Selective Synthesis of 5- or 6-Aryl Octahydrocyclopenta[*b*] pyrroles from a Common Precursor Through Control of Competing Pathways in a Pd-Catalyzed Reaction

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Abstract

The Pd/phosphine-catalyzed reaction of **1** with aryl bromides leads to the selective synthesis of either 6-aryl octahydrocyclopenta[*b*]pyrroles (**3**), the corresponding 5-aryl isomers **5**, diarylamine **2**, or hexahydrocyclopenta[*b*]pyrrole **4** depending on the structure of the phosphine ligand. These transformations are effective with a variety of different aryl bromides, and provide **3**-**5** with excellent levels of diastereoselectivity (dr ≥ 20:1). The changes in product distribution are believed to derive from the influence of Pd-catalyst structure on the relative rates of reductive elimination, β-hydride elimination, alkene insertion, and alkene dissociation processes in a mechanistically complex reaction. The effect of phosphine ligand structure on product distribution is described in detail, along with analysis of a proposed mechanism for these transformations.

Introduction

A significant challenge in the development of metal-catalyzed reactions is the suppression of competing mechanistic pathways without inhibiting desired steps in a catalytic cycle. In recent years several remarkable transformations have been effected through the use of palladium catalysts that minimize side reactions (e.g. β-hydride elimination) while still allowing reductive elimination or transmetalation processes to occur.[1] Despite these achievements, the factors that affect the relative rates of competing mechanistic pathways in catalytic reactions (e.g. reductive elimination vs. olefin insertion, or C-C vs. C-N bond-forming reductive elimination) are not well understood. If these fundamental processes could be controlled, the selective construction of a diverse array of products from common starting materials could be achieved under similar reaction conditions by varying catalyst structure.

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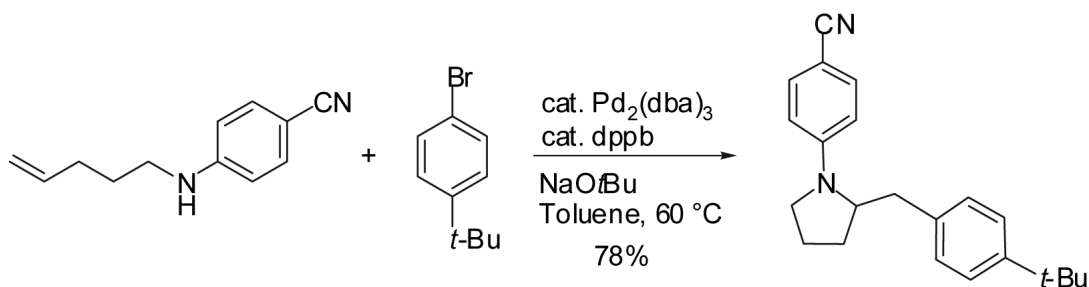
We recently described a new stereoselective synthesis of *N*-aryl pyrrolidines via Pd-catalyzed reactions of γ-(*N*-arylamino)alkenes with aryl bromides (eq 1).[2,3,4] These transformations lead to the formation of a C-C and a C-N bond along with up to two stereocenters in a single process. During the course of these studies, we noted that the Pd/P(*o*-tol)$_3$-catalyzed reaction of **1a** with 4-bromobiphenyl provides an unexpected mixture of four products (Scheme 1, **2-5**). We suggested that these products may derive from a common intermediate (**6**), which undergoes reductive elimination to afford **2**[,5] or intramolecular alkene insertion into the Pd-N bond[6,7,8] followed by: a) reductive elimination to afford **3**[,9] b) β-hydride elimination and alkene displacement to afford **4**, or c) β-hydride elimination, reinsertion, and reductive elimination to afford **5** (Scheme 1).[2] Despite the apparently complex mechanism of this reaction, we felt that selective formation of **2-5** might be achieved by altering the catalyst structure and/or the nitrogen nucleophilicity to control the relative rates (k_1-k_7) of each possible step in the catalytic cycle. This would provide access to a variety of products with a 2-azabicyclo[3.3.0]octane core, which is found in a number of biologically active molecules.[10,11] In this Article we present a detailed description of the effects of ligand structure, nitrogen nucleophilicity and aryl halide electronics on the ratios of products observed in reactions of **1** with aryl bromides. These studies have led to the selective synthesis of products **2-5** in good yields from a single precursor via the use of an appropriate catalyst for each transformation. The experiments described herein also provide further evidence to support the mechanistic hypothesis outlined in Scheme 1.

Results

Effect of Ligand Structure on Product Distribution

Prior to the start of our optimization studies, we sought to identify catalyst properties that might be expected to provide some degree of selectivity for each of the products **2-5**. The mechanistic proposal described above (Scheme 1) suggests that if the rate of reductive elimination from **6** (k_1) is fast relative to all other steps, then **2** should be obtained in high yield. Thus, we hypothesized that the selective synthesis of product **2** could be achieved in a straightforward manner by employing palladium catalysts supported by bulky, electron-rich phosphine ligands that are known to be highly effective at promoting C-N bond forming reductive elimination reactions.[5]

We reasoned that if the rates of all possible C-N and C-C bond forming reductive elimination steps (k_1, k_5, and k_7) could be minimized, the reaction may be directed towards product **4** provided that the rate of alkene insertion into the Pd-N bond is not completely inhibited. The two main classes of phosphines that are well documented in their ability to decrease the rate of reductive elimination reactions are small, electron-rich ligands (e.g. PMe$_2$Ph)[12] and chelating ligands with small bite angles (e.g. dppe).[12,13] Therefore, these types of ligands seemed to be potentially viable candidates for the selective formation of **4**.[14]

The selective formation of products **3** and **5** was more difficult to envision, as the formation of these products requires conditions that minimize C-N bond-forming reductive elimination without completely suppressing C-C bond-forming reductive elimination. In the case of product **3**, the rate of C-C bond forming reductive elimination of intermediate **7** would need to be faster than competing β-hydride elimination ($k_3 > k_4$). We reasoned that it might be feasible to achieve selectivity for **3** by employing chelating ligands with moderate to large bite angles (e.g. dppf, BINAP, or dpe-phos) to minimize the rate of β-hydride elimination[15] (k_4) while still allowing C-C bond forming reductive elimination[16] of **7** to occur at a reasonable rate (k_3).[17] If adequate control of the relative rates of C-N and C-C bond-forming reductive elimination could not be achieved through variation of phosphine ligand, we felt it should be possible to decrease the rate of C-N bond forming reductive elimination by employing an electron-deficient *N*-aryl substituent on the substrate **1**.[18]

The selective synthesis of **5** would require a scenario in which the rate of reversible β-hydride elimination[19] from **7** to afford **8** is fast relative to the rate of reductive elimination from **7** ($k_4>k_3$). In this scenario it seemed likely that the equilibrium between alkylpalladium complex **7** and π-complex **8** would lie far to the right, as examination of molecular models reveals a severe steric interaction between the *N*-aryl substituent and the metal fragment in **7** (Figure 1). In principle, **8** could undergo reversible reinsertion of the alkene into the Pd-H bond with opposite regiochemistry[19] to afford **9**; the position of the equilibrium between **8** and **9** is difficult to predict. However, if equilibration is rapid and the rate of reductive elimination from **9** is faster than the rate of the alkene displacement from **8** ($k_7>k_5$) then selective formation of **5** should occur. There was not sufficient literature precedent to allow us to predict how ligand variation would affect the relative rates of the required olefin insertion processes vs. reductive elimination reactions. However, the effects of ligand steric and electronic properties on the rates of reductive elimination reactions are well documented.[20] Additionally, we expected that increasing the size and electron-donor ability of the ligand should slow the rate of alkene displacement from **4**, which likely proceeds through an associative mechanism involving attack of an external nucleophile.[19,21,22,23] Thus, it seemed feasible that the correct combination of ligand steric and electronic properties could potentially provide good selectivity for **5**.

In order to probe the hypotheses described above, we examined the Pd-catalyzed reaction of **1a** with 4-bromotoluene in the presence of a variety of different phosphine ligands (eq 2). All reactions examined proceeded to completion with a catalyst loading of 1 mol % of $Pd_2(dba)_3$ except reactions conducted with PMe_3 and PEt_3, which both stopped at ca. 80% conversion. In all cases compounds **2-5** accounted for ≥95% of the products detected by GC and/or ^1H NMR analysis of the crude reaction mixtures, and products derived from oxidation of **1a** to the corresponding *N*-aryl imine via β-hydride elimination of **6**[5] were not observed in most reactions.

As shown in Table 1, experiments with monodentate trialkylphosphine ligands[24] demonstrated that selectivity is highly dependent on the steric bulk of the ligand, and that excellent selectivity for products **2**, **4**, and **5** can be achieved with the appropriate ligand. In general, the very bulky ligands (cone angle ≥178°) favored *N*-arylation, the medium-sized ligands (cone angle = 160-174°) favored the formation of **5**, and the very small ligands (cone angle ≤132°) favored the formation of **4**. Use of preformed L_2Pd complexes[1a,25] gave similar results to those obtained with $Pd_2(dba)_3$/phosphine mixtures.

(2)
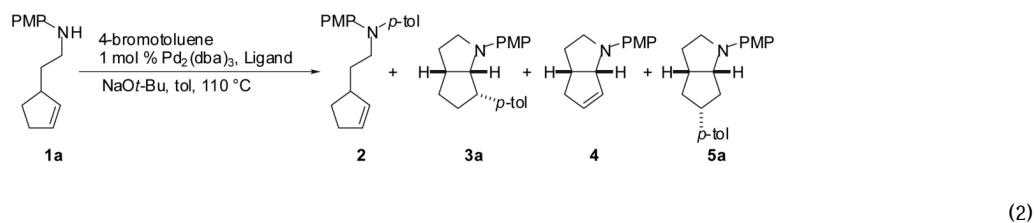
The selectivities observed in Pd-catalyzed reactions conducted with other monodentate phosphine ligands are shown in Table 2. In general, sterically bulky ligands favor the formation of **2** and/or **3**, whereas smaller ligands provide **4** and/or **5** as the major products. Of the ligands examined in this series, bulky, electron-rich phosphines provided the highest selectivity for **2**, and the selectivity for **4** increased with decreasing ligand size. Use of ligands that were extremely bulky (e.g tris[2,4,6-trimethoxyphenyl]phosphine), and/or extremely electron poor (e.g. $P[C_6F_5]_3$, $P[o\text{-}C_6H_4CF_3]_3$) resulted in low reactivity.[28]

To probe the effect of chelation and ligand bite angle on product distribution, a number of bidentate ligands were employed in the transformation shown in eq 1; the results are described

in Table 3. Systematic variation of ligand bite angle did not result in clear trends of product distribution. However, electronic effects similar to those described above for reactions involving monodentate ligands were observed within series of ligands that possess identical backbone structures. For example, reactions catalyzed by mixtures of $Pd_2(dba)_3$ and 1,2-bis (phosphino)ethane derivatives (entries 2-4 and 6) afforded increasing amounts of **4** and **5a** (relative to **2** and **3a**) as the electron-donicity of the phosphines increased. Similarly, use of 1,2-bis(diphenylphosphino)ferrocene as ligand afforded predominantly **2** and **3a**, whereas 1,2-bis(diisopropylphosphino)ferrocene provided **5a** as the major product (entries 10 and 11).

In summary, the best selectivity for **2** was obtained with the bulky, monodentate, electron-rich ligands $P(t\text{-}Bu)_3$ and $t\text{-}Bu_2P(o\text{-biphenyl})$ (**10**). Use of the small, monodentate electron-rich ligands PMe_3, PEt_3, and $PhPMe_2$ provided the best selectivity for **4**, whereas the medium-sized, electron-rich ligands $P(t\text{-}Bu)_2Me$ and PCy_3 provided the highest selectivity for **5a**. None of the ligands examined provided excellent selectivity for **3a**, however dppp provided modest selectivity for **3a**, with **2** formed as the major side product. The xantphos, $Cy_2P(o\text{-biphenyl})$, and 2-(diphenylphosphino)-2′-(*N,N*-dimethylamino)biphenyl (**11**) ligands also provided close to 1:1 ratios of **2**:**3a** with only small amounts of **4** and **5a** generated. Although the selectivity for **3a** was not ideal, we reasoned that we could further improve the ratio of **3a**:**2** by employing substrates bearing electron-withdrawing *N*-aryl substituents, which would slow the rate of competing C-N bond-forming reductive elimination (see below).[5]

Selective Synthesis of 5-Aryl Octahydrocyclopenta[*b*]pyrroles (3): Effect of Aryl Bromide Structure and *N*-Aryl Substituent

With optimized conditions in hand, we examined the reaction of several derivatives of **1** with a number of different aryl bromides; the results are summarized below. As shown in Table 4, the reaction of 4-bromotoluene with **1a** afforded a modest 44% isolated yield of **3a** in the presence of the $Pd_2(dba)_3$/dppp catalyst system (entry 1). Analysis of the crude reaction mixture showed that the four products (**2**, **3a**, **4**, and **5a**) were formed in a 25:65:10:0 ratio; the $Pd_2(dba)_3$/**11** catalyst provided a 48:48:2:2 ratio of **2**:**3a**:**4**:**5a** (entry 2). As expected, significantly higher yields of isomer **3** were obtained with substrates bearing electron-deficient *N*-aryl substituents (entries 3-5, and 7). For example, the reaction of substrate **1d** bearing a *N-para*-carbo-*tert*-butoxyphenyl group with 4-bromotoluene afforded a 75% yield of **3e** (entry 7). Use of **11** as ligand provided superior results in reactions of substrates **1c** and **1d**, which failed to react in the presence of the $Pd_2(dba)_3$/dppp catalyst system. Aryl halide electronics also had a significant effect on the selectivity with which products **3a-g** were formed. As noted above, the reaction of electron-deficient substrate **1d** with 4-bromotoluene afforded **3e** in 75% isolated yield as the sole detectable product (entry 7), whereas the reaction of **1d** with the electron-rich 4-bromoanisole afforded a separable 9:1 mixture of **3f:4d** (entry 8), and the reaction of **1d** with an aryl bromide bearing an electron-withdrawing substituent led to the formation of significant amounts of *N*-arylated side products (entry 9). In all cases examined, the 2-azabicyclo[3.3.0]octane derivatives **3a-g** were obtained with diastereomeric ratios of ≥20:1.

Selective Synthesis of 6-Aryl Octahydrocyclopenta[*b*]pyrroles (5): Effect of Aryl Bromide Structure and Nitrogen Electronics

As shown in Table 5, the selective synthesis of isomer **5** was achieved for a variety of different substrate combinations using the $Pd_2(dba)_3$/$P(t\text{-}Bu)_2Me\cdot HBF_4$ catalyst system. Good to excellent selectivities and yields were obtained in transformations of substrates bearing electron-rich, -neutral, or -poor *N*-substituents. The reactions also proceeded in good yield with aryl bromides of varying electronic properties, although the ratios of **5**:**3** decreased when certain electron-deficient or *o*-substituted aryl bromides were employed as coupling partners (entries

3, 4, and 6). Products **2** and **4** were not observed except in the reaction of **1c** with 3-bromopyridine (entry 5). In all cases the products **5a**-**g** were obtained with ≥ 20:1 dr.

Selective Synthesis of Oxidative Amination Product 4 and *N*-Arylated Product 2

The synthesis of oxidative amination[30] product **4** was achieved in 60% yield as shown in eq 3; the best results were obtained with PMe$_3$ as ligand. Although **4** is the sole product formed under these conditions, the reaction did not proceed beyond 80% consumption of starting material; use of 2 mol % Pd$_2$(dba)$_3$ led to only modest improvements in conversion and yield. Reactions in which PMePh$_2$, PMe$_2$Ph, or P(2-furyl)$_3$ were employed as ligands all provided similar isolated yields (44-54%) despite differences in selectivity due to the difficult chromatographic separation of **4** from **5**.[31]
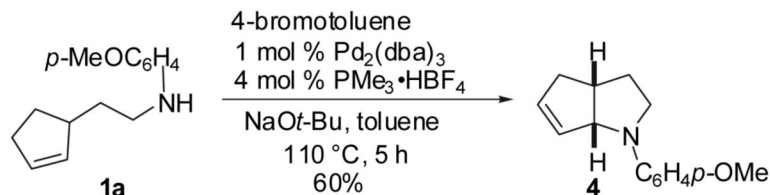
(3)

The *N*-arylated product **2** was obtained in 88% yield using the Pd$_2$(dba)$_3$/*t*-Bu$_2$P(*o*-biphenyl) (**10**) catalyst system (eq 4). The scope of this transformation was not explored due to the large body of existing literature on the effect of aryl bromide substitution on Pd-catalyzed *N*-arylation reactions.[5]
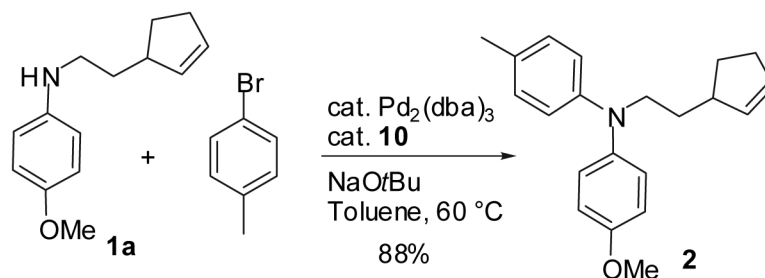
(4)

Discussion

Synthetic Scope and Limitations

The palladium-catalyzed reaction of *N*-aryl-2-(cyclopent-2-enyl)ethylamines **1** with aryl bromides provides 5- or 6-aryloctahydrocylopenta[*b*]pyrroles in moderate to good yields with excellent diastereoselectivity (>20:1 dr). The 5-aryl regioisomers **5a**-**g** are selectively formed in reactions that employ the medium-sized electron-rich phosphine P(*t*-Bu)$_2$Me as a ligand for palladium, whereas use of catalysts comprised of Pd$_2$(dba)$_3$ and either dppp or **11** leads to selective formation of the 6-aryl products **3a**-**g**. The yields obtained in reactions that afford predominantly 5-aryl products are not greatly affected by the electronics of either the amine *N*-aryl substituent or the aryl bromide. In contrast, reactions that afford 6-aryl products provide the highest yields when substrates bearing electron-poor *N*-aryl substituents are employed in combination with electron-neutral or slightly electron-rich aryl bromides. Functional groups such as non-enolizable nitriles, ketones, and esters are tolerated in these transformations, and

the synthesis of 5-aryl products bearing *o*-substituents or heterocylic groups is also feasible. The reaction of **1a** with 4-bromotoluene in the presence of a catalytic amount of $Pd_2(dba)_3/$ **10** leads to clean *N*-arylation of the substrate to afford **2**, whereas use of the $Pd_2(dba)_3/PMe_3$ catalyst system provides oxidative amination product **4** in moderate yield.

The results described above (Table 4 entry 1, Table 5 entry 1, and eq 3-4) demonstrate that a single starting material can be converted to four different products (**2-5**) in moderate to excellent yield by changing only the nature of the metal catalyst employed in the reaction. For example, in separate experiments **1a** was treated with 4-bromotoluene and an appropriate palladium catalyst to afford either **2** (88% yield), **3a** (44% yield), **4** (60% yield), or **5a** (74% yield). Although the selectivity for formation of **3a** was modest (a 65:35 ratio of **3a**: **2** + **4** + **5a** was obtained under optimal conditions)[32], products **2**, **4**, and **5a** were each obtained with excellent selectivity (≥94:6). High selectivity for isomer **3** was achieved by changing the substrate's *N*-aryl substituent to an electron-withdrawing p-$C_6H_4CO_2t$-Bu group. The reaction of this modified substrate (**1d**) with 4-bromotoluene and the $Pd_2(dba)_3/$**11** catalyst afforded **3e** in 75% yield with 100:0 selectivity (Table 4, entry 7).

Mechanism and Ligand Effects

In addition to the hypothesis outlined in Scheme 1, a number of other mechanistic pathways could potentially lead to the formation of products **3-5** (Scheme 2).[33] The ligand effects, stereoselectivity, and product stereochemistry described above can be used to evaluate the viability of the various possible mechanisms for this transformation. For example, product **3** could potentially derive from intermolecular carbopalladation of **1a** followed by C-N bond-forming reductive elimination (Scheme 2, Path A). However, this pathway is unlikely due to the high stereoselectivity for formation of products in which the aryl group is installed *syn* to the C-3 methylene. If the reactions were to occur via intermolecular carbopalladation without chelation of the amino group or formation of an amido complex it is likely that steric repulsion between the Pd(Ar)(X) complex and the alkyl chain would favor formation of the *anti*-diastereomer **12** (or at least would likely provide mixtures of diastereomers).[34] The formation of **3** via Wacker-type aminopalladation (Path B) can be ruled out, as this pathway would result in *anti*-addition of the heteroatom and the metal across the carbon-carbon double bond to provide **12** rather than the observed products **3a-g**.[35] The reductive Heck-arylation of **4** (Path C) can also be discounted as a possible mechanism for the generation of **3a** and/or **5a**, as the transformation of **4** to **3a** and/or **5a** is not observed under the conditions employed for the conversion of **1a** to **3a** or **5a**.[36]

The data described above also argue against insertion of the alkene into the Pd-C bond of **6** or a related mechanism involving amino chelate-directed carbopalladation from intermediate **6′**. As shown below (Scheme 3) alkene insertion into the Pd-C bond of **6** or **6′** would afford **13** or **13′**. In principle **13** or **13′** could be converted to **3a** via sp^3C-N bond-forming reductive elimination. However, C-C bond-forming alkene insertions are generally irreversible,[37] and this pathway could not provide either **4** or **5a** from intermediates **13** or **13′**. In addition, ligands that are known to slow the rate of C-C and sp^2C-N bond-forming reductive elimination (e.g. dppe or PMe_3)[12] would also be likely to slow the rate of sp^3C-N bond-forming reductive elimination. If the reductive elimination from **13** or **13′** were slowed, it is likely that β-hydride elimination of **13** or **13′** would afford product **14**. However, use of dppe or PMe_3 in the catalytic reactions leads instead to the formation of **4** as the major product. Thus, a mechanistic pathway involving intermediate **13** or **13′** cannot account for all products that are obtained and is also not consistent with the observed ligand effects.

In contrast, the data described above in Tables 1-5 can be explained using the mechanistic model outlined in Scheme 1. For example, the trends observed with trialkylphosphines show that as the steric bulk of the ligand is decreased, the product ratio shifts from predominantly

2 (P[*t*-Bu]$_2$Cy, P[*t*-Bu]$_3$) to **5** (PMe[*t*-Bu]$_2$, PCy$_3$, P[*t*-Bu]Cy$_2$) to **4** (PMe$_3$, PEt$_3$). The decrease in ligand size would be expected to slow the rate of reductive elimination from **6→2**,[5,20] which may lead to the formation of **7**. When medium-sized electron-rich ligands are employed it appears that β-hydride elimination from **7→8** occurs more rapidly than reductive elimination from **7**, but the conversion of **8→9→5** is fast relative to the rate of alkene displacement from **8**. This is presumably due to a combination of ligand steric and electronic properties that slow the associative ligand substitution process required to covert **8→4**.[19,21] In contrast, with the smaller ligands the metal becomes more sterically accessible for attack by an external nucleophile, and the rate of associative alkene displacement from **8** to afford **4** likely becomes fast relative to the rate of olefin reinsertion and reductive elimination. These arguments could also be used to explain similar trends observed in reactions that involve other monodentate ligands; the smaller ligands favor the formation of **4** (Table 2, entries 10-12) and larger ligands favor the formation of **2** and/or **3** (Table 2, entries 1-5). A comparison of reactions involving isosteric triphenylphosphine derivatives (Table 2, entries 7-9) reveals that increased amounts of products **2** and **3** are generated as phosphine basicity is decreased. This trend is also consistent with the mechanism described in Scheme 1, as ligands that increase the rate of C-N and/or C-C bond-forming reductive elimination[20] should favor the formation of **2** and **3** over products **4** and **5**, which are proposed to derive from β-hydride elimination processes.

Examination of the data shown in Table 3 does not reveal a clear relationship between bite angle of chelating ligands and product distribution. This may be due in part to the fact that the coordination chemistry of many of these ligands is complicated, and it is difficult to say whether or not some of the ligands are coordinated solely in a *cis*-bidentate fashion. For example, *trans*-chelated Pd-complexes of xantphos have been described,[38] and dppb is known to form bridging complexes with two palladium atoms.[39] However, ligands that are known to decrease the rate of reductive elimination (e.g. dppe)[12] disfavor the formation of **2** and **3**, which is consistent with our mechanistic hypothesis shown in Scheme 1. In addition, the electronic effects[20] observed within a structurally similar series of ligands are also consistent with the hypothesis described above. For example, use of the electron-poor dppe-*p*-CF$_3$ ligand resulted in the increased formation of **2** and **3** relative to dppe and, use of the electron-rich dppe-*p*-OMe led to a slight increase in the formation of **4**.

At the outset of these studies we hoped to be able to facilitate the selective formation of **3** by employing chelating ligands to minimize β-hydride elimination of **7**. Although we found several ligands (e.g dppp, dppf, xantphos, and dpp-benzene) that afforded high ratios of **2** + **3a**: **4** + **5a**, which suggests that chelation does affect the relative rates of reductive elimination vs. β-hydride elimination from **6** and **7**, we were unable to completely control the selectivity for formation of **3** over **2** by varying phosphine ligand structure. However, substitution of the nitrogen with an electron-deficient aryl group resulted in good to excellent selectivities for **3c**-**3g** with the pseudo-chelating ligand **11**,[40] which is consistent with an expected decrease in the rate of reductive elimination from **6** when the nitrogen nucleophilicity is decreased.[18]

The observed effects of aryl bromide substitution on product distribution are also consistent with the mechanistic hypothesis outlined in Scheme 1. The rates of stoichiometric C-N and C-C bond-forming reductive elimination reactions from L$_n$Pd(Ar)(NR$_2$) and L$_n$Pd(Ar)(R) complexes are known to decrease with increasing π-electron density on the aryl group.[18a,41] When **1d** is treated with the electron deficient *t*-butyl-4-bromobenzoate under conditions that favor formation of **3g**, increased amounts of *N*-arylated products **2** are formed compared to the amounts generated by reaction of **1d** with 4-bromotoluene (Table 4, entries 7 and 9). This presumably derives from an increase in the rate of reductive elimination of intermediate **6**. In contrast, reaction of **1d** with the electron-rich 4-bromoanisole leads to increased formation of **4d** (Table 4, entry 8), which is consistent with a decrease in the rate of reductive elimination from intermediates **6**, **7**, and **9**. Similarly, reactions of **1b** or **1e** with aryl bromides bearing

para-carbonyl functionality under conditions that favor formation of **5** also provided small amounts of regioisomeric side product **3**, which may derive from an increase in the rate of reductive elimination from **7** (Table 5, entries 3 and 6). This effect was not observed in the reaction of **1e** with of 4-bromobenzonitrile, which provided **5g** with essentially complete selectivity. Although this latter result is somewhat surprising, previous studies have shown that the rates of reductive elimination reactions often do not follow simple linear free energy relationships with the σ-values of arene substituents.[18a,41]

In addition to providing further support for our mechanistic hypothesis shown in Scheme 1, the results described above illustrate several important concepts that are potentially relevant to the future development of other new Pd-catalyzed reactions. First of all, these results demonstrate that the rate of both C-N and C-C bond-forming reductive elimination can be minimized without completely suppressing alkene insertion processes, which are required to transform **1** into **3**-**5**. Furthermore, since C-N bond forming reductive elimination reactions require larger ligands than are needed to effect C-C bond forming reductive elimination,[5] it is possible to minimize the rate of C-N bond-forming reductive elimination without completely suppressing C-C bond-forming reductive elimination. This allows for the selective synthesis of **3** and **5**. These results also reaffirm the notion that phosphines have a large impact on the relative rates of reductive elimination and β-hydride elimination, and that the appropriate choice of ligand can be used to favor either transformation over the other. Finally, our data also suggests that steric and electronic properties of phosphine ligands may have a large impact on the rate of alkene displacement from Pd(II) complexes. Medium-sized electron-rich ligands appear to slow the rate of alkene displacement from a Pd(II)-alkene complex to a greater degree than they decrease the rate of C-C bond-forming reductive elimination, which facilitates the selective preparation of **5** and minimizes the formation of side product **4**. However, as the size of the ligand decreases, a near complete reversal in selectivity is observed such that the formation of **4** is favored over **5** (Table 1, entries 1-7).

Conclusion

In conclusion, we have demonstrated that the selective conversion of **1** to four different products can be achieved by using ligand effects to control the relative rates of C-N and C-C bond-forming reductive elimination, β-hydride elimination, alkene insertion, and alkene displacement in a mechanistically complex process. These transformations allow for synthesis of a variety of 5- or 6-aryl octahydrocyclopenta[*b*]pyrroles (**5** and **3**, respectively) in good yield with high regioselectivity and diastereoselectivity. The observed effects of ligand structure on product ratio provide further evidence to support our mechanistic hypothesis and suggest that palladium(aryl)amido complex **6** is a plausible common intermediate in the conversion of **1** to **2**, **3**, **4**, and **5**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

References and Notes

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(2). A portion of this work has been previously communicated. See:Ney JE, Wolfe JP. Angew. Chem. Int. Ed 2004;43:3605–3608.3608

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(14). Our previous studies showed that use of certain electron-rich phosphines (e.g 2-dicyclohexylphosphinobiphenyl) provided acceptable yields in the Pd-catalyzed carboamination reactions of γ-aminoalkenes. Thus, it seemed possible that the alkene insertion into the Pd-N bond may also potentially proceed with other electron-rich phosphines. See reference 2.

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(22). Rates of associative ligand substitution should decrease as the electron density on the metal center increases due to electron-electron repulsion between the metal and the incoming nucleophile.

(23). Increased π-backbonding from the electron-rich metal to the alkene may also play a role in decreasing the rate of alkene dissociation. For a discussion of πbackbonding in electron-rich Pd(II)-alkene complexes, see:Miki K, Shiotani O, Kai Y, Kasai N, Kanatani H, Kurosawa H. Organometallics 1983;2:585–593.593

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(31). The use of PMe$_2$Ph, PMePh$_2$, or P(2-furyl)$_3$ as ligands afforded isolated yields of 54%, 44%, and 53%, respectively.

(32). The 65:35 ratio of products was determined by ^{1}H NMR analysis of the crude reaction mixture and differs slightly from the 58:42 ratio measured by GC analysis of the crude reaction mixture (Table 3, entry 7). Similarly small differences were observed for the product ratios described in Table 2, entry 4 (measured by GC) as compared to Table 4, entry 2 (measured by ^{1}H NMR). The small

differences in the product ratios for these are likely due to experimental error associated with the measurement techniques.

(33). The mechanism for Pd-catalyzed *N*-arylation reactions of amines is well documented and is believed to proceed via intermediate palladium(aryl)(amido) complexes such as **6**. For lead references, see: (a) reference 5.(b)Alcazar-Roman LM, Hartwig JF. J. Am. Chem. Soc 2001;123:12905–12906.12906 [PubMed: 11749551](c)Singh UK, Streiter ER, Blackmond DG, Buchwald SL. J. Am. Chem. Soc 2002;124:14104–14114.14114 [PubMed: 12440909](d)Guari Y, van Strijdonck GPF, Boele MDK, Reek JNH, Kamer PCJ, van Leeuwen PWNM. Chem. Eur. J 2001;7:475–482.482(e) Hartwig JF. Synlett 1997:329–340.340

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(40). Ligand **11** is believed to act as a bidentate ligand via π-complexation of the aromatic ring bearing the dimethylamino group. See:Yin J, Rainka MP, Zhang X-X, Buchwald SL. J. Am. Chem. Soc 2002;124:1162–1163.1163 [PubMed: 11841272]and references cited therein.

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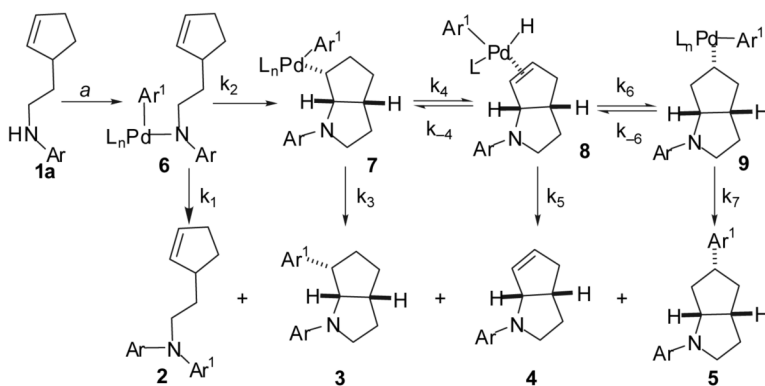
Scheme 1.
(a) Conditions: 1.0 equiv **1a**, 1.2 equiv 4-Ph(C_6H_4)Br, 1.4 equiv NaO*t*Bu, 1 mol % $Pd_2(dba)_3$, 4 mol % P(*o*-tol)$_3$, toluene, 110 °C. Isolated yield: **2** (19%), **3** (32%), **4** (5%), **5** (12%) for Ar = 4-methoxyphenyl, Ar^1 = 4-(phenyl)phenyl.
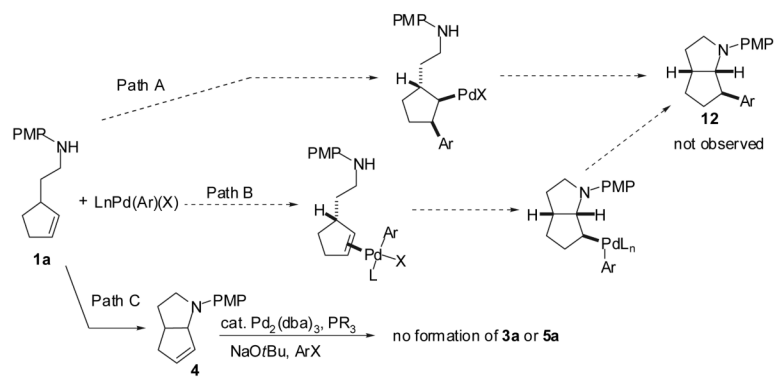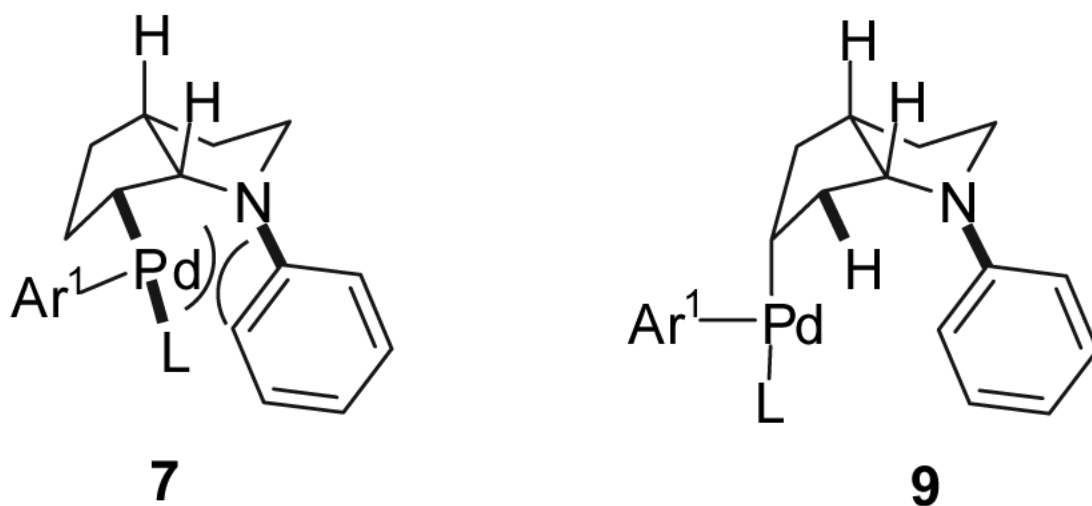
Scheme 2.
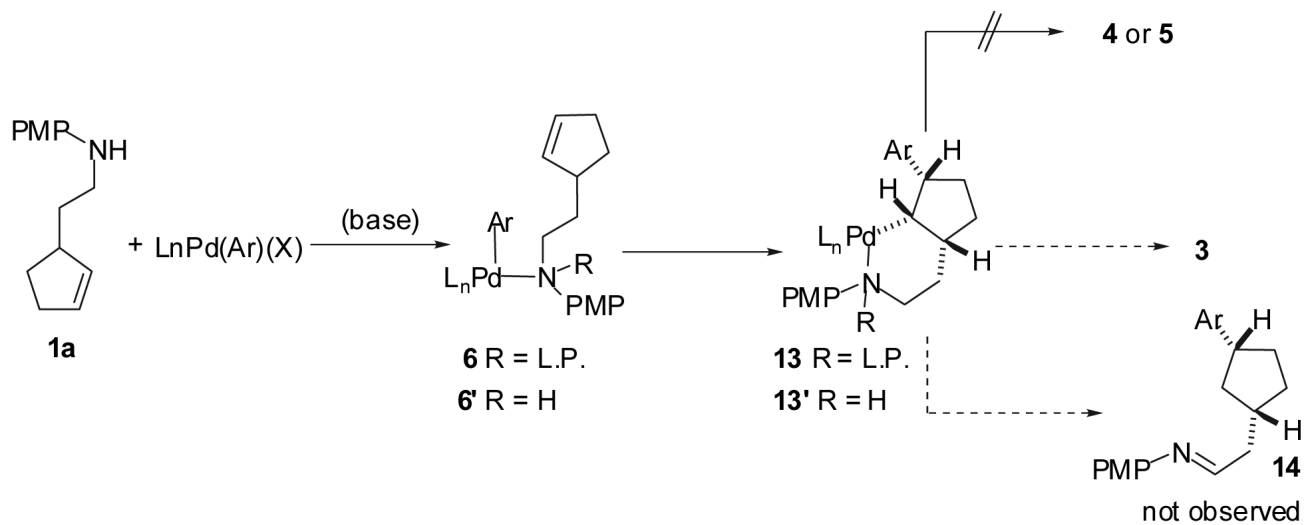
Scheme 3.

Figure 1.

Table 1

Trialkylphosphine Ligand Effects[(a)]

Entry	Ligand	Cone Angle	2	3a	4	5a
1[(b),(c)]	PMe$_3$·HBF$_4$	118[26a]	0	0	**98**	2
2[(b),(c)]	PEt$_3$·HBF$_4$	132[26a]	0	0	**92**	8
3	P(t-Bu)$_2$Me·HBF$_4$	161[26b]	0	0	0	**100**
4	Pd[PMe(t-Bu)$_2$]$_2$	161[26b]	0	0	0	**100**
5	Pd[PCy$_3$]$_2$	170[26a]	1	2	1	**96**
6	PCy$_3$	170[26a]	2	2	6	**90**
7	Pd[P(t-Bu)Cy$_2$]$_2$	174[27]	6	6	0	**88**
8	Pd[P(t-Bu)$_2$Cy]$_2$	178[27]	**81**	5	0	14
9	Pd[P(t-Bu)$_3$]$_2$	182[26a]	**100**	0	0	0
10[(b)]	P(t-Bu)$_3$·HBF$_4$	182[26a]	**98**	2	0	0

(a)Conditions: 1.0 equiv **1a**, 2.0 equiv 4-bromotoluene, 1.2 equiv NaOtBu, 1 mol % Pd$_2$(dba)$_3$, 4 mol % ligand, toluene (0.25 M), 110 °C. The product ratios refer to GC ratios of products **2-5** that have been corrected for GC response factor. All reactions proceed to completion unless otherwise noted.

(b)The reaction was conducted with 1.4 equiv 4-bromotoluene.

(c)The reaction proceeded to 80% conversion.

Table 2

Effect of Other Monodentate Phosphine Ligands[a]

Entry	Ligand	Cone Angle	2	3a	4	5a
1	t-Bu₂P(o-biphenyl) (**10**)		**94**	6	0	0
2	2-(Dicyclohexylphosphino)-2'-(N,N-dimethylamino)biphenyl		**76**	24	0	0
3	Cy₂P(o-biphenyl)		**52**	39	1	8
4	2-(Diphenylphosphino)-2'-(N,N-dimethylamino)biphenyl (**11**)		**56**	40	2	2
5	P(o-tol)₃	194[26a]	18	42	9	31
6	P[C₆H₄(m-CF₃)]₃	165[26c]	4	31	32	33
7	P[C₆H₄(p-CF₃)]₃	145[26d]	3	28	26	43
8	PPh₃	145[26a]	3	9	**55**	33
9	P[C₆H₄(p-OMe)]₃	145[26c]	0	5	**59**	36
10	P(2-furyl)₃		0	8	**82**	10
11	Ph₂PMe	136[26a]	0	0	**86**	14
12[b]	PhPMe₂	122[26a]	0	0	**92**	8

[a]Conditions: 1.0 equiv **1a**, 2.0 equiv 4-bromotoluene, 1.2 equiv NaOtBu, 1 mol % Pd₂(dba)₃, 4 mol % ligand, toluene (0.25 M), 110 °C. The product ratios refer to GC ratios of products **2–5** that have been corrected for GC response factor. All reactions proceed to completion unless otherwise noted.

[b]The reaction was conducted with 1.4 equiv 4-bromotoluene.

Table 3

Effect of Chelating Phosphine Ligands

Entry	Ligand	Bite Angle[c]	2	3a	4	5a
1	dppm	73[29a]	12	11	**51**	26
2	dppe-p-CF$_3$	86[d]	20	25	28	27
3[g]	dppe	86[29a]	5	7	**63**	25
4	dppe-p-OMe	86[d]	3	4	**69**	24
5	dpp-benzene	87[e],29b	**87**	3	7	4
6	dcpe	87[29c]	11	4	19	**66**
7	dppp	91[29a]	31	**58**	8	3
8	BINAP	93[29d]	32	9	37	22
9[g]	dppb	94[29e]	4	10	**56**	30
10	dppf	99[29f]	27	42	12	19
11	dppf-i-Pr	103[29g]	13	12	0	**75**
12	dpe-phos	104[f],29h	19	27	37	17
13	xantphos	108[f],29h	**54**	46	0	0

[a]Conditions: 1.0 equiv **1a**, 2.0 equiv 4-bromotoluene, 1.2 equiv NaOtBu, 1 mol % Pd2(dba)3, 2 mol % ligand, toluene (0.25 M), 110 °C. The product ratios refer to GC ratios of products **2-5** that have been corrected for GC response factor. All reactions proceed to completion unless otherwise noted.

[b]The reaction was conducted with 1.4 equiv 4-bromotoluene.

[c]Bite angles were obtained from crystal structures of bis(phosphine)PdCl2 complexes.

[d]The bite angle was estimated based on analogy to dppe.

[e]The bite angle was obtained from a crystal structure of the bis(phosphine)PdBr2 complex.

[f]The bite angle was obtained from a crystal structure of the bis(phosphine)Pd(1,1-dimethylallyl)tetrafluoroborate complex.
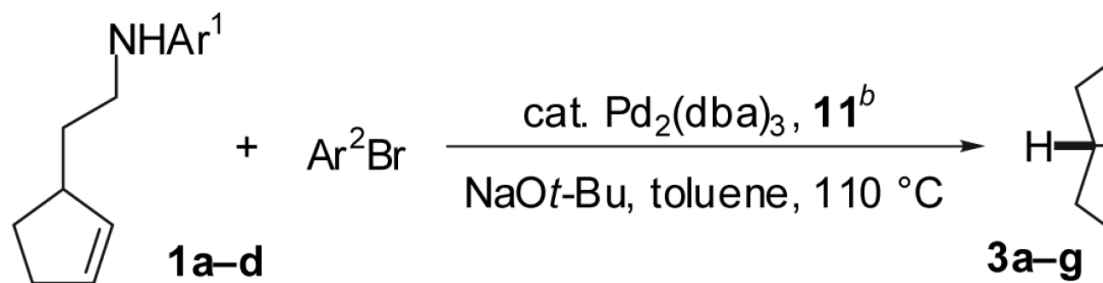
[g]Approximately 3% of an imine side product derived from substrate oxidation was detected by GC and GC/MS analysis of the crude reaction mixture.

Table 4

Selective Synthesis of 3
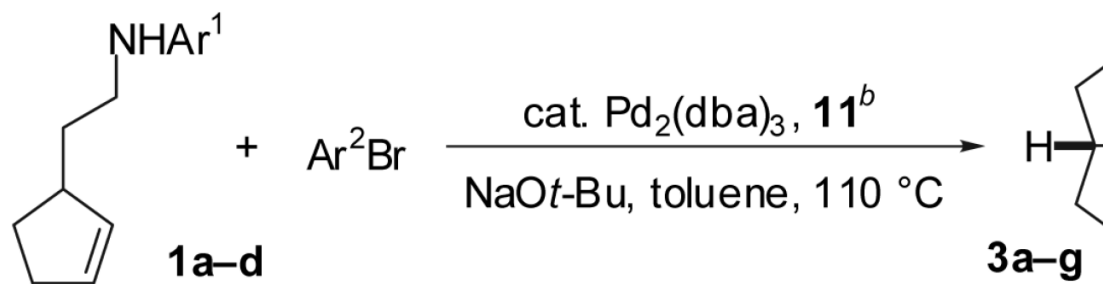
Entry	Substrate[c]	Crude Ratio 2:3:4:5	Product
1	**1a**	25:65:10:0	
2	**1a**	48:48:2:2	**3a**
3	**1b**	20:70:10:0	
4	**1b**	30:65:2:3	**3b**
5	**1c**	10:80:10:0	**3c**

Entry	Substrate[c]	Crude Ratio 2:3:4:5	Product
6	**1c**	0:100:0:0	**3d**
7	**1d**	0:100:0:0	**3e**
8	**1d**	0:90:10:0	**3f**
9	**1d**	30:60:10:0	**3g**

[a] Conditions: 1.0 equiv amine, 1.4 equiv Ar^{2}Br, 1.2 equiv NaOt-Bu, 1 mol % Pd$_2$(dba)$_3$, 2 mol % **11**, toluene (0.25 M), 110 °C.

[b] **11** = 2-diphenylphosphino-2′-(*N,N*-dimethylamino)biphenyl.

[c] **1a**: Ar = p-(MeO)C$_6$H$_4$; **1b**: Ar = p-(Cl)C$_6$H$_4$; **1c** : Ar = p-(NC)C$_6$H$_4$; **1d**: Ar = p-(t-BuO$_2$C)C$_6$H$_4$.

[d] Ligand = dppp.

(e)This material contained 7 % of **4c** as an inseparable impurity.

Table 5

Selective Synthesis of 5
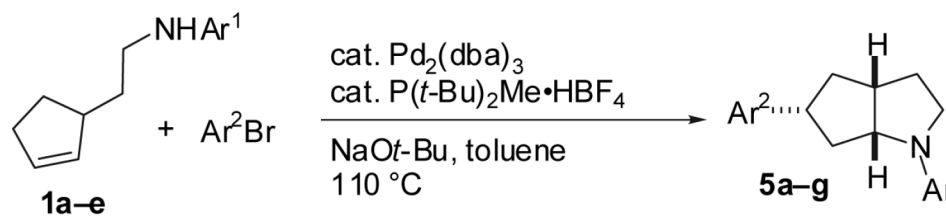
Entry	Substrate[b]	Crude Ratio 2:3:4:5	Product
1	**1a**	0:0:0:100	
2	**1a**	0:0:0:100	
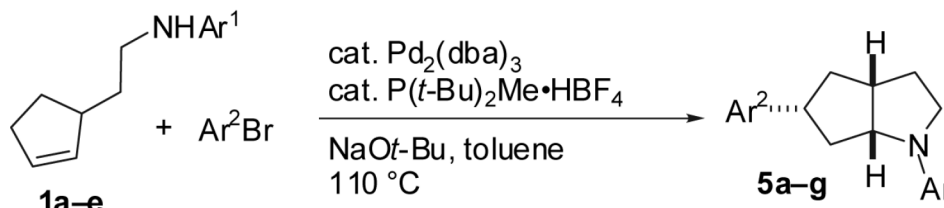
Entry	Substrate[b]	Crude Ratio 2:3:4:5	Product
3	**1b**	0:15:0:85	
4	**1d**	0:10:0:90	
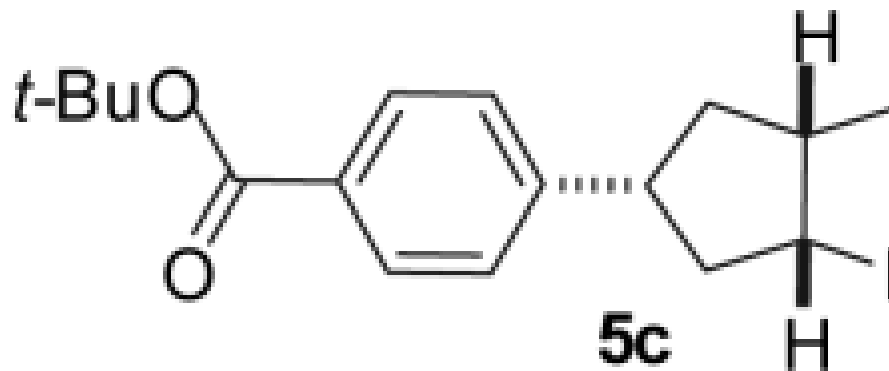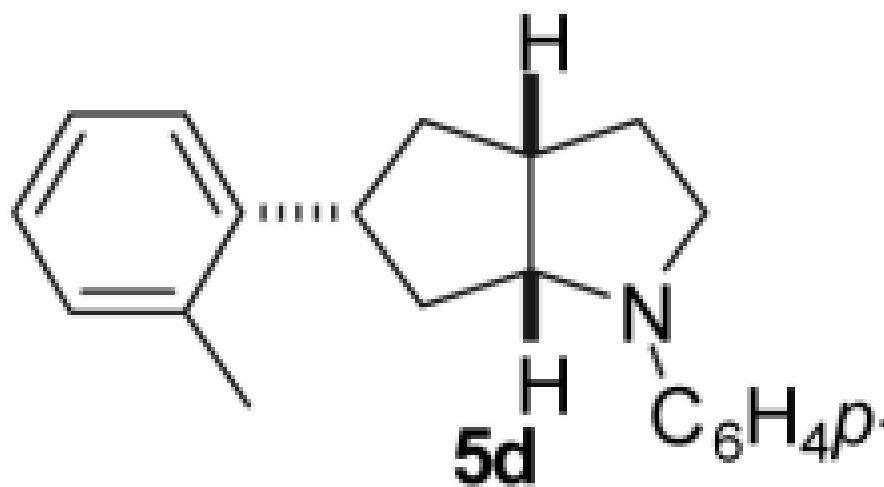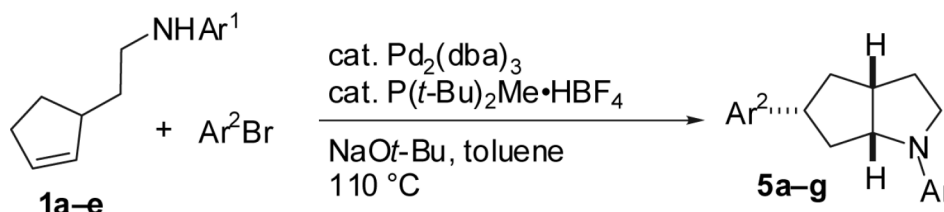
Entry	Substrate[b]	Crude Ratio 2:3:4:5	Product
5	**1c**	5:10:10:75	
6	**1e**	0:10:0:90	
7	**1e**	0:0:0:100	
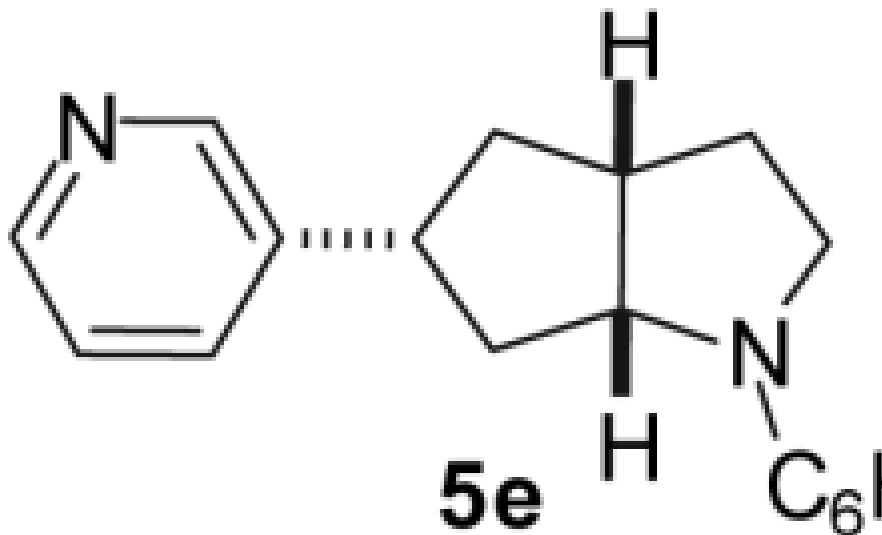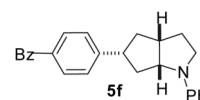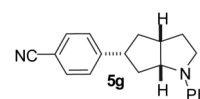
[a]Conditions: 1.0 equiv amine, 1.4 equiv Ar^2Br, 1.2 equiv NaOt-Bu, 1 mol % $Pd_2(dba)_3$, 2 mol % P(t-Bu)$_2$Me·HBF$_4$, toluene (0.25 M), 110 °C.

[b]**1a** : Ar = p-(MeO)C$_6$H$_4$; **1b**: Ar = p-(Cl)C$_6$H$_4$; **1c**: Ar = p-(NC)C$_6$H$_4$; **1d**: Ar =p-(t-BuO$_2$C)C$_6$H$_4$; **1e** Ar = Ph.

[c]This material contained 7 % of isomer **3** as an inseparable impurity.