CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.201101011

Mechanistic Studies on the Pd-catalyzed Direct C–H Arylation of 2-Substituted Thiophene Derivatives with Arylpalladium Bipyridyl Complexes

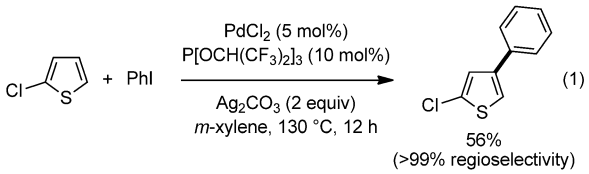
Marc Steinmetz,[a] Kirika Ueda,[c] Stefan Grimme,*[b] Junichiro Yamaguchi,[c] Sylvia Kirchberg,[a] Kenichiro Itami,*[a] and Armido Studer*[a]

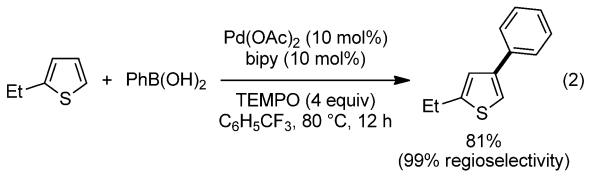
Abstract: Direct C–H phenylation of 2-ethylthiophene and 2-chlorothiophene with PhPdI(bipy) complex to form either the corresponding 4-phenyl or 5-phenylthiophene derivative is studied under stoichiometric conditions using various Lewis acids as additives. It is shown that reactions occur via the corresponding cationic Pd complex ($PhPdbipy^+$) and that the counteranion determines the regioselectivity. High-level DFT calculations reveal that C–C bond formation occurs via a carbopalladation pathway and not via electrophilic palladation. These calculations give some indications regarding the regioselectivity of the thiophene arylation.

Keywords: catalysis · C–H activation · cross-coupling · DFT calculations · palladium

Introduction

The development of synthetic methods for direct C–H arylation of arenes and heteroarenes is a highly active and modern research area. In most cases transition metals have been used as catalysts to conduct such C–C bond forming reactions.[1–5] Heteroarenes occur as structural key entities in many drugs and drug candidates. Importantly, the construction of such arylated heteroarenes via direct C–H arylation offers economic advantages over the more traditional cross-coupling approaches where both coupling partners, the heteroarene and also the arene, have to be prefunctionalized. However, in contrast to the classical cross-coupling processes, where the reactive positions in both partners are predetermined by the location of their functional groups, the direct C–H arylation of heteroarenes poses a regiochemistry problem if the heteroarene contains more than one aromatic C–H bond. An important goal in this field is the development of specific reagents that allow highly regioselective C–H bond arylation of heteroarenes. The most difficult task is, of course, the direct C–H arylation of intrinsically less reactive C–H bonds in a heteroarene. Along this line, we have initiated a program towards Pd-catalyzed selective C(4)-arylation of 2-substituted thiophene derivatives.[4] C–H Arylation of 2-substituted thiophenes at the most reactive C(5)-position is well established.[6] The C(4)-position in such systems can be addressed by installing an *ortho*-directing group at C(5).[7,8] However, the directing groups need to be installed and removed (if possible) after successful arylation and that route is therefore economically not ideal.





We have developed two protocols that allow for selective functionalization of thiophene at the 4-position via direct C–H arylation.[4] For example, 2-chlorothiophene reacted with iodobenzene under the action of $PdCl_2/P[OCH(CF_3)_2]_3/Ag_2CO_3$ catalysis to give 2-chloro-4-phenylthiophene with virtually complete regioselectivity [Eq. (1)].[4b] We also found that 2-ethylthiophene reacted with $PhB(OH)_2$[9] under oxidative $Pd(OAc)_2$/bipyridyl catalysis using 2,2,6,6-tetrame-

[a] M. Steinmetz, Dr. S. Kirchberg, Prof. Dr. K. Itami, Prof. Dr. A. Studer
Westfälische Wilhelms-Universität Münster
Organisch-Chemisches Institut
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 281-833-6523
E-mail: studer@uni-muenster.de

[b] Prof. Dr. S. Grimme
Mulliken Center for Theoretical Chemistry
University of Bonn
E-mail: grimme@thch.uni-bonn.de

[c] K. Ueda, Dr. J. Yamaguchi
Department of Chemistry
Graduate School of Science
Nagoya University
Chikusa, Nagoya 464-8602 (Japan)
Fax: (+81) 52-788-6098

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201101011.

thylpiperidine-*N*-oxyl radical (TEMPO)[10,11] as an oxidant with excellent regioselectivity and high yield to the corresponding C(4)-phenylated thiophene [Eq. (2)].[4c] Very recently, Bach and co-workers also published on Pd-catalyzed oxidative coupling of 3-substituted thiophenes with aryl boronic acids at the C(4)-position.[12]

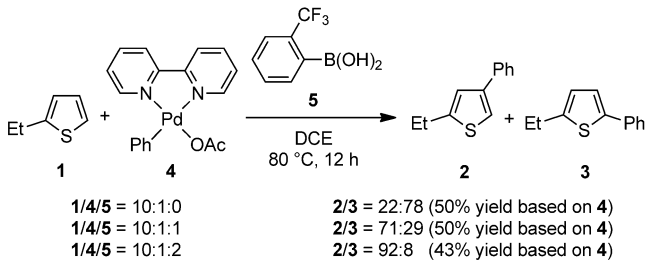
Herein we report mechanistic studies on the C(4)-selectivity of the direct C–H arylation of thiophene with arylpalladium bipyridyl complexes. Moreover, we will present high-level density functional theory (DFT) calculations to support our experimental findings.

Results and Discussion

Effect of the Counteranion in Cationic PhPd Bipyridyl Complexes on the C(4)/C(5) Selectivity.

As a first test reaction, we chose the phenylation of 2-ethylthiophene (**1**) to give 2-ethyl-4-phenylthiophene (C(4)-product **2**) and/or its regioisomeric congener, 2-ethyl-5-phenylthiophene (C(5)-product **3**).

We prepared Pd complex **4**[13] and studied the direct phenylation of 2-ethylthiophene in 1,2-dichloroethane (DCE) at 80 °C for 12 hours, mimicking the conditions applied under catalysis [see Equation (2)]. Surprisingly, we found that reaction of **1** with Pd complex **4** (10 mol %) afforded the C(5)-regioisomer as the major product (C(4)/C(5) = 22:78, Scheme 1). Note that the catalytic process delivered the

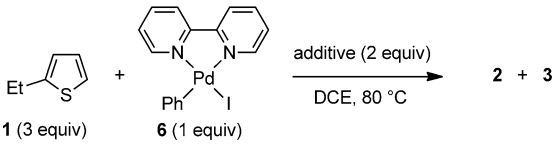


Scheme 1. Effect of free arylboronic acid on the regioselectivity.

C(4)-phenylated product with high regioselectivity. The difference to the arylation shown in equation 2 was the absence of any free arylboronic acid. We have previously communicated that TEMPO used in the catalytic process did not influence the regioselectivity.[4c] Repeating the same experiment in the presence of 2-$CF_3C_6H_4B(OH)_2$ (10 mol %), an arylboronic acid that does not undergo any transmetalation, led to the inversed regioselectivity also noted in catalysis (C(4)/C(5) = 71:29). It was obvious that the free arylboronic acid affected the regioselectivity. It is important to mention that in the experiments run under catalytic conditions, we always used a large excess of the arylboronic acid. We previously suggested that the free arylboronic acid is able to sequester the acetate anion deriving from **4** to generate a borate complex of the type $ArylB(OH)_2OAc^-$, which is, as compared to the acetate anion, certainly less basis. We therefore assumed that the basicity of the counteranion generated during C–H arylation must be responsible for the regiochemical outcome of the direct thiophene arylation.

To further support this assumption, we decided to study the effect of a series of counteranions with different basicity on the regioselectivity of the phenylation of **1**. To this end, we reacted 2-ethylthiophene (**1**, 3 equiv) with PhPdI(2,2′-bipy) complex **6** (1 equiv)[14] in the presence of an additive (2 equiv) in DCE at 80 °C for 14–15 hours (Table 1).

Table 1. Effect of the counteranion on the C(4)/C(5) selectivity.



Additive	*t* [h]	Yield [%][a]	Ratio (**2**:**3**)[a]	Ph_2 [%][b]
$AgPF_6$	14	74	97:3	<1
$AgPF_6$	14	78[c]	97:3	<1
Ag_2CO_3	14	19	18:82	36
AgOAc	14	67	10:90	15
AgOTf	14	91	99:1	10
$Cu(BF_4)_2/6H_2O$	15	74	96:4	1
$Sc(OTf)_3$	15	41	96:4	4
BF_3/Et_2O	15	17	97:3	13

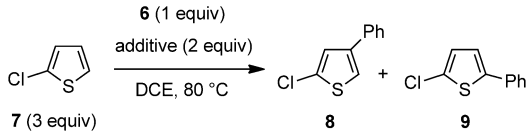
[a] The yield and the selectivity were determined by GC and ^1H NMR spectroscopy. [b] The yield was determined based on the amount of Pd complex used. [c] 5 Equivalents of 2-ethylthiophene were used.

With $AgPF_6$ as an additive, phenylation occurred in 74 % yield with high C(4)-selectivity (97:3). The yield slightly improved to 78 % upon increasing the amount of **1**. Biphenyl, which was observed in all other experiments, was not identified in these two reactions. With Ag_2CO_3 a lower yield was observed. Importantly, the regioselectivity was reversed (C(5)/C(4) = 82:18). A similar C(5)-selectivity was obtained with AgOAc as an additive (90:10). The use of AgOTf resulted in an excellent C(4)-selectivity (99:1). Other non-silver-containing Lewis acids such as $Cu(BF_4)_2/6H_2O$, $Sc(OTf)_3$, and BF_3/Et_2O also provided very high C(4)-selectivity. In the absence of any additive, no reaction took place. Based on these experiments we conclude that C(4)-selectivity is obtained for Lewis acids leading to non-basic anions (PF_6^-, OTf^-, BF_4^-, and BF_3I^-), whereas C(5)-selectivity is achieved for additives providing basic counteranions (carbonate and acetate).

To check whether electronic effects exerted by the substrate influence the regioselectivity, we also studied the phenylation of 2-chlorothiophene (**7**) with complex **6** under stoichiometric conditions (Table 2). Reactions were conducted in DCE at 80 °C and various additives were tested. In comparison to the more electron-rich 2-ethylthiophene, reactions with **7** gave rise to low yields. The more electron-deficient thiophene **7** also revealed the strong counteranion effect on the regioselectivity observed for **1**. Hence, with additives leading to basic counteranions such as AgOAc and Ag_2CO_3 high C(5)-selectivity was obtained. Additives lead-

CHEMISTRY
AN ASIAN JOURNAL

Table 2. Regioselective phenylation of 2-chlorothiophene with **6**.



Additive	t [h]	Yield [%][a]	Ratio (**8**:**9**)[a]	Ph_2 [%][b]
$AgPF_6$	15	17	>99:1	19
Ag_2CO_3	16	14	6:94	22
AgOAc	16	21	7:93	15
AgOTf	15	13	>99:1	31
$Cu(BF_4)_2/6H_2O$	16	19	>99:1	8
$Sc(OTf)_3$	15	6	>99:1	8
BF_3/Et_2O	15	5	>99:1	20

[a] The yield and the selectivity were determined by GC. [b] The yield was determined based on the amount of Pd complex used.

ing to non-basic counteranions provided regioisomer **8** as the major compound with perfect regioselectivity.

To gain more insight into the mechanism, we then investigated the Pd-catalyzed direct thiophene phenylation by computational chemistry.

Analysis of the Mechanism by DFT Calculations.

DFT calculations were performed with two different dispersion-corrected density functionals, which yield qualitatively the same picture. However, for the discussion only the results including corrections to (relative) free reaction energies at the B2PLYP-D3/QZVPP//TPSS-D3/TZVP[15–17] level in kcal mol^{-1} were used (Figure 1). As a model reaction, phenylation of thiophene with the cationic PhPdbipy complex was investigated. To simplify the system, calculations were conducted on unsubstituted thiophene.

Calculations clearly revealed that dissociation of the acetate from the [Pd(bipy)(Ph)OAc] complex preceded the C–C bond-forming event. Hence, the reactive complex in these phenylations must be the cationic PhPdbipy species. This

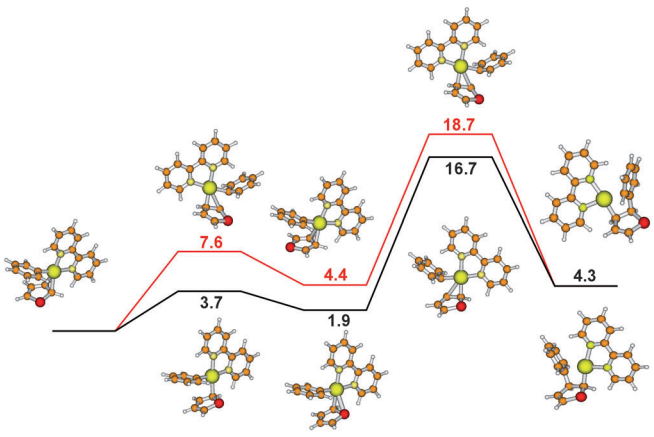


Figure 1. Calculated relative free energy (ΔG^{353}) at the B2PLYP-D3/QZVPP level for the reaction of thiophene with the cationic PhPdbipy complex in kcal mol^{-1}. The structures shown represent the corresponding stationary points on each potential energy surface (PES).

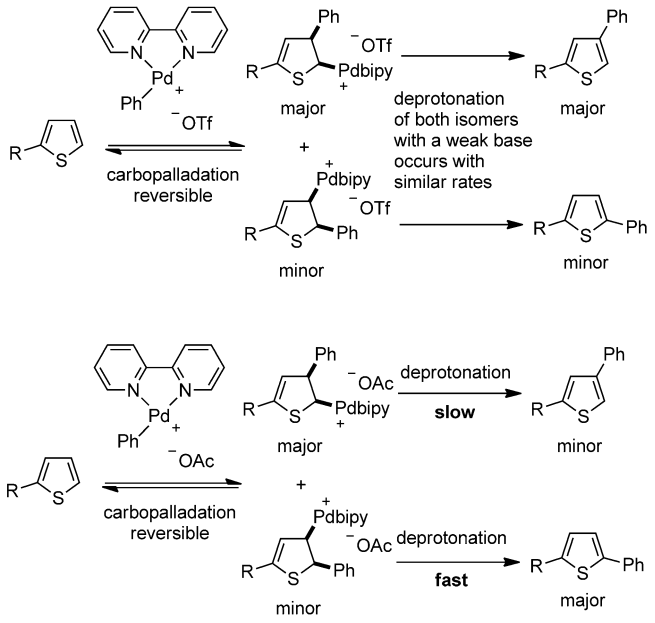
was in agreement with the experimental results discussed above that showed the necessity for activation of the Pd complex by an Ag-, Cu-, Sc-, or B-based Lewis acid. The calculations showed that the cationic Pd complex generated after acetate or iodide abstraction from PhPdXbipy (**4**, **6**) first forms a cationic π-complex with thiophene. The Pd thereby interacts with C(2) and C(3) of thiophene (Figure 1). The C(3)-reaction pathway then passes a transition state (TS, +3.7 kcal mol^{-1}) in which the Pd is bound to C(2) of thiophene via a σ-complex to end up as new cationic π-type complex (intermediate) with thiophene where Pd binds to S and C(2) of thiophene. This intermediate is slightly higher in energy (+1.9 kcal mol^{-1}). As an important result, we found that the subsequent C–C bond-forming reaction is a carbopalladation (TS = +16.7 kcal mol^{-1}) to give the C(3)-phenylated thiophene where the Pd remains bound to the C(2) atom of the thiophene as a σ-complex (+4.3 kcal mol^{-1}). The complex is further stabilized via interaction of Pd with the phenyl substituent.

Electrophilic palladation,[2] which is often suggested to occur in direct arene C–H arylation reactions, can be ruled out. Contrary to a previous supposition, a carbopalladation pathway needs to be taken into consideration for the C–H arylation of thiophenes.[18] The reaction pathway leading to the C(2)-phenylated Pd intermediate also follows a similar mechanism (see Figure 1). The precomplex that undergoes the carbopalladation is in that case a Pd π-complex in which Pd binds to C(3) and C(4) of the thiophene (+4.4 kcal mol^{-1}). The transition state for the subsequent C(2)-carbopalladation is 2.0 kcal mol^{-1} higher in energy as compared to the TS for the C(3)-carbopalladation.

To conclude the theoretical part, we can state that C–C bond formation occurs via a carbopalladation and that the C(3)-arylated intermediate is formed as the major isomer. Importantly, carbopalladation of thiophene with the cationic PhPdbipy complex is endothermic (+4.3 kcal mol^{-1}). Therefore, reversibility must be considered to explain the follow-up chemistry (aromatization). Interestingly, both carbopalladation intermediates have the same energy.

Since selectivity depended on the base/counteranion (see above), it is obvious that the deprotonation/rearomatization step must be included in the discussion on the regiochemical outcome of our thiophene arylation reactions. Unfortunately, due to the complexity of the system, we were not able to adequately analyze the deprotonation step using computational chemistry.

Considering the experimental and theoretical findings we noted that in the presence of weak bases as counteranions of the cationic Pd complex, the regioselectivity deduced from the calculations for the initial carbopalladation is well reflected by the isomer ratio for the two regioisomeric phenylated product thiophenes obtained in the experiment. Therefore, we assume that both carbopalladation isomers must further react with similar rates to the corresponding phenylated thiophenes (Scheme 2). The mechanism for the rearomatization with weakly basic counteranions is currently not fully understood. However, in the presence of a stronger



Scheme 2. Postulated mechanism.

base, we assume that the minor C(5)-phenylated carbopalladation complex gets selectively deprotonated in a fast process, whereas the major C(4)-phenylated Pd complex is deprotonated much slower. Assuming the initial carbopalladation as a reversible step (see above) and the deprotonation of the initially formed major C(4)-phenylated Pd complex as a high-energy reaction pathway, the minor C(5)-isomer can be selectively further transformed into the C(5)-phenylated thiophene, as observed in the experiment. Thus, by switching from a weak to a stronger base as a counteranion of the Pd complex, we currently assume a change in the regiochemistry-determining step from the carbopalladation in the former to the aromatization step in the latter case.

Conclusions

We showed that the direct C–H arylation of 2-ethylthiophene or 2-chlorothiophene with PhPdIbipy complex **6** under stoichiometric conditions either delivers the C(4)-phenylated thiophene or its C(5)-congener depending on the additive used. Reactions occur via the cationic PdPhbipy complex, and the regioselectivity is determined by the counteranion of the Pd complex. For counteranions that are weak bases, such as OTf^- and BF_4^-, the C(4)-phenylated product was formed with excellent regioselectivity. However, in the presence of a basic counteranion, the reaction afforded the C(5)-phenylated thiophene. DFT calculations revealed that the cationic Pd complex **6** is the reactive species, which reacts via a carbopalladation to give the C(4)-phenyl Pd complex as the major intermediate. The experimentally observed selectivities are well reflected by the regioselectivities calculated for the initial carbopalladation reaction under "base-free" conditions. However, in the presence of stronger bases as counteranions, such as acetate or carbonate, deprotonation becomes the regioselectivity-determining step and the isomer ratio set in the preequilibrium, assuming the carbopalladation as a reversible step, is not important for the regioselectivity.

Experimental Section

Computational Details

All calculations were carried out with the TURBOMOLE 6.3 program package.[19] The geometry optimizations were performed with the TPSS density functional[16] together with the Ahlrichs' type triple-ζ basis set def2-TZVP.[17] For the single-point calculations the double hybrid functional B2PLYP[15] and the large quadruple-ζ basis set def2-QZVPP[17] were employed. In the case of the TPSS calculations, the resolutions of identity (RI-J) approximation[20] were applied. For the DFT part of B2PLYP the RI-JK approximation[21] was adapted and for the perturbative part the RI approximation[22] was used as well. All auxiliary basis sets were taken from the TURBOMOLE basis set library.[23] In all calculations the recently developed DFT-D3[24] together with the Becke–Johnson (BJ) damping function[25] was added, as indicated by the appended "-D3" to the functional name. Furthermore, to simulate solvent effects, COSMO was used in all calculations with a dielectric constant of $\varepsilon = 10.125$ (DCE). The harmonic vibrational frequencies were obtained as numerical derivatives of analytically calculated gradients employing a modified version of the program SNF11.[26] This was done at the TPSS level only, and the derived ΔG353 values were also used for B2PLYP. In the case of the product with the phenyl group in position 3, the first and second transition states exhibit an imaginary frequency of 46 cm^{-1} and 343 cm^{-1}, respectively, and are thus characterized as first-order transition states. This also holds for the route leading to the product with a phenyl group in position 2. Here, the corresponding imaginary frequencies for the first and second maxima are 23.33 cm^{-1} and 352.32 cm^{-1}, respectively.

Typical Procedure for the Stoichiometric Reactions

Pd complex **6** (47 mg, 0.1 mmol, 1.0 equiv), 2-ethylthiophene **1** (34 μL, 0.3 mmol, 3 equiv), and silver trifluoromethanesulfonate (52 mg, 0.2 mmol, 2.0 equiv) were dissolved in DCE (0.4 mL) and stirred in a sealed tube at 80 °C for 14 h. The mixture was filtrated over silica gel (eluent: EtOAc, 50 mL), and the volatiles were removed under reduced pressure. Analysis by GC gave a yield of 91 % by using undecane as an internal standard, and the ratio of isomers was found to be **2**/**3** = 99:1.

Acknowledgements

We thank the DFG and the JSPS for supporting our research within the framework of the IRTG Münster/Nagoya.

[1] Recent reviews on catalytic C–H bond functionalization: a) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; b) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335; c) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013.

[2] Catalytic C–H bond arylation of aromatics and heteroaromatics. For excellent recent reviews, see: a) L. Ackermann, R. Vincente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; b) B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949. For selected recent breakthroughs, see: c) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172; d) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593; e) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013; f) J. Norinder, A. Matsumoto, N. Yoshikai, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 5858; g) H.-Q. Do, R. M. K. Khan, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 15185; h) L. Ackermann, A. Althammer, S. Fenner, *Angew. Chem.* **2009**, *121*, 207;

Angew. Chem. Int. Ed. **2009**, *48*, 201; i) L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 3291; j) C. Wang, I. Piel, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 4194; k) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 9651; l) C. Huang, V. Gevorgyan, *J. Am. Chem. Soc.* **2009**, *131*, 10844; m) M. Tobisu, I. Hyodo, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 12070; n) M. Kim, J. Kwak, S. Chang, *Angew. Chem.* **2009**, *121*, 9097; *Angew. Chem. Int. Ed.* **2009**, *48*, 8935; o) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677; p) B. Xiao, Y. Fu, J. Xu, T.-J. Gong, J.-J. Dai, J. Yi, L. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 468; q) T. Nishikata, A. R. Abela, B. H. Lipshutz, *Angew. Chem.* **2010**, *122*, 793; *Angew. Chem. Int. Ed.* **2010**, *49*, 781; r) M. Wasa, B. T. Worrell, J.-Q. Yu, *Angew. Chem.* **2010**, *122*, 1297; *Angew. Chem. Int. Ed.* **2010**, *49*, 1275; s) F. Vallée, J. J. Mousseau, A. B. Charette, *J. Am. Chem. Soc.* **2010**, *132*, 1514; t) W. Liu, H. Cao, A. Lei, *Angew. Chem.* **2010**, *122*, 2048; *Angew. Chem. Int. Ed.* **2010**, *49*, 2004; u) P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu, J. You, *J. Am. Chem. Soc.* **2010**, *132*, 1822; v) H. Hachiya, K. Hirano, T. Satoh, M. Miura, *Angew. Chem.* **2010**, *122*, 2248; *Angew. Chem. Int. Ed.* **2010**, *49*, 2202.

[3] a) S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, *J. Am. Chem. Soc.* **2006**, *128*, 11748; b) S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, *Tetrahedron* **2008**, *64*, 6073; c) I. Ban, T. Sudo, T. Taniguchi, K. Itami, *Org. Lett.* **2008**, *10*, 3607; d) J. Canivet, J. Yamaguchi, I. Ban, K. Itami, *Org. Lett.* **2009**, *11*, 1733; e) B. Join, T. Yamamoto, K. Itami, *Angew. Chem.* **2009**, *121*, 3698; *Angew. Chem. Int. Ed.* **2009**, *48*, 3644; f) J. Bouffard, K. Itami, *Top. Curr. Chem.* **2010**, *292*, 231; g) K. Itami, *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 1132. See also: h) S. Yanagisawa, K. Ueda, T. Taniguchi, K. Itami, *Org. Lett.* **2008**, *10*, 4673; i) G. Deng, K. Ueda, S. Yanagisawa, K. Itami, C.-J. Li, *Chem. Eur. J.* **2009**, *15*, 333.

[4] a) S. Yanagisawa, K. Ueda, H. Sekizawa, K. Itami, *J. Am. Chem. Soc.* **2009**, *131*, 14622; b) K. Ueda, S. Yanagisawa, J. Yamaguchi, K. Itami, *Angew. Chem.* **2010**, *122*, 9130; *Angew. Chem. Int. Ed.* **2010**, *49*, 8946; c) S. Kirchberg, S. Tani, K. Ueda, J. Yamaguchi, A. Studer, K. Itami, *Angew. Chem.* **2011**, *123*, 2435; *Angew. Chem. Int. Ed.* **2011**, *50*, 2387.

[5] a) S. Kirchberg, T. Vogler, A. Studer, *Synlett* **2008**, *18*, 2841; b) S. Kirchberg, R. Fröhlich, A. Studer, *Angew. Chem.* **2009**, *121*, 4299; *Angew. Chem. Int. Ed.* **2009**, *48*, 4235.

[6] a) J. Roger, A. L. Gottumukkala, H. Doucet, *ChemCatChem* **2010**, *2*, 20; b) For Pd-catalyzed C–H bond arylation of thiophenes with haloarenes, see: B. Liégault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, *J. Org. Chem.* **2009**, *74*, 1826 and references therein.

[7] Examples of β-arylation of thiophenes having metal-coordinating groups; a) T. Okazawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 5286; b) T. Vogler, A. Studer, *Org. Lett.* **2008**, *10*, 129.

[8] M. Nakano, H. Tsurugi, T. Satoh, M. Miura, *Org. Lett.* **2008**, *10*, 1851.

[9] Pd-catalyzed oxidative coupling of aromatic compounds with organoboron compounds. For an excellent review, see Ref. [2o]. For representative examples, see: a) X. Wan, Z. Ma, B. Li, K. Zhang, S. Cao, S. Zhang, Z. Shi, *J. Am. Chem. Soc.* **2006**, *128*, 7416; b) X. Chen, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 12634; c) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510; d) Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, B. Cao, C. Qin, Y. Wang, *Angew. Chem.* **2007**, *119*, 5650; *Angew. Chem. Int. Ed.* **2007**, *46*, 5554; e) S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li, Z.-J. Shi, *Angew. Chem.* **2008**, *120*, 1495; *Angew. Chem. Int. Ed.* **2008**, *47*, 1473; f) D.-H. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 17676; g) K. Mochida, K. Kawasumi, Y. Segawa, K. Itami, *J. Am. Chem. Soc.* **2011**, *133*, 10716; h) M. Wasa, K. S. L. Chan, J.-Q. Yu, *Chem. Lett.* **2011**, *40*, 1004; i) K. M. Engle, P. S. Thuy-Boun, M. Dong, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 18183. See also: j) S. Yang, B. Li, X. Wan, Z. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 6066.

[10] For reviews on the use of TEMPO in synthesis, see: a) T. Vogler, A. Studer, *Synthesis* **2008**, 1979; b) L. Tebben, A. Studer, *Angew. Chem.* **2011**, *123*, 5138; *Angew. Chem. Int. Ed.* **2011**, *50*, 5034.

[11] For the use of TEMPO as an oxidant in oxidative bond forming reactions, see: a) M. S. Maji, T. Pfeifer, A. Studer, *Angew. Chem.* **2008**, *120*, 9690; *Angew. Chem. Int. Ed.* **2008**, *47*, 9547; b) M. S. Maji, A. Studer, *Synthesis* **2009**, 2467; c) J. Guin, S. De Sarkar, S. Grimme, A. Studer, *Angew. Chem.* **2008**, *120*, 8855; *Angew. Chem. Int. Ed.* **2008**, *47*, 8727; d) S. Kirchberg, R. Fröhlich, A. Studer, *Angew. Chem.* **2010**, *122*, 7029; *Angew. Chem. Int. Ed.* **2010**, *49*, 6877; e) M. S. Maji, T. Pfeifer, A. Studer, *Chem. Eur. J.* **2010**, *16*, 5872.

[12] I. Schnapperelle, S. Breitenlechner, T. Bach, *Org. Lett.* **2011**, *13*, 3640.

[13] Pd complex **4** was prepared according to the following literature procedure: Y.-T. Tsoi, Z. Zhou, A. S. C. Chan, W.-Y. Yu, *Org. Lett.* **2010**, *12*, 4506.

[14] Generated by reacting $Pd(dba)_2$, PhI (1.43 equiv) and 2,2′-bipyridyl (1.29 equiv) in benzene at 50 °C for 0.5 h, see the Experimental Section.

[15] S. Grimme, *J. Chem. Phys.* **2006**, *124*, 034108.

[16] J. Tao, J. P. Perdew, V. N. Staroverov, G. E. Scuseria, *Phys. Rev. Lett.* **2003**, *91*, 146401.

[17] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.

[18] Though in a different reaction, Fu and coworkers recently reported a DFT calculation study on one of our β-selective C–H arylation of thiophenes (equation 1), in which a carbopalladation mechanism is suggested. S.-Y. Tang, Q.-X. Guo, Y. Fu, *Chem. Eur. J.* **2011**, *17*, 13866.

[19] TURBOMOLE V6.3 2011, a program package developed at the University of Karlsruhe and at the Forschungszentrum Karlsruhe GmbH from 1989–2007, and at TURBOMOLE GmbH since 2007; available from http://www.turbomole.com.

[20] K. Eichkorn, F. Weigend, O. Treutler, R. Ahlrichs, *Theor. Chem. Acc.* **1997**, *97*, 119.

[21] F. Weigend, *Phys. Chem. Chem. Phys.* **2002**, *4*, 4285.

[22] C. Hättig, F. Weigend, *J. Chem. Phys.* **2000**, *113*, 5154.

[23] F. Weigend, M. Häser, H. Patzelt, R. Ahlrichs, *Chem. Phys. Lett.* **1998**, *294*, 143.

[24] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104.

[25] S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* **2011**, *32*, 1456.

[26] C. Kind, M. Reiher, J. Neugebauer, B. A. Hess, *SNF version 2.2.1*, University of Erlangen, **2002**.

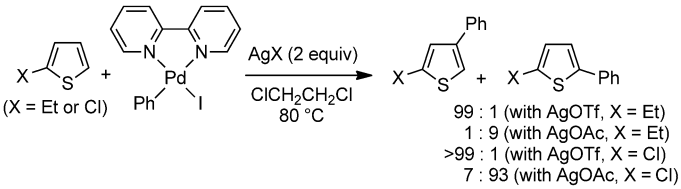
Received: December 15, 2011
Published online: ■■ ■■, 0000

FULL PAPERS

C–H Arylation

Marc Steinmetz, Kirika Ueda, Stefan Grimme, Junichiro Yamaguchi, Sylvia Kirchberg, Kenichiro Itami,* Armido Studer**

Mechanistic Studies on the Pd-catalyzed Direct C–H Arylation of 2-Substituted Thiophene Derivatives with Arylpalladium Bipyridyl Complexes



The counteranion does the job! Reactions of 2-substituted thiophenes with cationic PhPdbipy complexes afforded either the corresponding C(4) or C(5)-phenylated thiophene derivatives depending on the counteranion present. DFT calculations revealed that reactions occur via carbopalladation and not via electrophilic palladation.