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Palladium-Catalyzed C(sp^3)–H Arylation of Diarylmethanes at Room Temperature: Synthesis of Triarylmethanes via Deprotonative-Cross-Coupling Processes

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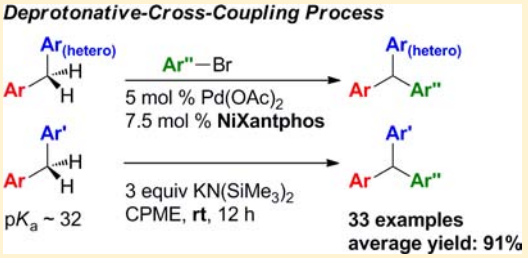
Supporting Information

ABSTRACT: Although metal-catalyzed direct arylation reactions of non- or weakly acidic C–H bonds have recently received much attention, chemists have relied heavily on substrates with appropriately placed directing groups to steer reactivity. To date, examples of intermolecular arylation of unactivated C(sp^3)–H bonds in the absence of a directing group remain scarce. We report herein the first general, high-yielding, and scalable method for palladium-catalyzed C(sp^3)–H arylation of simple diarylmethane derivatives with aryl bromides at room temperature. This method facilitates access to a variety of sterically and electronically diverse hetero- and nonheteroaryl-containing triarylmethanes, a class of compounds with various applications and interesting biological activity. Key to the success of this approach is an in situ metalation of the substrate via C–H deprotonation under catalytic cross-coupling conditions, which is referred to as a deprotonative-cross-coupling process (DCCP). Base and catalyst identification were performed by high-throughput experimentation (HTE) and led to a unique base/catalyst combination [$KN(SiMe_3)_2$/Pd–NiXantphos] that proved to efficiently promote the room-temperature DCCP of diarylmethanes. Additionally, the DCCP exhibits remarkable chemoselectivity in the presence of substrates that are known to undergo O-, N-, enolate-, and C(sp^2)–H arylation.

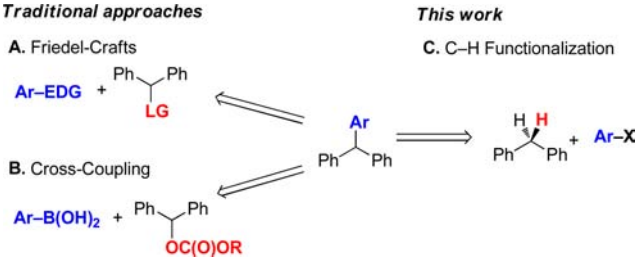


1. INTRODUCTION

Triarylmethane derivatives are well-known substructures in several areas, including leuco dye precursors,[1] photochromic agents,[2] and applications in materials science.[3] They are also important in medicinal chemistry as antitubercular,[4] anticancer,[5] and antiproliferative[6] agents, among others.[7,8] For the past decade, advances in the catalytic synthesis of triarylmethanes were largely based on two approaches:[9] (1) Friedel–Crafts-type arylations of diarylmethanols or diarylmethylamines (Scheme 1A)[10,11] and (2) cross-coupling reactions between diarylmethyl carbonates with arylboronic acids (Scheme 1B).[12] Despite the popularity of these methods, both have drawbacks. Friedel–Crafts-type arylations typically have significant electronic and steric limitations, being largely limited to electron-rich and unhindered nucleophiles. Additionally, mixtures of regioisomeric products are often obtained. Cross-coupling methods require prefunctionalization of the coupling partners and occasionally give moderate yield, complicated by formation of homocoupling byproducts.[12a]

We recently introduced a novel approach toward the catalytic synthesis of di- and triarylmethanes based on an η^6-arene-activation strategy. Initial studies employed readily available (η^6-$PhCH_2Z$)$Cr(CO)_3$ complexes (Z = Ph, H, OR, NR_2, eq 1).[13] Arylations of η^6-coordinated toluene, diphenylmethane,

Scheme 1. Synthetic Approaches to Triarylmethanes: (A) Friedel–Crafts Reaction, (B) Cross-Coupling, and (C) Nondirected C(sp^3)–H Arylation (EDG is an Electron-Donating Group; LG is a Leaving Group)



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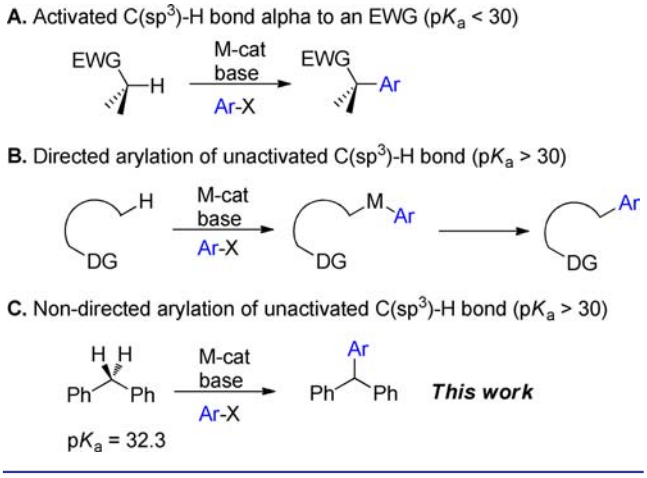
benzyl ethers, and benzyl amines were readily achieved. Although proof of concept of this approach was demonstrated, the stoichiometric use of chromium precludes large-scale applications of this chemistry. As outlined in Scheme 1C, we envisioned a chromium-free direct arylation approach involving C(sp^3)–H bonds of diphenylmethane derivatives.

Although metal-catalyzed cross-coupling reactions to form C–C bonds have become a mainstay in organic synthesis,[14] metal-catalyzed direct arylation reactions of C(sp^3)–H bonds possess distinct advantages.[15,16] Compared with traditional cross-coupling reactions with prefunctionalized partners (Scheme 1B), C–H arylation reactions are efficient, atom-economical, and minimize the costs of prefunctionalization. Great progress has been made in direct arylations of activated C(sp^3)–H bonds α to electron-withdrawing groups, such as ketones, esters, and amides, among others (Scheme 2A).[15] In

Scheme 2. Catalytic C(sp^3)–H Arylations



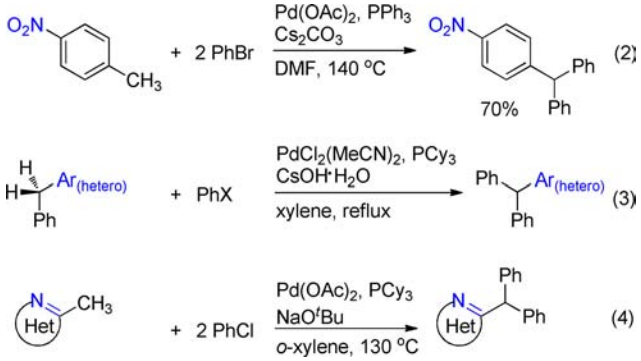
contrast, much less success has been achieved with the more challenging functionalization of non- or weakly acidic C(sp^3)–H bonds. To facilitate reactions at the unactivated C(sp^3)–H bonds (those with pK_a > 30[16d]), chemists have relied heavily on substrates with appropriately placed directing groups to steer reactivity (Scheme 2B).[16a–d] Although this approach avoids classical prefunctionalization of substrates, the addition and removal of directing groups often offsets any gain in synthetic efficiency provided by the direct C(sp^3)–H functionalization. To date, intermolecular arylation of C(sp^3)–H bonds *in the absence of* directing groups remains a formidable challenge.[17]

To streamline the synthesis of triarylmethanes, we set out to develop a general *room-temperature* directing-group-free method employing simple *diarylmethane* derivatives. To increase the practicality and utility of the method, we restricted our efforts to in situ metalation of the substrate via C–H deprotonation under catalytic cross-coupling conditions, and we will refer to these transformations as deprotonative-cross-coupling processes (DCCP) (Scheme 2C). Herein we report a palladium-catalyzed DCCP that fulfills these requirements. The advantages of this method are mild and reversible substrate deprotonation simply by mixing diarylmethanes with KN($SiMe_3$)$_2$, good functional group tolerance and chemoselectivity, nearly stoichiometric ratios of coupling partners for most substrates (down to 1.2:1), and commercial availability of Pd source and ligand.

2. RESULTS AND DISCUSSION

The first objective toward developing DCCPs is to identify conditions for the deprotonation of diphenylmethane (Ph_2CH_2). Diphenylmethane is weakly acidic, with a pK_a of 32.3 in DMSO.[18] The benzylic C–H's in diphenylmethane have traditionally been deprotonated with *n*-BuLi at −78 °C[19] or $NaNH_2$ and KNH_2 in liquid ammonia.[20,21] These conditions were viewed as cumbersome and impractical because of the low temperature and strongly basic media. We therefore focused on identifying conditions for the reversible in situ deprotonation of diphenylmethane that would be mild and compatible with the catalyst, reagents, and products in the DCCP. The second challenge is the discovery of catalysts suitable for cross-coupling processes at room temperature.

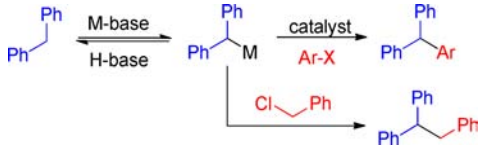
Prior reports on coupling with diarylmethane derivatives have employed various activation strategies to decrease the pK_a of the substrates. As mentioned above, we activated benzylic C–H's through coordination to $Cr(CO)_3$ (eq 1).[13,22] Inoh et al. have employed substrates bearing strong electron-withdrawing groups on the aryl ring, as exemplified by 4-nitrotoluene (pK_a 20.4, eq 2).[23] 2-Benzyl- (eq 3) and 2-methyl



heteroarenes (eq 4) are significantly more acidic than diphenylmethane and have been successfully employed in DCCPs.[17a,c] Deprotonation of these substrates can be facilitated by binding of the substrates' nitrogen to Lewis acidic species in solution. All three approaches required high temperatures (typically 130–150 °C). However, these methods fail with diarylmethane substrates such as 3-benzylpyridine and diphenylmethane itself.

2.1. Development of Room-Temperature Deprotonation/Benzylation of Diphenylmethane. We decided to separate the challenges of identifying the deprotonation conditions from the development and optimization of the catalyst. We, therefore, first examined diphenylmethane deprotonation step to determine the suitability of the substrate/base combinations. As a surrogate for the transmetalation step in the DCCP, we began with a deprotonation/benzylation reaction employing benzyl chloride (Scheme 3). A large number of variables for reagents and conditions were to

Scheme 3. Benzylation Used as Surrogate for the Transmetalation Step in DCCP



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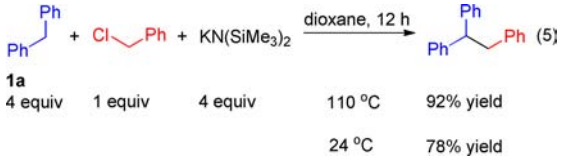
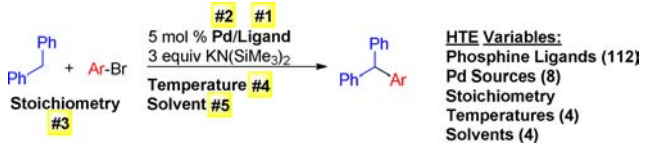
be simultaneously examined, including (1) base strength, (2) base nucleophilicity, (3) choice of main-group counterion (M = Li, Na, K), (4) stoichiometry, (5) solvent, (6) concentration, and (7) temperature. On the basis of our previous experience with DCCP of $(\eta^6\text{-PhCH}_2\text{Z})\text{Cr(CO)}_3$ complexes,[13,22] the choice of base would be critical for both deprotonation and cross-coupling. To perform this study in the most efficient manner, we employed low-barrier microscale high-throughput experimentation (HTE) techniques.[24] Using 12 diverse bases [$\text{LiN(SiMe}_3)_2$, $\text{NaN(SiMe}_3)_2$, $\text{KN(SiMe}_3)_2$, LiO-*t*-Bu, NaO-*t*-Bu, KO-*t*-Bu, LDA, LiH, KH, LiOH, KOH, and K_2CO_3] revealed that the combination of 4 equiv of diphenylmethane and 4 equiv of $\text{KN(SiMe}_3)_2$ with 1 equiv of benzyl chloride in dioxane at 110 °C was the most promising hit. Translation of this lead to laboratory scale (0.1 mmol) under the same conditions showed excellent reproducibility and rendered the benzylation product in 92% yield (eq 5). Surprisingly, results of



the HTE experiments indicated the *only* base leading to in situ deprotonation/benzylation product was $\text{KN(SiMe}_3)_2$. Neither $\text{LiN(SiMe}_3)_2$, $\text{NaN(SiMe}_3)_2$, nor MO-*t*-Bu (M = Li, Na, K) showed any reactivity (on both microscale or laboratory scale). Decreasing the reaction temperature from 110 to 24 °C resulted in 78% yield of the benzylation product (eq 5). Note that benzyl chloride did not react with bulky $\text{KN(SiMe}_3)_2$ on the time scale of the benzylation of diphenylmethane. Unlike bases previously used to deprotonate diphenylmethane (*n*-BuLi, $NaNH_2$, and KNH_2), $\text{KN(SiMe}_3)_2$ has a high likelihood of compatibility with catalyst, reagents, and products in catalytic DCCP (Scheme 3).[25]

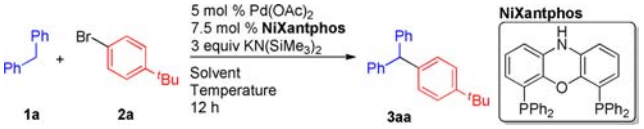
2.2. Development and Optimization of Palladium-Catalyzed DCCP of C(sp^3)–H of Diarylmethanes. We next turned our attention to the development of a Pd-catalyzed DCCP of C(sp^3)–H of diarylmethanes. Essential to accomplish this goal was the rapid identification of reagents and conditions from HTE on a 10 μmol scale. These efforts are summarized in Scheme 4, where the variables examined with cumulative HTE are numbered (see the Supporting Information for details).

Scheme 4. HTE Variables in Pd-Catalyzed DCCP of Diarylmethanes



We initially evaluated the reaction of diphenylmethane (**1a**) with 1-bromo-4-*tert*-butylbenzene (**2a**) using 112 sterically and electronically diverse, mono- and bidentate phosphine ligands and different Pd(0) and Pd(II) sources on a 10 μmol scale at 110 °C (see the Supporting Information for details). To our surprise, only one ligand from the entire collection, NiXantphos[26] (see Table 1 for the structure), afforded an excellent HPLC assay yield (AY) of the corresponding DCCP product **3aa** (93% AY from $\text{Pd(PPh}_3)_2\text{Cl}_2$/NiXantphos and

Table 1. Optimization of Pd-Catalyzed DCCP of 1a[a]



entry	1a:2a	solvent	temp (°C)	yield(%)[b]	HTE yield (%)[c]
1	4.0:1.0	dioxane	110	>95	100
2	2.0:1.0	dioxane	110	91	99
3	1.2:1.0	dioxane	110	77	77
4	1.2:1.0	dioxane	24	53	55
5	1.2:1.0	CPME	24	>95 (95[d])	96

[a]Reactions conducted on a 0.1 mmol scale using 1 equiv of **2a**, 3 equiv of $\text{KN(SiMe}_3)_2$, and **1a** at 0.1 M. [b]Yield determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c]HPLC assay yield of HTE conducted on a 10 μmol scale. [d]Isolated yield after chromatographic purification.

100% AY from Pd(OAc)_2/NiXantphos). These microscale reactions were successfully translated to laboratory scale (0.1 mmol) under the same conditions.

Although the combination of Pd(OAc)_2 and NiXantphos as precatalyst afforded the triarylmethane product **3aa** in excellent yield in the presence of 4 equiv of diphenylmethane (**1a**), 1 equiv of aryl bromide (**2a**), and 3 equiv of $\text{KN(SiMe}_3)_2$ in dioxane at 110 °C (Table 1, entry 1), further optimization was desired to reduce the equivalents of diphenylmethane and the reaction temperature.

Reducing the equivalents of diphenylmethane from 4 to 2 and 1.2 in dioxane at 110 °C resulted in a drop in triarylmethane yield from >95% to 77% (Table 1, entries 2–3). Furthermore, the reaction at 24 °C gave moderate yield compared with that at 110 °C (Table 1, entry 4 vs 3). To reduce both the equivalents of diphenylmethane and reaction temperature without compromising the yield, four ethereal solvents [dioxane, THF, 2-MeTHF, and CPME (cyclopentyl methyl ether)] and three temperatures (24, 50, and 70 °C) were examined. The best result was obtained when CPME was used as solvent, where the triarylmethane **3aa** was generated in >95% yield from 1.2 equiv of diphenylmethane, 1 equiv of aryl bromide **2a**, and 3 equiv of $\text{KN(SiMe}_3)_2$) at 24 °C (Table 1, entry 5). The triarylmethane **3aa** was ultimately isolated on laboratory scale in 95% yield after flash chromatography (Table 1, entry 5).

Control experiments conducted in the absence of any reagent, ligand, or palladium from the reaction mixture above resulted in no product. These optimized conditions were carried forward in the next phase of the project, which focused on the determination of the scope of diarylmethane derivatives in Pd-catalyzed DCCP.

2.3. Scope of Diarylmethanes in Palladium-Catalyzed DCCP. The scope of the DCCP with various diarylmethanes and 1-bromo-4-*tert*-butylbenzene (**2a**) is presented in Table 2. These reactions were conducted at 24 °C, except where noted. Substrates bearing various substituents on the diarylmethane exhibited excellent reactivity. Alkyl groups (**3ba**, **3ca**, **3da**), *ortho*-substituents (**3da**, **3ea**), electron-withdrawing (**3fa**, **3ga**), and electron-donating groups (**3ij**) were all well-tolerated. Although 4-methoxydiphenylmethane (**1i**) reacted with **2a** to give >95% conversion to the desired triarylmethane product **3ia** (as determined by ^{1}H NMR of the crude reaction mixture), **3ia** was inseparable from the starting diarylmethane (**1i**) by flash chromatography. The reaction of **1i** with 4-bromo-*N*,*N*-

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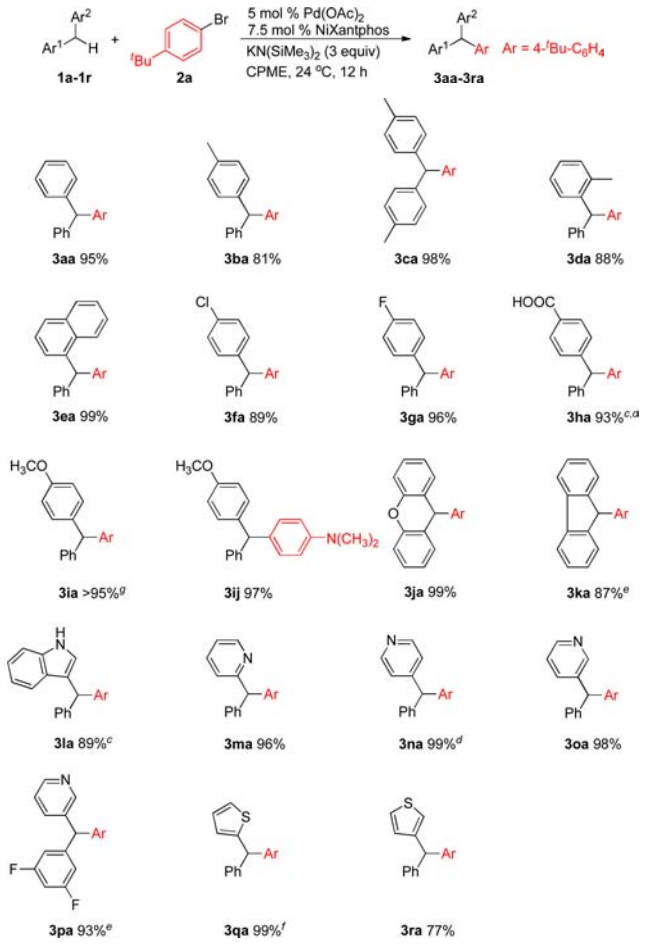
Table 2. Scope of Diarylmethanes in Pd-Catalyzed DCCP[a,b]



[a]Reactions conducted on a 0.1 mmol scale using 1 equiv of **2a**, 3 equiv of $KN(SiMe_3)_2$, and 1.2−3 equiv of **1** at 0.1 M. [b]Isolated yield after chromatographic purification. [c]4 equiv of $KN(SiMe_3)_2$. [d]110 °C. [e]85 °C in THF. [f]1.5 equiv of $KN(SiMe_3)_2$. [g]Yield determined by ^1H NMR spectroscopy of the crude reaction mixture.

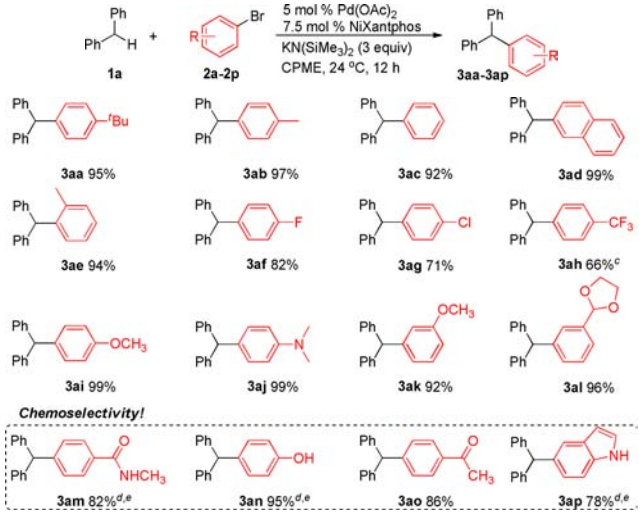
dimethylaniline (**2j**) afforded the desired triarylmethane product **3ij** in 97% isolated yield. Interestingly, 4-benzylbenzoic acid (**1h**) proved to be suitable substrate providing the corresponding product **3ha** in 93% yield at 110 °C. In addition to increasing the temperature, an extra equivalent of $KN(SiMe_3)_2$ was necessary to convert the starting acid into a potassium salt.

After demonstrating that our method was compatible with various diarylmethanes with different steric and electronic properties, we examined cyclic diarylmethane analogues. Both xanthene (**1j**) and fluorene (**1k**) proved to be good substrates, with corresponding products isolated in 99% (**3ja**) and 87% (**3ka**) yield. Note that the reaction with fluorene (**1k**) was run in THF at 85 °C due to solubility issues in CPME at 24 °C.

The next family of substrates examined was heteroaromatic diarylmethane derivatives, which are known for their utility in medicinal chemistry.[27] 3-Benzyl-1*H*-indole did not participate in the DCCP with **2a** under the optimized conditions, probably due to the decreased acidity of the benzylic hydrogens after deprotonation of the free N−H.[28a] Fortunately, DCCP proceeded with the *N*-Boc substrate in the presence of 4 equiv of $KN(SiMe_3)_2$ to furnish the indole-containing triarylmethane product **3la** in 89% isolated yield. Notably, **3la** was isolated in the deprotected 1*H*-indole form. The observed reactivity of 3-benzyl-1*H*-indole and its *N*-Boc analogue suggested that **3la** was formed via DCCP with subsequent *N*-Boc deprotection under the reaction conditions. Pyridine substrates bearing benzyl groups on different position were also examined. Isomeric 2-, 3-, and 4-benzylpyridine substrates all underwent DCCP smoothly to afford high yields of pyridine-containing triarylmethane products (**3ma**, **3na**, **3oa**, **3pa**). Although 2- and 4-benzylpyridine were known to participate in Pd-catalyzed DCCP at reflux in xylene, DCCP reactions with 3-benzylpyridine failed in prior studies even under vigorous conditions.[17a] The lack of reactivity of 3-benzylpyridine under previously reported conditions is likely due to its higher pK_a (30.1) compared with 2- and 4-benzylpyridines (pK_a = 28.2 and 26.7, respectively).[28b] It is noteworthy that 3-benzylpyridine affords the product in 98% yield at 24 °C with our procedure. In addition to 3-benzylpyridine, 3-(3,5-difluorobenzyl)pyridine (**1p**) was successfully arylated to afford **3pa** in 93% isolated yield. Elevated temperatures were required for 4-benzylpyridine to give **3na** (110 °C in CPME) and 3-(3,5-difluorobenzyl)-pyridine to furnish **3pa** (85 °C in THF), due to the low solubility of the substrates in CPME at 24 °C. In addition to nitrogen-containing substrates, 2-benzylthiophene (**1q**) and 3-benzylthiophene (**1r**) underwent DCCP at 24 °C to afford corresponding products **3qa** and **3ra** in 99% and 77% yield, respectively. To summarize, this method enables the synthesis of a variety of triarylmethanes from diarylmethanes bearing *ortho*-substitution and with electron-donating, electron-withdrawing, and heteroaryl groups.

2.4. Scope of Aryl Bromides in Palladium-Catalyzed DCCP. The scope of the DCCP with respect to aryl bromides was next explored with diphenylmethane (**1a**) (Table 3). Phenyl and 2-naphthyl bromides furnished **3ac** and **3ad** in 92% and 99% yield, respectively. Aryl bromides bearing various substituents exhibited good to excellent reactivity. Alkyl groups (**3aa**, **3ab**), *o*-methyl (**3ae**), electron-withdrawing groups (**3af**, **3ag**, **3ah**), and electron-donating groups (**3ai**, **3aj**, **3ak**) were all well-tolerated. 1-Bromo-4-chlorobenzene (**2g**) reacted with **1a**

Table 3. Scope of Aryl Bromides in Pd-Catalyzed DCCP[a,b]



[a]Reactions conducted on a 0.1 mmol scale using 1 equiv of aryl bromide, 3 equiv of $KN(SiMe_3)_2$, and 1.2−3 equiv of diphenylmethane at 0.1 M. [b]Isolated yield after chromatographic purification. [c]2 equiv of $KN(SiMe_3)_2$. [d]4 equiv of $KN(SiMe_3)_2$. [e]110 °C.

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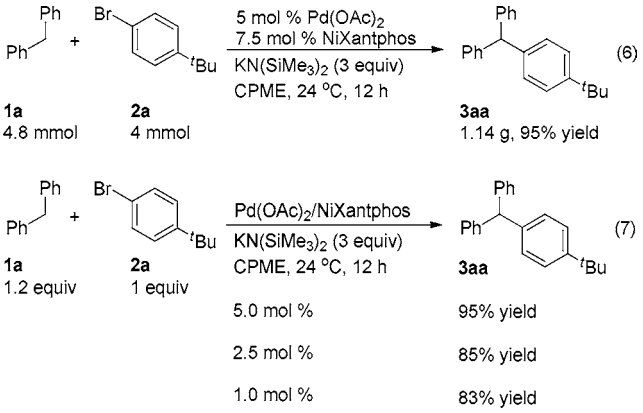
to produce **3ag** as the exclusive product in 71% isolated yield. No products derived from Ar−Cl oxidative addition were observed. The difference in reactivity of C−Cl and C−Br bonds in **2g** is in accordance with previous studies on oxidative addition of haloarenes.[29] To demonstrate the advantage of the mild conditions of our method over the previous deprotonation conditions using *n*-BuLi, $NaNH_2$, and KNH_2, we then tested substrates bearing sensitive functional groups. As shown in Table 3 remarkable chemoselectivity is observed with aryl bromides containing acetal, amide, phenol, acetyl, and 1*H*-indole moieties, which all underwent DCCP delivering the corresponding functionalized products in 78−96% yield (**3al**−**3ap**). Ketones are well-known to undergo 1,2-carbonyl addition reactions with reactive organometallics. 4-Bromoacetophenone might be expected to participate in competitive aldol chemistry[30] and α-arylation of the enolate derived from deprotonation[15] under the basic conditions of the reaction (pK_a of acetophenone in DMSO: 24.7[31]). Yet the triarylmethane **3ao** was produced in 86% yield. Phenols are known to undergo O- and C(sp^2)−H arylation[32] while 1*H*-indoles have been reported to react via N-arylation (Buchwald−Hartwig coupling),[33] C-2-, and C-3-arylation[34] in the presence of palladium catalysts and bases. Our method exhibits orthogonal chemoselectivity with arylation taking place selectively at the benzylic C(sp^3)−H's. These functional groups present opportunities to further functionalize the triarylmethane products. It is noteworthy that for 4-bromo-*N*-methylbenzamide (**2m**), 4-bromophenol (**2n**), and 5-bromoindole (**2p**), an extra equivalent of $KN(SiMe_3)_2$ as well as elevated temperature (110 °C) were employed to raise the yield to 82% (**3am**), 95% (**3an**), and 78% (**3ap**), respectively. For substrates giving less than 80% yield in Table 3 (**3ag**, **3ah**, **3ap**), ^{1}H NMR of the reaction mixture after work-up and removal of volatiles showed no byproduct formation. The DCCP products were easily separated from the unreacted diphenylmethane by flash chromatography.

To illustrate the practical utility of our method, we examined its scalability by conducting the reaction of **1a** with **2a** on a 4 mmol scale, which afforded 1.14 g of **3aa** (95% isolated yield, eq 6). We were also able to reduce the catalyst loading to 1.0 mol % with only a minor drop in yield (eq 7).



3. SUMMARY AND OUTLOOK

We have developed the first general, high-yielding, and scalable method for the palladium-catalyzed C(sp^3)−H arylation of diarylmethanes at room temperature. This method circumvents the traditional low-temperature deprotonation conditions with strong bases and the high-temperature cross-coupling conditions employed previously with more acidic, activated diarylmethane substrates. Our DCCP affords a variety of triarylmethane derivatives, a class of compounds with various applications and biological activity. Additionally, the DCCP exhibits remarkable chemoselectivity in the presence of substrates that are known to undergo O-, N-, enolate-, and C(sp^2)−H arylation.

The development of the DCCP was accomplished by solving two challenging interdependent problems: (1) to identify deprotonation conditions for diphenylmethane (pK_a 32.3) and related weakly acidic derivatives that would be amenable to catalysis and (2) to find a catalyst that would be compatible with the deprotonation conditions and promote the cross-coupling. Our approach to these two challenges was to separate them by employing a deprotonation/benzylation protocol as a surrogate for the deprotonation/transmetalation of the desired catalytic cycle. Interestingly, only a single base, $KN(SiMe_3)_2$, of the 12 examined, worked for the benzylation. Once the base had been identified, a search for a catalyst was conducted by screening 112 phosphine ligands and several palladium sources. The use of the HTE tools enabled rapid identification of the $Pd(OAc)_2$/NiXantphos combination as an excellent catalyst system for DCCP at room temperature. In hindsight, it is unlikely that we would have identified a reasonable catalyst system given that a single base/ligand combination was found to be successful. This translates to 1 out of 1344 combinations (12 bases × 112 ligands) of the two most important variables.

The broad scope and mild conditions of the DCCP outlined herein make it a valuable contribution to applications in nondirected transition metal-catalyzed arylation of C(sp^3)−H bonds for the synthesis of triarylmethanes. Mechanistic studies to understand how the $Pd(OAc)_2$/NiXantphos combination promotes the room-temperature DCCP of diarylmethanes are underway in our laboratory.

4. EXPERIMENTAL SECTION

Representative procedures are described herein. Full experimental details and characterization of all compounds are provided in the Supporting Information.

4.1. General Methods. All reactions were performed under nitrogen using oven-dried glassware and standard Schlenk or vacuum line techniques. Air- and moisture-sensitive solutions were handled under nitrogen and transferred via syringe. Anhydrous CPME, dioxane, and 2-MeTHF were purchased from Sigma-Aldrich and used as solvent without further purification. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were obtained from Sigma-Aldrich, Acros, TCI America, or Matrix Scientific, and solvents were purchased from Fisher Scientific. The progress of the reactions was monitored by thin-layer chromatography using Whatman Partisil K6F 250 μm precoated 60 Å silica gel plates and visualized by short-wavelength ultraviolet light as well as by treatment with ceric ammonium molybdate (CAM) stain or iodine. 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), 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. Melting points were

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determined on a Unimelt Thomas–Hoover melting point apparatus and are uncorrected.

4.2. General Procedure A: Room-Temperature Deprotonation/Benzylation of Diphenylmethane. An oven-dried 10 mL reaction vial equipped with a stir bar was charged with $KN(SiMe_3)_2$ (79.8 mg, 0.40 mmol, 4 equiv) under a nitrogen atmosphere followed by 1 mL of dry dioxane, and the reaction mixture was stirred for 5 min at 24 °C. Diphenylmethane (66.9 μL, 0.40 mmol, 4 equiv) was added to the reaction mixture followed by benzyl chloride (11.5 μL, 0.1 mmol, 1 equiv). The reaction mixture was stirred for 12 h at 24 °C (or 110 °C). The reaction mixture was quenched with two drops of H_2O, diluted with 3 mL of ethyl acetate, and filtered over a pad of $MgSO_4$ and silica. The pad was rinsed with additional ethyl acetate, and the solution was concentrated in vacuo. The crude material was loaded onto a silica gel column and purified by flash chromatography.

4.3. General Procedure B: Pd-Catalyzed DCCP of Diarylmethanes. An oven-dried 10 mL reaction vial equipped with a stir bar was charged with $KN(SiMe_3)_2$ (59.8 mg, 0.30 mmol, 3 equiv) under a nitrogen atmosphere. A solution (from a stock solution) of $Pd(OAc)_2$ (1.12 mg, 0.0050 mmol) and NiXantphos (4.14 mg, 0.0075 mmol) in 1 mL of dry CPME was taken up by syringe and added to the reaction vial. After stirring for 5 min at 24 °C, diphenylmethane (20.1 μL, 0.12 mmol, 1.2 equiv) was added to the reaction mixture followed by 1-bromo-4-*tert*-butylbenzene (17.3 μL, 0.1 mmol, 1 equiv). Note that the diarylmethane or aryl bromide in a solid form was added to the reaction vial prior to $KN(SiMe_3)_2$. The reaction mixture was stirred for 12 h at 24 °C, quenched with two drops of H_2O, diluted with 3 mL of ethyl acetate, and filtered over a pad of $MgSO_4$ and silica. The pad was rinsed with additional ethyl acetate, and the solution was concentrated in vacuo. The crude material was loaded onto a silica gel column and purified by flash chromatography.

4.4. Representative HTE Procedure C: Ligand Screening for Palladium-Catalyzed DCCP of Diphenylmethane. Experiments were set up inside a glovebox under a nitrogen atmosphere. A 96-well aluminum block containing 1 mL glass vials predosed with 96 ligands (1 μmol for bidentate ligands and 2 μmol for monodentate ligands) was treated with a solution of $Pd(OAc)_2$ (0.5 μmol) in THF. The solvent was evacuated to dryness using a Genevac vacuum centrifuge, and $KN(SiMe_3)_2$ (30 μmol) in THF was added to the ligand/catalyst mixture. The solvent was removed on the Genevac, and a parylene stir bar was then added to each reaction vial. 1-Bromo-4-*tert*-butylbenzene (10 μmol/reaction), diphenylmethane (12 μmol/reaction), and biphenyl (1 μmol/reaction) (used as an internal standard to measure HPLC yields) were then dosed together into each reaction vial as a solution in CPME (100 μL, 0.1 M). The 96-well plate was then sealed and stirred for 18 h at 110 °C. Upon opening the plate to air, 500 μL of acetonitrile was syringed into each vial. The plate was then covered again and the vials stirred for 20 min to extract the product and to ensure good homogenization. Into a separate 96-well LC block was added 700 μL of acetonitrile, followed by 40 μL of the diluted reaction mixtures. The LC block was then sealed with a silicon-rubber storage mat and mounted on HPLC instrument for analysis.

■ ASSOCIATED CONTENT

Supporting Information

Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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