Synthesis of triarylmethanols via tandem arylation/oxidation of diarylmethanes

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Abstract

A tandem arylation/oxidation of diarylmethanes for the convenient synthesis of unsymmetrical triarylmethanols bearing different aryl and heteroaryl groups is described. A Pd(OAc)$_2$–NiXantphos catalyst system efficiently catalyzed arylation of weakly acidic sp^3-hybridized C–H bonds of diarylmethanes with aryl bromides, and the arylation products were then oxidized in situ to carbinols by simply opening the reaction flasks to air. The triarylmethanol products were obtained in 35–98% yield.

Keywords

Tandem reaction; Diarylmethanes; Synthesis; One pot; Aryl bromides

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Supplementary Material
Supplementary data associated with this article can be found, in the online version, at:

Introduction

Triarylmethanol derivatives are well-known substructures in natural products.[1] They also find widespread applications in medicinal chemistry as antiproliferative agents,[2] Ca^{2+}-activated potassium ion channel blockers,[3] UDP-glucuronosyltransferase inhibitors,[4] anticancer agents,[5] androgen receptor antagonists,[6] HIV inhibitors,[7] and HCV helicase inhibitors,[8] among others.[9] Traditional approaches toward the synthesis of unsymmetrical triarylmethanols bearing 3 different aryl groups involves nucleophilic addition of organolithium or Grignard reagents to benzophenone derivatives (Scheme 1).[10] Despite the utility of this approach, these organometallic reagents have high reactivity and limited functional group tolerance, thus rendering their use less attractive.

Results and Discussion

We recently initiated a program in the catalytic functionalization of weakly acidic sp^3-hybridized C–H bonds. The reactions involve initial reversible C–H deprotonation under basic conditions and subsequent functionalization of the deprotonated species under catalytic conditions. Based on these features, we categorize such reactions as deprotonative cross-coupling processes (DCCP). We reported DCCP of weakly acidic substrates including diarylmethanes (Scheme 2A), sulfoxides, sulfones, and amides.[11-13] Diphenylmethane (pK_a =32.3[14]) and diarylmethane derivatives were arylated at room temperature with aryl bromides in the presence of $KN(SiMe_3)_2$ as base and a palladium catalyst bearing van Leeuwen's NiXantphos ligand.[15] We envisioned a tandem arylation/oxidation protocol toward the synthesis of triarylmethanols by first using our C–H arylation method to construct the $C(sp^3)$–$C(sp^2)$ bond and then subsequent oxidation under air to forge the $C(sp^3)$–O bond (Scheme 2B).

A related tandem arylation/oxidation strategy was applied to a significantly more acidic substrate, *N*-methyloxindole (pK_a=18.5[14]) by Willis and co-workers (Scheme 3A as the sole example).[16] During the course of our work, Shao and co-workers reported the tandem arylation/oxidation of fluorene (pK_a=22.6[14]) at 120° C in the presence of a Pd(NHC)-based catalyst in moderate to good yields (53–84%, Scheme 3B). They demonstrated the use of aryl chlorides as electrophiles with fluorene derivatives.[17] Herein we report the successful tandem arylation/oxidation protocol to synthesize unsymmetrical triarylmethanols from weakly acidic diarylmethanes (pK_a up to ~30) with aryl bromides at room temperature. Compared with traditional organometallic additions (Scheme 1A), the advantages of our method are: (1) atom-economy (C–C and C–O bond formations from 2 C–H bonds), (2) use of air as the oxidant, (3) room temperature reactions, (4) avoidance of storage or handling of organometallic reagents such as organolithium and Grignard reagents, and (5) commercial availability of diarylmethanes, aryl bromides, Pd source and the ligand.

We initially evaluated the reaction of 2-benzylpyridine (**1a**, pK_a=28.2[14]) with 1-bromo-4-*tert*-butylbenzene (**2a**) under the Pd-catalyzed reaction conditions related to our previous DCCP of aryl bromides.[12a] After completion of the DCCP by TLC (12 h), the reaction flask was opened to air at room temperature for 1 h or 3 h, providing the arylation/oxidation product in 60 and 75% yield, respectively (Table 1, entries 1 and 2). Changing the limiting

reagent from aryl bromide (**2a**) to 2-benzylpyridine (**1a**) (the best conditions for arylation of diarylmethane), resulted in a slight decrease in the yield (71%, entry 3). We noticed in entry 2 that 10% hydroperoxy byproduct was formed in the reaction along with the desired triarylmethanol. To reduce the peroxide to the desired alcohol, we examined PPh$_3$[18] and NaI[19] (entries 4 and 5) and found that the addition of 5 equiv NaI, followed by stirring at 100 °C for 10 min resulted in 86% yield of **3aa** with only trace hydroperoxy byproduct. Changing the palladium loading to 2.5 mol% resulted in decreased yield (75%, entry 6). The optimized conditions in entry 5 were carried forward in the next phase, which focused on the determination of the scope of heterocycle containing diarylmethanes and aryl bromides in the tandem arylation/oxidation sequence to produce triarylmethanols.

The scope of the room temperature tandem arylation/oxidation with respect to aryl bromides was explored with isomeric 2-, 3-, and 4-benzylpyridine substrates (Table 2). 2-Benzylpyridine (**1a**) exhibited good reactivity under our conditions. Electron donating 4-*tert*-butyl bromobenzene (**2a**) reacted with (**1a**) to give **3aa** in 83% isolated yield. 3-Bromobenzotrifluoride (**2b**) and 3-bromotoluene (**2c**) furnished tertiary aryl carbinols in 72 and 78% yield, respectively. In particular, 2-bromonaphthalene was an outstanding reagent, furnishing the product alcohol **3ad** in 93% isolated yield. Sterically more demanding 1-bromonaphthalene was also tolerated, affording the product **3ae** in 67% isolated yield. 4-Benzylpyridine (pK_a=26.7[14]) and 4-*tert*-butyl bromobenzene (**2a**) were coupled, furnishing the product **3ba** in 67% isolated yield. *N*-Methyl-5-bromoindole (**2f**) was employed to give desired product **3bf** in 54% yield. 3-Benzylpyridine (**1d**), with a pK_a=30.1,[14] was a challenging substrate. After significant optimization, an elevated oxidation temperature (100 °C) was found to provide the product **3da** in only 35% yield. This substrate is the least acidic of those giving product, and represents the pK_a limit for these conditions. Diphenylmethane underwent arylation only. No oxidation products were detected.

We then turned our attention to the substrate scope of aryl bromides with fluorene (**1c**) (Table 3). The parent bromobenzene (**2g**) reacted with (**1c**) to afford the triarylmethanol **3cg** in 93% yield. Aryl bromides containing electron-donating groups, such as 4-*t*Bu, 4-OMe, and 4-NMe$_2$, exhibited good to excellent reactivity, affording the corresponding product in 96%, 73%, and 83% yield, respectively. Good yields (81–82%) were obtained using aryl bromides bearing electron-withdrawing 4-chloro (**3j**) and 4-fluoro (**3k**) groups. Trifluoromethyl and methyl groups at *meta* position furnished **3cb** and **3cc** in 81% and 98% yield, respectively. 2-Bromonaphthalene participated in the tandem arylation/oxidation to produce the desired product in excellent yield (96%). Heterocyclic 5-bromo-1-methylindole (**2f**) was also tolerated in the reaction, furnishing the desired product in 95% yield. In general, we were pleased to find an average yield of 88% with fluorene as pronucleophile and a variety of aryl bromides. It is also noteworthy that the temperature employed in Table 2 is significantly lower than those used in Scheme 3B.[17]

In summary, we have developed a one-pot tandem arylation/oxidation of diarylmethane derivatives for the convenient synthesis of triarylmethanols bearing different aryl and heteroaryl groups under mild reaction conditions. The synthesis was accomplished via a Pd(OAc)$_2$–NiXantphos catalyzed C–H arylation of diarylmethanes with aryl bromides to construct the C(sp^3)–C(sp^2) bond, followed by subsequent oxidation under air to construct

the $C(sp^3)$–O bond (35–98% yield). Our method extends the reactivity to compounds that are 10 orders of magnitude less acidic than the procedure introduced by Willis and co-workers[16a] and provides a reliable low temperature method to access fluorene-containing triarylmethanols.

Given the well-established single-step transformations to convert trityl alcohols to the corresponding trityl cations as well as conversion of the trityl alcohols' C–O–H into C–OR, C–S, C–N, C–halide (halide=F, Cl, etc.), C–alkyl, C–aryl, C–heteroaryl, and C–H's, etc.,[20] we envision the triarylmethanols obtained from our method will enable rapid access to a wide variety of trityl-containing derivatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.
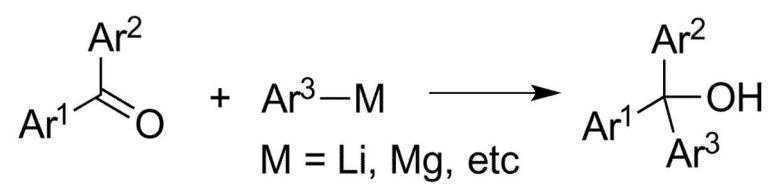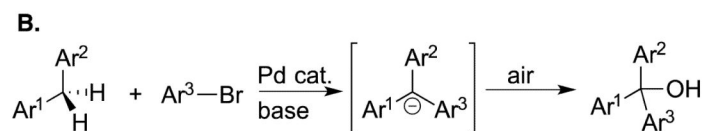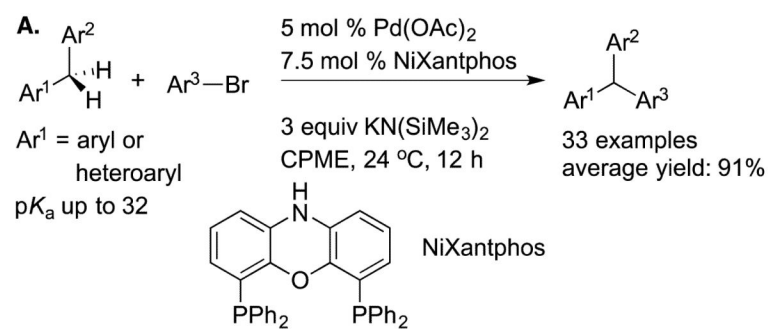
Acknowledgments

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We introduce a tandem catalytic arylation/oxidation with air as oxidant

NiXantPhos, a deprotonable ligand, is used with a palladium catalyst

This reaction is a deprotonative cross-coupling process (DCCP)

Triarylmethanols are efficiently synthesized

A carbo-alkoxylation is reported

$$Ar^1 \overset{Ar^2}{\underset{O}{\diagdown}} \quad + \quad Ar^3 - M \quad \longrightarrow \quad Ar^1 \overset{Ar^2}{\underset{Ar^3}{\diagdown}} OH$$

$$M = Li, Mg, etc$$

Scheme 1. Synthetic Approaches to Unsymmetrical Triarylmethanols

A.

Ar¹ = aryl or heteroaryl

pK_a up to 32

5 mol % Pd(OAc)$_2$
7.5 mol % NiXantphos

3 equiv KN(SiMe$_3$)$_2$
CPME, 24 °C, 12 h

33 examples
average yield: 91%

NiXantphos

B.

Scheme 2. Arylation of Diphenylmethane with Pd(NiXantphos)-based Catalyst and Tandem Arylation/Oxidation

A.

i) Ar—Br
Pd catalyst
KN(SiMe$_3$)$_2$
THF/Tol, 70 °C

ii) air

Ar = 4-C$_6$H$_4$-OMe

97% yield

B.

i) Ar—Cl
Pd catalyst
KO^{t}Bu, 120 °C

ii) air, rt, 1h

53-84% yield
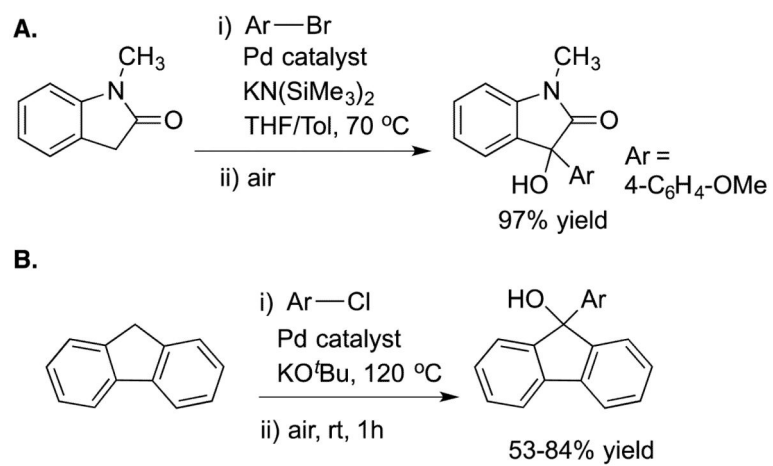
Scheme 3. Tandem Arylation/Oxidations

Table 1

Reaction Condition Screening [a]
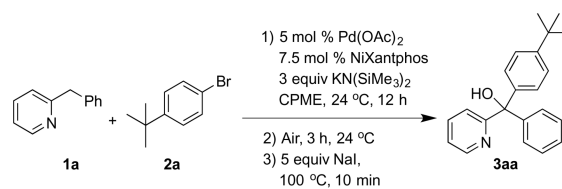
Entry	1a:2a	Oxidation condition	Reductant	Yield(%)[b]
1	1.2:1.0	Air, 1h	none	60
2	1.2:1.0	Air, 3h	none	75[c]
3	1.0:1.5	Air, 3h	none	71[c]
4	1.2:1.0	Air, 3h	PPh$_3$[d]	34
5	1.2:1.0	Air, 3h	NaI	86
6	1.2:1.0	Air, 3h	NaI	75[e]

[a] Reactions conducted on 0.1 mmol scale of (**2a**) at room temperature under nitrogen for 12 h and then the mixture was stirred under air for 3 h.

[b] Yields determined by ^{1}H NMR analysis of crude mixture with CH$_2$Br$_2$ as internal standard.

[c] 10% Hydroperoxide isolated.

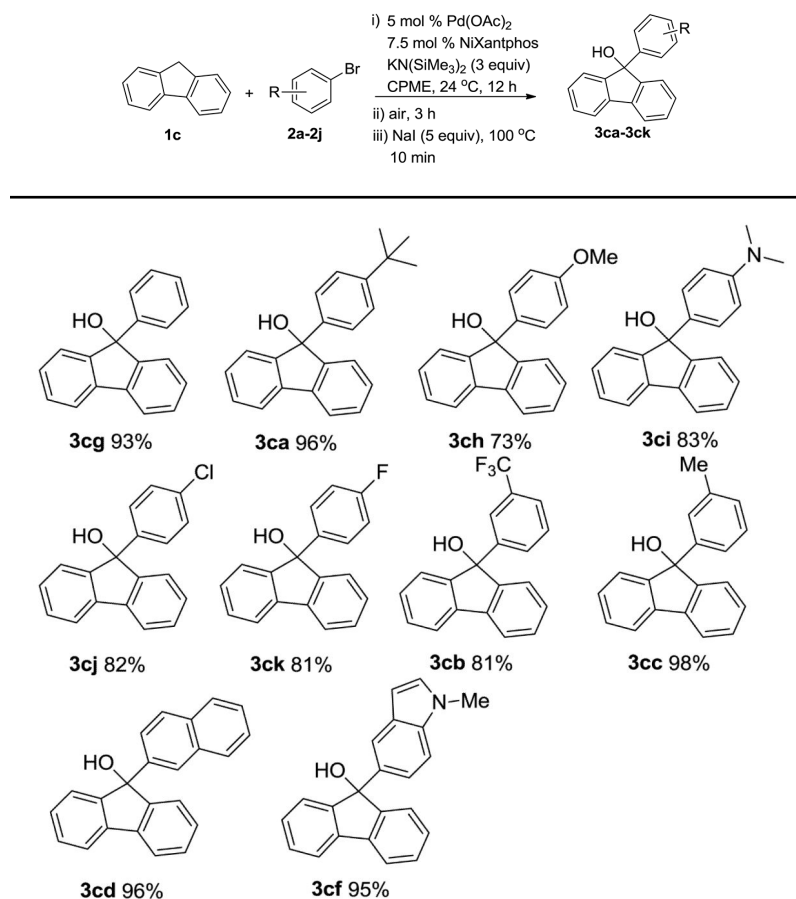[d] Reaction at rt for 2 h after 2 equiv PPh$_3$ was added.

[e] 2.5% catalyst.

Table 2

Scope of Aryl Bromides in Tandem Arylation/Oxidation using Benzylpyridyl Species[a]

Table 3

Scope of Aryl Bromides in Tandem Arylation/Oxidation using Fluorene[a]

3cg 93%   3ca 96%   3ch 73%   3ci 83%

3cj 82%   3ck 81%   3cb 81%   3cc 98%

3cd 96%   3cf 95%
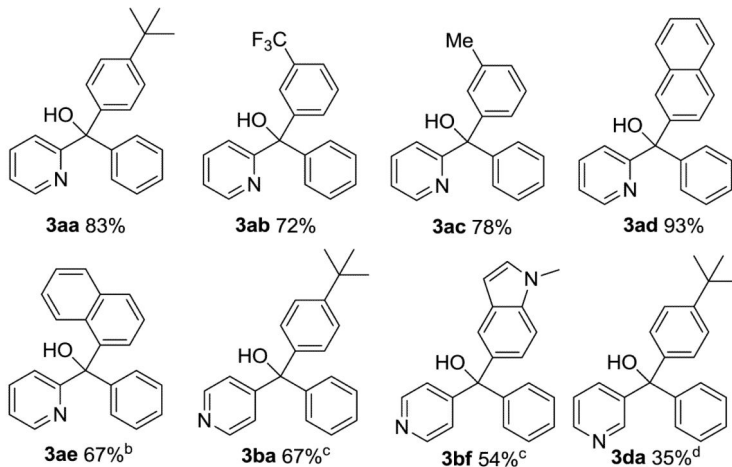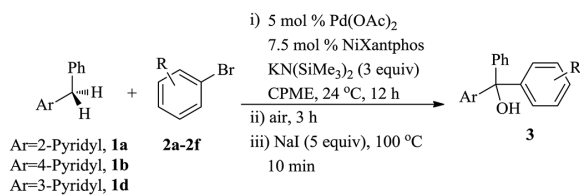
[a] Reactions conducted on a 0.1 mmol scale. Isolated yield.