Published in final edited form as:
Angew Chem Int Ed Engl. 2010 July 26; 49(32): 5541–5544. doi:10.1002/anie.201000957.

A Novel Approach to Polyarylated Methanes via Cross-coupling of Tricarbonylchromium-Activated Benzyllithiums**

Genette I. McGrew, **Jesada Temaismithi**, **Patrick J. Carroll**, and **Patrick J. Walsh**
UPenn/Merck HTE Laboratories, Department of Chemistry, University of Pennsylvania, 231 S. 34th St, Philadelphia, Pennsylvania, 19104, USA, Fax: (+) 1 215 573 6743, Homepage: http://titanium.chem.upenn.edu/walsh/index.html

Patrick J. Walsh: pwalsh@sas.upenn.edu

Keywords

C–C coupling; chromium; organolithium; palladium; triarylmethanes

Polyarylated methanes are attracting considerable attention due to their growing importance in developing medicinal agents for cancer[1] and vascular disease,[2, 3] as well as in leuco dye precursors,[4, 5] photochromic agents, and applications in materials science.[6, 7] Most syntheses of polyarylmethanes involve Friedel-Crafts-type (F-C) electrophilic aromatic substitution reactions,[5,6, 8–13] although there are some limited exceptions.[4, 14, 15] Recently, modified F-C processes,[9, 16] including a novel copper-catalyzed aza-Friedel-Crafts variant,[17] have been used in the preparation of differentially substituted triarylmethanes. The F-C approach, however, is limited by both reactivity and selectivity: the nucleophile must be electron-rich *and* unhindered for adequate reactivity and the selectivity is controlled by the relative directing abilities of the substituents. Thus, triarylmethanes with certain electron withdrawing groups and those with meta substitution, are largely inaccessible. A complementary and general route to polyarylated methanes that enables the synthesis of currently inaccessible members of this important structural class is needed.

A strategy that would circumvent the limitations of the F-C reaction is based on benzylic anion synthons. Traditionally, reagents for this synthon are based on metals such as boron, tin or zinc to temper reactivity.[18–20] An alternative approach to attenuate the reactivity of benzylic nucleophiles is η^6-coordination to a metal fragment such as $Cr(CO)_3$.[21–24] Along these lines, Kalinin and co-workers generated $(\eta^6\text{-}C_6H_5CH_2Li)Cr(CO)_3$, but were unable to effect palladium catalyzed cross-coupling reactions. After transmetallation to zinc the resulting $(\eta^6\text{-}C_6H_5CH_2ZnCl)Cr(CO)_3$ underwent palladium catalyzed single coupling with aryl halides to furnish diarylmethanes in low yield (average 37%).[25] The intermediate transmetallation to zinc prevents the realization of the tricarbonylchromium group's full potential: to activate more than one benzylic C–H bonds and open the door to multiple functionalizations via sequential deprotonation/coupling events.[26]

**This research was supported by the National Institutes of Health, General Medical Sciences (GM058101) and National Science Foundation (CHE-0848467). JT is a Vagelos Scholar.

Correspondence to: Patrick J. Walsh, pwalsh@sas.upenn.edu.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Herein we disclose a general, high-yielding cross-coupling method between $Cr(CO)_3$-activated toluene derivatives and aryl bromides to afford a broad range of di- and triarylmethanes that are difficult or impossible to access by known methods.

Our initial studies used tricarbonylchromium-complexed diphenylmethane (**1**, Scheme 1) and 4-bromotoluene as coupling partners. Use of alkoxide bases at room temperature resulted in no product (Table 1, entries 1 and 2). In contrast, $LiN(SiMe_3)_2$ combined with $PdCl_2(PPh_3)_2$ (3 mol %) afforded 70% isolated yield of the coupled product **2a** after 20 h at RT (entry 3) and 91% yield in 45 min at 60 °C (entry 4). On the other hand, stronger amide bases such as LDA, $NaN(SiMe_3)_2$, or $KN(SiMe_3)_2$ (entries 5–7), or related catalysts, including $Cl_2Pd(dppf)$(entries 8–10) were less effective. The optimized conditions in entry 4 were used to determine the substrate scope (Table 2).

The diphenylmethane complex **1** readily undergoes cross-coupling reactions with a variety of aryl bromides in 81–94% isolated yield of triarylmethane complexes **2a**–**2k** (Table 2). Electron-withdrawing (**2d**, **2e**), donating (**2f**–**2h**), and *ortho* substituted aryl bromides (**2h**–**2k**) were all successful coupling partners. Of medicinal relevance, our method enabled installation of a 4-substituted indole (**2k**).[27] In contrast, F-C chemistry strongly favours reaction of indole at the 3-position (or 2-position if the 3 is blocked).[5, 11–13, 17] Polyarylmethane derivatives bearing privileged indoles have attracted interest due to their widespread occurrence in biologically active compounds.

Next we examined reactions of (η^6-toluene)$Cr(CO)_3$ (**3**, Scheme 2). Although these reactions did not proceed well at room temperature, conversion to *triaryl*methane products **5a–f** (Table 3) was observed upon heating at 60 °C. Note that reaction with diarylmethane intermediate **4** is faster than the first coupling with **3**, probably due to the greater acidity of the benzlic C–H's of **4** over **3**.[28] In contrast, bulky 2,6-disubstitued aryl bromides afforded mono-coupled products **4g** and **4h**, likely due to steric hindrance.

Having demonstrated that two couplings could occur on a single methyl group, we wondered if one tricarbonylchromium center could activate multiple methyl groups in complexes of xylene and mesitylene. We were concerned that after the first methyl had undergone two arylations, the newly-formed triarylmethane moiety would be deprotonated and the resulting anion would inhibit further deprotonation and coupling at the remaining methyl groups. As shown in eq 2 and Table 4, this was not a serious issue. Subjecting (η^6-*p*-xylene)$Cr(CO)_3$ (**6**) to cross-coupling conditions with the bulky 1-bromo-2,4,6-triisopropylbenzene furnished di-coupled **7** in 73% yield. Employing 4-bromofluorobenzene gave tetracoupled **8** in 70% yield. Furthermore, the mesitylene complex **9** was coupled with 4-bromoanisole (Scheme 3) resulting in formation of the hexacoupled product **10** in 43% yield (over 86% for each C–C bond-forming event). The structure of the hexacoupled product is illustrated in Figure 1.[29] In the case of (η^6-*o*-xylene)$Cr(CO)_3$ (**11**), bulky 1-bromo-2,6-dimethylbenzene as coupling partner resulted in single arylation of each benzylic methyl to give the dicoupled product (**12**), in 85% yield. Use of the less sterocally demanding aryl bromide 4-bromo-*N,N*-dimethylaniline, however, led to either unsymmetrical di-coupled product (**13**, in which both aryl groups couple to a single methyl), or unsymmetrical tri-coupled product (**14**) by varying the amount of base and reaction time. Steric barriers to both deprotonation and transmetallation likely account for the absence of tetraarylated (symmetrical) coupling product. These polyarylation reactions highlight a significant advantage of this approach over others: the possibility of multiple coupling reactions.[16]

We also examined the possibility of coupling in the presence of α-heteroatoms and β–hydrogens using tricarbonylchromium-coordinated benzyl ether (**15**), *N,N*-

dimethylbenzylamine (**16**), and ethylbenzene (**17**). Benzyl ether complex **15** underwent coupling employing conditions similar to those in Scheme 2 to afford monocoupled products **18a–e** in 58–80% yield (Scheme 4). Surprisingly, further reaction, whether in the presence of the original aryl bromide or with a different aryl bromide after isolation, was found to give triarylmethyl ether complexes **19a–e**. *N,N*-Dimethylbenzyl amine complex **16** underwent single coupling to form diarylamines **20a–d** in 68–82% yield. No doubly coupled products were observed, possibly due to larger size of the dimethylamino group over the *n*-propyl ether in **15**. It is noteworthy that diarylmethylamines are important pharmacophores and are present in numerous medications.[30] Ethylbenzene complex **17** underwent single-coupling to generate the 1,1-diarylethane derivative **21** in 70% yield, despite the presence of β-hydrogens in the intermediate palladium complex. Interestingly, this reaction also produced 6% of the triarylmethane quaternary product **22**.

To exploit of the ability of $Cr(CO)_3$ to shield one face of the coordinated arene,[21] we also examined cross-coupling reactions with complexes of indane (**23**) and tetrahydronaphthalene (**24**) (Scheme 5). By adjusting the conditions, either mono- or diarylated product could be obtained, though yields of **25** and **26** were diminished due to partial conversion to diarylated product. In the case of the diarylation reactions to form **27** and **28**, *cis*-diaryl products were obtained in all cases (determined by ^1H NMR and X-ray diffraction of **27b**,[29] see Supporting Information).

To demonstrate the practical advantages to our method, double coupling of indane tricarbonylchromium (**23**) with PhBr, followed by exposure to light and air provided 79% isolated yield of *cis*-1,3-diphenylindane (**29**, Scheme 6). Existing syntheses of 1,3-diaryl indanes provide *cis*/*trans* mixtures.[31] The *cis*-1,3-diarylindane moiety is present in potent nonpeptide endothelin receptor antagonists.[2, 3] Performing the coupling of (η^6-toluene)$Cr(CO)_3$ (**3**) with 3-bromoanisole on a 5 mmol scale, followed by exposure to air and light afforded 1.4 g $PhCH(3\text{-}C_6H_4\text{-}OMe)_2$ (**30**) in 93% yield, a product inaccessible by standard F-C procedures with anisole.[32]

In summary, we have introduced an efficient method for benzylic coupling reactions leading to polyarylated methanes. This method is complementary to F-C approaches and enables the synthesis of polyarylmethanes that are not accessible through electrophilic aromatic substitution reactions alone. Activation of the benzylic protons of $(\eta^6\text{-}C_6H_5CH_2R)Cr(CO)_3$ allows a base of moderate strength, $LiN(SiMe_3)_2$, to be used for the in-situ generation of the benzyllithiums,[33] which directly participates in a palladium-catalyzed coupling reaction. Coordinated complexes can undergo multiple arylations, furnishing polyarylated products including unsymmetrically substituted triarylmethanes with quaternary carbon centers. Currently, efforts are underway to broaden the application of our method to the generation of quaternary polyarylmethanes and their enantioselective syntheses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Palchaudhuri R, Nesterenko V, Hergenrother PJ. J Am Chem Soc. 2008; 130:10274. [PubMed: 18611022]
2. Elliott JD, Lago MA, Cousins RD, Gao A, Leber JD, Erhard KF, Nambi P, Elshourbagy NA, Kumar C. J Med Chem. 1994; 37:1553. [PubMed: 8201588]
3. Ohlstein EH, Nambi P, Douglas SA, Edwards RM, Gellai M, Lago A, Leber JD, Cousins RD, Gao AM, Frazee JS, Peishoff CE, Bean JW, Eggleston DS, Elshourbagy NA, Kumar C, Lee JA, Yue TL,

Louden C, Brooks DP, Weinstock J, Feuerstein G, Poste G, Ruffolo RR, Gleason JG, Elliott JD. Proc Natl Acad Sci U S A. 1994; 91:8052. [PubMed: 8058755]

4. Muthyala R, Katritzky AR, Lan X. Dyes and Pigments. 1994; 25:303.
5. Katritzky AR, Gupta V, Garot C, Stevens CV, Gordeev MF. Heterocycles. 1994; 38:345.
6. Duxbury DF. Chem Rev. 2002; 93:381.
7. Shchepinov MS, Korshun VA. Chem Soc Rev. 2003; 32:170. [PubMed: 12792940]
8. Nair V, Thomas S, Mathew SC, Abhilash KG. Tetrahedron. 2006; 62:6731.
9. Lin S, Lu X. J Org Chem. 2007; 72:9757. [PubMed: 17999518]
10. Das SK, Shagufta, Panda G. Tetrahedron Lett. 2005; 46:3097.
11. Yadav JS, Reddy BVS, Sunitha S. Adv Syn & Catal. 2003; 345:349.
12. Ramesh C, Barerjee J, Pal R, Das B. Adv Syn & Catal. 2003; 345:557.
13. Nair V, Abhilash KG, Vidya N. Org Lett. 2005; 7:5857. [PubMed: 16354084]
14. For a complementary procedure involving vicarious nucleophilic substitution of nitroarenes see: Katritzky AR, Toader D. J Org Chem. 1997; 62:4137.
15. Katritzky AR, Lan X, Lam JN. Chem Ber. 1991; 124:1809.
16. Li YZ, Li BJ, Lu XY, Lin S, Shi ZJ. Angew Chem, Int Ed. 2009; 48:3817.
17. Esquivias J, Arrayás RG, Carretero JC. Angew Chem, Int Ed. 2006; 45:629.
18. Molander GA, Ellis N. Acc Chem Res. 2007; 40:275. [PubMed: 17256882]
19. Liégault B, Renaud JL, Bruneau C. Chem Soc Rev. 2008; 37:290. [PubMed: 18197345]
20. Imao D, Glasspoole BW, Laberge VS, Crudden CM. J Am Chem Soc. 2009; 131:5024. [PubMed: 19301820]
21. Uemura, M. Org React. Overman, LE., editor. Vol. 67. John Wiley; NJ: 2006. p. 217
22. Merlic CA, Walsh JC, Tantillo DJ, Houk KN. J Am Chem Soc. 1999; 121:3596.
23. Pfletschinger A, Dargel TK, Bats JW, Schmalz HG, Koch W. Chem Eur J. 1999; 5:537.
24. Kündig, EP. Topics in Organometallic Chemistry. Vol. 7. Berline; New York: 2004.
25. Kalinin VN, Cherepanov IA, Moiseev SK. J Organomet Chem. 1997; 536–537:437.
26. Brewer ARE, Drake AF, Gibson SE, Rendell JT. Org Lett. 2007; 9:3487. [PubMed: 17663561]
27. Sundberg, RJ. Indoles. Academic; San Diego: 1996.
28. When ^{1}H NMR deprotonation studies were conducted in THF with one equivalent of $LiN(SiMe_3)_2$, **1** exhibited approximately 50% deprotonation, whereas **3** was only 10% deprotonated.
29. CCDC 775771 (**10**) and 765716 (**27b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif
30. Yamada, K-i; Tomioka, K. Chem Rev. 2008; 108:2874. [PubMed: 18652515]
31. Lantaño B, Aguirre J, Finkielsztein ML, Alesso E, Brunet E, Moltrasio GY. Syn Commun. 2004; 34:625.
32. Alternately, the coordinated arene can be purified first and then simply decomplexed by exposure to light and air. A solution of coordinated arene **2a** exposed to light and air provided triphenylmethane in 98% isolated yield.
33. For cross-coupling reactions with organolithium reagents see: Murahashi SI. J Organomet Chem. 2002; 653:27.

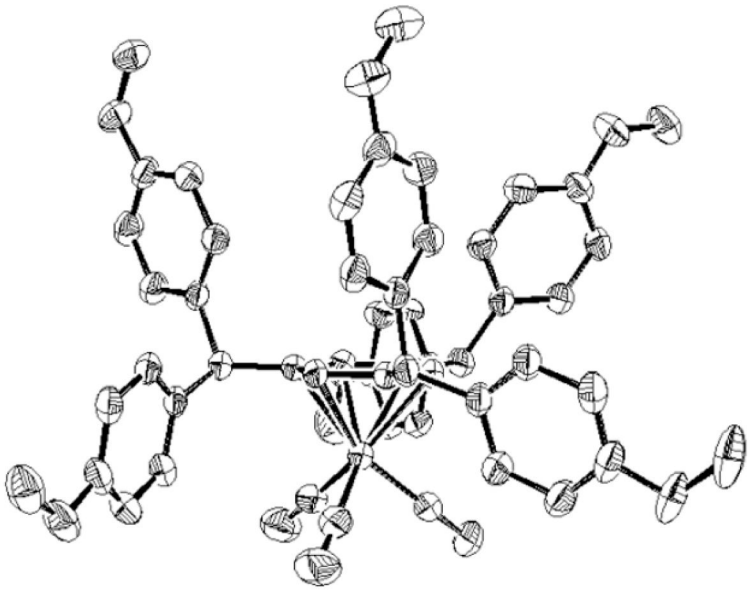
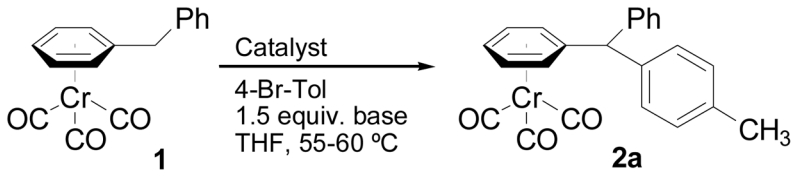
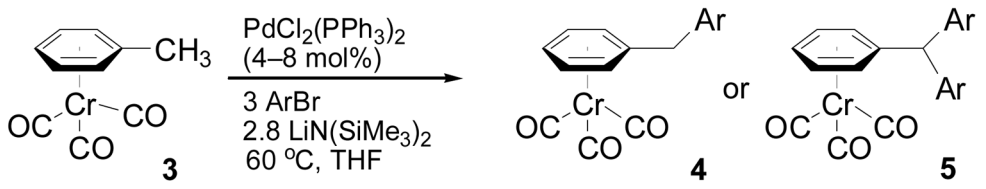


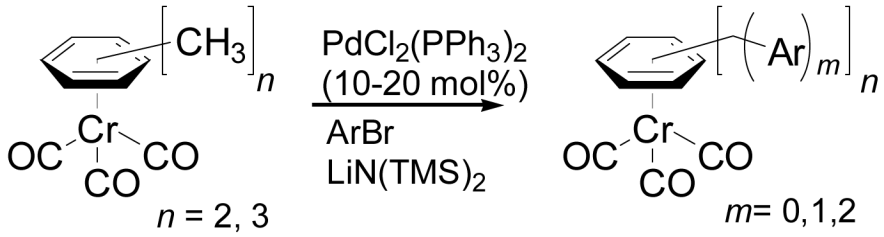
Figure 1.
ORTEP of hexa-arylated product (**10**).



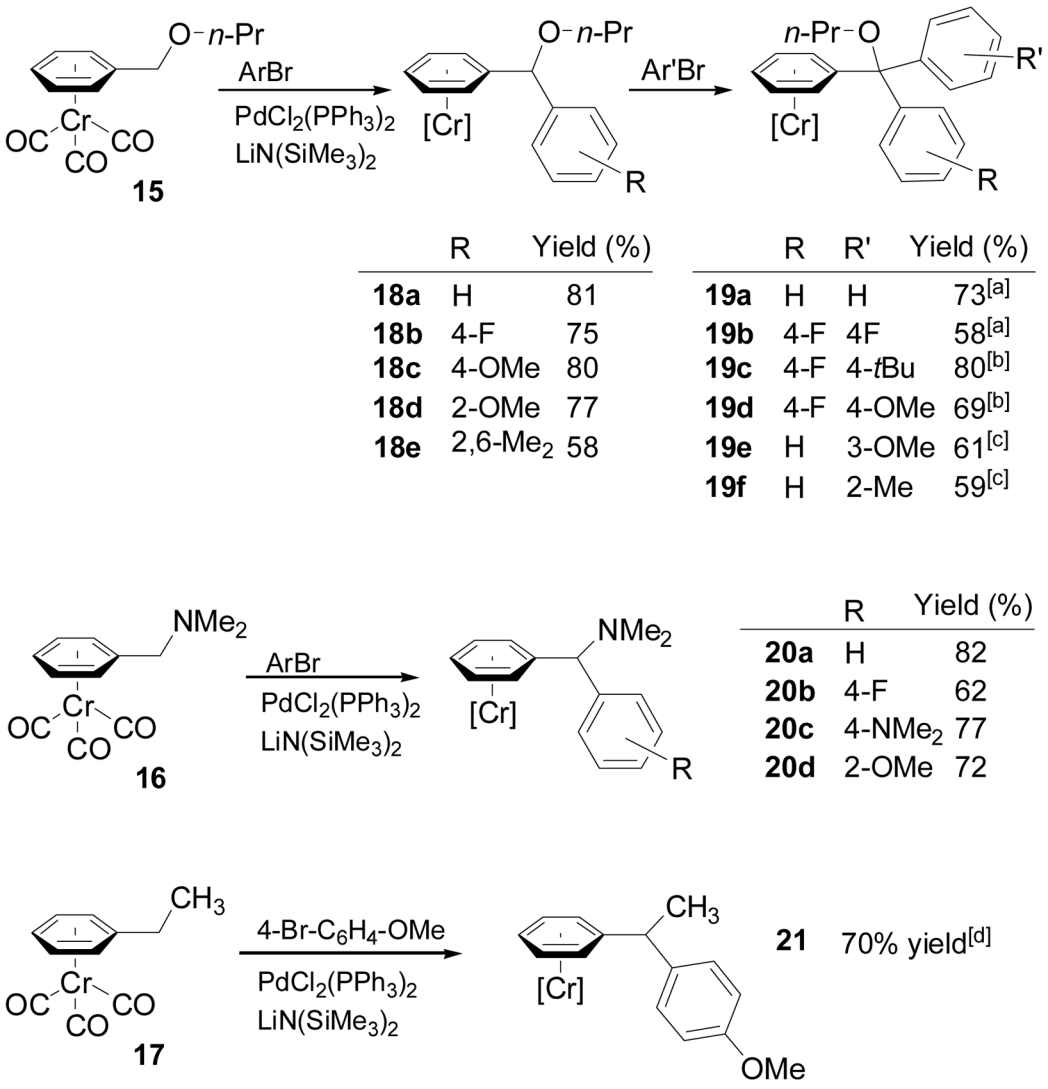
Scheme 1.
Coupling of diphenylmethane tricarbonylchromium **1** with aryl bromide



Scheme 2.
Cross-Coupling Reactions with (η^6-toluene)$Cr(CO)_3$ (**3**).



Scheme 3.
Cross-Coupling at multiple benzylic reaction sites.



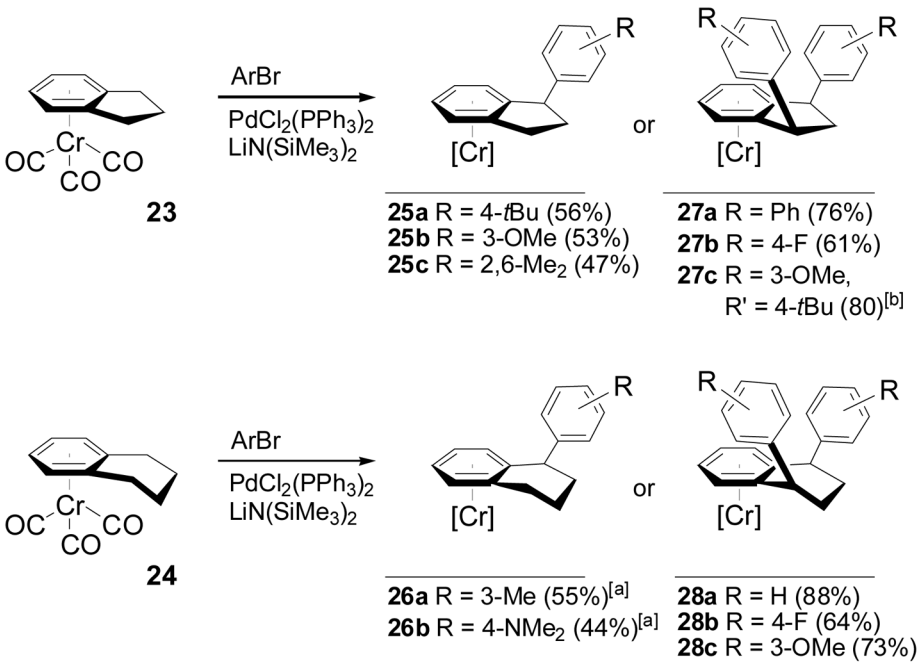
	R	Yield (%)
18a	H	81
18b	4-F	75
18c	4-OMe	80
18d	2-OMe	77
18e	2,6-Me$_2$	58

	R	R'	Yield (%)
19a	H	H	73[a]
19b	4-F	4F	58[a]
19c	4-F	4-*t*Bu	80[b]
19d	4-F	4-OMe	69[b]
19e	H	3-OMe	61[c]
19f	H	2-Me	59[c]

	R	Yield (%)
20a	H	82
20b	4-F	62
20c	4-NMe$_2$	77
20d	2-OMe	72

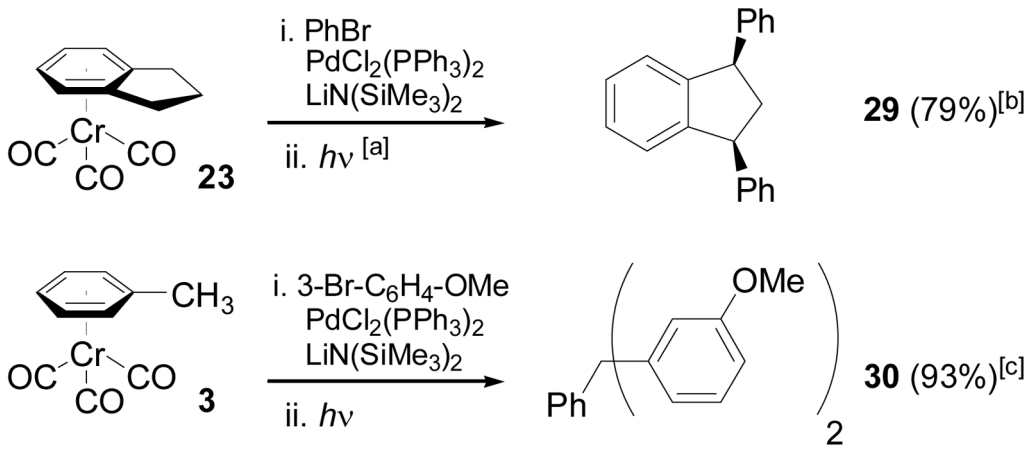
Scheme 4.

Coupling in the presence of heteroatoms and β–H's. [a] Product obtained directly from **15** [b] From isolated **18b**. [c] From isolated **18a**. [d] 6% doubly coupled product was also isolated.



Scheme 5.

Access to 1-Aryl-indanes and 1,3-*cis*-diaryl indanes. [a]40:60 Toluene:THF was used instead of pure THF to improve selectivity for monoarylation. [b] From isolated **25b**.



Scheme 6.

One-pot coupling and direct decomplexation of (η^6-Arene)$Cr(CO)_3$ complexes. [a] Reaction is exposed to light prior to purification. [b] Single (*cis*-) isomer observed. [c] Reaction was conducted on a 5 mmol scale.

Table 1

Optimization of reaction conditions (Scheme 1)

Catalyst	mol %	Base	time (h)[a]	yield[b]	SM[c]
1 $PdBr_2(PPh_3)_2$	10	LiO*t*-Bu	24	- [d]	-
2 $PdBr_2(PPh_3)_2$	5	NaO*t*-Bu	24	- [d]	67
3 $PdCl_2(PPh_3)_2$	3	$LiN(SiMe_3)_2$	20	70 [d]	trace
4 $PdCl_2(PPh_3)_2$	**3**	**$LiN(SiMe_3)_2$**	**0.75**	**91**	**0**
5 $PdCl_2(PPh_3)_2$	3	LDA	12	50	trace
6 $PdCl_2(PPh_3)_2$	5	$NaN(SiMe_3)_2$	18	26	38
7 $PdCl_2(PPh_3)_2$	5	$KN(SiMe_3)_2$	20	9	48
8 $NiCl_2(PPh_3)_2$	5	$LiN(SiMe_3)_2$	20	0	29
9 $Pd(PPh_3)_4$	5	$LiN(SiMe_3)_2$	17	67	12
10 $PdCl_2$(dppf)	5	$LiN(SiMe_3)_2$	19	78	14

[a] Conducted at 55–60 °C in THF solvent, except where otherwise noted

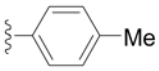
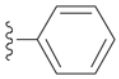
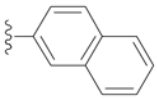
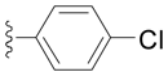
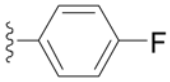
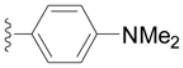
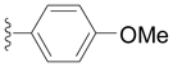
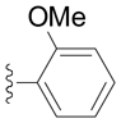
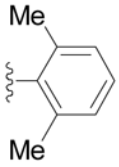
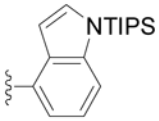
[b] % isolated yield

[c] % recovered SM

[d] Reaction conducted at RT.

Table 2

Single coupling of **1** with ArBr[a] (Scheme 1)

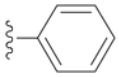
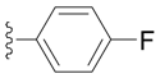
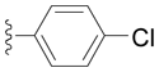
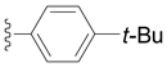
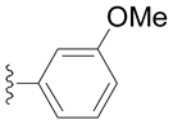
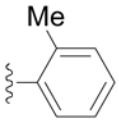
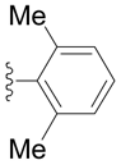
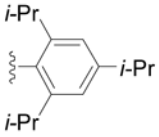
Entry	Ar =	yield[b]
2a		91
2b		92
2c		90
2d		83
2e		88
2f		91
2g		94
2h		91
2j		81
2k		89

[a]Conducted at 55–60 °C using 1.5 equiv. $LiN(SiMe_3)_2$, 1.5 equiv. ArBr, 3–5 mol % $PdCl_2(PPh_3)_2$, and THF as solvent

[b]Isolated yields.

Table 3

Double and Single Couplings of **3** with ArBr[a]

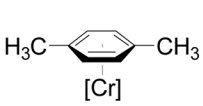
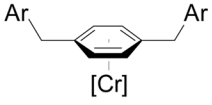
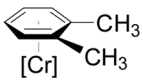
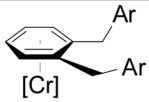
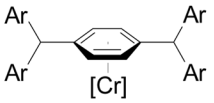
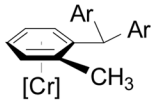
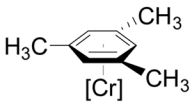
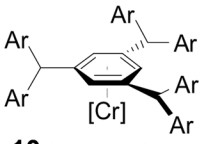
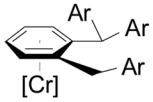
Entry	Ar =	yield[b]
5a		90
5b		83
5c		78
5d		82
5e		86
5f		88
4g		86
4h		81

[a]Conducted at 55–60 °C using 2.8 equiv. $LiN(SiMe_3)_2$, 3 equiv. ArBr, 4–8 mol % $PdCl_2(PPh_3)_2$, and THF as solvent.

[b]Isolated yields.

Table 4

Coupling reaction at multiple arylation sites[a]

Starting complex	Product (% yield)[b]	Starting complex	Product (% yield)
 **6**	 **7** (73% yield) Ar = 2,4,6-$C_6H_2(i\text{-}Pr)_3$	 **11**	 **12** (85% yield) Ar = 2,6-$C_6H_3Me_2$
6	 **8** (70% yield) Ar = *p*-C_6H_4-F	**11**	 **13** (64% yield) Ar = 4-C_6H_4-NMe_2
 **9**	 **10** (43% yield) Ar = 4-C_6H_4-OMe	**11**	 **14** (48% yield) Ar = 4-C_6H_4-NMe_2

[a] Conducted at 50–60 °C using 4–11 equiv. $LiN(SiMe_3)_2$, 3–10 equiv. ArBr, 10–20 mol % $PdCl_2(PPh_3)_2$, and THF as solvent.

[b] Isolated yields.