Synthetic Methods

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Palladium-Catalyzed C–H Arylation of α,β-Unsaturated Imines: Catalyst-Controlled Synthesis of Enamine and Allylic Amine Derivatives

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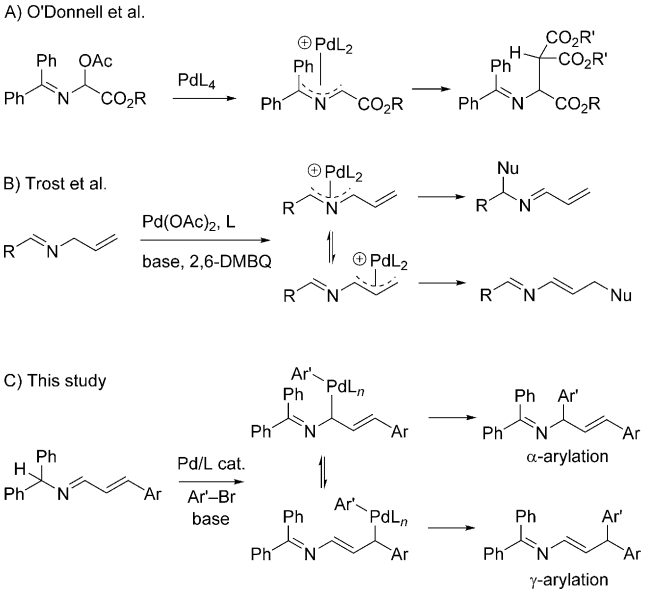
Abstract: *A unique chemo- and regioselective α- and γ-arylation of palladium azapentadienyl intermediates is presented. Two distinct catalysts and sets of conditions successfully controlled the regioselectivity of the arylation. These methods provide the first umpolung C–H functionalization of azapentadienyl palladium intermediates and enable the divergent synthesis of allylic amine and enamine derivatives, which are of significant interest in the pharmaceutical industry.*

Chemo- and regioselective allylic C–H functionalization of organic compounds by transition-metal-based catalysts has attracted considerable recent attention.[1] Beautiful applications of this approach to organic synthesis continue to emerge.[2] In contrast, the analogous C–H functionalization of azaallyl derivatives remains largely unexplored. Given that allylic amines and enamines[3] are valuable building blocks and are prevalent in bioactive compounds[4] (e.g. naftifine[4d] and flunarizine[4e]), the C–H functionalization of azaallyl systems has significant untapped potential.

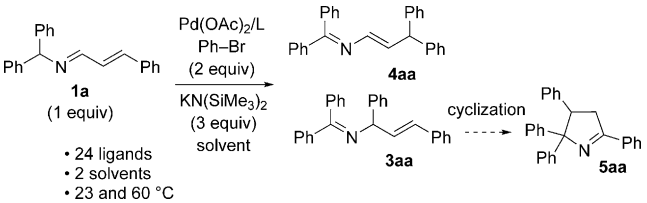
Early studies with azaallyl palladium intermediates were reported by O'Donnell et al.[5] and involved relatively sensitive hemiaminal precursors (Scheme 1 A). In 2015, Trost et al.[6] reported the use of readily available *N*-allyl imines in oxidative C–H functionalization reactions in the presence of 2,6-dimethylbenzoquinone (Scheme 1 B). This groundbreaking chemistry appears to generate equilibrating π-allyl intermediates that can be regioselectively trapped with nucleophiles with differing steric demand.

Owing to our interest in allylic C–H functionalization reactions[7] and the arylation of nitrogen-containing compounds,[8,9] we were inspired to investigate an umpolung approach to generate palladium azapentadienyl intermediates (Scheme 1 C). Our goal was to control the regioselectivity in the C–C bond-forming reductive-elimination step. If successful, such a method would enable access to arylated allylic amines and enamines. Herein, we disclose the first examples of umpolung allylic arylation that proceed with high levels of regioselectivity.



Scheme 1. Arylation of azaallyl anions.

We initiated our studies with aldimine **1a** and bromobenzene (**2a**) by microscale screening (0.01 mmol) with 24 electronically diverse mono- and bidentate phosphine ligands and two solvents [cyclopentyl methyl ether (CPME) and THF] at two temperatures (23 and 60 °C) with $Pd(OAc)_2$ and $KN(SiMe_3)_2$ (Scheme 2; see the Supporting Information for details). $P(tBu)_3HBF_4$ and Xantphos were identified as ligands favoring α-arylation to generate allylic amine derivative **3aa**. In sharp contrast, NiXantphos,[10] developed by van Leeuwen and co-workers, generated the γ-arylation product, enamine **4aa**. Cyclization of the α-arylation product led to by-product **5aa** in up to 50% yield.



Scheme 2. Reaction development and initial optimization.

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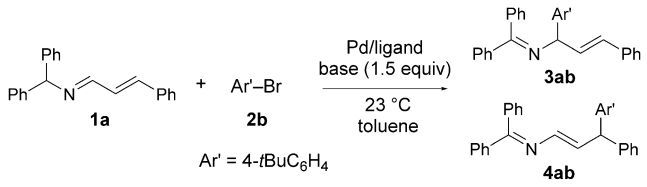
We suspected we could minimize the formation of the cyclic by-product **5aa** by using less of the base at the lower temperature (23 °C). With this in mind, we performed a series of microscale experiments (0.02 mmol) with 1.5 equivalents of the base, ligands P*t*Bu$_3$HBF$_4$, Xantphos, and NiXantphos, palladium complexes [Pd(dba)$_2$], Pd(OAc)$_2$, [{ClPd(2-methallyl)}$_2$], and [{ClPd(allyl)}$_2$], four solvents (THF, CPME, DME, toluene), and two bases [NaN(SiMe$_3$)$_2$ and KN(SiMe$_3$)$_2$; see the Supporting Information for details]. The most promising α-arylation screening result was obtained with [{ClPd(2-methallyl)}$_2$], P*t*Bu$_3$HBF$_4$, and KN(SiMe$_3$)$_2$ in toluene. Laboratory-scale optimization (0.1 mmol) led to α-arylation to give **3ab** in 84% assay yield (AY; Table 1, entry 1). At the optimal concentration of 0.05 M, excellent selectivity was observed (>20:1), and the product was isolated in 90% yield (Table 1, entry 2).

The leading screening result for the γ-arylation was with [Pd(dba)$_2$], NiXantphos, and NaN(SiMe$_3$)$_2$ in toluene, which gave the product in 72% AY on a laboratory scale (0.1 mmol; Table 1, entry 3). A slight increase in AY was observed at 0.05 M (75% assay yield; Table 1, entry 4). Buchwald precatalysts[8b,c] facilitate catalyst generation, often lead to increased activity, and allow a lower ligand loading. Therefore, we employed Buchwald-type[11] precatalysts **6** and **7** (with L = NiXantphos; Table 1, entries 5 and 6). The use of precatalyst **7** led to the γ-arylated product **4ab** in 85% AY with high selectivity (>20:1). A reduction in the reaction time to 6 h enabled the isolation of **4ab** in 88% yield (Table 1, entry 7). The assay yield dropped to 67% when we used KN(SiMe$_3$)$_2$ instead of NaN(SiMe$_3$)$_2$, but the regioselectivity was >20:1 (Table 1, entry 8). No reaction was observed with LiN(SiMe$_3$)$_2$ at room temperature, but at 60 °C γ-arylation predominated and afforded the product in 63% assay yield with 16:1 selectivity (Table 1, entry 9).

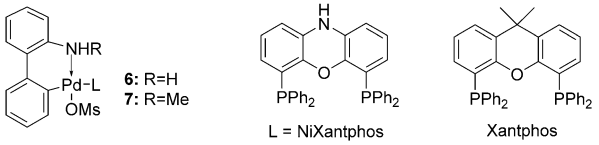
Having optimized the reaction conditions, we investigated the scope of the α-arylation with respect to the aryl bromide substrate (Scheme 3). High regioselectivity (α/γ 9:1 to >20:1) was observed in all cases. Bromobenzene and 1-bromo-4-*tert*-butylbenzene underwent coupling in excellent yield (85 and 90%, respectively). Efficient coupling of electron-donating 4-bromoanisole and 4-bromo-*N*,*N*-dimethylaniline afforded allylic amine derivatives **3ac** and **3ad** in 81 and 82% yield with 10:1 and 14:1 selectivity, respectively. Coupling reactions with sterically hindered 1-bromonaphthylene and 2-bromotoluene were more efficient with NaN(SiMe$_3$)$_2$ in CPME, under which conditions the products **3ae** and **3af** were obtained in 68 and 74% yield, respectively. Heterocyclic 5-bromobenzofuran and 5-bromo-*N*-methylindole were also good substrates: Products **3ag** and **3ah** were formed in 70 and 80% yield, respectively, both with excellent regioselectivity. The *meta*-substituted aryl bromides 3-bromotoluene and 3-bromo-*N*,*N*-dimethylaniline underwent coupling with **1a** in 80% yield with 9:1 and 10:1 selectivity, respectively. The coupling of 3-bromoanisole afforded **3ak** in 71% yield, and that of 2-bromonaphthalene afforded **3al** in 72% yield; in both cases, the regioselectivity was higher than 20:1. Unfortunately, the reaction with electron-withdrawing 1-bromo-4-fluorobenzene exhibited low selectivity.[12] To probe the scalability of the reaction, we carried out the synthesis of **3ab** on a 3 mmol scale with a catalyst loading of 5 mol%. The desired product was isolated in 86% yield (1.1 g, >20:1 regioselectivity).

Table 1: Optimization of arylation α and γ to the nitrogen atom of **1a** with **2b**.[a]

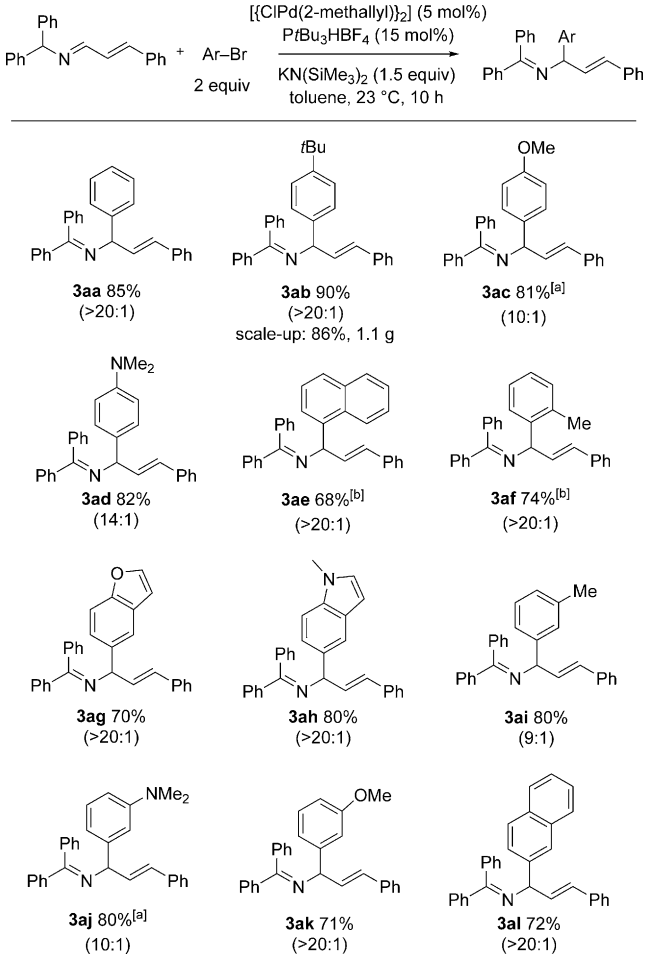


Entry	Pd (mol%)/L (mol%)	M in MN(SiMe$_3$)$_2$	*t* [h]	Conc. [M]	Yield [%][b] **3ab**	**4ab**
1	[{ClPd(2-methallyl)}$_2$] (5)/P*t*Bu$_3$ (15)	K	10	0.1	84	<5
2	[{ClPd(2-methallyl)}$_2$] (5)/P*t*Bu$_3$ (15)	K	10	0.05	93 (90)[c]	<5
3	[Pd(dba)$_2$] (10)/NiXantphos (20)	Na	10	0.1	<5	72
4	[Pd(dba)$_2$] (10)/NiXantphos (20)	Na	10	0.05	<5	75
5	precatalyst **6** (10)	Na	10	0.05	<5	82
6	precatalyst **7** (10)	Na	10	0.05	<5	85
7	precatalyst **7** (10)	Na	6	0.05	<5	89 (88)[c]
8	precatalyst **7** (10)	K	6	0.05	<5	67
9	precatalyst **7** (10)	Li	6	0.05	4	63[d]

[a] Reactions were conducted on a 0.1 mmol scale. [b] Assay yield determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Yield of the isolated product after chromatographic purification. [d] The reaction was carried out at 60 °C. dba = dibenzylideneacetone.



Having demonstrated the scope of the α-selective arylation with respect to the aryl bromide substrate, we next turned to the γ-arylation. High regioselectivity (>20:1) was observed in most cases with the NiXantphos-based catalyst (Scheme 4). Bromobenzene and 1-bromo-4-*tert*-butylbenzene provided products **4aa** and **4ab** in 86 and 88% yield, respectively. Aryl bromides with electron-withdrawing substituents, such as 4-F, 4-CF$_3$, and 3-CF$_3$, all underwent coupling in about 80% yield with >20:1 regioselectivity. The coupling of **1a** with aryl bromides containing electron-donating groups at the 3-position resulted in decreased yields (60–63%), partially as a result of the only moderate selectivity (7:1 and 3:1, respectively). Sterically more demanding 1-bromonaphthalene also exhibited catalyst-controlled reactivity and afforded the γ-arylated product in 68% yield with excellent regioselectivity. Finally,

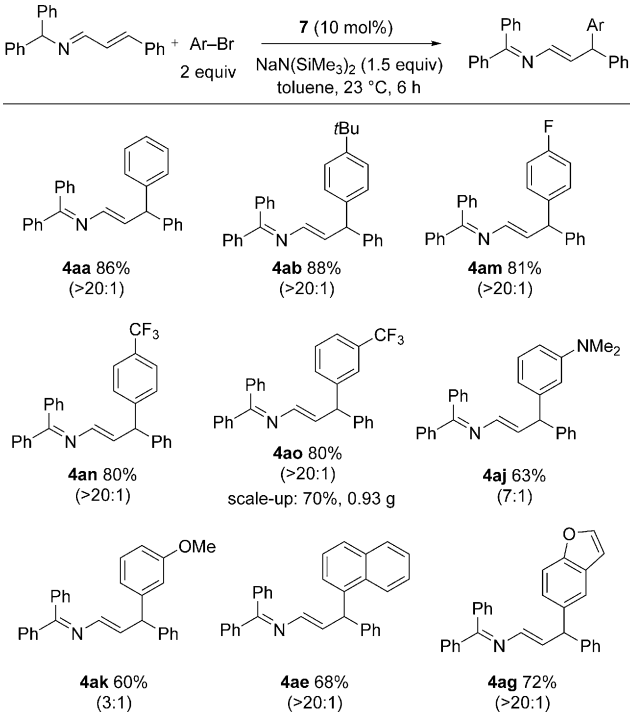


Scheme 3. Scope of the α-arylation with respect to the aryl bromide substrate. Reactions were conducted on a 0.1 mmol scale at 0.05 M. Yields are for the isolated product after chromatographic purification. The **3**/**4** product ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [a] CPME was used as the solvent. [b] The reaction was carried out with $NaN(SiMe_3)_2$ in CPME.

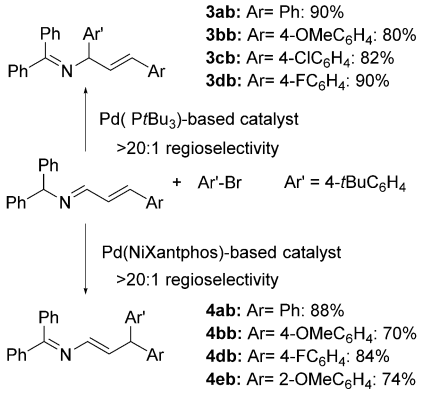
the coupling of **1a** with heterocyclic 5-bromobenzofuran gave the desired product in 72% yield. The reaction with 1-bromo-3-(trifluoromethyl)benzene was scaled up to 3 mmol with a catalyst loading of 5 mol%. The product was isolated in 70% yield (0.93 g, >20:1 regioselectivity).

We next surveyed a few cinnamaldehyde-derived aldimines (Scheme 5). The α-arylation of aldimines **1b** (Ar = 4-$OMeC_6H_4$), **1c** (Ar = 4-ClC_6H_4), **1d** (Ar = 4-FC_6H_4) with 1-bromo-4-*tert*-butylbenzene and the P*t*Bu_3-based catalyst afforded the corresponding products in 80–90% yield; the regioselectivity of the reactions was not affected by the different electronic properties of the substrates. Likewise, high regioselectivity (>20:1) and good yields (70–88%) were observed in the γ-arylation with the NiXantphos-based catalyst (Scheme 5).

Hydrolysis of the α-arylated product **3ab** gave the allylic amine (99% yield, Scheme 6). Similarly, the enamine derivative **4aj** was hydrolyzed to the aldehyde in 95% yield. As compared with traditional 1,2- or 1,4-addition reactions,[13] our method provides the first umpolung disconnection for such aldehydes.

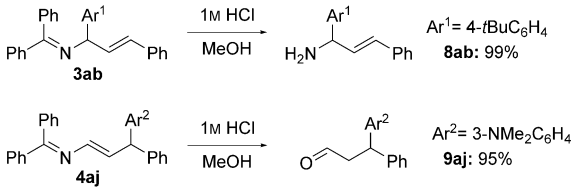


Scheme 4. Scope of the γ-arylation with respect to the aryl bromide substrate. Reactions were conducted on a 0.1 mmol scale at 0.05 M. Yields are for the isolated product after chromatographic purification. The **4**/**3** product ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.



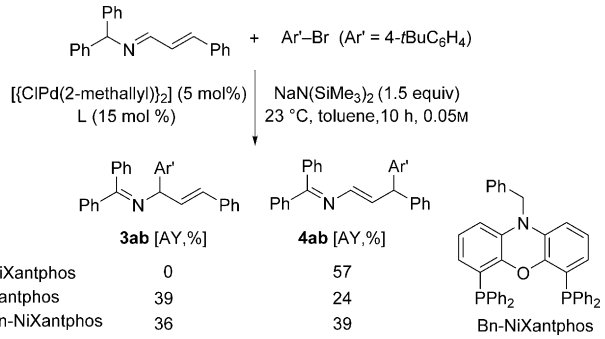
Scheme 5. Scope of the regioselective α- and γ-arylation reactions with respect to the aldimine substrate (see the Supporting Information for details). Reaction conditions for the α-arylation: **1** (1 equiv), aryl bromide (2 equiv), [{ClPd(2-methallyl)}$_2$] (5 mol%), P*t*Bu_3HBF_4 (15 mol%), $KN(SiMe_3)_2$ (1.5 equiv), toluene, 0.1 mmol scale, 0.05 M, 23 °C, 10 h. Reaction conditions for the γ-arylation: **1** (1 equiv), ArBr (2 equiv), precatalyst **7** (10 mol%), $NaN(SiMe_3)_2$ (1.5 equiv), toluene, 0.1 mmol scale, 0.05 M, 23 °C, 6 h. Yields are for the isolated product after chromatographic purification. Selectivity was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

Although a mechanistic study has not yet been performed, the ligand-screening results provide some food for thought. In particular, of the 24 ligands screened, 22 favor α-arylation, thus establishing the α position as the substrate-controlled arylation site. Only NiXantphos and bulky P(2-tolyl)$_3$ gave γ-



Scheme 6. Hydrolysis to afford allylic amine and aldehyde products. See the Supporting Information for optimization and experimental details. Yields are for the isolated product after chromatographic purification.

arylation. Additionally, there is an intriguing difference in selectivity between the Xantphos- and NiXantphos-based catalysts in this arylation reaction. Although both ligands are structurally similar (see Table 1), NiXantphos possesses an acidic N–H group ($pK_a \approx 21$), which we have shown to be deprotonated in other catalytic reactions[14] in the presence of silylamide bases, $MN(SiMe_3)_2$, to give a heterobimetallic catalyst. When the Pd(Xantphos) system was employed, the α-arylation product was favored over the γ-product (1.6:1, Scheme 7). In contrast, the NiXantphos-based catalyst provided exclusively the γ-arylation product. Moreover, when the NiXantphos N–H group was replaced with N–Bn, the resulting catalyst was unselective (Scheme 7). To rationalize this surprising shift in selectivity, we propose that the cation of the bimetallic NiXantphos-based catalyst forms a cation–π interaction with the aryl ring of the substrate (Figure 1),[15] thus forcing reductive elimination at the γ-position to form the enamine product with high selectivity. Our working model has a bridging $NaN(SiMe_3)_2$ moiety, and is thus similar to related crystal structures of deprotonated NiXantphos complexes.[14]



Scheme 7. Comparison of Pd complexes of NiXantphos, Xantphos, and Bn-NiXantphos. Bn = benzyl.

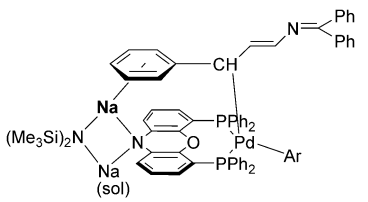


Figure 1. Proposed cation–π interaction guiding regioselectivity.

In summary, we have developed a remarkable catalyst-controlled chemo- and regioselective α- and γ-arylation of azaallyl anions. This umpolung C–H functionalization of azapentadienyl palladium intermediates enables the synthesis of allylic amine and enamine derivatives from common, readily accessible precursors. We propose that the high selectivity observed for the γ-arylation is the result of a cation–π interaction between the heterobimetallic Pd/Na NiXantphos-based catalyst and the substrate.

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Keywords: allylic amines · arylation · divergent synthesis · enamines · regioselectivity

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Angew. Chem. **2016**, *128*, 2875–2879

[1] For early examples, see: a) S. Hansson, A. Heumann, T. Rein, B. Aakermark, *J. Org. Chem.* **1990**, *55*, 975–984; b) H. Grennberg, V. Simon, J.-E. Bäckvall, *J. Chem. Soc. Chem. Commun.* **1994**, 265–266; c) M. S. Chen, M. C. White, *J. Am. Chem. Soc.* **2004**, *126*, 1346–1347; d) M. S. Chen, N. Prabagaran, N. A. Labenz, M. C. White, *J. Am. Chem. Soc.* **2005**, *127*, 6970–6971; for a recent example, see: e) F. Liron, J. Oble, M. M. Lorion, G. Poli, *Eur. J. Org. Chem.* **2014**, 5863–5883; f) "Allylic Oxidations: Palladium-Catalyzed Allylic Oxidation of Olefins": H. Grennberg, J.-E. Bäckvall in *Transition Metals for Organic Synthesis*, *Vol. 2*, 2nd ed. (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, pp. 243–255.

[2] For selected examples, see: a) E. M. Stang, M. C. White, *Nat. Chem.* **2009**, *1*, 547–551; b) E. M. Stang, M. C. White, *Angew. Chem. Int. Ed.* **2011**, *50*, 2094–2097; *Angew. Chem.* **2011**, *123*, 2142–2145; c) M. R. Luzung, C. A. Lewis, P. S. Baran, *Angew. Chem. Int. Ed.* **2009**, *48*, 7025–7029; *Angew. Chem.* **2009**, *121*, 7159–7163.

[3] a) G. Negri, C. Kascheres, A. J. Kascheres, *J. Heterocycl. Chem.* **2004**, *41*, 461–491; b) D. Liu, F. Xie, W. Zhang, *Tetrahedron Lett.* **2007**, *48*, 7591–7594; c) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; d) B. Maji, S. Lakhdar, H. Mayr, *Chem. Eur. J.* **2012**, *18*, 5732–5740; e) J. Xiao, *ChemCatChem* **2012**, *4*, 612–615; f) N. Gigant, L. Chausset-Boissarie, I. Gillaizeau, *Chem. Eur. J.* **2014**, *20*, 7548–7564.

[4] a) A. Stütz, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 320–328; *Angew. Chem.* **1987**, *99*, 323–331; b) A. Stütz, A. Georgopoulos, W. Granitzer, G. Petranyi, D. Berney, *J. Med. Chem.* **1986**, *29*, 112–125; c) S. M. Nanavati, R. B. Silverman, *J. Am. Chem. Soc.* **1991**, *113*, 9341–9349; d) G. Petranyi, N. S. Ryder, A. Stutz, *Science* **1984**, *224*, 1239–1241; e) J. Olesen, *J. Neurol.* **1991**, *238*, S23–S27.

[5] M. J. O'Donnell, X. Yang, M. Li, *Tetrahedron Lett.* **1990**, *31*, 5135–5138.

[6] B. M. Trost, S. Mahapatra, M. Hansen, *Angew. Chem. Int. Ed.* **2015**, *54*, 6032–6036; *Angew. Chem.* **2015**, *127*, 6130–6134.

[7] N. Hussain, G. Frensch, J. Zhang, P. J. Walsh, *Angew. Chem. Int. Ed.* **2014**, *53*, 3693–3697; *Angew. Chem.* **2014**, *126*, 3767–3771.

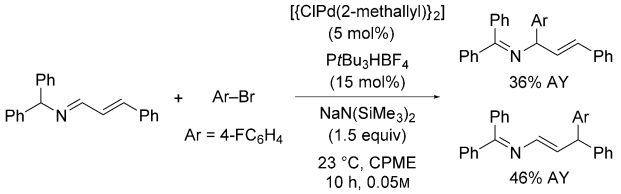
[8] a) G. I. McGrew, C. Stanciu, J. Zhang, P. J. Carroll, S. D. Dreher, P. J. Walsh, *Angew. Chem. Int. Ed.* **2012**, *51*, 11510 – 11513; *Angew. Chem.* **2012**, *124*, 11678 – 11681; b) M. Li, S. Berritt, P. J. Walsh, *Org. Lett.* **2014**, *16*, 4312 – 4315; c) M. Li, B. Yucel, J. Adrio, A. Bellomo, P. J. Walsh, *Chem. Sci.* **2014**, *5*, 2383 – 2391.

[9] For other examples of the use of azaallyl anions in palladium catalysis, see: a) E. C. Burger, J. A. Tunge, *J. Am. Chem. Soc.* **2006**, *128*, 10002 – 10003; b) W. H. Fields, J. J. Chruma, *Org. Lett.* **2010**, *12*, 316 – 319; c) W. H. Fields, A. K. Khan, M. Sabat, J. J. Chruma, *Org. Lett.* **2008**, *10*, 5131 – 5134; d) A. A. Yeagley, M. A. Lowder, J. J. Chruma, *Org. Lett.* **2009**, *11*, 4022 – 4025; e) G. Wolf, E.-U. Würthwein, *Tetrahedron Lett.* **1988**, *29*, 3647 – 3650; f) Y. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2014**, *136*, 4500 – 4503; g) T. Niwa, H. Yorimitsu, K. Oshima, *Org. Lett.* **2008**, *10*, 4689 – 4691; h) T. Niwa, T. Suehiro, H. Yorimitsu, K. Oshima, *Tetrahedron* **2009**, *65*, 5125 – 5131.

[10] L. A. van der Veen, P. H. Keeven, G. C. Schoemaker, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, M. Lutz, A. L. Spek, *Organometallics* **2000**, *19*, 872 – 883.

[11] a) N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci.* **2013**, *4*, 916 – 920; b) N. C. Bruno, N. Niljianskul, S. L. Buchwald, *J. Org. Chem.* **2014**, *79*, 4161 – 4166.

[12] Reaction with 1-bromo-4-fluorobenzene:



[13] K. Das, R. Shibuya, Y. Nakahara, N. Germain, T. Ohshima, K. Mashima, *Angew. Chem. Int. Ed.* **2012**, *51*, 150 – 154; *Angew. Chem.* **2012**, *124*, 154 – 158.

[14] J. Zhang, A. Bellomo, N. Trongsiriwat, T. Jia, P. J. Carroll, S. D. Dreher, M. T. Tudge, H. Yin, J. R. Robinson, E. J. Schelter, P. J. Walsh, *J. Am. Chem. Soc.* **2014**, *136*, 6276 – 6287.

[15] a) R. Kumpf, D. Dougherty, *Science* **1993**, *261*, 1708 – 1710; b) E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem. Int. Ed.* **2003**, *42*, 1210 – 1250; *Angew. Chem.* **2003**, *115*, 1244 – 1287; c) R. K. Raju, J. W. Bloom, Y. An, S. E. Wheeler, *ChemPhysChem* **2011**, *12*, 3116 – 3130.

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