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# Palladium-Catalyzed Triarylation of $sp^3$ C–H Bonds in Heteroarylmethanes: Synthesis of Triaryl(heteroaryl)methanes

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**Abstract.** A straightforward method for the palladium-catalyzed triarylation of heteroarylmethanes at the methyl group has been developed. The reaction works with a variety of aryl halides, enabling the rapid synthesis of triaryl(heteroaryl)methanes in moderate to excellent yields.

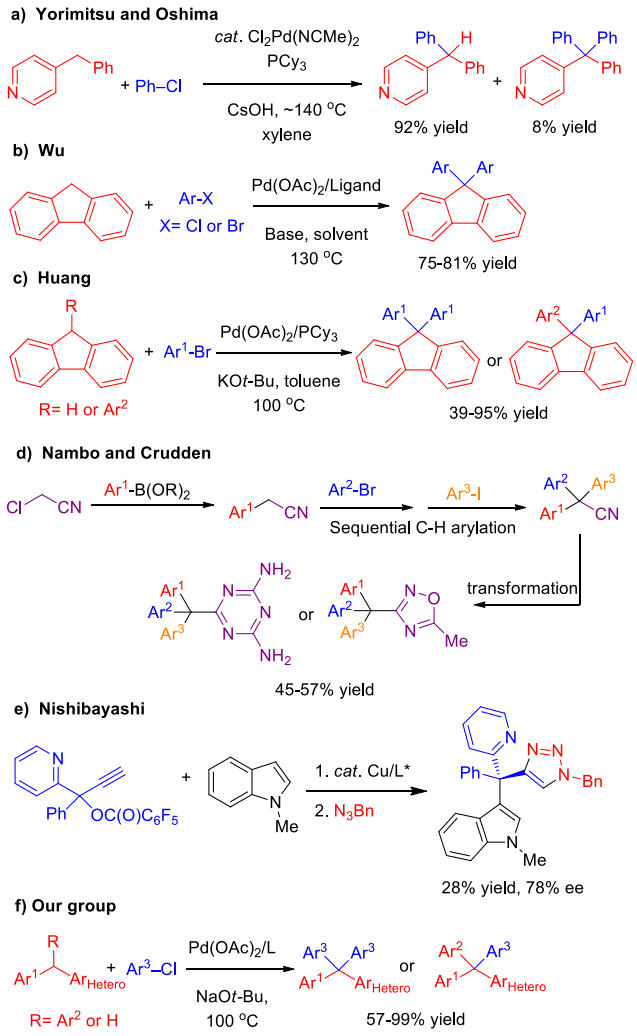
**Keywords:** palladium-catalyzed; aryl halides; triarylation; tetraarylmethanes

## Introduction

Tetraarylmethanes, and related derivatives, are ubiquitous building blocks and exhibit a wide range of applications.[1] Their synthesis, therefore, has attracted much attention. It is surprising, however, that transition metal-catalyzed C–H functionalization reactions, which are among the most versatile methods in organic synthesis, have witnessed only limited success in the synthesis of tetraarylmethanes.[2] We are aware of only a few relevant examples: Yorimitsu, Oshima and co-workers noted formation of 8% yield of a tetraarylmethane (Scheme 1a).[3] Wu and Huang (Scheme 1b and 1c) independently reported palladium-catalyzed arylations of fluorene and monoarylfluorene derivatives with aryl bromides for the synthesis of diarylfluorenes.[4] Nambo and Crudden outlined a sequential palladium-catalyzed arylation to generate triarylacetonitrile products. The triarylacetonitriles were subsequently transformed into triaryl(heteroaryl)methanes in 45–57% yield (Scheme 1d).[5] Nishibayashi presented a copper-catalyzed enantioselective propargylation of indoles with propargylic esters to construct all carbon quaternary stereocenters bearing an alkyne. Subsequent derivatization of the terminal alkyne with phenylazide generated enantioenriched all carbon substituted tetraarylmethanes with 28% yield and 78% ee (Scheme 1e).[6]

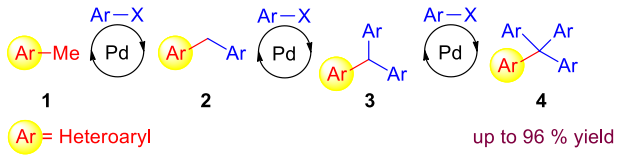
Our research group has been interested in the catalytic functionalization of weakly acidic $sp^3$-hybridized C–H bonds through deprotonative cross-coupling processes (DCCP),[7] which are mechanistically similar to carbonyl α-arylation reactions.[8] DCCP involve weakly acidic substrates (pKa > 25) that are reversibly deprotonated in the presence of the transition metal catalyst and subsequently functionalized. Based on this approach, we developed a palladium-catalyzed DCCP for direct arylation of aryl(heteroaryl)methanes and diaryl(heteroaryl)methanes with aryl chlorides using palladium catalysts based on tricyclohexyl phosphine ($PCy_3$) or cataCXium A ($Ad_2P$-*n*-Bu, Ad = adamantyl)[9] to construct triaryl(heteroaryl)methanes in good to excellent yields (Scheme 1f).[10]

General methods for the direct arylation of benzylic methyl groups to construct tetraarylmethanes have not been developed to our knowledge, although the diarylation of benzylic methyl groups to form triarylmethanes has been reported.[2e,11] Based on our prior studies,[10] we hypothesized that DCCP of benzylic methyl groups in the presence of a palladium catalyst should provide tetraarylmethanes via a tandem triarylation. The success of this process depends on identifying a catalyst that is able to perform arylations on 3 distinct coupling partners, as shown in Scheme 2. Herein, we present a novel palladium catalyzed triarylation of heteroaryl methyl groups for the efficient synthesis of tetraarylmethane derivatives (Scheme 2).




**Scheme 1.** Transition Metal Catalyzed Approaches to Tetraarylmethanes

Despite intensive efforts by medicinal chemists to prepare novel molecular scaffolds that exhibit biological activity, such structures are nearly always either linear or disk-shaped.[12] Very few examples of bioactive sphere-like molecules are known. We conjectured that the reason for this is that the synthesis of sphere-like molecules is more labor intensive. To address this issue, we initiated a program in the exhaustive arylation of benzylic C–H's.[10,13]




**Scheme 2.** Palladium Catalyzed Tandem Triarylation Reaction of Heteroaryl Methyl Groups to Generate Tetraarylmethane Derivatives.

## Results and Discussion

In light of the significance of heteroaryl groups in medicinal chemistry and material science,[14] we focused our studies on the coupling between 2-methylbenzothiazole **1a** and chlorobenzene **5a**. We initially examined the tandem triarylation reaction under conditions we previously reported for constructing triaryl(heteroaryl)methanes from benzyl-substituted heterocycles using $Pd(OAc)_2$, cataCXium A ($Ad_2P$-*n*-Bu), and NaO*t*-Bu in 1,4-dioxane for 12 h at 100 °C (Scheme 1f).[10] With 5.0 mol % $Pd(OAc)_2$ and 10.0 mol % cataCXium A, the arylation of 2-methylbenzothiazole (**1a**) with chlorobenzene led to tetraarylmethane in 14% assay yield (AY) and triarylmethane in 22% AY (AY determined by $^1H$ NMR analysis, Table 1, entry 1). With this promising lead, we screened three additional bases (KO*t*-Bu, LiHMDS and NaHMDS) under the same conditions. Unfortunately, all three bases led to decomposition products (entries 2–4). From our previous work[15] we found that solvents play an important role in DCCP. We, therefore, screened five additional solvents (DME, THF, CPME, toluene and *o*-xylene) at 100° C with a 12 h reaction time. Among these, DME and THF afforded 3 and 6% AY of triarylmethane, respectively (entries 5 and 6). CPME, toluene and *o*-xylene generated 11–23% AY of tetraarylmethane and 33–62% AY of triarylmethane (entries 7–9).

The results in entries 7–9 suggest that the reactions had not reached completion after 12 h at 100 °C. The temperature was, therefore, increased to 130 °C with *o*-xylene solvent. We were pleased to find that after 12 h at the higher temperature the tetraarylmethane product **4a** was obtained in 96% AY (entry 10). When the reaction time was reduced to 6 h, the tetraarylmethane was formed in 96% AY and 93% isolated yield (entry 11). A control reaction indicated that in the absence of the palladium catalyst, the reaction did not yield tetra-, tri-, or diarylation products (entry 12). It is noteworthy that no monoarylated product was detected in any of the entries. It is interesting that very similar reaction conditions [$Pd(OAc)_2$, $PCy_3$, Ph–Cl, 2-methylbenzothiazole, NaO*t*-Bu, 130 °C in *o*-xylene) were employed by Li and coworkers.[11b] Their reaction gave 96% of the diarylation product, however, with no formation of tetraarylmethane derivatives. The contrast between Li's publication and entry 10 of Table 1 highlights how relatively small changes in ligand structure can have a dramatic impact on reaction outcome.

**Table 1.** Optimization of Trisarylation of 2-Methylbenzothiazole with Chlorobenzene[a]

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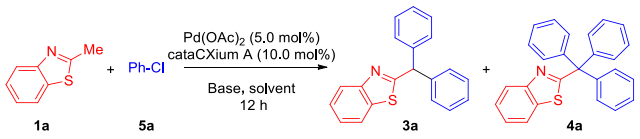
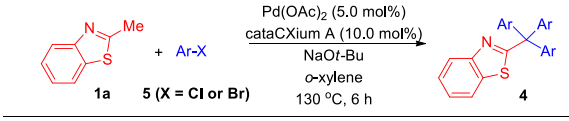


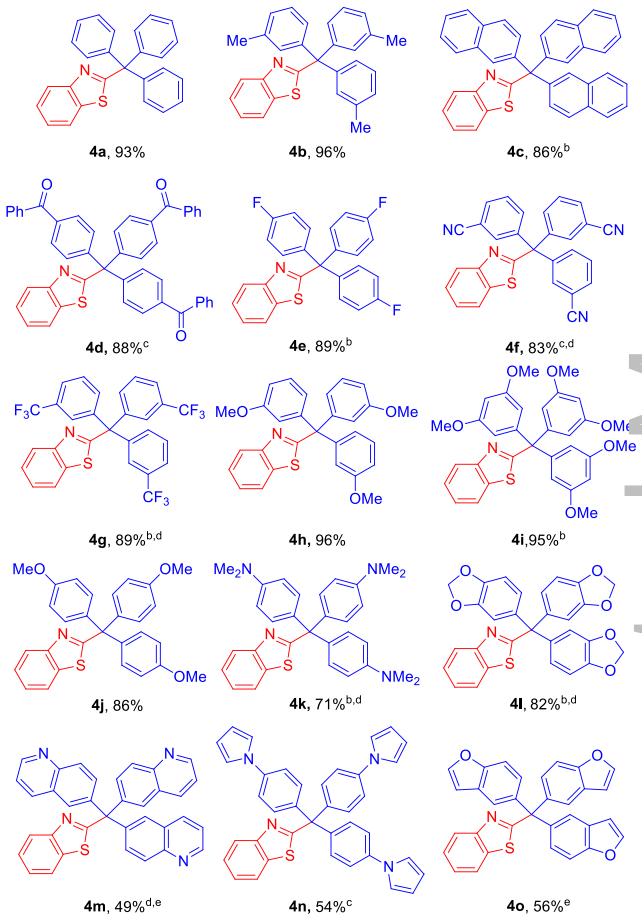

| Entry | Temp (°C) | Solvent | Base | **3a**[b] (%) | **4a**[b] (%) |
|---|---|---|---|---|---|
| 1 | 100 | 1,4-dioxane | NaO*t*-Bu | 21 | 14 |
| 2 | 100 | 1,4-dioxane | KO*t*-Bu | 0 | 0 |
| 3 | 100 | 1,4-dioxane | LiHMDS | 0 | 0 |
| 4 | 100 | 1,4-dioxane | NaHMDS | 0 | 0 |
| 5 | 100 | DME | NaO*t*-Bu | 3 | 0 |
| 6 | 100 | THF | NaO*t*-Bu | 6 | 0 |
| 7 | 100 | CPME | NaO*t*-Bu | 33 | 11 |
| 8 | 100 | toluene | NaO*t*-Bu | 55 | 11 |
| 9 | 100 | *o*-xylene | NaO*t*-Bu | 62 | 23 |
| 10 | 130 | *o*-xylene | NaO*t*-Bu | 0 | 96 |
| 11 | 130 | *o*-xylene | NaO*t*-Bu | 0 | 96(93)[c] |
| 12 | 130 | *o*-xylene | NaO*t*-Bu | 0 | 0[d] |

[a] Reaction conditions: All reactions were conducted on a 0.20 mmol scale using $Pd(OAc)_2$ (5.0 mol %), cataCXium A (10.0 mol %), 1.0 equiv of **1a**, 5.0 equiv of **5a** and 5.0 equiv of base in 2 mL of solvent for 12 h. [b] Assay yields determined by $^1$H NMR spectroscopy of the crude reaction mixtures with internal standard $CH_2Br_2$. [c] The reaction time is 6 h and isolated yield. [d] Without palladium and ligand, reaction time is 6 h.

With the optimized reaction conditions in hand [2-methylbenzothiazole (**1a**, 1.0 equiv), aryl chloride (**5**, 5.0 equiv), NaO*t*-Bu (5.0 equiv), $Pd(OAc)_2$/cataCXium A (5.0 mol %/10.0 mol %), *o*-xylene (0.10 M) at 130 °C], we explored the scope of aryl chlorides in their coupling with 2-methylbenzothiazole (Table 2). Overall, a variety of aryl chlorides led to the formation of triaryl(heteroaryl)methanes (**4**) with moderate to excellent yields (49–96%). The DCCP was compatible with aryl chlorides bearing alkyl or neutral substituents giving the desired products in 86–96% yield (**4a**–**4c**). A range of aryl chlorides, bearing both electron-withdrawing and electron-donating groups, was suitable for coupling with 2-methylbenzothiazole. Thus, aryl chlorides bearing 4-COPh, 4-F, 3-CN and 3-$CF_3$ groups resulted in tetraarylmethane products **4d**–**4g** in 83–89% yield. Reactions with 3-chloroanisole and 1-chloro-3,5-dimethoxybenzene furnished the products **4h** and **4i** in 96 and 95% yield, respectively. Good yields were obtained using electron rich aryl chlorides with 4-OMe, 4-$NMe_2$ and a protected catechol (**4j**–**4l**, 71–86% yield). Heteroaryl halides such as 6-bromoquinoline, 1-(4-chlorophenyl)-*1H*-pyrrole and 5-bromobenzofuran proved to be suitable electrophiles and underwent coupling with 2-methylbenzothiazole to furnish products (**4m**–**4o**) in 49–56% yield. It is noteworthy that aryl chlorides bearing more sensitive groups, such as 4-COPh, 3-CN and 1-(4-chlorophenyl)-*1H*-pyrrole, required LiO*t*-Bu as base to afford the desired products. Use of NaO*t*-Bu resulted in decomposition with no products isolable. In general, when yields for the triarylation are low, no significant byproducts derived from mono- or diarylation were observed by $^1$H NMR. We attribute the low yields to decomposition of the starting aryl halides under the basic reaction conditions. Despite considerable effort, heteroaryl halides 5-bromo-1-methyl-*1H*-indole and 3-bromopyridine[16] were not successfully coupled under our current conditions.

**Table 2.** Scope of Aryl Halides **5** in Benzylic C–H Arylation of 2-Methylbenzothiazole **1a**[a]



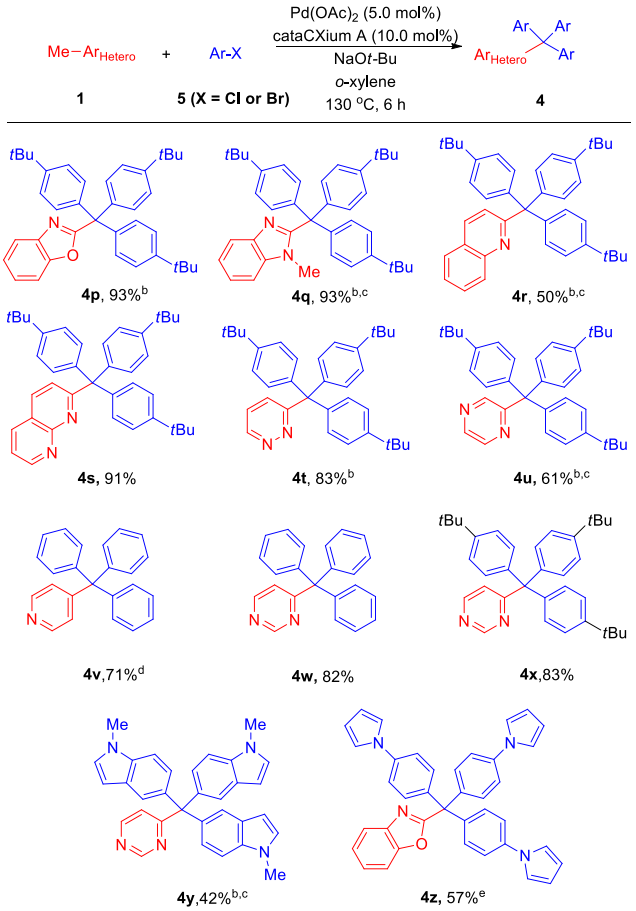




[a] Isolated yield on 0.20 mmol scale; Reactions conducted using **1a** (1.0 equiv), aryl chloride (5.0 equiv) and NaO*t*-Bu (5.0 equiv) in *o*-xylene (0.10 M) at 130 °C. [b] Reactions conducted using aryl chloride (6.0 equiv) and NaO*t*-Bu (6.0 equiv). [c] Reactions conducted using aryl chloride (6.0 equiv) and LiO*t*-Bu (6.0 equiv). [d] Reaction time 18 h. [e] Reactions conducted using aryl bromide (6.0 equiv) and NaO*t*-Bu (6.0 equiv).

After demonstrating the broad scope of the triarylation of 2-methylbenzothiazole we examined the

triarylation of other methyl heteroaromatics (**1**) with aryl halides **5** (Table 3). Under our optimized conditions, 2-methylbenzoxazole, *N*-methyl 2-methylbenzimidazole and 2-methylquinoline readily coupled with 1-bromo-4-*tert*-butylbenzene to afford the coupling products in good yields (**4p**–**4r**, 50–93% yield). 2-Methyl-1,8-naphthyridine, 3-methylpyridazine and 2-methylpyriazine also underwent facile coupling with 1-chloro- or 1-bromo-4-*tert*-butylbenzene to furnish the desired products (**4s**–**4u**, 61–91% yield). 4-Methylpyrimidine was a suitable substrate, undergoing coupling with 1-chloro-4-*tert*-butylbenzene and chlorobenzene to produce the triarylated products **4w** and **4x** in 82 and 83% yield, respectively. When using stronger base, KO*t*-Bu, 4-methylpyridine also coupled with chlorobenzene to obtain the corresponding compound **4v** in 71% yield. This result indicates that the use of heteroarylmethanes with *ortho*-directing groups is not necessary for successful coupling.

**Table 3**. Scope of Aryl Halides **5** in Benzylic C–H Arylation of Methyl Heteroaromatics **1**[a]

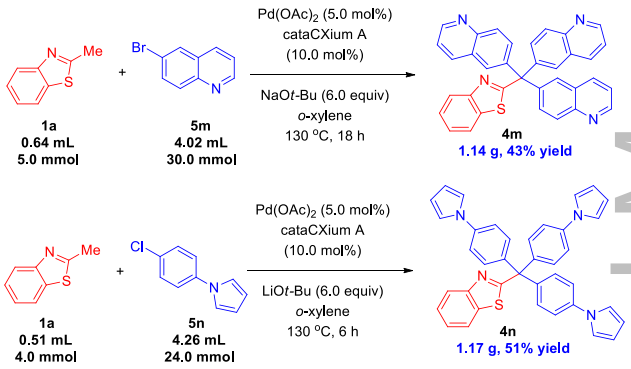



[a] Isolated yield on 0.20 mmol scale; Reactions conducted using **1** (1.0 equiv), aryl chloride (5.0 equiv) and NaO*t*-Bu (5.0 equiv) in *o*-xylene (0.10 M) at 130 °C. [b] Reactions conducted using aryl bromide (6.0 equiv) and NaO*t*-Bu (6.0 equiv). [c] Reaction time 18 h. [d] Reactions conducted using $Pd(OAc)_2$ (10 mol%), cataCXium A (20 mol%), aryl chloride (6.0 equiv) and KO*t*-Bu (6.0 equiv). [e] Reactions conducted using aryl chloride (6.0 equiv) and LiO*t*-Bu (6.0 equiv).

Heteroaryl halides such as 5-bromo-1-methyl-*1H*-indole underwent coupling with 4-methylpyrimidine to afford the products **4y** in 42% yield. When the coupling of 2-methylbenzoxazole was conducted with 1-(4-chlorophenyl)-*1H*-pyrrole and NaO*t*-Bu, no desired products were detected. Switching to the milder base LiO*t*-Bu, however, resulted in 57% yield. Although some of the yields in Tables 2 and 3 are only moderate, it must be borne in mind that they represent the sum of 3 distinct coupling events (Scheme 2).

To demonstrate the potential utility of this method, the gram scale reactions of 2-methylbenzothiazole (**1a**) with 6-bromoquinoline (**5m**) and 1-(4-chlorophenyl)-*1H*-pyrrole (**5n**) were performed. The desired products **4m** and **4n** were obtained in 43 and 51% yield, respectively (Scheme 3), suggesting the reaction is scalable, even with heteroaryl substrates.

**Scheme 3.** Triarylation of 2-methylbenzothiazole (**1a**) with 6-bromoquinoline (**5m**) and 1-(4-chlorophenyl)-*1H*-pyrrole (**5n**) on gram scale




## Conclusion

In summary, a palladium-catalyzed deprotonative cross-coupling process (DCCP) for direct arylation of methyl substituted heteroaromatics with aryl halides to synthesize triaryl(heteroaryl)methanes has been developed. Under our reaction conditions, a broad scope of methyl substituted heteroaromatics and aryl halides have successfully been coupled. It is impressive that a single catalyst can promote the efficient arylation of the starting material ($Ar_{Hetero}$-$CH_3$) and intermediates [$CH_2(Ar_{Hetero})Ar$ and $CH(Ar_{Hetero})Ar_2$] to yield tetraarylmethane derivatives in up to 96% yield. We anticipate that this method will enable rapid assembly of tetraarylmethane derivatives previously difficult to prepare and will be useful in the synthesis of sphere-like molecules for examination in medicinal chemistry.

# Experimental Section

**General Methods**

All reactions were conducted under an inert atmosphere of dry nitrogen. Dry solvents were purchased from Sigma-Aldrich and used without further purification. Unless otherwise stated, reagents were commercially available and used as purchased. Chemicals were obtained from Sigma-Aldrich, Acros, Alfa-Aesar, TCI and solvents were purchased from Fisher Scientific. TLC was performed with Merck TLC Silicagel60 $F_{254}$ plates with detection under UV light at 254 nm. Silica gel (230–400 mesh, Silicycle) was used for flash chromatography. The $^{1}H$ NMR and $^{13}C\{^{1}H\}$ NMR spectra were obtained using a Brüker AM-500 Fourier-transform NMR spectrometer at 500 and 125 MHz, respectively. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS, δ 0.00 ppm) for $^{1}H$ NMR, $CDCl_3$ (δ 77.16 ppm) and $^{13}C\{^{1}H\}$ NMR and all coupling constants are reported in hertz. The infrared spectra were obtained with KBr plates using a Perkin-Elmer Spectrum 100 Series FTIR spectrometer. High resolution mass spectrometry (HRMS) data were obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte.

**General Procedure for the Pd-catalyzed Triarylation of Methyl Heteroaromatics**

An oven-dried 8 mL reaction vial equipped with a stir bar was charged with methyl heteroaromatics (**1**, 0.20 mmol, 1.0 equiv) and aryl halides (**5**, 5.0–6.0 equiv) in a glove box under a nitrogen atmosphere at room temperature. A stock solution containing $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5.0 mol %) and cataCXium A (7.2 mg, 0.02 mmol, 10.0 mol %) in 2 mL of dry *o*-xylene was taken up by syringe and added to the reaction vial under nitrogen. Next, NaO*t*-Bu (5.0–6.0 equiv) was added to the reaction mixture. The vial was capped, removed from the glove box, and stirred for 6 h at 130 °C. After cooling to room temperature, the reaction mixture was opened to air. Water (10 mL) was then added and the solution was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over $Na_2SO_4$ and was concentrated in vacuo. The crude material was loaded onto a deactivated silica gel column and purified by flash chromatography to afford the products.

# Acknowledgements

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[16] When using 3-bromopyridine as the substrate, there was only triarylmethane formed in 77% AY under the same reaction conditions.

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FULL PAPER

# Palladium-Catalyzed Triarylation of $sp^3$ C–H Bonds in Heteroarylmethanes: Synthesis of Triaryl(heteroaryl)methanes

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