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Palladium-Catalyzed Diarylmethyl $C(sp^3)-C(sp^2)$ Bond Formation: A New Coupling Approach toward Triarylmethanes

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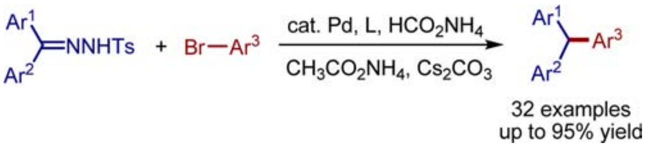
ABSTRACT



Palladium-catalyzed reductive coupling reactions between *N*-tosylhydrazones and aryl halides lead to the formation of $C(sp^3)-C(sp^2)$ bonds. This approach provides a general route for the synthesis of triarylmethanes.

Triarylmethanes and their derivatives have found widespread applications in material sciences and medicinal chemistry.[1,2] However, general methods for the synthesis of unsymmetrical triarylmethanes are less developed.[3] The traditional methods to synthesize triarylmethanes are Friedel–Crafts reactions[3a] and their variants.[3b,c] Such an approach is limited by the following drawbacks: (1) in general, electron-donating substituents on the aromatic ring are required to promote the transformation; (2) the regioselectivity largely depends on the electronic property of the substituents. Consequently, it is difficult to synthesize triarylmethanes containing electron-withdrawing groups or *meta*-substitutents with this type of reactions.

Pd-catalyzed cross-coupling reactions have become one of the most powerful and practical methodologies for the C–C bond construction.[4,5] The Pd-catalyzed diarylmethyl $C(sp^3)-C(sp^2)$ bond formation has been demonstrated to be a straightforward approach for the synthesis of triarylmethane derivatives.[6–8] Kuwano and co-workers reported a Suzuki–Miyaura coupling of diarylmethyl carbonates

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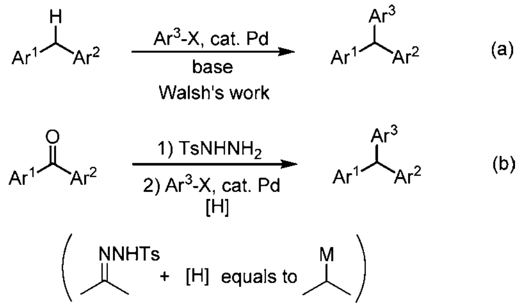
with arylboronic acids.[6] However, this method requires the preparation of the diarylmethyl coupling partners and uses stoichiometric organometallic reagents. The reaction in some cases only gives moderate yields of the desired products with formation of homocoupling byproducts. In 2012, Walsh and co-workers reported an elegant approach to triarylmethanes by the coupling of aryl bromides and diarylmethanes (Scheme 1a).[7] Notably, this deprotonative-cross-coupling process employs diarylmethanes as diarylmethyl metallic reagent equivalents, transforming the benzylic C–H bonds into the $C(sp^3)-C(sp^2)$ bonds.

Recently, *N*-tosylhydrazones have emerged as a new type of organometallic reagent equivalent in transition metal-catalyzed cross-coupling reactions.[9,10] Since *N*-tosylhydrazones are easily prepared through the corresponding carbonyl compounds, these reactions can be formally considered as transformation of C=O bonds. The previous work in this area has employed *N*-tosylhydrazone as a vinyl metallic reagent equivalent to form $C(sp^2)-C(sp^2)$ double bonds, as first demonstrated by Barluenga and co-workers.[10a] To the best of our knowledge, there is no report on using *N*-tosylhydrazone as an alkyl metallic reagent equivalent in Pd-catalyzed $C(sp^3)-C(sp^2)$ single bond formations.[11] Here, we demonstrate that under reductive conditions, *N*-tosylhydrazones derived from diarylmethanones can be served as diarylmethyl metallic reagent equivalent in Pd-catalyzed coupling reactions (Scheme 1b). Since diarylmethanones are easily available, this transformation constitutes a practical and general approach toward various triarylmethanes.

Scheme 1. Triarylmethane Synthesis by Pd-Catalyzed Coupling Reactions



At the outset of this investigation, benzophenone *N*-tosylhydrazone **1a** and 4-*tert*-butylphenyl bromide **2a** were used as the substrates in the reductive Pd-catalyzed coupling reaction (Table 1). In the presence of 5 mol % $Pd(OAc)_2$, 15 mol % PPh_3, and 1.2 equiv of HCO_2NH_4 as the reductant, we first tested two bases: LiO^tBu and Cs_2CO_3,[12] and we found Cs_2CO_3 could afford the desired product triarylmethane **3** in 29% yield (entry 2). With this initial result, we then screened the ligand of this transformtion. We found that XPhos, SPhos, and tri(2-furyl)phosphine were ineffective ligands in this reaction (entries 3–5). Change of PPh_3 to more electron-rich ligand $CyPPh_2$ resulted in a similar yield (entry 6). Then, it was found that the less hindered ligand than XPhos or SPhos, such as **L3**, could increase the yield to 34% (entry 7). Further modification of the substituents on the phosphine led us find that **L5** was a more efficient ligand (entry 9).

We then turned our attention to alternative hydride sources, however, both triethylsilane[13a] and isopropanol[13b] were found ineffective in this reaction (entries 10 and 11). We next inspected the effect of solvent (entries 12 and 13). Interestingly, it was found that *tert*-pentanol was a more suitable solvent, increasing the yield to 61% (entry 13). Under such conditions, the major byproduct was the direct reduction of **2a** to *tert*-butylbenzene. We were delighted to find that ammonium acetate could significantly suppress the side reaction, and the desired product **3** could be obtained in 85% yield (entry 14). Finally, by increasing the amount of ammonium acetate to 1.5 equiv, the yield was further improved (entry 15).

With the optimized reaction conditions, the scope of this palladium-catalyzed reductive coupling reaction was then examined by using a series of diarylmethanone *N*-tosylhydrazones **1a–j** and aryl bromides **2a–t**. As illustrated in Scheme 2, this transformation proceeds smoothly over a wide range of substrates, providing the triarylmethane with moderate to excellent yields. For the aryl bromides, the substituents on the *para* or *meta* position of the aryl ring marginally affect this reaction, affording the corresponding triarylmethanes in 66–95% yields (**3–15**).

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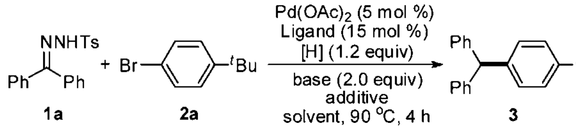
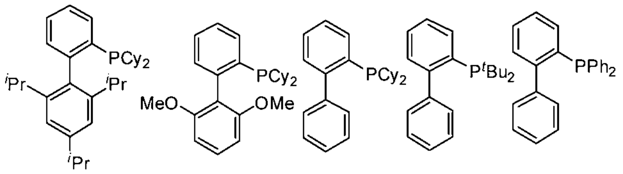
Table 1. Optimization of Reaction Conditions[a]



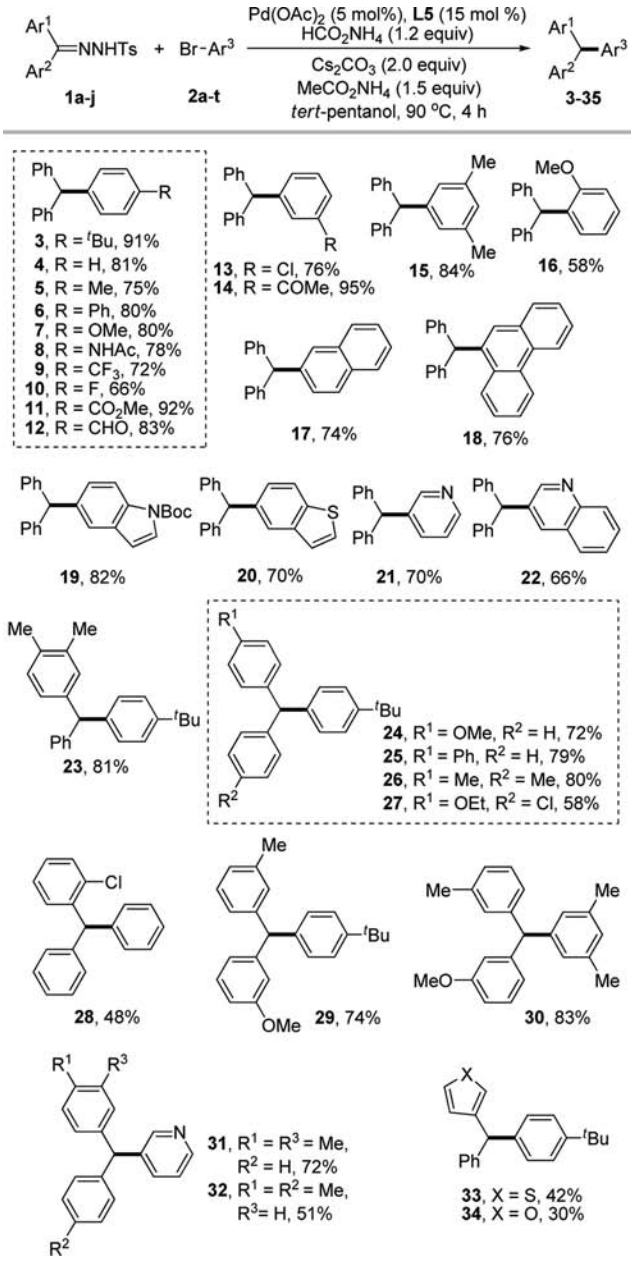
entry	ligand	base	solvent	[H]	additive	yield (%)[b]
1	PPh_3	LiOᵗBu	toluene	HCO_2NH_4	–	*trace*
2	PPh_3	Cs_2CO_3	toluene	HCO_2NH_4	–	29
3	**L1**	Cs_2CO_3	toluene	HCO_2NH_4	–	*trace*
4	**L2**	Cs_2CO_3	toluene	HCO_2NH_4	–	*trace*
5	P(2-furyl)$_3$	Cs_2CO_3	toluene	HCO_2NH_4	–	*trace*
6	$CyPPh_2$	Cs_2CO_3	toluene	HCO_2NH_4	–	27
7	**L3**	Cs_2CO_3	toluene	HCO_2NH_4	–	34
8	**L4**	Cs_2CO_3	toluene	HCO_2NH_4	–	*trace*
9	**L5**	Cs_2CO_3	toluene	HCO_2NH_4	–	43
10	**L5**	Cs_2CO_3	toluene	$HSiEt_3$	–	*trace*
11	**L5**	Cs_2CO_3	toluene	ⁱPrOH	–	*trace*
12	**L5**	Cs_2CO_3	dioxane	HCO_2NH_4	–	31
13	**L5**	Cs_2CO_3	*tert*-pentanol	HCO_2NH_4	–	61
14[c]	**L5**	Cs_2CO_3	*tert*-pentanol	HCO_2NH_4	$CH_3CO_2NH_4$	85
15[d]	**L5**	Cs_2CO_3	*tert*-pentanol	HCO_2NH_4	$CH_3CO_2NH_4$	91



L1 (XPhos) **L2** (SPhos) **L3** **L4** (JohnPhos) **L5**

[a] The reaction was carried out with 0.36 mmol of *N*-tosylhydrazone and 0.30 mmol of aryl halide in 3 mL of solvent. [b] Isolated yield. [c] 1.0 equiv of $CH_3CO_2NH_4$ was used. [d] 1.5 equiv of $CH_3CO_2NH_4$ was used.

Scheme 2. Scope of the Pd-Catalyzed Reductive Coupling Reactions[a]



[a] Reactions were carried out with *N*-tosylhydrazone (0.36 mmol) and aryl bromide (0.3 mmol) in the presence of $Pd(OAc)_2$ (5 mol %), **L5** (15 mol %), $HCONH_4$ (0.36 mmol), $MeCO_2NH_4$ (0.45 mmol), and Cs_2CO_3 (0.6 mmol) in *tert*-pentanol (3.0 mL) at 90 °C for 4 h.[b] Isolated yield.

Remarkably, some sensitive substituents or functional groups, such as amide, ester, aldehyde, chloride and ketone, are all tolerated well under the reductive coupling conditions. Aryl bromide bearing an *ortho* substituent results in a slightly lower yield (**16**). In addition, The bromonaphthalene and bromophenanthrene are also suitable substrates in the process, and the such generated products (**17** and **18**) may have interesting applications in medicinal chemistry.[2d,e,g]

It is noteworthy that the reaction conditions can also tolerate the heteroaryl bromides, affording the coressponding heteroaryl-containing triarylmethanes smoothly (**19**–**22**). Meanwhile, a range of diarylmethanone *N*-tosylhydrazones were also investigated in this reductive coupling reaction, leading to the corresponding products in moderate to good yields (**23**–**34**). Notably, this reaction affords a route to the synthesis of all *meta*-substituted unsymmetric triarylmethane (**30**), which cannot be obtained through the classical Friedel–Crafts reactions.[3] Moreover, pyridine-containing triarylmethanes could be obtained smoothly in this reaction (**31** and **32**). Finally, the thiophene and furan contained *N*-tosylhydrazones can also participate in the coupling, albeit moderate yields were obtained, such products may find potential applications in medicinal chemistry (**33** and **34**).[2f]

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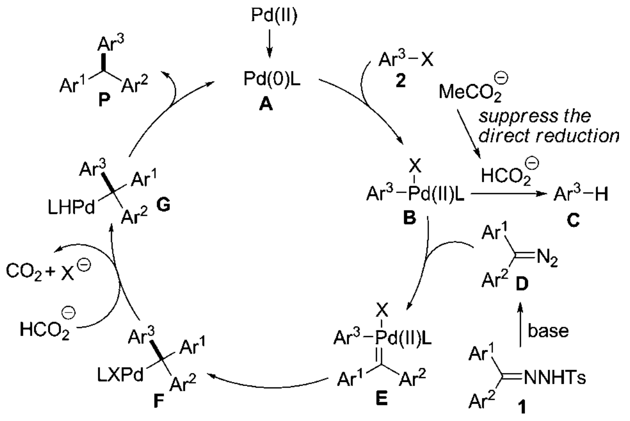
A plausible mechanism is proposed as shown in Scheme 3. The reaction might start with the oxidative addition of the aryl halide to the Pd(0) **A** to afford aryl palladium complex **B**. Meanwhile, the diazo compound **D** is generated in situ from *N*-tosylhydrazone **1** in the presence of the base. Reaction of the diazo compound with aryl palladium complex **B** leads to palladium carbene **E**.[14] Subsequent migratory insertion of an aryl group to the carbenic carbon produces intermediate **F**, which might undergo ligand exchange with the formate anion and decarboxylation gives the palladium-hydride complex **G**.[11] Finally, the reductive elimination of **G** would provide the product **P** and regenerate the Pd(0) catalyst. In this transformation, the direct reduction of **2** to give **C** is the major side reaction. An interesting observation of this study is that this side reaction can be suppressed by the addition of ammonium acetate. Although there are no reports on such a phenomenon, we speculate that it is similar to the common-ion effect.

Scheme 3. Proposed Mechanism



In conclusion, we have developed a Pd-catalyzed reductive coupling reaction between diarylmethanone *N*-tosylhydrazones and aryl halides. This reaction provides a novel method for the synthesis of various triarylmethanes and their hetereoatom-containing analogues in moderate to good yields from easily available starting materials. Moreover, from a mechanistic point of view, in the previously reported Pd-catalyzed coupling reaction involving *N*-tosylhydrazones as coupling partners, the *N*-tosylhydrazones are employed as vinyl metallic reagent equivalents to generate C═C double bonds,[10] while this work provides the first example in which *N*-tosylhydrazones are used as alkyl metallic reagent equivalents, leading to the formation of $C(sp^3)-C(sp^2)$ single bonds. Further investigation will focus on asymmetric catalysis as well as the extension of this concept to other types of *N*-tosylhydrazones and organic halides. The results will be reported in due course.

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Supporting Information Available. Representative experimental procedures, characterization data, and NMR spectra of all allene products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.