Palladium Catalysis

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Modular Synthesis of Triarylmethanes through Palladium-Catalyzed Sequential Arylation of Methyl Phenyl Sulfone**

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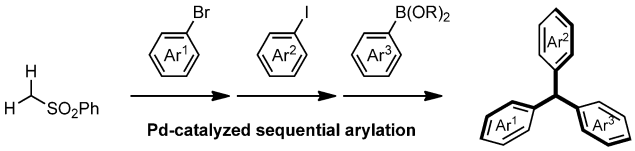
Abstract: *Triarylmethanes, which are valuable structures in materials, sensing and pharmaceuticals, have been synthesized starting from methyl phenyl sulfone as an inexpensive and readily available template. The three aryl groups were installed through two sequential palladium-catalyzed C–H arylation reactions, followed by an arylative desulfonation. This method provides a new synthetic approach to multisubstituted triarylmethanes using readily available haloarenes and aryl boronic acids, and is also valuable for the preparation of unexplored triarylmethane-based materials and pharmaceuticals.*

The synthesis of triarylmethanes and related structures has attracted much attention in the area of medicinal chemistry and materials science.[1] Indeed, the triarylmethane motif is ubiquitous in dyes,[1a,2] fluorescent probes,[3] natural products,[4] and biologically active compounds.[5] Although the Friedel–Crafts reaction is a simple and widely employed method for the construction of triarylmethane structures,[6] this reaction is only applicable to nucleophilic and electron-rich arenes and often results in the formation of undesired regioisomers. The reductive dehydroxylation of triarylmethanol derivatives is another common method for the multi-step synthesis of triarylmethanes.[7] Recently, a few transition-metal-catalyzed routes have been developed that begin to address these shortcomings.[8,9] Complementary to these methods that require prefunctionalization for the preparation of suitable coupling partners to promote these catalytic reactions, we report a new method that employs methyl phenyl sulfone as a simple and readily available starting material for the synthesis of triarylmethanes. Three sequential catalytic arylations are employed to transform methyl phenyl sulfone into valuable triarylmethane products. The present method involves two types of catalytic transformations: Two stepwise C–H arylation reactions are followed by a simultaneous, Pd-catalyzed desulfonation/arylation process (Scheme 1).



Scheme 1. Synthesis of triarylmethanes through Pd-catalyzed sequential arylations.

To accomplish the modular synthesis of triarylmethanes with sufficient generality, we focused on the unique properties of the sulfonyl group: Its electron-withdrawing character dramatically increases the acidity of the protons that are attached to the sp^3-hybridized carbon atom in the α-position of the SO_2 group,[10] and this functional group simultaneously has the potential to behave as a leaving group for organic reactions.[11] Inspired by recent progress in Pd-catalyzed arylation of acidic C(sp^3)–H bonds[8e–i,12] and aryl substitution of alkyl electrophiles,[7a–b] we envisioned that these reactions could be used to accomplish the direct installation of three aryl groups on the α-carbon atom of the sulfonyl group, which results in a modular straightforward synthesis of triarylmethanes from readily available building blocks.

Building on the pioneering work of Zhou et al.[12f] and Walsh and co-workers,[13] we chose methyl phenyl sulfone as our building block for the synthesis of triarylmethanes because of the high acidity of the protons at the α-position of the sulfone ($pK_a \approx 29$ in DMSO).[10a] For the first arylation, we focused on the mono-selective arylation of methyl phenyl sulfone, with the considerable challenge that after arylation, the α-protons are significantly more acidic, which can lead to the formation of undesired diarylated products. The use of $Pd(OAc)_2$ and XPhos[14] as the catalyst precursors resulted in exclusive mono-arylation, which is crucial for the introduction of three different aryl groups and the synthesis of unsymmetric triarylmethanes (Table 1).

Several key features of this reaction can be seen in Table 1. First, as observed by Walsh and co-workers,[13] whereas lithium and sodium bases effectively promoted the reaction, no product was observed when KO*t*Bu was employed (entries 3–5). This could be ascribed to a counterion effect on the transmetalation of the sulfone enolate to palladium.[15] Second, the most selective and highest yielding transformation was observed when XPhos (L5) was employed as the ligand for palladium. In this case, the desired product was obtained in 92%, and the diarylated product was not

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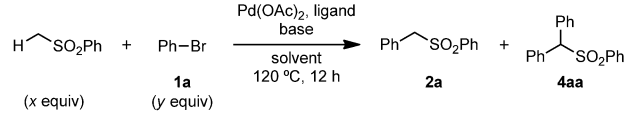
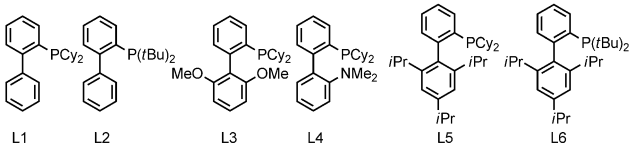
Supporting information for this article, including experimental procedures, characterization data for all arylation products, and the CIF file of **6hhh,** is available on the WWW under http://dx.doi.org/10.1002/anie.201307019.

Table 1: Optimization of the first C–H arylation of methyl sulfone.[a]



Entry	*x*:*y*	Ligand	Base	Solvent	**2a**[b] [%]	**4aa**[b] [%]
1	1:2	L1	LiO*t*Bu	CPME	72	5
2	2:1	L1	LiO*t*Bu	CPME	61	3
3	3:1	L1	LiO*t*Bu	CPME	68	2
4	3:1	L1	NaO*t*Bu	CPME	54	1
5	3:1	L1	KO*t*Bu	CPME	<1	<1
6	3:1	L1	LiO*t*Bu	dioxane	39	6
7	3:1	L1	LiO*t*Bu	toluene	37	2
8	3:1	L1	LiO*t*Bu	DMF	<1	<1
9	3:1	L2	LiO*t*Bu	CPME	57	<1
10	3:1	L3	LiO*t*Bu	CPME	84	2
11	3:1	L4	LiO*t*Bu	CPME	70	4
12	3:1	L5	LiO*t*Bu	CPME	92	<1
13	3:1	L6	LiO*t*Bu	CPME	79	<1

[a] Conditions: methyl phenyl sulfone, PhBr, $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), base (3 equiv), solvent (0.15 M), 120°C, 12 h. [b] Determined by GC analysis using dodecane as the internal standard. CPME = cyclopentyl methyl ether.

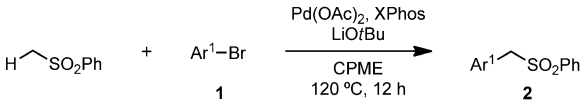


observed.[16] When an even bulkier ligand, namely *t*BuXPhos (L6), was employed, the diarylated product was not observed, but the yield of the desired product also decreased. These results corroborate that steric factors control the degree of arylation, with more sterically hindered ligands preventing the second arylation. Consistent with this, when product **2a** was re-exposed to the reaction conditions of the first arylation, only 15% of the diarylated product **4aa** was observed after twelve hours of reaction (Supporting Information, Table S1, entry 2).

With reasonable conditions in hand for the mono-selective reaction between methyl phenyl sulfone and bromobenzene, we examined the scope of this reaction (Table 2). Bromoarenes that bear electron-donating (entries 2–4) or electron-withdrawing groups (entries 5 and 6) all reacted to afford the corresponding mono-arylated products in good yield. Sterically hindered substrates, such as 1-bromonaphthalene (**1g**), also reacted efficiently (entry 7). Furthermore, heteroaromatic substrates, such as 3-bromothiophene, were also converted into the corresponding products, albeit in lower yields (entry 8).

Next, we investigated the C–H arylation of mono-arylated methyl sulfones with aryl halides (2nd arylation). Similar sulfone derivatives have been employed in Pd-catalyzed C–H arylations with aryl halides by the groups of Yorimitsu, Oshima,[17] and Walsh.[13] Building on these results, we focused on the effect of base, ligand, and solvent, and were ultimately able to effect the Pd-catalyzed C–H arylation of benzyl

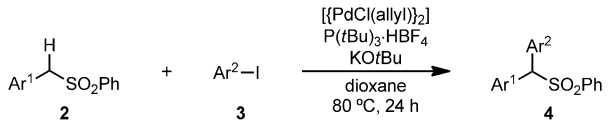
Table 2: Scope of the Pd-catalyzed C–H arylation of methyl phenyl sulfone with bromoarenes.[a]



Entry	Ar^1	**2**	Yield[b] [%]
1	C_6H_5 (**1a**)	**2a**	86
2	*p*-MeC_6H_4 (**1b**)	**2b**	78
3	*p*-$MeOC_6H_4$ (**1c**)	**2c**	74
4	*p*-$BnOC_6H_4$ (**1d**)	**2d**	70
5	*p*-FC_6H_4 (**1e**)	**2e**	82
6	*p*-$CF_3C_6H_4$ (**1f**)	**2f**	56
7	1-naphthyl (**1g**)	**2g**	79
8[c]	3-thienyl (**1h**)	**2h**	34

[a] Conditions: methyl phenyl sulfone (3 equiv), Ar^1Br (1 equiv), $Pd(OAc)_2$ (10 mol%), XPhos (20 mol%), LiO*t*Bu (3 equiv), CPME (0.15 M), 120°C, 12 h. [b] Yields of isolated products. [c] Reaction time: 24 h. Bn = benzyl.

Table 3: Scope of the Pd-catalyzed C–H arylation of mono-arylated sulfones with iodoarenes.[a]



Entry	Ar^1	Ar^2	**4**	Yield[b] [%]
1[c]	C_6H_5 (**2a**)	C_6H_5 (**3a**)	**4aa**	82
2	C_6H_5 (**2a**)	*p*-$MeOC_6H_4$ (**3c**)	**4ac**	68
3	C_6H_5 (**2a**)	*p*-FC_6H_4 (**3e**)	**4ae**	46
4	*p*-MeC_6H_4 (**2b**)	C_6H_5 (**3a**)	**4ba**	83
5	*p*-$MeOC_6H_4$ (**2c**)	*p*-$MeOC_6H_4$ (**3c**)	**4cc**	75
6	*p*-$BnOC_6H_4$ (**2d**)	*p*-$MeOC_6H_4$ (**3c**)	**4dc**	66
7	*p*-FC_6H_4 (**2e**)	*p*-MeC_6H_4 (**3b**)	**4eb**	78
8[d]	*p*-$CF_3C_6H_4$ (**2f**)	C_6H_5 (**3a**)	**4fa**	86
9	*p*-$CF_3C_6H_4$ (**2f**)	*p*-$CF_3C_6H_4$ (**3f**)	**4ff**	47
10[c]	1-naphthyl (**2g**)	C_6H_5 (**3a**)	**4ga**	79
11	3-thienyl (**2h**)	C_6H_5 (**3a**)	**4ha**	42
12[e]	3-thienyl (**2h**)	3-thienyl (**3h**)	**4hh**	30

[a] Conditions: mono-arylated sulfone (1 equiv), Ar^2I (1.5 equiv), $[\{PdCl(allyl)\}_2]$ (5 mol%), $P(tBu)_3{\cdot}HBF_4$ (20 mol%), KO*t*Bu (3 equiv), dioxane (0.19 M), 80°C, 12 h. [b] Yields of isolated products. [c] Reaction time: 12 h. [d] Reaction conducted at 60°C. [e] Reaction conducted at 120°C with Ar^2I (3 equiv).

phenyl sulfone (**2a**) with iodobenzene (**3a**) at 80°C in dioxane using $P(tBu)_3$ as the ligand and KO*t*Bu as the base.[18]

Under these optimized reaction conditions, the second arylation could be carried out with a considerable variety of iodoarenes (Table 3). Electron-neutral or electron-rich aryl iodides, such as phenyl (**3a**), *p*-tolyl (**3b**), or *p*-anisyl iodide (**3c**), yielded the corresponding diarylmethyl phenyl sulfones in good yields (entries 1, 2, 4–7). On the other hand, *para*-fluoro- and *p*-trifluoromethyl-substituted iodobenzenes (**3e** and **3f**) gave the desired products in lower yields (entries 3 and 9). However, this differential reactivity was not problematic, as electron-withdrawing groups were well tolerated on the sulfone component. For example, *para*-(trifluoromethyl)-

benzyl phenyl sulfone (**2f**) reacted with iodobenzene (**3a**) in high yield at 60 °C (entry 8). The increase in reactivity could arise from the higher acidity of the C–H bond in **2e**. The phenylation of sterically hindered 1-naphthylmethyl phenyl sulfone (**2g**) provided the product in high yield (entry 10). 3-Thienylmethyl phenyl sulfone (**2h**) was also reactive, but the products were formed in lower yields (entries 11 and 12).

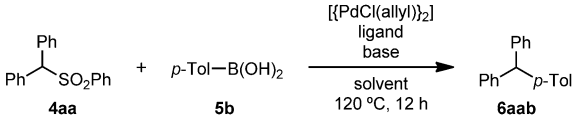
The final challenge that remained to complete our synthesis of triarylmethanes, namely conversion of the C–SO_2Ph moiety into a C–Ar group with complete regioselectivity, had very little precedent.[19] Arylboron compounds, which are air-stable, shelf-stable, functional-group-compatible, and commercially available compounds, were our first choice as a nucleophile. To rule out the possibility that Pd-catalyzed desulfonylative arylation of diarylmethyl phenyl sulfones may lead to diarylphenylmethenes, *p*-tolylboronic acid (**5b**) was selected as a coupling partner (Table 4). In early experiments, it was found that the use of typical phosphine (monodentate and bidentate) and amine ligands did not give the desired arylation product (entries 1–6). Our first "hit" came with the use of the N-heterocyclic carbene SIPr, which was employed as its HCl salt in the presence of LiO*t*Bu (3.0 equiv). Under these conditions, the desired product was obtained in 49% yield (entry 7). Whereas the use of K_3PO_4 as a mild base showed similar reactivity (entry 8), replacement of SIPr with other NHC ligands, such as IMes, ICy, and IAd, resulted in lower reactivity (entries 9–11).

The use of aqueous solutions of NaOH was also effective (entry 12), and the yield of the product was improved to 93% when the reaction was conducted at higher concentrations (entry 13). With this system, we successfully reduced the amount of **5b** without loss of reactivity (92%, entry 14). Commercially available Pd NHC complexes, such as PEPPSI-IPr,[20] showed similar reactivity (entry 15). The pinacol ester of *p*-tolylboronic acid also gave the arylated product in excellent yield (entry 16).[21]

With optimized conditions in hand, the variation of the aryl boronic acid in the arylation of **4aa** was assessed (Table 5). The reaction took place with electronically and structurally diverse aryl boronic acids, with high yields in almost all cases. Aryl boronic acids with an electron-donating group, such as *p*-methyl, *p*-methoxy, or *p*-*N*,*N*-dimethylamino, all reacted in high yield. Although the electron-poor *para*-(trifluoromethyl)phenylboronic acid (**5e**) showed lower reactivity under standard conditions, simply increasing the temperature by 30 °C gave the desired product in good yield (entry 6). Functional groups, such as trimethylsilyl and acetyl, were well tolerated (entries 7, 8). The reaction with bulky *ortho*-tolylboronic acid (**5l**) was improved by the use of PEPPSI-IPr as the catalyst (entry 9). Notably, heteroaryl moieties, such as 3-thienyl, 3-furyl, and 3-pyridyl substituents, could also be installed in good to moderate yields (entries 10–12).

After the third arylation had been demonstrated with diphenyl substrate **4aa**, we examined the synthesis of

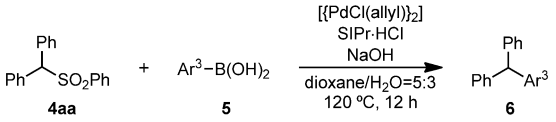
Table 4: Optimization of the Pd-catalyzed arylation of **4aa** with *p*-tolylboronic acid (**5b**).[a]



Entry	Ligand (mol%)	Base	Solvent	**6aab**[b] [%]
1	PPh_3 (20)	LiO*t*Bu	dioxane	<1%
2	XPhos (20)	LiO*t*Bu	dioxane	<1%
3	$P(tBu)_3{\cdot}HBF_4$ (20)	LiO*t*Bu	dioxane	<1%
4	dppe (10)	LiO*t*Bu	dioxane	<1%
5	dppf (10)	LiO*t*Bu	dioxane	<1%
6	2,2′-bpy (10)	LiO*t*Bu	dioxane	<1%
7	SIPr·HCl (10)	LiO*t*Bu	dioxane	49%
8	SIPr·HCl (10)	K_3PO_4	dioxane	46%
9	IMes·HCl (10)	K_3PO_4	dioxane	23%
10	$ICy{\cdot}HBF_4$ (10)	K_3PO_4	dioxane	8%
11	$IAd{\cdot}HBF_4$ (10)	K_3PO_4	dioxane	<1%
12	SIPr·HCl (10)	NaOH	dioxane/H_2O = 10:3	69%
13[c]	SIPr·HCl (10)	NaOH	dioxane/H_2O = 5:3	93%
14[c,d]	SIPr·HCl (10)	NaOH	dioxane/H_2O = 5:3	92% (85%)[e]
15[c,d]	PEPPSI-IPr	NaOH	dioxane/H_2O = 5:3	91%
16[c,d,f]	SIPr·HCl (10)	NaOH	dioxane/H_2O = 5:3	93%

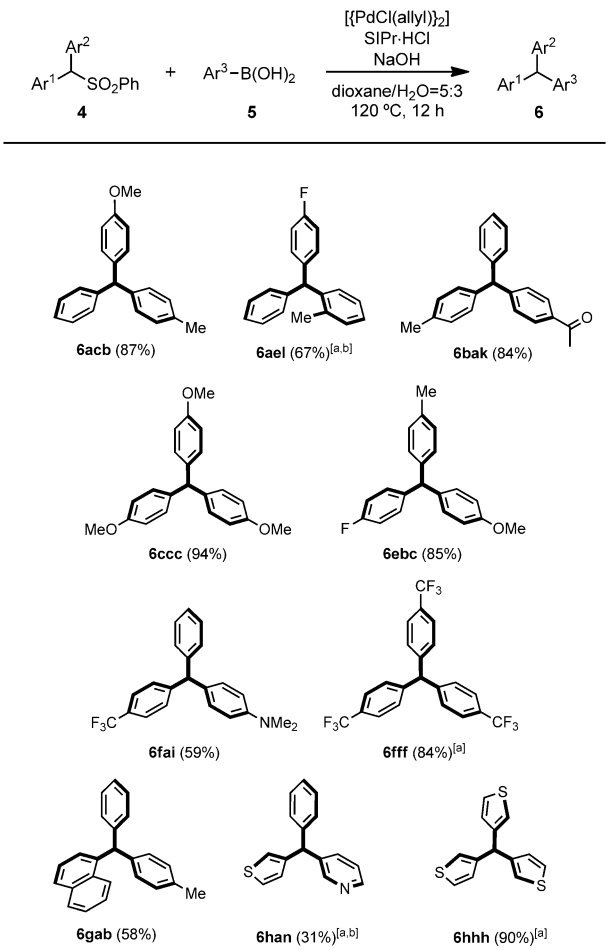
[a] Conditions: **4aa** (1 equiv), **5b** (3 equiv), [{PdCl(allyl)}$_2$] (10 mol%), ligand, base (3 equiv), solvent (0.1 M), 120 °C, 12 h. [b] Yield determined by GC analysis using dodecane as the internal standard. [c] Concentration: 0.13 M. [d] **5b** (2 equiv). [e] Yield of isolated product given in parentheses. [f] The pinacol ester of *p*-tolylboronic acid (2 equiv) was used. 2,2′-bpy = 2,2′-bipyridine, dppe = 1,2-bis(diphenylphosphino)-ethane, dppf = diphenylphosphinoferrocene, IAd = 1,3-di(adamantyl) imidazol-2-ylidene, ICy = *N*,*N*′-(dicyclohexyl) imidazol-2-ylidene, IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene, SIPr = *N*,*N*′-bis(2,6-(diisopropyl)phenyl)imidazolin-2-ylidine, PEPPSI-IPr = [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

Table 5: Scope of the arylation of **4aa** with aryl boronic acid **5**.[a]



Entry	Ar^3	**6**	Yield[b] [%]
1	C_6H_5 (**5a**)	**6aaa**	90
2	*p*-MeC_6H_4 (**5b**)	**6aab**	85
3	*p*-$MeOC_6H_4$ (**5c**)	**6aac**	92
4	*p*-$Me_2NC_6H_4$ (**5i**)	**6aai**	88
5	*p*-FC_6H_4 (**5e**)	**6aae**	89
6[c]	*p*-$CF_3C_6H_4$ (**5f**)	**6aaf**	83
7	*p*-$TMSC_6H_4$ (**5j**)	**6aaj**	80
8	*p*-AcC_6H_4 (**5k**)	**6aak**	82
9[c,d]	*o*-MeC_6H_4 (**5l**)	**6aal**	60
10[c]	3-thienyl (**5h**)	**6aah**	70
11[c]	3-furyl (**5m**)	**6aam**	52
12[c]	3-pyridyl (**5n**)	**6aan**	45

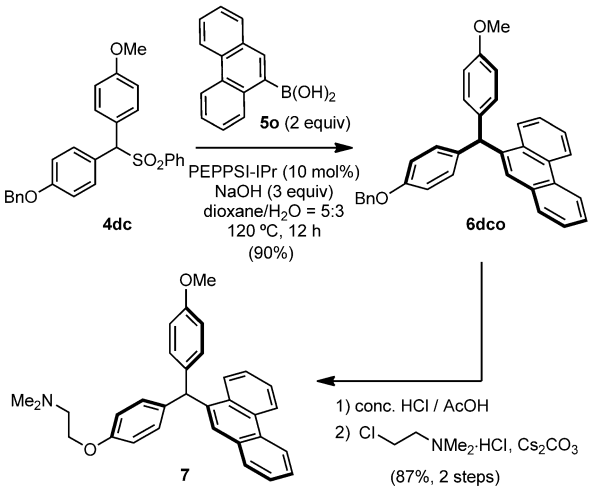
[a] Conditions: **4aa** (1 equiv), **5** (2 equiv), [{PdCl(allyl)}$_2$] (5 mol%), SIPr·HCl (10 mol%), NaOH (3 equiv), dioxane/H_2O = 5:3, 120 °C, 12 h. [b] Yields of isolated products. [c] Reaction conducted at 150 °C. [d] PEPPSI-IPr (10 mol%) was used as the catalyst. TMS = trimethylsilyl.



Scheme 2. Synthesis of unsymmetric triarylmethanes by Pd-catalyzed arylative desulfonylation. Conditions: **4** (1 equiv), **5** (2 equiv), [{PdCl(allyl)}$_2$] (5 mol%), SIPr·HCl (10 mol%), NaOH (3 equiv), dioxane/H_2O = 5:3, 120 °C, 12 h. [a] Reaction conducted at 150 °C. [b] PEPPSI-IPr (10%) was used as the catalyst.

unsymmetric triarylmethanes (Scheme 2). Electronically and structurally diverse triarylmethanes can be prepared in good to excellent yields using this simple and straightforward procedure. Importantly, triarylmethanes that possess thienyl, furyl, or pyridyl groups, which are difficult to install using typical Friedel–Crafts reaction conditions, were readily prepared. The structure of tris(3-thienyl)methane **6hhh** was confirmed by single-crystal X-ray diffraction analysis (for details, see the Supporting Information).

The utility of this method was demonstrated by the concise synthesis of an anti-breast-cancer agent (**7**; Scheme 3).[22] The reaction of (*para*-benzyloxyphenyl)(*para*-methoxyphenyl)methyl phenyl sulfone (**4dc**) with 9-phenanthreneboronic acid (**5o**) gave triarylmethane **6dco** in 90% yield. Removal of the benzyl group followed by alkylation gave **7** in 87% yield. Overall, compound **7** was obtained in 36% yield from **1d** in five steps. This result indicates that this method can provide facile access to biologically active compounds and can be employed to generate unique chemical libraries that are based on triarylmethanes for the screening of biologically active compounds.



Scheme 3. Synthesis of anti-breast-cancer agent **7**.

In summary, we have shown that a variety of triarylmethanes can be synthesized by Pd-catalyzed C–H arylation followed by arylative desulfonylation. This method does not only provide a new synthetic approach to multisubstituted triarylmethanes starting from readily available haloarenes and aryl boronic acids, but is also applicable to the preparation of unexplored triarylmethane-based materials and pharmaceuticals. During this study, we have developed a unique Pd-catalyzed substitution of the sulfonyl group with an aryl moiety, which could become a more general carbon–carbon bond-forming reaction. Investigations of the mechanism and the applicability of this reaction towards the syntheses of biologically active molecules are currently ongoing in our laboratory.

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[1] For reviews, see: a) D. F. Duxbury, *Chem. Rev.* **1993**, *93*, 381; b) M. S. Shchepinov, V. A. Korshun, *Chem. Soc. Rev.* **2003**, *32*, 170; c) V. Nair, S. Thomas, S. C. Mathew, K. G. Abhilash, *Tetrahedron* **2006**, *62*, 6731.

[2] a) C. D. Mason, F. F. Nord, *J. Org. Chem.* **1951**, *16*, 722; b) V. V. Ghaisas, B. J. Kane, F. F. Nord, *J. Org. Chem.* **1958**, *23*, 560; c) M. Irie, *J. Am. Chem. Soc.* **1983**, *105*, 2078; d) R. Muthyala, A. R. Katritzky, X. F. Lan, *Dyes Pigm.* **1994**, *25*, 303.

[3] For selected examples, see: a) T. Miura, Y. Urano, K. Tanaka, T. Nagano, K. Ohkubo, S. Fukuzumi, *J. Am. Chem. Soc.* **2003**, *125*, 8666; b) R. P. Haugland, *The Handbook. A Guide to Fluorescent Probes and Labeling Technologies*, 10th ed., Molecular Probes, Eugene, OR, USA, **2005**; c) Y. Urano, M. Kamiya, K. Kanada, T. Ueno, K. Hirose, T. Nagano, *J. Am. Chem. Soc.* **2005**, *127*, 4888; d) H. Abe, J. Wang, K. Furukawa, K. Oki, M. Uda, S. Tsuneda, Y. Ito, *Bioconjugate Chem.* **2008**, *19*, 1219; e) H. N. Kim, M. H. Lee, H. J. Kim, J. S. Kim, J. Yoon, *Chem. Soc. Rev.* **2008**, *37*, 1465; f) M. Beija, C. A. M. Afonso, J. M. G. Martinho, *Chem. Soc. Rev.*

2009, *38*, 2410; g) A. C. Bhasikuttan, J. Mohanty, W. M. Nau, H. Pal, *Angew. Chem.* **2007**, *119*, 4198; *Angew. Chem. Int. Ed.* **2007**, *46*, 4120.

[4] a) R. D. Bindal, J. T. Golab, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1990**, *112*, 7861; b) L. Bai, N. Masukawa, M. Yamaki, S. Takagi, *Phytochemistry* **1998**, *47*, 1637; c) C. Jin, R. G. Michetich, M. Daneshtalab, *Phytochemistry* **1999**, *50*, 505; d) K. Baba, K. Maeda, Y. Tabata, M. Doi, M. Kozawa, *Chem. Pharm. Bull.* **1988**, *36*, 2977.

[5] a) H. Jendralla, E. Granzer, B. Von Kerekjarto, R. Krause, U. Schacht, E. Baader, W. Bartman, G. Beck, A. Bergmann, K. Kesseler, G. Wess, L.-J. Chen, S. Granata, J. Herchen, H. Kleine, H. Schüssler, K. Wager, *J. Med. Chem.* **1991**, *34*, 2962; b) P. Wang, J. Kozlowski, M. Cushman, *J. Org. Chem.* **1992**, *57*, 3861; c) N. Mibu, K. Yokomizo, M. Uyeda, K. Sumoto, *Chem. Pharm. Bull.* **2003**, *51*, 1325; d) R. A. Al-Qawasmeh, Y. Lee, M.-Y. Cao, X. Gu, A. Vassilakos, J. A. Wright, A. Young, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 347; e) R. Palchaudhuri, V. Nesterenko, P. J. Hergenrother, *J. Am. Chem. Soc.* **2008**, *130*, 10274; f) M. Y. Cao, Y. Lee, N. P. Feng, R. A. Al-Qawasmeh, S. Viau, X. P. Gu, L. Lau, H. Jin, M. Wang, A. Vassilakos, J. A. Wright, A. H. Young, *J. Pharmacol. Exp. Ther.* **2004**, *308*, 538.

[6] For selected examples, see: a) J. Esquivias, R. G. Arrayás, J. C. Carretero, *Angew. Chem.* **2006**, *118*, 645; *Angew. Chem. Int. Ed.* **2006**, *45*, 629; b) P. Thirupathi, S. S. Kim, *J. Org. Chem.* **2009**, *74*, 7755; c) G. K. S. Prakash, C. Panja, A. Shakhmin, E. Shah, T. Mathew, G. A. Olah, *J. Org. Chem.* **2009**, *74*, 8659; d) S. Lin, X. Lu, *J. Org. Chem.* **2007**, *72*, 9757; e) P. Thirupathi, S. S. Kim, *Eur. J. Org. Chem.* **2010**, 1798; f) P. Thirupathi, S. S. Kim, *J. Org. Chem.* **2010**, *75*, 5240; g) P. Thirupathi, L. N. Neupane, K.-H. Lee, *Tetrahedron* **2011**, *67*, 7301.

[7] a) A. Ono, N. Suzuki, J. Kamimura, *Synthesis* **1987**, 736; b) T. J. Mizoguchi, S. J. Lippard, *J. Am. Chem. Soc.* **1998**, *120*, 11022; c) V. Gevorgyan, M. Rubin, S. Benson, J.-X. Liu, Y. Yamamoto, *J. Org. Chem.* **2000**, *65*, 6179; d) R. Rathore, C. L. Burns, I. A. Guzei, *J. Org. Chem.* **2004**, *69*, 1524; e) S. Sawadjoon, A. Lundstedt, J. S. M. Samec, *ACS Catal.* **2013**, *3*, 635.

[8] For interesting advances in Pd-catalyzed cross coupling reactions, see: a) J.-Y. Yu, R. Kuwano, *Org. Lett.* **2008**, *10*, 973; b) A. López-Pérez, J. Adrio, J. C. Carretero, *Org. Lett.* **2009**, *11*, 5514; c) L.-L. Cao, X.-N. Li, F.-Y. Meng, G.-F. Jiang, *Tetrahedron Lett.* **2012**, *53*, 3873; d) Y. Xia, F. Hu, Z. Liu, P. Qu, R. Ge, C. Ma, Y. Zhang, J. Wang, *Org. Lett.* **2013**, *15*, 1784; for metal-catalyzed C–H arylations, see: e) T. Niwa, H. Yorimitsu, K. Oshima, *Org. Lett.* **2007**, *9*, 2373; f) Y.-Z. Li, B.-J. Li, X.-Y. Lu, S. Lin, Z.-J. Shi, *Angew. Chem.* **2009**, *121*, 3875; *Angew. Chem. Int. Ed.* **2009**, *48*, 3817; g) G. I. McGrew, J. Temaismithi, P. J. Carroll, P. J. Walsh, *Angew. Chem.* **2010**, *122*, 5673; *Angew. Chem. Int. Ed.* **2010**, *49*, 5541; h) J. Zhang, A. Bellomo, A. D. Creamer, S. D. Dreher, P. J. Walsh, *J. Am. Chem. Soc.* **2012**, *134*, 13765; i) A. Bellomo, J. Zhang, N. Trongsiriwat, P. J. Walsh, *Chem. Sci.* **2013**, *4*, 849.

[9] For enantioselective routes, see: a) B. L. H. Taylor, M. R. Harris, E. R. Jarvo, *Angew. Chem.* **2012**, *124*, 7910; *Angew. Chem. Int. Ed.* **2012**, *51*, 7790; b) M. R. Harris, L. E. Hanna, M. A. Greene, C. E. Moore, E. R. Jarvo, *J. Am. Chem. Soc.* **2013**, *135*, 3303; c) Q. Zhou, H. D. Srinivas, S. Dasgupta, M. P. Watson, *J. Am. Chem. Soc.* **2013**, *135*, 3307.

[10] a) W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, N. R. Vanier, *J. Am. Chem. Soc.* **1975**, *97*, 7006; b) F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456.

[11] For transition-metal-catalyzed coupling reactions with allyl sulfones, see: a) M. Julia, A. Righini-Tapif, J.-N. Verpeaux, *Tetrahedron* **1983**, *39*, 3283; b) A. N. Kasatkin, A. N. Kulak, G. A. Tolstikov, S. I. Lomakina, *Izv. Akad. Nauk SSSR Ser. Khim.* **1988**, 2159; c) J. Clayden, M. Julia, *J. Chem. Soc. Chem. Commun.* **1994**, 1905; d) D. Seomoon, K. Lee, H. Kim, P. H. Lee, *Chem. Eur. J.* **2007**, *13*, 5197; e) J.-C. Wu, L.-B. Gong, Y. Xia, R.-J. Song, Y.-X. Xie, J.-H. Li, *Angew. Chem.* **2012**, *124*, 10047; *Angew. Chem. Int. Ed.* **2012**, *51*, 9909.

[12] For selected examples, see: a) J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, **2004**; b) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082; c) J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360; d) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234; e) J. B. Grimm, M. H. Katcher, D. J. Witter, A. B. Northrup, *J. Org. Chem.* **2007**, *72*, 8135; f) G. Zhou, P. C. Ting, R. G. Aslanian, *Tetrahedron Lett.* **2010**, *51*, 939.

[13] B. Zheng, T. Jia, P. J. Walsh, *Org. Lett.* **2013**, *15*, 1690.

[14] Zhou et al. employed similar conditions, but required LiHMDS and stoichiometric Zn salts; see Ref. [12f].

[15] The yield of the reaction severely decreased (from 92% to 10%) when KBF_4 was added to a reaction promoted by LiO*t*Bu. The special reactivity of LiO*t*Bu in comparison to other salts, including KO*t*Bu, is documented for C–H arylations; see: T. Yamamoto, K. Muto, M. Komiyama, J. Canivet, J. Yamaguchi, K. Itami, *Chem. Eur. J.* **2011**, *17*, 10113. This observation may arise from different levels of ion separation in the potassium and lithium enolates. For a discussion of counterion effects on transmetallation, see: C. Amatore, A. Jutand, G. Le Duc, *Chem. Eur. J.* **2012**, *18*, 6616 – 6625.

[16] The aryl bromide was completely consumed at the end of the reaction, and few byproducts were observed, except, on occasion, biphenyl.

[17] H. Yorimitsu, K. Oshima, *Tetrahedron* **2009**, *65*, 1971.

[18] Traces of the aryl iodide are observed at the end of the reaction, and neither reduction of the aryl halide nor the formation of biaryl byproducts were observed under optimized conditions. The reaction is sensitive to heat; when the reaction was conducted at 100 °C, the yield decreased from 86% to 66%.

[19] Although Pd-catalyzed C–SO_2 bond arylation using aryl boronic acids has been reported (Ref. [8c]), substrates are limited to sulfones that bear a 3-indolyl substituent on the methyl group to assist the elimination of the sulfonyl group. The reaction that we have developed proceeds without these electron-rich aryl substituents and is therefore likely to proceed through a different mechanism.

[20] a) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749; b) C. J. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Eur. J. Org. Chem.* **2010**, 4343.

[21] At the end of the reaction, the sulfone was completely converted, and 19% of 4,4′-dimethylbiphenyl (derived from $ArB(OH)_2$) was observed by GC even under optimized conditions.

[22] Shagufta, A. K. Srivastava, R. Sharma, R. Mishra, A. K. Balapure, P. S. R. Murthy, G. Panda, *Bioorg. Med. Chem.* **2006**, *14*, 1497.

