloromethane were purified using a GlassContour solvent purification system. THF used in kinetic experiments was stirred as a dark purple solution of sodium/benzophenone overnight under vacuum and then vacuum transferred before use. 2-fluorotoluene, 4-fluorotoluene, and pentane were distilled from CaH_2. CD_2Cl_2, acetic acid-d_4, and THF-d_8 were obtained from Cambridge Isotope Laboratories and used as received. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted. The yields reported in the experimental section describe the result of a single experiment, whereas all kinetic data has been averaged over

duplicate experiments. All kinetic experiments were set up in a glovebox under nitrogen atmosphere. All glassware and microsyringes associated with kinetics experiments were oven dried at 120 °C overnight before use. ^{31}P NMR shifts are given relative to an 85% H_3PO_4 external standard. ^{1}H NMR shifts for the experimental section are reported downfield of TMS in $CDCl_3$ or referenced to residual protia in THF-d_8. ^{19}F NMR shifts for the experimental section are referenced to residual protia in $CDCl_3$, or to an internal standard of 2-fluorotoluene (–117.2 ppm) or 4-fluorotoluene (–117.9 ppm) in THF-d_8.

Preparation and Characterization of Potassium Amide Substrates General Procedure 6: Conversion of *N*-aryl-pent-4-enamides to *N*-aryl-pent-4-enylamines.

A flame-dried flask equipped with a magnetic stirbar was charged with the appropriate *N*-aryl-pent-4-enamide (1.0 equiv) and purged with nitrogen for 5 min. THF (4 mL/mmol substrate) was added and the resulting solution was cooled to 0 °C. To this solution, a 1 M solution of $LiAlH_4$ in diethyl ether (1.2 equiv) was added slowly over 10 min. The reaction mixture was stirred at 0 °C for 15 min then warmed to rt and stirred overnight (ca. 16 h). The reaction mixture was cooled to 0 °C, then water (0.05 mL/mmol substrate), 6 M NaOH (0.05 mL/mmol substrate) and additional water (0.15 mL/mmol substrate) were sequentially added. The resulting white suspension was stirred vigorously for 30 min, then filtered through glass wool and the white precipitate was washed with diethyl ether (3 × 30 mL). The filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting product was purified by flash chromatography on silica gel.

General Procedure 7: Conversion of *N*-aryl-pent-4-enylamines to Potassium *N*-aryl-pent-4-enyl Amides. A flame-dried flask equipped with a magnetic stirbar was charged with the appropriate *N*-aryl-pent-4-enylamine (1.3 equiv) and purged with nitrogen for 5 min. In the glovebox, a separate flame-dried Schlenk flask equipped with a magnetic stirbar was charged with solid KHMDS (1.0 equiv), capped with a septum, removed from the glovebox, and connected to a vacuum/nitrogen manifold. Toluene (5 mL/mmol KHMDS) was added to each flask to afford clear solutions. Subsequently the amine solution was added dropwise to the KHMDS solution at rt to afford a bright yellow solution. The solution was stirred for 1.5 h at rt, over which time the solution became progressively more cloudy. The solvent was removed under high vacuum to afford a crude solid, which was taken into the glovebox under vacuum. The crude solid was purified on a medium glass frit via rinsing/trituration with pentane (4 × 10 mL) The resulting potassium *N*-aryl-pent-4-enyl amides were determined to contain ca. 0.1–2.7% KHMDS as judged by ^{1}H NMR analysis. This material was used without further purification.

Potassium (4-*tert*-butylphenyl)(pent-4-enyl)amide (IV-6b). The conversion of 4-pentenoic acid (2.0 mL, 19.6 mmol) and 4-*tert*-butylaniline (6.3 mL, 40 mmol) to *N*-(4-*tert*-butylphenyl)pent-4-enamide was accomplished using a procedure analogous to that employed above for the preparation of *N*-(4-fluorophenyl)pent-4-enamide. This procedure afforded 3.10 g (68%) of *N*-(4-*tert*-butylphenyl)pent-4-enamide as a fluffy white solid, m.p. 103–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.40 (m, 2 H), 7.35–7.28 (m, 3 H), 5.93–5.81 (m, 1 H), 5.12 (dd, *J* = 1.6, 16.8 Hz, 1 H), 5.04 (d, *J* = 10.4 Hz,

1 H), 2.52–2.40 (m, 4 H), 1.30 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 147.4, 137.1, 135.4, 126.0, 119.9, 116.1, 37.0, 34.6, 31.6, 29.7.

N-(4-*tert*-Butylphenyl)pent-4-enamide (1.50 g, 6.5 mmol) was reduced according to General Procedure 6 to afford 1.14 g (81%) of 4-*tert*-butyl-*N*-(pent-4-enyl)aniline (**IV-1b**) as a pale orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.16 (m, 2 H), 6.58–6.52 (m, 2 H), 5.90–5.77 (m, 1 H), 5.09–5.01 (m, 1 H), 5.01–4.96 (m, 1 H), 3.50 (s, br, 1 H), 3.10 (t, *J* = 7.2 Hz, 2 H), 2.20–2.11 (m, 2 H), 1.69 (quint, *J* = 7.2 Hz, 2 H), 1.27 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 140.0, 138.3, 126.1, 115.2, 112.6, 43.8, 34.0, 31.7, 31.5, 28.9; IR (film) 3411 cm^{-1}. MS (EI) 217.1832 (217.1830 calcd for $C_{15}H_{23}N$).

General Procedure 7 was used for the conversion of 4-*tert*-butyl-*N*-(pent-4-enyl)aniline (306 mg, 1.4 mmol) to 159 mg (59%) of the title compound as a yellow powder containing 0.3% KHMDS. ^{1}H NMR (400 MHz, THF-d_8) δ 6.82 (d, *J* = 9.2 Hz, 2 H), 6.04 (d, *J* = 9.2 Hz, 2 H), 6.02–5.90 (m, 1 H), 5.10–5.01 (m, 1 H), 4.95–4.88 (m, 1 H), 2.97–2.88 (m, 2 H), 2.25–2.16 (m, 2 H), 1.82–1.71 (m, 2 H), 1.18 (s, 9 H); ^{13}C NMR (100 MHz, THF-d_8) δ 159.8, 141.2, 130.1, 126.9, 113.9, 110.7, 52.1, 34.2, 34.0, 33.9, 32.7.

Potassium (4-methoxyphenyl)(pent-4-enyl)amide (IV-6c). The conversion of 4-pentenoic acid (2.0 mL, 19.6 mmol) and *p*-anisidine (4.93 g, 40 mmol) to *N*-(4-methoxyphenyl)pent-4-enamide was accomplished using a procedure analogous to that described above for the preparation of *N*-(4-fluorophenyl)pent-4-enamide. This procedure afforded 3.28 g (81%) of *N*-(4-methoxyphenyl)pent-4-enamide as a white solid, m.p. 91–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.36 (m, 2 H), 7.30 (s, br, 1 H), 6.90–6.81 (m,

2 H), 5.94–5.81 (m, 1 H), 5.12 (dd, *J* = 1.6, 16.8 Hz, 1 H), 5.05 (d, *J* = 10.4 Hz, 1 H), 3.78 (s, 3 H), 2.52–2.39 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 156.6, 137.1, 131.2, 122.0, 116.0, 114.3, 55.7, 36.8, 29.7.

N-(4-Methoxyphenyl)pent-4-enamide (1.50 g, 7.3 mmol) was reduced according to General Procedure 6 to afford 1.27 g (91%) of 4-methoxy-*N*-(pent-4-enyl)aniline (**IV-1c**) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81–6.74 (m, 2 H), 6.60–6.53 (m, 2 H), 5.90–5.76 (m, 1 H), 5.10–4.96 (m, 2 H), 3.73 (s, 3 H), 3.35 (s, br, 1 H), 3.07 (td, *J* = 7.2, 1.6 Hz, 2 H), 2.20–2.12 (m, 2 H), 1.69 (quintd, *J* = 1.6, 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 142.9, 138.3, 115.1, 115.0, 114.1, 55.9, 44.5, 31.5, 28.9; IR (film) 3393, 1236 cm^{-1}. MS (EI) 191.1305 (191.1310 calcd for $C_{12}H_{17}NO$).

General Procedure 7 was used for the conversion of 4-methoxy-*N*-(pent-4-enyl)aniline (304 mg, 1.6 mmol) to 118 mg (44%) of the title compound as a light green powder containing 0.4% KHMDS. ^{1}H NMR (400 MHz, THF-d_8) δ 6.48 (d, *J* = 7.6 Hz, 2 H), 6.02–5.90 (m, 3 H), 5.03 (dd, *J* = 1.6, 17.2 Hz, 1 H), 4.91 (d, *J* = 10.4 Hz, 1 H), 3.53 (s, 3 H), 2.90–2.81 (m, 2 H), 2.25–2.16 (m, 2 H), 1.82–1.70 (m, 2 H); ^{13}C NMR (100 MHz, THF-d_8) δ 158.2, 144.9, 141.2, 118.1, 113.9, 110.2, 57.7, 52.9, 34.21, 34.16.

Potassium pent-4-enyl(phenyl)amide (IV-6d). *N*-Phenylpent-4-enamide[4] (1.50 g, 8.6 mmol) was reduced according to General Procedure 6 to afford 1.20 g (86%) of *N*-(pent-4-enyl)aniline (**IV-1d**) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.11 (m, 2 H), 6.71–6.64 (m, 1 H), 6.62–6.54 (m, 2 H), 5.90–5.71 (m, 1 H), 5.09–4.95 (m, 2 H), 3.58 (s, br, 1 H), 3.10 (td, *J* = 1.6, 7.2 Hz, 2 H), 2.19–2.11 (m, 2 H), 1.69 (quintd, *J* = 1.6,

7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 138.2, 129.4, 117.3, 115.2, 112.9, 43.5, 31.4, 28.8; IR (film) 3411 cm^{-1}. MS (EI) 161.1201 (161.1204 calcd for $C_{11}H_{15}N$).

General Procedure 7 was used for the conversion of *N*-(pent-4-enyl)aniline (305 mg, 1.9 mmol) to 213 mg (72%) of the title compound as an off-white powder containing 0.1% KHMDS. ^{1}H NMR (400 MHz, THF-d_8) δ 6.76–6.68 (m, 2 H), 6.03 (d, *J* = 8.4 Hz, 2 H), 6.01–5.87 (m, 1 H), 5.67 (t, *J* = 6.8 Hz, 1 H), 5.03 (dd, *J* = 1.6, 17.2 Hz, 1 H), 4.94–4.87 (m, 1 H), 2.92–2.84 (m, 2 H), 2.20 (q, *J* = 7.2 Hz, 2 H), 1.75 (quint, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, THF-d_8) δ 161.6, 141.1, 130.3, 113.9, 111.4, 105.0, 51.8, 34.1, 33.9.

Potassium (4-chlorophenyl)(pent-4-enyl)amide (IV-6e). The conversion of 4-pentenoic acid (1.5 mL, 15.0 mmol) and 4-chloroaniline (4.78 g, 37.5 mmol) to *N*-(4-chlorophenyl)pent-4-enamide was accomplished using a procedure analogous to that described above for the preparation of *N*-(4-fluorophenyl)pent-4-enamide. This procedure afforded 1.78 g (58%) of *N*-(4-chlorophenyl)pent-4-enamide as a white solid, m.p. 86–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, br, 1 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 8.8 Hz, 2 H), 5.91–5.80 (m, 1 H), 5.11 (d, *J* = 16.4 Hz, 1 H), 5.05 (d, *J* = 10.4 Hz, 1 H), 2.51–2.41 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 136.9, 136.6, 129.4, 129.2, 121.4, 116.2, 36.9, 29.5.

N-(4-Chlorophenyl)pent-4-enamide (1.50 g, 7.2 mmol) was reduced according to General Procedure 6 to afford 1.28 g (91%) of 4-chloro-*N*-(pent-4-enyl)aniline (**IV-1e**) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12–7.06 (m, 2 H), 6.52–6.45 (m, 2 H),

5.88–5.75 (m, 1 H), 5.05 (d, J = 17.2 Hz, 1 H), 4.99 (d, J = 10.0 Hz, 1 H), 3.60 (s, br, 1 H), 3.06 (t, J = 7.2 Hz, 2 H), 2.14 (q, J = 7.2 Hz, 2 H), 1.67 (quint, J = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 138.0, 129.1, 121.7, 115.4, 113.9, 43.6, 31.4, 28.6; IR (film) 3417 cm^{-1}. MS (EI) 195.0820 (195.0815 calcd for $C_{11}H_{14}ClN$).

General Procedure 7 was used for the conversion of 4-chloro-*N*-(pent-4-enyl)aniline (392 mg, 2.0 mmol) to 240 mg (64%) of the title compound as a yellow-green powder containing 1.1% KHMDS. ^{1}H NMR (400 MHz, THF-d_8) δ 6.60 (d, J = 8.8 Hz, 2 H), 5.98–5.86 (m, 3 H), 5.02 (d, J = 17.6 Hz, 1 H), 4.90 (d, J = 10.0 Hz, 1 H), 2.87–2.78 (m, 2 H), 2.23–2.13 (m, 2 H), 1.77–1.66 (m, 2 H); ^{13}C NMR (100 MHz, THF-d_8) δ 160.5, 141.0, 129.6, 114.0, 111.8 (br), 107.7, 52.2, 34.0, 33.8.

Potassium (4-chlorophenyl)(4-deuteriopent-4-enyl)amide (IV-6v). A flame-dried flask equipped with magnetic stirbar was charged with $Cp_2Zr(D)Cl$ (501 mg, 1.9 mmol) and purged with nitrogen for 5 min. CH_2Cl_2 (6 mL) was added to afford a white suspension. Subsequently a solution of pent-4-ynyl-4-methylbenzenesulfonate (454 mg, 1.9 mmol) in CH_2Cl_2 (2 mL) was added and the suspension clarified instantly. The resulting solution was stirred for 20 min at rt and then cooled to 0 °C. The chilled solution was treated with 1 M aqueous HCl (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The drying agent was filtered off through glass wool and the filtrate was concentrated *in vacuo*. Purification by flash chromatography afforded 328 mg (71%) of 4-deuteriopent-4-enyl 4-methylbenzenesulfonate as a colorless oil with >95% deuterium incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2 H), 7.35 (d, J = 7.5

Hz, 2 H), 4.96–4.93 (m, 2 H), 4.04 (t, J = 6.5 Hz, 2 H), 2.45 (s, 3 H), 2.08 (t, J = 7.0 Hz, 2 H), 1.74 (quint, J = 7.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 136.5 (t, $J_{C\text{-}D}$ = 24.1 Hz), 133.4, 130.0, 128.1, 115.9, 70.0, 29.5, 28.2, 21.9; MS (ESI) 242.0951 (242.0961 calcd for $C_{12}H_{15}DO_3S + H^+$).

The alkylation of 4-chloroaniline (327 mg, 2.6 mmol) with 4-deuteriopent-4-enyl 4-methylbenzenesulfonate (298 mg, 1.2 mmol) was accomplished using a procedure analogous to that described above for the preparation of (*E*)-4-chloro-*N*-(5-deuteriopent-4-enyl)aniline. This procedure afforded 211 mg (87%) of 4-chloro-*N*-(4-deuteriopent-4-enyl)aniline (**IV-1v**) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.08 (m, 2 H), 6.54–6.48 (m, 2 H), 5.07–5.03 (m, 1 H), 5.02–4.98 (m, 1 H), 3.63 (s, br, 1 H), 3.10 (t, J = 6.8 Hz, 2 H), 2.16 (t, J = 7.2 Hz, 2 H), 1.70 (quint, J = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 137.8 (t, $J_{C\text{-}D}$ = 23.1 Hz), 129.2, 121.9, 115.3, 113.9, 43.7, 31.3, 28.7; IR (film) 3416 cm^{-1}. MS (EI) 196.0886 (196.0878 calcd for $C_{11}H_{13}DClN$).

General Procedure 7 was used for the conversion of 4-chloro-*N*-(4-deuteriopent-4-enyl)aniline (177 mg, 0.9 mmol) to 77 mg (47%) of the title compound as a yellow-green powder containing 1.6% KHMDS. ^{1}H NMR (400 MHz, THF-d_8) δ 6.61 (d, J = 8.8 Hz, 2 H), 5.95 (d, J = 9.2 Hz, 2 H), 5.01 (s, 1 H), 4.90 (s, 1 H), 2.87–2.78 (m, 2 H), 2.17 (t, J = 7.2 Hz, 2 H), 1.71 (quint, J = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, THF-d_8) δ 160.1, 140.6 (t, $J_{C\text{-}D}$ = 23.1 Hz), 129.6, 113.9, 111.9 (br), 108.2, 52.0, 33.9, 33.6.

Potassium (4-methylpent-4-enyl)(phenyl)amide (IV-6w). A flame-dried flask equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with aniline

(1.1 g, 11.8 mmol) and THF (10 mL). A solution of MeMgBr in diethyl ether (3.9 mL, 11.7 mmol, 3.0 M) was added slowly at rt. The resulting mixture was stirred at rt for 30 min, then a solution of ethyl 4-methylpent-4-enoate (1.5 g, 10.6 mmol) in THF (5 mL) was added slowly. The resulting solution was stirred at rt for 3 h upon which time H_2O (30 mL) and EtOAc (25 mL) were added. The layers were separated, the aqueous layer was extracted with EtOAc (1 × 50 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. The drying agent was filtered off through glass wool and the filtrate was concentrated *in vacuo.* Purification by flash chromatography afforded 908 mg (46%) of 4-methyl-*N*-phenylpent-4-enamide as a as a white solid, m.p. 82–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 2 H), 7.44 (s, br, 1 H), 7.30 (t, *J* = 8.0 Hz, 2 H), 7.09 (t, *J* = 7.2 Hz, 1 H), 4.80 (s, 1 H), 4.76 (s, 1 H), 2.55–2.40 (m, 4 H), 1.77 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 144.6, 138.1, 129.2, 124.4, 120.1, 111.0, 36.0, 33.3, 22.7.

4-Methyl-*N*-phenylpent-4-enamide (735 mg, 3.9 mmol) was reduced according to General Procedure 6 to afford 548 mg (81%) of *N*-(4-methylpent-4-enyl)aniline (**IV-1w**) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.12 (m, 2 H), 6.71–6.65 (m, 1 H), 6.61–6.55 (m, 2 H), 4.75 (s, 1 H), 4.72 (s, 1 H), 3.57 (s, br, 1 H), 3.09 (t, *J* = 7.6 Hz, 2 H), 2.10 (t, *J* = 7.6 Hz, 2 H), 1.78–1.65 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 145.3, 129.4, 117.2, 112.8 110.5, 43.7, 35.4, 27.5, 22.5; IR (film) 3411 cm^{-1}. MS (EI) 175.1360 (175.1361 calcd for $C_{12}H_{17}N$).

General Procedure 7 was used for the conversion of *N*-(4-methylpent-4-enyl)aniline (299 mg, 1.7 mmol) to 189 mg (65%) of the title compound as an off-white

powder containing 1.7% KHMDS. ^{1}H NMR (400 MHz, THF-d_8) δ 6.75–6.67 (m, 2 H), 6.02 (d, J = 8.0 Hz, 2 H), 5.65 (t, J = 6.8 Hz, 1 H), 4.75 (s, 1 H), 4.68 (s, 1 H), 2.90–2.82 (m, 2 H), 2.20–2.12 (m, 2 H), 1.86–1.76 (m, 5 H); ^{13}C NMR (100 MHz, THF-d_8) δ 162.1, 147.9, 130.3, 111.4 (br), 109.7, 104.5, 52.5, 38.0, 32.9, 23.2.

Potassium (*Z*)-hex-4-enyl(phenyl)amide (IV-6x). A flame-dried flask equipped with magnetic stirbar was charged with (*Z*)-*tert*-butyl hex-4-enylcarbamate (702 mg, 3.5 mmol), $Pd(OAc)_2$ (25 mg, 0.1 mmol), X-Phos (105 mg, 0.2 mmol), Cs_2CO_3 (2.56 g, 7.9 mmol), and bromobenzene (1.1 mL, 10.4 mmol) and purged with nitrogen for 5 min. Toluene (15 mL) was added and the resulting mixture was heated to 100 °C for 15 h . The mixture was cooled to rt and saturated aqueous NH_4Cl (10 mL) and EtOAc (10 mL) were added. The layers were separated, the aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. The drying agent was filtered off through glass wool and the filtrate was concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (5 mL) and trifluoroacetic acid (1 mL). The solution was stirred at rt for 2 h upon which time the solution was cooled to 0 °C and quenched with saturated aqueous Na_2CO_3 (15 mL). Water (10 mL) and CH_2Cl_2 (10 mL) were added, the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The drying agent was filtered off through glass wool and the filtrate was concentrated *in vacuo* to afford a crude oil, which was purified by flash chromatography to give 174 mg (28%) of (*Z*)-*N*-(hex-4-enyl)aniline (**IV-1x**) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.12 (m, 2 H), 6.72–6.65 (m, 1 H), 6.63–6.57 (m, 2 H), 5.55–5.35 (m, 2 H), 3.60 (s, br, 1

H), 3.12 (t, *J* = 6.8 Hz, 2 H), 2.16 (q, *J* = 7.2 Hz, 2 H), 1.68 (quint, *J* = 6.8 Hz, 2 H), 1.64–1.60 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 129.9, 129.4, 124.9, 117.3 112.9, 43.7, 29.5, 24.6, 13.0; IR (film) 3410 cm^{-1}. MS (EI) 175.1360 (175.1361 calcd for $C_{12}H_{17}N$).

General Procedure 7 was used for the conversion of (*Z*)-*N*-(hex-4-enyl)aniline (128 mg, 0.7 mmol) to 32 mg (26%) of the title compound as a tan powder containing 2.7% KHMDS. ^{1}H NMR (400 MHz, THF-d_8) δ 6.77–6.66 (m, 2 H), 6.09–6.00 (m, 2 H), 5.74–5.64 (m, 1 H), 5.57–5.45 (m, 1 H), 5.45–5.34 (m, 1 H), 2.94–2.81 (m, 2 H), 2.25–2.10 (m, 2 H), 1.80–1.60 (m, 5 H); ^{13}C NMR (100 MHz, THF-d_8) δ 161.3, 132.7, 130.2, 123.5, 111.4 (br), 105.2, 51.8, 34.4, 26.9, 13.1.

Potassium (*E*)-hex-4-enyl(phenyl)amide (IV-6y). A flame-dried flask equipped with magnetic stirbar was charged with 3-butene-2-ol (3.6 mL, 42 mmol), triethyl orthoacetate (15.2 mL, 84 mmol), and neat acetic acid (200 μL, 2.5 mmol). The flask was attached to a short-path distillation head, the system purged with nitrogen, and the mixture heated with stirring at 90 ºC for 45 min. The heat was gradually increased to 120 ºC over 75 min and the reaction was allowed to proceed for 14 h under those conditions before being cooled to rt. To the reaction flask was added 1M HCl (40 mL) and Et_2O (40 mL), and the resulting mixture was stirred vigorously for 1 h. The layers were separated and the aqueous layer extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography of the crude oil afforded 4.2 g (72%) of (*E*)-ethyl hex-4-enoate

which contained traces of chromatography solvent which was difficult to remove due to product volatility. This material was used without further purification.

A flame dried flask equipped with a magnetic stir bar was charged with aniline (3.3 mL, 35 mmol) sealed with a septum and purged with nitrogen. THF (30 mL) was added and the solution cooled to 0 ºC, then a solution of MeMgBr (3.0 M in Et_2O, 11 mL, 33 mmol) was added slowly via syringe. The ice bath was removed and a solution of crude (*E*)-ethyl hex-4-enoate (4.2 g, 30 mmol) in THF was added dropwise. The resulting solution was stirred 5 h at rt, quenched with water (30 mL), diluted with EtOAc (30 mL) and the layers separated. The aqueous layer was extracted with EtOAc (3 × 50 mL), the combined organic layers washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography of the crude oil afforded (*E*)-*N*-(phenyl)-hex-4-enamide containing residual aniline, which was carried on without further purification.

The crude (*E*)-*N*-(phenyl)-hex-4-enamide was reduced according to General Procedure 6 to afford 1.28 g (91%) of (*E*)-*N*-(hex-4-enyl)aniline (**IV-1y**) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19–7.13 (m, 2 H), 6.71–6.66 (m, 1 H), 6.62–6.57 (m, 2 H), 5.52–5.40 (m, 2 H), 3.61 (s, br, 1 H), 3.11 (t, J = 7.0 Hz, 2 H), 2.14–2.06 (m, 2 H), 1.71–1.64 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 130.5, 129.2, 125.6, 117.1, 112.7, 43.5, 30.1, 29.3, 17.9; IR (film) 2930, 1603, 1508 cm^{-1}. MS (EI) 175.1361 (175.1361 calcd for $C_{12}H_{17}N$).

General Procedure 7 was used for the conversion of (*E*)-*N*-(hex-4-enyl)aniline (500 mg, 2.85 mmol) to 380 mg (78%) of the title compound as a yellow powder containing 2.0% KHMDS. ^{1}H NMR (500 MHz, THF-d_8) δ 6.71–6.68 (m, 2 H), 6.00 (d, *J* = 8.0 Hz, 2 H), 5.64 (t, *J* = 7.0 Hz, 1 H), 5.91–5.53 (m, 1 H), 5.48–5.41 (m, 1 H), 2.85–2.82 (m, 2 H), 2.12 (q, br, *J* = 7.0 Hz, 2 H), 1.73–1.67 (m, 2 H), 1.64 (dd, *J* = 1.0, 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, THF-d_8) δ 162.2, 133.7, 130.3, 123.3, 111.3, 104.3, 52.2, 34.7, 23.9, 18.4.

Synthesis of Authentic Samples of Pyrrolidine Products formed in Kinetic Runs

General Procedure 8: Pd-Catalyzed Carboamination of γ-(*N*-arylamino)alkenes with Aryl Bromides. An oven or flame-dried Schlenk tube was cooled under a stream of argon or nitrogen and charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), dppf (2 mol %), NaO*t*-Bu (1.0 equiv), and the ArBr (1.5 equiv). The tube was purged with argon or nitrogen and a solution of the amine substrate (1.0 equiv) in toluene (4 mL/mmol aryl bromide) was added. The mixture was heated to 60–110 °C with stirring until the starting material had been consumed as judged by GC or ^{1}H NMR analysis. The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (2 mL) and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

1-(4-*tert*-Butylphenyl)-2-(4-fluorobenzyl)pyrrolidine (IV-2b). General Procedure 8 was used for the coupling of 4-*tert*-butyl-*N*-(pent-4-enyl)aniline (52 mg, 0.24 mmol) with 1-bromo-4-fluorobenzene (38 μL, 0.35 mmol) to afford 48 mg (65%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 2 H), 7.23–7.14 (m, 2 H), 7.03–6.94 (m, 2 H), 6.71–6.62 (m, 2 H), 3.98–3.82 (m, 1 H), 3.48–3.36 (m, 1 H), 3.24–3.10 (m, 1 H), 3.00 (dd, *J* = 2.8, 13.6 Hz, 1 H), 2.56 (dd, *J* = 9.2, 13.6 Hz, 1 H), 1.95–1.76 (m, 4 H), 1.31 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5 (d, *J* = 243 Hz), 144.8, 138.2, 135.2, 130.7 (d, *J* = 7.6 Hz), 126.1, 115.1 (d, *J* = 21.0 Hz), 111.4, 59.9, 48.6, 38.1, 33.7, 31.6, 29.5, 23.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –117.2; IR (film) 1222 cm^{-1}. MS (ESI) 312.2137 (312.2128 calcd for $C_{21}H_{26}FN$, M + H^+).

1-(4-Methoxyphenyl)-2-(4-fluorobenzyl)pyrrolidine (IV-2c). General Procedure 8 was used for the coupling of 4-methoxy-*N*-(pent-4-enyl)aniline (50 mg, 0.26 mmol) with 1-bromo-4-fluorobenzene (43 μL, 0.39 mmol) to afford 32 mg (43%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.13 (m, 2 H), 7.02–6.94 (m, 2 H), 6.92–6.86 (m, 2H), 6.66–6.60 (m, 2 H), 3.90–3.83 (m, 1 H), 3.77 (s, 3 H), 3.42–3.34 (m, 1 H), 3.17–3.07 (m, 1 H), 2.97 (dd, *J* = 3.0, 13.8 Hz, 1 H), 2.58 (dd, *J* = 9.0, 13.8 Hz, 1 H), 1.94–1.74 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5 (d, *J* = 244 Hz), 150.7, 141.9, 135.1 (d, *J* = 3.5 Hz), 130.7 (d, *J* = 7.6 Hz), 115.2, 115.1 (d, *J* = 20.7 Hz), 112.6, 60.0, 56.0, 49.1, 38.0, 29.6, 23.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –117.3; IR (film) 1241 cm^{-1}. MS (ESI) 286.1610 (286.1607 calcd for $C_{18}H_{20}FN$, M + H^+).

1-(Phenyl)-2-(4-fluorobenzyl)pyrrolidine (IV-2d). General Procedure 8 was used for the coupling of *N*-(pent-4-enyl)aniline (50 mg, 0.31 mmol) with 1-bromo-4-fluorobenzene (51 μL, 0.46 mmol) to afford 58 mg (74%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.19 (m, 2 H), 7.1–7.10 (m, 2 H), 6.99–6.91 (m, 2 H), 6.69–6.61 (m, 2 H), 3.96–3.85 (m, 1 H), 3.41–3.32 (m, 1 H), 3.19–3.07 (m, 1 H), 2.99 (dd, *J* = 3.4, 13.8 Hz, 1 H), 2.59 (dd, *J* = 9.2, 13.6 Hz, 1 H), 1.92–1.70 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5 (d, *J* = 244 Hz), 146.9, 135.0 (d, *J* = 3.0 Hz), 130.7 (d, *J* = 8.0 Hz), 129.3, 115.6, 115.1 (d, *J* = 21.0 Hz), 111.8, 59.6, 48.4, 37.7, 29.4, 23.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –117.1; IR (film) 1221 cm^{-1}. MS (ESI) 256.1508 (256.1502 calcd for $C_{17}H_{18}FN$, M + H^+).

1-(4-Chlorophenyl)-2-(4-fluorobenzyl)pyrrolidine (IV-2e). General Procedure 8 was used for the coupling of 4-chloro-*N*-(pent-4-enyl)aniline (32 mg, 0.16 mmol), with 1-bromo-4-fluorobenzene (25 μL, 0.23 mmol) to afford 33 mg (69%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.10 (m, 4 H), 7.02–6.94 (m, 2 H), 6.59–6.52 (m, 2 H), 3.96–3.86 (m, 1 H), 3.38–3.31 (m, 1 H), 3.18–3.08 (m, 1 H), 2.92 (dd, *J* = 2.8, 14.0 Hz, 1 H), 2.59 (dd, *J* = 8.8, 14.0 Hz, 1 H), 1.95–1.70 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, *J* = 244 Hz), 145.7, 134.9 (d, *J* = 3.8 Hz), 130.9 (d, *J* = 7.7 Hz), 129.3, 120.6, 115.4 (d, *J* = 21.4 Hz), 113.1, 60.0, 48.8, 37.8, 29.8, 23.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –117.0 (m); IR (film) 1222 cm^{-1}. MS (ESI) 290.1107 (290.1112 calcd for $C_{17}H_{17}ClFN$ + H^+).

1-(4-Fluorophenyl)-2-(4-*tert*-butylbenzyl)pyrrolidine (IV-2g). General Procedure 8 was used for the coupling of 4-fluoro-*N*-(pent-4-enyl)aniline (52 mg, 0.29 mmol) with 4-*tert*-butyl-bromobenzene (75 μL, 0.43 mmol) to afford 59 mg (65%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 2 H), 7.18–7.13 (m, 2 H), 7.01–6.93 (m, 2 H), 6.62–6.54 (m, 2 H), 3.93–3.84 (m, 1 H), 3.44–3.37 (m, 1 H), 3.13 (q, *J* = 8.2 Hz, 1 H), 2.99 (dd, *J* = 3.2, 13.6 Hz, 1 H), 2.49 (dd, *J* = 9.4, 13.8 Hz, 1 H), 1.99–1.80 (m, 4 H), 1.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7 (d, *J* = 232 Hz), 149.0, 143.7, 136.3, 128.9, 125.3, 115.6 (d, *J* = 22.2 Hz), 112.1 (d, *J* = 6.8 Hz), 60.2, 48.8, 38.1, 34.4, 31.4, 29.7, 23.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –131.0 (m); IR (film) 1227 cm^{-1}. MS (ESI) 312.2124 (312.2128 calcd for $C_{21}H_{26}FN$, M + H^+).

1-(4-Fluorophenyl)-2-(4-methoxybenzyl)pyrrolidine (IV-2h). General Procedure 8 was used for the coupling of 4-fluoro-*N*-(pent-4-enyl)aniline (49 mg, 0.27 mmol) with 4-bromoanisole (50 μL, 0.40 mmol) to afford 64 mg (82%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.10 (m, 2 H), 7.01–6.93 (m, 2 H), 6.88–6.82 (m, 2 H), 6.61–6.53 (m, 2 H), 3.90–3.83 (m, 1 H), 3.80 (s, 3 H), 3.41–3.32 (m, 1 H), 3.16–3.07 (m, 1 H), 2.93 (dd, *J* = 3.2, 13.6 Hz, 1 H), 2.52 (dd, *J* = 9.2, 13.6 Hz, 1 H), 1.95–1.80 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 154.7 (d, *J* = 232 Hz), 143.7, 131.3, 130.2, 115.6 (d, *J* = 21.8 Hz), 113.8, 112.2 (d, *J* = 7.2 Hz), 60.2, 55.2, 48.9, 37.7, 29.6, 23.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –130.9; IR (film) 1247, 1226 cm^{-1}. MS (ESI) 286.1614 (286.1607 calcd for $C_{18}H_{20}FN$, M + H^+).

1-(4-Fluorophenyl)-2-benzylpyrrolidine (IV-2i). General Procedure 8 was used for the coupling of 4-fluoro-*N*-(pent-4-enyl)aniline (48 mg, 0.27 mmol) with bromobenzene (43 μL, 0.41 mmol) to afford 55 mg (81%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 2 H), 7.26–7.18 (m, 3 H), 7.03–6.94 (m, 2 H), 6.62–6.55 (m, 2 H), 3.95–3.85 (m, 1 H), 3.43–3.35 (m, 1 H), 3.18–3.08 (m, 1 H), 3.01 (dd, *J* = 3.2, 13.6 Hz, 1 H), 2.56 (dd, *J* = 9.4, 13.8 Hz, 1 H), 1.96–1.80 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8 (d, *J* = 232 Hz), 143.7, 139.3, 129.3, 128.4, 126.2, 115.6 (d, *J* = 21.7 Hz), 112.1 (d, *J* = 6.9 Hz), 60.1, 48.8, 38.6, 29.6, 23.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –130.9 (m); IR (film) 1226 cm^{-1}. MS (ESI) 256.1503 (256.1502 calcd for $C_{17}H_{18}FN$, M + H^+).

***N*-(4-Chlorophenyl)-2-deuterio-2-(*p*-fluorobenzyl)pyrrolidine (IV-2v).** In a nitrogen-filled glovebox, **IV-5a** (106 mg, 0.127 mmol) and dppf (142 mg, 0.256 mmol) were dissolved in THF (10 mL). To this solution was added a solution of **IV-6v** (29.4 mg, 0.125 mmol) and 2-fluorotoluene (50 μL, 0.235 mmol) in THF (3 mL). The reaction was sealed, removed from the glovebox, and allowed to react for 4 h at rt with periodic shaking. After 4 h, the liquid was removed from a precipitate by pipette and concentrated in vacuo to give a red paste, which was triturated with hexanes:EtOAc (96:4, 3 × 3 mL). The combined extracts were purified by chromatography afford 17.9 mg (49%) of the title compound as a viscous colorless oil.

A second sample was prepared for ^{13}C NMR spectroscopy following General Procedure 8 for the reaction of **IV-1v** with 1-bromo-4-fluorobenzene. The catalytic reaction with this substrate gave a mixture of ca 2.5:1 **IV-2v**:**III-4c** (with no

stereochemical information). ^{13}C NMR signals for **IV-2v** were assigned from this mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.16 (m, 2 H), 7.14–7.10 (m, 2 H), 7.00–6.95 (m, 2 H), 6.57–6.53 (m, 2 H), 3.36–3.31 (m, 1 H), 3.12 (q, *J* = 8.5 Hz, 1 H), 2.90 (d, *J* = 14.0 Hz, 1 H), 2.58 (d, *J* = 14.0 Hz, 1 H), 1.93–1.73 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6 (d, *J* = 243 Hz), 145.5, 134.7 (d, *J* = 3.4 Hz), 130.7 (d, *J* = 7.8 Hz), 129.1, 120.3, 115.2 (d, *J* = 20.9 Hz), 112.8, 48.6, 37.4, 29.4, 23.0 (the expected triplet signal at or about 59 ppm for C–D was obscured); ^{19}F NMR (376 MHz, $CDCl_3$) δ –117.0 (m); IR (film) 1598, 1498, 1223 cm^{-1}. MS (ESI) 291.1161 (291.1175 calcd for $C_{17}H_{16}DClFN$, M + H^+).

***N*-(Phenyl)-2-methyl-2-(*p*-fluorobenzyl)pyrrolidine (IV-2w).** General Procedure 8 was used for the coupling of *N*-(4-methyl-pent-4-enyl)aniline (30 mg, 0.17 mmol) with 1-bromo-4-fluorobenzene (28 μL, 0.26 mmol) to afford the title compound as a colorless oil containing ~12% unidentified isomeric materials. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.23 (m, 2 H, obscured by $CHCl_3$), 7.03–6.99 (m, 2 H), 6.91–6.86 (m, 2 H), 6.83 (d, *J* = 9.0 Hz, 2 H), 6.69 (t, *J* = 6.5 Hz, 1 H), 3.37 (d, *J* = 13.5 Hz, 1 H), 3.29 (app q, *J* = 7.8 Hz, 1 H), 3.13–3.08 (m, 1 H), 2.81 (d, *J* = 14.0 Hz, 1 H), 2.10–2.04 (m, 1 H), 1.75–1.60 (m, 2 H), 1.48 (s, 3 H), 1.22–1.16 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6 (d, *J* = 243 Hz), 146.5, 134.5 (d, *J* = 3.5 Hz), 131.7 (d, *J* = 7.4 Hz), 129.0, 120.1, 114.7 (d, *J* = 21.0 Hz), 113.8, 64.0, 50.7, 43.1, 40.9, 26.1, 21.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ –117.3 (m); IR (film) 1598, 1506, 1353, 1222 cm^{-1}. MS (ESI) 270.1647 (270.1653 calcd for $C_{18}H_{20}FN$, M + H^+). Resonances for the isomeric material were detected at: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.26 (m), 7.13–7.08 (m), 7.07–7.03 (m), 6.72 (t, *J* = 7.0 Hz),

3.18 (d, J = 9.0 Hz), 3.03 (d, J = 8.5 Hz), 2.90 (d, J = 8.5 Hz), 2.64 (dd, J = 1.5, 15 Hz), 1.52 (s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.8, 129.1, 124.2 (d, J = 7.4 Hz), 121.6, 115.6, 115.2 (d, J = 21.4 Hz), 114.9, 44.4, 44.0, 26.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ –118.4 (m).

Preparation and Characterization of Pd-Complexes

General Procedure 9: Preparation of a Palladium Arylbromide Dimer. A flame-dried flask equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 equiv), and P(*o*-tol)$_3$ (2.5 equiv). The flask was purged with nitrogen for 5 min, toluene [40 mL/mmol $Pd_2(dba)_3$] and the appropriate ArBr (5 equiv) were added, and the resulting dark purple-brown solution was stirred at 25 °C for 1–3 h. At this time the solution had changed to a dark purple-yellowish color and was subsequently filtered through celite eluting with diethyl ether (ca. 100 mL) to obtain a yellow-orange filtrate. The filtrate was concentrated *in vacuo* to ca. 15 mL, layered with 60 mL pentane and transferred to an Erlenmeyer flask. The stoppered, layered solution was then allowed to settle at rt for 2 h upon which time significant formation of a yellow precipitate had occurred. The mixture was filtered to isolate an {[(*o*-tol)$_3$P]Pd(Ar)(Br)}$_2$ complex as a fluffy yellow powder that was subsequently used without further purification.

General Procedure 10: Preparation of (L–L)Pd(Ar)Br.

A flame-dried flask equipped with magnetic stir bar was charged with the appropriate {[(*o*-tol)$_3$P]Pd(Ar)(Br)}$_2$ complex (1 equiv) and the appropriate P–P ligand (2 equiv). The flask was purged with nitrogen for 5 min and CH_2Cl_2 (6 mL/0.1 mmol Pd complex) was

added. The resulting solution was stirred for 1 h at rt and then concentrated *in vacuo* to ca. 0.5 mL. Diethyl ether (7 mL) was added, the resulting slurry was stirred for 1 min and then allowed to settle for 1 h at rt. The mixture was then filtered and washed with diethyl ether (3 × 8 mL) and pentane (3 × 8 mL) to yield the desired (L–L)Pd(Ar)(Br) complex, which was used without additional purification.

(dppf)Pd(4-*tert*-butylphenyl)(Br) (IV-5g). General Procedure 9 was employed for the reaction of $Pd_2(dba)_3$ (496 mg, 0.54 mmol), P(*o*-tol)$_3$ (584 mg, 1.9 mmol) and 1-bromo-4-*tert*-butylbenzene (950 μL, 5.4 mmol) in CH_2Cl_2 (30 mL) at 30 °C for 1 h, and palladium black was removed by cannula filtration to afford a yellow solution. To the solution, dppf (302 mg, 0.54 mmol) was added and the reaction vessel purged with nitrogen and the reaction stirred for 2 h. Work-up according to General Procedure 10 afforded 280 mg (59% over 2 steps) of the title compound as an orange solid, m.p. 175 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–8.02 (m, 4 H), 7.50–7.30 (m, 12 H), 7.07 (td, *J* = 2.0, 9.6 Hz, 4 H), 6.82 (td, *J* = 2.4, 6.4 Hz, 2 H), 6.58 (dd, *J* = 1.2, 6.8 Hz, 2 H), 4.68–4.65 (m, 2 H), 4.47–4.45 (m, 2 H), 4.12–4.09 (m, 2 H), 3.59–3.56 (m, 2 H), 1.07 (s, 9 H); ^{13}C NMR (100.7 MHz, CD_2Cl_2) δ 153.8 (dd, *J* = 2.3, 135 Hz), 145.0, 136.0 (d, *J* = 12.4 Hz), 135.5 (dd, *J* = 2.0, 5.1 Hz), 134.7 (d, *J* = 11.7 Hz), 133.9 (d, *J* = 33.3 Hz), 133.8 (d, *J* = 41.1 Hz), 130.7 (app. t, *J* = 2.5 Hz), 128.7, 128.6 (d, *J* = 9.3 Hz), 128.4 (d, *J* = 10.9 Hz), 125.2 (dd, *J* = 1.5, 9.2 Hz), 77.5 (dd, *J* = 7.4, 49.5 Hz), 76.6 (d, *J* = 12.4 Hz), 75.6 (dd, *J* = 2.3, 36.3 Hz), 74.8 (d, *J* = 8.6 Hz), 74.0 (d, *J* = 7.9 Hz), 72.8 (d, *J* = 5.4 Hz), 34.2, 31.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.8 (d, *J* = 34.3 Hz), 8.8 (d, *J* = 34.3 Hz); IR (film) 1481, 1435 cm^{-1}. Anal calcd for $C_{44}H_{41}BrFeP_2Pd$: C, 60.47; H, 4.73. Found: C, 60.19; H, 4.65.

(dppf)Pd(4-methoxyphenyl)(Br) (IV-5h). General Procedure 9 was used for the reaction of $Pd_2(dba)_3$ (197 mg, 0.22 mmol), P(*o*-tol)$_3$ (262 mg, 0.86 mmol) and 4-bromoanisole (275 μL, 2.2 mmol) for 1 h to afford 79 mg of {[(*o*-tol)$_3$P]Pd(*p*-C_6H_4OMe)(Br)}$_2$ as fluffy yellow powder.

General Procedure 10 was used for the reaction of {[(*o*-tol)$_3$P]Pd(*p*-C_6H_4OMe)(Br)}$_2$ (60 mg, 0.050 mmol) with dppf (56 mg, 0.10 mmol) to give 56 mg (17% over 2 steps) of the title compound as an orange solid , m.p. 165 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.00 (m, 3 H), 7.49–7.43 (m, 6 H), 7.40–7.22 (m, 5 H), 7.17–7.10 (m, 6 H), 6.83–6.75 (m, 2 H), 6.30–6.23 (m, 2 H), 4.68–4.64 (m, 2 H), 4.50–4.45 (m, 2 H), 4.16–4.12 (m, 2 H), 3.67–3.63 (m, 2 H), 3.56 (s, 3 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2) δ 156.6, 146.7 (d, *J* = 2.4 Hz), 145.4, 136.0 (d, *J* = 11.6 Hz), 134.7 (d, *J* = 12.4 Hz), 134.0 (d, *J* = 34.0 Hz), 133.8 (d, *J* = 55.9 Hz), 131.7 (d, *J* = 10.1 Hz), 130.8, 128.6 (d, *J* = 9.2 Hz), 128.4 (d, *J* = 10.9 Hz), 114.3 (dd, *J* = 2.0, 9.2 Hz), 77.5 (dd *J* = 7.3, 50.2 Hz), 76.6 (d, *J* = 11.7 Hz), 75.6 (dd, *J* = 2.8, 36.3 Hz), 74.8 (d, *J* = 8.6 Hz), 74.0 (d, *J* = 7.0 Hz), 72.9 (d, *J* = 4.7 Hz), 55.6 (s); ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.7 (d, *J* = 31.7 Hz), 9.5 (d, *J* = 31.7 Hz); IR (film) 1480, 1435, 1231 cm^{-1}. Anal calcd for $C_{41}H_{35}BrFeOP_2Pd$: C, 58.08; H, 4.16. Found: C, 57.66; H, 4.10.

(dppf)Pd(Ph)(Br) (IV-5i). General Procedure 9 was used for the reaction of $Pd_2(dba)_3$ (197 mg, 0.22 mmol), P(*o*-tol)$_3$ (265 mg, 0.87 mmol) and bromobenzene (230 μL, 345 mg, 2.2 mmol) for 1 h to afford 131 mg of {[(*o*-tol)$_3$P]Pd(Ph)(Br)}$_2$ as a fluffy yellow powder that was used without further purification.

General Procedure 10 was used for the reaction of {[(*o*-tol)$_3$P]Pd(Ph)(Br)}$_2$ (100 mg, 0.088 mmol) with dppf (98 mg, 0.18 mmol) to give 30 mg (11% over 2 steps) of the title compound as an orange solid, m.p. 176 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11–8.02 (m, 4 H), 7.50–7.05 (m, 16 H), 6.99–6.89 (m, 2 H), 6.60–6.45 (m, 3 H), 4.70–4.65 (m, 2 H), 4.51–4.46 (m, 2 H), 4.16–4.12 (m, 2 H), 3.66–3.61 (m, 2 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2) δ 158.7 (dd, *J* = 2.0, 123 Hz), 136.2 (d, *J* = 3.0 Hz), 136.0 (d, *J* = 12.2 Hz), 134.6 (d, *J* = 12.3 Hz), 133.9 (d, *J* = 34.4 Hz), 133.6 (d, *J* = 55.0 Hz), 130.8, 130.7, 128.6 (d, *J* = 9.9 Hz), 128.4 (d, *J* = 10.7 Hz), 127.8 (d, *J* = 9.1 Hz), 122.5, 77.4 (dd, *J* = 7.3, 51.1 Hz), 76.6 (d, *J* = 11.2 Hz), 75.5 (dd, *J* = 3.1, 38.8 Hz), 74.8 (d, *J* = 8.4 Hz), 74.0 (d, *J* = 7.7 Hz), 72.9 (d, *J* = 4.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.7 (d, *J* = 34.2 Hz), 9.3 (d, *J* = 33.6 Hz); IR (film) 1482, 1435 cm^{-1}. Anal calcd for $C_{40}H_{33}BrFeP_2Pd$: C, 58.75; H, 4.07. Found: C, 58.62; H, 4.19.

(dppf)Pd(4-trifluoromethylphenyl)(Br) (IV-5j). General Procedure 9 was used for the reaction of $Pd_2(dba)_3$ (501 mg, 0.547 mmol), P(*o*-tol)$_3$ (582 mg, 1.9 mmol) and 4-trifluoromethylbromobenzene (763 μL, 5.46 mmol) for 3 h and palladium black was removed by cannula filtration to afford a yellow solution. To the solution, solid dppf (302 mg, 0.54 mmol) was added and the reaction vessel purged with nitrogen and the reaction stirred for 1 h. Work-up according to General Procedure 10 afforded 376 mg (79% over 2 steps) of the title compound as a red-orange solid containing ca 1.5% Et_2O by mass as estimated by ^{1}H NMR, m.p. 194 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–7.99 (m, 4 H), 7.47 (s, br, 6 H), 7.34–7.28 (m, 6 H), 7.14–7.05 (m, 6 H), 6.75 (d, br, *J* = 7.2 Hz, 2 H), 4.68 (s, 2 H), 4.49 (s, 2 H), 4.14 (s, 2 H), 3.61 (s, 2 H); ^{19}F NMR (376

MHz, $CDCl_3$) δ –62.1 (s); ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.2 (d, *J* = 32.7 Hz), 10.1 (d, *J* = 31.3 Hz); IR (film) 1585, 1436, 1324 (strong, CF_3), 1154 cm^{-1}. Anal calcd for $C_{41}H_{32}BrF_3FeP_2Pd$: C, 55.59; H, 3.64. Found: C, 55.61; H, 3.70.

(dppf)Pd(4-cyanophenyl)(Br) (IV-5k). General Procedure 9 was employed for the reaction of $Pd_2(dba)_3$ (503 mg, 0.55 mmol), P(*o*-tol)$_3$ (580 mg, 1.9 mmol) and 4-bromobenzontrile (996 mg, 5.5 mmol) in CH_2Cl_2 (20 mL) at 30 °C for 2 h, and palladium black was removed by cannula filtration to afford a yellow solution. To the solution, solid dppf (303 mg, 0.55 mmol) was added and the reaction vessel purged with nitrogen and the reaction was stirred for 2 h. Work-up according to General Procedure 10 afforded 402 mg (44% over 2 steps) of the title compound as an orange solid, m.p. 189 °C (decomp). ^1H NMR (400 MHz, $CDCl_3$) δ 8.08–7.98 (m, 4 H), 7.52–7.44 (m, 7 H), 7.39–7.30 (m, 6 H), 7.18–7.11 (m, 5 H), 6.83–6.76 (m, 2 H), 4.73–4.68 (m, 2 H), 4.55–4.51 (m, 2 H), 4.19–4.15 (m, 2 H), 3.63–3.59 (m, 2 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2) δ 170.8 (dd, *J* = 2.4, 131 Hz), 136.8 (d, *J* = 3.4 Hz), 135.9 (d, *J* = 11.9 Hz), 134.5 (d, *J* = 12.0 Hz), 133.3 (d, *J* = 36.3 Hz), 132.9 (d, *J* = 54.6 Hz), 131.2 (d, *J* = 2.3Hz), 131.0, 129.8 (d, *J* = 9.3 Hz), 128.7, 128.6 (d, *J* = 2.7 Hz), 120.5, 105.8, 76.8 (d, *J* = 12.0 Hz), 76.1 (d, *J* = 6.9 remaining Cp signals from carbons α to phosphorus obscured), 75.0 (d, *J* = 8.4 Hz), 74.3 (d, *J* = 7.7 Hz), 73.1 (d, *J* = 4.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.9 (d, *J* = 32.1 Hz), 10.6 (d, *J* = 32.1 Hz); IR (film) 2218, 1472, 1435 cm^{-1}. Anal calcd for $C_{41}H_{32}BrFeNP_2Pd$: C, 58.43; H, 3.83; N, 1.66. Found: C, 58.46; H, 4.05; N, 1.67.

(dppe)Pd(4-fluorophenyl)(Br) (IV-5l). Complex **IV-5l** was prepared according to General Procedure 10 for the reaction of dppe with $\{[(o\text{-tol})_3P]Pd(p\text{-}C_6H_4F)(Br)\}_2$, but could not be isolated in analytically pure form. Available NMR spectral data is provided. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, br, 4 H), 7.55–7.30 (m, 16 H), 6.95 (s, br, 2 H), 6.50 (s, br, 2 H), 2.56–2.39 (m, 2 H), 2.27–2.13 (m, 2 H); ^{19}F NMR (376.3 MHz, $CDCl_3$) δ –123.3 (s); ^{31}P NMR (162 MHz, $CDCl_3$) δ 52.7 (d, J = 25.6 Hz), 34.0 (d, J = 25.9 Hz).

(dpp-Benzene)Pd(4-fluorophenyl)(Br) (IV-5m). General Procedure 9 was modified for reaction of $Pd_2(dba)_3$ (500 mg, 0.55 mmol), $P(o\text{-tol})_3$ (578 mg, 1.9 mmol) and 1-bromo-4-fluorobenzene (600 μL, 5.5 mmol) in CH_2Cl_2 (25 mL) at 30 °C for 2 h, and palladium black was removed by cannula filtration to afford a yellow solution. To the solution, solid dpp-benzene (242 mg, 0.54 mmol) was added and the reaction vessel purged with nitrogen and the reaction was stirred for 2 h. Work-up according to General Procedure 10 afforded 324 mg (41% over 2 steps) of the title compound as a white solid, m.p. 218 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.67 (m, 5 H), 7.63–7.39 (m, 11 H), 7.33–7.26 (m, 8 H), 6.96–6.87 (m, 2 H), 6.57–6.50 (m, 2 H); ^{13}C NMR (100.7 MHz, CD_2Cl_2) δ 160.7 (dd, J = 2.4, 239 Hz), 151.7 (dd, J = 2.2, 135 Hz), 144.3 (dd, J = 47.2, 49.5 Hz), 141.0 (dd, J = 34.0, 41.2 Hz), 137.0 (m), 134.3 (d, J = 14.7 Hz), 133.9 (d, J = 14.5 Hz), 133.8 (dd, J = 2.3, 17.3 Hz), 133.4 (d, J = 12.5 Hz), 132.1 (m), 131.2 (d, J = 37.9 Hz), 131.1 (d, J = 2.3 Hz), 130.8 (d, J = 2.3 Hz), 129.4 (d, J = 55.3 Hz), 128.8 (d, J = 10.1 Hz), 128.7 (d, J = 11.7 Hz), 113.8 (ddd, J = 1.5, 11.6, 18.6 Hz), one signal obscured; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ –123.1 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 53.9 (d, J = 28.2 Hz),

43.8 (d, J = 26.7 Hz); IR (film) 1475, 1435, 1210 cm^{-1}. Anal calcd for $C_{36}H_{28}BrFP_2Pd$: C, 59.40; H, 3.88. Found: C, 59.54; H, 3.95.

(dppp)Pd(4-fluorophenyl)(Br) (IV-5n). Complex **IV-5n** was prepared according to General Procedure 10 for the reaction of dppp with $\{[(o\text{-tol})_3P]Pd(p\text{-}C_6H_4F)(Br)\}_2$, but could not be isolated in analytically pure form. Available NMR spectral data is provided. ^{19}F NMR (376.3 MHz, THF-d_8) δ –125.9 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 16.2 (d, J = 50.7 Hz), –8.3 (d, J = 50.4 Hz).

[(*rac*)-BINAP]Pd(4-fluorophenyl)(Br) (IV-5o). General procedure 10 was used for the reaction of $\{[(o\text{-tol})_3P]Pd(p\text{-}C_6H_4F)(Br)\}_2$ (100 mg, 0.0852 mmol) with (*rac*)-BINAP (106 mg, 0.170 mmol) to give 129 mg (84%) of the title compound as an off-white solid, m.p. 180 °C (decomp). ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, J = 8.8, 10.8 Hz, 1 H), 7.82–7.76 (m, 2 H), 7.71 (dd, J = 1.6, 8.4 Hz, 1 H), 7.59–7.46 (m, 6 H), 7.45–7.29 (m, 6 H), 7.18–7.12 (m, 2 H), 7.07–6.93 (m, 6 H), 6.77–6.58 (m, 6 H), 6.52–6.47 (m, 2 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –123.4 (s, br); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.8 (d, J = 36.3 Hz), 12.5 (d, J = 36.6 Hz); IR (film) 1474, 1436, 1212, 742, 696 cm^{-1}.

(DPE-Phos)Pd(4-fluorophenyl)(Br) (IV-5p). General procedure 10 was used for the reaction of $\{[(o\text{-tol})_3P]Pd(p\text{-}C_6H_4F)(Br)\}_2$ (201 mg, 0.172 mmol) with DPE-Phos (184 mg, 0.341 mmol) to give 189 mg (67%) of the title compound as a tan solid, m.p. 143 °C (decomp). ^1H NMR (400 MHz, C_6D_6) δ 7.96 (s, br, 2 H), 7.20–6.60 (m, partially obscured by solvent signal), 6.52 (t, J = 9.0 Hz, 2 H), 6.39 (s, br, 2 H); ^{19}F NMR (376 MHz, THF-

d_8) δ –124.2 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 14.2 (d, J = 30.8 Hz), 5.0 (d, J = 33.2 Hz); IR (film) 1435, 1096, 694 cm^{-1}.

(xantphos)Pd(4-fluorophenyl)(Br) (IV-5q). General procedure 10 was used for the reaction of {[(*o*-tol)$_3$P]Pd(*p*-C$_6$H$_4$F)(Br)}$_2$ (200 mg, 0.17 mmol) with xantphos (197 mg, 0.34 mmol) to give 223 mg (40% over 2 steps) of the title compound as an off-white solid, m.p. 216 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 2.0, 6.8 Hz, 2 H), 7.34 (s, br, 8 H), 7.29–7.21 (m, 4 H), 7.18–7.09 (m, 12 H), 6.43 (s, br, 2 H), 5.91 (t, J = 9.2 Hz, 2 H), 1.79 (s, 6 H); ^{13}C NMR (100.7 MHz, CD_2Cl_2) δ 159.9 (d, J = 238 Hz), 155.7 (app t, J = 5.8 Hz), 149.7, 135.0 (m), 134.6 (m), 132.1, 131.6 (app t, J = 22.6 Hz), 129.9, 128.1 (app t, J = 5.0 Hz), 127.4, 124.5 (app t, J = 3.1 Hz), 122.1 (app t, J = 20.9 Hz), 113.3 (d, J = 19.3 Hz), 36.37, 36.35, 28.8 (s, br); ^{19}F NMR (376 MHz, $CDCl_3$) δ –126.1 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 9.1 (s); IR (film) 1474, 1434, 1211 cm^{-1}. Anal calcd for $C_{45}H_{36}BrFOP_2Pd$: C, 62.84; H, 4.22. Found: C, 62.94; H, 4.34.

(*N*-Me-NiXantphos)Pd(4-fluorophenyl)(Br) (IV-5r). General procedure 10 was used for the reaction of {[(*o*-tol)$_3$P]Pd(*p*-C$_6$H$_4$F)(Br)}$_2$ (149 mg, 0.25 mmol) with *N*-Me-NiXantphos (145 mg, 0.26 mmol) to give 139 mg (65% over 2 steps) of the title compound as a yellow powder, m.p. 195 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.30 (s, br, 6 H), 7.29–7.22 (m, br, 6 H), 7.16–7.10 (m, br, 8 H), 6.96 (t, J = 7.8 Hz, 2 H), 6.82 (dd, J = 1.2, 8.0 Hz, 2 H), 6.72–6.68 (m, 2 H), 6.46–6.34 (s, br, 2 H), 5.92–5.84 (m, br, 2 H), 3.27 (s, 3 H); ^{13}C NMR (100.7 MHz, CD_2Cl_2) δ 159.9 (d, J = 235 Hz), 149.5 (app. t, J =6.2 Hz), 137.7 (app t, J = 3.9 Hz), 134.8 (m), 134.2 (m), 131.0 (app t, J

= 22.4 Hz), 129.7, 127.9 (app t, J = 5.1 Hz), 125.6, 124.6 (app t, J = 3.9 Hz), 121.8 (app t, J = 21.6 Hz), 114.5, 113.0 (d, J = 19.5 Hz) 31.9; ^{19}F NMR (376.9 MHz, $CDCl_3$) δ broad baseline signal centered at –129 (at 25 °C); ^{31}P NMR (162.1 MHz, $CDCl_3$) δ 7.32; IR (film) 1474, 1208 cm^{-1}. Anal calcd for $C_{43}H_{33}BrFNOP_2Pd$: C, 60.98; H, 3.93, N 1.65. Found: C, 60.95; H, 3.97, N 1.59.

(dppf-CF_3)Pd(4-fluorophenyl)(Br) (IV-5s). General procedure 10 was used for the reaction of {[(*o*-tol)$_3$P]Pd(*p*-C_6H_4F)(Br)}$_2$ (101 mg, 0.086 mmol) with dppf-CF_3 (141 mg, 0.17 mmol) to give 102 mg (28% over 2 steps) of the title compound as an orange solid, m.p. 191 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.89 (m, 4 H), 7.76 (d, J = 7.2 Hz, 4 H), 7.50–7.40 (m, 8 H), 6.80–6.71 (m, 2 H), 6.45–6.37 (m, 2 H), 4.67–4.63 (m, 2 H), 4.63–4.59 (m, 2 H), 4.33–4.29 (m, 2 H), 3.76–3.72 (m, 2 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2) δ 161.0 (d, J = 240 Hz), 149.0 (dm, J = 129 Hz), 137.6 (d, J = 32.4 Hz), 137.3 (d, J = 53.0 Hz), 136.3 (d, J = 12.3 Hz), 136.0–135.8 (m), 134.8 (d, J = 12.2 Hz), 133.0 (qd, J = 2.3, 32.5 Hz), 132.9 (qd, J = 2.3, 32.4 Hz), 126.0–125.4 (m), 124.3 (q, J = 270 Hz, partially obscured), 124.2 (q, J = 270 Hz, partially obscured), 115.3 (ddd, J = 1.5, 10.3, 19.4 Hz), 76.6 (d, J = 12.2 Hz), 75.1 (d, J = 7.7 Hz), 74.9 (d, J = 8.7 Hz), 74.6 (d, J = 7.3 Hz, partially obscured), 73.9 (d, J = 5.3 Hz), 73.5 (dd, J = 2.4, 38.2 Hz), one signal obscured; ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.2 (m, 12 F), –123.0 (m, 1 F); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.6 (d, J = 32.5 Hz), 9.3 (d, J = 34.3 Hz); IR (film) 1475, 1324, 1168 cm^{-1}. Anal calcd for $C_{44}H_{28}BrF_{13}FeP_2Pd$: C, 47.71; H, 2.55. Found: C, 47.91; H, 2.55.

(dppf-OMe)Pd(4-fluorophenyl)(Br) (IV-5t). General procedure 10 was used for the reaction of {[(*o*-tol)$_3$P]Pd(*p*-C$_6$H$_4$F)(Br)}$_2$ (101 mg, 0.086 mmol) with dppf-OMe (116 mg, 0.17 mmol) to give 83 mg (27% over 2 steps) of the title compound as an orange solid , m.p. 175 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.93 (m, 4 H), 7.29–7.22 (m, 4 H), 6.98 (dd, *J* = 1.2, 8.4 Hz, 4 H), 6.89–6.81 (m, 2 H), 6.67 (dd, *J* = 2.4, 8.8 Hz, 4 H), 6.39 (td, *J* = 9.8, 2.0 Hz, 2 H), 4.61–4.58 (m, 2 H), 4.46–4.43 (m, 2 H), 4.16–4.13 (m, 2 H), 3.86 (s, 6 H), 3.79 (s, 6 H), 3.69–3.66 (m, 2 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2) δ 161.9, 161.8, 160.6 (d, *J* = 249 Hz), 153.1 (dm, *J* = 128 Hz), 137.4 (d, *J* = 13.1 Hz), 136.3 (m), 136.1 (d, *J* = 13.8 Hz), 125.0 (d, *J* = 35.1 Hz), 124.5 (d, *J* = 55.7 Hz), 114.1 (d, *J* = 10.0 Hz), 114.0 (d, *J* = 12.2 Hz), 78.5 (dd *J* = 6.9, 51.8 Hz), 76.6 (d, *J* = 2.3 Hz, partially obscured), 76.2 (d, *J* = 12.3 Hz), 74.7 (d, *J* = 8.4 Hz), 73.8 (d, *J* = 7.6 Hz), 72.8 (d, *J* = 5.4 Hz), 55.93, 55.88, signal for the aryl carbons β to fluorine obscured; ^{19}F NMR (376 MHz, $CDCl_3$) δ –124.8 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.4 (d, *J* = 32.1 Hz), 7.3 (d, *J* = 32.1 Hz); IR (film) 1500, 1253, 1209, 1028 cm^{-1}. Anal calcd for $C_{44}H_{40}BrFFeO_4P_2Pd$: C, 55.29; H, 4.22. Found: C, 55.34; H, 4.20.

***In Situ* Formation of Pd-Amido Complexes IV-3 and Conversion to IV-2.**

(dppf)Pd(C$_6$H$_4$-*p*-F)[N(C$_6$H$_4$-*p*-*tert*-butyl)(CH$_2$CH$_2$CH$_2$CH=CH$_2$)] (IV-3b): ^{1}H NMR (400 MHz, THF-d_8) δ 8.01–7.90 (m), 7.72–7.64 (m), 7.59–7.39 (m), 7.22–6.98 (m), 6.71–6.59 (m), 6.11–6.04 (m), 5.60 (tdd, *J* = 6.8, 10.0, 16.8 Hz, 1 H), 4.87–4.77 (m, 2 H), 4.57 (s, 2 H), 4.44 (s, 2 H), 4.41 (s, 1 H), 4.31 (s, 1 H), 4.22 (s, partially obscured), 4.16 (s, 1 H), 4.12 (s, 1 H), 2.66–2.55 (m, 1 H), 2.40–2.32 (m, partially obscured, 1 H), 1.70–

1.62 (m, partially obscured, 2 H), 1.33–1.26 (m, partially obscured, 1 H), 1.16 (s, 9 H), 1.05–0.95 (m, 1 H); ^{19}F NMR (376 MHz, THF-d_8) δ –123.9 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 23.7 (dd, J = 2.6, 38.1 Hz), 8.6 (d, J = 38.1 Hz).

(dppf)Pd(C_6H_4-*p*-F){CH_2[$\overline{CHCH_2CH_2CH_2N(C_6H_4\text{-}p\text{-}tert\text{-butyl})}$]} (IV-4b): ^{19}F NMR (376 MHz, THF-d_8) δ –124.3 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 20.7 (d, J = 22.8 Hz), 16.1 (dd, J = 2.6, 22.8 Hz).

(dppf)Pd(C_6H_4-*p*-F)[N(C_6H_4-*p*-OMe)($CH_2CH_2CH_2CH{=}CH_2$)] (IV-3c): ^{1}H NMR (400 MHz, THF-d_8) δ 7.95–7.79 (m), 7.57–7.39 (m), 7.23–7.10 (m), 7.09–6.94 (m), 6.61–6.52 (m, 2 H), 6.29 (d, J = 7.6 Hz, 2 H), 6.05 (t, J = 8.6 Hz, 2 H), 5.62 (tdd, J = 6.4, 10.0, 16.4 Hz, 1 H), 4.87–4.80 (m, 2 H), 4.57 (s, 1 H), 4.47 (s, 1 H), 4.44 (s, 1 H), 4.42 (s, 1 H), 4.35 (s, 1 H), 4.32 (s, 1 H), 4.20 (s, 1 H), 4.16 (s, 1 H), 3.52 (s, 3 H), 2.45 (m, 1 H), 2.17 (m, 2 H), 1.70 (m, partially obscured by THF signal), 1.45 (m, 1 H), 1.20 (m, 1 H); ^{19}F NMR (376 MHz, THF-d_8) δ –124.1 (s); ^{31}P NMR (162 MHz, THF-d_8) δ 24.8 (d, J = 40.7 Hz), 7.9 (d, J = 39.5 Hz).

(dppf)Pd(C_6H_4-*p*-F){CH_2[$\overline{CHCH_2CH_2CH_2N(C_6H_4\text{-}p\text{-}OMe)}$]} (IV-4c): ^{19}F NMR (376 MHz, THF-d_8) δ –124.3 (s); ^{31}P NMR (162 MHz, THF-d_8) δ 21.3 (d, J = 24.1 Hz); 16.4 (dd, J = 2.4, 24.1 Hz).

(dppf)Pd(C_6H_4-*p*-F)[N(C_6H_5)($CH_2CH_2CH_2CH{=}CH_2$)] (IV-3d): ^{1}H NMR (400 MHz, THF-d_8) δ 7.93–7.86 (m), 7.84–7.74 (m), 7.57–7.38 (m), 7.27 (m), 7.20–7.08 (m), 6.66

(q, *J* = 7.2 Hz, 2 H), 6.58 (s, br, 1 H), 6.08 (t, *J* = 8.8 Hz, 2 H), 5.63 (tdd, *J* = 6.4, 10.4, 16.8 Hz, 1 H), 4.90–4.77 (m, 2 H), 4.51–4.49 (m, 2 H), 4.45 (s, 1 H), 4.41 (s, 1 H), 4.37 (s, 1 H), 4.32, (s, 1 H), 4.21 (obscured by dppf), 2.53–2.42 (m, 1 H), 2.29–2.20 (m, 1 H), 1.70 (m, obscured by THF), 1.50–1.38 (m, 1 H), 1.18–1.04 (m, 1 H); ^{19}F NMR (376 MHz, THF-d_8) δ –123.9 (s); ^{31}P NMR (162 MHz, THF-d_8) δ 24.3 (d, *J* = 36.8 Hz), 9.9 (d, *J* = 36.8 Hz).

(dppf)Pd(C_6H_4-*p*-F){CH_2[$\overline{CHCH_2CH_2CH_2N(C_6H_5)}$]} (IV-4d): ^{19}F NMR (376 MHz, THF-d_8) δ –124.4 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 20.7 (d, *J* = 23 Hz), 16.1 (dd, *J* = 2.6, 22.8 Hz).

(dppf)Pd(C_6H_4-*p*-F)[N(C_6H_4-*p*-Cl)($CH_2CH_2CH_2CH=CH_2$)] (IV-3e): ^{1}H NMR (400 MHz, THF-d_8) δ 7.88–7.79 (m), 7.74 (t, *J* = 8.6 Hz), 7.56–7.41 (m), 7.23-7.12 (m, partially obscured), 6.67 (app q, *J* = 6.8 Hz, 2 H), 6.50 (d br, *J* = 6.8 Hz, 2 H), 6.12 (t, *J* = 8.8 Hz, 2 H), 5.67–5.58 (m, 1 H), 4.89–4.79 (m, 2 H), 4.59 (s, 1 H), 4.49 (s, 2 H), 4.41 (s, 1 H), 4.39 (s, 1 H), 4.34 (s, 1 H), 2.50–2.45 (m, br, 1 H), 2.26–2.13 (m, 1 H), 1.73–1.61 (m, partially obscured by THF, 2 H), 1.51–1.38 (m, br, 1 H), 1.14–1.03 (m, br, 1 H); ^{19}F NMR (376 MHz, THF-d_8) δ –123.4; ^{31}P NMR (162 MHz, THF-d_8) δ 24.4 (d, *J* = 35.6 Hz), 10.8 (d, *J* = 35.6 Hz).

(dppf)Pd(C_6H_4-*p*-F){CH_2[$\overline{CHCH_2CH_2CH_2N(C_6H_4\text{-}p\text{-}Cl)}$]} (IV-4e): ^{19}F NMR (376 MHz, THF-d_8) δ –124.0 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 21.2 (d, *J* = 22.8 Hz), 16.8 (dd, *J* = 2.6, 24.1 Hz).

(dppf)Pd(C_6H_4-*p*-*tert*-butyl)[N(C_6H_4-*p*-F)($CH_2CH_2CH_2CH{=}CH_2$)] (IV-3g): ^{1}H NMR (400 MHz, THF-d_8) δ 7.89 (t, *J* = 8.4 Hz, 2 H), 7.82 (t, *J* = 8.6 Hz, 2 H), 7.67 (t, *J* = 8.6 Hz, 2 H), 7.53–7.44 (m), 7.16–7.03 (m), 6.65 (t, *J* = 7.6 Hz, 2 H), 6.39 (d, *J* = 7.2 Hz, 2 H), 6.31 (t, *J* = 8.2 Hz, 2 H), 5.62 (tdd, *J* = 6.8, 10.0, 16.8 Hz, 1 H), 4.86–4.79 (m, 2 H), 4.49 (s, 1 H), 4.42–4.39 (m, 3 H), 4.33 (s, 1 H), 4.16 (s, 1 H), 4.16 (s, 1 H), 2.56–2.50 (m, 1 H), 2.36–2.23 (m, obscured by internal standard), 1.73–1.60 (m, obscured by THF), 1.54–1.44 (m, 1 H), 1.08 (s, 9 H), 1.03–0.92 (m, partially obscured by *t*-Bu signal, 1 H); ^{19}F NMR (376 MHz, THF-d_8) δ –138.3 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 24.0 (d, *J* = 36.8 Hz), 9.0 (d, *J* = 36.9 Hz).

(dppf)Pd(C_6H_4-*p*-*tert*-butyl){CH_2[$CHCH_2CH_2CH_2N(C_6H_4\text{-}p\text{-}F)$]} (IV-4g): ^{19}F NMR (376 MHz, THF-d_8) δ –133.6 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 20.5 (d, *J* = 22.8 Hz), 16.6 (d, *J* = 22.8 Hz).

(dppf)Pd(C_6H_4-*p*-OMe)[N(C_6H_4-*p*-F)($CH_2CH_2CH_2CH{=}CH_2$)] (IV-3h): ^{1}H NMR (400 MHz, THF-d_8) δ 7.88–7.71 (m), 7.52–7.38 (m), 7.22–6.93 (m), 6.53 (t, *J* = 7.8 Hz, 2 H), 6.33 (t, *J* = 8.4 Hz, 2 H), 5.98 (d, *J* = 8.0 Hz, 2 H), 5.65 (tdd, *J* = 6.4, 10.0, 16.4 Hz, 1 H), 4.89–4.82 (m, 2 H), 4.46 (s, 2 H), 4.44 (s, 1 H), 4.39 (s, 2 H), 4.31 (s, 1 H), 4.21 (s,

obscured by dppf), 3.44 (s, 3 H), 2.50–2.44 (m, 1 H), 2.24–2.14 (m, 1 H), 1.70 (m, obscured by THF), 1.62–1.52 (m, 1 H), 1.19–1.08 (m, 1 H); ^{19}F NMR (376 MHz, THF-d_8) δ –137.9 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 24.0 (d, J = 36.8 Hz), 9.2 (d, J = 34.2 Hz).

(dppf)Pd(C$_6$H$_4$-*p*-OMe){CH$_2$[CHCH$_2$CH$_2$CH$_2$N(C$_6$H$_4$-*p*-F)]} (IV-4h): ^{19}F NMR (376 MHz, THF-d_8) δ –133.7 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 21.1 (d, J = 22.8 Hz), 16.1 (d, J = 22.8 Hz).

(dppf)Pd(C$_6$H$_5$)[N(C$_6$H$_4$-*p*-F)(CH$_2$CH$_2$CH$_2$CH=CH$_2$)] (IV-3i): ^{1}H NMR (400 MHz, THF-d_8) δ 7.92–7.81 (m), 7.78–7.71 (m), 7.55–7.40 (m), 7.21–7.14 (m), 7.13–7.01 (m), 6.74–6.67 (m), 6.42–6.25 (m), 5.63 (tdd, J = 6.8, 10.0, 16.8 Hz, 1 H), 4.89–4.80 (m, 2 H), 4.51 (s, 1 H), 4.44 (s, 2 H), 4.41 (s, 2 H), 4.33 (s, 1 H), 4.21 (s, 1 H), 4.18–4.14 (m, 1 H), 2.59–2.47 (m, 1 H), 2.27–2.13 (m, 1 H), 1.70 (m, obscured by THF), 1.54–1.42 (m, 1 H), 1.18–1.07 (m, 1 H); ^{19}F NMR (376 MHz, THF-d_8) δ –137.9 (s); ^{31}P NMR (162 MHz, THF-d_8) δ 24.5 (d, J = 36.8 Hz), 8.8 (d, J = 36.8 Hz).

(dppf)Pd(C$_6$H$_5$){CH$_2$[CHCH$_2$CH$_2$CH$_2$N(C$_6$H$_4$-*p*-F)]} (IV-4i): ^{19}F NMR (376.9 MHz, THF-d_8) δ –133.6 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 20.9 (d, J = 22.8 Hz), 16.6 (d, J = 22.8 Hz).

(dppf-CF$_3$)Pd(C$_6$H$_4$-*p*-F)[N(C$_6$H$_4$-*p*-F)(CH$_2$CH$_2$CH$_2$CH=CH$_2$)] (IV-3s′): ^{1}H NMR (400 MHz, THF-d_8) δ 8.37–8.26 (m), 8.02 (d, J = 7.6 Hz), 7.95 (d, J = 7.6 Hz), 7.90–7.78

(m), 7.38 (d, J = 7.6 Hz), 7.28–7.21 (m), 6.97 (app dt, br, J = 1.6, 8.8 Hz), 6.59 (app q, J = 7.6 Hz), 6.40 (app t, br, J = 8.4 Hz), 6.15 (app t, br, J = 8.4 Hz), 5.54 (ddt, J = 6.8, 10.8, 16.0 Hz, 1 H), 4.98–4.89 (m, 2 H), 4.82–4.75 (m, br, 2 H), 4.70–4.63 (m, br, 1 H), 4.61 (s, br, 1 H), 4.57 (s, br, 1 H), 4.52–4.46 (m, br, 2 H), 4.40 (s, br, 1 H; partially obscured by free ligand), 2.83–2.72 (m, 1 H), 2.39–2.30 (m, 1 H, partially obscured by internal standard), 1.72–1.64 (m, 2 H, partially obscured by THF), 1.12 (t, J = 7.2 Hz, 1 H), 0.89 (t, J = 7.0 Hz, 1 H); ^{19}F NMR (376 MHz, THF-d_8) δ –61.89 s, 3 F), –61.95 (s, 3 F), –61.97 (s, 3 F), –62.03 (s, 3 F), –122.7 (m, 1 F), –135.8 (s, 1 F); ^{31}P NMR (162 MHz, THF-d_8) δ 27.0 (d, J = 38.1 Hz), 8.2 (d, J = 38.1 Hz).

(dppf-CF_3)Pd(C_6H_4-*p*-F){CH_2[$\overline{CHCH_2CH_2CH_2N}$($C_6H_4$-*p*-F)]} (IV-4s′): ^{19}F NMR (376.9 MHz, THF-d_8) δ –123.1 (s, 1 F), –132.7 (s, 1 F) – CF_3 signals for **IV-4s′** could not be identified among the more prominent signals of free ligand, Pd(dppf-CF_3)$_2$, and **IV-3s′**; ^{31}P NMR (162 MHz, THF-d_8) δ 22.3 (d, J = 22.9 Hz), 17.7 (d, J = 25.4 Hz).

(dppf-OMe)Pd(C_6H_4-*p*-F)[N(C_6H_4-*p*-F)($CH_2CH_2CH_2CH=CH_2$)] (IV-3t′): ^{1}H NMR (400 MHz, THF-d_8) δ 7.98 (app t br, J = 8.6 Hz), 7.86–7.73 (m), 7.65 (app t, J = 8.6 Hz), 7.38–7.24 (m), 7.07–6.96 (m), 6.76–6.70 (m), 6.69–6.60 (m), 6.41–6.33 (m), 6.32–6.23 (m), 6.16–6.09 (m), 5.62 (ddt, J = 16.8, 10.0, 6.8 Hz, 1 H), 4.88–4.79 (m, 2 H), 4.67 (s, 1 H), 4.55 (s, 1 H), 4.51 (s, 1 H), 4.43 (s, 2 H), 4.41 (s, 1 H), 4.37 (s, 1 H), 4.31 (s, 1 H), 3.75 (s, 12 H), 2.61-2.50 (m, 1 H), 2.26-2.13 (m, 1 H), 1.7–1.65 (m, obscured by THF),

1.25–1.24 (m, 1 H), 1.20-1.08 (m, 1 H); ^{19}F NMR (376 MHz, THF-d_8) δ –123.9 (m), –137.9 (s); ^{31}P NMR (162 MHz, THF-d_8) δ 22.0 (d, J = 38.1 Hz), 6.3 (d, J = 39.4 Hz).

(dppf-OMe)Pd(C$_6$H$_4$-*p*-F){CH$_2$[$\overline{\text{CHCH}_2\text{CH}_2\text{CH}_2\text{N}}$(C$_6H_4$-*p*-F)]} (IV-4t′): ^{19}F NMR (376.9 MHz, THF-d_8) δ –124.4 (s), –133.4 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 18.4 (d, J = 24.2 Hz), 13.9 (dd, J = 24.2, 2.6 Hz).

(dppf)Pd(C$_6$H$_4$-*p*-F)[N(C$_6$H$_4$-*p*-Cl)(CH$_2$CH$_2$CH$_2$CD=CH$_2$)] (IV-3v): ^{1}H NMR (400 MHz, THF-d_8) δ 7.90–7.77 (m), 7.74 (app t, J = 8.8 Hz), 7.52–7.45 (m), 7.41 (app t, J = 6.0 Hz), 7.23–7.10 (m), 6.68 (app q, J = 7.6 Hz), 6.56–6.42 (m), 6.12 (app t, J = 8.4 Hz), 4.88–4.83 (m, 2 H), 4.49 (s, br, 2 H), 4.46 (s, br, 1 H), 4.41 (s, br, 1 H), 4.39 (s, br, 1 H), 4.34 (m, 1 H), 2.53–2.43 (m, 1 H), 2.26–2.12 (m, 1 H), 1.74–1.61 (m, 2 H, partially obscured by THF), 1.50–1.37 (m, 1 H), 1.16–1.03 (m, 1 H), remaining Cp signals obscured by free ligand; ^{19}F NMR (376 MHz, THF-d_8) δ –123.4 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 24.1 (d, J = 35.7 Hz), 10.5 (d, J = 35.7 Hz).

(dppf)Pd(C$_6$H$_4$-*p*-F){CH$_2$[$\overline{\text{CDCH}_2\text{CH}_2\text{CH}_2\text{N}}$(C$_6H_4$-*p*-Cl)]} (IV-4v): ^{19}F NMR (376 MHz, THF-d_8) δ –124.0 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 20.9 (d, J = 24.2 Hz), 16.5 (dd, J = 3.1, 23.0 Hz).

(dppf)Pd(C$_6$H$_4$-*p*-F){N(C$_6$H$_5$)[CH$_2$CH$_2$CH$_2$C(CH$_3$)=CH$_2$]} (IV-3w): ^{1}H NMR (400 MHz, THF-d_8) δ 7.86–7.77 (m), 7.71 (app t, J = 8.8 Hz), 7.55–7.40 (m), 7.35 (app t, J = 7.2 Hz), 6.67 (app q, J = 7.2 Hz), 6.59 (s, br), 6.08 (app t, J = 9.2 Hz), 4.79–4.71 (m, 2

H), 4.60 (s, 1 H), 4.54 (s, br, 3 H), 4.45 (s, 1 H), 4.41–4.33 (m, 4 H), 4.31 (s, 1 H), 2.42–2.33 (m, 1 H), 2.26–2.17 (m, 1 H), 1.73–1.62 (m, 2 H), 1.59 (s, 3 H), 1.17–1.08 (m, 1 H), remaining alkyl signal obscured; ^{19}F NMR (376 MHz, THF-d_8) δ –123.8 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 23.5 (d, J = 36.8 Hz), 10.4 (d, J = 36.8 Hz).

(dppf)Pd(C_6H_4-*p*-F){CH_2[$\overline{C(CH_3)CH_2CH_2CH_2N(C_6H_5)}$]} (IV-4w): ^{19}F NMR (376 MHz, THF-d_8) δ –124.6 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 20.2 (d, J = 22.8 Hz), 14.0 (dd, J = 2.1, 23.2 Hz).

(dppf)Pd(C_6H_4-*p*-F)[N(C_6H_5)((*Z*)-$CH_2CH_2CH_2CH$=$CHCH_3$)] (IV-3x): ^{1}H NMR (400 MHz, THF-d_8) δ 7.97–7.90 (m), 7.86–7.73 (m), 7.52–7.46 (m), 7.46–7.38 (m), 7.19–7.13 (m), 7.13–7.02 (m), 6.88 (app t, J = 7.8 Hz), 6.66 (app q, J = 7.2 Hz), 6.58 (s, br), 6.08 (app. t, J = 8.4 Hz), 5.38–5.29 (m, 1 H), 5.25–5.16 (m, 1 H), 4.54 (m, 1 H), 4.48 (s, 1 H), 4.44 (s, 1 H), 4.41 (s, 1 H), 4.38 (s, 1 H), 4.32 (s, 1 H), 4.23–4.18 (m, 2 H), 2.56–2.45 (m, 1 H), 2.28–2.18 (m, 1 H – partially obscured), 1.70–1.63 (m, 2 H – partially obscured by THF), 1.46–1.34 (m, 1 H), 1.18–1.08 (m, 1 H); ^{19}F NMR (376 MHz, THF-d_8) δ –123.9 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 23.1 (d, J = 35.7 Hz), 8.5 (d, J = 38.3 Hz).

(dppf)Pd(C_6H_4-*p*-F)[N(C_6H_5)((*E*)-$CH_2CH_2CH_2CH$=$CHCH_3$)] (IV-3y): ^{1}H NMR (400 MHz, THF-d_8) δ 7.95–7.88 (m), 7.86–7.74 (m), 7.51–7.45 (m), 7.44–7.40 (m), 7.19–7.14 (m), 7.13–7.01 (m), 6.88 (app t, J = 7.8 Hz), 6.66 (app q, J = 7.6 Hz), 6.57 (s, br), 6.07 (app t, J = 8.6 Hz), 5.53–5.40 (m, 1 H), 5.32–5.19 (m, 1 H – partially obscured), 4.54 (s, 1 H), 4.48 (s, 1 H), 4.45 (s, 1 H), 4.41 (s, 1 H), 4.39 (s, 1 H), 4.32 (s, 1 H), 4.20 (s, 1 H), 4.19 (s, 1 H), 2.52–2.42 (m 1 H), 2.27–2.16 (m, 1 H), 1.69–1.58 (m, 5 H – partially

obscured), 1.46–1.34 (m, 1 H), 1.18–1.06 (m, 1 H); ^{19}F NMR (376 MHz, THF-d_8) δ –123.9 (m); ^{31}P NMR (162 MHz, THF-d_8) δ 23.0 (d, J = 37.0 Hz), 8.3 (d, J = 36.8 Hz).

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([113]) Ligand substitution reactions of d^8-Pd(II) complexes generally occur via associative pathways. See: (a) Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 2056. (b) Shultz, L. H.; Tempel, D. J.; Brookhart, M. *J. Am. Chem. Soc.* **2001**, *123*, 11539 and references cited therein. For rare exceptions, which involve very large, sterically bulky ligands, see: (c) Bartolome, C.; Espinet, P.; Martin-Alvarez, J. M; Villafane, F. *Eur. J. Inorg. Chem.* **2004**, 2326. (d) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598.

([114]) Prior studies by Hartwig have shown that cyclometallated four-coordinate [*t*-$Bu_2PCH_2C_6H_4$]Pd(NAr_2)(ethylene) complexes undergo very fast insertion of the alkene into the Pd–N bond at temperatures as low as –40 °C. See reference 12.

([115]) Although the wide bite angle ligands DPE-Phos, xantphos, and *N*-Me-nixantphos are more electron-rich than dppf, the trends observed with *p*-substituted dppf derivatives (complexes **IV-3s** and **IV-3t**) suggest the large bite angle is responsible for the rate enhancement rather than electronic properties. The electron-rich complex **IV-3t** reacts at a slower rate than **IV-3s**. In addition, DPE-Phos and xantphos have similar electronic properties, but the complexes bearing these ligands have considerably different reactivities.

([116]) The lability of a chelating ligand has previously been observed to influence the rate of carbopalladation in (L–L)Pd(Me)[$PPh_2(C_6H_4$-*o*-$CH=CH_2)$] complexes. See: Cavell, K. J.; Jin, H. *J. Chem. Soc., Dalton Trans.* **1995**, 4081.

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