Published in final edited form as:
Tetrahedron. 2010 June 26; 66(26): 4811–4815. doi:10.1016/j.tet.2010.03.111.

Amide-Directed Arylation of sp³ C-H Bonds using Pd(II) and Pd(0) Catalysts

Masayuki Wasa and **Jin-Quan Yu***
Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

Abstract

Protocols to effect *β*-arylation of sp^3 C–H bonds *via* Pd(II)/(IV) and Pd(0)/(II) catalytic cycles have been achieved using a newly developed monodentate $CONHC_6F_5$ directing group. These reactions provide an unprecedented means to functionalize sp^3 C–H bonds in aliphatic carboxylic acid–derived substrates.

Keywords

Amide; palladium; arylation; sp^3 C; H activation

1. Introduction

Pd–catalyzed C–H activation/functionalization reactions have emerged as powerful synthetic tools for converting ubiquitous sp^2 and sp^3 C–H bonds into desired chemical functional groups.[1] Methods for effecting the functionalization of aryl and heretoaryl sp^2 C–H bonds have been extensively investigated and have found impressive applications in natural products synthesis and drug discovery.[2] In contrast, the functionalization of more inert sp^3 C–H bonds still represents a tremendous challenge in organic synthesis and remains at an early stage of development.

The majority of sp^3 C–H activation methods utilize heteroatom-containing functional groups that can coordinate the metal and direct C–H insertion.[3] Indeed, reactions that proceed *via* cleavage of sp^3 C–H bonds directed by heteroatom-directing groups such as oximes,[4] oxazolines,[5] and pyridines[6] have been well-documented. Recent investigations in the area of directed C–H functionalization focus on utilizing more synthetically practical functional groups, such as amino,[7] amide[8] and carboxyl[9] groups as directing groups. Using the directing group approach, a number of sp^3 C-H activation/C-C bond forming reactions have been reported.[2] One important class of these reactions concerns the Pd-catalyzed arylation of unactivated sp^3 C-H bonds with aryl halides which was developed *via* two distinct catalytic pathways: Pd(II)/(IV) catalysis which uses aryl iodides and requires external oxidant for reoxidation, and Pd(0)/(II) homogeneous catalysis which accommodates organophosphine or NHC ligands and aryl halides (Scheme 1).[1,2]

*Corresponding author., Tel.: +1 858 784 7942;, fax: +1 858 784 7949;, yu200@scripps.edu.

The redox chemistry involving Pd(IV) has been poorly understood in its early stage and gained much attention in recent years.[10] A number of reactions have been developed using the Pd(II)/(IV) catalysis which includes acetoxylation, amination, arylation, halogenation, among others.[1,2] For instance, Chen reported an interesting arylation of aldehydic C-H bonds with $[Ph_2I]Br$ which could involve the Pd(II)/(IV) catalysis.[11] Sanford and Daugulis independently developed general approaches using directed C-H activation and $[Ph_2I]PF_6$[12] or $[Ph_2I]BF_4$[6d] for arylation of sp^2 C–H bonds. Building on these studies, Daugulis *et al.* went on to develop a highly efficient C–H arylation reaction using readily available aryl iodides and applied these conditions to effect arylation of sp^3 C–H bonds (Scheme 2).[6b, 6c] Notably, despite numerous evidence for Pd(II)/Pd(IV) catalysis reported in literature,[1–4] the involvement of Pd(II)/Pd(III) catalysis has also been invoked with substantial experimental support.[13] It is possible the competition between these two catatlytic pathways may vary with substrates.

Their initial reports described the arylation of an sp^3 C–H bond in 2-ethylpyridine **(2)** using catalytic amounts of $Pd(OAc)_2$ and stoichiometric AgOAc.[6b] A subsequent report by the same group demonstrated impressive examples of *β*-arylation using an effective bisdentate directing group such as **3)**.[6c] Notably, this reaction represents a rare example of catalytic methylene C–H activation in Pd chemsitry. Corey *el al.* have used this directing group and these reaction conditions to functionalize sp^3 C–H bonds in natural amino acid derivatives **(4)** (Scheme 3).[14] A related investigation by our group described *β*-arylation of simple aliphatic acids without installing a directing group **(5)**; however the yields were low (40–70%) and the reaction temperature was higher (130 °C).[9b] We found, by converting the carboxylic acids into structurally analogous hydroxamic acids **(6)**, the yields could be greatly improved (>80 %), and the reaction could be carried out at lower temperature (60 °C).[15] However, substrates containing α-hydrogens were not reactive with either carboxylic acids or this directing group.

Pd(0)-catalyzed arylation of C–H bonds using phosphine or NHC ligands and aryl halides represents another class of C–H activation/arylation reactions that has been extensively studied in recent decades.[16–18] Compared to the aforementioned Pd(II)/Pd(IV) C–H arylation reactions, this mode of catalysis does not require stoichiometric silver salts, which is a significant practical advantage. Both intra- and intermolecular arylation of aryl and heteroaryl sp^2 C–H bonds has proven to be highly successful.[16–18] On the other hand, only a limited number of sp^3 C–H arylation reactions *via* Pd(0)/Pd(II) catalysis have been achieved to date (Scheme 4).[19] In this manuscript, we describe Pd-catalyzed sp^3 C–H arylation protocols using a recently developed amide directing group and two modes of catalysis, Pd(0)/(II) and Pd(II)/(IV). (Scheme 5). Notably, the use of this particular directing group allowed for a significant expansion in substrate scope such that carboxylic acid derivatives containing α-hydrogen atoms could be tolerated.

2. Results and Discussion

2.1. Arylation of sp^3 C–H bonds via Pd(II)/(IV) catalysis

In 2007, we reported that the *β*-methyl groups of aliphatic carboxylic acids could be cross-coupled with aryl iodides *via* sp^3 C–H bond activation in the presence of stoichiometric Ag_2CO_3 (Scheme 3).[9b] However, the carboxylate moiety proved to be a poor directing group for activation of inert sp^3 C–H bonds, as it required high reaction temperatures and gave low yields. Additionally, we found that this reaction was incompatible with aliphatic carboxylic acids that contained *α*-hydrogen atoms, a problem that could not be remedied by converting the carboxylate to other directing groups, such as oxazoline[5] or hydroxamic acid **(6)**.[8d] Thus, the substrate scope was limited to compounds that contained quaternary *α*-

carbon atoms. In an effort to overcome both of these issues, we sought to develop a novel directing group that would enhance the reactivity and broaden the substrate scope.

Based on previous reports, we were aware that bis-coordinating pyridine-containing directing groups such as **3** and **4** were capable of directing C–H activation with substrates that contained *α*-hydrogen atoms.6c, 14 However, we thought that a simpler monodentate directing group could provide both the reactivity and *α*-hydrogen tolerance that we sought. Based on the high reactivity observed with hydroxamic acids (6),[8d] we hypothesized that replacing the methoxy group with functional group in which the steric and electronic properties could be readily adjusted could prove to be highly useful in developing an improved directing group. Given that a wide variety of substituted anilines are commercially available, we identified *N*-aryl amides as a class of potential directing groups that would be easily tunable. To test this idea, we initially converted pivalic acid into several *N*-arylpivalamides to examine whether the amide group was capable of directing C–H activation (Scheme 6 and Table 1).

We were encouraged by the initial observation of trace amount of the desired arylation products using simple aniline-derived amide with Cs_2CO_3 in neat PhI (Table 1, entry 2). Further screening revealed that electron-withdrawing, fluorine-substituted directing groups showed dramatically higher reactivity (Table 1, entries 3 and 5). The addition of base was found to be crucial for the arylation reaction (as no product was obtained in absence of base) (Table 1, entries 1 and 4) with Cs_2CO_3 giving the highest yield.

To test if the reaction would be compatible with substrates containing *α*-hydrogen atoms, we converted isobutyric acid to an array of different *N*-arylisobutyramides. Gratifyingly, we obtained a mixture of mono- and di-arylation products in high yields. The reaction was optimized using various directing groups. Among those screened, $CONHC_6F_5$ gave the best results (Table 2).

A variety of carboxylic acid derivatives were arylated in reasonable to excellent yields under the optimized reaction conditions (Table 3). *β*-Amino acid substrate **15**, as well as substrates derived from commercial drugs, such as **16** (from Gemfibrozil) and **17** (from Ibuprofen), were also compatible. For substrate **17**, both *β*-arylation of the methyl group and *γ*-arylation of the arene were observed in the major product. For substrate **14**, it was possible to reduce the reaction temperature to 100 °C, though the yield decreased to 64 % even after 12 h.

2.2. Arylation of sp^3 C–H bonds via Pd(0)/(II) catalysis

Despite the remarkable efficiency of these Pd(II)/(IV)-catalyzed arylation reactions, the need for superstoichiometric amount of AgOAc is a major drawback. In contrast, Pd(0)-catalyzed homogeneous reactions accommodates phosphine or NHC ligands and do not require a co-oxidants or silver salts, which are significant practical advantages. Miura and Daugulis have previously reported pioneering examples of $Pd(0)/PR_3$-catalyzed sp^2 C–H arylation reactions directed by amides[18a] and carboxylic acids, [18c] respectively. We have recently reported $CONHC_6F_5$-directed arylation of sp^3 C–H bonds (Scheme 7).[8f] This work will be summarized briefly here to allow for comparison to our Pd(II)/(IV) C–H arylation data, as both reactions rely upon the same directing group.

Based on the successful development of Pd(II)/(IV)-catalyzed arylation directed by $CONHC_6F_5$ group, we initiated our investigation of Pd(0)-catalyzed activation of sp^3 C–H bonds. Our initial experiment using substrate **12** gave trace quantities of the desired mono-arylated product with PPh_3 as the ligand and Cs_2CO_3 as the base (Scheme 8). To improve this result, systematic screening of ligands, bases, solvents and coupling partners was undertaken.

Among the bases tested, only CsF gave appreciable amounts of the desired product. Buchwald ligands, protected as HBF_4 salts using Fu's strategy,[20] were found to give considerably better yield than PPh_3. To our surprise, the reaction was only found to proceed when aryl iodides were used; aryl bromides, chlorides, triflates, and tosylates did not give any of the desired product. The oxidative insertion of Pd(0) into an aryl-halide bond is the most facile for aryl iodides. However, Fagnou and others have established that the use of aryl iodides typically results in poor reactivity due to the accumulation of iodide anions in reaction mixture, which ultimately leads to catalyst poisoning.[21] Indeed, higher catalyst and ligand loadings (10 and 20 mol%, respectively) were needed to obtain high product yields, which could be attributed to the poisoning phenomenon. With the optimized conditions in hand, we obtained **12a** in 34% and **12b** in 54% yield (Scheme 9).

Through the development of sp^3 C–H arylation protocols *via* Pd(0)/(II) and Pd(II)/(IV) catalysis, we learned there are inherent advantages and disadvantages of both catalytic cycles. C–H arylation reactions *via* Pd(II)/(IV) catalysis went to completion in shorter reaction times (<3h) and gave generally higher product yields than did Pd(0)/(II) catalysis for the same set of substrates. Nevertheless, Pd(0)/(II)-catalyzed C–H arylation was found to proceed under milder reaction conditions and did not require stoichiometric silver salts, though the current conditions did require higher catalyst and ligand loadings due to potential catalyst poisoning. Further optimization is currently underway for the Pd(0)/(II) reaction, in an effort to utilize other aryl halides in order to suppress catalyst poisioning.

3. Conclusions

β-Arylation of inert sp^3 C–H bonds *via* two catalytic pathways has been achieved using a newly developed monodentate amide directing group. These studies have allowed for the discovery of an unprecedented C–H activation reaction of carboxylic acid–derived substrates that contain *α*-hydrogen atoms. Follow-up studies to further tune the directing group and to develop asymmetric sp^3 C–H arylation of *gem*-dimethyl groups using chiral phosphine ligands are underway in our laboratory.

Experimental

3.1. General experimental—Solvents were obtained from Sigma-Aldrich and used directly without further purification. ^1H and ^{13}C NMR spectra were recorded on a Varian instrument (400 MHz and 100 MHz, respectively) and internally referenced to the $SiMe_4$ signal. Exact mass spectra for new compounds were recorded on a VG 7070 high resolution mass spectrometer. Analytical GC-MS was performed on a Hewlett-Packard G1800C instrument connected to an electron ionization detector using a MS-5 GC column (30 × 0.25 mm). Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrometer.

Carboxylic acids, anilines and phosphine ligands were purchased from Aldrich, Acros and Strem and were used as received without further purification. $Pd(OAc)_2$ was received from Alfa Aesar.

3.2. Preparation of amide substrates—An acid chloride (20 mmol), prepared from the corresponding carboxylic acid and oxalyl chloride, was added to a vigorously stirred solution of 2,3,4,5,6-pentafluoroaniline (22 mmol) in toluene (50 mL). The reaction mixture was stirred for 12 h under reflux, and then stirred at room temperature for 4 h. The product mixture was concentrated under vacuum and was recrystallized from ethyl acetate/hexane (100 °C to 0 °C) to give the amide.

3.3. General procedure for palladium-catalysed arylation of sp^3 C-H bonds via Pd(II)/(IV) catalysis—Substrate (0.2 mmol), aryl iodide (0.5 mL), AgOAc (0.8 mmol),

and Cs_2CO_3 (0.24 mmol) were added in a 25 mL glass pressure vessel. $Pd(OAc)_2$ (0.02 mmol) was added to the reaction mixture, tightly capped and heated to 130 °C with vigorous stirring. The reaction was stopped after it completely turned black (typically 3h). The black solid was filtered off, and the solvent was removed in a rotary evaporator. The purification was done by silica gel column chromatography using 1–5% diethyl ether/hexane as an eluting solvent.

3.3.1. 2-methyl-N-(perfluorophenyl)-3-phenylpropanamide (12a): Substrate **12** was arylated following the general procedure. After purification by column chromatography, **12a** was obtained as a colorless solid (27.1 mg, 41 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.10 (m, 5H), 6.72 (bs, 1H), 3.10-2.97 (m, 1H), 2.83-2.71 (m, 2H), 1.31 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 139.3, 129.2, 129.0, 127.0, 44.1, 40.7, 18.1; IR (neat) ν 3256, 2927, 1682, 1498 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{16}H_{12}F_5NO$ (MH^+): 330.0912; found: 330.0907.

3.3.2. 2-benzyl-N-(perfluorophenyl)-3-phenylpropanamide (12b): Substrate **12** was arylated following the general procedure. After purification by column chromatography, **12b** was obtained as a colorless solid (36.6 mg, 45 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.20 (m, 8H), 6.12 (bs, 1H), 3.12-3.05 (m, 2H), 2.95-2.79 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 139.2, 129.2, 129.0, 127.1, 53.4, 39.5; IR (neat) ν 3231, 2919, 1674, 1526, 1450 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{22}H_{16}F_5NO$ (MH^+): 406.1225; found: 406.1235.

3.3.3. *N*-(perfluorophenyl)-3-phenylpropanamide (13a): Substrate **13** was arylated following the general procedure. After purification by column chromatography, **13a** was obtained as a colorless solid (43.0 mg, 68 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.20 (m, 4H), 6.89 (bs, 1H), 3.05 (t, J = 7.6 Hz, 2H), 2.75 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 143.3, 129.0, 128.6, 126.9, 38.3, 31.6; IR (neat) ν 3264, 2921, 1680, 1530, 1495 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{15}H_{10}F_5NO$ (MH^+): 316.0755; found: 316.0755.

3.3.4. 2-benzyl-N-(perfluorophenyl)pentanamide (14a): Substrate **14** was arylated following the general procedure. After purification by column chromatography, **14a** was obtained as a colorless solid (62.3 mg, 84 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.15 (m, 4H), 6.49 (bs, 1H), 2.95-2.82 (m, 1H), 2.82-2.80 (m, 1H), 2.61-2.54 (m, 1H), 2.04-1.99 (m, 1H), 1.88-1.68 (m, 1H), 1.53-1.32 (m, 4H), 0.93 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 139.5, 129.1, 129.0, 126.9, 105.1, 44.2, 39.7, 36.2, 33.1, 23.0, 14.25; IR (neat) ν 3274, 2901, 1650, 1520 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{19}H_{18}F_5NO$ (MH^+): 371.1309; found: 371.1310.

3.3.5. 2-benzyl-3-(1,3-dioxoisoindolin-2-yl)-N-(perfluorophenyl)propanamide (15a): Substrate **15** was arylated following the general procedure. After purification by column chromatography, **15a** was obtained as a colorless solid (62.7 mg, 66 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.73 (m, 4H), 7.30-7.16 (m, 4H), 6.74 (bs, 1H), 4.18-4.13 (m, 1H), 3.92-3.86 (m, 1H), 3.51-3.39 (m, 1H), 3.15-3.09 (m, 1H), 2.96-2.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 168.6, 138.1, 134.6, 134.6, 129.1, 127.2, 123.8, 48.1, 40.6, 37.2; IR (neat) ν 3268, 2918, 2850, 1716, 1522, 1495 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{24}H_{15}F_5N_2O$ (MH^+): 475.1076; found: 475.1075.

3.3.6. 2-benzyl-6-(2,5-dimethylphenyl)-2-methyl-N-(perfluorophenyl)hexanamide (16a): Substrate **16** was arylated following the general procedure. After purification by column chromatography, **16a** was obtained as a colorless solid (33.5 mg, 34 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.30-7.24 (m, 5H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.77 (s, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 3.99 (t, *J* = 6.0 Hz, 3H), 3.16 (d, *J* = 13.2 Hz, 2H), 2.80 (d, *J* = 13.2 Hz, 2H), 2.80 (s, 3H), 2.10 (s, 3H) 1.98-1.40 (m, 6H), 1.30 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 175.4, 157.0, 137.1, 137.0, 130.7, 130.6, 127.2, 123.8, 121.3, 112.5, 92.6, 68.0, 48.3, 46.7, 36.6, 25.1, 21.5, 16.1 cm^{-1}; IR (neat) ν 3296, 2924, 2869, 1675, 1523, 1490 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{27}H_{26}F_5NO_2$ (MH^+): 492.1956; found: 492.1959.

3.3.7. 2,2-dibenzyl-6-(2,5-dimethylphenyl)-N-(perfluorophenyl)hexanamide (16b): Substrate **16** was arylated following the general procedure. After purification by column chromatography, 16b was obtained as a colorless solid (44.3 mg, 39 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.21 (m, 10H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.76-6.59 (m, 3H), 4.00 (t, *J* = 5.6 Hz, 2H), 3.27 (d, *J* = 13.6 Hz, 2H), 2.94 (d, *J* = 13.6 Hz, 2H), 2.28 (s, 3H), 2.20-2.08 (m, 2H), 1.96 (s, 3H), 1.87-1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 156.8, 137.0, 137.0, 130.6, 130.6, 128.7, 127.2, 123.7, 121.5, 112.4, 105.1, 67.8, 42.9, 30.1, 28.5, 21.7, 16.1; IR (neat) ν 3299, 2924, 2856, 1676, 1523, 1453 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{33}H_{30}F_5NO_2$ (MH^+): 568.2269; found: 568.2269.

3.3.8. 2-(5-isobutylbiphenyl-2-yl)-N-(perfluorophenyl)-3-phenylpropanamide (17a): Substrate **17** was arylated following the general procedure. After purification by column chromatography, **17a** was obtained as a colorless solid (67.0 mg, 64 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.59-7.16 (m, 9H), 6.99-6.93 (m, 4H), 6.28 (s, 1H), 3.97 (t, *J* = 7.6 Hz, 1H), 3.49-3.45 (m, 1H), 3.06-3.03 (m, 1H), 2.47 (d, *J* = 7.2 Hz, 2H), 1.90-1.85 (m, 1H), 0.93 (d, *J* = 2.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 142.5, 141.4, 141.4, 139.4, 133.4, 131.2, 129.6, 129.5, 129.4, 128.8, 128.6, 127.8, 127.6, 126.7, 50.7, 45.3, 39.8, 30.5, 22.7; IR (neat) ν 3260, 2950, 2929, 1700, 1512, 1489, 1411 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{31}H_{26}F_5NO$ (MH^+): 523.1945; found: 523.1944.

Acknowledgments

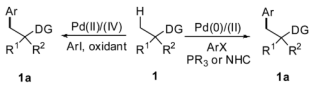
We gratefully acknowledge The Scripps Research Institute, the National Institutes of Health (NIGMS, 1 R01 GM084019-02), Amgen and Eli Lilly for financial support. We thank the A. P. Sloan Foundation for a fellowship (J.-Q.Y.), and the Bristol Myers Squibb for graduate fellowships (M. W.).

References and notes

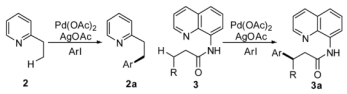
1. For reviews, see; (a) Yu JQ, Giri R, Chen X. Org Biomol Chem. 2006; 4:4041. [PubMed: 17312954] (b) Dick AR, Sanford MS. Tetrahedron. 2006; 62:2439. (c) Daugulis O, Zaitsev VG, Shabashov D, Pham QN, Lazareva A. Synlett. 2006:3382. (d) Alberico D, Scott ME, Lautens M. Chem Rev. 2007; 107:174. [PubMed: 17212475] (e) Chen X, Engle KM, Wang DH, Yu JQ. Angew Chem Int Ed. 2009; 48:5094.
2. For reviews, see; (a) Hassan J, Sévignon M, Gozzi C, Shultz E, Lemaire M. Chem Rev. 2002; 102:1359. [PubMed: 11996540] (b) Kakiuchi F, Murai S. Acc Chem Res. 2002; 35:826. [PubMed: 12379135] (c) Campeau L-C, Fagnou K. Chem Commun. 2006:1253. (d) Alberico D, Scott ME, Lautens M. Chem Rev. 2007; 107:174. [PubMed: 17212475] (e) Seregin IV, Gevorgyan V. Chem Soc Rev. 2007; 36:1173. [PubMed: 17576484] (f) Kakiuchi F, Kochi T. Synthesis. 2008:3013.
3. (a) Ryabov AD. Chem Rev. 1990; 90:403. (b) Yu JQ, Giri R, Chen X. Org Biomol Chem. 2006; 4:4041. [PubMed: 17312954] (c) Ackermann L. Top Organomet Chem. 2007; 24:35. (d) Kalyani D, Sanford MS. Top Organomet Chem. 2007; 24:85.
4. (a) Desai LV, Hull KL, Sanford MS. J Am Chem Soc. 2004; 126:9542. [PubMed: 15291549] (b) Thu HY, Yu WY, Che CM. J Am Chem Soc. 2006; 128:9048. [PubMed: 16834374] (c) Desai LV, Malik HA, Sanford MS. Org Lett. 2006; 8:1141. [PubMed: 16524288]
5. (a) Giri R, Liang J, Lei JG, Li JJ, Wang DH, Chen X, Naggar IC, Guo C, Foxman BM, Yu JQ. Angew Chem Int Ed. 2005; 44:7420. (b) Giri R, Chen X, Hao XS, Li JJ, Liang J, Fan ZP, Yu JQ. Tetrahedron: Asymmetry. 2005; 16:3502. (c) Giri R, Chen X, Yu JQ. Angew Chem Int Ed. 2005; 44:2112. (d) Giri R, Wasa M, Breazzano SP, Yu JQ. Org Lett. 2006; 8:5685. [PubMed: 17134247] (e) Chen X, Li JJ, Hao XS, Goodhue CE, Yu JQ. J Am Chem Soc. 2006; 128:78. [PubMed: 16390130]

6. (a) Kalyani D, Sanford MS. Org Lett. 2005; 7:4149. [PubMed: 16146374] (b) Shabashov D, Daugulis O. Org Lett. 2005; 7:3657. [PubMed: 16092843] (c) Zaitsev VG, Shabashov D, Daugulis O. J Am Chem Soc. 2005; 127:13154. [PubMed: 16173737] (d) Kalyani D, Deprez NR, Desai LV, Sanford MS. J Am Chem Soc. 2005; 127:7330. [PubMed: 15898779] (e) Chen X, Goodhue CE, Yu JQ. J Am Chem Soc. 2006; 128:12634. [PubMed: 17002342] (f) Hull KL, Lanni EL, Sanford MS. J Am Chem Soc. 2006; 128:14047. [PubMed: 17061885] (g) Hull KL, Anani WQ, Sanford MS. J Am Chem Soc. 2006; 128:7134. [PubMed: 16734446]
7. Lazareva A, Daugulis O. Org Lett. 2006; 8:5211. [PubMed: 17078680]
8. (a) Zaitsev VG, Daugulis O. J Am Chem Soc. 2005; 127:4156. [PubMed: 15783182] (b) Yang S, Li B, Wan X, Shi Z. J Am Chem Soc. 2007; 129:6066. [PubMed: 17455938] (c) Shabashov D, Daugulis O. J Org Chem. 2007; 72:7720. [PubMed: 17824657] (d) Wang DH, Wasa M, Giri R, Yu JQ. J Am Chem Soc. 2008; 130:7190. [PubMed: 18479089] (e) Wasa M, Yu JQ. J Am Chem Soc. 2008; 130:14058. [PubMed: 18834119] (f) Wasa M, Engle KM, Yu JQ. J Am Chem Soc. 2009; 131:9886. [PubMed: 19580277]
9. (a) Miura M, Tsuda T, Satoh T, Pivsa-Art S, Nomura M. J Org Chem. 1998; 63:5211. (b) Giri R, Maugel N, Li JJ, Wang DH, Breazzano SP, Saunders LB, Yu JQ. J Am Chem Soc. 2007; 129:3510. [PubMed: 17335217] (c) Chiong HA, Pham QN, Daugulis O. J Am Chem Soc. 2007; 129:9879. [PubMed: 17649995] (d) Giri R, Yu JQ. J Am Chem Soc. 2008:130, 14082. (e) Wang DH, Mei TS, Yu JQ. J Am Chem Soc. 2008; 130:17676. [PubMed: 19067651] (f) Zhang YH, Shi BF, Yu JQ. Angew Chem Int Ed. 2009; 48:6097. (g) Zhang YH, Yu JQ. J Am Chem Soc. 2009; 131:14654. [PubMed: 19788192] (h) Wang D-H, Engle KM, Shi B-F, Yu J-Q. Science. 2009 ASAP. (i) Shi B-F, Zhang Y-H, Lam JK, Wang D-H, Yu J-Q. J Am Chem Soc. 2009 ASAP.
10. For early proposal of formation of Pt(IV) complexes, see: (a) Pope WJ, Peachy S. J Proc Chem Soc London. 1907; 23:86.For oxidation of Pt(II) to Pt(IV) by O_2 see: (b) Rostovtsev VV, Henling LM, Labinger JA, Bercaw JE. Inorg Chem. 2002; 41:3608. [PubMed: 12099863] (c) Uson R, Fornies J, Navarro R. J Organomet Chem. 1975; 96:307. (d) Trost BM, Tanoury GJ. J Am Chem Soc. 1987; 109:4753. (e) Canty AJ. Acc Chem Res. 1992; 25:83.
11. Xia M, Chen ZC. Syn Commun. 2000; 30:531.
12. Daugulis O, Zaitsev VG. Angew Chem Int Ed. 2005; 44:4046.
13. (a) McAuley A, Whitcombe TW. Inorg Chem. 1988; 27:3090. (b) Hull KL, Anani WQ, Sanford MS. J Am Chem Soc. 2006; 128:7134. [PubMed: 16734446] (c) Cotton FA, Koshevoy IO, Lahuerta P, Murillo CA, Sanaú M, Ubeda MA, Zhao QL. J Am Chem Soc. 2006; 128:13674. [PubMed: 17044680] (d) Kaspi AW, Yahav-Levi A, Goldberg I, Vigalok A. Inorg Chem. 2008; 47:5. [PubMed: 18052157] (e) Furuya T, Ritter T. J Am Chem Soc. 2008; 130:10060. [PubMed: 18616246] (f) Mei TS, Wang X, Yu JQ. J Am Chem Soc. 2009; 131:10806. [PubMed: 19606861]
14. Reddy BVS, Reddy LR, Corey EJ. Org Lett. 2006; 8:3391. [PubMed: 16836413]
15. Unpublished results..
16. For arylation of heterocycles see: (a) Nakamura N, Tajima Y, Sakai K. Heterocycles. 1982; 17:235. (b) Akita Y, Ohta A. Heterocycles. 1982; 19:329. (c) Pivsa-Art S, Satoh T, Kawamura Y, Miura M, Nomura M. Bull Chem Soc Jpn. 1998; 71:467. (d) Park CH, Ryabova V, Seregin IV, Sromek AW, Gevorgyan V. Org Lett. 2004; 6:1159. [PubMed: 15040747]
17. For pioneering work on Pd(0)-catalyzed arylation of arenes see: (a) Hennings DD, Iwasa S, Rawal VH. J Org Chem. 1997; 62:2. [PubMed: 11671356] (b) Satoh T, Kawamura Y, Miura M, Nomura M. Angew Chem Int Ed. 1997; 36:1740.
18. For Pd(0)-catalyzed intermolecular arylation of sp^2 C–H bonds see: (a) Kametani Y, Satoh T, Miura M, Nomura M. Tetrahedron Lett. 2000; 41:2655. (b) Lafrance M, Fagnou K. J Am Chem Soc. 2006; 128:16496. [PubMed: 17177387] (c) Chiong HA, Pham Q-N, Daugulis O. J Am Chem Soc. 2007; 129:9879. [PubMed: 17649995]
19. (a) Dyker G. Angew Chem Int Ed. 1992; 31:1023. (b) Baudoin O, Herrbach A, Guéritte F. Angew Chem Int Ed. 2003; 42:5736. (c) Zhao J, Campo M, Larock RC. Angew Chem Int Ed. 2005; 44:1873. (d) Barder TE, Walker SD, Martinelli JR, Buchwald SL. J Am Chem Soc. 2005; 127:4685. [PubMed: 15796535] (e) Lafrance M, Gorelsky SI, Fagnou K. J Am Chem Soc. 2007; 129:14570. [PubMed: 17985911]
20. Netherton MR, Fu GC. Org Lett. 2001; 3:4295. [PubMed: 11784201]

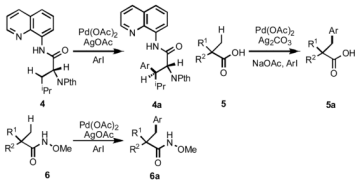
21. Campeau LC, Parisien M, Jean A, Fagnou K. J Am Chem Soc. 2006; 128:581. [PubMed: 16402846]



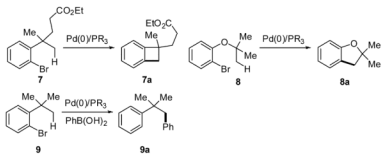
Scheme 1.
Two catalytic cycles to effect Pd-mediated arylation of sp^3 C–H bonds.



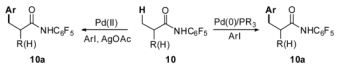
Scheme 2.
Arylation of sp^3 C–H bonds using aryl iodides.



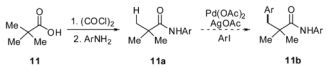
Scheme 3.
Pd(II)/Pd(IV) catalysis for sp^3 C–H arylation.



Scheme 4.
Arylation of sp^3 C–H bonds *via* Pd(0)/(II) catalysis.

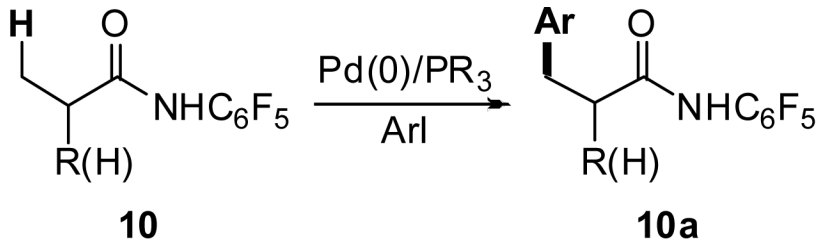


Scheme 5.
Amide-directed arylation of sp^3 C–H bonds *via* two modes of catalysis.



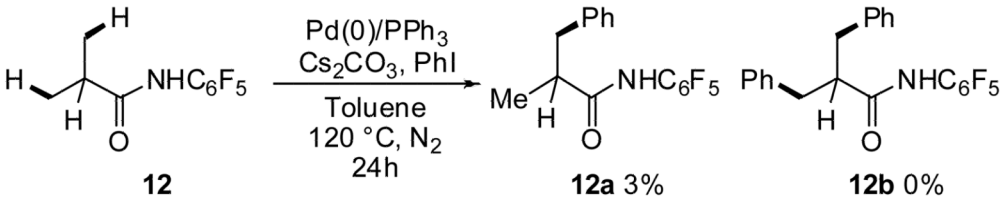
11 11a 11b

Scheme 6.
Preparation of amide substrates.

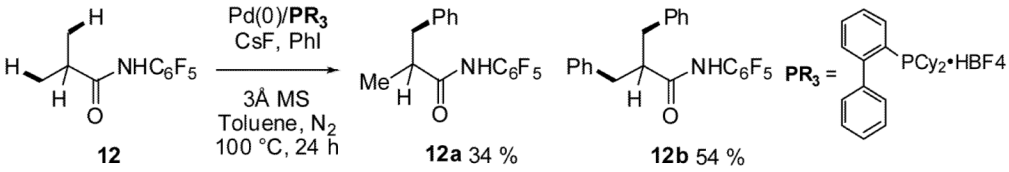


10 10a

Scheme 7.
$Pd(0)/PR_3$-catalyzed arylation of sp^3 C–H bonds.



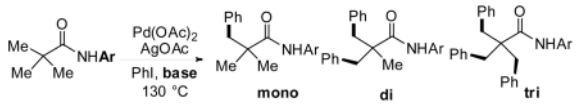
Scheme 8.
Initial experiments with Pd(0)/PR_3-catalyzed sp^3 C–H arylation.



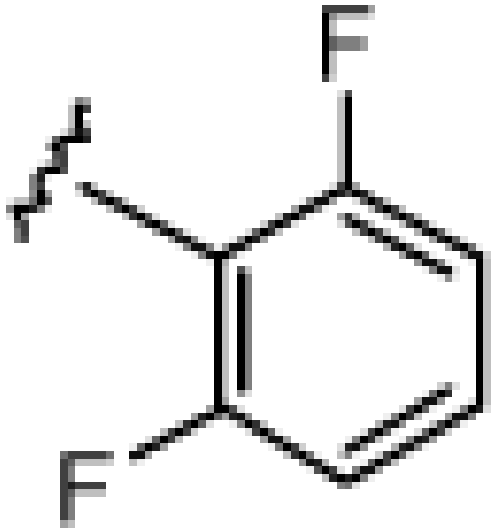
Scheme 9.
Optimized conditions.

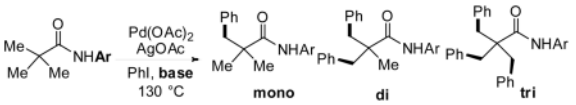
Table 1

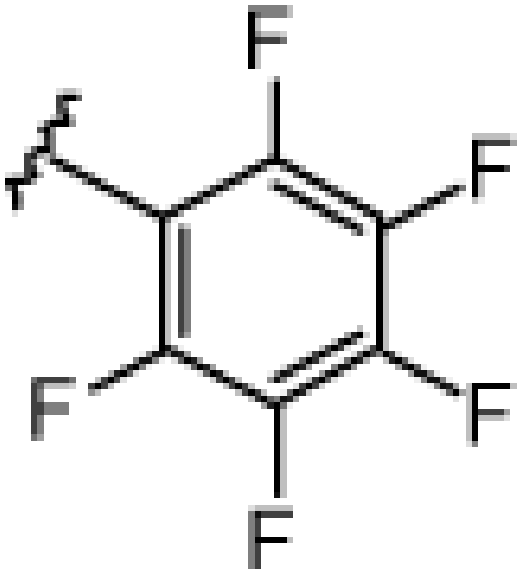
Arylation of *N*-phenylpivalamides[a, b]



			yield (%)			
Entry	**Ar**	**base**	**sm**	**mono**	**di**	**tri**
1	Ph	none	100	0	0	0
2		Cs_2CO_3	91	7	2	0
3		Cs_2CO_3	39	41	12	8





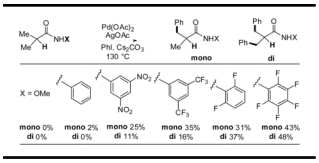
Entry	Ar	base	yield (%) sm	mono	di	tri
4		none	100	0	0	0
5		Cs_2CO_3	12	32	40	16

[a]Reaction conditions: 0.2 mmol substrate, 10 mol% $Pd(OAc)_2$, 4 equiv AgOAc, 1.2 equiv Cs_2CO_3, 0.5 mL iodobenzene, 130°C,3 h, air.

[b]Yield was determined by ^1H NMR analysis of crude product using CH_2Br_2 as the internal standard.

Table 2

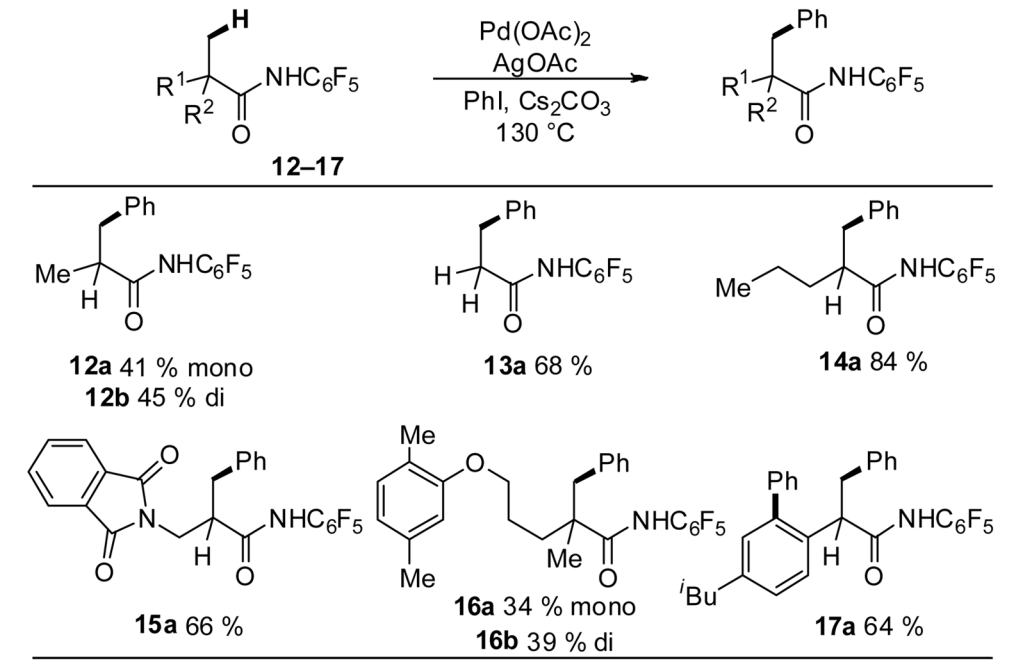
Screening of directing groups for α-hydrogen-containing substrates [a]



[a]The reaction conditions are identical to those described in Table 1.

Table 3

Arylation of *N*-phenylpivalamides[a, b]



[a]The reaction conditions are identical to those described in Table 1.

[b]Isolated yield.