C–H Activation

Anilide *ortho*-Arylation by Using C–H Activation Methodology**

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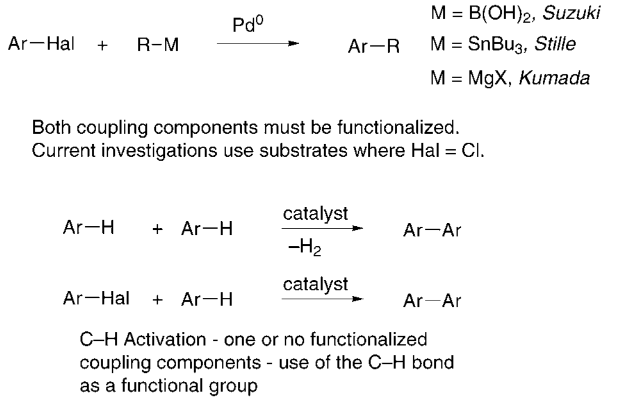
With few exceptions, the current methodology for biaryl formation utilizes functionalization on both components of the coupling process (Scheme 1).[1] Ideally, one would like to selectively and efficiently couple two C–H bonds to give the corresponding product (Scheme 1). From a thermodynamic point of view, however, this latter process is quite often unfavorable (for example, the coupling of benzene to give biphenyl and hydrogen is unfavorable by 13.8 kJ mol^{-1}).[2] Given the potentially large number of C–H bonds in both reactants, it is also problematic to achieve the desired regioselectivity of coupling.

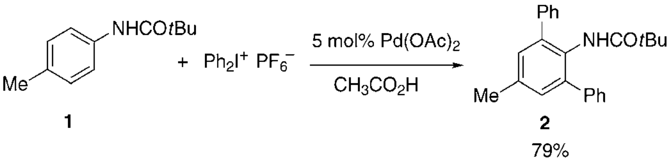


Scheme 1. C–X bond activation versus C–H bond activation.

The R–X coupling with R–H is viable, but this variation has not been extensively investigated. Phenols and heterocycles have been *ortho*-arylated with aryl bromides through Pd^0–Pd^{II} catalytic cycles.[3] Benzanilides have been *ortho*-arylated on the benzoyl moiety under similar conditions.[4] Simple arenes may be arylated with aryl iodides under Ir catalysis, and *ortho*-arylation of aromatic ketones and imines by using Ru catalysis has been shown.[5] A few other examples of coupling reactions between Ar–H and Ar–Hal have been reported, mostly proceeding through a Pd^0–Pd^{II} catalytic cycle.[6]

Tremont, Liebeskind and co-workers have shown that anilide and aromatic imine coupling with alkyl iodides is promoted by Pd^{II}.[7] This alkylation is mechanistically distinct from the processes described above since it proceeds either through a σ-bond methathesis pathway or a Pd^{II}–Pd^{IV} couple.[7a] Inspired by this work, we have investigated the Pd-catalyzed arylation of arenes containing *ortho*-directing groups, in the hope of developing a general method for arene *ortho*-arylation under C–H activation conditions. We report herein the Pd-catalyzed *ortho*-arylation of anilides. 2,6-Diarylanilines are useful for the synthesis of ligands employed in Brookhart-type transition-metal-catalyzed polymerizations and currently are synthesized only from highly functionalized starting materials.[8]

The screening reactions were performed with respect to the arylating agent and the solvent. Reaction of 4-methylpivalanilide (**1**) with 4-methylphenyldiazonium tetrafluoroborate gave only minor amounts of coupling product under the tested conditions in a variety of solvents. Arylation of **1** with the commercially available Ph$_2$I$^+$PF$_6^-$ was successful in acetic acid and allowed the isolation of the diphenylated product **2** in 79 % yield (Scheme 2; Table 1, entry 12).[9]



Scheme 2. Amide arylation with iodonium salts.

Unfortunately, diphenyliodonium salts are the only ones commercially available, thus limiting the scope of this reaction. In addition, these salts are very expensive and have to be used in excess for complete conversion into the product.

We were pleased to find out that the combination of aryl iodides and AgOAc is effective in catalytically arylating the anilides by using palladium acetate. The reaction proceeds well in acetic acid, but the fastest rates were observed in trifluoroacetic acid and thus further investigations were carried out in this solvent.

A number of anilides could be arylated by using this methodology (Table 1). Generally, the pivaloyl derivatives gave the cleanest reactions; however, acetamides (entry 11) are also compatible with the reaction conditions. In this case more optimization is needed due to a competitive side reaction.[10] The reaction is highly tolerant with respect to substituents on the anilide: any halogenes, including iodine (entries 4, 9), are tolerated. The reaction is also compatible with bromo substituents on the aryl iodide (entries 2, 5). This allows construction of scaffolds that could be functionalized further by using conventional Pd^0 coupling processes. Ester groups are also tolerated (entries 7, 8). The use of *meta*-substituted anilides results in the selective addition of one aryl

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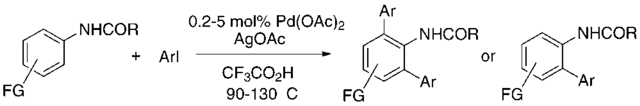
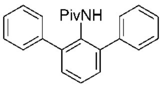
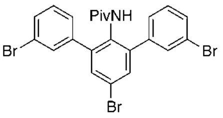
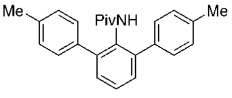
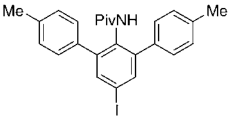
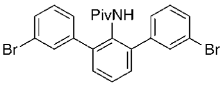
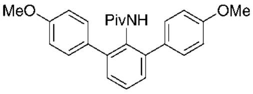
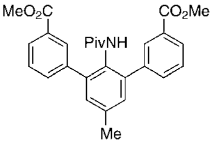
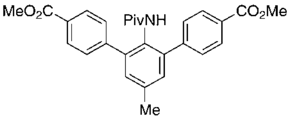
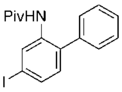
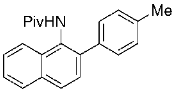
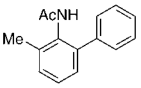
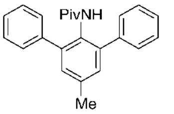
[**] This work was supported by the Welch Foundation and the University of Houston Small Grants Program. The authors are grateful to Prof. Maurice Brookhart (University of North Carolina, Chapel Hill, NC) for helpful comments.

Supporting Information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/ange.200500589

Table 1: Iodoarene coupling with amides[a]



Entry	Amide FG	Ar	Product	Yield [%]
1	H	C_6H_5		91
2	4-Br	3-Br-C_6H_4		95
3	H	4-Me-C_6H_4		95
4	4-I	4-Me-C_6H_4		92
5	H	3-Br-C_6H_4		55
6	H	4-MeO-C_6H_4		67
7	4-Me	3-MeO_2C-C_6H_4		85
8	4-Me	4-MeO_2C-C_6H_4		96
9	3-I	C_6H_5		83
10	[b]	4-Me-C_6H_4		62
11	[c]	C_6H_5		76
12	4-Me	[d]		79

[a] Substrate (1 equiv), ArI (2–9 equiv), AgOAc (1 equiv per coupled Ar), $Pd(OAc)_2$ (0.2–5 mol%). In entries 1–10 and 12 R = *t*Bu, in entry 11 R = Me. Yields are given for isolated products. See the Experimental Section and Supporting Information for details. [b] 1-Naphthyl-*N*-pivalamide. [c] 2-Methylacetanilide. [d] $Ph_2I^+PF_6^-$ was used instead of ArI, with CH_3CO_2H as the solvent, and no AgOAc was added.

group (entry 9). High turnover numbers have been achieved: Entry 3 was run with 0.2 mol% Pd and complete conversion (according to GC) was observed, a result indicating a turnover number of 1000. This is a remarkably high turnover number for a C–H activation process.[11]

At this point only a speculative discussion about the reaction mechanism is possible. Qualitatively, the reactions are faster for ArI containing electron-donating groups, a result which sets this process apart from the conventional Pd-catalyzed couplings.[12] As expected for an electrophilic C–H activation process, the reactions are faster for anilides possessing donor substituents.[13] It has been shown that diaryliodonium trifluoromethanesulfonates can transfer Ar^+ to nitrogen-ligated Pd^{II}, thereby leading to the formation of unstable Pd^{IV} species that decompose through reductive elimination pathways.[14] This finding of Canty and co-workers may be relevant to the mechanism of this arylation procedure; however, at this point a σ-bond metathesis pathway can not be ruled out.

Finally, we include a note regarding the use of silver salts in this coupling process: the silver acetate price per mole is about twice that of the price of cesium carbonate, a base widely used for Pd-catalyzed coupling reactions. However, in many cases several equivalents of Cs_2CO_3 are used for the reactions, as opposed to the one equivalent of AgOAc per introduced aryl group for this method.

In conclusion, we have developed a new anilide arylation process based on C–H activation. The method is highly tolerant to functional groups and allows the presence of any halogens on the anilide moiety and bromo substituents on the aryl iodide. Up to 1000 turnovers have been demonstrated for this reaction. Recently, we have verified that the reaction developed here is quite general and allows for the arylation of other arenes containing *ortho*-directing groups. 2-Arylpyridines and imines derived from substituted benzaldehydes can be arylated using this methodology. The results of these latter investigations will be published separately.

Experimental Section

General considerations: The coupling reactions were performed without special precautions in 2-dram screw-cap vials. Flash chromatography was performed by using 60-Å silica gel (Sorbent Technologies) or acidic, Brockmann I, aluminum oxide (Aldrich). GC analyses were performed on a Shimadzu GC-2010 chromatograph equipped with a Restek column (Rtx-5, 15 m, 0.25 mm inner diameter). The ^1H and ^{13}C NMR spectra were recorded on a GE QE-300 spectrometer by using the residual solvent peak as a reference. IR spectra were obtained by using a ThermoNicolet Avatar 370 FT-IR instrument. Melting points were measured on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA.

2,6-Di(4-methylphenyl)pivalanilide (Table 1, entry 3): A solution of pivalanilide (0.53 g, 3.0 mmol), 4-iodotoluene (3.30 g, 15.0 mmol), palladium acetate (1.3 mg, 0.006 mmol), and silver acetate (1.00 g, 6.0 mmol) in trifluoroacetic acid (TFA; 2 mL) in a 2-dram screw-cap vial was heated at 90 °C for 3 days. At that point, the conversion was observed by GC analysis to be > 99%. During this time, a dark-yellow precipitate was formed and the supernatant became clear dark red. The reaction mixture was diluted with toluene (30 mL), the solution was decanted, and the precipitate was washed with toluene (2 × 5 mL). The combined organic solutions were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (toluene, then dichloromethane/toluene (1:1)) to give the product as a white solid (1.02 g, 95%): m.p. 239–240 °C (pentane); $R_f = 0.35$ (dichloromethane/pentane (1:1)); ^{1}H NMR ($CDCl_3$): $\delta = 0.87$ (s, 9H), 2.37 (s, 6H), 6.74 (brs, 1H), 7.17 (d, $J = 7.8$ Hz, 4H), 7.25 (d, $J = 7.8$ Hz, 4H), 7.25–7.40 ppm (m, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 21.2$, 27.1, 38.7, 127.1, 128.6, 128.7, 129.5, 131.6, 136.7, 136.8, 140.6, 176.3 ppm; FT-IR: $\tilde{\nu} = 1642$ (C=O), 3250 cm^{-1} (N–H); elemental analysis: calcd (%) for $C_{25}H_{27}NO$: C 83.99, H 7.61, N 3.92; found: C 83.47, H 7.64, N 4.00.

Silver iodide (1.37 g, 5.82 mmol) obtained after drying the precipitate in vacuo and in the dark dissolved completely in 28–30% ammonia (100 mL).

2,6-Di(3′-bromophenyl)-4-bromopivalanilide (Table 1, entry 2): A solution of 3-bromoiodobenzene (130 μL, 1.0 mmol), 4-bromopivalanilide[15] (64 mg, 0.25 mmol), palladium acetate (1.5 mg, 0.007 mmol), and silver acetate (87 mg, 0.5 mmol) in TFA (0.5 mL) was heated at 120 °C for 2 h. Workup as above followed by purification by flash chromatography (toluene, then dichloromethane) afforded the product as an off-white solid (135 mg, 95%): m.p. 206–207 °C (colorless crystals, from pentane); $R_f = 0.35$ (dichloromethane/pentane (1:2)); ^{1}H NMR ($CDCl_3$): $\delta = 0.90$ (s, 9H), 6.66 (brs, 1H), 7.20–7.30 (m, 4H), 7.40–7.55 ppm (m, 6H); ^{13}C NMR ($CDCl_3$): $\delta = 27.1$, 38.9, 121.0, 122.0, 127.5, 129.9, 130.8, 130.9, 131.5, 132.6, 140.1, 141.4, 176.7 ppm; FT-IR: $\tilde{\nu} = 1639$ (C=O), 3280 cm^{-1} (N–H); elemental analysis: calcd (%) for $C_{23}H_{20}Br_3NO$: C 48.80, H 3.56, N 2.47; found: C 48.91, H 3.48, N 2.54.

Received: February 17, 2005
Published online: May 24, 2005

Keywords: biaryls · C–C coupling · C–H activation · homogeneous catalysis · palladium

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