JOC Article

Application of Secondary Alkyl Halides to a Domino Aryl Alkylation Reaction for the Synthesis of Aromatic Heterocycles

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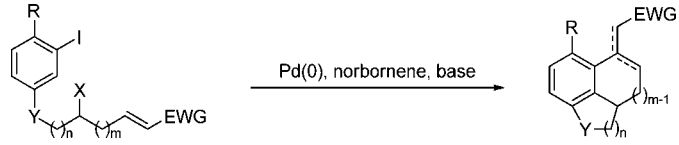
Received September 29, 2008



A palladium-catalyzed, norbornene-mediated *ortho*-alkylation reaction of aryl iodides with secondary alkyl halides is described. Intermolecular or intramolecular *ortho*-alkylation proceeds in a domino process with various termination steps, generating two new carbon−carbon or carbon−nitrogen bonds in one pot, to afford an array of polycyclic heterocycles. The use of enantioenriched substrates has shown that this palladium-catalyzed reaction is stereospecific, proceeding with minimal erosion of ee.

Introduction

Over the last three decades, transition metal catalysis has become an indispensable tool for the formation of new carbon−carbon bonds. A multitude of methods now exist for the coupling of sp-, sp^2- and sp^3-carbon nucleophiles with aryl or alkenyl electrophiles (Csp^2−X, where X = I, Br, Cl, OMs, OTf, N_2). Metals such as palladium and nickel have played a central role in this endeavor.[1] The transition metal catalyzed cross-coupling of β-hydrogen-containing alkyl electrophiles is an inherently more difficult task than it is for aryl or alkenyl electrophiles. The Csp^3−X bond is more electron-rich than the Csp^2−X bond, making oxidative addition of the metal more difficult. If oxidative addition does occur, then the alkylmetal species that results is prone to competing side reactions such as β-hydride elimination and hydrodehalogenation. Despite these difficulties, the cross-coupling reactions of primary alkyl electrophiles (Csp^3−X) have seen significant advances.[2] In contrast, the reaction of secondary alkyl electrophiles remains underdeveloped. Only within the last five years has there been reliable methods that successfully use secondary alkyl halides in cross-coupling reactions. The bulk of these methods have been developed with nickel, iron or cobalt catalysis and it is believed that radical mechanisms are operative. Coupling reactions of secondary alkyl halides with palladium catalysis are far less known.[3] A seminal report by Sustmann in 1986 showed that palladium-catalyzed Stille couplings using a secondary benzylic bromide are possible.[4] Simultaneously, Castle and Widdowson disclosed their results on a palladium-catalyzed reaction of a secondary alkyl iodide with Grignard reagents,[5] which was later disputed by Yuan and Scott.[6] A few reports of cabonylation reactions with secondary alkyl electrophiles were published between 1989−1991.[7] More recently, Glorius reported a Sonogashira coupling of unactivated secondary alkyl bromides[8] and in 2007, Asensio reported the Suzuki coupling of activated secondary bromo sulfoxides.[9] While these advances are sig-

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(4) Sustmann, R.; Lau, J.; Zipp, M. *Tetrahedron Lett.* **1986**, *27*, 5207–5210.

(5) Castle, P. L.; Widdowson, D. A. *Tetrahedron Lett.* **1986**, *27*, 6013–6016.

(6) Yuan, K.; Scott, W. J. *Tetrahedron Lett.* **1989**, *30*, 4779–4782.

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(8) Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925–2928.

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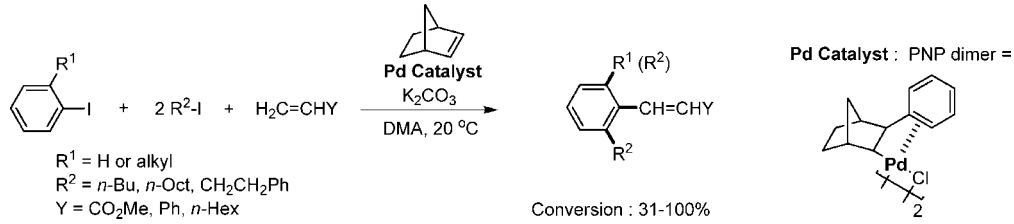
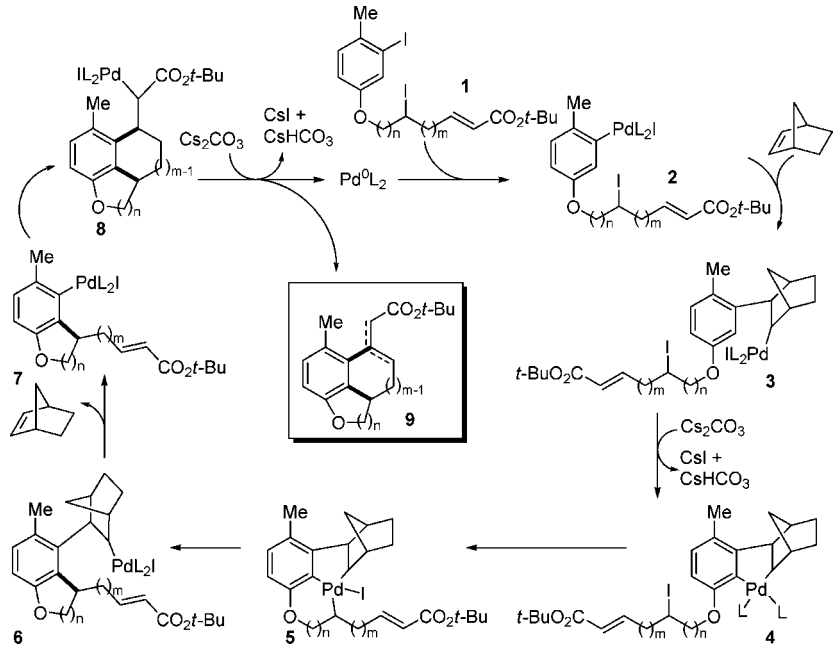
10.1021/jo802180h CCC: $40.75
Published on Web 11/14/2008

SCHEME 1. Catellani Reaction



SCHEME 2. Proposed Reaction Mechanism



nificant, substantial effort still needs to be invested in discovering new and efficient strategies.

Within the realm of transition metal catalyzed carbon−carbon bond formation, the development of domino and/or tandem processes to generate complex molecules from simple substrates is ideal. Unlike stepwise bond formation, domino processes allow for rapid access to target molecules in fewer steps and with reduced waste.[10] In particular, coupling reactions that achieve carbon−carbon bond formation from the direct activation of an aromatic carbon−hydrogen bond are extremely attractive, as they avoid the need for the prefunctionalization of substrates.[11] A particular reaction that incorporates both of these features was first described by Catellani, wherein the *ortho*-carbon−hydrogen bonds of an aryl halide are alkylated, followed by a terminating Heck reaction, to generate functionalized arenes (Scheme 1).[12] This process is catalyzed by palladium and mediated by norbornene to generate up to three carbon−carbon bonds in one pot.

Our focus has been to develop practical reactions, particularly related to the synthesis of functionalized heterocycles.[13] Previously reported methodologies have focused on the use of primary alkyl halides to achieve *ortho*-alkylation of the aryl halide. Catellani has shown in two separate instances that *ortho*-alkylation of the aryl halide is possible with isopropyl iodide.[14] When isopropyl iodide was used in a 4−7 fold excess, up to 71% yield[15] of the desired product was achieved. Herein we report our results on the first examples of intramolecular *ortho*-alkylation reaction of aryl iodides with secondary alkyl iodides and bromides and we also illustrate the scope of the intermolecular process.[16] We have extended the scope of this domino *ortho*-alkylation reaction to include a terminating Heck reaction, the direct arylation of heterocycles and a Buchwald−Hartwig amination to form two new carbon−carbon bonds or a new

(10) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

(11) *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005.

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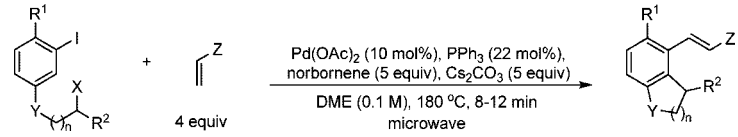
(13) For selected examples with the Heck reaction, see: (a) Piguel, S.; Lautens, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045–1046. (b) Pache, S.; Lautens, M. *Org. Lett.* **2003**, *5*, 4827–4830. (c) Alberico, D.; Paquin, J.-F.; Lautens, M. *Tetrahedron* **2005**, *61*, 6283–6297. With cyanation, see: (d) Mariampillai, B.; Alberico, D.; Bidau, V.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372–15379. With direct arylation, see: (e) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148–13149. (f) Martins, A.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 4827–4829. (g) Blaszykowski, C.; Aktoudianakis, E.; Alberico, D.; Bressy, C.; Hulcoop, D. G.; Jafarpour, F.; Joushaghani, A.; Laleu, B.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 1888–1897. For reduction of the aryl halide bond, see: (h) Wilhelm, T.; Lautens, M. *Org. Lett.* **2005**, *7*, 4053–4056.

(14) (a) Catellani, M.; Cugini, F. *Tetrahedron* **1999**, *55*, 6595–6602. (b) Catellani, M.; Motti, E.; Minari, M. *Chem. Commun.* **2000**, 157–158.

(15) GC yield based on the amount of charged aryl iodide.

(16) For preliminary communications see: (a) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485–1488. (b) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255–5258.

TABLE 1. Synthesis of Bicyclic Heterocycles *via* an *ortho*-Alkylation/Heck Reaction Sequence



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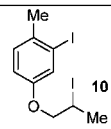
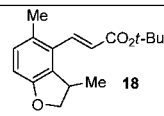
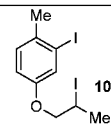
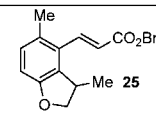
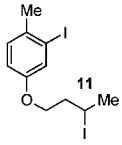
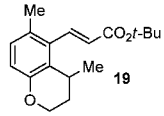
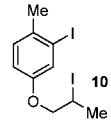
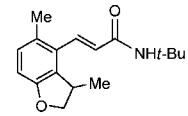
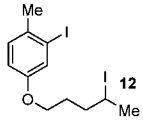
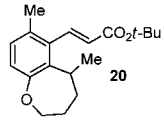
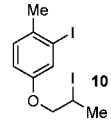
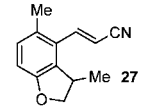
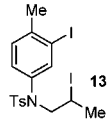
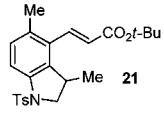
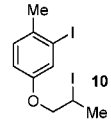
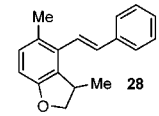
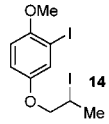
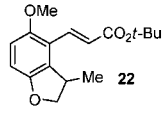
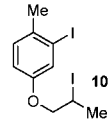
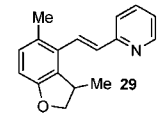
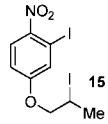
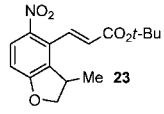
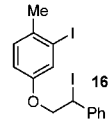
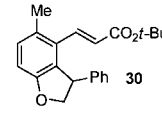
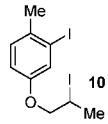
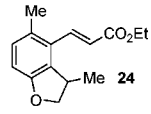
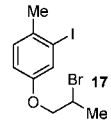
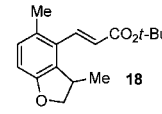
1		CO_2t-Bu		75	8		CO_2Bn		57
2		CO_2t-Bu		49	9		C(O)NHt-Bu		66
3		CO_2t-Bu		0	10		CN		44
4[a]		CO_2t-Bu		54	11		Ph		35
5		CO_2t-Bu		40	12		2-pyridyl		58
6		CO_2t-Bu		0	13		CO_2t-Bu		0
7		CO_2Et		79	14		CO_2t-Bu		24[b] 49[c]

[a] Conditions (unoptimized): $Pd(OAc)_2$ (20 mol%), PPh_3 (44 mol%), *tert*-butyl acrylate (4 equiv), norbornene (5 equiv), Cs_2CO_3 (3 equiv), DME (0.1 M), 180 °C, oil bath, 12 min. [b] Recovered starting material 45%. Yield of **18** brsm = 44%. [c] Conditions (unoptimized): $Pd(OAc)_2$ (10 mol%), TFP (22 mol%), *tert*-butyl acrylate (4 equiv), norbornene (5 equiv), Cs_2CO_3 (5 equiv), CH_3CN (0.1 M), 180 °C, microwave, 8 min.

carbon−carbon and carbon−nitrogen bond in one pot. The resulting products are polycyclic heterocycles containing up to five fused rings.

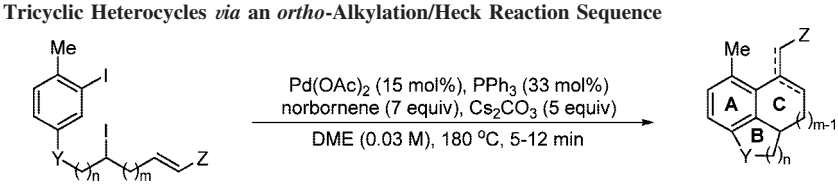
Results and Discussion

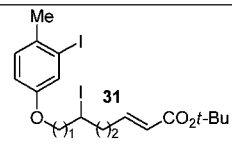
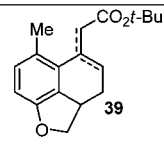
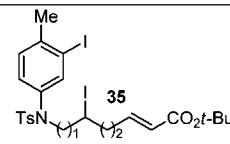
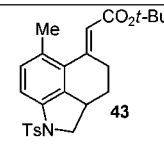
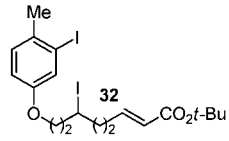
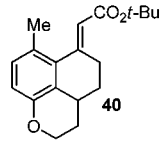
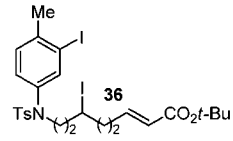
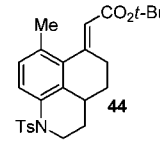
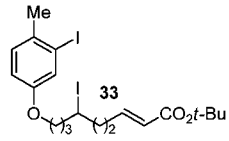
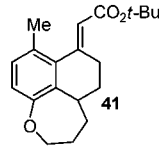
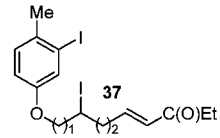
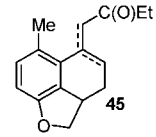
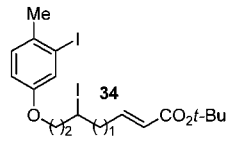
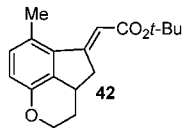
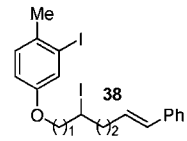
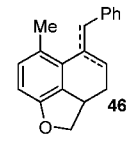
Reaction Mechanism. The proposed reaction mechanism of a representative secondary alkyl halide substrate, based upon the findings of Catellani is shown in Scheme 2.[12] The reaction begins with the oxidative addition of Pd(0) to **1** to form arylpalladium iodide **2**. Carbopalladation of norbornene follows to form *cis*-,*exo*-complex **3**.[17] Due to the lack of *syn*-β-hydrogens, **3** preferentially forms palladacycle **4** *via* the activation of an aromatic *ortho*-carbon−hydrogen bond, rather than undergo *anti*-β-hydride elimination. Oxidative addition of palladium to the alkyl iodide follows to form Pd(IV) complex **5**, which quickly reductively eliminates to form the first carbon−carbon bond in Pd(II) intermediate **6**. Norbornene is then extruded from the system forming Pd(II) intermediate **7**, which undergoes a Heck coupling (or other palladium-mediated process, *vide infra*) to form the final product **9**.

Intramolecular *ortho*-Alkylation/Intermolecular Heck Reaction for the Synthesis of Bicyclic Heterocycles. We originally hypothesized that an intramolecular *ortho*-alkylation of secondary alkyl halides would be a more facile process than an intermolecular reaction. Moreover, only one equivalent of

(17) In the presence of an external Heck acceptor, coordination of norbornene to intermediate **2** is preferred due to the steric strain relief associated with carbopalladation to form intermediate **3**. While norbornene is theoretically required in catalytic amounts, often stoichiometric quantities are used to moderate the competitive reactions in the system, namely direct Heck reaction of intermediate **2**. For further information, see ref 12d.

TABLE 2. Synthesis of Tricyclic Heterocycles *via* an *ortho*-Alkylation/Heck Reaction Sequence



entry	substrate	product	yield (%)	entry	substrate	product	yield (%)
1			78[a]	5[c]			68
2			74	6[c]			62
3			13	7			75[d]
4[b]			12	8			53[e]

[a] Ratio of *exo*:*endo* double bond isomers (**39a**:**39b**), 5:1. [b] Reaction run in the microwave at 180 °C, for 8 min. [c] Conditions: $Pd(OAc)_2$ (20 mol%), PPh_3 (44 mol%), norbornene (7 equiv), Cs_2CO_3 (3 equiv), DME (0.03 M), 150 °C, oil bath, 12 min. [d] $Pd(OAc)_2$ (10 mol%), PPh_3 (22 mol%), norbornene (7 equiv), Cs_2CO_3 (5 equiv), DME (0.03 M), 180 °C, microwave, 11 min. Ratio of *exo*:*endo* double bond isomers (**45a**:**45b**), 1:1.5. [e] $Pd(OAc)_2$ (10 mol%), PPh_3 (22 mol%), norbornene (7 equiv), Cs_2CO_3 (5 equiv), DME (0.03 M), 180 °C, microwave, 11 min. Ratio of *exo*:*endo* double bond isomers (**46a**:**46b**), 5:1.

the alkyl halide is required, thereby preventing the use of a large excess of reagents. Good yields of the desired product would indicate that competing side reactions such as β-hydride elimination and hydrodehalogenation had mostly been suppressed. To test this hypothesis, we tethered a secondary alkyl iodide *via* an oxygen or nitrogen linker, to the aryl iodide. In the presence of palladium, norbornene, base and an external Heck acceptor, we could form oxygen- and nitrogen-containing functionalized bicyclic heterocycles (Table 1).

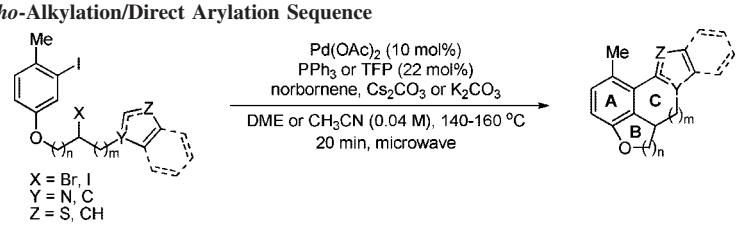
In all cases, the *ortho*′-position of the aryl iodide has been blocked by an alkyl or functional group. *ortho*-Alkylation to form five- and six-membered rings (Table 1, entries 1 and 2) proceeded in moderate to good yields, where alkylation to form a seven-membered ring did not produce any of the desired product (entry 3). Substituting aniline for phenol on the aryl iodide (entry 4) gave the desired product in moderate yield, although 20 mol% of Pd was necessary in this case. Substituting the methyl *ortho*-blocker for methoxy (entry 5) lead to a decrease in yield and a nitro-*ortho*-blocker did not afford the desired product (entry 6). We next investigated the scope of Heck acceptors that could be used in this reaction (entries 7−12). Most of the desired products were isolated in moderate to good yields and even unactivated acceptors such as styrene (entry 11) worked well in this reaction. Product **27** from the reaction with acrylonitrile (entry 10) easily isomerizes to the *cis*- isomer when exposed to light. The reaction of a secondary benzylic iodide **16** under the standard reaction conditions gave a messy reaction and none of the desired product **30** was isolated (entry 13). Reaction of secondary alkyl bromide **17** under the optimized conditions gave 24% yield of the desired product, with 45% of starting material being recovered (entry 14). Changing the ligand to tri-2-furylphoshine (TFP) and the solvent to acetonitrile afforded product **18** in 49% yield.

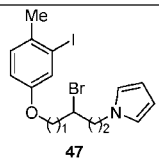
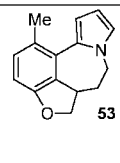
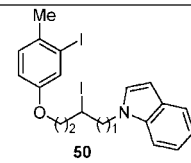
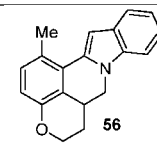
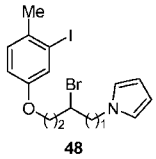
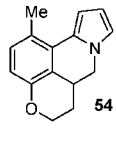
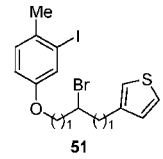
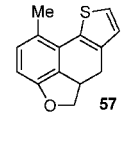
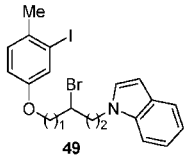
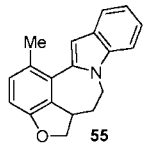
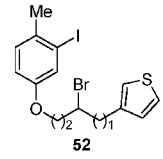
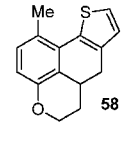
Intramolecular *ortho*-Alkylation/Heck Reaction for the Synthesis of Tricyclic Heterocycles. Tethering the Heck acceptor to the alkyl halide would allow for a domino intramolecular *ortho*-alkylation/intramolecular Heck reaction sequence to afford functionalized tricyclic heterocycles (Table 2).

Products with 6,5,6- or 6,6,6-ring systems (A,B,C-ring system as depicted in scheme above) were afforded in good yield (Table 2, entries 1, 2, 5, 6). Product **43** is particularly interesting as it closely resembles the core of lysergic acid.[18] *ortho*-Alkylation of substrate **33** to make a 6,7,6-annulated product **41** proceeded in poor yield (entry 3). The major byproduct in this case was the incorporation of norbornene on the aromatic ring, suggesting that reductive elimination of palladium to form the norbornene aduct outcompetes the rate of intramolecular cyclization to form a seven-membered ring. Substrate **34** underwent the annulation reaction to afford 6,6,5-ring system **42** in poor yield (entry 4). Elimination of HI from **34** occurred preferentially to give the conjugated dieneone. A limited Heck acceptor scope was also investigated for this domino cyclization. Substrates bearing ethyl vinyl ketone (**37**) and styrene (**38**) as Heck acceptors proceeded

(18) Rehacek, Z.; Sajdi, P. *Ergot Alkaloids: Chemistry, Biological Effects, Biotechnology*; Elsevier Science: Amsterdam, 1990.

TABLE 3. Intramolecular *ortho*-Alkylation/Direct Arylation Sequence



entry	substrate	product	yield (%)	entry	substrate	product	yield (%)
1[a]	 **47**	 **53**	84	4[c]	 **50**	 **56**	33
2[b]	 **48**	 **54**	54	5[d]	 **51**	 **57**	90
3[a]	 **49**	 **55**	87	6[d]	 **52**	 **58**	29

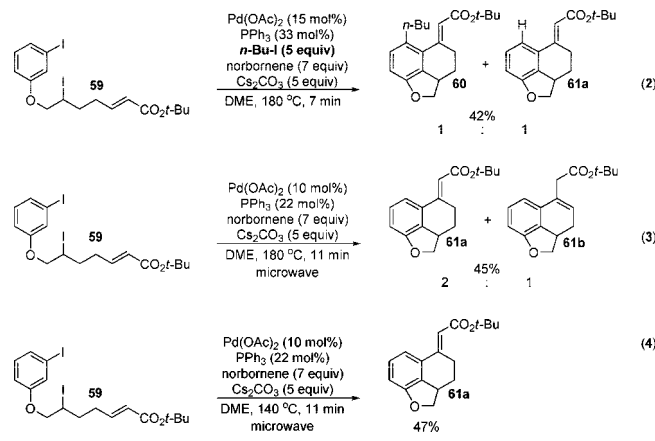
[a] Conditions: $Pd(OAc)_2$ (10 mol%), TFP (22 mol%), norbornene (5 equiv), Cs_2CO_3 (3 equiv), CH_3CN (0.04 M), 160 °C, microwave, 20 min. [b] Conditions: $Pd(OAc)_2$ (10 mol%), TFP (22 mol%), norbornene (5 equiv), K_2CO_3 (3 equiv), CH_3CN (0.04 M), 160 °C, microwave, 20 min. [c] Conditions: $Pd(OAc)_2$ (10 mol%), PPh_3 (22 mol%), norbornene (7 equiv), Cs_2CO_3 (5 equiv), DME (0.04 M), 140 °C, microwave, 20 min. [d] Conditions: $Pd(OAc)_2$ (10 mol%), TFP (22 mol%), norbornene (5 equiv), Cs_2CO_3 (2 equiv), CH_3CN (0.04 M), 160 °C, microwave, 20 min.

to afford the expected products in moderate to good yields (entries 7 and 8). Interestingly, only those products with an oxygen-containing five-membered B-ring (**39**, **45**, **46**, entries 1, 7, 8) were obtained as separable mixtures of exo- and endocyclic double bond isomers.

Intramolecular *ortho*-Alkylation/Direct Arylation Sequence for the Synthesis of Tetra- and Pentacyclic Heterocycles. To further expand the scope of the intramolecular *ortho*-alkylation of secondary alkyl halides, we chose to investigate the direct arylation of various heterocycles[13e−g,19] as a termination step to the reaction (Table 3). This reaction sequence would involve two carbon−hydrogen activation steps to form two new carbon−carbon bonds in one pot, affording novel tetra- and pentacyclic heterocycles.

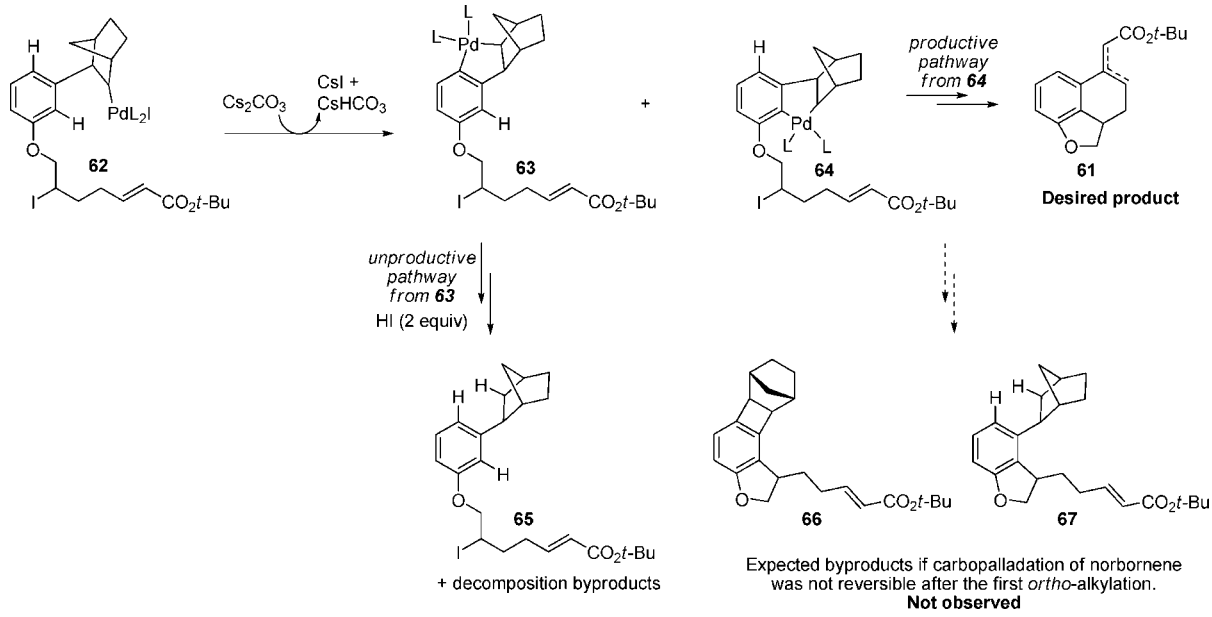
The direct arylation works with pyrrole, indole and thiophene. Other heterocycles such as pyrazole and furan were not attempted, although they have been previously shown to work in the reaction of primary alkyl halides.[13f,g] *ortho*-Alkylation to form five-membered rings is facile and the yield of these systems appears to be independent of the ring size formed during the direct arylation step (Table 3, entries 1, 3, 5). The yield of the desired compounds drops significantly when *ortho*-alkylation to form six-membered rings was attempted (entries 2, 4, 6). Secondary alkyl bromides in these systems gave better isolated yields overall, except in the case of substrate **50** (entry 4) which uses a secondary alkyl iodide.

Reaction of an Unsubstituted *ortho′*- Subtrate. We wished to investigate the reaction of substrate **59**, where the *ortho′*-position is unsubstituted, in the presence of an intermolecular primary alkyl halide (eq 2). During our preliminary screening of reaction conditions using 1-iodobutane as the intermolecular alkyl halide, we isolated the desired product **60** and another annulated compound **61a**, where the butyl chain had not been incorporated into the *ortho′*-position. This result was noteworthy as it is the first report of a synthetically useful single *ortho*-functionalization in an *ortho*-unsubstituted substrate. Removing 1-iodobutane from the reaction lead to a 45% yield of the annulated products **61a** and **61b** as a 2:1 (*exo*:*endo*) mixture of double bond isomers (eq 3). When the reaction temperature was reduced to 140 °C, **61a** was isolated solely in 47% yield (eq 4).



Closer inspection of the proposed mechanism for this reaction allows us to rationalize our observations and draw some new conclusions (Scheme 3). Reaction intermediate **62** is analogous

SCHEME 3. Mechanistic Rationale for the Reaction of *ortho′*-Unsubstituted Substrate 59



to intermediate **3** in Scheme 1. This intermediate results from the oxidative addition of Pd(0) to the aryl iodide bond, followed by carbopalladation of norbornene. Because intermediate **62** contains two *ortho*-hydrogens, palladacycles **63** and **64** can be formed, although it is unknown if they are formed with equal probability.[20] Further reaction of palladacycle **64** can be labeled as a "productive pathway" leading to the desired product **61**. Reaction of **63** can be labeled as an "unproductive pathway" and is likely the reaction pathway leading to isolated byproduct **65**. (It should be noted that byproduct **65** can also arise from the reduction of intermediates **62** or **64**). The reduction of palladacycles (such as **63**) by HI had been previously documented by Catellani.[12d] An interesting piece of mechanistic information gained from this reaction involves the extrusion of norbornene from the reaction intermediates. From the original mechanistic investigations done by Catellani, it was proposed that if both *ortho*-positions of the aryl iodide were unsubstituted, palladacycle formation/*ortho*-alkylation would occur successively until both *ortho*-positions were alkylated. Norbornene would finally be extruded from the system due to the steric congestion caused by the two substituted *ortho*-positions.[12d] The isolation of product **61** and the absence of expected byproducts **66** and **67** would indicate that norbornene extrusion can occur prior to the second *ortho*-alkylation.

Intermolecular *ortho*-Alkylation/Buchwald−Hartwig Amination Sequence for the Synthesis of Substituted Indolines. During our investigations toward the synthesis of substituted indolines *via* an intermolecular *ortho*-alkyation/Buchwald-Hartwig amination of primary bromoethylamines,[16b] we discovered that a major byproduct of the reaction was the intramolecular cyclization of the bromoethylamines to form aziridines. We envisioned that one way to impede this intramolecular aziridine formation would be to use secondary bromoethylamines (Table 4).

While we attempted to reduce the rate of intramolecular aziridination of the bromoethylamines, the added steric bulk of the secondary alkyl bromide also reduces the rate of oxidative addition.[21] Nevertheless, we saw the development of this reaction as a worthwhile endeavor, as it would add to the body of evidence on couplings of secondary alkyl halides. Furthermore, the development of new methods for the synthesis of substituted indolines is important as they are biologically active motifs found in alkaloids and pharmaceuticals.[22] Proper protection of the primary amine was vital for the success of this reaction. While the ethyl carbamate gave us low yields of the desired product (entry 1), the use of a *p*-nitrophenyl protecting group[16b] gave us the best yields of our model system (entry 2). Although **71** is isolated in moderate yield, this remains the first example of an intermolecular reaction of a secondary alkyl halide in this palladium-catalyzed process to be achieved in synthetically useful isolated yields. Notably, this was accomplished with only one equivalent of the alkyl halide. However, expansion of the reaction scope to incorporate various substituted aryl iodides was limited. Reaction of 1-iodonaphthalene (entry 3) afforded product **72** in moderate yield, while the reaction of an aryl iodide bearing an electron-withdrawing group gave the desired product in lower yield (entry 4). The use of electron-donating 1-iodo-2-methoxybenzene did not afford any of the desired product (entry 5).

Reaction of Enantioenriched Substrates. Our next goal was to investigate the use of enantioenriched substrates to test

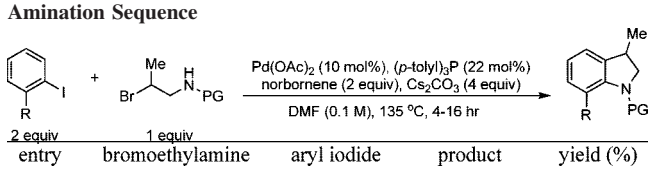
(19) For reviews on direct arylation, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (c) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35–41. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (e) Godula, K.; Sames, D. *Science* **2006**, *312*, 67–72. (f) Miura, M.; Satoh, T. *Top. Organomet. Chem.* **2005**, *14*, 55–83. (g) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625–655. (h) Echavarren, A. M.; Gómez-Lor, B.; González, J. J.; de Frutos, O. *Synlett* **2003**, 585–59. (i) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211–241. (j) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699–1712.

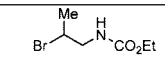
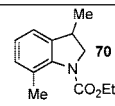
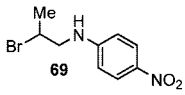
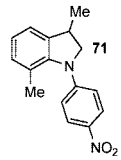
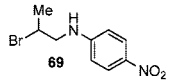
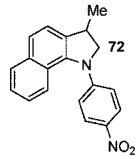
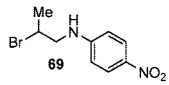
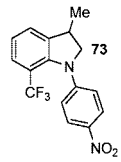
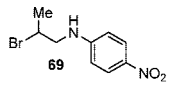
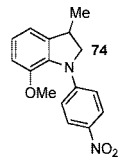
(20) Previous studies by Catellani on palladacycle formation with analogous 1-iodo-3-methoxybenzene show that reaction at the C−H bond next to the methoxy group is preferred, see: (a) Catellani, M.; Chiusoli, G. P.; Ricotti, S. *J. Organomet. Chem.* **1985**, *296*, C11−C15. (b) Catellani, M.; Ferioli, L. *Synthesis* **1996**, 769–772.

(21) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749–5752.

(22) For example, see: (a) Sunazuka, T.; Shirahata, T.; Tsuchiya, S.; Hirose, T.; Mori, R.; Harigaya, Y.; Kuwajima, I.; Ōmura, S. *Org. Lett.* **2005**, *7*, 941–943. (b) Sakashita, H.; Akahoshi, F.; Yoshida, T.; Kitajima, H.; Hayashi, Y.; Ishii, S.; Takashina, Y.; Tsutsumiuchi, R.; Ono, S. *Bioorg. Med. Chem.* **2007**, *15*, 641–655.

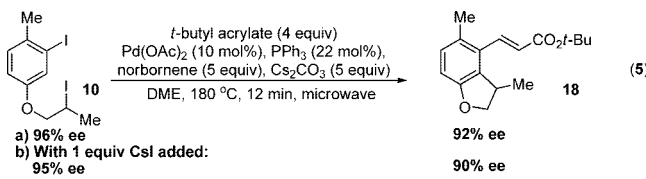
TABLE 4. Intermolecular *ortho*-Alkylation/Buchwald−Hartwig Amination Sequence

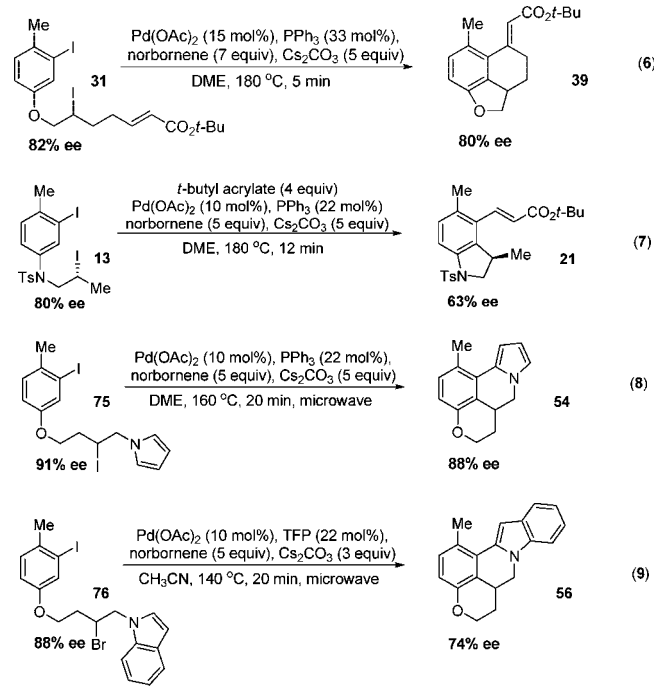


entry	bromoethylamine	aryl iodide	product	yield (%)
1[a]	 **68**		 **70**	24
2	 **69**		 **71**	55
3	 **69**		 **72**	31
4	 **69**		 **73**	19
5	 **69**		 **74**	0

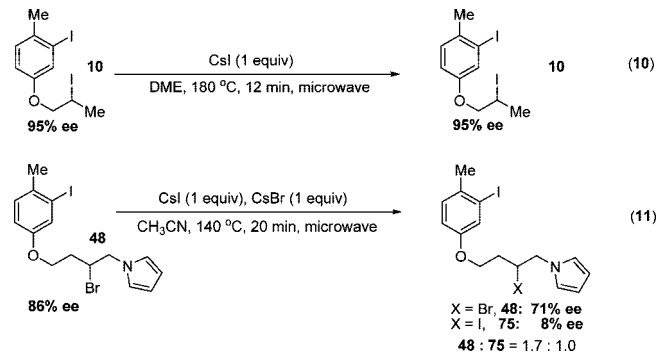
[a] Conditions: $Pd(OAc)_2$ (10 mol%), TFP (22 mol%), norbornene (2 equiv), Cs_2CO_3 (4 equiv), CH_3CN (0.1 M), 135 °C, 16 hrs.

whether this palladium-catalyzed process proceeds in a stereospecific manner and if so, whether the reaction proceeds with overall inversion or retention of configuration. Several model systems were synthesized, including phenol (eq 5, 6, 8, 9) and aniline (eq 7) analogues, secondary alkyl iodides (eqs 5–8) and bromides (eq 9) as well as those bearing pendant Heck acceptors (eq 6) or heterocycles (eq 8, 9) for a terminating direct arylation reaction. The reaction of secondary alkyl iodide substrates tethered through the phenol proceeded to give the annulated products with minimal erosion of ee (eq. 5, 6, 8). Secondary alkyl iodide substrate **13** tethered through the aniline, gave the desired product, but in diminished ee (eq. 7). Similarly, secondary alkyl bromide substrate **76** also proceeded to give the annulated product in diminished ee (eq. 9).





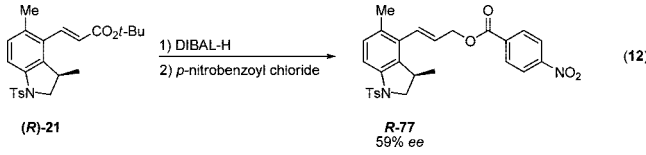
Because the greater extent of erosion in ee occurs with aniline-tethered secondary iodide **13** (eq 7) as compared to the analogous phenol-tethered secondary iodide **10** (eq 5), this indicates that the loss in ee may be due to anchimeric assistance of the heteroatom. However, we cannot rule out the possibility that the two equivalents of CsI generated during the reaction may also be responsible for the loss in ee in the annulated products. To determine the cause for the erosion in ee, we added one equivalent of CsI in the annulation reaction of **10** (eq 5b), but no further erosion in ee was detected. Speculating that CsI may not be soluble in DME to racemize **10**, we heated **10** in the presence of one equivalent of CsI in DME at 180 °C for 12 min (eq 10). Substrate **10** was recovered with the same level of enantioenrichment, indicating that under the palladium-catalyzed reaction conditions, any erosion in ee likely arises form anchimeric assistance of the heteroatom. Because we observed more of an erosion in ee with secondary bromide **76** (eq 9), we speculate that the reaction conditions may play an important role in the enantioenrichment observed in the annulated product. As the reaction of **76** was run in acetonitrile, the two equivalents of CsX (one equivalent each of CsBr and CsI) generated during the reaction may be more soluble in this solvent than in DME. Moreover, anchimeric assistance of the phenolic oxygen in this



case is less likely, as it would involve the formation of a four-membered ring. To test this hypothesis, we also heated

secondary bromide substrate **48** with one equivalent each of CsI and CsBr in acetonitrile at 140 °C for 20 min (eq 11). The results of this experiment indicate the reaction conditions are important for maintaining the levels of enantioenrichment in the annulated products. Presumably due to the higher solubility of CsI in acetonitrile, a portion of substrate **48** is converted to the corresponding iodide **75**, in nearly racemic form (8% ee). Substrate **75** is also able to react under the palladium-catalyzed conditions to form the same final product. The ee of remaining **48** was eroded at a much slower rate (71% ee remaining), within the given reaction time.

In order to determine whether the palladium-catalyzed annulation proceeded with overall inversion or retention of configuration, we aimed to obtain the crystal structures for an enantioenriched substrate and the corresponding annulated product. Derivatization of product **21** gave a crystalline product **77** (eq 12) that could be analyzed by X-ray crystallography. Along with the X-ray structure of substrate **13**, we determined that the palladium-catalyzed annulation depicted in equation 7 proceeded with inversion of configuration at the chiral center.[16a]



(12)

Investigations on the stereochemical course of palladium-catalyzed reactions are scarce in the literature and most are restricted to oxidative addition to zerovalent palladium species. From the pioneering work of Stille, it was shown indirectly that oxidative addition to Pd(0) occurred with inversion of configuration at the stereogenic center.[23] Further studies done by Netherton and Fu[24] on the Suzuki coupling of chiral primary deuterated tosylates also showed that oxidative addition to Pd(0) proceeds with inversion of configuration. Asensio and coworkers reported that the Suzuki coupling of boronic acids to chiral secondary 1-bromoethyl arylsulfoxides proceeded with an overall inversion of configuration, although they were unable to directly prove at which step of the catalytic cycle the inversion of configuration occurs.[9] Previous investigations of transmetalation[25] to Pd(II) and have shown that the stereochemistry may depend on substrate class[22a] and/or reaction conditions.[22b]

To our knowledge, the only report in the literature on the stereochemistry of oxidative addition/reductive elimination in a Pd(II)/(IV) system, which is a proposed mechanistic pathway for this reaction (intermediates **4**−**6**, Scheme 1), is again limited to the pioneering work of Stille.[26] In his investigations, it was found that oxidative addition of a chiral primary deuterated benzyl bromide to Pd(II) proceeded with inversion of configuration while reductive elimination from Pd(IV) occurs with retention of configuration. Regarding this investigation, if we assume that reductive elimination from Pd(IV) species **5** (Scheme 1) of the palladium-catalyzed annulation also proceeds with retention of configuration, then we propose that the inversion of stereochemistry in this reaction likely occurs during the oxidative addition of the secondary alkyl halide to Pd(II) intermediate **4** to form Pd(IV) intermediate **5**. This is consistent with oxidative addition of palladium occurring by an S_N2 mechanism.[27]

Conclusions

We have developed a route to polycyclic heterocycles using a palladium-catalyzed norbornene-mediated domino process involving the intramolecular or intermolecular *ortho*-alkylation of aromatic carbon−hydrogen bonds with secondary alkyl iodides and bromides. We have significantly expanded the scope of this reaction to include a number of terminating reactions such as a Heck reaction, direct arylation of heterocycles and a Buchwald-Hartwig amination. The process creates up to two new carbon−carbon bonds or a carbon−nitrogen bond in one pot and can form products of medicinal value, with up to five fused rings. The products are rapidly accessed within minutes using microwave irradiation or heating in an oil bath. Furthermore, the reaction of enantioenriched substrates occurs in a stereospecific manner to give the desired products with little loss in ee. X-ray crystallography has shown that the reaction proceeded with an overall inversion of configuration at the chiral center, suggesting that oxidative addition of the alkyl halide to our proposed Pd(II) intermediate occurred via an S_N2 mechanism and reductive elimination from Pd(IV) proceeds with retention of configuration. To our knowledge, this is one of the few stereochemical investigations of a Pd(II)/(IV) catalytic cycle, outside of the pioneering discoveries of Stille. Investigations toward the development of an asymmetric process from racemic substrates is currently underway.

Experimental Section

The following is a representative experimental procedure for the palladium-catalyzed norbornene-mediated annulations reaction of secondary alkyl halides. Specific experimental details and characterization data for the aforementioned compounds and other new compounds can be found in the Supporting Information.

General Procedure for the Palladium-Catalyzed Annulation Reaction. To a 2−5 mL microwave vial was added the substrate (0.1−0.2 mmol, 1 equiv), base (Cs_2CO_3 or K_2CO_3, 2−5 equiv), $Pd(OAc)_2$ (10−20 mol%), ligand (22−44 mol%), norbornene (2−7 equiv) and if applicable, a Heck acceptor (4 equiv) or an aryl iodide (2 equiv). The vial was sealed with a septum and flushed with nitrogen. Solvent (2−7 mL) was added and the reaction mixture was stirred at room temperature for 2−5 min. The reaction vessel was then placed in a preheated oil bath, or in a microwave reactor and heated to 135−180 °C for 5 min to 16 h. The reaction mixture was then cooled to ambient temperature, diluted with

(23) (a) Lau, K. S. Y.; Fries, R. W.; Stille, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 4983–4986. (b) Stille, J. K.; Lau, K. S. Y. *J. Am. Chem. Soc.* **1976**, *98*, 5841–5849.

(24) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910–3912.

(25) (a) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666–15667. (b) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461–470. (c) Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458–460. (d) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1–5. (e) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793–7794. (f) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129–6137. (g) Bäckvall, J. E.; Åkermark, B. *J. Chem. Soc., Chem. Commun.* **1975**, 82–83.

(26) For a review of oxidative addition and reductive elimination, including stereochemical issues regarding Pd(II)−Pd(IV) intermediates, see: (a) Stille, J. K. *The Chemistry of the Metal-Carbon Bond*; Vol. 2; Hartley, F. R., Patai, S., Eds.; Wiley: New York, 1985; Chapter 9. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981–4991. (c) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992–4998.

(27) For a discussion regarding S_N2 vs. direct insertion pathways of oxidative addition, see: (a) Collman, J. P.; Hegedus, L. S. L. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1980; Chapter 4. See also: (b) Byers, P. K.; Canty, A. J.; Crespo, M.; Puddephatt, R. J.; Scott, J. D. *Organometallics* **1988**, *7*, 1363–1367. (c) Aye, K.-T.; Canty, A. J.; Crespo, M.; Puddephatt, R. J.; Scott, J. D.; Watson, A. A. *Organometallics* **1989**, *8*, 1518–1522.

diethyl ether and filtered over celite. The filtrate was concentrated and the crude product was purified by flash chromatography.

Acknowledgment. We gratefully acknowledge the financial support of the Natural Sciences and Engineering Research Council (NSERC) of Canada, the Merck Frosst Centre for Therapeutic Research for an Industrial Research Chair, and the University of Toronto. We thank Dr. Alan Lough (University of Toronto) for X-ray analysis. We also thank Sylvia Xin Nie for the preparation of starting materials. A.R. thanks NSERC for a Canada Graduate Scholarship. N.R. thanks the Deutsche Forschungsgemeinschaft (DFG) for a postdoctoral fellowship. M.-O.T.-S. thanks NSERC for an Undergraduate Student Research Award.

Supporting Information Available: Experimental details crystallography and characterization data for all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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