Arylations with Nitroarenes for One-Pot Syntheses of Triarylmethanols and Tetraarylmethanes

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ABSTRACT: Triarylmethanols are well-known core structures in natural products and pharmacologically relevant compounds. In general, transition metal-based catalysts or highly reactive organometallics are employed for the synthesis of these compounds. Herein, we report the regioselective tandem C(sp^3)–H arylation/oxidation of diarylmethanes with nitroarenes to generate arylated alcohols. The present method is general, mild, green, and conducted in air at room temperature. Furthermore, use of triarylmethanes as pro-nucleophiles provides straightforward access to select tetraarylmethanes through a cross-dehydrogenative coupling process.

Triarylmethanol derivatives are well-known frameworks and are common in polymers and natural products.[1] These motifs constitute an important pharmacophore in medicinal chemistry, with applications as anticancer agents,[2] HIV inhibitors,[3] Ca^{2+}-activated potassium ion channel blockers,[4] HCV helicase inhibitors,[5] androgen receptor antagonists,[6] and UDP-glucuronosyltransferase inhibitors,[7] among others.[8] Traditionally, triarylmethanols are synthesized by nucleophilic addition of organolithium or Grignard reagents to benzophenone derivatives (Scheme 1A).[9] Drawbacks to this approach include the use of air- and water-sensitive preformed organometallic reagents, special handling techniques and equipment and poor chemoselectivity.

Our team has been interested in the synthesis of triarylmethanols and tetraarylmethanes by an approach involving the palladium catalyzed coupling of weakly acidic pro-nucleophiles under basic conditions.[10] Based on this idea, we recently developed a tandem arylation/oxidation of diarylmethanes for the synthesis of triarylmethanols (Scheme 1B).[11] We were also able to apply a coupling tactic to the arylation of triarylmethane derivatives to furnish tetraarylmethanes (Scheme 1C).[12] Despite the convenience of these methods, a shortcoming is the use of an expensive metal catalyst (Pd) and phosphine ligands.

The development of environmentally-friendlier and practical methods for the synthesis of triarylmethanols and tetraarylmethanes, therefore, remains in demand. Ideally, it would be best to avoid the use of transition metals. In a relevant study for the synthesis of triarylmethane intermediates, Cao and co-workers introduced a transition-metal free arylation of diarylmethanes with fluoroarenes in the presence of LDA (lithium diisopropylamide).[13] This chemistry was shown to involve benzyne intermediates and suffers from the associated difficulties with regioselective addition of nucleophiles to arynes.[14]

Recently, the use of nitroarenes has attracted significant attention as amine sources and arylating agents.[15] Nitroarenes represent one of the most versatile building blocks in organic synthesis and are easily available by nitration of the parent arenes. In 2013, Kürti and co-workers reported an impressive transition metal-free cross-dehydrogenative coupling (CDC) alkylation of nitroarenes with ketone enolates under basic conditions (Scheme 2A).[16] Subsequently, several other transition metal-free CDC reactions incorporating nitroarenes as aryl electrophiles were developed by Kumar,[17] Xiao,[18] Li,[19] and the team of Ess, Kürti and Gao[20] (Scheme 2A). The nucleophiles used in these transformations were generally enolates. Arylation of non-carbonyl containing pro-nucleophiles include Xiao's arylation of heteroaryl benzylic methyl groups[18] (Scheme 2b) and two examples with 4-benzylpyridine by Ess, Kürti and Gao (Scheme 2C).[20]

Given our past efforts in metal catalyzed arylation of weakly acidic pro-nucleophiles and use of weakly acidic pro-nucleophiles under transition metal-free conditions,[21] we were attracted to the use of nitroarenes as arylating reagents. We envisioned developing straightforward approaches for the synthesis of triarylmethanols and tetraarylmethanes using nitroarene electrophiles. Herein we report a facile one-pot conversion of diarylmethanes to triarylmethanols via a tandem arylation/oxidation under mild conditions. The net transformation is a cross-dehydrogenative-coupling (CDC) arylation of diarylmethanes followed by an air oxidation of the corresponding intermediates (Scheme 2D). This method provides a convenient, simple, and environmentally benign synthetic route to triarylmethanols with excellent yields. In addition, tetraarylmethanes are also generated when triarylmethanes are employed as pro-nucleophiles, expanding the scope of this method and providing rapid access to spherical molecules.

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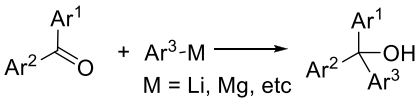
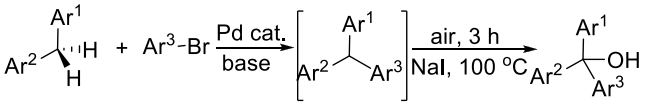
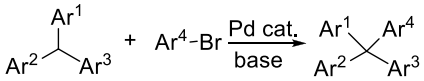
A: Classic Grignard addition approach



B: One-pot arylation/oxidation of diarylmethanes

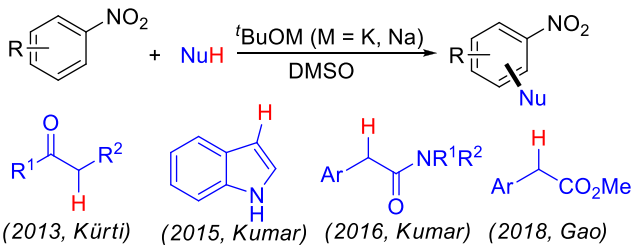


C: Arylation of triarylmethanes

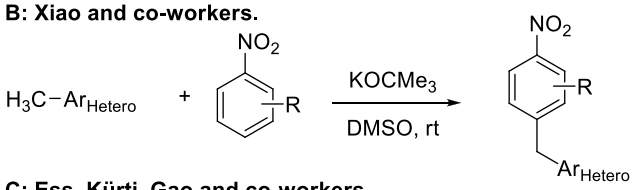


Scheme 1. Arylation reactions. A. Aryl organometallic additions to ketones to make triarylmethanols. B. Transition metal catalyzed arylation/oxidation of diarylmethanes to afford triarylmethanols. C. Pd-catalyzed arylation of triarylmethanes to give tetraarylmethanes.

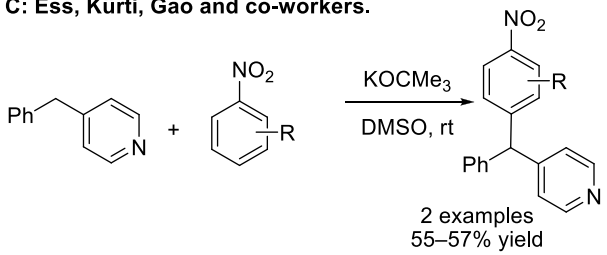
A: TM-free arylation/alkylation of nitroarenes



B: Xiao and co-workers.

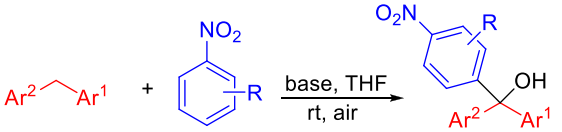


C: Ess, Kürti, Gao and co-workers.

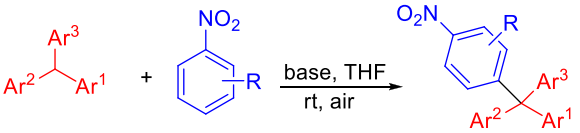


D: This Work

Base mediated tandem arylation/oxidation of diarylmethanes



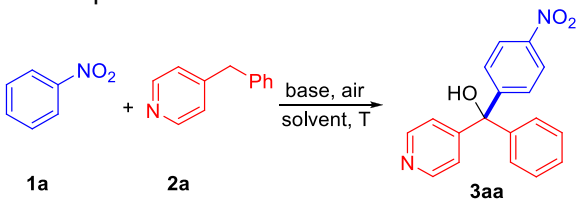
Arylation/oxidation of triarylmethanes



Scheme 2. Arylation with nitroarenes. A. Transition metal-free arylation/alkylation with nitroarenes. B. Xiao's arylation of heteroaryl benzylic methyl groups. C. Ess, Kürti, and Gao's arylation of 4-benzyl pyridine. D. This work: arylation/oxidation to form triarylmethanols and arylations to give tetraarylmethanes.

We initiated our studies of the tandem arylation/oxidation reaction using nitrobenzene (**1a**) and 4-benzylpyridine (**2a**) under air. We examined different bases [NaN(SiMe$_3$)$_2$, KN(SiMe$_3$)$_2$, LiN(SiMe$_3$)$_2$, *t*-BuOLi, *t*-BuONa, *t*-BuOK] using THF as the solvent at 60 °C for 12 h (Table 1, entries 1–6). Of the six bases screened, the silyl amide bases KN(SiMe$_3$)$_2$ and NaN(SiMe$_3$)$_2$ gave the desired product in 52% and 61% respectively. Subsequently, four solvents [THF, 1,4-dioxane, DME, and toluene] were tested in this transformation with KN(SiMe$_3$)$_2$ at 60 °C for 12 h. As shown in Table 1, the reaction in THF outperformed the other solvents by ≥ 25% yield (entries 2 vs. 7–9). Further examination of reaction temperatures indicated that room temperature was most appropriate, affording the triarylmethanol product in 82% yield. The excess amount of base is crucial in this reaction. When 2 equiv. of KN(SiMe$_3$)$_2$ were employed, the triarylmethanol product was produced in 41% yield, whereas only 26% yield was obtained with an equivalent KN(SiMe$_3$)$_2$. Finally, Kürti and Kumar's optimal reaction conditions were employed in this transformation and the target product was furnished in 52–59% yield (entries 16 and 17).

Table 1. Optimization of the reaction conditions[a]



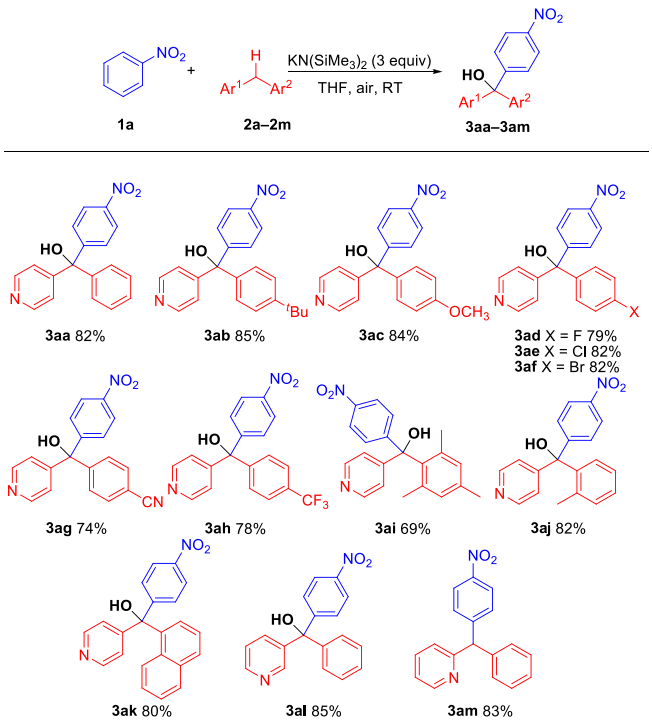
entry	solvent	base	temp (°C)	yield[b] (%)
1	THF	NaN(SiMe$_3$)$_2$	60	52
2	THF	KN(SiMe$_3$)$_2$	60	61
3	THF	LiN(SiMe$_3$)$_2$	60	NR
4	THF	LiO*t*-Bu	60	NR
5	THF	NaO*t*-Bu	60	NR
6	THF	KO*t*-Bu	60	NR
7	dioxane	KN(SiMe$_3$)$_2$	60	29
8	DME	KN(SiMe$_3$)$_2$	60	35
9	Toluene	KN(SiMe$_3$)$_2$	60	43
10	THF	KN(SiMe$_3$)$_2$	80	45
11	THF	KN(SiMe$_3$)$_2$	40	71
12	THF	KN(SiMe$_3$)$_2$	rt	82
13	THF	KN(SiMe$_3$)$_2$	0	67
14[c]	THF	KN(SiMe$_3$)$_2$	rt	41
15[d]	THF	KN(SiMe$_3$)$_2$	rt	26
16	DMSO	NaO*t*-Bu	rt	52
17	DMSO	KO*t*-Bu	rt	59

[a]Reactions were conducted on a 0.2 mmol scale using 1 equiv of **1a**, 3 equiv of base, and 1 equiv of **1a** at 0.1 M. [b]Isolated yield after chromatographic purification. [c]2 equiv of base. [d]1 equiv of base.

With the optimized conditions in hand, we next examined the scope of diarylmethanes in this arylation/oxidation tandem reaction with nitrobenzene (**1a**). As shown in Table 2, diarylmethanes bearing electronically-diverse substituents on the phenyl group afforded the desired triarylmethanols in good yields (74–85%). 4-Benzylpyridines bearing alkyl (4-*t*Bu, **3ab**, 85% yield), electron-donating (4-OMe; **3ac**, 84% yield) and electronegative or electron-withdrawing substituents (4-F, **3ad**; 4-Cl, **3ae**; 4-Br, **3af**; 4-CN, **3ag**; 4-CF_3, **3ah**) provided the desired products in 74–82% yield. Substituting the phenyl group in 4-benzylpyridine with more sterically hindered mesityl (**3ai**, 69% yield), *ortho*-tolyl (**3aj**, 82% yield), or 1-naphthyl (**3ak**, 80% yield) did not substantially impact the yield of the triarylmethanols. Furthermore, less acidic 3-benzylpyridine was also viable in this protocol, furnishing the product **3al** in 85% yield. It is noteworthy that use of 2-benzyl pyridine did not form the expected triarylmethanol product, instead giving the triarylmethane **3am** in 83% yield under the standard reaction conditions. Although the origin of this difference in reactivity is not clear, the result was reproduced several times.

To test the scalability of this protocol, we conducted the tandem reaction of nitrobenzene (**1a**) and 4-benzylpyridine (**2a**) on a 5 mmol scale. The triarylmethanol product **3aa** was isolated in 71% yield.

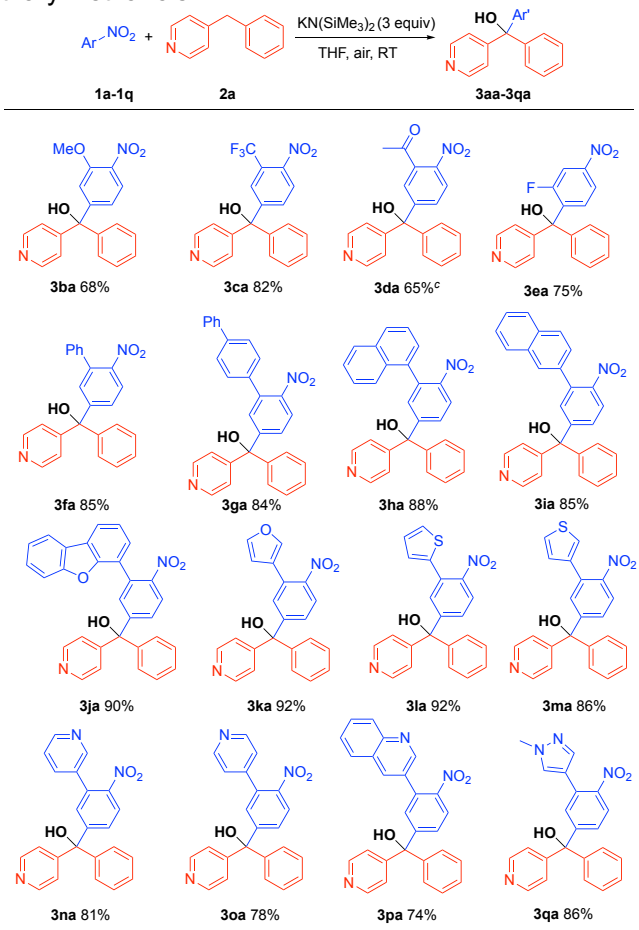
Table 2. Scope of diarylmethanes for the synthesis of triarylmethanols[a,b]



[a]Reactions were conducted on a 0.1 mmol scale using 1 equiv of **1a**, 3 equiv of $KN(SiMe_3)_2$, and 1 equiv of diarylmethanes at 0.1 M. [b]Isolated yield after chromatographic purification. [c]Reaction conducted on 5 mmol scale.

Next, we set out to determine the generality of nitroarenes in the tandem reaction of 4-benzylpyridine (**2a**) with $KN(SiMe_3)_2$ (Table 3) Nitroarenes bearing electronically-diverse substituents (2-OMe, 2-CF_3, 2-Ac, and 3-F) afforded the desired triarylmethanols (**3ba**, **3ca**, **3da**, **3ea**) in 65–82% yield. Nitroarenes possessing phenyl, biphenyl, 1-naphthyl, and 2-naphthyl groups provided **3fa**–**3ia** in 84–88% yield. Notably, nitroarenes bearing heterocyclic groups, such as dibenzofuran (**3ja**), furan (**3ka**), thiofuran (**3la**, **3ma**), pyridine (**3na**, **3oa**), quinoline (**3pa**), and pyrazole (**3qa**) were all well-tolerated in this transformation, giving the product with diverse functional groups in 74–92% yield.

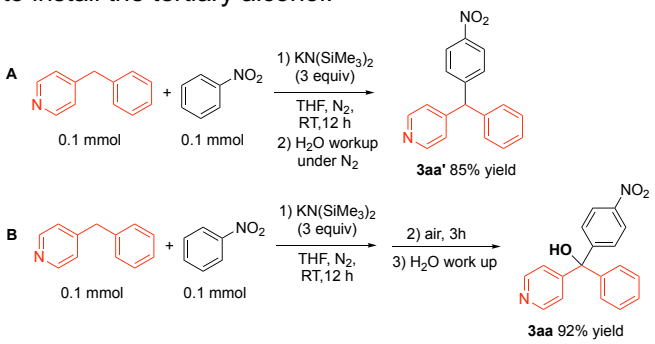
Table 3. Scope of nitroarenes for the synthesis of triarylmethanols[a,b]



[a]Reactions were conducted on a 0.1 mmol scale using 1 equiv of nitroarene, 3 equiv of $KN(SiMe_3)_2$, and 1 equiv of **2a** at 0.1 M. [b]Isolated yield after chromatographic purification.[c]3 equiv of $LiN(SiMe_3)_2$ instead of $KN(SiMe_3)_2$

A few control experiments were performed to better understand the reaction. To probe the role of air in the tandem process, two reactions were initiated under N_2 in the absence of air. The first reaction under N_2 was conducted under otherwise standard conditions and quenched with water under N_2 after 12 h at rt. In this case, triarylmethane **3aa'** was isolated in 85% yield (Scheme 3A, top). The second reaction was likewise

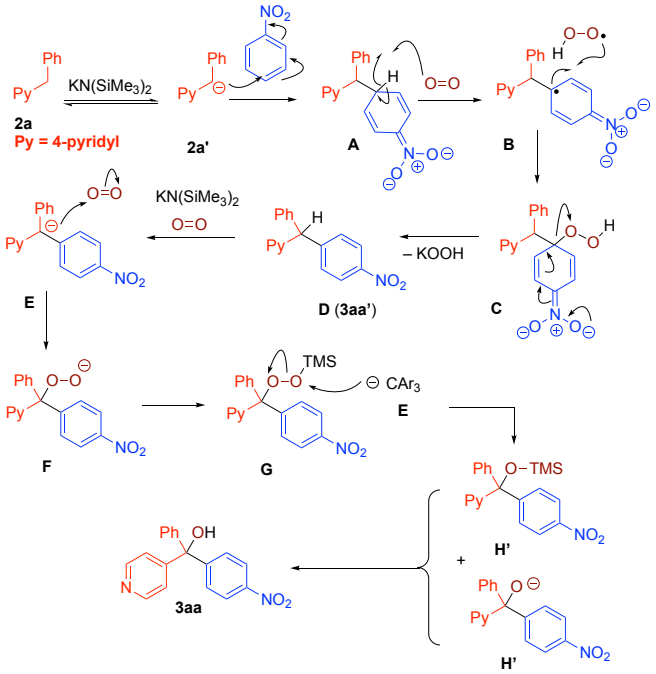
conducted under N_2 for 12 h, then removed from the glove box and exposed to air for 3 h. This reaction led to the oxidation product **3aa** in 92% yield (Scheme 3B). These results indicate that the deprotonation and addition to the nitroarene take place under N_2 or air and that the dioxygen in air is responsible for the oxidation to install the tertiary alcohol.



Scheme 3. Control experiments

Based on our control experiments, literature precedence (especially the calculations performed by Ess and Kürti),[16] and our past experience in reactions of organometallic reagents with dioxygen,[22] a plausible pathway is outlined in Scheme 4. We envisioned that 4-benzylpyridine is deprotonated by $KN(SiMe_3)_2$ and the deprotonated pronucleophile **2a'** attacks the *para*-position of nitrobenzene to furnish the resonance stabilized pentadienyl intermediate **A**. Intermediate **A** reacts with dioxygen via hydrogen atom transfer (HAT) to generate an organic radical and hydroperoxyl radical. Radical-radical coupling is proposed to give the hydroperoxide **C**. Hydroperoxide intermediate **C** undergoes HOO^- elimination to form triarylmethane **D**. Intermediate **D**, or specifically **3aa'** in the case of Scheme 3A, was observed when the reaction was conducted under a nitrogen atmosphere and quenched with water in the absence of dioxygen. It is proposed that after addition of water, intermediate **A** reacts with dioxygen to give **D**, but further deprotonation/oxidation is not possible because the base has been quenched.

When the reaction is conducted under oxygen in the presence of excess $KN(SiMe_3)_2$, triarylmethane **D** is deprotonated and the resulting carbanions **E** reacts with dioxygen to form the peroxide anion **F**. While protonation of **F** under the basic reaction conditions seems less probable, silylation by the $HN(SiMe_3)_2$ is reasonable given the oxophilicity of silicon. The resulting silylated peroxide **G** can react with triarylmethyl carbanion (**E**) to form products **H** and **H'**. Both these species would form the triarylmethanols (**3aa**) upon acidic aqueous workup. We note that at this early stage of this research, we cannot rule out single electron transfer routes between carbanion **2a'** and the nitroarene, followed by radical-radical coupling to give intermediate **A**.



Scheme 4. Proposed reaction pathway

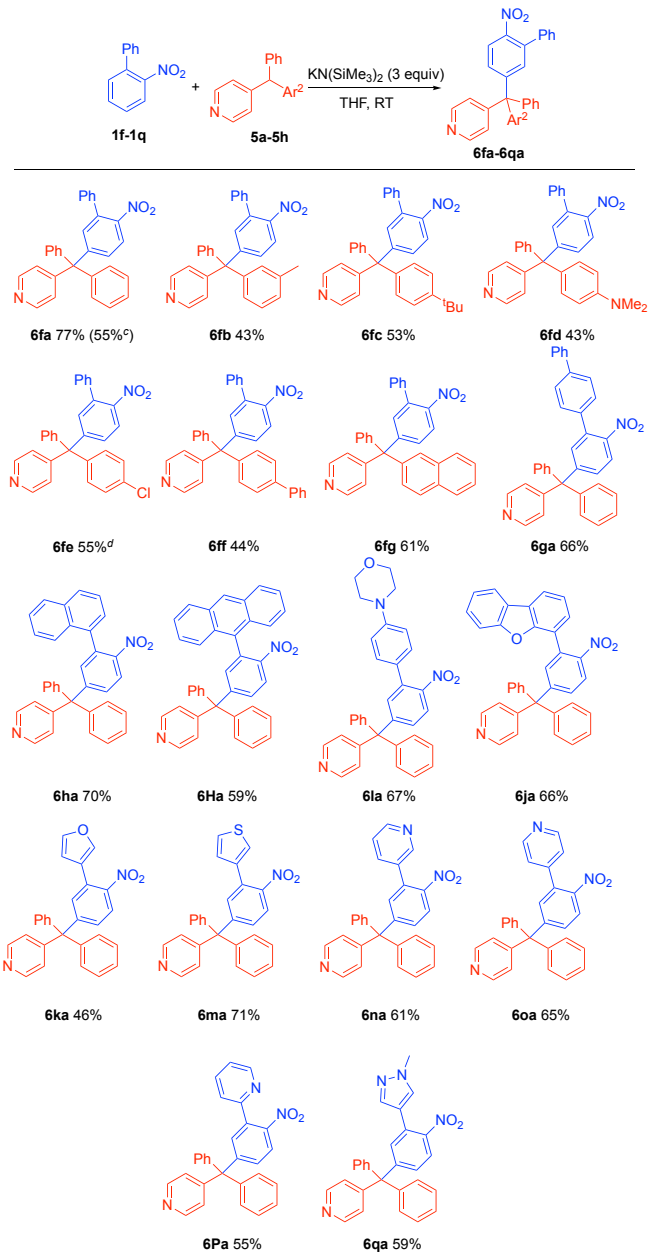
In a bid to broaden the application of this base-mediated $C(sp^3)$–H/$C(sp^2)$–H coupling reaction, triarylmethanes were next employed as substrates for the purpose of preparing tetraarylmethanes. Tetraarylmethanes are sphere-like molecules that are important building blocks with wide applications in drug delivery[23], translocation detection,[24] and molecular devices.[25] These 3-dimensional scaffolds, however, have not been greatly explored because of their long synthetic routes. Recently, we reported the use of diaryl- and triarylmethanes in palladium catalyzed cross-coupling reactions with aryl halides to generate tetraarylmethanes in good to excellent yields (Scheme 1C).[12a]

In the present investigation no transition metals are added to the reaction mixtures. As shown in Table 4, use of the same coupling reaction conditions introduced in Table 2 with 4-benzhydrylpyridine (**5a**) and 2-nitrobiphenyl provided tetraarylmethane **6fa** in 72% yield. Upon addition of an alkyl group to one of the phenyl groups in 4-benzhydrylpyridine, tetraarylmethane products were furnished in 43% (**6fb**) and 53% (**6fc**) yield. Substrates bearing electronically-diverse substituents on the phenyl group (4-OMe, 4-NMe_2, 4-Cl) were tolerated, giving the arylation products **6fd**–**6fe** in 43–55% yield. Replacement of one of the phenyl groups with biphenyl or 2-naphthyl showed similar reactivity, affording **6ff** and **6fg** in 44% and 61% yield, respectively.

The substrate scope of the nitroarene in arylation of 4-benzhydrylpyridine (**5a**) was next examined. As shown in Table 4, use of nitrobenzene derivatives with various of 2-aryl substituents [2-Ph, 2-biphenyl, 2-(α-naphthyl), or 2-(9-anthryl)] provided products **6fa**–**6ha** in 59–77% yield. The reaction using a morpholino-containing substrate furnished the product

in 67% yield (**6la**). Interestingly, heteroaryl substituents, such as in tetraarylmethanes bearing dibenzofuran (**6ja**), furan (**6ka**), and thiofuran (**6ma**) were all tolerated, furnishing products in 46–71% yield. The isomeric pyridinyl-substituted nitroarene substrates performed well in the base-mediated arylation to give the desired products in 55–65% yield (**6na**, **6oa**, **6pa**). Furthermore, 1-methyl-4-(2-nitrophenyl)-1*H*-pyrazole reacted to afford **6qa** in 59% yield. Overall, a series of tetraarylmethanes were synthesized in workable yields at room temperature without the addition of transition metal catalysts. It is noteworthy that nitro-substituted tetraarylmethanes are difficult to access through the traditional routes (Friedel-Crafts chemistry). Unfortunately, nitroarenes without a 2-aryl substituent are currently very low yielding under these reaction conditions. Efforts to understand and circumvent this limitation are underway.

Table 4. Scope of the synthesis of tetraarylmethanes[a,b]



[a]Reactions were conducted on a 0.1 mmol scale using 2 equiv of **1f**, 3 equiv of $KN(SiMe_3)_2$, and 1 equiv of triarylmethane at 0.1 M. [b]Isolated yield after chromatographic purification. [c]Reaction conducted on 5 mmol scale. [d]50 °C

To illustrate the scalability of this protocol, 5 mmol of 2-nitrobiphenyl (**1f**) was reacted with 4-benzhydrylpyridine (**5a**) and the tetraarylmethane product **6fa** was isolated in 55% yield (1.22 g). The mechanism for formation of tetraarylmethanes is likely to follow a similar reaction pathway to that in the early steps in Scheme 4.

CONCLUSION

In summary, we have developed a one-pot arylation/oxidation for the synthesis of triarylmethanols with nitroarenes. This sequence was accomplished via direct $C(sp^3)$–H/$C(sp^2)$–H coupling/oxidation tandem reaction under air and exhibits good scope. Employing triarylmethanes as pro-nucleophiles and nitroarene electrophiles, tetraarylmethanes were prepared *via* the $C(sp^3)$–H/$C(sp^2)$–H net cross-dehydrogenative coupling reaction. Tetraarylmethanes are underexplored scaffolds in medicinal chemistry, likely due to their lengthy syntheses. Compared to transition metal-catalyzed protocols, the reactions presented here are more environmentally-friendly and operationally simpler. Considering the significant role of triarylmethanols and tetraarylmethanes in various aspects of modern chemistry, we envision that this process will be of interest in chemical sciences and medicinal chemistry.

Conflict of interest

The authors declare no competing financial interest.

Acknowledgements

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