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Palladium-Catalyzed Synthesis of Diarylmethanes: Exploitation of Carbanionic Leaving Groups

Jason R. Schmink and Nicholas E. Leadbeater*

Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Storrs, Connecticut 06269-3060

nicholas.leadbeater@uconn.edu

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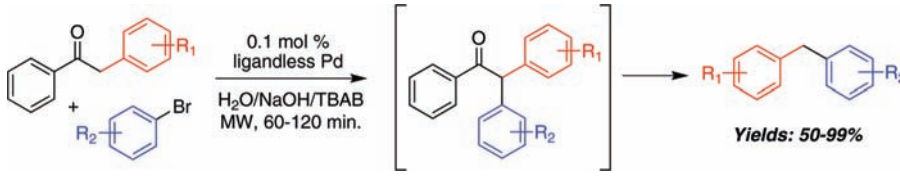
ABSTRACT



A novel route to the synthesis of diarylmethanes via a Pd-catalyzed α-arylation of benzyl ketones is reported. By harnessing the inherent reactivity of enolates, it is possible to circumvent the need for a transmetalating reagent such as boron for the coupling. Additionally, the two phenyl rings of the intermediate are exploited to stabilize the high-energy carbanionic leaving group in a straightforward synthesis.

Palladium-catalyzed carbon−carbon bond formation continues to be a powerful synthetic organic tool.[1] Thus, it is no surprise that the palladium-catalyzed synthesis of diarylmethanes has received much attention recently. The cross-coupling of arylboronic acids with benzyl halides[2,3] or benzyl phosphates,[4] coupling of aryltrifluoroborates with benzyl halides,[5] and the coupling of benzyl indium reagents with aryl iodides[6] illustrate a few recent approaches in the synthesis of diarylmethanes. Although the use of transmetallating reagents in palladium-catalyzed carbon−carbon bond formation continues to be a powerful synthetic technique, these reagents are often synthesized from the corresponding halides and thus reduce overall atom economy for the transformation. As a result, the development of selective cross-coupling reactions that avoid a transmetalating event is highly desirable. Given that the diarylmethane motif is found in a range of biologically active compounds and pharmaceuticals, in our laboratory we have been seeking approaches to their synthesis that avoid a transmetallating reagent and employ ligand-free palladium catalysts at low loadings (i.e., ≤ 0.1 mol %).

The simultaneous publications by Buchwald[7] and Hartwig[8] in 1997 describing palladium-catalyzed α-arylation of ketones illustrate an attractive approach to carbon−carbon bond formation, as it takes advantage of the inherent reactivity of enolates and avoids a transmetalating reagent. Despite the many advantages and further development of this chemistry over the past decade,[9] to our knowledge there is no report that avoids the use of either activating phosphine or N-heterocylic carbene ligands to affect this reaction. Thus, we wanted to probe the feasability of performing the α-arylation

(1) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 1.
(2) For the first reported example of a Suzuki−Miyaura coupling with a benzyl halide, see: Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501.
(3) For recent examples, see: (a) Nobre, S. M.; Montiero, A. L. *Tetrahedron Lett.* **2004**, *45*, 8225. (b) Burns, M. J.; Fairlamb, I. J. S.; Kapdi, A. R.; Sehnal, P.; Taylor, R. J. K. *Org. Lett.* **2007**, *9*, 5397.
(4) McLaughlin, M. *Org. Lett.* **2005**, *7*, 4875.
(5) Molander, G. A.; Elia, M. D. *J. Org. Chem.* **2006**, *71*, 9198.
(6) Chupak, L. S.; Wolkowski, J. P.; Chantigny, Y. A. *J. Org. Chem.* **2009**, *74*, 1388.
(7) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.
(8) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.
(9) For representative examples, see: (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (b) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P *Org. Lett.* **2002**, *4*, 4053. (c) Grasa, G. A.; Colacot, T. J. *Org. Lett.* **2007**, *9*, 5489. (d) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1545. (e) Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 10510.

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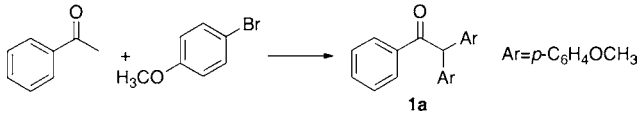
of ketones using simple ligandless palladium catalysts. Application of microwave heating in Suzuki and Heck couplings has allowed us to affect these similar palladium-catalyzed transformations rapidly and with extremely low loadings of ligandless palladium in aqueous reaction media.[10−12]

We began our studies by investigating the coupling of acetophenone with 2 equiv of 4-bromoanisole to form **1a**. We chose to perform the reactions under phase-transfer conditions in a water−sodium hydroxide−tetrabutylammonium bromide (TBAB) mix and using a commercially available palladium ICP standard solution as a convenient ligandless palladium source (0.1 mol %). Immediately, we noticed that whereas we were able to isolate diarylated product **1a** in moderate yield after 20 min of heating at 150 °C (Table 1, entry 1), extending the reaction time to 30 or 60 min resulted in a decrease in yield (Table 1, entries 2 and 3). Reducing the reaction temperature and catalyst loading while extending the time did, however, show an overall increase in isolated yields, leading to an optimized set of reaction conditions of 0.025 mol % Pd, 100 °C for 20 h, which provided a 95% isolated yield of the diarylated product (Table 1, entry 7). Although the reaction progresses at even lower catalyst loadings, it was deemed unreasonably sluggish (Table 1, entry 8).

Table 1. Optimization of Conditions for the Diarylation of Acetophenone with 4-Bromoanisole[a]



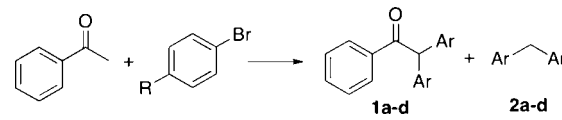
1a

entry	time (h)	temp[b]	Pd (mol %)[c]	yield (%)[d]
1	0.33	150	0.1	73
2	0.5	150	0.1	63
3	1	150	0.1	64
4	0.5	130	0.05	81
5	7	110	0.05	90
6	20	100	0.05	95
7	20	100	0.025	95
8	20	100	0.005	58/28/14[e]

[a] Conditions: 1.0 mmol of acetophenone, 2.1 mmol of 4-bromoanisole, 0.5 mmol of TBAB, 2.0 mL of 2.0 M NaOH(aq). [b] Entries 1−5 performed using microwave heating, entries 6−9 carried out in a thermostatted oil bath. [c] Loading based upon aryl bromide. [d] Isolated yields. [e] Relative ratio of diarylated product:monoarylated product:acetophenone.

Our next step was to perform a small screen of three additional substrates to probe the effects of changing the aryl bromide coupling partner. While the optimized conditions worked well for the electron-rich 4-bromoanisole (Table 2, entry a), when electron-neutral or electron-poor systems were used, the conversion to the diarylated products dropped significantly (Table 2, entries b−d). Of interest, however, was the observation of diarylmethanes as byproduct. Indeed, in the case of 1-bromo-4-fluorobenzene, a significant amount of 4,4′-difluorodiphenylmethane (**2d**) was isolated. This electron-poor system is likely better able to stabilize the carbanionic diarylmethane leaving group. This observation helped to explain why yields suffered initially when the reaction between acetophenone and 4-bromoanisole was performed at higher temperatures. While there are limited examples of isolating diarylmethanes from the corresponding ketone intermediates for characterization purposes,[13] the authors are not aware of any systematic approach employing this methodology in order to synthesize these moieties. As a result, we felt that this mechanistically interesting route to diarylmethanes warranted further exploration.

Table 2. Electronic Studies into the Diarylation of Acetophenone[a]



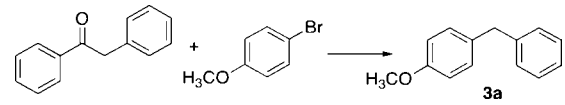
1a-d 2a-d

entry	R	conversion[b] to **1** (%)	conversion to **2** (%)[b]
A	-OCH_3	>95	tr
B	-H	91	9
C	-CH_3	89	11
D	-F	52	48

[a] Conditions: 1.0 mmol of acetophenone, 2.1 mmol of aryl bromide, 0.5 mmol of TBAB, 2.0 mL of 2.0 M NaOH(aq), 0.025 mol % $PdCl_2$ (based on aryl bromide), 100 °C, 20 h. [b] Ratios of **1**:**2** as determined by ^{1}H NMR; in all cases consumption of aryl bromide starting material was complete.

We moved from acetophenone to deoxybenzoin as the ketone coupling partner in order to optimize conditions for generating benzylated coupling product **3a**. We reasoned that additional equivalents of NaOH should not only accelerate the rate of the reaction but would be necessary because of

Table 3. Optimization of the Formation of 4-Methoxy-diphenylmethane from Deoxybenzoin and 4-Bromoanisole[a]



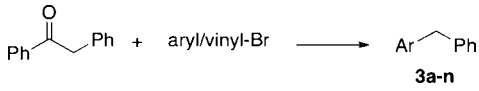
3a

entry	reaction time and temperature	conversion (%)[c]
1	150 °C, 60 min	90[b]
2	150 °C, 90 min	65
3	130 °C, 30 min; 160 °C, 30 min	>95 (91)[d]

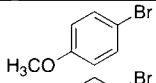
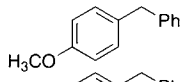
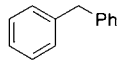
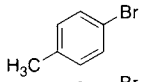
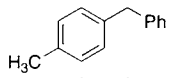
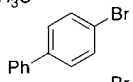
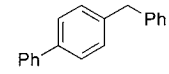
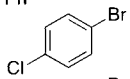
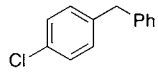
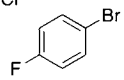
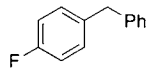
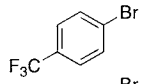
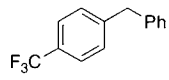
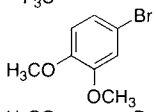
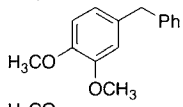
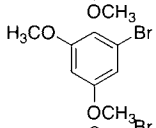
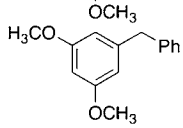
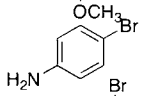
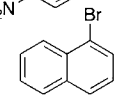
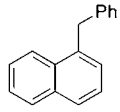
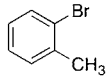
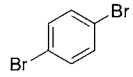
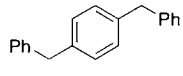
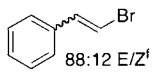
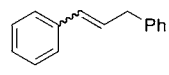
[a] Conditions: 1.1 mmol of deoxybenzoin, 1.0 mmol of 4-bromoanisole, 2.5 mL of 3.0 M NaOH(aq), 0.1 mol % $PdCl_2$. [b] 0.2 mol % $PdCl_2$. [c] Conversion to desired product relative to arylated intermediate determined by ^{1}H NMR; consumption of 4-bromoanisole was complete. [d] Isolated yield.

(10) For a review see: Leadbeater, N. E. *Chem. Commun.* **2005**, 2881.
(11) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161.
(12) Arvela, R. K.; Leadbeater, N. E. *J. Org. Chem.* **2005**, *70*, 1786.
(13) (a) Lagrave, R. *Ann. Chim.* **1927**, *8*, 363. (b) Koelsch, C. F. *J. Am. Chem. Soc.* **1931**, *53*, 1147.

Table 4. Synthesis of Diarylmethanes from Deoxybenzoin[a]



3a-n

entry	bromide S.M.	product	yield (%)[b]
a			91
b			91
c			99
d			98
e			78
f			97
g			84[c]
h			93
i			99
j		not observed	--
k			73[d]
l		not observed	--
m			89[e]
n	 88:12 E/Z[f]		61 92:8 E/Z[f]

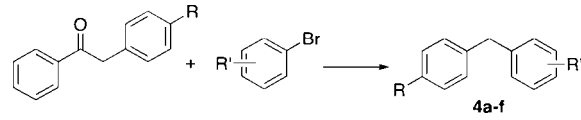
[a] Conditions: 1.0 mmol of aryl bromide, 1.1 mmol of deoxybenzoin, 0.5 mmol of TBAB, 2.5 mL of 3.0 M NaOH(aq), 0.1 mol % $PdCl_2$, microwave heating, 130 °C for 30 min followed by 160 °C for 30 min. [b] Isolated yields. [c] Additionally, 32 mg of 4,4′-bis(trifluoromethyl)biphenyl was isolated. [d] 60 min at 130 °C followed by 30 min at 160 °C. [e] 0.5 mmol dibromobenzene. [f] 1.0 mmol of deoxybenzoin, 2.4 mmol of β-bromostyrene, *E*/*Z* ratio assigned by ^{1}H NMR integrations of the β-bromostyrene and the isolated product.

the equivalent of benzoic acid that is generated as the reaction progresses. We undertook a screen of reaction conditions using 1 equiv of 4-bromoanisole and 3.0 M aqueous sodium hydroxide as solvent (Table 3). Our optimal conditions involved a two-stage process, namely, heating the reaction mixture to 130 °C and holding at this temperature for 30 min before increasing to 160 °C for a further 30 min (Table 3, entry 3).

With optimized conditions in hand, we screened a number of aryl bromides to probe the scope and limitations of this new methodology. A wide range of substrates could be used in the coupling with success, the notable exception being 4-bromoaniline (Table 4, entry j), which afforded no product nor any arylated intermediate, instead returning only starting materials. The methodology allowed for the chemoselective coupling of 1-bromo-4-chlorobenzene (Table 4, entry e), just the bromo functionality being involved in the reaction, although with slightly attenuated reactivity. Moderate conversion was achieved using 1-bromonaphthlene (Table 4, entry k), though there was no reaction with the more sterically demanding 2-bromo-toluene (Table 4, entry l).[14] The reaction could be extended to use a vinyl bromide coupling partner. Using β-bromostyrene afforded the desired β-benzylstyrene (**3n**) in moderate yield. However, due to competitive decomposition of the β-bromostyrene, 2.4 equiv of the vinyl bromide had to be used in order to ensure complete consumption of the deoxybenzoin starting material.

In order to gain further insight into the reaction, we sought to couple aryl bromides with substituted deoxybenzoins. It became apparent that the nature of the substituent on the deoxybenzoin had a more pronounced impact upon the rate of the reaction than that of the aryl bromide. Only the couplings with the electronically similar α-(4′-methylphenyl)acetophenone (Table 5, entries 1−3) resulted in complete

Table 5. Synthesis of Substituted Diarylmethanes[a]



4a-f

entry	R	R′	product	yield (%)[b]
1	CH_3	4-Cl	**4a**	50[c,d]
2	CH_3	4-Ph	**4b**	87[c]
3	CH_3	4-OCH_3	**4c**	83
4	Cl	4-F	**4d**	80
5	Cl	4-CH_3	**4a**	95
6	Cl	3-Cl	**4e**	62
7	Cl	OCH_3	**4f**	82
8	OCH_3	4-Cl	**4f**	(15/10/75)[e]
9	OCH_3	3,5-$(OCH_3)_2$	**4g**	(−/10/90)[e]

[a] Conditions: identical to Table 4, but 130 °C for 1 h followed by 160 °C for 1 h. [b] Isolated yields. [c] 130 °C for 30 min followed by 160 °C for 30 min. [d] 15 mg of the symmetric 4,4′-dichlorobiphenyl side product was isolated. [e] Relative conversion of product:arylated intermediate:starting deoxybenzoin as determined by ^{1}H NMR of the crude product mixture.

consumption of the starting aryl bromide after 60 min. All other reactions required longer reaction times and were run at 130 °C for 1 h followed by an additional 1 h at 160 °C in order to consume all of the starting aryl bromide. The attenuated reactivity of a slightly electron-rich deoxybenzoin versus a slightly electron-poor one can be seen in the two

(14) A trace of the arylated intermediate, 2-(2-methyl-phenyl)deoxybenzoin, in the crude mixture was detected by ^{1}H NMR.

orthogonal syntheses of **4f** (Table 5, entries 7 and 8). Placing the chlorine moiety on the deoxybenzoin and reacting with 4-bromoanisole (Table 5, entry 7) affords **4f** in a moderate 82% isolated yield, but reversal of the substitution pattern (Table 5, entry 8) reduces the reactivity dramatically, and after 2 h the crude reaction mixture contains only approximately 15% of **4f**. Similar effects are seen in the two syntheses of **4a**. Reacting 4-bromotoluene with the chlorinated deoxybenzoin (Table 5, entry 5) affords the product in 95% isolated yield, but upon reversal of the substitution pattern (Table 5, entry 1) only 50% of **4a** is isolated.

In conclusion, we have reported a novel, ligand-free, palladium-catalyzed route to the synthesis of diarylmethanes carried out in water. This route takes advantage of the inherent reactivity of enolates toward palladium-catalyed coupling, hence eliminating the need for a transmetalating reagent. The use of microwave heating facilitates the methodology and enables facile access to the elevated temperatures required. Computational and kinetic investigations are currently underway to explore this mechanism in greater detail, and the results will be reported in due course.

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Supporting Information Available: Experimental procedures and NMR spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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