Pure Appl. Chem., Vol. 78, No. 2, pp. 351–361, 2006.
doi:10.1351/pac200678020351

Palladium-catalyzed ring-forming reactions: Methods and applications*

Mark Lautens‡, Dino Alberico, Cyril Bressy, Yuan-Qing Fang, Brian Mariampillai, and Thorsten Wilhelm

Davenport Laboratories, Chemistry Department, University of Toronto, Toronto, Ontario M5S 3H6, Canada

Abstract: Several Pd-catalyzed cyclization methods were developed, including norbornene-mediated Catellani-type reactions, a Pd-catalyzed coupling reaction of aryl iodides and allyl moieties, and a tandem C–N/C–C coupling of *gem*-dihalovinyl systems. These ring-forming methods were applied to the synthesis of highly functionalized carbocyclic and heterocyclic compounds. Intermolecular Pd-catalyzed methods for synthesis of highly substituted arene compounds were also developed.

Keywords: palladium; tandem reactions; cyclization; coupling; indole; heterocycles; direct arylation.

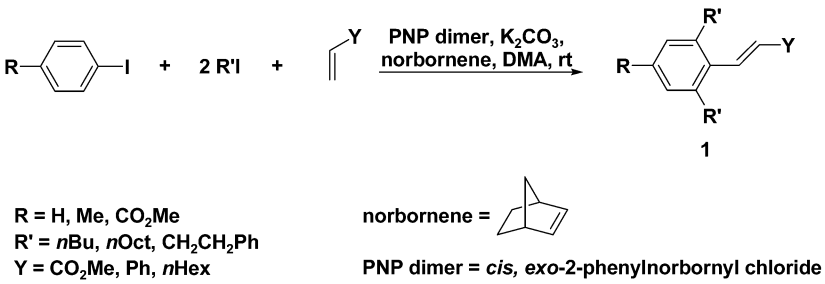
INTRODUCTION

For many years, Pd-catalyzed reactions have served as one of the most reliable and versatile methods for the synthesis of organic compounds [1]. In particular, great attention has been given to Pd-catalyzed ring-forming processes [2]. Our group has been interested in the development of new Pd-catalyzed cyclization methods for the synthesis of highly functionalized carbocyclic and heterocyclic compounds from relatively simple and readily accessible starting materials. The discussion below describes various Pd-catalyzed cyclization processes involving a broad range of substrates that result in an assortment of complex carbocycles and heterocycles. In addition, further application of these Pd-catalyzed methods to the development of highly functionalized arene compounds will also be presented.

THE CATELLANI REACTION

Catellani discovered a remarkable norbornene-mediated Pd-catalyzed reaction whereby three carbon–carbon bonds are formed in one-pot [3]. In this process, an aryl iodide reacts with an alkyl halide and a Heck acceptor in the presence of norbornene, a Pd catalyst and a base to form *ortho,ortho'*-disubstituted vinylarenes **1** (Scheme 1). The norbornene is crucial to the reaction in that it acts as a scaffold involved in the assembly of the molecule, yet is not incorporated in the final product.

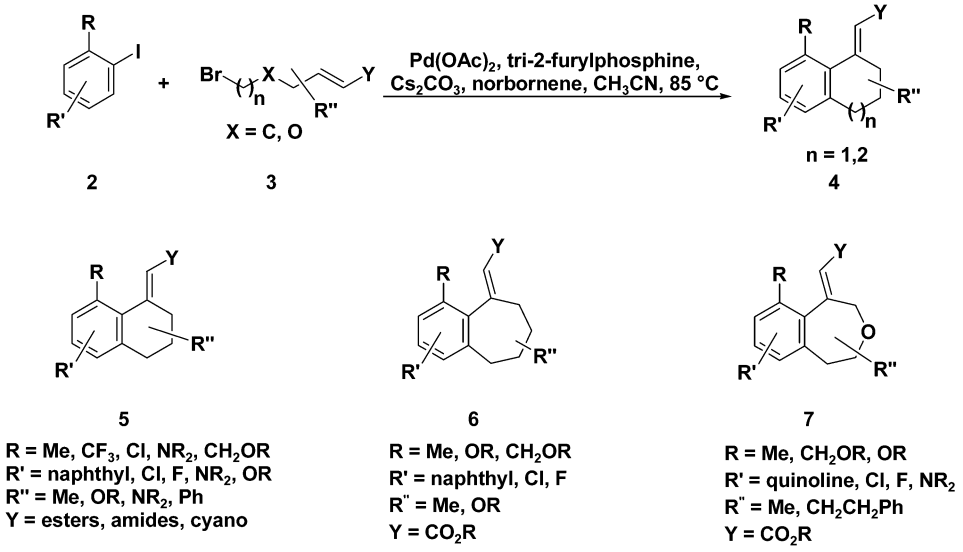
Pure Appl. Chem.* **78, 197–523. An issue of reviews and research papers based on lectures presented at the 13th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-13), Geneva, Switzerland, 17–21 July 2005.
‡Corresponding author



Scheme 1

PALLADIUM-CATALYZED TANDEM INTERMOLECULAR *ORTHO* ALKYLATION/INTRAMOLECULAR HECK REACTION

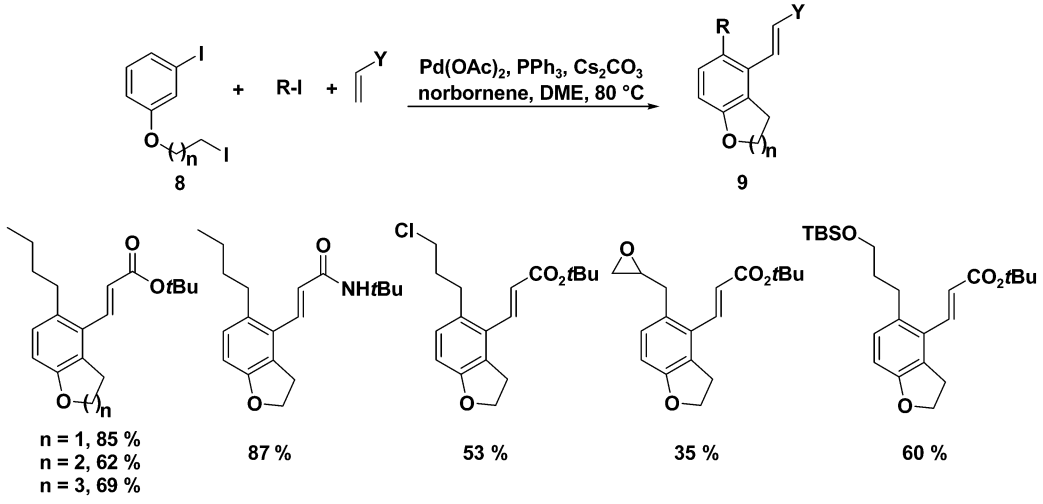
Our group modified the reaction conditions and extended the methodology by using a difunctional acceptor (**3**) so that an intramolecular Heck reaction can follow the *ortho* alkylation leading to fused aromatic compounds **4** (Scheme 2) [4–7]. We initially demonstrated that numerous six- and seven-membered fused aromatic carbocycles (**5**) can be easily prepared using our optimized reaction conditions: iodoarene (1 equiv), $Pd(OAc)_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), norbornene (2 equiv), and bromoenoate (2 equiv) in acetonitrile at 85 °C for 12 h [4]. Various functional groups at different positions on the aryl iodide as well as a variety of Heck acceptors are tolerated [5]. We then showed that a variety of functional groups along the chain on the bromoenoate are compatible, affording highly substituted six- (**5**) and seven-membered (**6**) fused aromatic rings in moderate to good yields [6]. This procedure was also extended to the formation of benzoxepines (**7**) [7].



Scheme 2

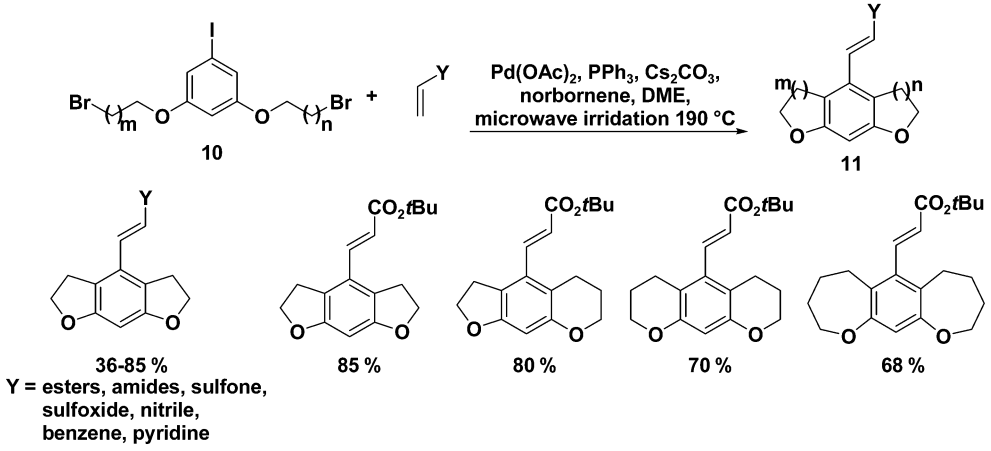
PALLADIUM-CATALYZED TANDEM INTRAMOLECULAR *ORTHO* ALKYLATION/INTERMOLECULAR HECK REACTION

We also reported a three-component norbornene-mediated Pd-catalyzed coupling reaction involving a haloalkyl aryl iodide (**8**), an alkyl halide, and a Heck acceptor (Scheme 3) [8]. The reaction involves an intramolecular *ortho* alkylation, an intermolecular *ortho* alkylation, and a Heck reaction. This process is particularly appealing since the *ortho* positions of the iodoarene are alkylated with different alkyl halides. A variety of polysubstituted five- and six-membered bicyclic oxacycles (**9**) were synthesized in good yields from readily accessible starting materials.



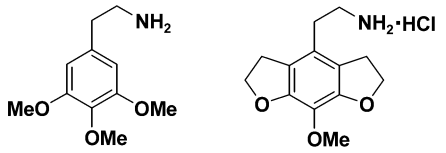
Scheme 3

We have extended this methodology such that two intramolecular *ortho* insertions followed by an intermolecular Heck reaction can be achieved (Scheme 4) [9]. Using this approach, both symmetrical and unsymmetrical substituted tricyclic heterocycles (**11**) were easily prepared in moderate to good yields from a Heck acceptor and an aryl iodide containing two tethered alkyl bromides (**10**).



Scheme 4

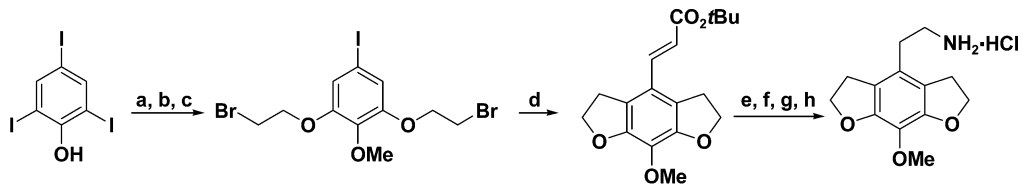
Tricyclic compounds of this type are found in natural products [10] and exhibit notable biological and pharmaceutical properties [11]. For example, mescaline analog **13**, containing tetrahydrobenzodifuran functionalities as rotationally restricted bioisosteres of the aromatic methoxy groups in mescaline **12**, showed an enhanced affinity for 5-HT_2 receptors with decreased hallucinogenic activity [11a,b].



12 13

Fig. 1

We applied this methodology to the synthesis of mescaline analog **13** (Scheme 5) [9]. Our synthesis began with the preparation of aryl iodide **15** in three steps from commercially available 2,4,6-triiodophenol **14**. The one-pot Pd-catalyzed *bis*-intramolecular *ortho* alkylation of **15** and subsequent Heck reaction with *tert*-butyl acrylate afforded the tricyclic heterocycle **16** in 81 % yield. Subsequent functional group interconversions resulted in the desired tricyclic product **13**. An overall 27 % yield was achieved in eight steps with an average yield per step of 85 %. An advantage of this approach is that a variety of rotationally restricted mescaline analogs with varying ring sizes should be easily accessed.

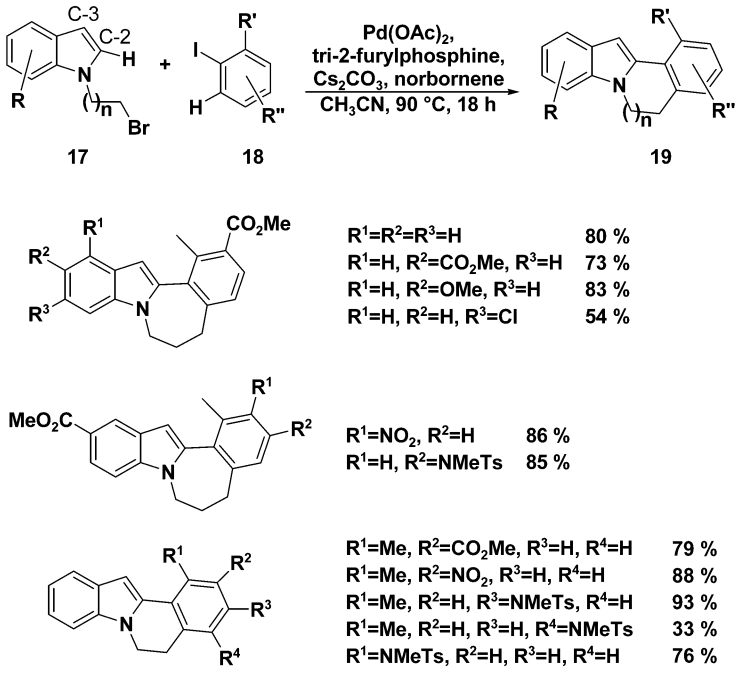


14 15 16 13

Scheme 5 Reagents and conditions: (a) MeI, K_2CO_3, acetone, reflux, 3 h, 98 %; (b) [i] *n*BuLi, ether, –78 °C, 1 h, [ii] $B(OMe)_3$, –78 °C to rt, 18 h, [iii] peracetic acid solution, 0 °C to rt, 30 min, 77%; (c) 1,2-dibromoethane, K_2CO_3, acetone, reflux, 48 h, 84 %; (d) $Pd(OAc)_2$, PPh_3, Cs_2CO_3, norbornene, *tert*-butyl acrylate, DME, microwave, 190 °C, 5 min, 81 %; (e) Pd/C, H_2, MeOH/EtOAc, rt, 12 h, 98 %; (f) TFA, CH_2Cl_2, rt, 12 h, 87 %; (g) DPPA, Et_3N, benzyl alcohol, toluene, reflux, 12 h, 65 %; (h) [i] Pearlman's catalyst, H_2, MeOH, rt, 12 h, [ii] HCl (1 M ether), rt, 1 h, 96 %.

PALLADIUM-CATALYZED TANDEM *ORTHO* ALKYLATION/DIRECT ARYLATION

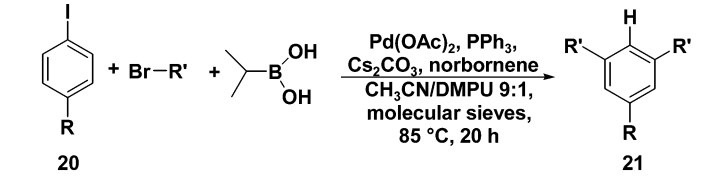
Over the past few years we mainly focused on Pd-catalyzed tandem *ortho* alkylation/Heck reaction processes. More recently, we modified this sequence by using bromoalkyl indole **17** so that an intramolecular direct arylation [12] can follow the *ortho* alkylation (Scheme 6) [13]. In this highly efficient approach, an alkyl–aryl bond and an aryl–heteroaryl bond are created from two carbon–hydrogen bonds in a one-pot process. A wide range of functionalized annulated indoles **19** can be rapidly synthesized in a convergent manner from relatively simple and accessible starting materials. New methods for functionalizng indoles are indispensable since many biologically active natural products as well as pharmaceutically important compounds contain this motif [14].



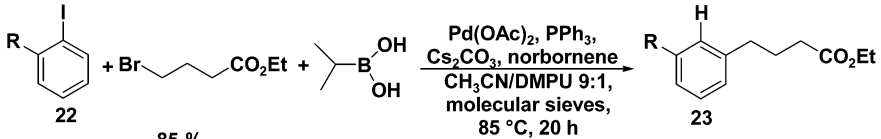
Scheme 6

PALLADIUM-CATALYZED TANDEM *ORTHO* ALKYLATION/HYDRIDE REDUCTION

In an effort to expand the scope of the reaction by developing processes with a final coupling step other than the Heck reaction, we attempted to terminate the reaction with a Suzuki coupling using alkyl boronic acids. [15] Although Catellani reported successful Suzuki coupling using aryl boronic acids, our endeavor using alkyl boronic acids resulted in an unusual hydride reduction product as the major product [16,17]. Labeling studies were conducted, and some insight into the mechanism was established. It is proposed that the final hydride reduction step in the catalytic cycle may involve two pathways occurring simultaneously. One pathway involves the alkyl boronic acid as the hydride source, and the other pathway involves the alkyl halide. Gratifyingly, this opportune result allowed for the formation of a vast array of polyfunctionalized *meta*-substituted arenes (**21** and **23**) (Scheme 7) [18] that are often difficult to prepare by other methods [19].



R=H, R'=$(CH_2)_3CO_2Me$	67 %	R=NMeTs, R'=$(CH_2)_3CO_2Me$	77 %
R=CH_3, R'=$(CH_2)_3CO_2Me$	65 %	R=NMeTs, R'=$(CH_2)_3CH_3$	86 %
R=OCH_3, R'=$(CH_2)_3CO_2Me$	89 %	R=NMeTs, R'=CH_2CH_3	75 %
R=Cl, R'=$(CH_2)_3CO_2Me$	64 %	R=NMeTs, R'=$(CH_2)_3Ph$	82 %
R=F, R'=$(CH_2)_3CO_2Me$	68 %	R=NMeTs, R'=$(CH_2)_3OTBS$	70 %
R=CF_3, R'=$(CH_2)_3CO_2Me$	54 %		
R=NO_2, R'=$(CH_2)_3CO_2Me$	51 %		



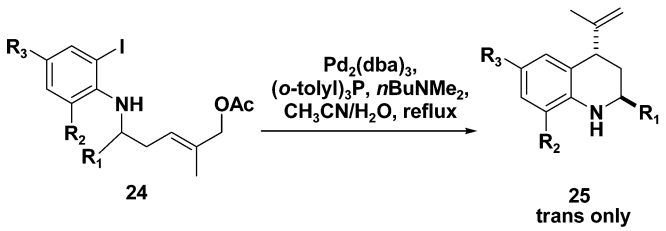
R=Me	85 %
R=CF_3	82 %
R=CH_2OTBS	60 %
R=Cl	45 %
R=NMeTs	71 %

Scheme 7

PALLADIUM-CATALYZED COUPLING BETWEEN ARYL IODIDES AND ALLYL MOIETIES

Intramolecular coupling

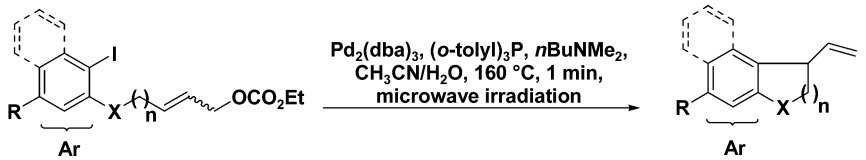
Our group has recently reported a Pd-catalyzed cyclization method involving a modified intramolecular Heck-type coupling of an aryl iodide with a tethered allylic acetate (**24**) using $Pd_2(dba)_3$, (*o*-tolyl)$_3$P, *n*BuNMe$_2$ in refluxing CH_3CN/H_2O [20]. The reaction differs from a traditional Heck reaction in that the terminating step involves the loss of a leaving group rather than β-hydride elimination. This results in a product containing a useful terminal olefin which allows for further functionalization. A variety of substituted tetrahydroquinolines (**25**) were obtained in good yields and excellent diastereoselectivity (Scheme 8).



R_1=Ph, R_2=H, R_3=H	76 %
R_1=4-Me-Ph, R_2=H, R_3=H	80 %
R_1=4-Cl-Ph, R_2=H, R_3=H	81 %
R_1=4-Br-Ph, R_2=H, R_3=H	73 %
R_1=Ph, R_2=Me, R_3= Me	79 %
R_1=Ph, R_2=H, R_3= Cl	88 %
R_1=Ph, R_2=OMe, R_3=H	77 %
R_1=COO-*c*-Hex, R_2=Me, R_3=Me	84 %

Scheme 8

We have expanded the scope of the reaction to other heterocyclic compounds. Microwave irradiation led to the rapid access of heterocyclic and carbocyclic compounds (**27**) of varying ring size in good yields (Scheme 9).

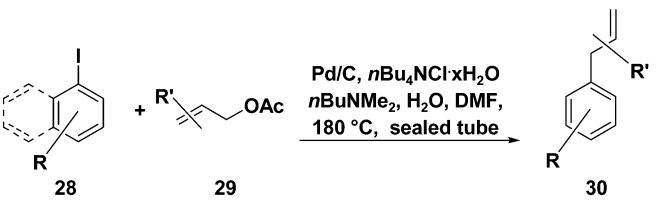


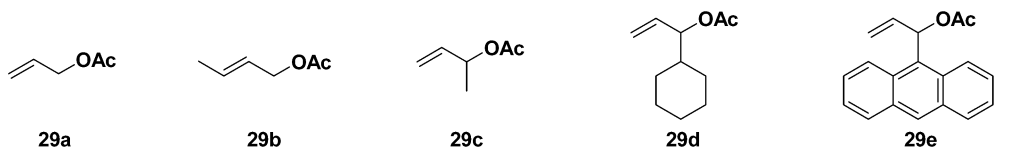
n=1, X=O, R=H, Ar=naphthyl	56 %	n=2, X=O, R=H, Ar=naphthyl	62 %
n=1, X=O, R=CF_3, Ar=Ph	61 %	n=3, X=O, R=H, Ar=naphthyl	72 %
n=1, X=O, R=CO_2Me, Ar=Ph	66 %	n=3, X=NTs, R=H, Ar=Ph	65 %
n=1, X=NTs, R=H, Ar=Ph	74 %	n=3, X=C(CO_2Et), R=H, Ar=Ph	73 %
n=1, X=C(CO_2Et), R=H, Ar=Ph	67 %		

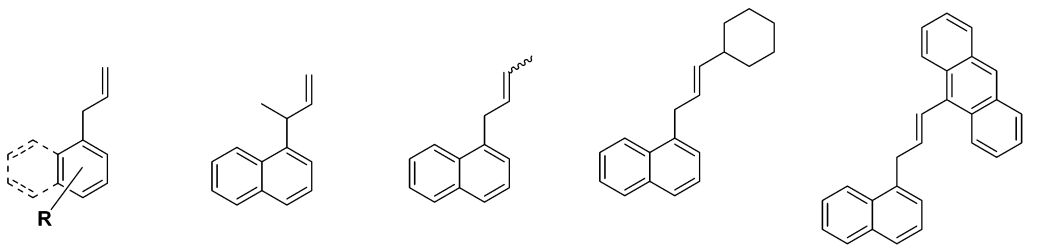
Scheme 9

Intermolecular coupling

Recently, we examined the intermolecular coupling of aryl iodides and allylic acetates [21]. A variety of electron-rich and -poor substituted aromatic compounds (**30**) were synthesized in moderate to good yields when **29a** was employed. A number of products arising from substituted allylic acetates (**29b–e**) were also synthesized, and it is apparent that the product outcome is highly dependent upon the steric bulk around the olefin (Scheme 10).





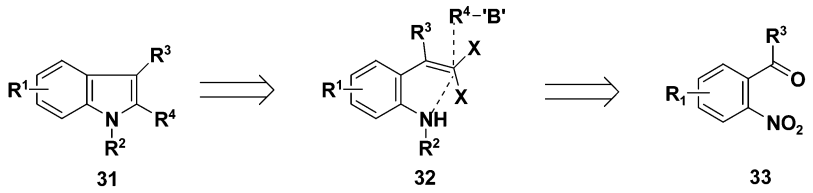


R=naphthyl 80 %	51 %	83 % (*E*/*Z* 2/1)	84 % (*E*/*Z* 12/1)	64 % (*E* only)
R=*m*-Br 79 %				
R=*p*-OMe 58 %				
R=*o*-Cl 54 %				
R=*p*-NMeTs 71 %				
R=CO_2Me 58 %				

Scheme 10

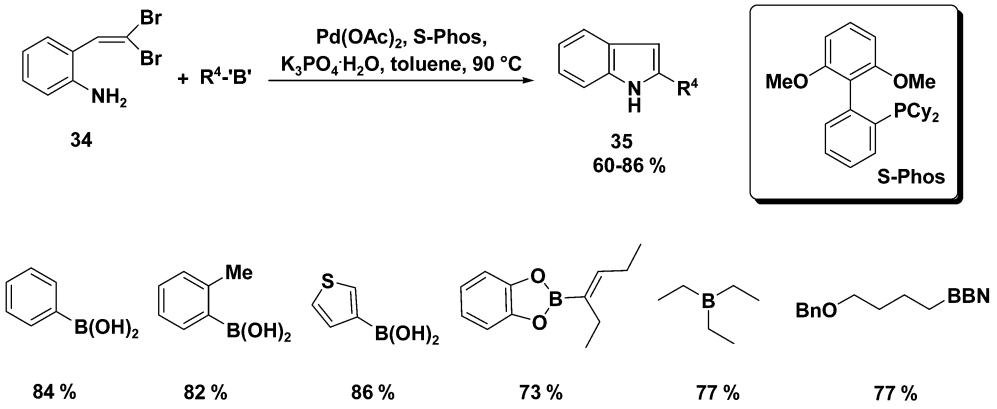
PALLADIUM-CATALYZED TANDEM C–N/C–C COUPLING OF *GEM*-DIHALOVINYL SYSTEMS

In continuing efforts to develop simple processes for accessing pharmaceutically and therapeutically important compounds, we developed a modular synthetic method for the synthesis of functionalized indole derivatives (**31**) [22]. By tethering a *gem*-dibromovinyl group *ortho* to aniline, we envisaged a modular indole synthesis via a tandem Pd-catalyzed intramolecular C–N (Buchwald–Hartwig amination) [23] and intermolecular C–C bond (Suzuki–Miyaura coupling) [24] formation (Scheme 11) [25]. Many *o*-*gem*-dibromovinylaniline (**32**) substrates can be conveniently obtained from the corresponding *o*-nitrobenzaldehydes or ketones (**33**) by Ramiraz–Corey olefination [26] followed by reduction using $SnCl_2 \cdot 2H_2O$ or Fe/HOAc.



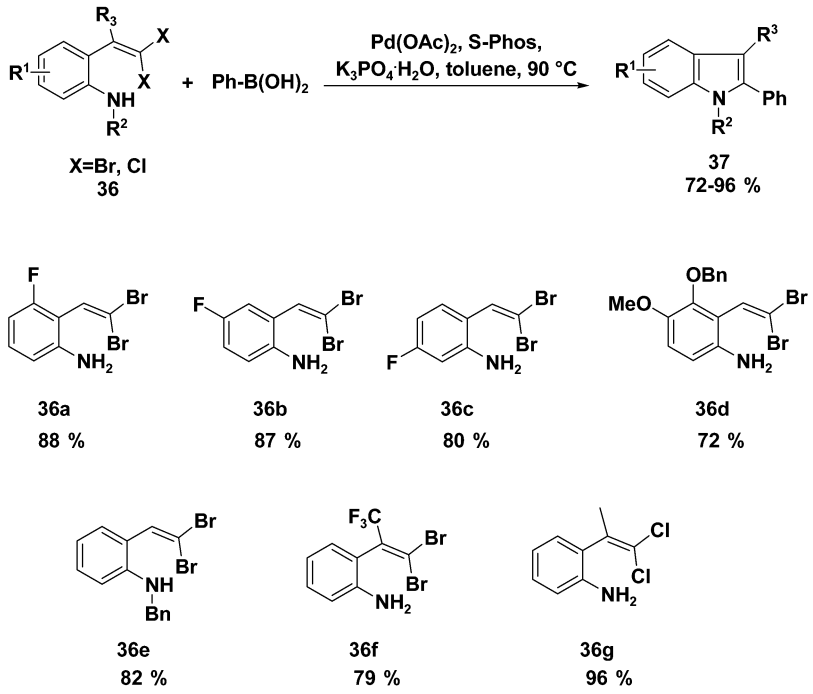
Scheme 11

Using our optimized reaction conditions {$Pd(OAc)_2$, S-Phos ligand [27] and $K_3PO_4 \cdot H_2O$ in toluene at 90–100 °C}, a broad scope of organoboron reagents successfully gave the expected 2-substituted indoles (**35**) in good isolated yields (60–86 % yield, >15 examples). These include substituted phenylboronic acids of different electronic and steric character, heteroarylboronic acids, alkenylboronic acids/esters, and alkylborane derivatives (Scheme 12).



Scheme 12

A broad spectrum of electron-withdrawing and -donating functionalities are compatible on the aniline substrates (**36a–d**) (Scheme 13). N-Benzylated secondary anilines (**36e**) worked nearly as well as the primary aniline substrate. In contrast, acylated or tosylated anilines gave low yields as well as some undesired by-products.



Scheme 13

This method was also extended to synthetically important 2,3-disubstituted indoles (**37**, R ≠ H). Indoles with this substitution pattern could be obtained from the corresponding dihalovinyl substrates (**36f,g**) in good to excellent yields using our standard conditions (Scheme 13). In particular, we note use of *ortho-gem*-dichlorovinylanilines (**36g**) gave near quantitative yields of the expected indole, suggesting that the two C–Cl bonds were more selective in the two new bond formations than their C–Br analogs [28].

CONCLUSIONS

We have developed new Pd-catalyzed cyclization methods based upon norbornene-mediated cyclizations, Heck-type coupling involving allyl moieties, and tandem C–N/C–C coupling of *gem*-dihalovinyl compounds. Application of these ring-forming methods allowed for rapid access of a large number of diverse carbocyclic and heterocyclic compounds in moderate to excellent yields. The methodology is not limited to ring formation, as demonstrated by the intermolecular Pd-catalyzed synthesis of highly functionalized arene compounds.

ACKNOWLEDGMENTS

We thank the Natural Sciences and Engineering Research Council (NSERC) of Canada and the Merck Frosst Centre for Therapeutic Research for an Industrial Research Chair, the University of Toronto for financial support, and the essential contributions of Marc Dahlmann, Christelle Herse, Sandrine Pache, Jean-François Paquin, Sandrine Piguel, and Eiji Tayama cited in the references.

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