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Palladium-Catalyzed Intermolecular Directed C−H Amidation of Aromatic Ketones

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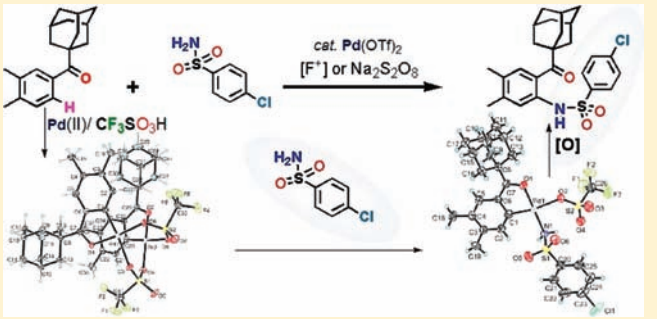
Supporting Information

ABSTRACT: Pd-catalyzed directed ortho C−H amidation of aromatic ketones with both sulfonamides and amides has been accomplished. The use of an electron-deficient Pd complex, $Pd(OTf)_2$, is crucial for the success of this transformation. Some key intermediates of the reaction, that is, the cyclopalladation complexes of ketones, have been characterized by X-ray crystallography. Experimental analysis of these palladacycles and also the experimental results with *N*-methyl sulfonamides indicate that the new reaction does not seem to proceed through a nitrene intermediate. The utility of the newly developed reaction was demonstrated for the synthesis of useful organic intermediates such as 2- and 3-alkyl indoles and 2-aminophenyl ketones.



1. INTRODUCTION

Recently, Pd-catalyzed chelation-directed C−H activation/cross-coupling reactions have emerged as powerful methods in organic synthesis.[1] Frequently used directing groups are nitrogen-containing moieties (e.g., amides,[2] *N*-heterocycles,[3] imines,[4] pyridine *N*-oxides,[5] and amines[6]), while recent studies expanded the scope to include more challenging substrates such as alcohols[7] and carboxylic acids.[8] The use of a ketone group as the directing group is also known, but most previous studies on ketone-directed C−H activation used Ru catalysts and only afforded the C−C coupling products.[9] In a pioneering study, Miura et al. discovered Pd-catalyzed multiple arylation of benzyl phenyl ketones with aryl bromides.[10] Recently, Cheng et al. described an important discovery of Pd-catalyzed C−H activation/C−C coupling of *sec*-alkyl aryl ketones with aryl iodides.[11]

Here, we report a practical Pd(II)-catalyzed ortho C−H amidation of aromatic ketones. This work was inspired by our recent success in Pd(II)-catalyzed C−H activation/coupling of phenol esters.[12] The significance of the present finding is 2-fold: (1) ortho-amino aryl ketones are very useful synthetic intermediates in medicinal chemistry; they can also be converted to other ortho-substituted aryl ketones and indoles (Scheme 1); and (2) the previous examples of Pd-catalyzed intermolecular directed C−H amination involve the functionalization of sp^2 and sp^3 C−H bonds in pyridine and oxime ether substrates, most likely via a nitrene insertion mechanism.[1b,4b] The present study provides an additional example[13−16] for Pd-catalyzed intermolecular directed C−H amination, and our experiments show that the new reaction may not involve a nitrene intermediate.

2. RESULTS AND DISCUSSION

2.1. Crystal Structures of the Reaction Intermediates. Our study began by synthesis of palladacycles of a model aryl ketone **1a** (Scheme 2). A yellow crystal of a palladacycle dimer **A** was obtained with two OTf^- anions bridging two Pd(II) atoms. When **A** was treated with 4-Cl−$C_6H_4SO_2NH_2$, a green crystal **B** was obtained in which the sulfonamide coordinates to Pd(II) unusually in its neutral form. Addition of an F^+ agent (i.e., *N*-fluoro-2,4,6-trimethyl-pyridinium triflate) or $Na_2S_2O_8$ converted **B** to the ortho C−H amidation product **2a** at 60 °C in 82% yield. In the absence of these oxidants, **B** did not afford any C−H amidation product even when heated to 100 °C. Addition of weaker oxidants (i.e., Cu(II), Ag(I), O_2, and benzoquinone) to **B** did not cause the C−H amidation, either. Besides, when TFA (trifluoroacetic acid) was used with HOTf, a palladacycle **C** similar to that reported by Cheng et al.[11] was obtained with two TFA anions bridging two Pd(II). It is interesting to note that **C** did not react with 4-Cl−$C_6H_4SO_2NH_2$ to produce **B**, but the reverse conversion of **B** to **C** occurred smoothly. In addition, treatment of both **A** and **C** with the nitrene precursor 4-Cl−$C_6H_4SO_2N$═IPh did not cause any C−H amidation. This result suggests against the involvement of nitrene insertion mechanism,[3f,4b] whereas previous stoichiometric reactions of related sulfonamide-coordinated palladacycles indicated that the conversion from **B** to **2a** may involve the intermediacy of a Pd(IV) imido complex.[3b,13b,c]

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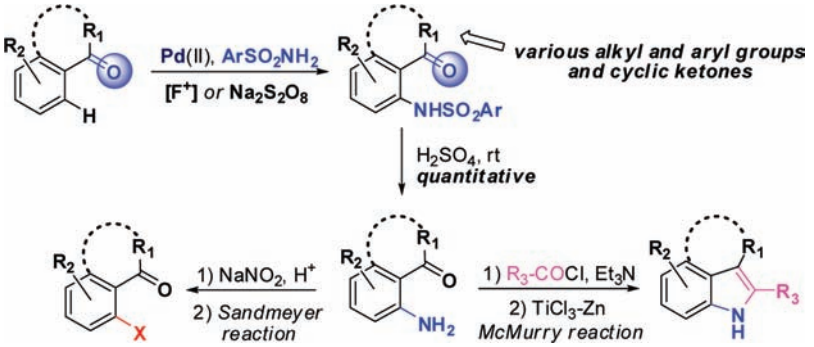
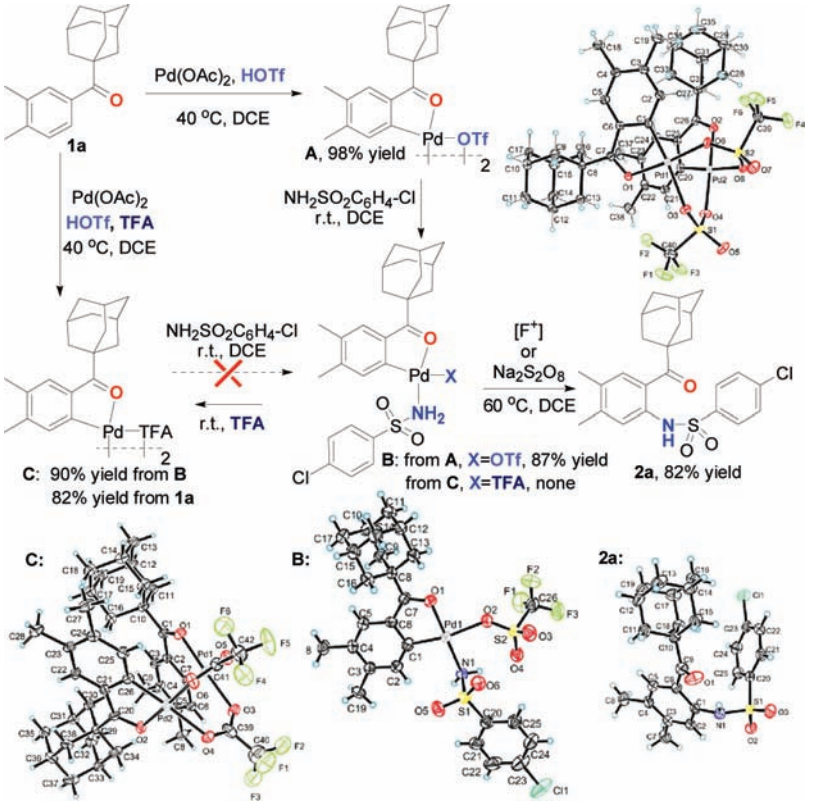
Scheme 1. Possible Use of Pd(II)-Catalyzed Ortho C−H Amidation of Aromatic Ketones



Scheme 2. Transformations under Stoichiometric Conditions



2.2. Reaction Scope. The above results indicate that the use of HOTf to tune the electrophilicity of Pd(II)[17] is a useful strategy to achieve difficult C−H activation. Subsequently, we developed a catalytic version of the above C−H amidation reaction. As shown in Scheme 3, stirring a solution of **1a** with 2 equiv of sulfonamide, 2 equiv of *N*-fluoro-2,4,6-trimethyl-pyridinium triflate, 10 mol % $Pd(OAc)_2$, and 0.5 equiv of HOTf at 80 °C in DCE afforded the desired product **2a** in 71% isolated yields. Other oxidants including Selectfluor and $Na_2S_2O_8$[18] could also be used in the reaction (Supporting Information). When $Pd(OTf)_2$ was used as catalyst, the yield improved to 85%. This observation is consistent with Yu's finding that the acetate anion may interfere with some C−H activation processes.[19] Moreover, we tested Cheng's Pd(II)/TFA conditions[11] in our amidation reaction but failed to obtain any desired product. This result is consistent with the above studies on the crystals showing that **B** can be easily converted to **C** but the **C**-to-**B** transformation is much more difficult.

Under the optimized conditions, ortho-amidation can occur smoothly with both alkyl aryl ketones and aryl aryl ketones carrying a number of substituents (Table 1). The alkyl groups in the ketones can be primary, secondary, or even tertiary alkyl groups so that the present reaction is not limited to nonenolizable ketones. Both electron-rich and electron-poor aromatic ketones can be converted, while a competition experiment shows that an electron-rich aromatic ketone reacts more rapidly than an electron-poor substrate (**2c′**). Importantly, the bromo and chloro substitutions (**2e**−**2f**, **2o**, **2y**) can

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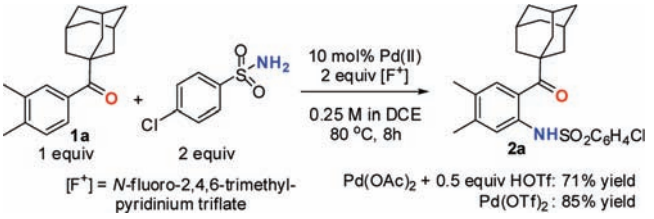
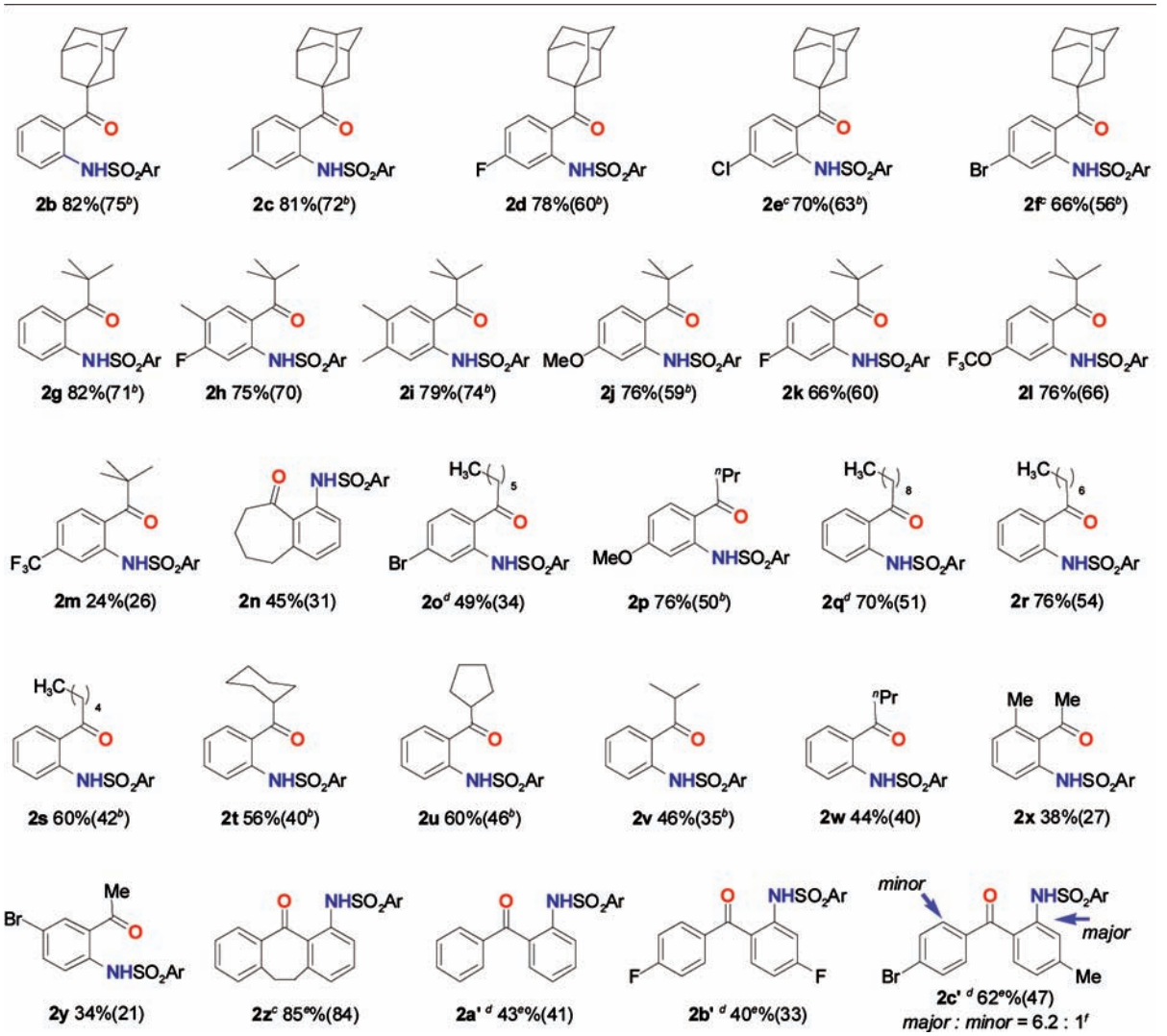
be well tolerated in this C−N coupling reaction, making possible additional modifications at the halogenated positions. Moreover, it is noteworthy that all the transformations in Table 1 are not sensitive to moisture or air so that these reactions can be readily conducted without any sophisticated operation.

Scheme 3. Catalytic Version of the C−H Amidation Reaction



Noteworthily, eletron-rich ketones tend to give higher yields than electron-poor ones in the reaction. Also, aryl alkyl ketones with tertiary alkyl groups tend to give higher yields than substrates with primary and secondary alkyl groups. To understand these observations, we carried out experiments to synthesize palladacycles of 4-trifluoromethylphenyl *t*-butyl ketone and 1-*o*-tolylethanone (Scheme 4) in the presence of $TsNH_2$. Instead of generating any palladacycle, we obtained a golden crystal corresponding to a TsNH-bridged Pd dimer. This result indicates that the sulfonamide can compete with the ketone for the coordination with Pd, which is consistent with the notion that a ketone group is a weak directing group in palladium catalysis. Comparing Schemes 2 and 4, we concluded that an electron-rich ketone exhibits a better performance in the C−H amidation reaction because it coordinates to Pd more strongly. This explanation also applies to the cases of ketones with tertiary alkyl groups, because a tertiary alkyl group is a better electron donor than a primary or secondary alkyl group.

Table 1. Catalytic Ortho C−H Amidation of Aromatic Ketones (Ar = 4-Cl−C_6H_4−)[a]



[a] Isolated yields for the reactions conducted with 10 mol % $Pd(OTf)_2$. Yields in the parentheses were obtained with 10 mol % $Pd(OAc)_2$ and 0.5 equiv of HOTf. [b] At 60 °C. [c] 4 equiv of $Na_2S_2O_8$ was used as oxidant. [d] 2 equiv of Selectfluor was used as oxidant. [e] 10 mol % $Pd(OTf)_2$ and 0.3 equiv of HOTf were used. [f] The ratio was determined by NMR.

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Further studies on the electronic effect in the transformation reveal an interesting Hammett relationship between the product distribution and the substituent electronic constants. As shown in Figure 1, the log value of the product distribution (i.e., $\log([P_1]/[P_2])$) is found to have a linear dependence on the Hammett susbtituent constants in the diphenyl ketone system. This observation again indicates that an electron-rich ketone exhibits a better performance in the C−H amidation reaction. In addition, by using an isotope labeled diphenyl ketone, we obtained a KIE (kinetic isotope effect) value of 4.9 (Scheme 5). This result indicates that C−H activation is the rate-limiting step of the present transformation.

As to the amide partner (Table 2), we found that both electron-rich and electron-poor arylsulfonamides can be used for the transformation (from **2g** to **2go**). The optimal yield (82%) is obtained for arylsulfonamides carrying a *para*-Cl (**2g**) or *para*-CF_3 (**2gi**) substitution. An alkylsulfonamide, that is, methanesulfonamide, can also be used in the reaction to give a modest yield (**2gp**, 51%). Moreover, several amides of electron-deficient carboxylic acids, pentafluorobenzamide (**2gq**, 37%), 2,3,5,6-tetrafluorobenzamide (**2gr**, 20%), and 2,6-bis(trifluoromethyl) benzamide (**2gs**, 17%), can be coupled with the aromatic C−H bonds, suggesting that sulfonamide is not necessary in this chemistry but the electronic nature of the amide is vital. Finally, it is important to note that several *N*-methyl arylsulfonamides (**2gv**, **2gw**, **2gx**) can be converted to the desired products. This observation provides a second evidence against the involvement of nitrene insertion mechanism,[3f,4b,15] because an *N*-methyl arylsulfonamide cannot generate any nitrene intermediate. On the other hand, the reaction with an *N*-methyl arylsulfonamide can be readily explained by a mechanism involving the intermediacy of a Pd(IV) imido complex (Figure 2).[3b,13b,c]

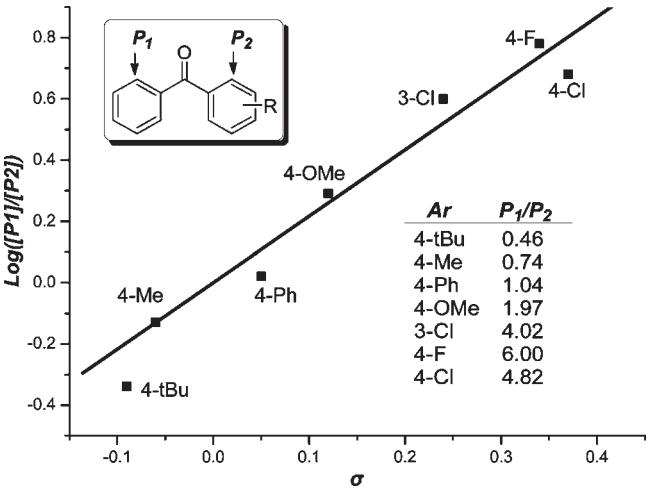
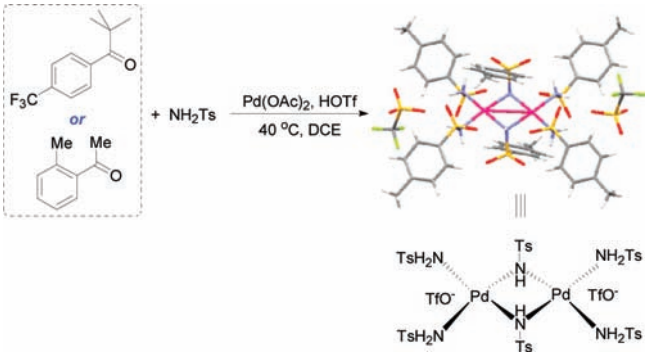


Figure 1. Hammett relationship in the C−H amidation reaction.

Scheme 4. Reactions with Less Electron-Rich Ketones



Finally, the reaction can be readily scaled up to gram-scale transformation (Scheme 6). Moreover, it is interesting to report that the reaction of a 3-indole ketone using the newly developed catalytic system causes C−H amidation at the 4-position (Scheme 7). The steric hindrance of the *N*-Ts group may be the reason for the occurrence of the C−H activation at the 4-position.

2.3. Applications. The utility of the new ortho C−H amidation reaction was examined for the synthesis of some useful organic intermediates. Shown in Scheme 8 is a new, alternative synthetic route to 2- or 3-substituted indoles from simple aryl alkyl ketones. The first step of the synthesis, that is, catalytic ortho C−H amidation, has already been shown in Table 1. As to the second step, we found that the aryl alkyl ketones with *n*Pr substitution (Table 3, entries 1,2) can be directly converted to 3-alkyl indoles (**3a**, **3b**) in good yields (80−83%) through a previously reported method[20] of TMSC(Li)N_2-mediated cyclization (Table 3). When the ketones carry longer side chains (Table 3, entries 3,4), the cyclization step produces the desired 3-alkyl indoles (**3c**, **3d**) in modest yields (49−58%). Besides, we also observed the formation of some *N*-sulfonyl-*o*-alkynylanilines (**4c**, **4d**) presumably through the rearrangement of the alkylidene carbene intermediates generated from TMSC(Li)N_2 and the ketones. CuI-catalyzed cyclization[21] is then conducted to convert the *N*-sulfonyl-*o*-alkynylanilines to the 2-alkyl indoles (**5c** and **5d**).

For aryl alkyl ketones carrying side chains with larger steric hindrance (Table 3, entries 5−10), it is interesting to find that the LDA/$TMSCHN_2$ treatment only produces *N*-sulfonyl-*o*-alkynylanilines (**4e**−**4j**) in high yields (78−88%). Subsequent CuI-catalyzed cyclization of the *N*-sulfonyl-*o*-alkynylanilines is also a highly efficient transformation providing the 2-alkyl indoles (**5e**−**5j**) in excellent yields (95−98%). Thus, the results in Table 3 show a new method for the preparation of either 2- or 3-alkyl indoles depending on the steric hindrance of the side chain. The advantage of this method is the easy synthesis of ortho amidated aromatic ketones directly from readily available aryl alkyl ketones.

Scheme 5. Kinetic Isotope Effect

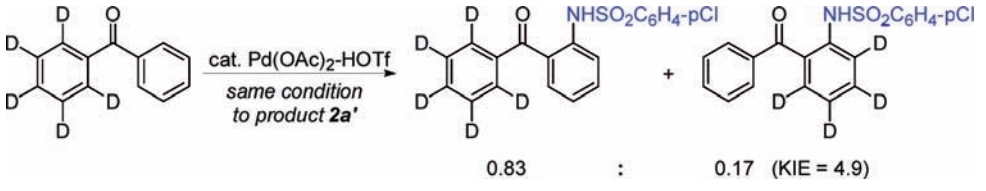


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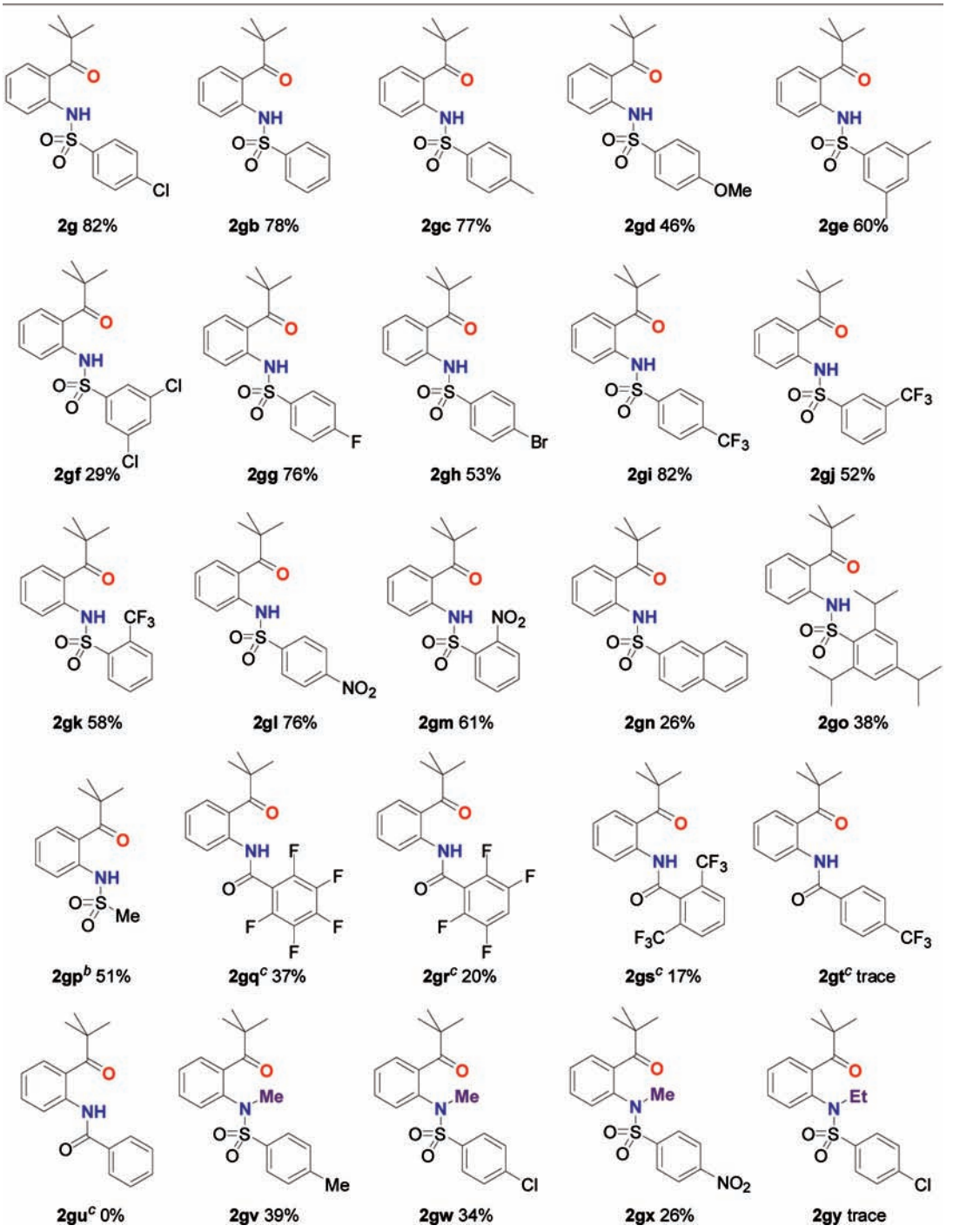
Table 2. Catalytic C−H Amidation with Different Amides[a]



[a] Isolated yields. [b] 100 °C. [c] 2 h at 120 °C; Selectfluor was used as oxidant.

Moreover, shown in Scheme 9 is a new, simple synthesis of a key intermediate[22] for the blood glucose-lowering drug Prandin in 52% yield through three steps from readily available isovalerophenone. In this example, a simple synthesis of 2-aminophenyl ketone from a phenyl ketone compares favorably with the previous methods that involve either reaction of 2-aminobenzonitrile with an alkyl Grignard reagent or ortho-metalation of *N*-acyl aniline followed by *C*-acylation.[20,22]

3. CONCLUSIONS

In summary, Pd-catalyzed directed ortho C−H amidation of aromatic ketones with sulfonamides and amides was accomplished. The use of an electron-deficient Pd complex, $Pd(OTf)_2$, was found to be crucial for the success of this transformation. Key intermediates of the reaction, that is, the cyclopalladation complexes of ketones, were characterized by X-ray crystallography. Experimental analysis of these palladacycles and also the experimental

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results with *N*-methyl sulfonamides indicated that the new reaction does not seem to involve a nitrene intermediate. The utility of the newly developed reaction was demonstrated for the synthesis of useful organic building blocks such as 2- and 3-alkyl indoles and 2-aminophenyl ketones.

4. EXPERIMENTAL SECTION

4.1. General Information. Dichloroethane (DCE) was purchased from a commercial source and used without further treatment. $Pd(OAc)_2$ (>99.9%) and HOTf was purchased from Aldrich and kept in a dry place. $Pd(OTf)_2 \cdot 2H_2O$ was synthesized according to the reported method.[23] Aryl ketones were commercially available or easily synthesized from acyl chlorides and Grignard reagents. ^{1}H NMR spectra were recorded on 400 MHz spectrometers. Chemical shifts of ^{1}H NMR spectra were reported in parts per million relative to tetramethylsilane ($\delta = 0$). ^{13}C NMR spectra were recorded on 100 MHz spectrometers. Chemical shifts were reported in parts per million relative to the solvent resonance as the internal standard ($CDCl_3$, δ 77.16 ppm). High-resolution mass spectra (HRMS) were recorded on a BRUKER VPEXII spectrometer with EI mode.

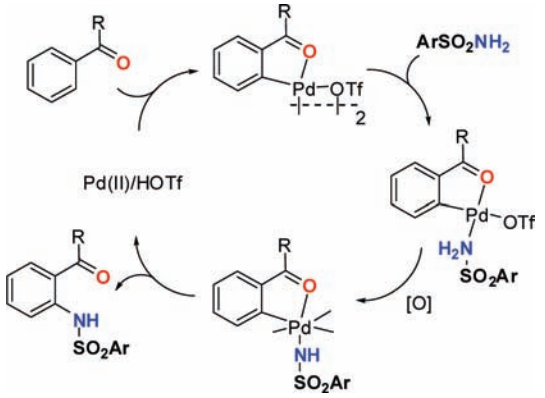
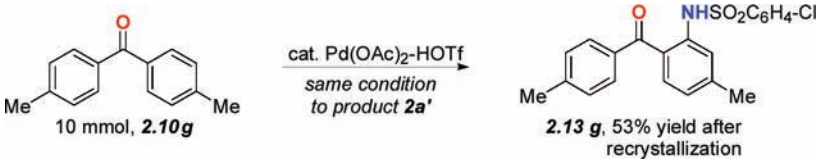


Figure 2. Proposed mechanism for the C−H amidation reaction.

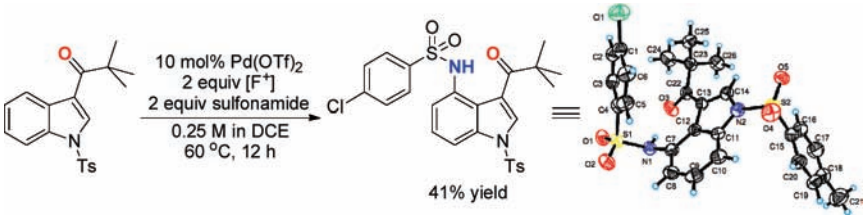
4.2. General Procedure for Synthesis of A. To a 10 mL vial were sequentially added $Pd(OAc)_2$ (56.5 mg, 0.25 mmol), adamantan-1-yl-(3,4-dimethyl-phenyl)-methanone (**1a**) (107.3 g, 0.4 mmol), and DCE (1 mL). The vial was stirred at 40 °C for 5 min. Next, HOTf (45 mg, 0.3 mmol) was added. The vial was stirred at the 40 °C for 2.5 min and then cooled to room temperature. The reaction mixture was filtered and washed with 2 mL of a mixture of petroleum ether/DCE (1:1) to give the desired OTf's bridged palladacycle product as yellow needles (128 mg, 98%) that can be characterized by X-ray crystallography. This palladacycle compound was stable at room temperature in the dry solid state for about 1 week but sensitive to moisture.

4.3. General Procedure for Synthesis of B. **A** (52.3 mg, 0.05 mmol) and 4-chloro-benzenesulfonamide (19.2 mg, 0.1 mmol) were stirred in 1 mL of DCE at room temperature for 1 h, during which period the palladacycle and sulfonamide dissolved. The resulting solution was kept in 15 °C for 8 h. The crystal was formed, filtered, and washed with 2 mL of a mixture of petroleum ether and DCE (1:1) to give **B**·DCE (71 mg, 87%) as light green needles, which were characterized by X-ray crystallography.

Scheme 6. Gram-Scale Reaction



Scheme 7. C−H Amidation of an Indole Substrate



Scheme 8. An Alternative Synthetic Route to 2- or 3-Substituted Indoles from Simple Aryl Alkyl Ketones

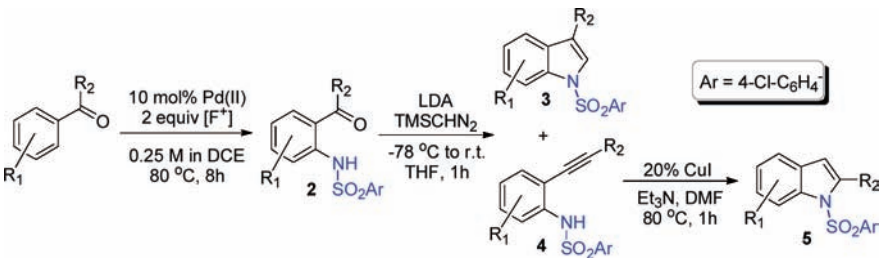


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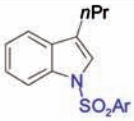
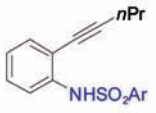
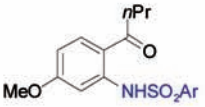
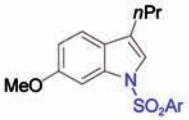
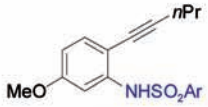
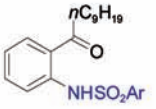
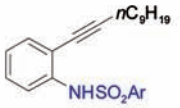
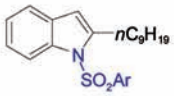
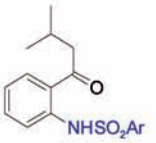
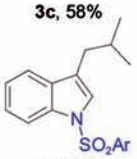
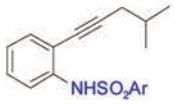
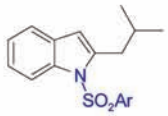
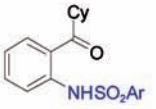
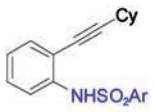
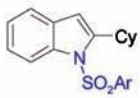
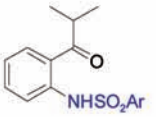
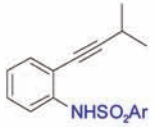
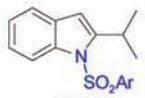
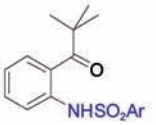
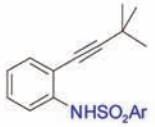
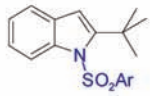
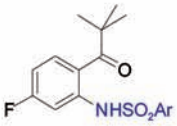
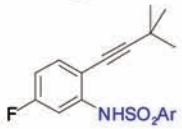
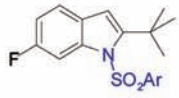
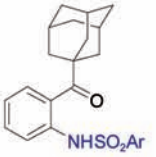
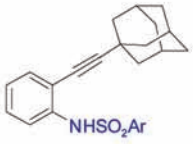
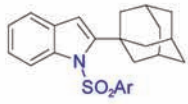
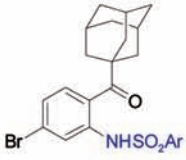
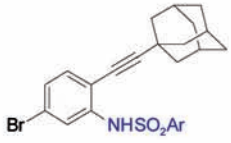
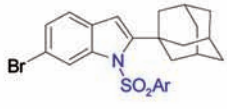
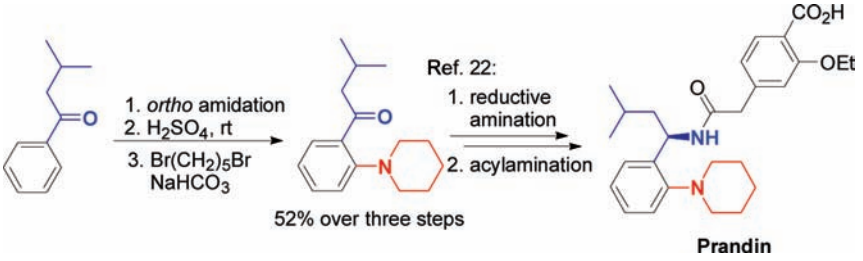
Table 3. Synthesis of 2- and 3-Alkyl Indoles[a]

entry	2	3	4	5 (yield from 4)
1		 **3a**, 83%	 **4a**, <10%	-
2		 **3b**, 80%	 **4b**, <10%	-
3		 **3c**, 58%	 **4c**, 35%	 **5c**, 96%
4		 **3d**, 49%	 **4d**, 40%	 **5d**, 95%
5		trace	 **4e**, 78%	 **5e**, 95%
6		trace	 **4f**, 82%	 **5f**, 98%
7		0%	 **4g**, 87%	 **5g**, 96%
8		0%	 **4h**, 85%	 **5h**, 98%
9		0%	 **4i**, 88%	 **5i**, 97%
10		0%	 **4j**, 84%	 **5j**, 98%

[a] Isolated yields.

dx.doi.org/10.1021/ja108450m |*J. Am. Chem. Soc.* 2011, 133, 1466–1474

Scheme 9. Synthesis of a Key Intermediate for Prandin



4.4. General Procedure for Synthesis of C. To a 10 mL vial were sequentially added $Pd(OAc)_2$ (56.5 mg, 0.25 mmol), adamantan-1-yl-(3,4-dimethyl-phenyl)-methanone (**1a**) (107.3 mg, 0.4 mmol), and DCE (1 mL). TFA (114 mg, 1 mmol) was added. The vial was stirred at 40 °C for 5 min, and then HOTf (45 mg, 0.3 mmol) was added. The vial was stirred at the 40 °C for 10 min and then cooled to room temperature. The reaction mixture was filtered and washed with 2 mL of a mixture of petroleum ether and DCE (1:1) to give the desired OTFA's bridged palladacycle **C** as orange needles (109 mg, 90%). **C** was much more stable than **A**, and no decomposition was observed even after staying in atmosphere for at least 4 weeks, which was characterized by X-ray crystallography without further recrystallization. When **C** and 4-chlorobenzenesulfonamide were stirred in DCE for 12 h (room temperature or 60 °C), the solid did not dissolve, and no product was observed after even 3 days. Conversely, when **B** was stirred in TFA, an orange solid was formed immediately to produce **C** according to NMR analysis.

4.5. General Procedure for C−H Amidation. To a 10 mL vial were added ketone (0.25 mmol), sulfonamide (0.5 mmol), *N*-fluoro-2,4,6-trimethyl-pyridinium triflate (145 mg, 0.5 mmol), $Pd(OTf)_2 \cdot 2H_2O$ (11 mg, 0.025 mmol, 10 mol %), and DCE (1 mL). The vial was sealed and heated at 80 °C for 8 h. After the completion of the reaction, the mixture was purified by flash chromatography (EtOAc/petroleum ether) to give the desired product as a white or pale yellow solid.

4.6. General Procedure for Synthesis of 3-Alkyl or 2-Alkyl Indoles (Table 3, Entry 4). To a solution of 4-chloro-*N*-[2-(3-methyl-butyryl)-phenyl]-benzene-sulfonamide (35.2 mg, 0.1 mmol) and $TMSCHN_2$ (2 M in *n*-hexane, 60 μL, 0.12 mmol) in 1 mL of THF at −78 °C under Ar was added LDA (1.8 M in THF, 140 μL, 0.25 mmol). The mixture was stirred at −78 °C for 30 min and warmed to room temperature. The reaction was quenched with aqueous NH_4Cl, extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography with EtOAc/petroleum ether (1:50) to give the 3-*i*Bu indole as a white solid (17.0 mg, 49%) and then EtOAc/petroleum ether (1:10) to give the *o*-ynylaniline (13.9 mg, 40%).

The *o*-ynylaniline (13.9 mg, 0.04 mmol) and CuI (1.5 mg, 0.2 equiv) were dissolved in 0.6 mL of DMF and 1 mL of Et_3N, and then heated to 80 °C for 1 h. The reaction was quenched with aqueous NH_4Cl, extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography with EtOAc/petroleum ether (1:50) to give the 2-*i*Bu indole as a white solid (13.2 mg, 95%).

■ ASSOCIATED CONTENT

Supporting Information. Experimental details and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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