Homogeneous Catalysis

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Palladium-Catalyzed Asymmetric Allylic Alkylations with Toluene Derivatives as Pronucleophiles

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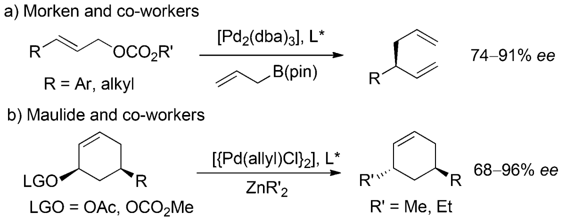
Abstract: *The first two highly enantioselective palladium-catalyzed allylic alkylations with benzylic nucleophiles, activated with $Cr(CO)_3$, have been developed. These methods enable the enantioselective synthesis of α-2-propenyl benzyl motifs, which are important scaffolds in natural products and pharmaceuticals. A variety of cyclic and acyclic allylic carbonates are competent electrophilic partners furnishing the products in excellent enantioselectivity (up to 99 % ee and 92 % yield). This approach was employed to prepare a non-steroidal anti-inflammatory drug analogue.*

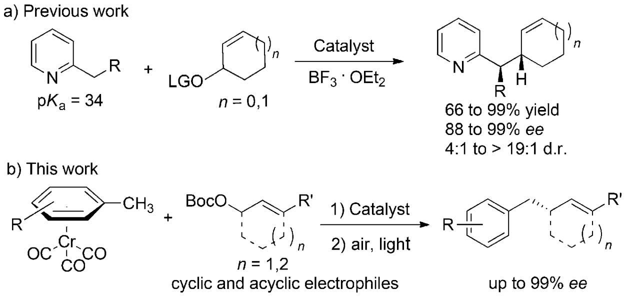


Scheme 1. Palladium-catalyzed AAA reaction with hard nucleophiles. dba = dibenzylideneacetone.

Transition-metal-catalyzed allylic substitution reactions have emerged as a powerful method to construct C–C bonds.[1] Of these, the palladium-catalyzed asymmetric allylic alkylation (AAA) reaction has attracted the greatest interest because of its applications in total synthesis and the preparation of bioactive compounds.[2] A wide variety of stabilized or "soft" nucleophiles (originally defined as pronucleophiles with $pK_a < 25$[3]) have been successfully employed in palladium-catalyzed AAA reactions, including malonates,[4] imides,[5] and many others.[6] In contrast, few palladium-catalyzed allylic substitution reactions with "hard" nucleophiles (generally defined as pronucleophiles with $pK_a > 25$) have materialized.[1a] Recent advances in palladium-catalyzed AAAs with hard nucleophiles have been reported by Morken and co-workers who employed allylboronates in allyl–allyl coupling reactions[7] (Scheme 1 a). Maulide and co-workers have also reported such reactions using dialkylzinc nucleophiles[8] (Scheme 1 b).

The most significant difference between soft- and hard-nucleophile classes in the Tsuji–Trost allylic substitution is their reaction pathways: soft nucleophiles react through a double inversion mechanism whereas hard nucleophiles are proposed to undergo single inversion,[9] wherein the nucleophile transmetallates to the palladium catalyst. Both reactions in Scheme 1 were shown to proceed by the hard-nucleophile pathway. As a valuable complement, Fletcher and co-workers reported a copper-catalyzed AAA reaction of alkylzirconium reagents (generated in situ from alkenes by hydrometallation) by dynamic kinetic asymmetric transformation.[10] The scope of this reaction, however, does not include simple benzylic nucleophiles.

To broaden the synthetic utility of the palladium-catalyzed AAA, researchers have focused on expanding the classes of nucleophiles which can undergo the more controllable double-inversion or soft-nucleophile reaction pathway. This approach entails softening hard nucleophiles by addition of activating agents to stabilize the resulting anionic charge. In pioneering studies, Trost and co-workers reported the highly enantioselective palladium-catalyzed AAA with 2-methylpyridine derivatives (Scheme 2 a, LG = leaving group).[11] Key to success of this approach was the addition of 1.3 equivalents of BF_3 to bind the nitrogen atom and acidify the sp^3-hybridized C–H units of 2-methylpyridine ($pK_a \approx 34$[12]). A different strategy is necessary for pronucleophiles bearing less acidic C–H units, such as toluene derivatives ($pK_a \approx 43$[13]). AAAs with benzyl anions as nucleophiles could



Scheme 2. Palladium-catalyzed AAA reactions with softened hard pronucleophiles. Boc = *tert*-butoxycarbonyl.

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potentially furnish benzylated substructures, which are important scaffolds in natural products and pharmaceuticals, such as FR181157,[14] sophoraflavanone G,[15] and dactylosponol[16] (Figure 1).

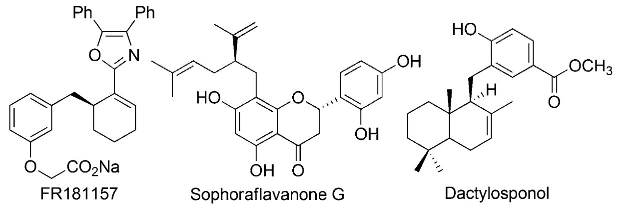
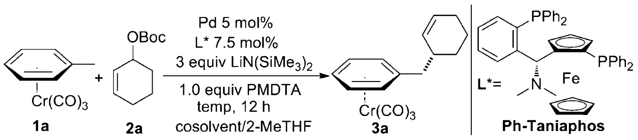


Figure 1. Selected natural products containing α-2-propenyl benzyl motifs.

Table 1: Optimization of the reaction parameters.[a]



Entry	Solvent with Tol (%)[b]	T [°C]	Pd source	Conc. [M]	Yield [%][c]	*ee* [%][d]
1	THF	0	$Pd(COD)Cl_2$	0.1	50	85
2	2-MeTHF	0	$Pd(COD)Cl_2$	0.1	61	85
3	2-MeTHF	25	$Pd(COD)Cl_2$	0.1	48	79
4	2-MeTHF	−10	$Pd(COD)Cl_2$	0.1	67	86
5	2-MeTHF	−20	$Pd(COD)Cl_2$	0.1	56	87
6	Tol (30)	−10	$Pd(COD)Cl_2$	0.1	79	86
7	Tol (30)	−10	$Pd(COD)Cl_2$	0.2	76	84
8	Tol (30)	−10	$Pd(COD)Cl_2$	0.05	84	86
9	Tol (30)	−10	$Pd(OAc)_2$	0.05	79	89
10	Tol (30)	−10	$Pd(NCPh)_2Cl_2$	0.05	64	86
11	Tol (30)	−10	$Pd(dba)_2$	0.05	72	87
12	Tol (30)	−10	$\{Pd(allyl)Cl\}_2$	0.05	72	88
13	Tol (30)	−20	$Pd(OAc)_2$	0.05	84	89
14	Tol (30)	−30	$Pd(OAc)_2$	0.05	87	91
15	Tol (30)	−40	$Pd(OAc)_2$	0.05	80	91
16	Tol (30)	−30	$Pd(OAc)_2$	0.05	63	91[e]
17	Tol (30)	−30	$Pd(OAc)_2$	0.05	92	92[f]

[a] Reactions performed using 1.0 equiv of **1a** and 2 equiv of **2a** on a 0.1 mmol scale. [b] Tol (30) indicates 30% toluene by volume in 2-MeTHF [c] Yields determined by ^{1}H NMR analysis of crude reaction mixture with CH_2Br_2 as an internal standard. [d] The *ee* value was determined by chiral-phase SFC. [e] 0.5 equiv PMDTA was used. [f] 1.5 equiv PMDTA was used. COD = 1,5-cyclooctadiene.

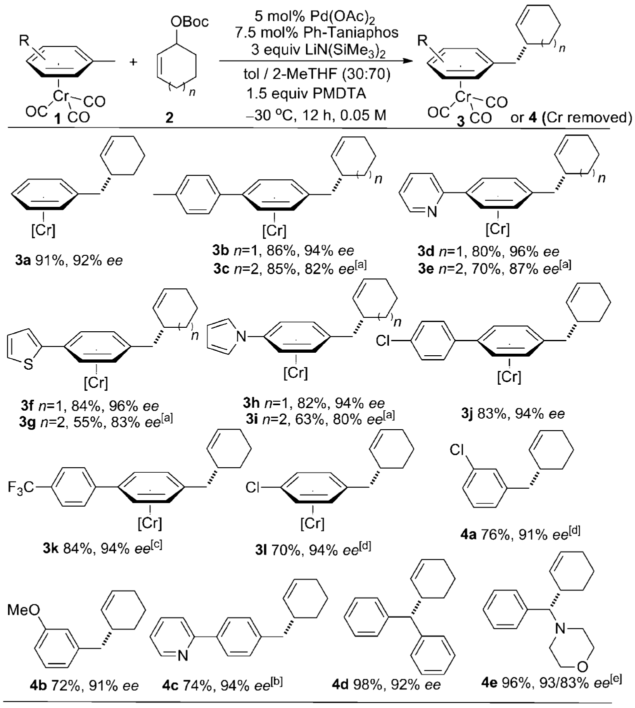
Herein we report the first palladium-catalyzed AAA reactions of toluene-based pronucleophiles. By activation of toluene derivatives with η^6-tricarbonylchromium, cyclic and acyclic allylic carbonates are benzylated with enantioselectivities as high as 96 and 99 %, respectively (Scheme 2 b).

Recently, our team introduced a strategy to employ (η^6-$C_6H_5CH_2R$)$Cr(CO)_3$ complexes as cross-coupling partners to produce di- and triarylmethanes,[17] and enantioenriched diarylmethylamines[18] by direct arylations.[19] Using these pronucleophiles, we also explored palladium-catalyzed allylic substitution of diverse cyclic and acyclic electrophiles to give racemic products.[20] Despite significant progress in palladium-catalyzed Tsuji–Trost reactions, highly enantioselective processes with benzylic nucleophiles (toluene derivatives) remain a limitation of this method. Our prior demonstration of a double-inversion reaction pathway with $Cr(CO)_3$-activated benzylic nucleophiles to afford racemic products inspired us to pursue palladium-catalyzed AAA reactions.[20]

Given the known difficulty of identifying chiral ligands which can moderate all of the steps of a complex catalytic cycle and provide useful enantioselectivity, we initially examined over 140 diverse enantioenriched mono- and bidentate phosphine ligands (see the Supporting Information for full ligand structures and results). We employed 1 equivalent of (η^6-$C_6H_5CH_3$)$Cr(CO)_3$ (**1a**) as the pronucleophile, 2 equivalents of *tert*-butyl cyclohex-2-enyl carbonate (**2a**), 3 equivalents of $LiN(SiMe_3)_2$, 1 equivalent of PMDTA (pentamethyldiethylenetriamine) as an additive,[21] 10 mol % Pd-(COD)Cl_2, and either 10 mol % of a chiral bidentate ligand or 20 mol % of a monodentate phosphine in THF at room temperature for 12 hours (Table 1). Surprisingly, out of 140 ligands, only the Ph-Taniaphos ligand[22] provided significant turnover and high enantioselectivity, thus highlighting the challenging nature of this reaction. Translation of this lead to the laboratory scale with Ph-Taniaphos at 0 °C afforded **3a** in a 50 % assay yield (AY) with 85 % *ee* (entry 1). The use of the solvent 2-MeTHF resulted in improvement to 61 % AY, while maintaining the *ee* value (entry 2). Next we screened the impact of the temperature on the reactivity and enantioselectivity in 2-MeTHF. By conducting the reaction at room temperature it resulted in a drop in the AY (48 %) and *ee* value (entry 3). As the temperature was decreased from 0 °C to −20 °C, the AY increased to 67 % at −10 °C (86 % *ee*), then decreased to 56 % at −20 °C (87 % *ee*; entries 4 and 5). We next examined the solvent composition.[18] Use of 30 % toluene as a cosolvent resulted in an increase in the AY to 79 % (entry 6). Changing the ratio of the toluene to 2-MeTHF had a dramatic impact on the yield but maintained the *ee* value (see the Supporting Information for details). Increasing the concentration from 0.1 M to 0.2 M had a detrimental impact (entry 7), whereas decreasing to 0.05 M led to an increase in assay yield (entry 8).

Palladium precursors can impact both activity and enantioselectivity in AAAs.[3] Varying the palladium source from $Pd(COD)Cl_2$ to $Pd(OAc)_2$, $Pd(dba)_2$, $Pd(NCPh)_2Cl_2$, {Pd-(ally)Cl}$_2$ (Table 1, entries 9–12) revealed that $Pd(OAc)_2$ resulted in the highest enantioselectivity (entry 9). With $Pd(OAc)_2$ we revisited the reaction temperature, and as the temperature was decreased from −10 °C to −40 °C, the enantioselectivity increased to 91 % at −30 °C (entry 14). When the additive PMDTA was decreased to 0.5 equivalents at −30 °C, the AY dropped to 63 % (entry 16). In contrast, the AY increased to 92 % with 1.5 equivalents of PMDTA (entry 17). The role of the PMDTA is likely to decrease the aggregation state of the $LiN(SiMe_3)_2$, thus facilitating the deprotonation of the arene complex.[23] The optimized reaction conditions in entry 17 afforded the AAA product in 92 % yield and 92 % *ee*, thus favoring the *R* enantiomer.[24]

With the optimized reaction conditions in hand, we next examined the scope of the nucleophiles in the AAA with

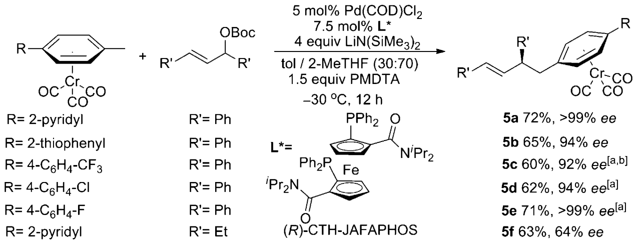


Scheme 3. Scope with respect to the pronucleophiles in AAA reactions. Yield is that of the isolated product. The *ee* values were determined by chiral-phase HPLC. [a] Reactions performed using 1.0 equivalent of **1**, 3 equivalents of **2b**, and 4 equivalents of LiN(SiNe$_3$)$_2$. [b] A two-step one-pot procedure was employed to afford the chromium-free product with only 2% *ee* erosion. [c] Reaction time was 4 h. [d] Reaction time was 2.5 h. [e] The d.r. value was 55:45.

cyclohexenyl-OBoc and cycloheptenyl-OBoc (Scheme 3). In addition to the toluene complex **3a**, a variety of substituents on the η^6-arene were well tolerated. To compare the selectivity of the (η^6-$C_6H_5CH_3$)Cr(CO)$_3$ with an unactivated tolyl group, the 4,4′-dimethylbiphenyl complex was examined. The AAA occurred exclusively at the chromium-activated position to give the product in 86% yield with 94% *ee* (**3b**). Substrates bearing 2-pyridyl, 2-thiophene, and *N*-pyrrolyl groups at the 4-position of the η^6-arene underwent AAA reaction, thus affording the desired product in 80–84% yield with excellent enantioselectivities (**3d**, **3f**, and **3h**). The aryl-chloride-containing substrate was also a good partner, thus giving the desired product in 83% yield and 94% *ee* (**3j**). The trifluoromethyl-containing biaryl substrate was compatible with this AAA reaction, thus furnishing the product with 84% yield and 94% *ee* (**3k**). Chromium complexes of aryl chlorides exclusively give the AAA products in excellent enantioselectivity (**3l**).[25] In addition to the cyclohexenyl-OBoc derivative, a seven-membered allylic carbonate (Scheme 3, $n = 2$) was also a competent electrophile. With the same set of pronucleophiles, the corresponding products were generated in 55–85% yields with 80–87% *ee* (**3c**, **3e**, **3g**, and **3i**).

To demonstrate the versatility of this approach, a two-step one-pot procedure to afford the chromium-free products was explored (Scheme 3). The {η^6-(3-chlorotoluene)}Cr(CO)$_3$ gave the demetallated product in 76% yield and 91% *ee* (**4a**).[25] The (η^6-3-methylanisole)Cr(CO)$_3$ complex gave 72% yield with 91% *ee* (**4b**). The 4-(2-pyridyl)-containing toluene complex was also a good substrate, thus providing the product in 74% yield upon isolation with 94% *ee* (**4c**). Comparison of metallated (**3d**) and demetallated (**4c**) products indicates that demetallation occurs with loss of 6% yield and only 2% erosion in the *ee* value. Diarylmethane derivatives are important motifs in pharmaceuticals and have found wide application in materials science.[26] The diphenylmethane complex (η^6-$C_6H_5CH_2Ph$)Cr(CO)$_3$ gave the AAA/demetallated product in 98% yield with 92% *ee* (**4d**). We also examined the benzyl amine complex, which afforded the allylation product as approximately a 1:1 ratio of diastereomers in 96% yield with 83 and 93% *ee* (**4e**). These different *ee* values suggest that the AAA products (**4e**) do not epimerize under the reaction conditions.

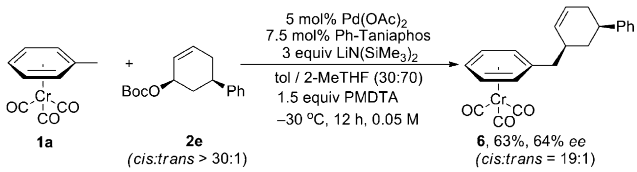
We next investigated palladium-catalyzed allylic substitutions with acyclic allylic substrates, starting with (*E*)-*tert*-butyl (1,3-diphenylallyl) carbonate (Scheme 4). Given the significant difference between acyclic and cyclic substrates, it is not surprising that Ph-Taniaphos did not give high enantioselectivity. After rescreening a subset of ligands (see the Supporting Information) we found that (*R*)-CTH-JAFAPHOS[27] was the leading hit. The (*E*)-*tert*-butyl (1,3-diphenylallyl) carbonate underwent the AAA to furnish the corresponding products **5a** (72% yield, >99% *ee*) and **5b** (65% yield, 94% *ee*). Substrates containing 4-CF$_3$, 4-Cl, and 4-F groups were also compatible with the AAA, thus affording the allylated products with excellent enantioselectivities (**5c–e**; 92 to >99% *ee*). The (*E*)-*tert*-butyl (1,3-diethylallyl) carbonate exhibited lower enantioselectivity (**5f**; 63% yield, 64% *ee*).



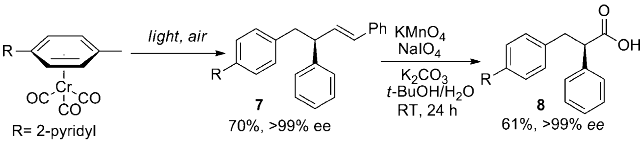
Scheme 4. Palladium/(*R*)-CTH-JAFAPHOS-catalyzed AAA with acyclic electrophiles. Yield is that of isolated product. The *ee* values were determined by either chiral-phase HPLC or SFC. [a] 10 mol% catalysis was used. [b] Reaction time was 4 h.

To determine if our organolithium nucleophiles react by the double-inversion pathway, the toluene complex was coupled with the *cis*-disubstituted stereoprobe (Scheme 5). The product **6** was obtained in 64% yield with 64% *ee* (unoptimized). Comparison of the ^{1}H NMR coupling constants with those of related compounds led to the conclusion that this reaction proceeded by the soft-nucleophile pathway.[20]

To demonstrate the utility of our protocol, a nonsteroidal *anti*-inflammatory drug analogue (NSAID)[28] was prepared in two steps (Scheme 6). Beginning with the pyridyl-contain-



Scheme 5. AAA reaction and mechanistic study with Ph-Taniaphos.



Scheme 6. Further transformations of the allylated product.

ing toluene complex **1c**, AAA/demetallation, as outlined in Scheme 3, gave the compound **7** in greater than 99 % *ee*. The allylated product **7** was then converted into the enantioenriched α-arylalkanoic acid **8** in 61 % yield with a greater than 99 % *ee* (Scheme 6).

In conclusion, we have successfully developed the first two catalysts for the palladium-catalyzed AAA employing toluene-derived pronucleophiles. This method provides ready access to the enantioenriched α-2-propenyl benzyl motifs and expands the classes of nucleophiles which can be employed in AAA reactions. It is noteworthy that the optimized catalysts for both AAA reactions advanced herein, and for our palladium(Cy-Mandyphos)-catalyzed enantioselective arylation of (η^6-$C_6H_5CH_2NR_2$)$Cr(CO)_3$ complexes,[18] all contain strongly coordinating tertiary amine or amide groups on the ligands, groups which can serve to bind the lithium counterions of the nucleophiles. This observation suggests a possible design feature for related enantioselective processes with strongly basic lithiated nucleophiles.

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Keywords: allylic compounds · arenes · chromium · enantioselectivity · palladium

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[1] a) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395 – 422; b) B. M. Trost, *Chem. Pharm. Bull.* **2002**, *50*, 1 – 14; c) T. Graening, H.-G. Schmalz, *Angew. Chem. Int. Ed.* **2003**, *42*, 2580 – 2584; *Angew. Chem.* **2003**, *115*, 2684 – 2688.

[2] a) B. M. Trost, O. Dirat, J. Dudash, Jr., E. J. Hembre, *Angew. Chem. Int. Ed.* **2001**, *40*, 3658 – 3660; *Angew. Chem.* **2001**, *113*, 3770 – 3772; b) B. M. Trost, J. Dudash, Jr., E. J. Hembre, *Chem. Eur. J.* **2001**, *7*, 1619 – 1629.

[3] J. F. Hartwig, *Organotransition Metal Chemistry: From Bonding to Catalysis*, University Science Books, Sausalito, **2011**.

[4] a) G. J. Dawson, C. G. Frost, J. M. J. Williams, S. J. Coote, *Tetrahedron Lett.* **1993**, *34*, 3149 – 3150; b) J. Sprinz, G. Helmchen, *Tetrahedron Lett.* **1993**, *34*, 1769 – 1772; c) B. M. Trost, R. C. Bunt, *J. Am. Chem. Soc.* **1994**, *116*, 4089 – 4090.

[5] a) B. M. Trost, A. C. Krueger, R. C. Bunt, J. Zambrano, *J. Am. Chem. Soc.* **1996**, *118*, 6520 – 6521; b) B. M. Trost, D. E. Patterson, *Chem. Eur. J.* **1999**, *5*, 3279 – 3284.

[6] B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921 – 2944.

[7] a) M. J. Ardolino, J. P. Morken, *J. Am. Chem. Soc.* **2014**, *136*, 7092 – 7100; b) P. Zhang, L. A. Brozek, J. P. Morken, *J. Am. Chem. Soc.* **2010**, *132*, 10686 – 10688; c) P. Zhang, H. Le, R. E. Kyne, J. P. Morken, *J. Am. Chem. Soc.* **2011**, *133*, 9716 – 9719.

[8] a) A. Misale, S. Niyomchon, M. Luparia, N. Maulide, *Angew. Chem. Int. Ed.* **2014**, *53*, 7068 – 7073; *Angew. Chem.* **2014**, *126*, 7188 – 7193; b) S. Niyomchon, D. Audisio, M. Luparia, N. Maulide, *Org. Lett.* **2013**, *15*, 2318 – 2321; c) D. Audisio, G. Gopakumar, L.-G. Xie, L. G. Alves, C. Wirtz, A. M. Martins, W. Thiel, C. Fares, N. Maulide, *Angew. Chem. Int. Ed.* **2013**, *52*, 6313 – 6316; *Angew. Chem.* **2013**, *125*, 6434 – 6438.

[9] a) B. M. Trost, T. R. Verhoeven, *J. Org. Chem.* **1976**, *41*, 3215 – 3216; b) H. Matsushita, E. Negishi, *J. Chem. Soc. Chem. Commun.* **1982**, 160 – 161.

[10] H. You, E. Rideau, M. Sidera, S. P. Fletcher, *Nature* **2015**, *517*, 351 – 355.

[11] a) B. M. Trost, D. A. Thaisrivongs, *J. Am. Chem. Soc.* **2008**, *130*, 14092 – 14093; b) B. M. Trost, D. A. Thaisrivongs, *J. Am. Chem. Soc.* **2009**, *131*, 12056 – 12057.

[12] P. M. Dewick, *Essentials of Organic Chemistry: For Students of Pharmacy, Medicinal Chemistry and Biological Chemistry*, Wiley, Chichester, **2006**.

[13] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456 – 463.

[14] A. Tanaka, K. Hattori, K. Taniguchi, O. Okitsu, S. Tabuchi, M. Nishio, Y. Nagakura, N. Maeda, H. Murai, J. Seki, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4861 – 4864.

[15] M. Sato, H. Tsuchiya, I. Takase, H. Kureshiro, S. Tanigaki, M. Iinuma, *Phytother. Res.* **1995**, *9*, 509 – 512.

[16] L. M. Murray, A. Johnson, M. C. Diaz, P. Crews, *J. Org. Chem.* **1997**, *62*, 5638 – 5641.

[17] a) G. I. McGrew, J. Temaismithi, P. J. Carroll, P. J. Walsh, *Angew. Chem. Int. Ed.* **2010**, *49*, 5541 – 5544; *Angew. Chem.* **2010**, *122*, 5673 – 5676; recently Larrosa and co-workers reported $Cr(CO)_3$-activated C–H arylation. See: b) P. Ricci, K. Kramer, I. Larrosa, *J. Am. Chem. Soc.* **2014**, *136*, 18082 – 18086.

[18] G. I. McGrew, C. Stanciu, J. Zhang, P. J. Carroll, S. D. Dreher, P. J. Walsh, *Angew. Chem. Int. Ed.* **2012**, *51*, 11510 – 11513; *Angew. Chem.* **2012**, *124*, 11678 – 11681.

[19] Kalinin and co-workers generated (η^6-$C_6H_5CH_2Li$)$Cr(CO)_3$ and transmetallated this nucleophile to zinc. See: V. N. Kalinin, I. A. Cherepanov, S. K. Moiseev, *J. Organomet. Chem.* **1997**, *536*, 437 – 455.

[20] J. Zhang, C. Stanciu, B. Wang, M. M. Hussain, C.-S. Da, P. J. Carroll, S. D. Dreher, P. J. Walsh, *J. Am. Chem. Soc.* **2011**, *133*, 20552 – 20560; for allylic substitution with basic carbanions, see: S.-C. Sha, J. Zhang, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2013**, *135*, 17602 – 17609.

[21] We heve previously demonstrated the use of additives in palladium-catalyzed reactions. See: A. Bellomo, J. Zhang, N. Trongsiriwat, P. J. Walsh, *Chem. Sci.* **2013**, *4*, 849 – 857. For use of pentamethyldiethylenetriamine as an additive see Ref. [18].

[22] a) T. Ireland, G. Grossheimann, C. Wieser-Jeunesse, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 3212 – 3215; *Angew. Chem.* **1999**, *111*, 3397 – 3400; b) T. Ireland, K. Tappe, G. Grossheimann, P. Knochel, *Chem. Eur. J.* **2002**, *8*, 843 – 852.

[23] V. H. Gessner, C. Daeschlein, C. Strohmann, *Chem. Eur. J.* **2009**, *15*, 3320 – 3334.

[24] Assignment based on comparison with reported optical rotation values after the chromium was removed. See: J.-B. Langlois, A. Alexakis, *Adv. Synth. Catal.* **2010**, *352*, 447 – 457.

[25] Chromium complexes of aryl chlorides exhibit increased susceptibility to reactions. See: M. Uemura, H. Nishimura, K. Kamikawa, K. Nakayama, Y. Hayashi, *Tetrahedron Lett.* **1994**, *35*, 1909 – 1912.

[26] D. Attwood, *J. Pharm. Pharmacol.* **1976**, *28*, 407 – 409.

[27] H. Jendralla, E. Paulus, *Synlett* **1997**, 471 – 472.

[28] M. F. Landoni, A. Soraci, *Curr. Drug Metab.* **2001**, *2*, 37 – 51.

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