C–H Activation

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Palladium(0)-Catalyzed Enantioselective C–H Arylation of Cyclopropanes: Efficient Access to Functionalized Tetrahydroquinolines**

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Cyclopropanes have been in the center of interest for both theoretical and practical purposes. As structural motifs, they are found in many natural products and bioactive compounds,[1] and as highly strained cycloalkanes they are versatile synthetic intermediates for ring-expansion or ring-opening reactions.[2] Moreover, cyclopropanes are used as molecular tools to constrain conformation[3] and to study reaction mechanisms.[4] Classical, robust methods that proceed via carbene or carbenoid intermediates, such as the Simmons–Smith reaction and transition-metal-catalyzed decomposition of stabilized diazoalkanes or Michael-type additions, have greatly facilitated synthetic access to this compound class.[5] However, the catalytic enantioselective construction of unfunctionalized cyclopropanes remote from functional groups remains problematic.

In stark contrast to the formation of cyclopropane rings, the direct functionalization of an existing cyclopropyl unit is largely underdeveloped. Mainly, such functionalization has been limited to metalations with stoichiometric amounts of strong bases, such as organo–magnesium or organo–lithium reagents.[6] Cyclopropane C–H bonds display enhanced acidity because of the orbital rehybridization that is imposed by the geometry of the cyclopropane ring,[7] and an adequate directing group is required in analogy to directed *ortho* metalations of arenes.[8] Stoichiometric amounts of sparteine as chiral modifier allowed an enantioselective deprotonation.[9] Recently, Yu and co-workers reported a directed palladium(II)-catalyzed process[10] that uses protected chiral amino acid derivatives as ligands for enantioselective C–H arylations of N-aryl cyclopropyl carboxamides.[10a]

Our interest to develop synthetic tools for asymmetric C–H functionalizations,[11] aiming to streamline the synthesis of complex molecules, drew our attention to the tetrahydroquinoline scaffold.[12] The tetrahydroquinoline core is an omnipresent and important structural subunit of natural products and synthetic compounds that display a vast range of relevant biological activities (Figure 1).[13]

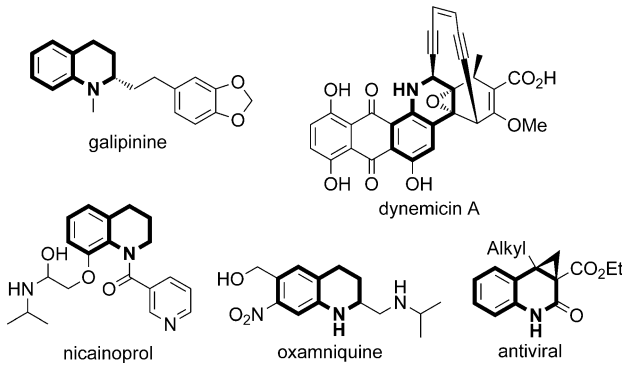
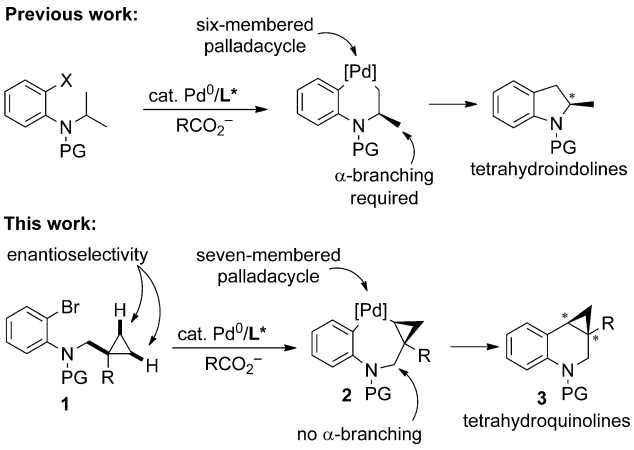


Figure 1. Tetrahydroquinoline-containing natural products and pharmaceuticals.

In this respect, a palladium(0)-catalyzed direct C(sp^3)–H arylation of unbiased cyclopropanes **1** would give direct access to the tetrahydroquinoline scaffold **3**, which bears a quaternary stereogenic center (Scheme 1). These intramolecular C(sp^3)–H functionalizations are strictly limited by a) the ring size of the intermediary palladacycle (five- or six-membered), and b) by substrates with a Thorpe–Ingold bias that requires substrate branching.[14] In addition, asymmetric



Scheme 1. Enantioselective synthesis of tetrahydroquinolines by palladium(0)-catalyzed C–H functionalization. L = ligand, PG = protecting group.

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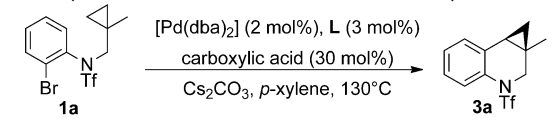
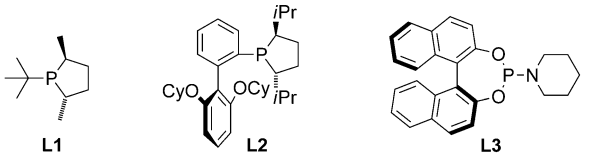
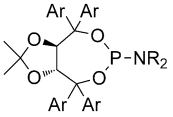
versions are often impeded by high reaction temperatures and the use of a monodentate ligand imposed by the concerted metalation–deprotonation (CMD) mechanism.[15] The process we envisioned would require the enantioselective formation of a rare seven-membered palladacycle[16] of an unbranched substrate (**2**), thus significantly expanding the boundaries of the current methodology. Among the very few reported catalytic asymmetric processes, all examples are limited to six-membered palladacyclic intermediates.[17]

The general feasibility of our hypothesis for the cyclopropane C(sp^3)–H bond functionalization was proven using aryl bromide **1a** and tricyclohexylphosphine as achiral ligand (Table 1, entry 1). The desired tetrahydroquinoline **3a** was obtained in excellent yield at 130 °C. For the development of an efficient asymmetric version, we first investigated related chiral and electron-rich monodentate phosphines. P-Alkyl phospholane **L1**[18] worked well with 2 mol % catalyst loading,

Table 1: Optimization of the enantioselective C–H arylation of **3a**.[a]







L4 ($R_2 = (CH_2)_5$, Ar = 3,5-dimethylphenyl)
L5 ($R_2 = (CH_2)_5$, Ar = Ph)
L6 ($R_2 = (CH_2)_5$, Ar = 3,5-di*tert*butylphenyl)
L7 ($R_2 = (CH_2)_4$, Ar = 3,5-dimethylphenyl)
L8 (R_2 = Me, Ar = 3,5-dimethylphenyl)
L9 (R_2 = Et, Ar = 3,5-dimethylphenyl)

Entry	Carboxylic acid	L	Yield [%][b]	e.r.[c]
1	pivalic acid	PCy_3[d,e]	95	–
2	pivalic acid	**L1**[e]	95	35.5:64.5
3	pivalic acid	**L2**	< 5[f]	–
4	pivalic acid	**L3**	< 5[f]	–
5	pivalic acid	**L4**	88	94.5:5.5
6	pivalic acid	**L5**	< 5[f]	–
7	pivalic acid	**L6**	91	62:38
8	pivalic acid	**L7**	97	94.5:4.5
9	pivalic acid	**L8**	98	96:4
10	pivalic acid	**L9**	86[f]	95:5
11	no acid	**L8**	58[f]	82:18
12	9*H*-xanthene-9-carboxylic acid	**L8**	59[f]	84.5:15.5
13	triphenylacetic acid	**L8**	75[f]	84:16
14	2,2-diphenylpropanoic acid	**L8**	62[f]	88.5:11.5
15	anthracene-9-carboxylic acid	**L8**	38[f]	90:10
16	cyclohexylcarboxylic acid	**L8**	92	91.5:8.5
17	adamantylcarboxylic acid	**L8**	94	95:5
18	pivalic acid	**L8**[g]	95	96:4

[a] Reaction conditions: **1a** (0.10 mmol), carboxylic acid (30.0 μmol), $[Pd(dba)_2]$ (2.00 μmol), **L** (3.00 μmol), Cs_2CO_3 (1.5 equiv), 0.30 M in *p*-xylene at 130 °C for 12 h. [b] Yields of isolated products. [c] Determined by GC on a chiral stationary phase. [d] With $Pd(OAc)_2$ (5 mol %) and PCy_3 (10 mol %). [e] Used as HBF_4 salt. [f] Incomplete conversion. [g] With $[Pd(dba)_2]$ (1 mol %). Cy = cyclohexyl, dba = *trans*,*trans*-dibenzylideneacetone.

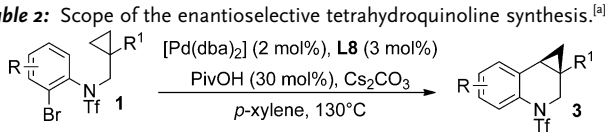
however, the enantioselectivity is modest (Table 1, entry 2). In contrast, SagePhos (**L2**), a ligand we previously introduced for related C–H functionalizations of aryl triflates leading to indolines,[17c] showed a very low reactivity with aryl bromides (Table 1, entry 3). We then turned our attention toward less-electron-rich phosphoramidites. While binol-based ligand **L3** did not promote the reaction at all (Table 1, entry 4), taddol-derived ligand **L4** gave excellent reactivity and selectivity, providing **3a** in 88 % yield and e.r. = 94.5:5.5 (Table 1, entry 5). A careful choice of aromatic substituents on the taddol backbone is critical for reactivity and selectivity.[19] Whereas the reactivity was very low with simple phenyl groups (**L5**; Table 1, entry 6), bulky 3,5-di-*tert*-butylphenyl groups (**L6**) are detrimental to the enantioselectivity (entry 7). In conjunction with a dimethylamino group, the 3,5-xylyl backbone (**L8**) gave **3a** almost quantitatively with e.r. = 96:4 (Table 1, entry 9). As we have previously demonstrated,[17c] the carboxylic acid co-catalyst plays a critical role on the enantioselectivity of the activation by relaying the chiral information of the phosphine ligand during the selectivity-determining CMD step. Without acid additive, the reaction proceeds sluggishly and with reduced selectivity (Table 1, entry 11). Contrasting our previous findings with aryl triflate substrates, bulky acids that bear aromatic groups are not as efficient, leading to incomplete conversions with 2 mol % of palladium catalyst (Table 1, entries 12–15), whereas aliphatic acids give rise to excellent yields (entries 16 and 17). Among them, pivalic acid displays the best enantioselectivity. Without affecting the reaction outcome negatively, the catalyst loading could be reduced to 1 mol % (Table 1, entry 18). Notably, such a low catalyst loading is quite uncommon in the field of C–H functionalization and demonstrates the efficiency of our catalytic system.

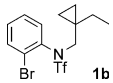
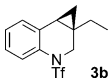
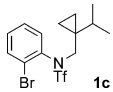
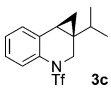
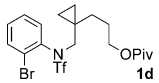
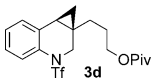
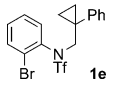
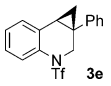
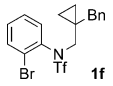
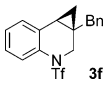
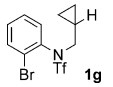
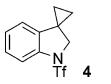
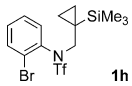
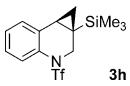
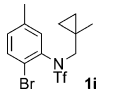
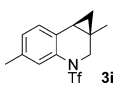
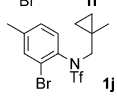
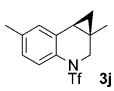
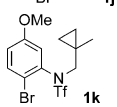
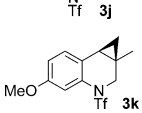
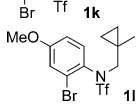
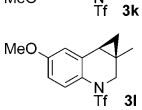
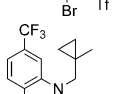
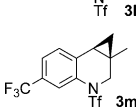
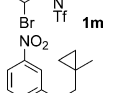
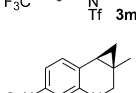
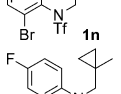
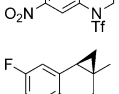
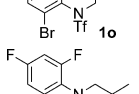
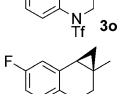
To explore the generality of the optimized process, we evaluated different substitution patterns on the cyclopropane ring. Several aliphatic and functional groups are tolerated (Table 2, entries 1–3). The yields and selectivities are consistently excellent. A phenyl and a benzyl group do not react in a competing C(sp^2)–H activation (Table 2, entries 4 and 5). With the unsubstituted cyclopropane **1g**, exclusively methine C–H activation occurs and gives rise to spirocycle **4** (Table 2, entry 6). The better accessibility of the six-membered palladacycle clearly overrides the preference for the less-substituted C–Pd bond. In contrast, silyl-substituted cyclopropane **1h** cleanly gives **3h**, offering further opportunities for functionalization (Table 2, entry 7). The aromatic portion of the substrates tolerates the most common electron-donating and electron-withdrawing groups (Table 2, entry 7–14). Both *meta* and *para* substitution with respect to the bromine atom have little influence on the reaction efficiency. Notably, tetrasubstituted substrate **1p** with a fluorine atom in *ortho* position to the nitrogen atom that disturbs the proper orientation of the cyclopropyl moiety most, is also tolerated (Table 2, entry 15). However, a somewhat lower enantioselectivity is observed for **3p**.

To showcase the practicality of the process, we carried out a gram-scale reaction using substrate **1e** and a catalyst loading of 1 mol % palladium (Scheme 2). The desired product **3e** was

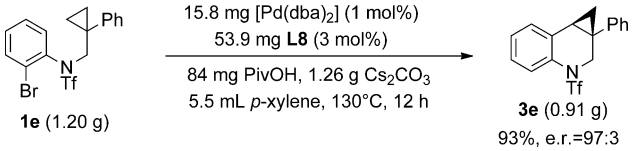
isolated in slightly higher yield of 93% and with the same selectivity (e.r. = 97:3).[20]

Table 2: Scope of the enantioselective tetrahydroquinoline synthesis.[a]



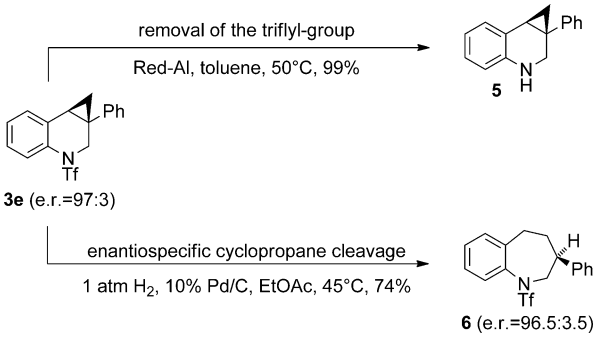
Entry	Aryl bromide **1**	Product **3**	Yield [%][b]	e.r.[c]
1	 **1b**	 **3b**	91	96:4
2	 **1c**	 **3c**	90	97:3
3	 **1d**	 **3d**	90	95.5:4.5
4	 **1e**	 **3e**	89	97:3
5	 **1f**	 **3f**	99	96:4
6	 **1g**	 **4**	95	–
7	 **1h**	 **3h**	80	96:4
8	 **1i**	 **3i**	93	96:4
9	 **1j**	 **3j**	91	92:8
10	 **1k**	 **3k**	94	94.5:5.5
11	 **1l**	 **3l**	95	92:8
12	 **1m**	 **3m**	93	95.5:4.5
13	 **1n**	 **3n**	90	96:4
14	 **1o**	 **3o**	86	95:5
15	 **1p**	 **3p**	89	93:7

[a] Reaction conditions: **1** (0.10 mmol), $[Pd(dba)_2]$ (2.00 μmol), **L8** (3.00 μmol), PivOH (30.0 μmol), Cs_2CO_3 (1.5 equiv), 0.30 M in *p*-xylene at 130°C for 12 h. [b] Yields of isolated products. [c] Determined by HPLC or GC on a chiral stationary phase. Bn = benzyl, Piv = pivaloyl, Tf = trifluoromethanesulfonyl.



Scheme 2. Gram-scale synthesis of tetrahydroquinoline **3e**.

To prove the utility of our methodology, the triflyl group was removed under reductive conditions with Red-Al, affording the corresponding free aniline **5** virtually quantitatively (Scheme 3). Furthermore, the cyclopropyl moiety is



Scheme 3. Modifications of the tetrahydroquinoline scaffold by deprotection and regioselective enantiospecific cyclopropane cleavage. Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride.

amenable to modifications. For instance, treatment of **3e** with H_2 and 10% Pd/C in ethyl acetate selectively reduces the highest-substituted C–C bond of the cyclopropane to give the ring-enlarged highly valuable benzazepine scaffold[21] (Scheme 3). Most notably, this reaction is completely stereospecific and the corresponding tetrahydrobenzoazepine **6** is obtained with an almost unchanged e.r. = 96.5:3.5.

In summary, we reported an enantioselective palladium(0)-catalyzed direct arylation of unbranched cyclopropylmethyl anilines, giving an efficient access to the valuable tetrahydroquinoline scaffold with excellent selectivities. The enantioselective CMD step occurs via a rare seven-membered palladacycle. We showed that the cooperative effect between the chiral phosphine ligand and the carboxylate base is a great handle to tune the selectivity. The reaction proceeds with catalyst loadings as low as 1 mol% and is well suited for gram-scale reactions. In addition, enantiospecific reduction of the cyclopropyl group provides a convenient access to the highly valuable chiral tetrahydrobenzoazepines.

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[1] a) J. Salaün, *Top. Curr. Chem.* **2000**, *207*, 1–67; b) R. Faust, *Angew. Chem.* **2001**, *113*, 2312–2314; *Angew. Chem. Int. Ed.* **2001**, *40*, 2251–2253; c) F. Gnad, O. Reiser, *Chem. Rev.* **2003**,

103, 1603 – 1623; A. de Meijere, S. I. Kozhushkov, H. Schill, *Chem. Rev.* **2006**, *106*, 4926 – 4996.
[2] For reviews, see: a) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151 – 1196; b) F. De Simone, J. Waser, *Synthesis* **2009**, 3353 – 3374; c) P. Tang, Y. Qin, *Synthesis* **2012**, 2969 – 2984.
[3] For some examples, see: a) P. D. Armstrong, G. J. Cannon, J. P. Long, *Nature* **1968**, *220*, 65 – 66; b) S. H. Stammer, *Tetrahedron* **1990**, *46*, 2231 – 2254; c) K. Shimamoto, Y. Ofune, *J. Med. Chem.* **1996**, *39*, 407 – 423; d) T. Sekiyama, S. Hatsuya, Y. Tanaka, M. Uchiyama, N. Ono, S. Iwayama, M. Oikawa, K. Suzuki, M. Okunishi, T. Tsuji, *J. Med. Chem.* **1998**, *41*, 1284 – 1298; e) S. F. Martin, M. P. Dwyer, B. Hartmann, K. S. Knight, *J. Org. Chem.* **2000**, *65*, 1305 – 1318.
[4] D. Griller, K. U. Ingold, *Acc. Chem. Res.* **1980**, *13*, 317 – 323.
[5] a) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977 – 1050; b) H. Pellissier, *Tetrahedron* **2008**, *64*, 7041 – 7095.
[6] a) P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016 – 8018; b) M.-X. Zhang, P. E. Eaton, *Angew. Chem.* **2002**, *114*, 2273 – 2275; *Angew. Chem. Int. Ed.* **2002**, *41*, 2169 – 2171.
[7] a) A. de Meijere, *Angew. Chem.* **1979**, *91*, 867 – 884; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 809 – 826; b) K. Exner, P. v. R. Schleyer, *J. Phys. Chem. A* **2001**, *105*, 3407 – 3416.
[8] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879 – 933.
[9] S. Lauru, N. S. Simpkins, D. Gethin, C. Wilson, *Chem. Commun.* **2008**, 5390 – 5392.
[10] a) M. Wasa, K. M. Engle, D. W. Lin, E. J. Yoo, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19598 – 19601; for related work, see: b) D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 7190 – 7191; c) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3680 – 3681; d) E. J. Yoo, M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 17378 – 17380.
[11] For our recent activities in C–H functionalizations, see: a) T. Seiser, O. A. Roth, N. Cramer, *Angew. Chem.* **2009**, *121*, 6438 – 6441; *Angew. Chem. Int. Ed.* **2009**, *48*, 6320 – 6323; b) M. Albicker, N. Cramer, *Angew. Chem.* **2009**, *121*, 9303 – 9306; *Angew. Chem. Int. Ed.* **2009**, *48*, 9139 – 9142; c) D. N. Tran, N. Cramer, *Angew. Chem.* **2010**, *122*, 8357 – 8360; *Angew. Chem. Int. Ed.* **2010**, *49*, 8181 – 8184; d) D. N. Tran, N. Cramer, *Angew. Chem.* **2011**, *123*, 11294 – 11298; *Angew. Chem. Int. Ed.* **2011**, *50*, 11098 – 11102; e) M. Pham, B. Ye, N. Cramer, *Angew. Chem.* **2012**, *124*, 10762 – 10766; *Angew. Chem. Int. Ed.* **2012**, *51*, 10610 – 10614; f) B. Ye, N. Cramer, *Science* **2012**, *338*, 504 – 506.
[12] M. Waibel, N. Cramer, *Angew. Chem.* **2010**, *122*, 4557 – 4560; *Angew. Chem. Int. Ed.* **2010**, *49*, 4455 – 4458.
[13] a) A. R. Katritzky, S. Rachwal, B. Rachwal, *Tetrahedron* **1996**, *52*, 15031 – 15070; b) D. Ellis, K. L. Kuhen, B. Anaclerio, B. Wu, K. Wolff, H. Yin, B. Bursulaya, J. Caldwell, D. Karanewsky, Y. He, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4246 – 4251.
[14] For general reviews about metal-catalyzed C(sp^3)-H activation see: a) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654 – 2672; b) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902 – 4911; for representative examples of palladium(0)-catalyzed functionalization of unactivated C(sp^3)–H bonds, see: c) G. Dyker, *Angew. Chem.* **1994**, *106*, 117 – 119; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 103 – 105; d) O. Baudoin, A. Herrbach, F. Gueritte, *Angew. Chem.* **2003**, *115*, 5914 – 5918; *Angew. Chem. Int. Ed.* **2003**, *42*, 5736 – 5740; e) M. Lafrance, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 14570 – 14571; f) J. Hitce, P. Retailleau, O. Baudoin, *Chem. Eur. J.* **2007**, *13*, 792 – 799; g) T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 1759 – 1762; h) M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J.-L. Peglion, E. Clot, O. Baudoin, *J. Am. Chem. Soc.* **2008**, *130*, 15157 – 15166; i) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886 – 9887; j) S. Rousseaux, S. I. Gorelsky, B. K. W. Chung, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 10692 – 10705; k) J. Pan, M. Su, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 8806 – 8810; *Angew. Chem. Int. Ed.* **2011**, *50*, 8647 – 8651; l) S. Rousseaux, B. Liégault, K. Fagnou, *Chem. Sci.* **2012**, *3*, 244 – 248.
[15] a) D. García-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880 – 6886; b) D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118 – 1126.
[16] A side product resulting from a palladium(0)-catalyzed C(sp^3)–H functionalization involving a seven-membered palladacycle was observed in reference [14l].
[17] a) M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, *Angew. Chem.* **2011**, *123*, 7576 – 7579; *Angew. Chem. Int. Ed.* **2011**, *50*, 7438 – 7441; b) S. Anas, A. Cordi, H. B. Kagan, *Chem. Commun.* **2011**, *47*, 11483 – 11485; c) T. Saget, S. Lemouzy, N. Cramer, *Angew. Chem.* **2012**, *124*, 2281 – 2285; *Angew. Chem. Int. Ed.* **2012**, *51*, 2238 – 2242; d) D. Katayev, M. Nakanishi, T. Bürgi, E. P. Kündig, *Chem. Sci.* **2012**, *3*, 1422 – 1425; e) N. Martin, C. Pierre, M. Davi, R. Jazzar, O. Baudoin, *Chem. Eur. J.* **2012**, *18*, 4480 – 4484; f) M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, *Chimia* **2012**, *66*, 241 – 243; for an enantioselective palladium(0)-catalyzed C(sp^3)–H functionalization operating by other mechanism, see: g) A. Renaudat, L. Jean-Gerard, R. Jazzar, C. E. Kefalidis, E. Clot, O. Baudoin, *Angew. Chem.* **2010**, *122*, 7419 – 7423; *Angew. Chem. Int. Ed.* **2010**, *49*, 7261 – 7265.
[18] P. A. Donets, T. Saget, N. Cramer, *Organometallics* **2012**, DOI: 10.1021/om3008772.
[19] For examples with similar influences of the aryl substituents, see: a) A. R. Woodward, H. E. Burks, L. M. Chan, J. P. Morken, *Org. Lett.* **2005**, *7*, 5505 – 5507; b) J. D. Sieber, J. P. Morken, *J. Am. Chem. Soc.* **2008**, *130*, 4978 – 4983; c) L. T. Kliman, S. M. Mlynarski, J. P. Morken, *J. Am. Chem. Soc.* **2009**, *131*, 13210 – 13211.
[20] The absolute configuration of **3e** was established by X-ray crystallographic analysis, see the Supporting Information.
[21] See M. Qadir, R. E. Priestley, T. W. D. F. Rising, T. Gelbrich, S. J. Coles. M. B. Hursthouse, P. W. Sheldrake, N. Whittal, K. K. Hii, *Tetrahedron Lett.* **2003**, *44*, 3675 – 3678, and references therein.

