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N_2 Extrusion and CO Insertion: A Novel Palladium-Catalyzed Carbonylative Transformation of Aryltriazenes

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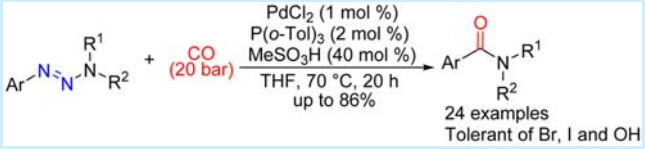
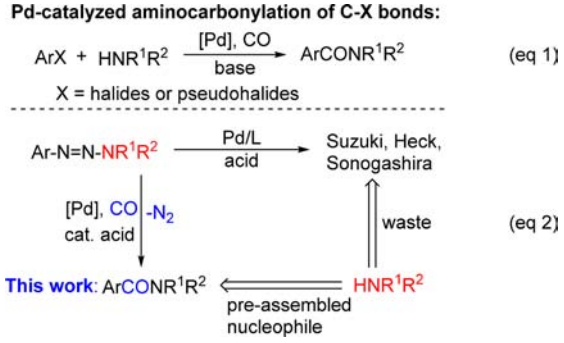
Supporting Information

ABSTRACT: A novel procedure for the replacement of N_2 with CO of aryltriazenes has been developed. Aryltriazenes were converted to the corresponding arylamides catalyzed by 1 mol % of $PdCl_2/P(o\text{-Tol})_3$ under CO pressure. In this process, aryldiazonium salts were generated in the presence of 40 mol % of $MeSO_3H$. Nitrogen was released from the substrates and CO formally inserted. Aryl bromides, iodides, alkynes, and free hydroxyl groups can be tolerated in this transformation.



Since the earliest report by Schoenberg and Heck in 1974,[1] palladium-catalyzed aminocarbonylation has evolved into a versatile and reliable tool for amide synthesis.[2] In these reactions, electrophilic halides or pseudohalides are coupled with nucleophilic amines in the presence of CO under basic reaction conditions (Scheme 1, eq 1). Recently, the applications of aryltriazenes in organic synthesis have witnessed a surge in interest due to their easy preparation, good stability, and ready conversion to other functional groups.[3] Most of the aryltriazenes could be easily synthesized from replacement of the proton of amines with aryldiazonium salts in good yields.[4] Alternatively, they could also be prepared from the addition of organometallic reagents to aryl azides.[5] More recently, some modified procedures have been reported regarding their synthesis.[3h,6] Notably, the excellent nucleofugality of the dialkylaminoazo groups in the presence of a Lewis or Brønsted acid renders the aryltriazenes highly electrophilic species and active partners for many palladium-catalyzed cross-couplings,[7] wherein these reactions are usually performed under acidic conditions which allow unique functional group tolerance compared with basic cases.

Scheme 1. State of the Art on Aminocarbonylation



For the known coupling reactions involving aryltriazenes as coupling partners, the aliphatic secondary amino groups were unexceptionally degraded into waste which usually contaminated the desired products. With respect to the carbonylation reactions, the only existing example of transformation of aryltriazenes was reported by Tamao and co-workers in 2004 in the carbonylative Suzuki reaction.[7f] Since then, triazenes have scarcely been used in palladium-catalyzed carbonylation reactions. Recently, we have succeeded in the carbonylative synthesis of alkenone from aryl halides and alkenes. As the advantages of using aryltriazenes as substrates are known, we have become interested in developing a palladium-catalyzed carbonylative Heck reaction of triazenes and olefins.[8]

Initially, 1-(phenyldiazenyl)pyrrolidine (**1a**) and styrene were tested under several different conditions, but only a trace amount of chalcone was detected. To our surprise, *N*-benzoylpyrrolidine (**2a**) was detected by GC−MS, which has not been reported. In this paper, we wish to report this discovery in detail: palladium-catalyzed tandem denitrogen/CO insertion process, which allows for the direct conversion of aryltriazenes to arylamides (Scheme 1, eq 2). One interesting feature of this transformation is that the dialkylamino groups (R^1R^2N) functioned as preassembled nucleophiles rather than waste.

Upon the observation of the unintended amide product benzoylpyrrolidine (**2a**), we embarked on the optimization of this new type of catalytic transformation (Table 1). Compound **1a** and 1 equiv of BF_3·OEt were reacted in the presence of 1 mol % of $Pd(OAc)_2$ in THF, but no **2a** was detected after 15 h (Table 1, entry 1). After screening of several other acids including HOAc and CF_3COOH, we found that 1 equiv of $MeSO_3H$ led to 39% yield of **2a** (Table 1, entry 2). Therefore, we tried to improve the yield by adding some ligand with $MeSO_3H$ as the activator. Bidentate phosphine like dppp inhibited the reaction, and only 9% yield of **2a** was obtained (Table 1, entry 3). When a monophosphine like *n*-BuPAd$_2$ was used, a quantum leap in the yield of **2a** (79%) was observed

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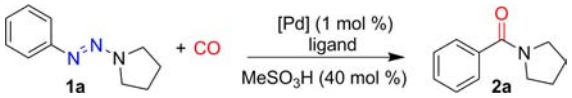
Table 1. Selective Optimization of the Reaction Conditions[a]



entry	[Pd]	ligand	solvent	yield[b] (%)
1	$Pd(OAc)_2$	no	THF	0[c]
2	$Pd(OAc)_2$	no	THF	39[d]
3	$Pd(OAc)_2$	dppp	THF	9
4	$Pd(OAc)_2$	*n*-BuPAd$_2$	THF	79
5	$Pd(OAc)_2$	PCy_3	THF	74
6	$Pd(OAc)_2$	PPh_3	THF	65
7	$Pd(OAc)_2$	P(*p*-MeO-Ph)$_3$	THF	66
8	$Pd(OAc)_2$	P(*p*-F-Ph)$_3$	THF	74
9	$Pd(OAc)_2$	P(*o*-MeO-Ph)$_3$	THF	51
10	$Pd(OAc)_2$	P(*o*-Tol)$_3$	THF	87 (50)[d]
11	$Pd(OAc)_2$	P(*o*-Tol)$_3$	DMSO	44
12	$Pd(OAc)_2$	P(*o*-Tol)$_3$	MeCN	71
13	$Pd(OAc)_2$	P(*o*-Tol)$_3$	dioxane	55
14	$Pd(OAc)_2$	P(*o*-Tol)$_3$	CH_2Cl_2	66
15	$PdCl_2(PPh_3)_2$		THF	10
16	$Pd(PPh_3)_4$		THF	56
17	Pd/C	P(*o*-Tol)$_3$	THF	40
18	$Pd(TFA)_2$	P(*o*-Tol)$_3$	THF	84
19	$PdCl_2$	P(*o*-Tol)$_3$	THF	90 (86)[e]
20	$PdCl_2$	P(*o*-Tol)$_3$	THF	64[f]
21	$PdBr_2$	P(*o*-Tol)$_3$	THF	69
22	$Ni(CO)_2(PPh_3)_2$		THF	39[d]
23	$CuCl_2$	PPh_3	THF	0

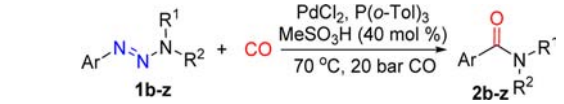
[a]Reaction conditions: **1a** (52.6 mg, 0.3 mmol), $MeSO_3H$ (7.8 μL, 0.12 mmol), solvent (1.5 mL), 20 bar of CO, 70 °C for 15 h. [b]GC yield using hexadecane as the internal standard. [c]40 mol % of $BF_3{\cdot}OEt_2$ was used instead of $MeSO_3H$. [d]1.0 equiv of $MeSO_3H$ was used. [e]Isolated yield. [f]0.2 equiv of $MeSO_3H$ was used.

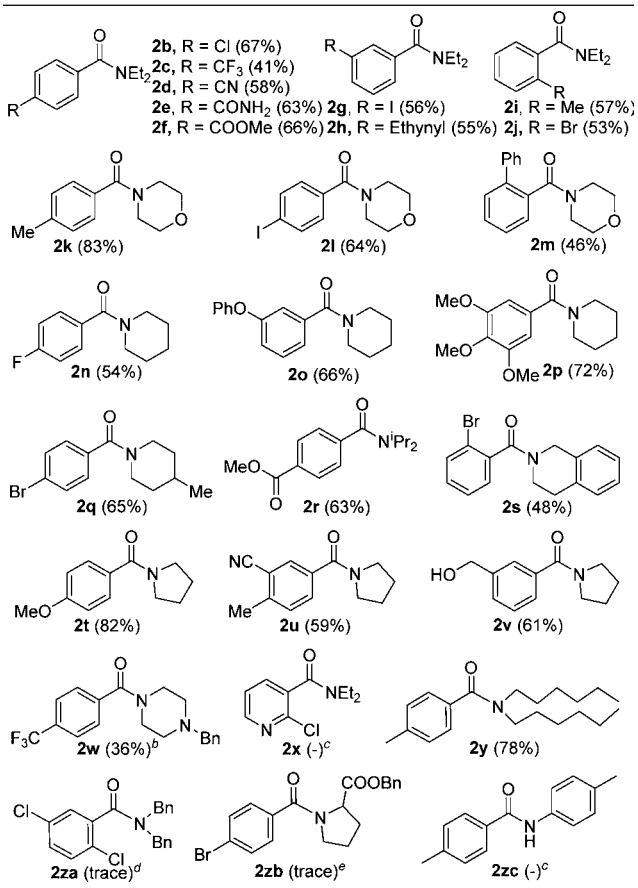
(Table 1, entry 4). The electron-rich ligand tricyclohexlphosphine also led to 74% yield (Table 1, entry 5). Triphenylphosphine and *p*-methoxy- or fluoro-substituted triphenylphosphines gave no better results (Table 1, entries 6−8). When tri(*o*-anisyl)phosphine was used, the yield of **2a** was even lower (Table 1, entry 9). To our satisfaction, the yield of **2a** was further increased to 87% when tri(*o*-tolyl)phosphine was employed as the ligand (Table 1, entry 10).

It was also note-worthy that when 1 equiv of $MeSO_3H$ was used, the yield of **2a** dropped from 87% to 50% (Table 1, entry 10). In addition, the reaction was much less efficient in other solvents like DMSO, MeCN, dioxane, and CH_2Cl_2 (Table 1, entries 11−14). Therefore, THF was selected as the optimized solvent and tri-*o*-tolylphosphine as the best ligand. Other palladium precursors were also tested (Table 1, entries 15−21), and $PdCl_2$ was proved the best, which enabled 90% yield of **2a** (Table 1, entry 19). Fewer equivalents of $MeSO_3H$ caused an obvious decrease in the yield (Table 1, entry 19 vs 20). Other metals like nickel and copper were much less active for this carbonylation reaction (Table 1, entries 22 and 23). On the basis of these screening results, the optimized reaction conditions were specified as the following: the combination of $PdCl_2$ and P(*o*-Tol)$_3$ as the catalyst and 0.4 equiv of $MeSO_3H$ was used as the additive.

The scope of the carbonylative conversion of triazenes to amides was then investigated with various substituted triazenes under the optimized conditions. The triazenes **1b−j** with different *ortho*, *meta*, and *para* substituents were smoothly

Table 2. Palladium-Catalyzed Carbonylative Conversion of Aryltriazenes[a]





[a]Reaction conditions: **1** (0.6 mmol), $MeSO_3H$ (16 μL, 0.24 mmol), solvent (3 mL), 20 bar of CO, 70 °C for 20 h. [b]1.4 equiv of $MeSO_3H$ was added. [c]No reaction. [d]*p*-Dichlorobenzene and dibenzylamine were the main decomposition products for **1za**. [e]Bromobenzene and benzyl prolinate were the main decomposition products for **1zb**.

converted to the diethylamides in moderate to good yields (**2b−j**). Triazenes bearing a strong electron-withdrawing group like trifluoromethyl (**1c**) gave lower yields than other *para*-substituted substrates.[9] Iodo (**1g**) and bromo (**1j**) on the phenyl group remained unreactive during the transformation, which would be reactive under common aminocarbonylation conditions. Besides, morpholinyl (**2k−m**) and piperidinyl (**2n−p**) were also obtained from the corresponding triazenes. 1-Aryl-3,3-diisopropyltriazenes are usually very stable under strong acidic or basic conditions,[10] whereas **2r** was obtained in 63% yield under our conditions. The bromide in **1s** remained untouched, and the product 2-*N*-(2-bromobenzoyl)-tetrahydroisoquinoline (**2s**) can be further elaborated to form some biologically active heterocylces.[11] It was noteworthy that unprotected hydroxyl group (**1v**) was not affected in this acidic carbonylation. The synthesis of amides with a benzyl alcohol group like **2v** usually employed a circuitous route.[12] For triazene with a *N*-benzylpiperazine group (**1w**), 1.4 equiv of $MeSO_3H$ was needed to ensure the full conversion. Long alkylamides (**2y**) was also obtained in good yield from the corresponding dialkyltriazenes. Unfortunately, the triazene with

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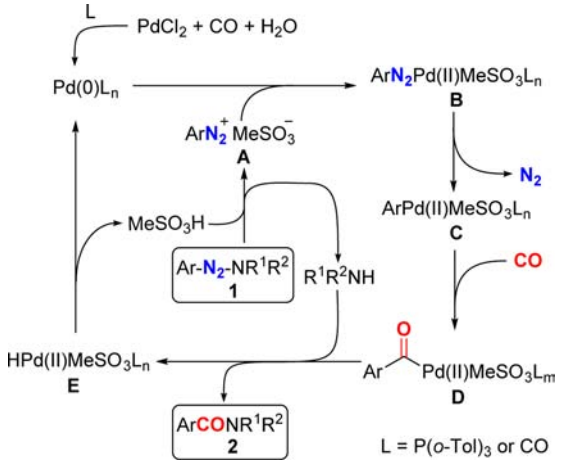
pyridine group (**1x**) was unreactive for the transformation. Besides, substrates bearing a dibenzylamino group (**1za**) and 2-(benzoxycarbonyl)pyrrolidinyl group (**1zb**) could not be carbonylated to **2za** and **2zb**, respectively, mainly due to the poorer nucleophility of dibenzylamine and benzyl prolinate. The triazene with a primary amino group like 3-di-*p*-tolyltriaz-1-ene (**1zc**) was recovered under these conditions.

Finally, a possible reaction pathway was proposed on the basis of the reported mechanism of palladium-catalyzed carbonylation reactions involving aryl diazonium salts (Scheme 2).[13] First, aryltriazene (**1**) decomposed to aryldiazonium

Scheme 2. Proposed Reaction Mechanism



methanesulfonate (**A**) and the free amine (R^1R^2NH) activated by $MeSO_3H$. The diazonium salt **A** easily undergoes oxidative addition onto Pd(0), which was reduced from $PdCl_2$ by CO,[14] to form intermediate **B**. The ensuing extrusion of N_2 led to the formation of arylpalladium species **C**, which undergoes CO insertion to produce an acylpalladium species **D**. Next, the attack from the released amine onto **D** would form the amide **2**. The $MeSO_3^-$ itself worked as a base to regenerate Pd(0), and $MeSO_3H$ was released whereby to activate another molecule of triazene substrate. Therefore, only substoichiometric amount of $MeSO_3H$ was required. When 1 equiv of acid was employed, the released amine in the first step was largely protonated and the nucleophilic attacking became difficult.

In summary, we successfully realized a new type of catalytic conversion of *N*,*N*-dialkylaryltriazenes to corresponding amides by palladium-catalyzed carbonylations in the presence of substoichimetric amount of $MeSO_3H$. The dialkylamino groups were preassembled as the nucleophiles in these substrates, and nitrogen was the only side product for this transformation. Some unstable or reactive functional groups for traditional $C(sp^2)$–X bond based aminocarbonylation reactions could be well tolerated under these conditions. Therefore, this new transformation of aryltriazenes may find some unique applications in multistep synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details for the preparation of triazenes and ^1H and ^{13}C NMR spectra for the substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) We tried to improve the yield by adding some free amines to the reaction system according to one reviewer's suggestion that the low yield may be resulted from the incomplete reentry of amines once formed by the decomposition of triazenes. However, the isolated yield of **2c** decreased from 41% to 17% after 30 mol % Et_2NH was added. Similarly, after 30 mol % pyrrolidine was added, the GC yield of **2a** dropped form 90% (entry 19, Tabe 1) to 50% under otherwise the identical conditions. We guessed that the added free amines would nuturalize the $MeSO_3H$, which was essential for the activation of the triazenes.

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