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$Pd(TFA)_2$-catalyzed oxidative coupling of anilides with olefins through C–H bond activation under non-acidic conditions

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ABSTRACT

C–H bond activation is an important issue. The Pd-catalyzed and non-coordinating anion improved C–H bond activation was realized through the oxidative coupling reaction of anilides with olefins under non-acidic conditions. Additionally, the catalytic activity of palladium catalysts is enhanced by non-coordinating anions, further proving that non-coordinating anion can be used in palladium-involved reactions.

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1. Introduction

Very weakly coordinating anions (WCAs) and non-coordinating anions (NCAs) are an important topic and sometimes they have important effects in modern organic chemistry and medical synthesis [1]. In the past, many transformations and reactions were explored through the help of WCAs and NCAs [2]. Recently, we found and verified that the catalytic activity of rhodium catalyst is obviously improved and changed by non-coordinating anions, which provide an efficient method that allows the rhodium to become a good chemoselectivity catalyst in selective C–H bond activation of anilides [3].

The past twenty years evidenced the extremely rapid development of C–H activation, which has been considered to be one of the most efficient methods in modern organic chemistry and medical synthesis, because it provides an atom and step-economical path to the many natural products or intermediates [4]. One typical model is anilides, particularly in the study of C–H activation with Pd, Rh, Ru as a catalyst (Scheme 1) [5]. An early important example is the Pd-catalyzed ortho C–H bond activation of anilides developed by de Vries and van Leeuwen with acid as solvent [6]. Recently, Rovis et al. reported the cycloaddition of benzamides and alkynes through Rh-catalyzed C–H activation [7]. Ackermann et al. showed the alkenylations of anilides and benzamides with water as solvent [8]. Based on these excellent examples and results (Chang [9], Fagnou [10], Glorius [11], Cui [12], Li [13], Shi [14], Ge [15], Yu [16], Ma [17], Chatani [18] and others [19]), herein, we found that NCAs could still promote Pd-catalyzed C–H bond activation of anilides with moderate yields under non-acidic conditions. This transformation could proceed under non-acidic conditions and thus acid-sensitive functional groups can be tolerated during the reaction, which provides an much milder reaction conditions for the simplifying workup procedures and has better adaptability to the environment.

2. Results and discussion

Recently, we reported the Rh-catalyzed selective C–H bond activation of diaryl substituted anilides, which revealed that *N*-aryl ring product was discovered under non-coordinating anion conditions, while *C*-aryl ring product was obtained in the absence of non-coordinating anion with rhodium as a catalyst [3]. When palladium was used as a catalyst, only *N*-aryl ring product was achieved with (or without) non-coordinating anion conditions, which is very different to our previous results (Scheme 2). The obvious difference was that the yield was enhanced under non-

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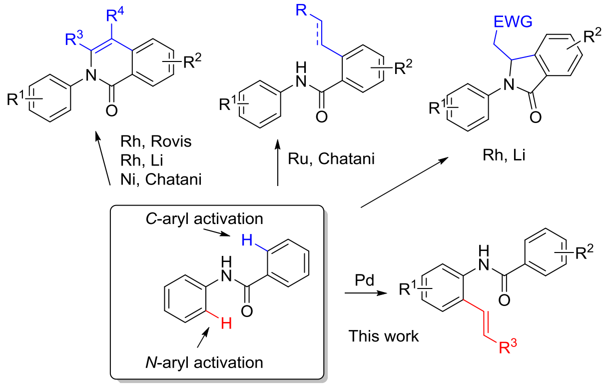
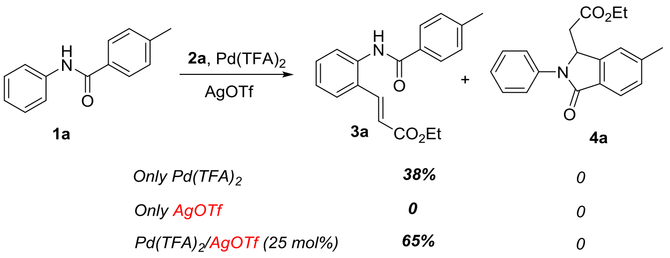
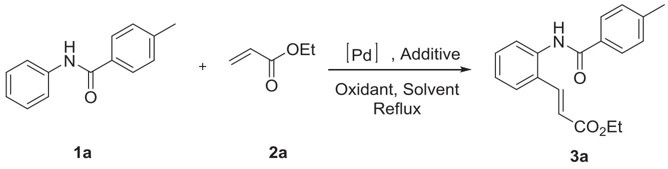


Scheme 1. C–H Activation with Anilides as Directing Group.



Scheme 2. The C–H activation with non-coordinating anions and different catalyst.

Table 1
Screening of reaction conditions.[a]



Entry	Catalyst	Oxidant	Solvent	Yield [%][b]
1[c]	$Pd(PPh_3)_2Cl_2$	$Cu(OAc)_2$	DMF	<5
2[c]	Pd/C	$Cu(OAc)_2$	DMF	<5
3[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	Toluene	<5
4[c]	$Pd(TFA)_2$	$Cu(OAc)_2$	Toluene	17
5[c]	$Pd(TFA)_2$	TBHP	Toluene	31
6	$Pd(TFA)_2$	TBHP	Toluene	65
7	$Pd(TFA)_2$	$K_2S_2O_8$	Toluene	<5
8	$Pd(TFA)_2$	Ag_2CO_3	Toluene	27
9	$Pd(TFA)_2$	$Cu(OAc)_2$	Toluene	19
10	$Pd(TFA)_2$	$K_2Cr_4O_7$	Toluene	48
11	$Pd(TFA)_2$	MnO_2	Toluene	36
12	$Pd(TFA)_2$	*m*CPBA	Toluene	53
13	$Pd(TFA)_2$	TBHP	DCE	44
14	$Pd(TFA)_2$	TBHP	Dioxane	11
15	$Pd(TFA)_2$	TBHP	THF	<5
16	$Pd(TFA)_2$	TBHP	DMF	<5

[a] Conditions: **1a** (0.50 mmol, 1.0 equiv.), **2a** (0.70 mmol, 1.4 equiv.), [Pd] (5%), AgOTf (25%), oxidant (1.5 equiv.), solvent (3 mL), reflux, 24 h.
[b] Isolated yields.
[c] Without AgOTf.

coordinating anion conditions. As the continuing research about the non-coordinating anion to C–H bond activation in our group [3,20], we seek to discern the details of this transformation with palladium as a catalyst under non-acidic conditions.

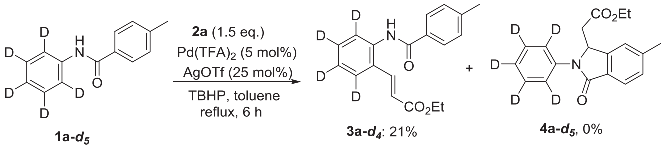
Concurrently, in order to demonstrate this clearly, the substrate **1a**-d_5 was used to test the reaction. The results showed that only **3a**-d_4 was achieved at 21% yield, while **4a**-d_5 was not found. Therefore, this clearly revealed that only the *N*-aryl ring product was obtained with palladium as a catalyst (Scheme 3).

Next, the screening reaction conditions were carried out to obtain a better yield. The results showed that the best reaction was achieved in toluene with TBHP as the oxdidant (Table 1).

Thus, with the best reaction conditions in hand, we explored the scope of the C–H bond activation reaction of anilides with ester acrylate. The results are summarized in Table 2. Generally, all the anilides were converted into the corresponding products with moderate to good yields. The anilides with various electron-donating groups could be worked well to produce the corresponding products.

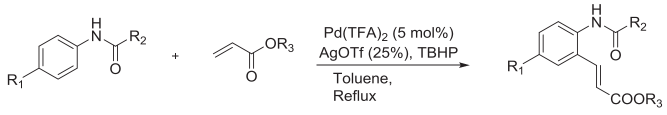
To unambiguously elucidate this reaction, a preliminary mechanism exploration was conducted. TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was thought to be an effective radical scavenger with which to check the reaction pathway. Thus, the control reaction for the C–H bond activation reaction of anilides with ester acrylate was carried on under 1.0 equiv of TEMPO amid optimized conditions. The result showed that the corresponding product was obtained with a slightly low yield, which revealed that this transformation does not constitute radical progress (Scheme 4). However, the reaction mechanism for this transformation is not yet clear.

Furthermore, in order to better under reaction mechanism, the kinetic isotope effects (KIE) experiments were carried out. It was found that the KIE ($K_H/K_D = 3.17$) was observed from the isotope



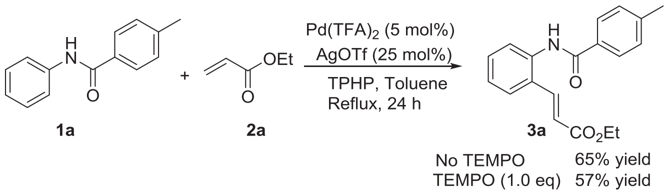
Scheme 3. Deuteration experiments.

Table 2
Substrate expansion experiment.[a]



Entry	R^1	R^2	R^3	Yield [%][b]
1	H	*p*-Me-Ph	Et	65 **(3a)**
2	Me	Ph	Et	71 **(3b)**
3	F	Ph	Me	67 **(3c)**
4	CF_3	Ph	Me	70 **(3d)**
5	Cl	Ph	Me	65 **(3e)**
6	H	*p*-OMe-Ph	Et	74 **(3f)**
7	H	Ph	Et	68 **(3g)**
8	OMe	Ph	Me	85 **(3h)**
9	OMe	Ph	Et	78 **(3i)**
10	Cl	Ph	Et	66 **(3j)**
11	NO_2	*p*-OMe-Ph	Me	82 **(3k)**
12	OMe	*p*-NO_2- Ph	Me	76 **(3l)**
13	H	*P*-OMe-Ph	Me	64 **(3m)**
14	F	Me	Me	77 **(3n)**
15	Cl	Me	Me	73 **(3o)**
16	OMe	Me	Me	78 **(3p)**

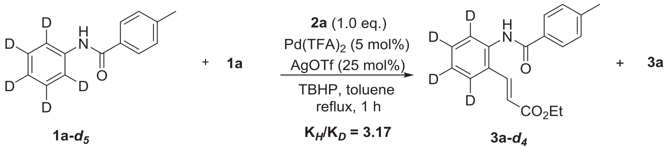
[a] Conditions: **1** (0.50 mmol, 1.0 equiv.), **2** (0.70 mmol, 1.4 equiv.), $Pd(TFA)_2$ (5%), AgOTf (25%), TBHP (1.5 equiv.), toluene (3 mL), 24 h.
[b] Isolated yields.



Scheme 4. Control experiments.

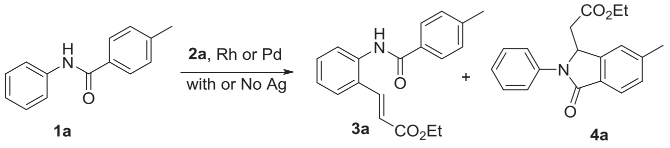
experiment (Scheme 5). This revealed that the radical reaction process is not involved in this reaction.

The “silver effect” in gold catalysis was disclosed by the Shi group in 2012, which led to the reconsideration of some silver-involved reactions [21]. Many transformations involving silver actually consist of silver-assisted metal catalysis or bimetallic catalysis. In some cases, AgCl or silver nanoparticles may play a decisive role. Based on this consideration, we conducted a series of “silver effect” experiments and the results were concluded in Table 3. The experiments showed that the reaction didn't occur only with AgOTf conditions. Sodium chloride has no effect in this reaction (Table 3, entry 8). Nearly the same yield was achieved, when the catalyst was carefully filtered with a pad of paper in order to remove the AgCl. This revealed that non-coordinating anions slightly improved catalytic activity of palladium catalysts, while silver does not play a role in this transformation. It should be noted that other non-coordinating anions produced different results (entries 3, 10–12). Importantly, when NaOTf was used to this reaction, almost the same result was achieved (entry 13).



Scheme 5. The isotope effect experiments.

Table 3
The “silver effect” test experiments.[a,b]



Entry	Catalyst	Conditions	**3a**:**4a**[%]
1	none	–	0:0
2	[Cp*RhCl$_2$]$_2$	–	0:58
3	[Cp*RhCl$_2$]$_2$	–	0:93[b]
4	[Cp*RhCl$_2$]$_2$/AgOTf	–	88:0
5	AgOTf	–	0:0
6	Pd(TFA)$_2$	–	38:0
7	Pd(TFA)$_2$/AgOTf	–	65:0
8	Pd(TFA)$_2$/AgOTf/NaCl	No filtration	65:0
9	Pd(TFA)$_2$/AgOTf/NaCl	After filtration	61:0
10	Pd(TFA)$_2$/AgBF$_4$	–	47:0
11	Pd(TFA)$_2$/AgSbF$_6$	–	31:0
12	Pd(TFA)$_2$/AgNTf$_2$	–	54:0
13	Pd(TFA)$_2$/NaOTf	–	63:0

[a] Conditions: **1** (0.5 mmol, 1.0 equiv.), **2** (0.70 mmol, 1.4 equiv.), Pd(TFA)$_2$ or [Cp*RhCl$_2$]$_2$ (5%), AgOTf (25%), oxidant (1.5 equiv.), toluene or DCE (3 mL), 24 h, isolated yields.

[b] CH$_3$CN was used.

3. Conclusions

In summary, the Pd-catalyzed and non-coordinating anion improved C–H bond activation was realized through the oxidative coupling reaction of anilides with olefins under non-acidic conditions. Additionally, the catalytic activity of palladium catalysts is enhanced by non-coordinating anions, which provide further proof that non-coordinating anion can be used in palladium-involved reactions.

4. Experimental section

4.1. General experiments

The obtained products were characterized by ^{1}H NMR spectra. NMR spectra were obtained on Bruker Advance 400 and -300; Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), multiplet (m); TLC was performed using commercially prepared 100–400 mesh silica gel plates (GF$_{254}$), and visualization was effected at 254 nm; All the reagents were purchased from commercial sources (J&KChemic, TCI, Fluka, Acros, SCRC), and used without further purification.

4.2. Typical procedure for the synthesis of compound ***3a***

The mixture of 4-methyl-*N*-phenylbenzamide (**1a**) (0.5 mmol), ethyl acrylate (**2a**) (0.7 mmol), AgOTf (25 mol%) and TBHP (1.5 equiv.) in toluene (3 mL) was stirred at 120 °C under air for 24 h. Upon completion, the reaction mixture was removed the solvents to give the residue. The residue was then purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1:10) to provide the corresponding product as white solid **3a**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (s, 1H), 7.91–7.85 (m, 2H), 7.82 (d, $J = 8.4$ Hz, 2H), 7.60 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.47–7.40 (m, 1H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.25 (t, $J = 7.6$ Hz, 1H), 6.43 (d, $J = 16.0$ Hz, 1H), 4.24 (q, $J = 7.2$ Hz, 2H), 2.44 (s, 3H), 1.32 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.8, 166.1, 142.8, 139.5, 136.2, 131.6, 131.0, 129.6, 128.1, 127.4, 126.0, 125.4, 121.0, 60.8, 21.7, 14.4. IR (KBr): 3265, 2988, 1712, 1647, 1614, 1521, 1506, 1482, 1449, 1368, 1315, 1301, 1261, 1178, 1032, 987, 864, 762 cm^{-1}.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2016.08.025.

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