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Palladium-Catalyzed Carbonylative Synthesis of Amides from Aryltriazenes under Additive-free Conditions

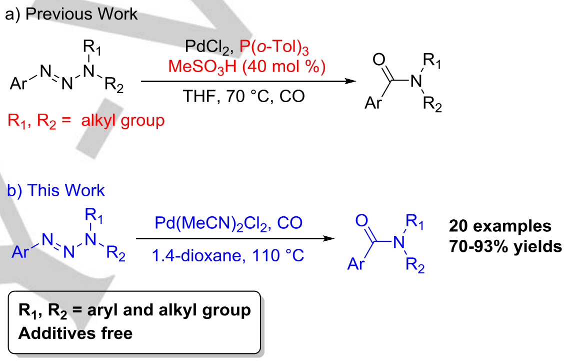
Zhiping Yin,[a] Zechao Wang,[a] and Xiao-Feng Wu*[a]

Abstract: An interesting palladium-catalyzed carbonylative synthesis of amides from aryltriazenes has been developed. By using $Pd(MeCN_2)Cl_2$ as the catalyst precursor under CO pressure via N_2 extrusion/CO insertion sequence, broad range of aryltriazenes were transformed into the corresponding amides in good yields with excellent functional groups tolerance. Remarkably, no additives such as acid or phosphine ligand are required here.

Among all the carboxylic acid derivatives, amides are attractive due to their numerous applications in advanced materials and pharmaceutical molecules.[1] The traditional procedure for their construction is based on the combination of their parent carboxylic acid derivatives with amines. Although various alternative methodologies have been established during the past decades, challenges such as complexed reaction system, limited substrates scope, low functional group tolerance and/or low reaction efficiency are still existing.[2] Hence, new synthetic procedures which can overcome one or some of the mentioned drawbacks will be still under demand.[3]

On the other hand, transition metal-catalyzed carbonylative transformations have experienced decades of developments and proven to be a powerful toolbox for the synthesis of carbonyl-containing molecules. By introducing one or two molecules of carbon monoxide into the parent compounds, values added chemicals can be effectively formed. In the known carbonylation reactions, amides can be selectively produced via aminocarbonylation of aryl halides with amines as the coupling partner.[4]

Aryltriazenes are considered as an analogue of stabilized aryl diazonium salts and have been extensively explored in organic synthesis.[5] They have advantages including easy preparation, good stability and readily conversion to other functional groups. However, in general, most of these transformations need Lewis acids or Brønsted acid as the additive to activate the aryltriazenes.[5,6] In 2015, we reported a new palladium-catalyzed carbonylative reaction of aryltriazenes (Scheme 1, eq. a).[7a] Nevertheless, besides the necessity of $MeSO_3H$ addition, only *N*-alkyl benzamides can be produced as the terminal products. Under these backgrounds, we find it would be interesting if we could develop a new procedure to overcome the mentioned drawbacks (Scheme 1, eq. b).



Scheme 1. Carbonylation transformation of triazenes.

Initially, the reaction was performed using diphenyltriazene **1a** as the model substrate with $Pd(OAc)_2$ as the catalyst in DMF under the pressure of CO (20 bar) at 110°C. To our delight, diphenyltriazene **1a** was transformed into the desired *N*-phenyl benzamide in 30% yield without any acid additive or phosphine ligand (Table 1, entry 1). With this exciting result in hand, we continued to optimize this new reaction. Then different palladium(II) catalyst precursors were tested under identical reaction conditions (Table 1, entries 2-7). As we expected, *N*-phenyl benzamide can be detected in all the cases and the best yield can be reached by using $Pd(MeCN)_2Cl_2$ as the catalyst (Table 1, entry 7; 65% yield). The yield can be further improved to 87% by using 1.4-dioxane as the reaction media (Table 1, entry 10). Other solvents, such as DCE and MeCN were all inferior to 1.4-dioxane. Then the loading of $Pd(MeCN)_2Cl_2$ was checked as well, up to 82% of the desired amide can be obtained with even 2 mol% of the palladium catalyst (Table 1, entry 11). Additionally, no significant reaction efficiency decreasing was observed with decreased CO pressure or reaction temperature (Table 1, entry 12-14). Finally, we found that the combination of 5 mol% $Pd(MeCN)_2Cl_2$ in 1.4-dioxane under CO atmosphere (20 bar) at 110°C for 16 hours can provide the best outcome of the target amide (88% isolated yield; Table 1, entry 10).

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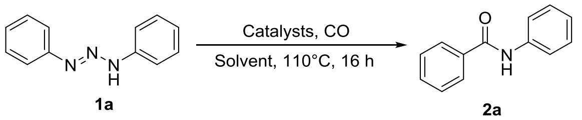
Table 1. Optimization of the reaction conditions.[a]



1a **2a**

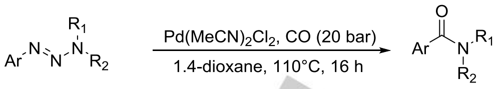
Entry	Catal.	Solvent	CO	Yield[b]
1	Pd(OAc)$_2$	DMF	20 bar	30%
2	Pd(dba)$_2$	DMF	20 bar	8%
3	Pd(CF$_3$CO$_2$)$_2$	DMF	20 bar	57%
4	[Pd(cinnamyl)Cl]$_2$	DMF	20 bar	62%
5	PdCl$_2$(cod)	DMF	20 bar	40%
6	PdCl$_2$	DMF	20 bar	61%
7	Pd(MeCN)$_2$Cl$_2$	DMF	20 bar	65%
8	Pd(MeCN)$_2$Cl$_2$	DCE	20 bar	32%
9	Pd(MeCN)$_2$Cl$_2$	MeCN	20 bar	69%
10	Pd(MeCN)$_2$Cl$_2$	1.4-dioxane	20 bar	87% (88%)[c]
11	Pd(MeCN)$_2$Cl$_2$	1.4-dioxane	20 bar	82%[d]
12	Pd(MeCN)$_2$Cl$_2$	1.4-dioxane	10 bar	85%
13	Pd(MeCN)$_2$Cl$_2$	1.4-dioxane	5 bar	74%
14	Pd(MeCN)$_2$Cl$_2$	1.4-dioxane	20 bar	76%[e]

a: Reaction conditions: **1a** (0.20 mmol), [Pd] (0.01 mmol, 5 mol%) , solvent (2 mL), CO, 110 °C, 16 h. b: GC yields were determined by using hexadecane as the internal standard. c: isolated yield, obtained in separate runs. d: Pd(MeCN)$_2$Cl$_2$ (2 mol%). e: 100 ^{o}C. DCE = 1,2-Dichloroethane; DMF = *N*,*N*-Dimethylmethanamide.

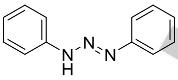
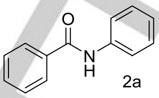
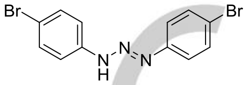
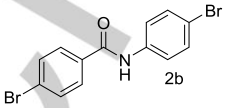
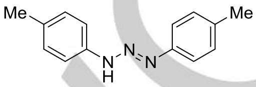
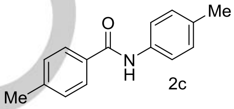
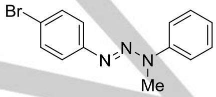
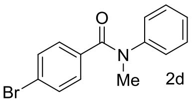
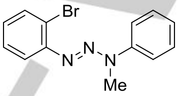
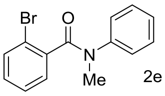
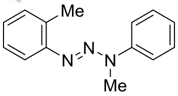
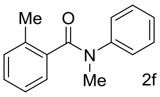
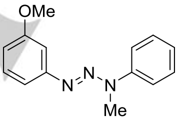
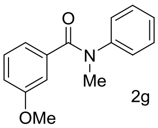
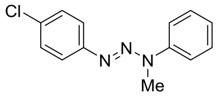
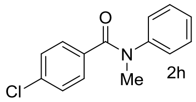
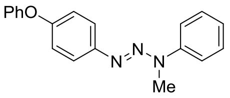
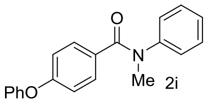
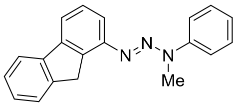
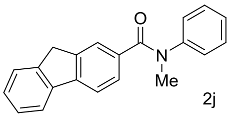
With the optimized reaction conditions in hand, we examined the substrates scope of this transformation with a range of aryltriazenes (Tables 2 and 3). As shown in Table 2, the desired amide products were formed in good yields in general with the aryltriazenes tested. Both electron-withdrawing and electron-donating substituted aryltriazene can provide the desired *N*-aryl arylamides products in good to excellent yields. Notably, halogen functional groups can be well tolerated as well, good yields of the desired amides were isolated (Table 2, entries 2, 4, 5, 8). These halogen functional group containing amides products are ready for further modifications via cross-coupling reactions.

Furthermore, by using dialkylamines as the starting materials, various dialkyl-aryltriazenes were prepared and tested under our reaction conditions. As shown in Table 3, aryltriazenes **1k-1p** with different substituents at *ortho, meta* and *para* were smoothly converted into the desired aryl(piperidin-1-yl)methanonethes in high yields (Table 3, entries 1-6). Moreover, good yields can also be observed from the reaction of other alkylamine substrates such as morpholine, diethyl and 4-methyl-piperidine (Table 3, entries 7-10).

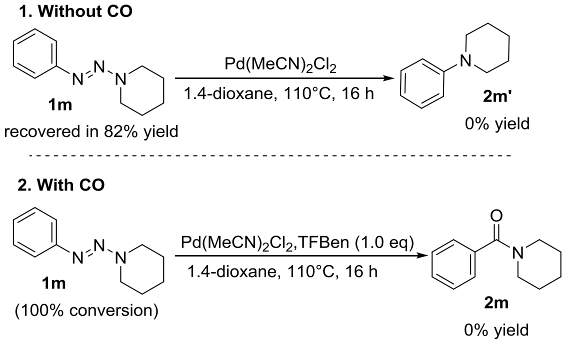
Table 2. Substrate scope of aryltriazenes.[a]



1a-1j **2a-2j**

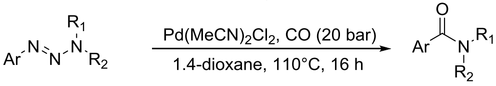
Entry	Substrate	Product	Yield[b]
1		 2a	87%
2		 2b	82%
3		 2c	80%
4		 2d	88%
5		 2e	93%
6		 2f	84%
7		 2g	90%
8		 2h	82%
9		 2i	83%
10		 2j	78%

[a] Reaction conditions: **1a** (0.20 mmol), Pd(MeCN)$_2$Cl$_2$ (0.01 mmol, 2.6 mg) , 1.4-dioxane (2 mL), CO (20 bar), 110 °C, 16 h. [b] Isolated yields.

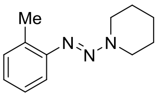
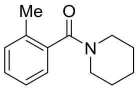
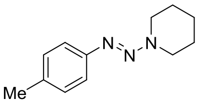
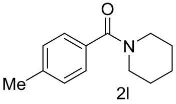
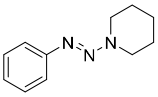
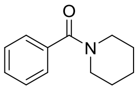
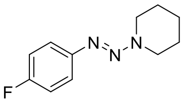
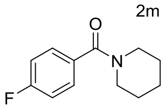
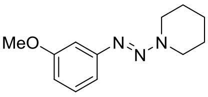
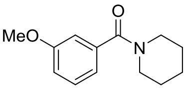
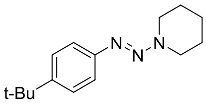
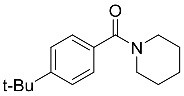
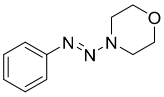
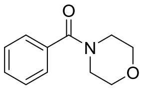
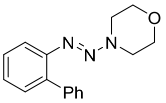
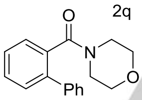
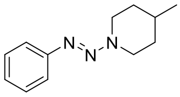
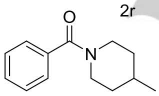
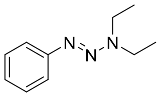
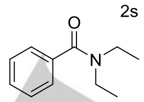


Scheme 2. Control experiments.

Table 3. Substrate scope of additional aryltriazenes.[a]

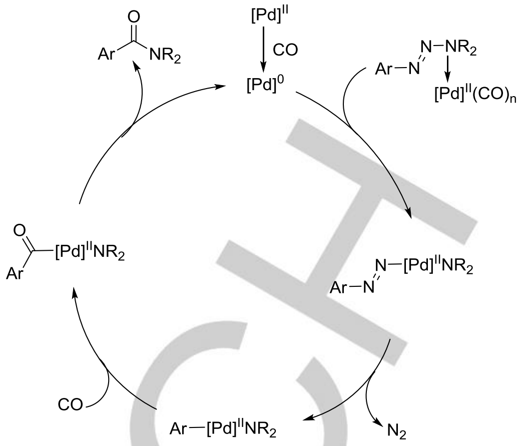


1k-1t **2k-2t**

Entry	Substrate	Product	Yield[b]
1		 2k	89%
2		 2l	91%
3		 2m	74%
4		 2n	70%
5		 2o	84%
6		 2p	89%
7		 2q	76%
8		 2r	79%
9		 2s	86%
10		 2t	85%

[a] Reaction conditions: **1a** (0.20 mmol), Pd(MeCN)$_2$Cl$_2$ (0.01 mmol, 2.6 mg) , 1.4-dioxane (2 mL), CO (20 bar), 110 °C, 16 h. [b] Isolated yields.

Finally, in order to get some insight of the reaction pathway of this procedure, control experiments were performed. As shown in scheme 2, the start material **1m** was recovered in 82% yield when the reaction was conducted under the same reaction condition but in the absence of CO. However, the start material can be fully converted when some CO source (TFBen: benzene-1,3,5-triyl triformate) was introduced but no desired amide product could be detected.[8] Hence we propose that CO has three roles in this transformation (Scheme 3): 1) as ligand and coordinates with palladium to increase its Lewis acidity which then activates triazenes; 2) as reductant to reduce Pd(II) to Pd(0) which then starts the catalytic cycle; 3) as carbonyl source to replace N$_2$ and produce amides.



Scheme 3. Proposed reaction mechanism.

In summary, a new palladium(II)-catalyzed N$_2$ extrusion/CO insertion reaction of aryltriazenes has been developed. With Pd(MeCN)$_2$Cl$_2$ as the only catalyst, a series of *N*-aryl and *N*-alkyl benzamides were synthesized in good to excellent yields from the corresponding triazenes. Notably, no additives such as acid or phosphine ligand are required here.

Experimental Section

General procedure of Pd-catalyzed carbonylative reaction of aryltriazenes: To each screw-cap vial (4 mL) equipped with a septum, a small cannula, and a stirring bar was added aryltriazene substrates (0.20 mmol), Pd(MeCN)$_2$Cl$_2$ (2.6 mg, 0.01 mmol) and 1.4-dioxane (2 mL). The vials then were purged with argon three times before placed on an alloy plate and transferred into a 300 mL autoclave of the 4560 series from Parr instruments under air. After flushing the autoclave three times with CO, a pressure of 20 bar CO was set and the reaction was performed for 16 hours at 110°C. Afterwards, the autoclave was cooled to room temperature and the pressure was released carefully. The solvent was removed under reduced pressure and the crude products were purified by column chromatography on silica gel (eluent: pentane/ethyl acetate = 2:1).

Acknowledgements

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Keywords: amides • aryltriazenes • palladium • carbonylation • cascade process

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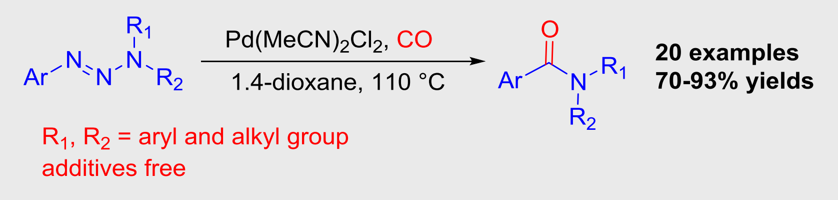

Self-activated: A new palladium-catalyzed carbonylation reaction of aryltriazenes has been developed. With Pd(MeCN)$_2$Cl$_2$ as the catalyst, a series of *N*-aryl and *N*-alkyl benzamides were synthesized in good to excellent yields from the corresponding triazenes. Notably, no additives such as acid or phosphine ligand are required here.

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Palladium-Catalyzed Carbonylative Synthesis of Amides from Aryltriazenes under Additive-free Conditions