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The Concise Synthesis of Unsymmetric Triarylacetonitriles via Pd-Catalyzed Sequential Arylation: A New Synthetic Approach to Tri- and Tetraarylmethanes

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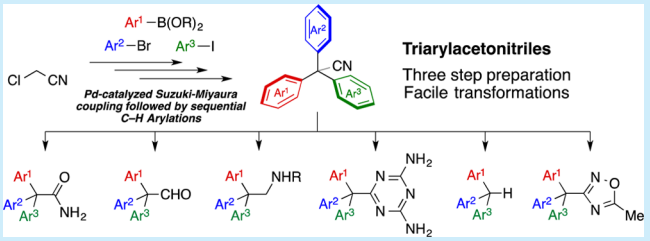
Supporting Information

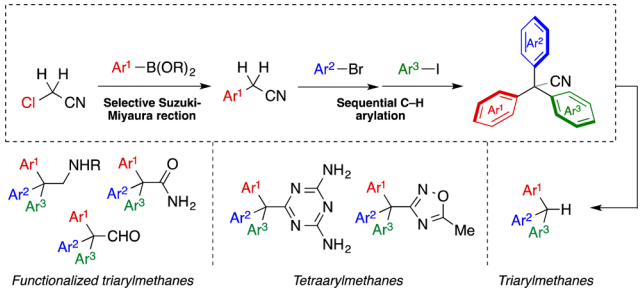
ABSTRACT: The selective synthesis of multiarylated acetonitriles via sequential palladium-catalyzed arylations of chloroacetonitrile is reported. The three aryl groups are installed via a Pd-catalyzed Suzuki–Miyaura cross coupling reaction followed by back-to-back C–H arylations to afford triarylacetonitriles in three steps with no over-arylation at any step. The triarylacetonitrile products can be converted into highly functionalized species including tetraarylmethanes. This new strategy provides rapid access to a variety of unsymmetrical tri- and tetraarylmethane derivatives from simple, readily available starting materials.



The triarylmethane motif is a privileged structure in functional materials[1] including organic dyes,[2] fluorescent probes for bioimaging,[3] and sensors for metal ions.[4] This substructure is finding new applications in medicinal chemistry including as antitubercular and anticancer agents,[5] and potassium ion channel blockers,[6] making versatile, modular routes to these species increasingly important.

As a part of our program aiming at establishing practical methods for the synthesis of multiply arylated methane derivatives,[7] we describe herein a straightforward and modular synthesis of privileged triarylacetonitrile structures using chloroacetonitrile as a simple and readily available template.[8] Three different aryl groups are introduced via an initial Pd-catalyzed Suzuki–Miyaura coupling followed by sequential and selective C–H arylations (Scheme 1). The newly established protocol is very different from classical triarylmethane syntheses, which typically employ the Friedel–Crafts reaction.[9] This approach is typically restricted to electron-rich aromatics, and suffers from regioselectivity issues. Our method permits the introduction of three distinct aryl groups without over-arylation, and the reaction is applicable to a range of aromatic substituents including electron-neutral and -poor substrates. Importantly, the nitrile group can be converted into various functional groups, providing access to a number of untapped, densely functionalized molecules of significant interest. For example, unsymmetrical tetraarylmethanes, which are exceptionally difficult to make by other routes, can be synthesized in 1–2 steps from the triarylacetonitrile products. Conditions were also developed to remove the nitrile, providing a viable route to the parent triarylmethanes (Scheme 1).

Scheme 1. Synthesis of Triarylacetonitriles and Derivatives via Pd-Catalyzed Sequential Arylation and Transformations



The transition-metal-catalyzed arylation of acidic sp^3 C–H bonds α to electron-withdrawing substituents has proven to be a very effective method for the introduction of one or two aryl groups.[10] Although these reactions are highly effective and have broad scope, the introduction of three aryl groups is unprecedented, likely due to steric constraints in the last arylation.[11] Thus, acetonitrile attracted our attention as an interesting potential building block. However, it became quickly obvious that the small size and high activating power of the nitrile was problematic, since diarylation products were always observed,[12] which would be problematic in the synthesis of completely unsymmetrical triarylacetonitriles.[13]

Chloroacetonitrile thus became our preferred starting material in order to avoid C–H arylation at the first step and then rely on steric effects to prevent over-arylation in subsequent C–H functionalizations.[14] For the Suzuki–Miyaura coupling of phenylboronic acid with chloroacetonitrile, we found that

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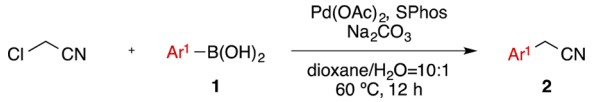
$Pd(OAc)_2$ and SPhos along with aqueous Na_2CO_3 provided monoaryl acetonitriles **2** in good to excellent yields. The more expensive bromoacetonitrile gave the desired product in lower yield (22%) under these conditions. Pinacol esters and trifluoroborate salts could be employed giving approximately the same yield (see Supporting Information).

The scope of this reaction is summarized in Table 1. Electron-rich *p*-tolyl- and *p*-anisylboronic acids (**1b** and **c**) give the

Table 1. Scope of First Pd-Catalyzed Arylation of Chloroacetonitrile with Arylboronic Acids 1[a]

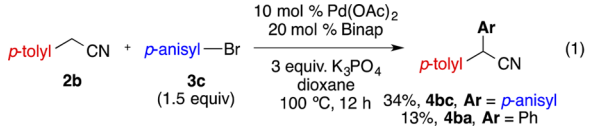


entry	Ar^1	2	yield[b] (%)
1	C_6H_5 (**1a**)	**2a**	85
2	*p*-MeC_6H_4 (**1b**)	**2b**	85
3	*p*-$MeOC_6H_4$ (**1c**)	**2c**	81
4	*p*-FC_6H_4 (**1d**)	**2d**	80
5[c]	*p*-$CF_3C_6H_4$ (**1e**)	**2e**	84
6	*p*-$MeO_2CC_6H_4$ (**1f**)	**2f**	87
7	*p*-$BocNHC_6H_4$ (**1g**)	**2g**	53
8[c]	*p*-$NO_2C_6H_4$ (**1h**)	**2h**	65
9	1-naphthyl (**1i**)	**2i**	93
10	*o*-MeC_6H_4 (**1j**)	**2j**	89
11[c]	3-thienyl (**1k**)	**2k**	53
12	4-pyridyl (**1l**)	**2l**	<1

[a]Conditions: chloroacetonitrile (1 equiv), $Ar^1B(OH)_2$ (1.5 equiv), $Pd(OAc)_2$ (2.5 mol %), SPhos (5 mol %), Na_2CO_3 (1.5 equiv), dioxane/H_2O = 10:1, 60 °C, 12 h. [b]Isolated yield. [c]100 °C

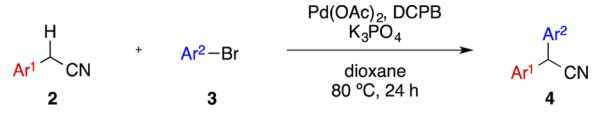
expected monoarylation products in good yields (entries 2 and 3). Although arylboronic acids bearing electron-withdrawing groups are less efficient, reasonable yields can be obtained at moderately higher reaction temperatures (entries 5, 8, and 10). Ester and *N*-Boc-amino groups are also well tolerated. Bulky 1-naphthylboronic acid (**1i**) and *o*-methylphenylboronic acid (**1j**) provide the desired products in excellent yields (entries 9, 10). Heteroaromatic substituents such as the 3-theinyl group (**1k**) can be introduced, albeit in slightly lower yield, however, 4-pyridineboronic acid (**1l**) did not give desired coupling product (entry 12).

The second C–H arylation[12,15] was carried out using a modified literature condition.[12a] Using bromobenzene as the electrophilic component, $Pd(OAc)_2$, *rac*-BINAP, and K_3PO_4 in dioxane emerged as the best conditions. However, when bromo*arenes* were employed instead of bromo*benzene*, it became rapidly obvious that BINAP-derived phenyl groups were being incorporated into the final product.[16] For example, when attempting to introduce a *p*-methoxylphenyl substituent during arylation of *p*-tolylacetonitrile (**2b**), the corresponding phenylated compound **4ba** was detected in 13% yield (eq 1).[16]



In order to avoid this side reaction, a variety of ligands were screened, and 2,2′-bis(dicyclohexylphosphino)-1,1′-biphenyl (DCPB) emerged as the best. This ligand could be easily handled in air and is commercially available or easily prepared (see Supporting Information). Using DCPB under optimized conditions, as shown in Table 2, aryl groups having electron-

Table 2. Second C–H Arylation of Arylacetonitriles 2[a]



entry	Ar^1	Ar^2	4	yield[b] (%)
1	C_6H_5 (**2a**)	C_6H_5 (**3a**)	**4aa**	89
2	C_6H_5 (**2a**)	*p*-$MeOC_6H_4$ (**3c**)	**4ac**	84
3	C_6H_5 (**2a**)	*p*-FC_6H_4 (**3d**)	**4ad**	74
4	*p*-MeC_6H_4 (**2b**)	C_6H_5 (**3a**)	**4ba**	76
5	*p*-MeC_6H_4 (**2b**)	*p*-$MeOC_6H_4$ (**3c**)	**4bc**	91
6[c]	*p*-MeC_6H_4 (**2b**)	*p*-$CF_3C_6H_4$ (**3e**)	**4be**	43
7	*p*-$MeOC_6H_4$ (**2c**)	*p*-$MeOC_6H_4$ (**3c**)	**4cc**	80
8	*p*-FC_6H_4 (**2d**)	3-thienyl (**3k**)	**4dk**	66
9[c,d]	*p*-$CF_3C_6H_4$ (**2e**)	C_6H_5 (**3a**)	**4ea**	41
10	*p*-$MeO_2CC_6H_4$ (**2f**)	*p*-MeC_6H_4 (**3b**)	**4fb**	66
11	3-thienyl (**2k**)	C_6H_5 (**3a**)	**4ka**	75

[a]Conditions: arylacetonitrile (1 equiv), Ar^2Br (1.5 equiv), $Pd(OAc)_2$ (5 mol %), DCPB (10 mol %), K_3PO_4 (3 equiv), dioxane, 80 °C, 24 h. [b]Isolated yield. [c]10 mol % catalyst was used. [d]Reaction conducted at 100 °C for 12 h.

donating or -withdrawing substituents can be installed in good to excellent yields (entries 1–4, 5, 7). Sensitive functional groups such as methoxylcarbonyl were tolerated (entry 10). Electron-withdrawing substituents such as CF_3 resulted in decreased yields (entries 6 and 9) while thiophene rings were tolerated in the nitrile or bromide component (entries 8, 11).

Using $Pd(OAc)_2$ and Cs_2CO_3 in dioxane, we investigated the effect on the the critical third and final arylation of diphenylacetonitrile (**4aa**) (see Supporting Information). Typical mono- and bidentate arylphosphines, amines, and *N*-heterocyclic carbenes were all inactive. Although the use of PCy_3 as a ligand gave no observable product, $P(t\text{-}Bu)_3$ afforded the desired triphenylacetonitrile (**6aaa**) in 94% isolated yield (Table 3, entry 1). Remarkably, replacing one *tert*-butyl group on the phosphine with a methyl or 2-biphenyl group shut down the reaction completely. The use of Cs_2CO_3 was also critical for this reaction, as other carbonates or related Cs bases such as CsOAc and CsF gave virtually no product. Although the precise reason for this effect is unclear, the Cs cation may stabilize the enolate form of the diarylacetonitrile prior to transmetalation. Bromobenzene gave comparable reactivity (90%), but chlorobenzene was poorer (58%).

With reaction conditions optimized, we examined the scope of the reaction (Table 3). Aryl groups having electron-donating or -withdrawing substituents can be installed in good to excellent yields (entries 1–6). The structurally hindered *o*-iodotoluene also afforded the product without loss of reactivity (entry 7). In addition, sensitive functional groups such as methoxylcarbonyl and formyl groups were compatible (entries 8 and 9). Electron-withdrawing substituents such as CF_3 were well tolerated, as were heteroaromatic groups such as 5-*N*-methylindolyl and 4-pyridyl groups, with only 3-thienyl giving reduced yields (entry 10). As shown in Figure 1, this method could be applied to the synthesis of entirely unsymmetrical triarylacetonitriles with a large variety of substituents in good to excellent yields.

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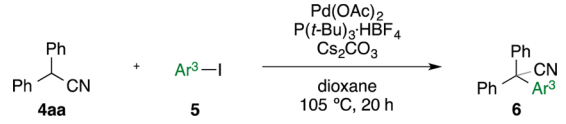
Table 3. Scope of Third Arylation of 4aa with Iodoarenes 5[a]



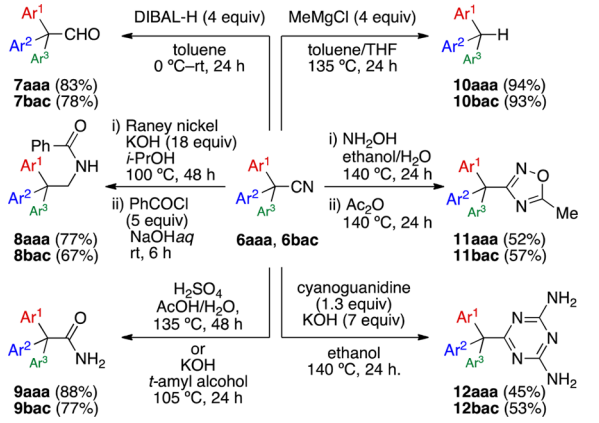
entry	Ar^3	6	yield[b] (%)
1	C_6H_6 (**5a**)	**6aaa**	94
2	*p*-MeC_6H_4 (**5b**)	**6aab**	91
3	*p*-$MeOC_6H_4$ (**5c**)	**6aac**	93
4[c]	*p*-$Me_2NC_6H_4$ (**5o**)	**6aao**	89
5	*p*-FC_6H_4 (**5d**)	**6aad**	82
6	*p*-$CF_3C_6H_4$ (**5e**)	**6aae**	88
7	*o*-MeC_6H_4 (**5j**)	**6aaj**	73
8	*p*-$MeO_2CC_6H_4$ (**5f**)	**6aaf**	91
9	*p*-formylC_6H_4 (**5m**)	**6aam**	86
10	3-thienyl (**5k**)	**6aak**	43
11[c]	*N*-methyl-5-indolyl (**5n**)	**6aan**	83
12	4-pyridyl (**5l**)	**6aal**	77

[a]Conditions: diphenylacetonitrile **4aa** (1 equiv), iodoarene **5** (1.5 equiv), $Pd(OAc)_2$(10 mol %), P(*t*-Bu)$_3$·HBF_4 (30 mol %), Cs_2CO_3 (2 equiv), dioxane (0.5 M), 105 °C, 20 h. [b]Isolated yield. [c]Aryl bromide was used as a coupling partner.

Finally, we explored the reactivity of the nitrile functionality. As shown in Scheme 2, treatment of either triphenylacetonitrile (**6aaa**) or (*p*-methoxyphenyl)(*p*-methylphenyl)phenyl-acetonitrile (**6bac**) with DIBAL-H afforded the corresponding triarylated acetaldehydes **7** in ca. 80% yields. Reduction with Raney Ni followed by reaction with benzoyl chloride gave amides **8aaa** and **8bac** in good yields, and acidic or basic hydrolysis gave triarylacetamides **9aaa** and **9bac** in high yields.[12f]

In addition to these transformations, treatment with MeMgCl at elevated temperature removed the cyano group yielding triarylmethane derivatives **10aaa** and **10bac** in excellent yields (94% and 93%).[17] This provides an interesting and still concise synthesis of the parent triarylmethanes. Finally the nitrile functional group can be converted into heteroaromatics, resulting in a remarkably concise synthesis of tetraarylmethane derivatives **11aaa**, **11bac**, **12aaa**, and **12bac**.

Scheme 2. Transformations of Triarylacetonitriles 6



In summary, we have established a facile and modular synthesis of unsymmetric triarylacetonitriles from chloroacetonitrile through sequential Pd-catalyzed arylation reactions. This method enables the selective introduction of three different aryl groups using readily available arylboronic acids and aryl halides. The triarylacetonitrile products can be transformed into a wide array of compounds including aldehydes, amines, amides, triarylmethanes, and tetraarylmethanes, which are of interest in medicinal chemistry and materials science.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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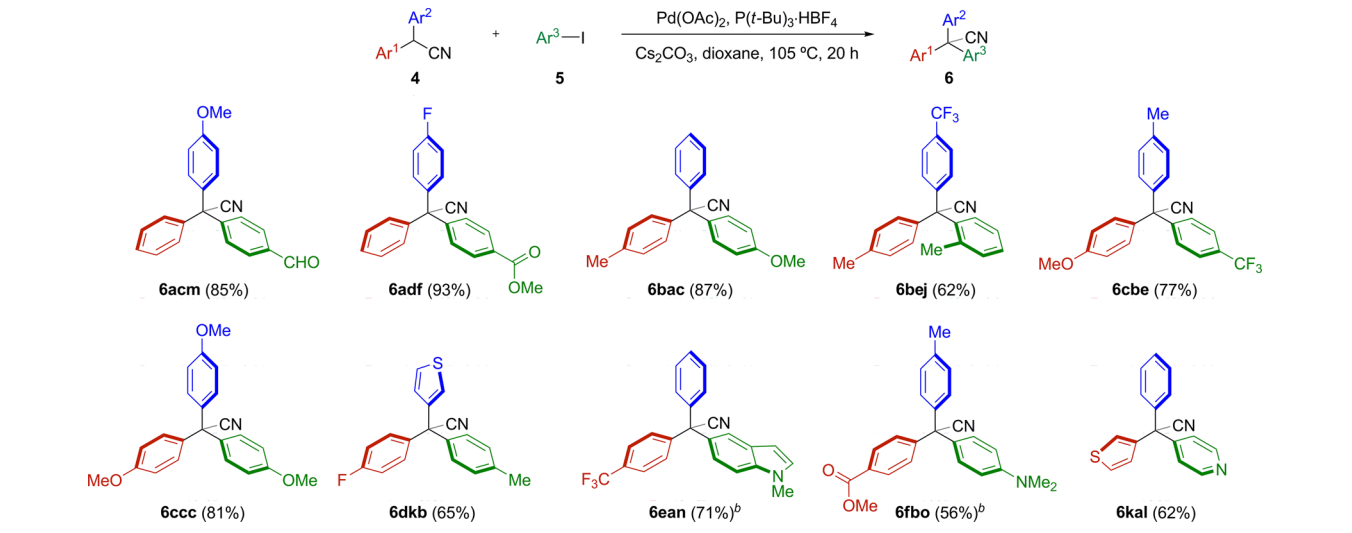

Figure 1. Synthesis of triarylacetonitriles **6**. Conditions: diarylacetonitrile **4** (1 equiv), iodoarene **5** (1.5 equiv), $Pd(OAc)_2$ (10 mol %), P(*t*-Bu)$_3$·HBF_4 (30 mol %), Cs_2CO_3 (2 equiv), dioxane (0.5 M), 105 °C, 20 h. The number in parentheses is the isolated yield. For **6ean** and **6fbo**, the corresponding aryl bromide was used as a coupling partner.

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Notes

The authors declare no competing financial interest.

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