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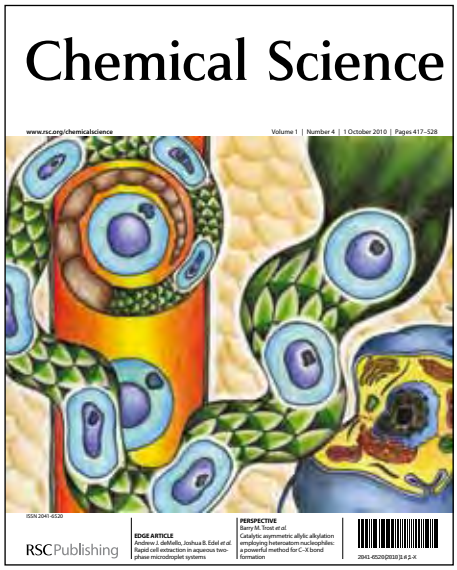

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ARTICLE TYPE

Additive Effects on Palladium-Catalyzed Deprotonative-Cross-Coupling Processes (DCCP) of sp^3 C–H Bonds in Diarylmethanes

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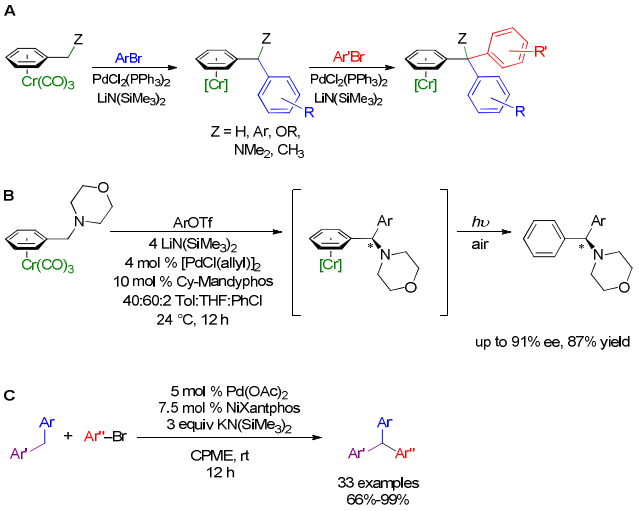
Palladium-catalyzed cross-coupling reactions have become one of the most useful tools in modern organic chemistry. Current methods to achieve direct functionalization of sp^3 C–H bonds of arenes and heteroarenes often employ substrates with appropriately placed directing groups to enable reactivity. Examples of intermolecular arylation methods of weakly acidic sp^3 C–H bonds in the absence of directing groups, however, are still limited. We describe herein a study on the use of additives in Pd-catalyzed deprotonative-cross-coupling processes (DCCP) of sp^3 C–H bonds of diarylmethanes with aryl bromides at room temperature. These studies resulted in development of four new efficient Pd-catalyzed DCCP using additives that enabled the generation of a range of sterically and electronically diverse aryl- and heteroaryl containing triarylmethanes in good to excellent yields. Additive identification and optimization of all reaction conditions (additive loading, solvent and temperature) were performed using high-throughput experimentation (HTE). The approach outlined herein is expected to be generalizable to other C–H functionalization reactions involving the deprotonation of weakly acidic C–H bonds.

1. Introduction

Transition-metal-catalyzed cross-coupling reactions are among the most straightforward and versatile methods in organic synthesis.[1] These reactions typically involve two prefunctionalized coupling partners, such as a vinyl or aryl halide and an organometallic reagent. More recently, the synthetic community has focused on direct functionalization of C–H bonds of arenes and heteroarenes, because C–H functionalizations are more atom-economical and minimize the costs of prefunctionalization. Currently, much of this effort has been concentrated on direct functionalization of sp^3 C–H bonds.[2] Despite this effort, the intermolecular arylation of weakly acidic sp^3 C–H bonds in the absence of directing groups remains challenging.[3]

Our initial approach to direct functionalization and arylation of weakly acidic benzylic sp^3-hybridized C–H bonds (ArCH_2-Z, Z=H, Ph NR_2, OR) relied on acidification of the benzylic C–H's by coordination of the arene substrates to $Cr(CO)_3$ in the form of (η^6-ArCH_2–Z)$Cr(CO)_3$ complexes (Scheme 1A).[4] This strategy was amenable to the first catalytic asymmetric arylation of benzylic amines (Scheme 1B).[5] The novelty of this approach, however, was moderated by the use of stoichiometric chromium. To circumvent this issue, we recently reported the first palladium-catalyzed deprotonative-cross-coupling process (DCCP) for sp^3 C–H arylation of unactivated diarylmethane derivatives in the absence of chromium. This protocol enables the synthesis of a variety of sterically and electronically diverse aryl- and heteroaryl containing triarylmethanes (Scheme 1C).[6] Triarylmethane derivatives exhibit interesting applications in material science and are also important in medicinal chemistry.[6]

It is noteworthy that the reaction can be conducted at room temperature with most substrates and that only 1.2 equiv diarylmethane is necessary in the majority of cases. The catalyst system is very effective, providing an average yield of >90% for the 33 triarylmethanes synthesized in the initial study. High throughput experimentation (HTE) techniques[7] were used to optimize parameters in this reaction leading to a unique base/catalyst combination (Scheme 1C).

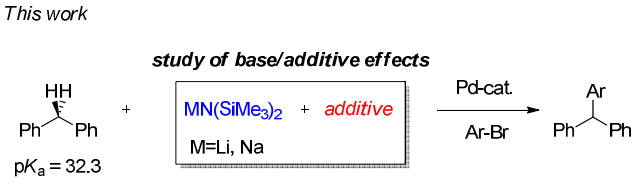


Scheme 1 Palladium-catalyzed sp^3 C–H arylation approaches developed by our group.

Surprisingly, of the 12 bases examined during the development and optimization of this reaction,[6] only $KN(SiMe_3)_2$ afforded the desired DCCP products in good to excellent yields (Scheme 1C). Related alkali metal-bis(trimethylsilyl)amide bases [$MN(SiMe_3)_2$, M=Li, Na] as well as *tert*-butoxide bases [MO-*t*-Bu, M=Li, Na, K] failed to show even trace conversion.

We hypothesized that additives might influence the

performance of $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$ and potentially other bases and turn on the DCCP to afford triarylmethane products (Scheme 2). Additionally, we hoped the use of additives would improve reaction yields of problematic substrates and result in milder reaction conditions. A search of the additive literature led to an unexpected result: despite the enormous number of palladium catalyzed processes published in the last 20 years, we were not able to find previous systematic studies on the use of Lewis basic additives for the Pd-catalyzed cross-coupling processes with weakly acidic sp^3 C–H bonds. Yet these reactions are increasingly popular in the efficient and economical synthesis of biologically active compounds.[2a, 2e] Thus, inspired by the use of additives in different types of reactions, we set out to evaluate the impact of additives on the DCCP in Scheme 2. We now disclose four conditions with different additives and bases that not only turn on the DCCP with previously unreactive $LiN(SiMe_3)_2$ and $NaN(SiMe_3)_2$, but actually afford better reaction conditions with certain challenging substrates relative to our original additive-free conditions.[6]



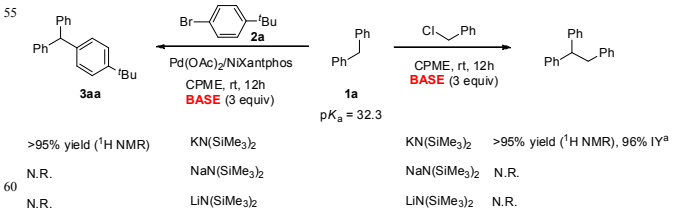
Scheme 2 Study of additive effects on the DCCP for sp^3 C–H arylation of weakly acidic diarylmethanes.

2. Results and discussion

2.1. Probing the Role of the Base in the Absence of Additives

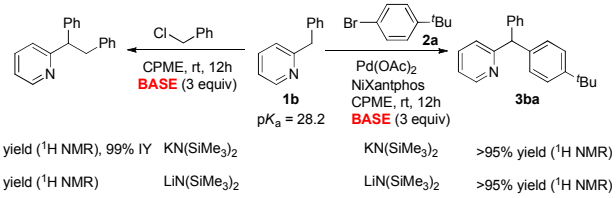
Before selecting additives for use in the DCCP (Scheme 2), a better understanding of the role of the base in room-temperature (23 °C) Pd-catalyzed DCCP was necessary. There are two widely accepted pathways for the C–H cleavage step in transition metal-catalyzed C–H arylation reactions: (1) C–H activation *via* a base-induced, concerted metallation-deprotonation (CMD) pathway[2c, 8] and (2) C–H deprotonation by base without participation of the transition metal. The former is common for unactivated sp^3 C–H arylations while the latter is widespread for activated sp^3 C–H arylations.

To gain insight into the role of the base, we compared different bases of the type $MN(SiMe_3)_2$ (M=Li, Na, K) by employing them in the DCCP of diphenylmethane (**1a**) with 4-*tert*-butyl bromobenzene (**2a**) (Scheme 3, left). Only $KN(SiMe_3)_2$ afforded the DCCP product **3aa** with excellent yield. In sharp contrast, $LiN(SiMe_3)_2$ and $NaN(SiMe_3)_2$ showed no conversion. To understand why these three alkali metal counterions exhibited dramatic differences in the DCCP, we carried out deprotonation/benzylation experiments with these three bases in cyclopentylmethyl ether (CPME) at room temperature (Scheme 3, right). Again, only $KN(SiMe_3)_2$ afforded the benzylation product while $LiN(SiMe_3)_2$ and $NaN(SiMe_3)_2$ failed to produce detectable amounts of product. The results in the room temperature deprotonation/benzylation (Scheme 3) are consistant with the room-temperature DCCP and suggest a reaction pathway for the DCCP involving direct deprotonation of the substrate without the participation of the palladium catalyst.



Scheme 3 Deprotonation/benzylation and DCCP experiments with diphenylmethane (**1a**). [a]IY: isolated yield.

To further test the hypothesis above, we compared $KN(SiMe_3)_2$ and $LiN(SiMe_3)_2$ in the room-temperature deprotonation/benzylation and DCCP experiments with 2-benzylpyridine (**1b**, Scheme 4). The benzylic hydrogens of 2-benzylpyridine are considerably more acidic (pK_a=28.2)[3g, 3k, 9] than those of diphenylmethane (pK_a=32.3),[10] which should facilitate room-temperature deprotonation/benzylation process with either of the two bases. In agreement with our expectations, 2-benzylpyridine underwent benzylation in excellent yield in the presence of either $KN(SiMe_3)_2$ or $LiN(SiMe_3)_2$. Both of the metallated 2-benzylpyridine species (organopotassium and organolithium) also participated in the catalytic DCCP to furnish the triarylmethane derivative **3ba** in >95% yield. These experiments point to the reactivity of the base and the acidity of the substrate as a key feature in the DCCP of diarylmethanes and lead us to hypothesize that additives that increase the reactivity of the base will have a beneficial impact on formation of the DCCP product.



Scheme 4 Deprotonation/benzylation and DCCP experiments with 2-benzylpyridine (**1b**).

2.2. Additives Background

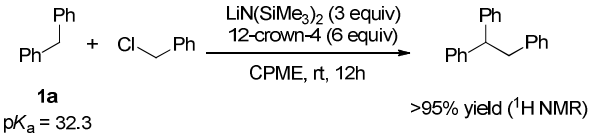
Several important contributions outlining the use of additives on various processes guided our choice of starting points. In the past decade, advances have been made in exploiting the use of additives to improve synthetic performance in late transition metal-catalyzed reactions.[11] In 2001 Beller's group reported a detailed study on the effect of halide additives on the Heck reaction.[12] Recently, the groups of Nakamura,[13] Fürstner,[14] Cahiez,[15] Cossy[16] and Jacobi von Wangelin[17] have described the use of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) on the

Fe-catalyzed cross-coupling reactions between Grignard reagents and alkyl halides while Hu[18] reported its use in the Ni-catalyzed sp^3-sp^2 Kumada-Corriu-Tamao cross-coupling reaction. Evano *et al.*[19] as well as Shang and co-workers[20] also explored TMEDA in cross-coupling reactions using alkynylcopper reagents. We employed *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDTA) and TMEDA in the enantioselective DCCP of (η^6-$ArCH_2$–NR_2)$Cr(CO)_3$ complexes.[5] Another diamine, dimethylethylenediamine (DMEDA) has been described to significant accelerate Cu-catalyzed C–N cross-coupling reactions.[21] In several of these systems the role of these additives is unclear, although it has been suggested that in iron-catalyzed processes the TMEDA can function as the ligand for the iron center[22] while in Cu-catalyzed processes the role of DMEDA has been rationalized not only as acting as a ligand to copper but also helping to solublize the base and possibly serving as reducing agent.[21b] A Perspective published in 2010 by Buchwald[23] discusses the use of diamine ligands in Cu catalysis. Myristic acid[24] as well as acetic acid[25] were also reported by Buchwald as additives; the first in Cu-catalyzed C–N coupling methods and the latter facilitating activation of the catalyst in Pd-catalyzed *N*-arylation reactions. Moreover, Buchwald highlighted the remarkable effect of catalytic amounts of phenolic additives on the Cu-catalyzed α-arylation of malonates[26] and ketone enolates.[27]

Considering organolithium chemistry, Collum's group has studied the impact of diamines on organolithium and lithium amide bases.[28] Furthermore, they have outlined the beneficial effect of LiCl in accelerating *ortho*-lithiation reactions.[29] Knochel and co-workers developed a new class of mixed magnesium bisamides in combination with LiCl as active bases for the direct magnesiation[30] and zincation[31] of arenes and heteroarenes and they recently introduced the use of Lewis acids to promote the deprotonation of a variety of aromatic and heteroaromatic substrates for benzylic cross-coupling reactions.[32] In this same area, Hartwig's research group had shown the accelerating effect of Lewis acids in Pd-catalyzed aminations[33] and the effect of zinc additives[34] and metal fluorides[35] on palladium complexes to catalyze the arylation of trimethylsilyl enolates. Finally, Trost has also shown the beneficial effect of Lewis acids like BF_3•OEt_2 in Pd-catalyzed asymmetric allylic substitutions.[36] These reports inspired our approach to identification of additives for the DCCP in Scheme 2.

2.3. Examination of Additives in Deprotonation/Benzylation Studies

To gain insight into the lack of reactivity of $LiN(SiMe_3)_2$ with diphenylmethane in both the benzylation and DCCP (Scheme 3), we decided to explore the use of additives, initially focusing on crown ethers. It is well-known that 12-crown-4 has a high affinity for lithium cations.[37] We, therefore, added 12-crown-4 to the reaction mixture of diphenylmethane (**1a**), $LiN(SiMe_3)_2$, and benzyl chloride in CPME at room temperature (Scheme 5). Under these conditions, the benzylation occurred in >95% assay yield, indicating that binding the lithium cation by the crown ether dramatically increased the kinetic basicity of $LiN(SiMe_3)_2$. The enhanced reactivity in the presence of the crown ether is presumably due to the reduced degree of aggregation of the resulting lithium amide species.[38]

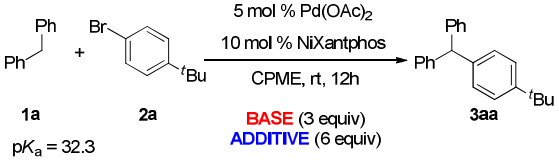


Scheme 5 Crown ether effect on the deprotonation/benzylation reaction with diphenylmethane (**1a**) using $LiN(SiMe_3)_2$.

With these results in hand, we decided to determine the range of additives that would increase the reactivity of $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$ and potentially other bases and thus generate the triarylmethane products starting from weakly acidic diphenylmethane substrates.

Recently HTE techniques have emerged as a powerful approach for the discovery of new and more active catalysts, and milder reaction conditions, for a wide variety of transformations. We, therefore, decided to examine the impact of additives in the cross-coupling reaction between 4-*tert*-butyl bromobenzene (**2a**) and diphenylmethane (**1a**) against a range of bases and solvents using HTE techniques. The additives were selected based on their ability to coordinate to the main-group counterions of the bases.

As a starting point, we employed our previously optimized additive-free conditions for the DCCP of **1a** and **2a** (5 mol % $Pd(OAc)_2$, 7.5 mol % NiXantphos in CPME at rt).[6] In the present study, 6 different bases [$KN(SiMe_3)_2$, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, KO*t*Bu, LiO*t*Bu and NaO*t*Bu] and 11 diverse additives including crown ethers (12-crown-4, 15-crown-5, 18-crown-6) and various amines and nitrogen-containing ligands [NEt_3, TMEDA, *N,N,N',N'*-tetramethyl-1,3-propanediamine (TMPDA), *N,N'*-diisopropylethylenediamine, *N,N*-diethylethylenediamine, *N,N'*-dibenzylethylenediamine (DBED), PMDTA, 2,2'-bipyridine (bipy), 1,10-phenanthroline and 1,4-diazabicyclo[2.2.2]octane (DABCO)] were screened (Scheme 6).



Scheme 6. HTE study on the impact of additives in the cross-coupling reaction between 4-*tert*-butyl bromobenzene (**2a**) and diphenylmethane (**1a**) against a range of bases.

The 72-reaction additive screening was carried out by dosing diphenylmethane (**1a**, 12 μmol), 4-*tert*-butyl bromobenzene (**2a**, 10 μmol), and internal standard (biphenyl, 1 μmol) in 100 μL of CPME into a 96 well plate containing 72-1 mL reaction vials. The vials had been predosed with $Pd(OAc)_2$ (5 mol %), NiXantphos (10 mol %), base (30 μmol) and additive (60 μmol, except for the control reactions). The plate was prepared inside a glovebox under a nitrogen atmosphere and sealed for the reaction period. The plate was then stirred for 12 h at room temperature outside the glovebox, opened to air, diluted with acetonitrile and the reaction mixtures subjected to HPLC analysis. The product

standard, starting materials, and internal standard were previously analyzed to determine their retention times and UV/vis spectra. In an effort to identify the most generalized set of conditions, we focused our analysis on reactions generating coupled triarylmethane product **3aa** in ≥10% HPLC assay yield (AY, Figure 1). These leads would then be further optimized in subsequent experiments.

The results of this study are illustrated graphically in Figure 1. Reactions in column 1 are the control reactions conducted without additive. Wells B1, C1, D1, E1 and F1 contained only unreacted starting material and no triarylmethane product. In contrast, $KN(SiMe_3)_2$ formed triarylmethane in >90% AY in the absence of additive (A1). These results are consistent with our earlier report.[6] The combination of $LiN(SiMe_3)_2$/12-crown-4 (B2) and $NaN(SiMe_3)_2$/15-crown-5 (C2) rendered product **3aa** in 97% and 91% AY, respectively, whereas 18-crown-6 was detrimental to the AY with $KN(SiMe_3)_2$ (A1 vs. A2). Amines are known to bind to lithium and increase the reactivity of lithium bases such as LDA[28] and $LiN(SiMe_3)_2$.[38d, 39] Among the amine additives examined, reactions with TMEDA (C4), *N,N′*-diisopropylethylenediamine (C6) and PMDTA (C9) provided triarylmethane product in the presence of $NaN(SiMe_3)_2$, albeit in low yield (10–12% AY). None of the other bases generated the DCCP product with or without the additives (see Supporting Information for details). It is interesting to note that all additives employed in this initial study had a negative impact on reactions with $KN(SiMe_3)_2$ relative to the control reaction.

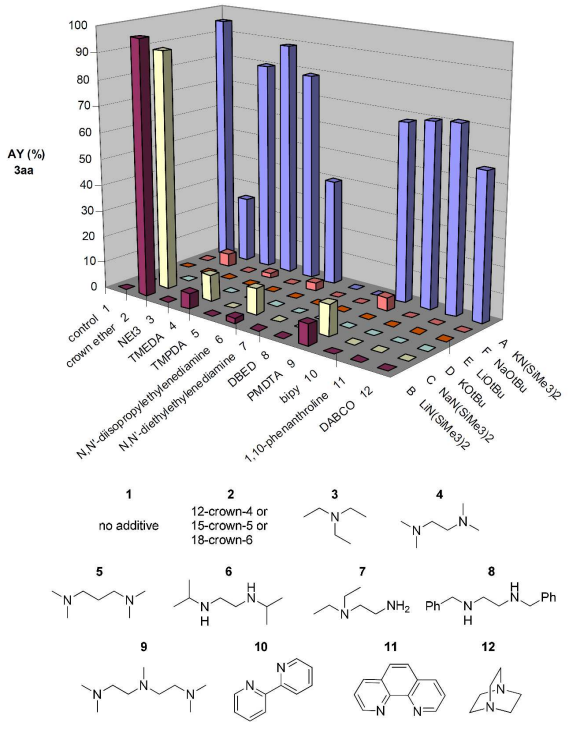


Fig. 1 Results of initial screen of additives. Column 1 is the control reaction without additives.

After identification of the leads above, we performed multiparallel screening in 1 mL reaction vials to evaluate additive stoichiometry by employing 1, 2, 3, 6 and 8 equiv additive in the presence of $LiN(SiMe_3)_2$ and $NaN(SiMe_3)_2$. The effect of temperature on AY was also examined. We found that the loading of the crown ethers could be reduced from 6 equiv to 1 equiv at rt without dramatically impacting the reaction yield.

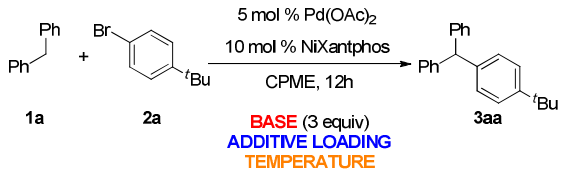
Reactions with amine additives performed better at high temperature (110 °C compared to rt) using $NaN(SiMe_3)_2$ with 1 equiv PMDTA (45% AY) being more promising than 6 equiv TMEDA (32% AY) and 6 equiv *N,N′*-diisopropylethylenediamine (15% AY) (see Supporting Information for details).

Based on the observation that the triamine PMDTA was more effective than the diamine TMEDA and the monoamine NEt_3, we decided to evaluate the tetramine 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA). A new screen using $NaN(SiMe_3)_2$ and several tetramine loadings in CPME at room temperature and 110 °C revealed that 6 equiv HMTETA at rt resulted in generation of the desired product in good to excellent yields (80% AY when 1.2 equiv of diphenylmethane was used and 97% AY with 3 equiv; see Supporting Information for details). Collectively, the results above indicate that the presence of crown ethers and amine additives enhance reactivity in the DCCP with Li- and $NaN(SiMe_3)_2$ bases.

With the successful identification of crown ethers as additives with $LiN(SiMe_3)_2$ and $NaN(SiMe_3)_2$ bases, we decided to examine solvents resembling crown ethers, such as DME (1,2-dimethoxyethane) and diglyme. Thus, we screen the initial 6 bases at three temperatures (rt, 50 °C and 110 °C) in CPME, DME and diglyme and in combination with various additive loadings (see Supporting Information for details). The most promising results obtained from HTE screen are summarized in Table 1. The combination of 6 equiv of 12-crown-4 with 3 equiv of $LiN(SiMe_3)_2$ in CPME rendered the desire product in 97% AY (95% isolated yield) at rt (Table 1, entry 2). Unfortunately, we were not able to make the DCCP work as efficient with lower loadings of 12-crown-4 (Table 1, entries 3 and 4). The use of *substoichiometric amounts of 15-crown-5 (30 mol %)* with $NaN(SiMe_3)_2$, rendered the highest yield (quantitative AY, 96% isolated yield) of the desired product in CPME at rt (Table 1, entry 9). Attempts to decrease the additive loading to 15 mol % or 3 mol % at rt was detrimental to the yield (Table 1, entries 11 and 14). When the reactions were conducted at 110 °C and the amount of diphenylmethane was increased to 3 equiv, however, better assay yields was obtained (Table 1, entries 13 and 16). The use of 6 equiv HMTETA and $NaN(SiMe_3)_2$ at rt in CPME rendered 80% AY (86% isolated yield, Table 1, entry 17). Of significance, HMTETA is inexpensive and can be easily removed from the reaction mixture during the purification of the product. The coordinating solvent diglyme rendered good results (see Supporting Information) but due to its reported toxicity (based on the MSDS), we used it as an additive instead of solvent. Thus, diglyme (6 equiv) with $NaN(SiMe_3)_2$ at rt was the most suitable conditions, generating the desired product in 88% AY (78% isolated yield, Table 1, entry 20). Bases MO-*t*-Bu did not show promising results even in the presence of the additives explored (see Supporting Information).

It is of note that the microscale screening results (10 μmol) outlined above translated to laboratory scale (0.1 mmol) with excellent reproducibility. The isolated yields are given in the last column of Table 1 in parentheses.

Table 1 Selected results from HTE screen using different bases and additive loadings. Isolated yields are shown in parenthesis for the best conditions obtained.



Entry	MN(SiMe$_3$)$_2$ M=	Additive, loading	T (°C)	1a (equiv.)	AY (%) HTE[a]	AY (%) Lab scale[b]
1	Li	-	23	1.2	NR	NR
2	Li	**12-crown-4, 6 equiv**	**23**	**1.2**	**97**	**97 (95)**[c]
3	Li	12-crown-4, 1 equiv	23	1.2	79	70
4	Li	12-crown-4, 1 equiv	50	1.2	78	70
5	Na	-	23	1.2	NR	NR
6	Na	-	50	1.2	NR	2
7	Na	-	110	3	35	38
8	Na	15-crown-5, 6 equiv	23	1.2	91	96
9	Na	**15-crown-5, 30 mol %**	**23**	**3**	**102**	**quant. (96)**[c]
10	Na	15-crown-5, 30 mol %	50	1.2	90	85
11	Na	15-crown-5, 15 mol %	23	1.2	41	-[d]
12	Na	15-crown-5, 15 mol %	50	1.2	74	90
13	Na	15-crown-5, 15 mol %	110	3	79	-[d]
14	Na	15-crown-5, 3 mol %	23	1.2	NR	-[d]
15	Na	15-crown-5, 3 mol %	50	1.2	17	-[d]
16	Na	15-crown-5, 3 mol %	110	3	67	65
17	Na	**HMTETA, 6 equiv**	**23**	**1.2**	**80**	**89 (86)**[c]
18	Na	HMTETA, 3 equiv	50	1.2	76	46
19	Na	HMTETA, 30 mol %	110	1.2	65	64
20	Na	**diglyme, 6 equiv**	**23**	**1.2**	**88**	**70 (78)**[c]
21	Na	diglyme, 3 equiv	50	1.2	89	72
22	Na	diglyme, 30 mol %	110	1.2	41	43

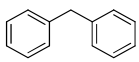
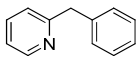
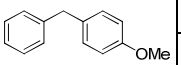
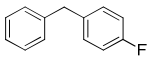
Conditions: 5 mol % Pd(OAc)$_2$, 10 mol % NiXantphos, base (3 equiv) in CPME; [a]HPLC analysis on 10 µmol scale; [b]yield determined by ^{1}H NMR spectroscopy of the crude reaction mixture on a 0.1 mmol scale; [c]isolated yield; [d]not determined. NR: no reaction (SM unreacted).

As illustrated in Table 1 four promising sets of conditions utilizing additives (Table 1, entries 2, 9, 17 and 20) were discovered (Conditions A: [LiN(SiMe$_3$)$_2$/6 equiv 12-crown-4]; Conditions B: [NaN(SiMe$_3$)$_2$/30 mol % 15-crown-5]; Conditions C: [NaN(SiMe$_3$)$_2$/6 equiv HMTETA] and Conditions D: NaN(SiMe$_3$)$_2$/6 equiv diglyme]). We were interested in testing the substrate generality with these new Conditions A–D. We investigated the DCCP of 5 aryl bromides (**2a2e**) bearing electron-donating and electron-withdrawing groups as well as one sterically hindered aryl bromide (**2f**) with four diphenylmethane derivatives (**1a**–**1d**) under the four sets of conditions highlighted in Table 1. The reactions were conducted in a 96 well-plate, worked up and assay yields (based on ^{1}H NMR spectroscopy and HPLC analysis) were obtained for all of the reactions. Table 2 outlines the results obtained for each combination of aryl bromide and diarylmethane (see Supporting Information for details). One of the triarylmethanes was prepared from two different sets of coupling partners, giving a total of 23 unique triarylmethane derivatives.

Overall, 21 of the 23 coupling combinations examined resulted in generation of triarylmethane products in fair to excellent yields (48–99%) with at least one of the conditions used. This is particularly impressive because unactivated diphenylmethanes were not viable substrates in the absence of additives with the LiN(SiMe$_3$)$_2$ and NaN(SiMe$_3$)$_2$. More specifically, 12 of these 20 triarylmethanes (**3aa**, **3ad**, **3ae**, **3ba**, **3bb**, **3bd**, **3be**, **3bf**, **3da**, **3dd**, **3de** and **3df**) were obtained in ≥90% yield using the additives. *p*-Bromobenzotrifluoride (**2c**) was reacted following our previous conditions.[6] A decrease in the amount of base along with an increase in the nucleophile loading were essential to avoid decomposition of the triarylmethane product formed.

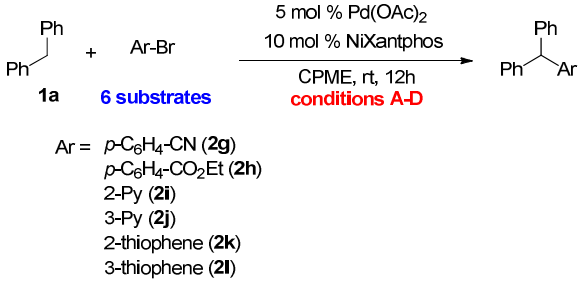
Control reactions were conducted in the presence of KN(SiMe$_3$)$_2$ in CPME at rt for all substrate combinations. Comparison of the results in Table 2 with the control experiments indicated that, in several cases the products were generated in comparable yields with the additive Conditions A–D and with the KN(SiMe$_3$)$_2$ control (see Supporting Information for details). The most significant improvements were seen in the formation of 4 new compounds (**3bb**, **3bc**, **3cb** and **3db**), which were accessed in higher yields employing the additive systems than with the controls with KN(SiMe$_3$)$_2$. Specifically, product **3bb** was obtained in 99% isolated yield with Conditions B [NaN(SiMe$_3$)$_2$/30 mol % 15-crown-5] vs. 68% AY with KN(SiMe$_3$)$_2$, **3bc** was accessed in 78% isolated yield with Conditions A [LiN(SiMe$_3$)$_2$/6 equiv 12-crown-4] vs. 5% AY with KN(SiMe$_3$)$_2$, **3cb** was achieved in 51% isolated yield with Conditions A [LiN(SiMe$_3$)$_2$/6 equiv 12-crown-4] vs. 17% AY with KN(SiMe$_3$)$_2$, and **3db** was produced in 76% isolated yield using Conditions A [LiN(SiMe$_3$)$_2$/6 equiv 12-crown-4] vs. 50% AY with KN(SiMe$_3$)$_2$ (see Supporting Information for details). Importantly, scale-up to laboratory scale using 0.1 mmol of substrates were similar to those determined in microscale experiments.

Table 2 Scope of aryl bromides and diarylmethanes in the DCCP under the four sets of conditions identified by HTE.[a]

Diarylmethanes		Conditions[a]	Ar-Br: 2a (4-tBu-C6H4-Br)	2b (4-F-C6H4-Br)	2c[b] (4-CF3-C6H4-Br)	2d (4-MeO-C6H4-Br)	2e (4-Me2N-C6H4-Br)	2f (1-Br-naphthalene)
			Results					
 1a	A	$LiN(SiMe_3)_2$, 6 equiv 12-C-4	87 (97)	6	25	106 (99)	66	9
	B	$NaN(SiMe_3)_2$, 30 mol % 15-C-5	96 (99)	54 (63)	18	118 (97)	105 (99)	91 (77)
	C	$NaN(SiMe_3)_2$, 6 equiv HMTETA	80 (86)	25	4	2	2	36
	D	$NaN(SiMe_3)_2$, 6 equiv diglyme	88 (78)	12	0	28	23	19
		Product	**3aa**	**3ab**	**3ac**	**3ad**	**3ae**	**3af**
 1b	A	$LiN(SiMe_3)_2$, 6 equiv 12-C-4	82	76	81 (78)	92	10	0
	B	$NaN(SiMe_3)_2$, 30 mol % 15-C-5	26	73 (99)	21	112 (99)	99 (94)	73 (99)
	C	$NaN(SiMe_3)_2$, 6 equiv HMTETA	37	31	19	66	83	27
	D	$NaN(SiMe_3)_2$, 6 equiv diglyme	95 (99)	87	multiple products	16	97	0
		Product	**3ba**	**3bb**	**3bc**	**3bd**	**3be**	**3bf**
 1c	A	$LiN(SiMe_3)_2$, 6 equiv 12-C-4	61 (52)	39 (51)	multiple products	59 (48)	48 (61)	55 (63)
	B	$NaN(SiMe_3)_2$, 30 mol % 15-C-5	30	10	multiple products	30	27	25
	C	$NaN(SiMe_3)_2$, 6 equiv HMTETA	8	2	0	6	0	0
	D	$NaN(SiMe_3)_2$, 6 equiv diglyme	1	0	0	3	4	1
		Product	**3ca**	**3cb**	**3cc**	**3cd**	**3ce**	**3cf**
 1d	A	$LiN(SiMe_3)_2$, 6 equiv 12-C-4	60	74 (76)	12	101	0	82 (88)
	B	$NaN(SiMe_3)_2$, 30 mol % 15-C-5	6	44	8	101 (99)	109 (99)	103
	C	$NaN(SiMe_3)_2$, 6 equiv HMTETA	73 (99)	47	0	58	83	56
	D	$NaN(SiMe_3)_2$, 6 equiv diglyme	49	2	0	41	32	32
		Product	**3da**	**3db**	**3dc**	**3dd = 3cb**	**3de**	**3df**

[a]All reactions were conducted in CPME at rt. Numbers in brackets correspond to isolated yields on laboratory scale. [b]3 equiv of diarylmethane and 2 equiv of base were used with substrate **2c**.

We next decided to probe the utility of the four sets of additive conditions and explore the cross-coupling reaction with six challenging aryl bromides (**2g**–**2l**) that failed or gave very low yields of desired products with diphenylmethane (**1a**) under the original conditions using $KN(SiMe_3)_2$ in CPME.[6] HTE in 1 mL vials was used to screen these 24 reactions (Scheme 7).



Scheme 7 DCCP of aryl bromides **2g**–**2l** with **1a** using Conditions A–D.

Figure 2 shows the most promising results obtained from the HTE screen. We observed that *p*-bromobenzonitrile (**2g**) and 2-bromopyridine (**2i**) rendered the desired product in good assay yield (high ratio product/internal standard) with at least one set of conditions used. The promising leads were then scaled to laboratory scale. Conditions A [$LiN(SiMe_3)_2$/6 equiv 12-crown-4] with *p*-bromobenzonitrile (**2g**) was the most effective affording 67% isolated yield of the desired coupled product (**3ag**). In contrast, 34% isolated yield was obtained with Conditions B [$NaN(SiMe_3)_2$/30 mol % 15-crown-5]. These results represented a significant improvement over those of the control using $KN(SiMe_3)_2$, which afforded the corresponding triarylmethane **3ag** in only 16% isolated yield.

Because functionalization of pyridines and related heterocycles is very important in medicinal chemistry,[32] we examined heteroaryl bromide substrates **2i**–**2l**. 2-Bromopyridine (**2i**) successfully underwent DCCP affording 75% isolated yield of desired product **3ai** with Conditions A and 37% isolated yield with Conditions B. No product was observed with the control, $KN(SiMe_3)_2$ or in the absence of the palladium catalyst with $KN(SiMe_3)_2$. In the case of *p*-Br-C_6H_4-CO_2Et (**2h**), the only product observed in moderate yield corresponded to the attack of the diphenylmethyl anion on the carbonyl group of ester. With

substrates 3-bromopyridine, 2-bromothiophene, or 3-bromothiophene (**2j–l**), no triarylmethane products were observed in the presence or absence of additives under our current DCCP conditions and remain challenging.

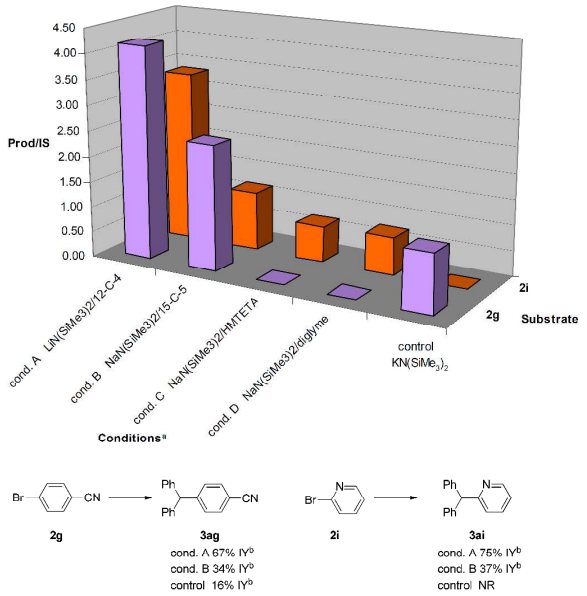
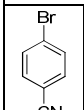
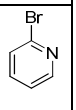
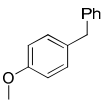
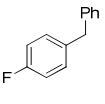


Fig. 2 Most promising results from HTE screen under different conditions. Substrates **2g** and **2i** showed better reactivity than the control reaction. [a]Conditions A: $LiN(SiMe_3)_2$, 6 equiv 12-crown-4, CPME, rt; Conditions B: $NaN(SiMe_3)_2$, 30 mol % 15-crown-5, CPME, rt; Conditions C: $NaN(SiMe_3)_2$, 6 equiv HMTETA, CPME, rt; Conditions D: $NaN(SiMe_3)_2$, 6 equiv diglyme, CPME, rt. [b]IY: isolated yield on laboratory scale.

Having proved that substrates **2g** and **2i** successfully underwent DCCP with diphenylmethane (**1a**) under Conditions A and B, we decided to explore their reactivity with diarylmethanes **1b**–**1d** using Conditions A–D. HTE in 1 mL vials was employed to screen these 24 reactions. Table 3 summarizes the results obtained from this screening. Assay yields (based on ^{1}H NMR spectroscopy and HPLC analysis) were obtained for each combination of aryl bromide and diarylmethane (see Supporting Information for details).

Table 3 Cross-coupling reaction of aryl bromides **2g** and **2i** with diarylmethanes **1b**–**1d** under Conditions A-D.

			ArBr	
			 **2g**	 **2i**
$ArCH_2Ar'$	**Conditions[a]**		**Results[b]**	
 **1b**	A	$LiN(SiMe_3)_2$, 6 equiv 12-C-4	92 (86)	95
	B	$NaN(SiMe_3)_2$, 30 mol % 15-C-5	83	83
	C	$NaN(SiMe_3)_2$, 6 equiv HMTETA	69	107 (96)
	D	$NaN(SiMe_3)_2$, 6 equiv diglyme	54	44
	CONTROL - $KN(SiMe_3)_2$		20	74
	Product		**3bg**	**3bi**
 **1c**	A	$LiN(SiMe_3)_2$, 6 equiv 12-C-4	0	<6
	B	$NaN(SiMe_3)_2$, 30 mol % 15-C-5	0	0
	C	$NaN(SiMe_3)_2$, 6 equiv HMTETA	0	0
	D	$NaN(SiMe_3)_2$, 6 equiv diglyme	0	0
	CONTROL - $KN(SiMe_3)_2$		0	0
	Product		**3cg**	**3ci**
 **1d**	A	$LiN(SiMe_3)_2$, 6 equiv 12-C-4	0	83 (85)
	B	$NaN(SiMe_3)_2$, 30 mol % 15-C-5	18 (26)	60
	C	$NaN(SiMe_3)_2$, 6 equiv HMTETA	3	0
	D	$NaN(SiMe_3)_2$, 6 equiv diglyme	0	0
	CONTROL - $KN(SiMe_3)_2$		14	0
	Product		**3dg**	**3di**

[a]All reactions were conducted in CPME at rt; [b]Results correspond to assay yields based on ^{1}H NMR of the crude mixture. Control results correspond to ^{1}H NMR yields from the crude mixture on laboratory scale. Numbers in brackets correspond to isolated yields on laboratory scale.

The additive systems enabled access to four new products (**3bg**, **3bi**, **3dg** and **3di**) in good to excellent yields and in all cases, superior results were obtained compared to control conditions with $KN(SiMe_3)_2$ (see Table 3). *p*-Bromobenzonitrile (**2g**) showed excellent reactivity with diarylmethane **1b** under Conditions A and B. The product (**3bg**) was obtained in 86% isolated yield using Conditions A. No reactivity was observed when **2g** was allowed to react with **1c** while only Conditions B rendered product **3dg** although in poor yield (26% isolated yield). Substrate **2i** gave the corresponding product **3bi** in high yield under Conditions A–C with C being the most promising (96% isolated yield). Product **3di** was achieved in 85% isolated yield using Conditions A but no desired product was observed for the reaction of **2i** with diarylmethane **1c**. Substrate **1c** is the least acidic diarylmethane of those examined in this study.

Overall, twenty six triarylmehtane derivatives were synthesized in good to excellent yields using the additives. In particular, ten of the compounds prepared showed better results with the additive conditions than under the control conditions using $KN(SiMe_3)_2$ in CPME in the absence of additive.[6] This is impressive when it is considered that in the original study of 33 substrate combinations with the $KN(SiMe_3)_2$, the triarylmethane products were isolated with an average yield of 91%.

Conclusions

Lewis basic additives can dramatically alter the outcome of reactions by coordination to reagents that possess main-group metals. Despite the well known beneficial impact of additives in a diverse range of chemical transformations, we are not aware of thorough studies concerning the effect of Lewis basic additives on metal-catalyzed C–H arylation reactions involving deprotonation of substrates possessing weakly acidic C–H bonds. This class of reactions is very important and includes enolate C-arylation processes and the DCCP of diarylmethanes, among others.

In this report, we have conducted a study on the use of additives in the DCCP of sp^3 C–H bonds of diphenylmethane derivatives with aryl bromides to form synthetically useful triarylmethanes. A number of potential mono- and polydentate Lewis basic additives were selected for examination. High-throughput experimentation techniques were employed on microscale to rapidly identify the most promising additives and guide the optimization of the reaction conditions (additive stoichiometry, base, solvent and temperature). These studies have resulted in development of four efficient Pd-catalyzed procedures that rely on additives to enable the generation of a range of aryl- and heteroaryl containing triarylmethanes. The most useful additives discovered for this process are polydentate ethers (12-crown-4, 15-crown-5, and diglyme), and the tetradentate amine 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA). A benefit of these additives is that all are commercially available and relatively inexpensive. It is particularly noteworthy that the bases used in these new procedures, $LiN(SiMe_3)_2$ and $NaN(SiMe_3)_2$, fail to promote formation of detectable amounts of triarylmethane coupling products with unactivated diarylmethanes in the absence of the additives. Presumably these additives enhance the reactivity of $LiN(SiMe_3)_2$ and $NaN(SiMe_3)_2$ by coordination to the main group metal and reducing their aggregation state.[38] It is interesting to note that in the combination of $NaN(SiMe_3)_2$ with 15-crown-5, the crown ether is used in sub stoichiometric quantity (30 mol %). In contrast to $LiN(SiMe_3)_2$ and $NaN(SiMe_3)_2$, the use of $KN(SiMe_3)_2$ with additives gives inferior results relative to reactions without additives. Finally, it is important to mention that the new procedures employing additives result in a significant improvement in the reaction yields with certain substrates. In the most striking example, 2-bromopyridine, which failed to undergo DCCP under the original conditions with $KN(SiMe_3)_2$, resulted in 75% yield with $LiN(SiMe_3)_2$ and 12-crown-4.

Because a variety of important C–H functionalizations involve a deprotonation step (Sonogashira reaction, α-arylation of carbonyl compounds, benzylic C–H arylations of aromatics and heteroaromatics, etc) we envision potential applications of the additives outlined herein to facilitating these classes of reactions and thus enabling increased access to chemical diversity and to the discovery of new reactions.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Data for new compunds, experimental procedures, copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/b000000x/

1 a) A. de Meijere and F. E. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley- VCH: Weinheim, 2004; b) F. Diederich and P. J. Stang, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH: Weinheim, 1998; c) N. Miyaura, *Cross-Coupling Reactions. A Practical Guide*, Springer: Berlin, 2002; d) E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, John Wiley & Sons: New York, 2002.

2 a) P. Novak and R. Martin, *Curr. Org. Chem.*, 2011, **15**, 3233; b) L. Ackermann, *Chem. Commun.*, 2010, **46**, 4866; c) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; d) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem. Int. Ed.*, 2009, **48**, 9792; e) F. Bellina and R. Rossi, *Chem. Rev.*, 2010, **110**, 1082; f) D. A. Culkin and J. F. Hartwig, *Acc. Chem. Res.*, 2003, **36**, 234; g) C. C. C. Johansson and T. J. Colacot, *Angew. Chem. Int. Ed.*, 2010, **49**, 676; h) F. Kakiuchi and T. Kochi, *Synthesis*, 2008, 3013; i) G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447; j) C. J. Scheuermann, *Chem. Asian J.*, 2010, **5**, 436; k) J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; l) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; m) J.-Q. Yu, R. Giri and X. Chen, *Org. Biomol. Chem.*, 2006, **4**, 4041.

3 a) O. Baudoin, *Chem. Soc. Rev.*, 2011, **40**, 4902; b) R. G. Bergman, *Nature*, 2007, **446**, 391; c) X. Chen, K. M. Engle, D. H. Wang and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2009, **48**, 5094; d) O. Daugulis, H. Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; e) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem. Eur. J.*, 2010, **16**, 2654; f) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; g) T. Niwa, H. Yorimitsu and K. Oshima, *Organic Lett.*, 2007, **9**, 2373; h) C. L. Sun, B. J. Li and Z. J. Shi, *Chem. Rev.*, 2011, **111**, 1293; i) M. Tobisu and N. Chatani, *Angew. Chem. Int. Ed.*, 2006, **45**, 1683; j) M. Wasa, K. M. Engle and J.-Q. Yu, *Isr. J. Chem.*, 2010, **50**, 605; k) G. Song, Y. Su, X. Gong, K. Han and X. Li, *Organic Lett.*, 2011, **13**, 1968; l) H. Li, B.-J. Li and Z.-J. Shi, *Catal. Sci. Technol.*, 2011, **1**, 191.

4 a) G. I. McGrew, J. Temaismithi, P. J. Carroll and P. J. Walsh, *Angew. Chem. Int. Ed.*, 2010, **49**, 5541; b) J. Zhang, C. Stanciu, B. Wang, M. M. Hussain, C.-S. Da, P. J. Carroll, S. D. Dreher and P. J. Walsh, *J. Am. Chem. Soc.*, 2011, **133**, 20552.

5 G. I. McGrew, C. Stanciu, J. Zhang, P. J. Carroll, S. D. Dreher and P. J. Walsh, *Angew. Chem. Int. Ed.*, 2012, doi: 10.1002/anie.201201874.

6 J. Zhang, A. Bellomo, A. D. Creamer, S. D. Dreher and P. J. Walsh, *J. Am. Chem. Soc.*, 2012, **134**, 13765.

7 a) A. Bellomo, N. Celebi-Olcum, X. Bu, N. Rivera, R. T. Ruck, C. J. Welch, K. N. Houk and S. D. Dreher, *Angew. Chem. Int. Ed.*, 2012, **51**, 6912; b) I. W. Davies and C. J. Welch, *Science*, 2009, **325**, 701; c) S. D. Dreher, P. G. Dormer, D. L. Sandrock and G. A. Molander, *J. Am. Chem. Soc.*, 2008, **130**, 9257; d) J. Kobayashi, Y. Mori, K. Okamoto, R. Akiyama, M. Ueno, T. Kitamori and S. Kobayashi, *Science*, 2004, **304**, 1305; e) A. McNally, C. K. Prier and D. W. C. MacMillan, *Science*, 2011, **334**, 1114; f) G. A. Molander, S. L. J. Trice and S. D. Dreher, *J. Am. Chem. Soc.*, 2010, **132**, 17701; g) M. T. Reetz, K. M. Khling, A. Deege, H. Hinrichs and D. Belder, *Angew. Chem.*, 2000, **112**, 4049; h) D. W. Robbins and J. F. Hartwig, *Science*, 2011, **333**, 1423; i) O. Trapp, S. K. Weber, S. Bauch and W. Hofstadt, *Angew. Chem.*, 2007, **119**, 7447.

8 a) D. Balcells, E. Clot and O. Eisenstein, *Chem. Rev.*, 2010, **110**, 749; b) Y. Boutadla, D. L. Davies, S. A. Macgregor and A. I. Poblador-Bahamonde, *Dalton Trans.*, 2009, 5820; c) Y. Boutadla, D. L. Davies, S. A. Macgregor and A. I. Poblador-Bahamonde, *Dalton Trans.*, 2009, 5887; d) D. L. Davies, S. M. A. Donald and S. A. Macgregor, *J. Am. Chem. Soc.*, 2005, **127**, 13754; e) D. Garcia-Cuadrado, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2006, **128**, 1066; f) D. Garcia-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2007, **129**, 6880; g) S. I. Gorelsky, D. Lapointe and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 10848; h) M. Lafrance, C. N. Rowley, T. K. Woo and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 8754; i) D. Lapointe and K. Fagnou, *Chem. Lett.*, 2010, **39**, 1119.

9 F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456.

10 F. G. Bordwell, W. S. Matthews and N. R. Vanier, *J. Am. Chem. Soc.*, 1975, **97**, 442.

11 E. Hevia and R. E. Mulvey, *Angew. Chem.*, 2011, **50**, 6448.

12 A. Zapf and M. Beller, *Chem. Eur. J.*, 2001, **7**, 2908.

13 M. Nakamura, K. Matsuo, S. Ito and E. Nakamura, *J. Am. Chem. Soc.*, 2004, **126**, 3686.

14 R. Martin and A. Fürstner, *Angew. Chem. Int. Ed.*, 2004, **43**, 3955.

15 G. Cahiez, V. Habiak, C. Duplais and A. Moyeux, *Angew. Chem. Int. Ed.*, 2007, **46**, 4364.

16 A. Guérinot, S. Reymond and J. Cossy, *Angew. Chem. Int. Ed.*, 2007, **46**, 6521.

17 W. M. Czaplik, M. Mayer and A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.*, 2009, **48**, 607.

18 O. Vechorkin, V. Proust and X. Hu, *J. Am. Chem. Soc.*, 2009, **131**, 9756.

19 K. Jouvin, J. Heimburger and G. Evano, *Chem. Sci.*, 2012, **3**, 756.

20 M.-G. Wang, J. Wu and Z.-C. Shang, *Synlett*, 2012, **23**, 589.

21 a) E. Zuidema and C. Bolm, *Chem Eur J*, 2010, **16**, 4181; b) P.-F. Larsson, C. Bolm and P.-O. Norrby, *Chem. Eur. J.*, 2010, **16**, 13613.

22 D. Noda, Y. Sunada, T. Hatakeyama, M. Nakamura and H. Nagashima, *J. Am. Chem. Soc.*, 2009, **131**, 6078.

23 D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2010, **1**, 13.

24 J. C. Antilla and S. L. Buchwald, *Organic Lett.*, 2001, **3**, 2077.

25 M. A. McGowan, J. L. Henderson and S. L. Buchwald, *Organic Lett.*, 2012, **14**, 1432.

26 E. J. Hennessy and S. L. Buchwald, *Organic Lett.*, 2002, **4**, 269.

27 J. L. Rutherford, M. P. Rainka and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 15168.

28 a) A. Ramirez, X. Sun and D. B. Collum, *J. Am. Chem. Soc.*, 2006, **128**, 10326; b) J. F. Remenar and D. B. Collum, *J. Am. Chem. Soc.*, 1998, **120**, 4081; c) J. F. Remenar, B. L. Lucht and D. B. Collum, *J. Am. Chem. Soc.*, 1997, **119**, 5567.

29 L. Gupta, A. C. Hoepker, K. J. Singh and D. B. Collum, *J. Org. Chem.*, 2009, **74**, 2231.

30 G. C. Clososki, C. J. Rohbogner and P. Knochel, *Angew. Chem. Int. Ed.*, 2007, **46**, 7681.

31 S. H. Wunderlich and P. Knochel, *Angew. Chem. Int. Ed.*, 2007, **46**, 7685.

32 S. Duez, A. K. Steib, S. M. Manolikakes and P. Knochel, *Angew. Chem. Int. Ed.*, 2011, **50**, 7686.

33 a) Q. Shen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 7734; b) T. Hama, D. A. Culkin and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 4976.

34 X. Liu and J. F. Hartwig, *J. Am. Chem. Soc.*, 2004, **126**, 5182.

35 W. Su, S. Raders, J. G. Verkade, X. Liao and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2006, **45**, 5852.

36 a) B. M. Trost and D. A. Thaisrivongs, *J. Am. Chem. Soc.*, 2008, **130**, 14092; b) B. M. Trost and D. A. Thaisrivongs, *J. Am. Chem. Soc.*, 2009, **131**, 12056.

37 a) D. J. Cram, *J. Inclusion Phenom.*, 1988, **6**, 397; b) D. J. Cram and J. M. Cram, *Science*, 1974, **183**, 803; c) D. J. Cram, R. C. Helgeson, L. R. Sousa, J. M. Timko, M. Newcomb, P. Moreau, F. de Jong, G. W. Gokel, D. H. Hoffman, L. A. Domeier, S. C. Peacock, M. Khorshed and L. Kaplan, *Pure Appl. Chem.*, 1975, **43**, 327; d) J.-M. Lehn, *J. Inclusion Phenom.*, 1988, **6**, 351; e) J. M. Lehn, *Acc. Chem. Res.*, 1978, **11**, 49; f) C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **89**, 7017; g) C. J. Pedersen, *J. Inclusion Phenom.*, 1988, **6**, 337; h) P. P. Power, *Acc. Chem. Res.*, 1988, **21**, 147; i) P. P. Power and X. Xu, *J. Chem. Soc., Chem. Commun.*, 1984, 358.

38 a) V. H. Gessner, C. Daschlein and C. Strohmann, *Chem. Eur. J.*, 2009, **15**, 3320; b) R. A. Gossage, J. Jastrzebski and G. van Koten, *Angew. Chem. Int. Ed.*, 2005, **44**, 1448; c) A. C. Jones, A. W. Sanders, M. J. Bevan and H. J. Reich, *J. Am. Chem. Soc.*, 2007, **129**, 3492; d) B. L. Lucht, M. P. Bernstein, J. F. Remenar and D. B. Collum, *J. Am. Chem. Soc.*, 1996, **118**, 10707; e) B. L. Lucht and D. B. Collum, *Acc. Chem. Res.*, 1999, **32**, 1035.

39 a) B. L. Lucht and D. B. Collum, *J. Am. Chem. Soc.*, 1996, **118**, 2217; b) B. L. Lucht and D. B. Collum, *J. Am. Chem. Soc.*, 1996, **118**, 3529; c) P. Zhao and D. B. Collum, *J. Am. Chem. Soc.*, 2003, **125**, 4008.

Chemical Science

TABLE OF CONTENTS

Additive Effects on Palladium-Catalyzed Deprotonative-Cross-Coupling Processes (DCCP) of sp^3 C–H Bonds in Diarylmethanes

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We describe the use of additives in Pd-catalyzed DCCP of unactivated sp^3 C–H bonds of diarylmethanes with aryl bromides.