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Palladium-catalyzed carbonylative Sonogashira coupling between aryl triazenes and alkynes†

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We developed a palladium-catalyzed carbonylative Sonogashira reaction with aryl triazenes and alkynes as substrates and methanesulfonic acid as the additive. A series of α,β-ynones were synthesized by this alternative procedure. Notably, bromides, iodides and hydroxyl groups could be well-tolerated under these reaction conditions.

α,β-Ynones are an important class of compounds with many special biological activities.[1] Besides, they provide versatile intermediates for numerous heterocycle[2] and natural product syntheses.[3] Traditionally, these structures were obtained from the nucleophilic addition of acetylide reagents to aldehydes[4] or carboxylic acid derivatives,[5] which required either a two-step procedure or laborious work-up. The cross-coupling between acid chlorides and alkynes or alkynylboronates under metal-catalyzed[6] or metal-free[7] conditions represents a more convenient way to their synthesis, but the poor substrate stability and narrow functional group tolerance often curtailed this methodology for synthetic applications.

Since the seminal work by Kobayashi and Tanaka in 1981,[8] palladium-catalyzed carbonylative Sonogashira coupling using aryl (pseudo)halides has become an efficient route to α,β-ynones.[9] Aryl amines are relatively inexpensive and abundantly available chemicals and usually act as nucleophiles in many organic reactions. However, after being converted to diazonium salts by some well-known procedures, they become more active than aryl halides in many palladium-catalyzed cross-coupling reactions.[10] One of the practical concerns while dealing with diazonium salts is their instability and explosive potential.[11] To overcome these disadvantages, in 2011, some of us developed a carbonylative Sonogashira protocol with *in situ* generated diazonium salts from aryl amines and *tert*-butyl nitrite in the presence of acetic acid.[12] Recently, the use of triazenes as diazonium precursors or directing groups has attracted much attention due to their easy preparation and

good stability and facile conversion to other functional groups.[13] For example, aryl triazenes have often been employed in the Sonogashira reactions for the synthesis of some phenylacetylene oligomers,[14] molecular wires[15] and annulenes.[16] To the best of our knowledge, carbonylative Sonogashira coupling using aryl triazenes has been hitherto unreported in the literature. Herein, we report the palladium-catalyzed carbonylation of aryl triazenes with alkynes and carbon monoxide.

At the outset, we carried out carbonylation between 3,3-diethyl-1-(*p*-tolyl)triaz-1-ene (**1a**) and phenylacetylene (**2a**) as the model reaction in the presence of a catalytic amount of Pd(OAc)$_2$ to optimize the reaction conditions. When the Lewis acid BF$_3$·OEt$_2$ was added as the activator for **1a**, only a trace amount of 3-phenyl-1-(*p*-tolyl)prop-2-yn-1-one (**3aa**) was detected on a GC (entry 1, Table 1). Under the same ligand-

Table 1 Optimization of the reaction conditions^a

Entry	Acid	Ligand	Solvent	Yield^b (%)
1	BF$_3$·OEt$_2$	No	Dioxane	Trace
2	HCOOH	No	Dioxane	Trace
3	CH$_3$COOH	No	Dioxane	Trace
4	CF$_3$COOH	No	Dioxane	33
5	TsOH·H$_2$O	No	Dioxane	48
6	MeSO$_3$H	No	Dioxane	55
7	MeSO$_3$H	DPPP	Dioxane	11
8	MeSO$_3$H	DPEPhos	Dioxane	5
9	MeSO$_3$H	XantPhos	Dioxane	7
10	MeSO$_3$H	*n*-BuPAd$_2$	Dioxane	51
11	MeSO$_3$H	PPh$_3$	Dioxane	60
12	MeSO$_3$H	P(*p*-FC$_6$H$_5$)$_3$	Dioxane	41
13	MeSO$_3$H	P(*p*-OC$_6$H$_5$)$_3$	Dioxane	57
14	MeSO$_3$H	PCy$_3$	Dioxane	58
15	MeSO$_3$H	P(*o*-tolyl)$_3$	Dioxane	66
16	MeSO$_3$H	P(*o*-tolyl)$_3$	^{t}BuOMe	11
17	MeSO$_3$H	P(*o*-tolyl)$_3$	DME	55
18	MeSO$_3$H	P(*o*-tolyl)$_3$	THF	76^c (71^d)

^{a} Reaction conditions: **1a** (57.4 mg, 0.3 mmol), **2a** (50 μL, 0.45 mmol), MeSO$_3$H (20 μL, 0.33 mmol), Pd(OAc)$_2$ (2.02 mg, 9 μmol) and solvent (2 mL). 20 bar CO, 70 °C. ^{b} Determined by GC using *n*-hexadecane as the internal standard. ^{c} Corresponds to 73% isolated yield. ^{d} The CO pressure was 10 bar.

Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a, 18059 Rostock, Germany. E-mail: xiao-feng.wu@catalysis.de
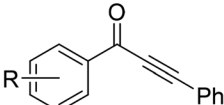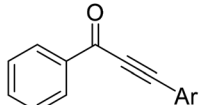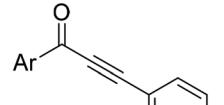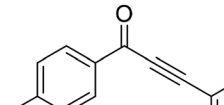†Electronic supplementary information (ESI) available: NMR spectra and data, and the reaction procedure. See DOI: 10.1039/c5ob00502g
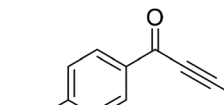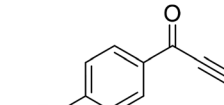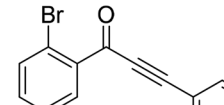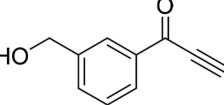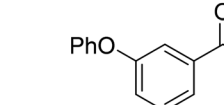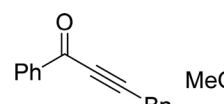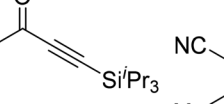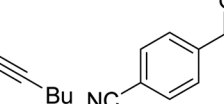
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free conditions, several other protic acids were screened (entries 2–6, Table 1). Formic acid and acetic acid were as inefficient as $BF_3 \cdot OEt_2$. Trifluoroacetic acid, which has often been used as an activator for triazenes, led to only 33% yield of **3aa** (entry 4, Table 1). Finally we discovered that sulfonic acids were more effective than other acids and $MeSO_3H$ was the best additive, which furnished **3aa** in 55% yield (entry 6, Table 1).

To further improve the yield of **3aa**, we tried to add some ligands to the catalytic system. When bidentate phosphine
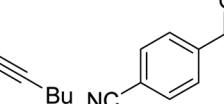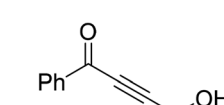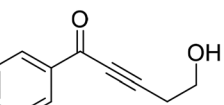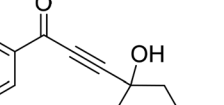
Table 2 Palladium-catalyzed carbonylative Sonogashira coupling of various aryl triazenes and alkynes[a]


R′ = Et
1a (Ar = 4-Me-Ph)
1b (Ar = 4-Cl-Ph)
1c (Ar = 4-CF₃-Ph)
1d (Ar = 4-CN-Ph)
1e (Ar = 4-COOMe-Ph)

R′ = Et
1f (Ar = 3-I-Ph)
1g (Ar = 2-MePh)
1h (Ar = 2-Br-Ph)
1i (Ar = 1-Naphthyl)

R′ = –(CH₂)₄
1j (Ar = Ph)
1k (Ar = 3-CH₂OH-Ph)
1l (Ar = 4-MeO-Ph)
1m (Ar = 4-Me-5-CN-Ph)

R′ = –(CH₂)₅
1n (Ar = 4-I-Ph)
1o (Ar = 3,4,5-tri-MeO-Ph)
1p (Ar = 3-PhO-Ph)
NR′₂ = 4-methylpiperidiyl
1q (Ar = 4-Br-Ph)

Structure of the alkynes **2a–s**
2a (R = Ph)
2b (R = 3-Me-Ph)
2c (R = 4-Et-Ph)
2d (R = 4-n-Pr-Ph)
2e (R = 4-n-Bu-Ph)

2f (R = 4-n-Hex-Ph)
2g (R = 2-Br-Ph)
2h (R = 4-CF₃-Ph)
2i (R = 4-Ac-Ph)
2j (R = 1-naphthyl)

2k (R = 3-thienyl)
2l (R = ferrocenyl)
2m (R = Bn)
2n (R = TIPS)
2o (R = n-Bu)

2p (R = CH₂OPh)
2q (R = CH₂OH)
2r (R = (CH₂)₂OH)
2s (R = (1-cyclohexanol)yl)

3ja (R=H), 70%
3ga (R=2-Me), 47%
3ba (R=4-Cl), 74%
3ca (R=4-CF₃), 77%
3da (R=4-CN), 84%
3ea (R=4-COOMe), 75%

3jb (Ar=3-Me-Ph), 73%
3jc (Ar=4-Et-Ph), 69%
3jf (Ar=4-Hexyl-Ph), 71%
3jj (Ar=1-Naphthyl), 87%
3jl (Ar=Ferrocenyl), 49%

3ld (Ar=4-MeO-Ph, R=n-Pr), 72%
3oe (Ar=3,4,5-tri-MeO-Ph, R=n-Bu), 52%
3ie (Ar=1-Naphthyl, R=n-Bu), 57%

3ne, 56%
3bg, 52%
3qh, 71%

3hi, 42%
3ki, 50%[b]
3pk, 65%

3jm, 62%
3en, 59%
3mo, 41%
3dp, 55%

3jq, 31%
3br, 33%
3ds, 37%

[a] Reaction conditions: **1** (0.6 mmol), **2** (0.9 mmol), $MeSO_3H$ (40 μL, 0.66 mmol), Pd(OAc)₂ (4.04 mg, 18 μmol), P(o-Tol)₃ (11.0 mg, 36 μmol), and solvent (4 mL), 70 °C, 20 h. Isolated yield. [b] The product was contaminated with some unreacted **2i**.

ligands like DPPP, DPEPhos and XantPhos were employed, the yield of **3aa** decreased to a very low level (entries 7–9, Table 1). Therefore, we tried to use some monophosphines instead. *n*-BuPAd₂, which has been used in many palladium-catalyzed carbonylations of aryl halides,[17] led to a somewhat lower yield of **3aa** (51% *vs.* 55%) than ligand-free conditions (entry 10, Table 1). Substituted triphenylphosphines with either electron-donating or electron-withdrawing groups on the phenyl rings did not show much improvement for this reaction (entries 11–13, Table 1). The electron-richer ligand like tricyclohexyl-phosphine (PCy₃) led to 58% yield of **3aa**. To our satisfaction, when P(*o*-tolyl)₃ was used in place of PPh₃, the yield of **3aa** increased from 60% to 66% under the same conditions (entry 11 *vs.* 15, Table 1). When the solvent was changed from dioxane to THF, the yield of **3aa** was increased further to 76%. But in other ether solvents like *t*BuOMe and DME, the yields were much lower (entries 16 and 17, Table 1). At an elevated temperature of 80 °C, the yield in THF dropped from 76% to 65%, which may be caused by the partial decomposition of the diazonium methanesulfonate that was likely to be presented as an intermediate during the reaction. In other solvents like MeCN, toluene and DMSO, the yields of **3aa** were 44, 15 and 62% respectively. Therefore, THF was the optimal solvent for the carbonylation between **1a** and **2a**. Besides, the lower CO pressure caused a decrease in the yield.

Having the optimized reaction conditions in hand, we next examined the substrate scope of the above procedure with other triazenes and commercially available alkynes (Table 2). These triazenes (**1a–q**) were easily prepared from the corresponding anilines and secondary amines in high yields (see the Experimental section). Firstly, we carried out the reactions between several *ortho* and *para*-substituted aryl triazenes and phenyl acetylenes. Obvious lower yields were found when *ortho* substituents were on the phenyl group. Aryl triazenes with some electron-withdrawing groups on *para* positions gave higher yield of the products. These may be attributed to the less stability of these aryl triazenes with electron rich or *ortho* groups.[11] Next, 1-(phenyldiazenyl)pyrrolidine (**1j**) was reacted with several substituted phenyl acetylenes and good to excellent yields were obtained. For example, when 1-ethynyl naphthene (**2j**) was employed, **3jj** was isolated in 87% yield. Notably, **3jl** was obtained from ferrocenylethyne (**2l**) in 49% yield, which has some potential applications in photoactive semiconductors and liquid crystals.[18] More investigation on the substituent effect on both aryl triazenes and aryl alkynes was performed and we were glad to see that aryl iodide (**1n**) and bromides (**1h**, **1q**, **2g**) were well tolerated. These aryl halides could undergo further palladium-catalyzed cross-couplings to introduce various functional groups.[19] The free hydroxyls in **1k** and **2q–s** were also tolerated under these acidic conditions. Unfortunately, some basic functional groups like pyridines and amines were not tolerated under our conditions.

Finally, we tried the carbonylative Sonogashira reactions with some aliphatic alkynes (**2m–s**) and the yields were in overall lower than the aryl counterparts. The masked form
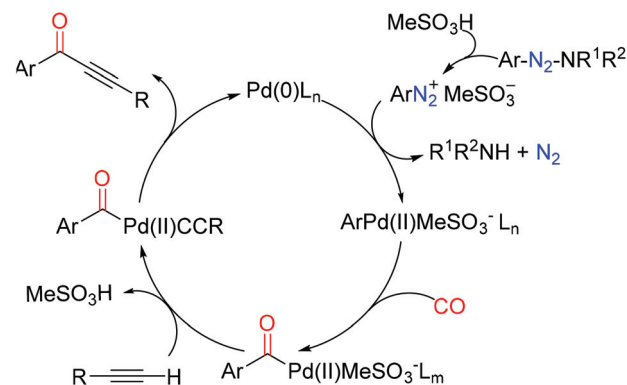
Scheme 1 Proposed reaction mechanism.

of gaseous acetylene, (triisopropylsilyl)acetylene (**2n**), was smoothly converted to a protected aryl ethynyl ketone, which is a very versatile intermediate for many organic syntheses.[20] Besides, the alkynols (**2q–s**) were also coupled with aryl triazenes but the yields were even lower.

Based on these results, a most possible reaction mechanism has been proposed. As shown in Scheme 1, the aryl triazenes were first transformed into the corresponding aryl diazonium salts with the assistance of methane sulfonic acid. Then the formed aryl diazonium salts underwent oxidative addition with Pd(0) to give an arylpalladium complex which gave the acylpalladium intermediate after the coordination and insertion of one molecule of CO. Then the terminal alkynes were produced which formed a new Pd–C bond with the assistance of MeSO₃⁻, which gave the desired alkynones after reductive elimination and also Pd(0) for the next catalytic cycle. In this procedure, methane sulfonic acid might have three roles: (1) producing aryl diazonium salts from aryl triazenes; (2) MeSO₃⁻ deprotonates terminal alkynes and re-forms methane sulfonic acid; (3) the regenerated methane sulfonic acid reacts with the pre-released free amines to avoid the nucleophilic attack of the amines to the acylpalladium intermediate and produce non-desired amides.

Conclusions

In conclusion, we have developed a carbonylative Sonogashira procedure for the synthesis of α,β-ynones using aryl triazenes, which have been transformed to aryl diazonium salts in the presence of methane sulfonic acid. This procedure has the following features: (1) acidic conditions are used instead of basic conditions and aryl bromides and iodides remained unreactive; (2) aryl triazenes are easily prepared and stable to be stored for a long time; (3) free alcohols in the substrates can be tolerated. Owing to these advantages, we believe that this alternative method will be useful in the synthesis of some special functionalized ynones for multiple step synthesis.

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Acknowledgements

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