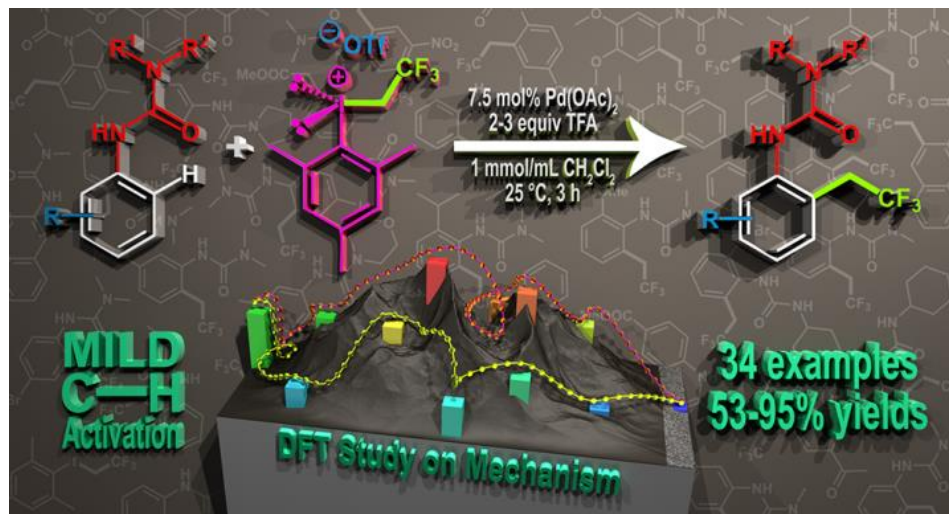


Graphical Abstract



Abstract: Development of direct late-stage installation of key fluorinated functional groups into aromatic systems is an important and challenging task of current organic chemistry. Herein, we report a novel palladium catalyzed trifluoroethylation process by C-H activation for the access of *ortho* trifluoroethylated aromatic ureas. The application of novel, highly active trifluoroethyl(mesityl)iodonium salt enables the efficient introduction of the trifluoroethyl group at 25 °C in 3 hours in high yields (up to 95%) with good functional group tolerance.

Direct *ortho*-Trifluoroethylation of Aromatic Ureas by Palladium Catalyzed C-H activation: A Missing Piece of Aromatic Substitutions

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Abstract: Development of direct late-stage installation of key fluorinated functional groups into aromatic systems is an important and challenging task of current organic chemistry. Herein, we report a novel palladium catalyzed trifluoroethylation process by C-H activation for the access of *ortho* trifluoroethylated aromatic ureas. The application of novel, highly active trifluoroethyl(mesityl)iodonium salt enables the efficient introduction of the trifluoroethyl group at 25 °C in 3 hours in high yields (up to 95%) with good functional group tolerance.

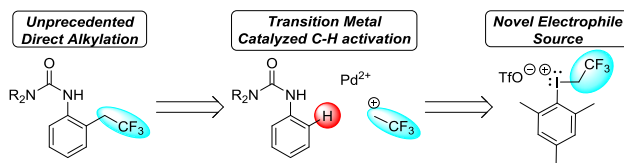
Functionalization of aromatic systems for the construction of new carbon-carbon bond is one of the most important transformations in organic chemistry. The traditional Friedel-Crafts-type and cross-coupling reactions offer several synthetic tools to achieve the desired C-C bond formations efficiently. Recently, the activation of C-H bond by transition metal catalysts using directing groups has become an important tool for the functionalization of aromatic compounds.¹ Beside various groups capable for coordination, the urea function serves as excellent *ortho* directing functional group. With their utilization, the implementation of direct *ortho* arylation,² carbonylation,³ alkenylation⁴ and cyclization⁵ is straightforwardly achievable, even under mild reaction conditions. Interestingly, the direct alkylation of

aromatic ureas is unprecedented, considering not only the modern transition metal mediated C-H activation reactions, but the classic organic synthetic tools.

Fluorine substituted alkyl groups have great importance in medicinal and agricultural chemistry due to their desirable biological and chemical effects.⁶ In fact, a large number of robust trifluoromethylation methods have been developed.⁷ In contrast the introduction of trifluoroethyl group into aromatic systems is less investigated. In the literature only limited number of examples can be found for the installation of trifluoroethyl group into the aromatic systems with the aid of transition metal catalysis via cross-coupling⁸ and C-H activation⁹ under relatively harsh reaction conditions, and via radical functionalization.¹⁰

In our research, we aimed to develop a novel, mild and simple alkylation procedure for the direct functionalization of aromatic ureas in the aromatic core, focusing on the introduction of trifluoroethyl group. The importance of this methodology is two-fold. It provides a new synthetic tool for organic chemistry, and offers a possibility for the late-stage functionalization of arylurea derivatives having biological activity for medicinal chemistry.¹¹ To fulfill our goals, we intended to utilize hypervalent iodonium salts.¹² Among the available versatile reagents the mesityl(2,2,2-trifluoroethyl)iodonium salt as an excellent fluoroalkylating agent, developed in our laboratory for mild C-H functionalization (Scheme 1).¹³ We envisioned that the chemical properties of the reagent could enable straightforward palladium catalyzed trifluoroethylation of the target arylurea derivatives by C-H activation under mild reaction conditions.

Scheme 1. Desired direct alkylation of arylureas



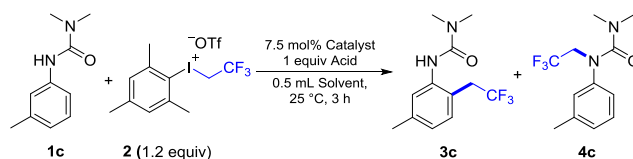
During the optimization phase, in the model reaction of *N,N*-dimethyl-*N'*-(3-methylphenyl)urea and mesityl(trifluoroethyl)-iodonium triflate we tested the feasibility of several protic and aprotic solvents,

different catalysts and additives to find the optimal reaction conditions for this transformation. The reaction of **1c** with the iodonium salt in dichloromethane (DCM) without catalyst resulted in only the *N*-trifluoroethylated by-product **4c** in 94% conversion (Table 1, Entry 1). The application of Pd(OAc)₂ catalyst provided the *ortho* substituted product **3c** in 50% and 45% **4c**. The presence of acetic acid (AcOH) as additive did not affect the coupling. Changing the acid to trifluoroacetic acid (TFA) caused significant improvement and the desired product was formed in 99:1 ratio with full conversion. Screening the different solvents, we found that beside DCM, ethyl acetate (EtOAc) and toluene are also suitable for the reaction, but the conversions are slightly lower. Different palladium sources were also tested in the trifluoroethylation: PdCl₂ did not catalyze the reaction, while Pd₂dba₃ and palladium(II) trifluoroacetate gave similar results to Pd(OAc)₂ catalyst. The application of 2 equivalent of TFA resulted in selectively the trifluoroethylated product with full conversion after 3 hours.

After the thorough optimization we tested the applicability of the developed trifluoroethylation method using a wide variety of *N,N*-dimethyl-*N'*-arylureas in DCM at 25 °C, in the presence of 7.5% Pd(OAc)₂ and 2 equivalents of TFA (Scheme 2). In the case of *para* substituted arylureas we used 1.05 equivalent of iodonium salt to avoid the formation of bis(trifluoroethyl) product.

The urea containing unsubstituted phenyl ring reacted smoothly with **2** to form the trifluoroethylated product **3a** in 74% yield. Electron donating methyl- and methoxy groups in *ortho*, *meta* and *para* positions were well tolerated and the corresponding products formed in good and excellent yield (**3b-g**).

Remarkably, sterically more hindered *isopropyl* and *benzyl* moiety in *ortho* and *para* position on the phenyl ring were also feasible for the transformation, and the reaction provided products **3h-j** in excellent and good yields. The coupling of electron rich dimethoxy derivative (**1k**) afforded the mono-trifluoroethylated product in 70% yield. In the case of substrate **1l** the *O*-protecting *benzyl* group was not stable under the reaction conditions and we obtained the free hydroxy derivative of the trifluoroethylated product (**3l**) in 53% yield.

Table 1. Optimization of the reaction conditions^a

Entry	Catalyst	Solvent	Acid	GC yield (%) ^b	
				3c	4c
1	-	DCM	-	0	94
2	Pd(OAc) ₂	DCM	-	50	45
3	Pd(OAc) ₂	DCM	AcOH	46	47
4	Pd(OAc) ₂	DCM	TFA	99	1
5	Pd(OAc) ₂	MeOH	TFA	0	0
6	Pd(OAc) ₂	THF	TFA	32	23
7	Pd(OAc) ₂	EtOAc	TFA	90	7
8	Pd(OAc) ₂	toluene	TFA	96	3
9	PdCl ₂	DCM	TFA	12	44
10	Pd ₂ dba ₃	DCM	TFA	96	4
11	Pd(OTFA) ₂	DCM	TFA	80	13
12^c	Pd(OAc)₂	DCM	TFA	100	0

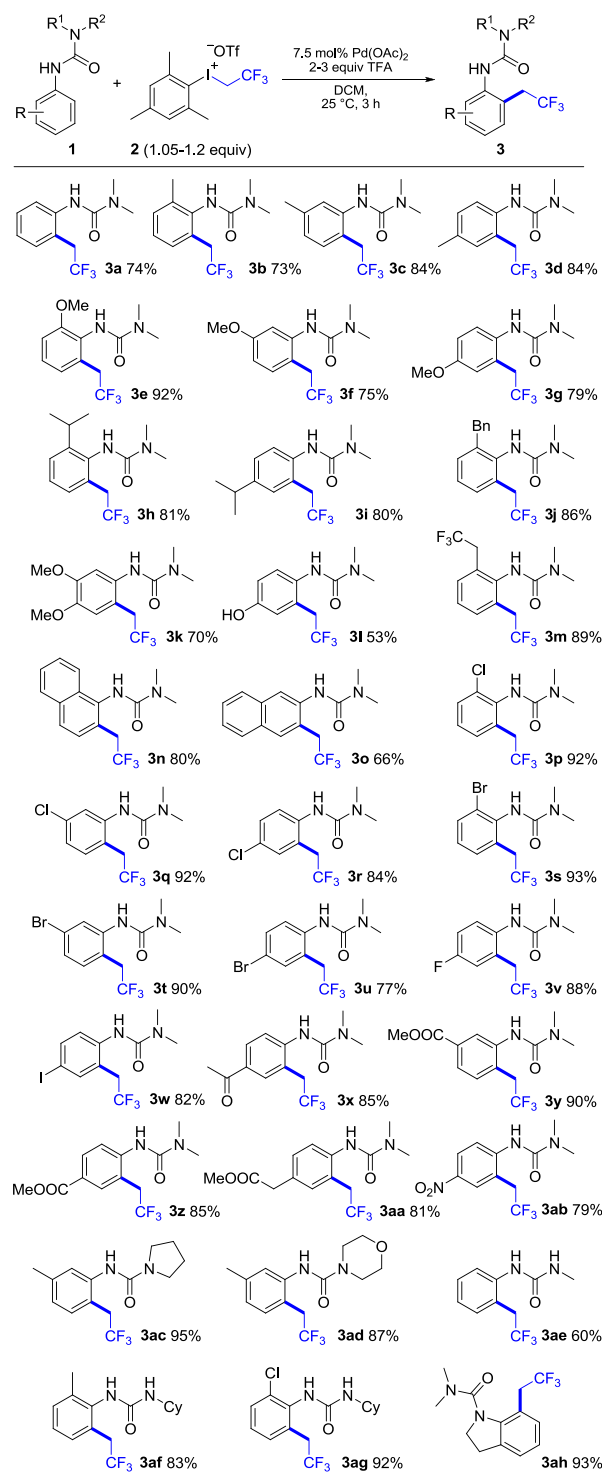
^a Reaction conditions: **1c** (0.05 mmol, 1 equiv), **2** (1.2 equiv), Pd(OAc)₂ (7.5 mol%), acid (1 equiv), solvent (0.5 mL), 25 °C, 3 hours. ^b

Conversions determined by GC-MS analysis. ^c 2 equiv TFA was used, TFA: trifluoroacetic acid.

The trifluoroethylation of **3a** was achieved and the appropriate 2,6-bis(trifluoroethyl)phenylurea derivative (**3m**) was isolated in 89% yield. Naphthylureas were also successfully applied in the reaction, and products **3n** and **3o** were prepared with 80% and 66% yields, respectively. Halide substituted arylureas were also utilized in this C-H bond activation reaction to obtain cross-coupling-ready 2-trifluoroethylarylurea building blocks. Chloro- and bromo substituents were well tolerated in each positions of the aromatic ring and the trifluoroethylated derivatives were obtained in good to excellent

yields (**3p-u**). To our delight, 4-iodo- and 4-fluorophenylureas also underwent this fluoroalkylation reaction.

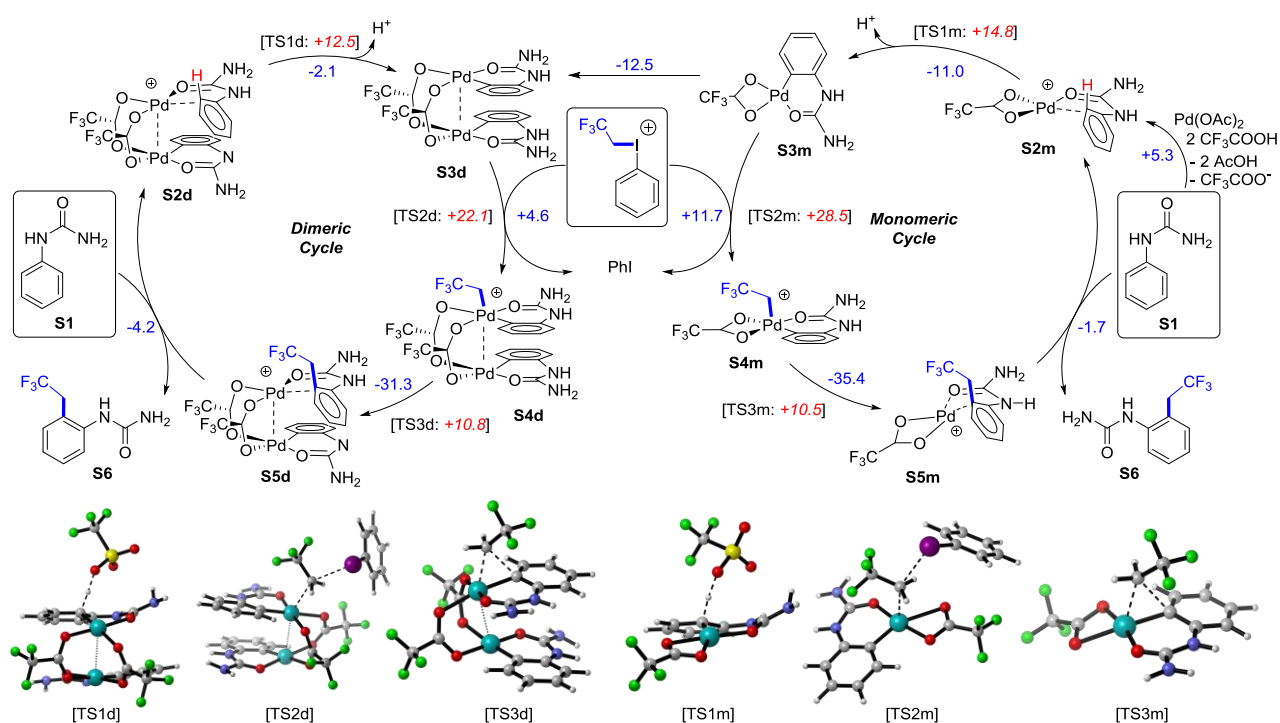
Scheme 2. Palladium catalyzed trifluoroethylation of *N,N*-dimethyl *N'*-arylureas^a



^a Reaction conditions: **1** (1 mmol, 1 equiv), **2** (1.05-1.2 equiv), Pd(OAc)₂ (7.5 mol%), TFA (2-3 equiv), DCM (0.5 mL), 25 °C, 3 hours.

Electron withdrawing acetyl-, ester- and nitro- groups in *meta* and *para* positions of the aromatic moiety were remarkably suitable for the reaction and the desired products **3x-ab** were formed in 79-90% yields. Next, we investigated the application of ureas equipped with different alkyl substituents on the nitrogen atom. Changing the dimethylamino moiety to cyclic diamines had no influence on the coupling and thereby piperidine and morpholine urea derivatives reacted excellently to provide **3ac** and **3ad** in 95% and 87% yields.

Scheme 3. Mechanistic proposals for the catalytic process. Reaction (blue) and transition-state (TS) Gibbs free energies (red, kcal/mol) are indicated. They are consistently referenced to the energy of the preceding stable state

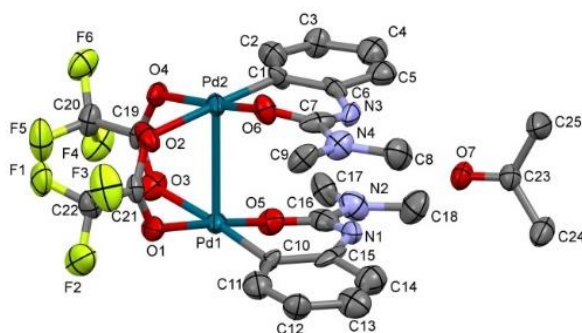


In preparation of the starting ureas primer amines were also studied. We found that *N*-methyl and *N*-cyclohexyl ureas can be transformed smoothly under the catalytic conditions (**3ae-3ag**). Trifluoroethylation of heterocyclic indoline structure (**1ah**) was also achieved effectively and the transformation selectively provided the product (**3ah**) in 93% yield.

In order to understand the mechanism of the process, we have performed theoretical calculations applying density functional theory (DFT).¹⁴ We examined the reaction between *N*-phenylurea and phenyl(trifluoroethyl)-iodonium triflate in the presence of Pd(OAc)₂ and TFA in DCM solvent. Earlier studies have convincingly shown that in palladium catalyzed C-H activation processes, various forms of the Pd catalyst, in particular the more likely binuclear forms show high reactivity.¹⁵ Therefore, we sought feasible reaction routes featuring both monomeric and dimeric Pd complexes and compare the solvent corrected free energy profiles of the reaction paths. Based on the experiments we have constructed reaction routes, which are depicted in Scheme 3. The reaction free energy changes and barrier heights are given in Scheme 3 while full profiles can be found in the SI. The reaction is initiated by the formation of the catalytically more reactive Pd(OTFA)₂ species from the initial compound Pd(OAc)₂ in the presence of excess TFA,¹⁶ which then forms complex **S2m** with substrate **S1** in a slightly endergonic process (+5.3 kcal/mol). The oxidative C-H insertion step takes place in a concerted fashion (featuring a single TS, 14.8 kcal/mol) where a triflate anion assists the metalation process by deprotonating the aryl ligand via an outer-sphere mechanism. The reaction can then propagate in two different directions: **S3m** proceeds along the monomeric cycle or after dimerization (-12.5 kcal/mol) **S3d** enters into the dimeric cycle. In both catalytic cycles the next step is the electrophilic attack of the iodonium cation and the transfer of the CF₃CH₂ ligand to palladium forming high-valent **S4m** and **S4d** with 28.5 and 22.1 kcal/mol activation energy, respectively.¹⁵ The following step is the rapid reductive elimination step yielding intermediates **S5m** or **S5d** where migration of the trifluoroethyl group from the Pd centers to the aryl ring requires moderate activation energy (9-10 kcal/mol) with high exergonicity on both paths. The **S2** complexes are recovered by ligand exchange reaction on the palladium center, when a reactant **S1** replaces the coordinated product **S6**. In agreement with the monomeric route, along the dimer path the C-H activation takes place in a concerted fashion on the dimeric Pd center in an intermolecular fashion. Small activation energy (12.5 kcal/mol) is necessary for this C-H activation, where a triflate anion serves as base to capture the detaching proton when the Pd-C bond is forming because the available CF₃COO⁻ anion is limited by

the catalyst. Comparison of the monomeric and dimer profiles shows that the dimeric route is more favorable than the monomeric one. This is primarily due to the exergonic formation of **S3d** complex from the monomeric **S3m** species (-12.5 kcal/mol). In addition, the Pd-Pd interaction has beneficial effect on the energetics of both the C-H activation and the CF₃CH₂ ligand transfer: for both steps, the dimer route features remarkably lower activation barriers. Comparison of the barriers for the C-H activation and the trifluoroethyl migration steps along the dimer route shows that the rate-determining step is the CF₃CH₂ group transfer from the iodonium salt to the palladium center with an energetic span of 22.1 kcal/mol. This is in nice accord with earlier experimental¹⁸ and theoretical predictions for analogous reactions.^{17d,19} As a proof of the favored formation of the dimeric palladium species, we were able to prepare the desired complex from the reaction of arylurea and palladium(II) acetate in the presence of trifluoroacetic acid. The crystals were grown from hexane acetone solution mixture. The structure of the obtained dimeric palladium complex (**5**, *N,N*-dimethyl-substituted analogue of **S3d**) was established by X-ray crystallography (Figure 1). In order to study the reactivity of complex **5**, it was reacted with the trifluoroethyliodonium salt (**2**) in DCM at 25 °C. After couple of minutes reaction time we observed complete consumption of the palladium complex and the formation of the trifluoroethylated urea.¹⁴

Figure 1. Molecular structure of compound 5.²⁰ Displacement ellipsoids are drawn at the 50% probability level²¹



In summary, we have developed a novel procedure for the trifluoroethylation of aromatic ureas with hypervalent iodonium salt via palladium catalyzed C-H activation. This synthetic strategy allows the simple, direct, late-stage fluoroalkylation of urea derivatives with high efficiency and excellent functional

group tolerance, under mild reaction conditions. We proposed catalytic cycles for the transformation with DFT calculations. The mechanistic studies revealed that the formation of bimetallic palladium species (5) is a crucial step of the reaction, which has an important role in the mild catalytic transformation.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, NMR spectra, crystallographic data, computational details, full free energy profiles, structures and energetics of the calculated compounds.

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Author Contributions

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Notes

The authors declare no competing financial interests.

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REFERENCES

- (1) For reviews on C-H activations: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 114. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (c) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (d) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236. (e) Zheng, C.; You, S.-L. *RSC Adv.* **2014**, *4*, 6173. (f) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107. (g) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900.
- (2) (a) Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 4978. (b) Nishikata, T.; Abela, A. R.; Lipshutz, B. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 781. (c) Jiang, Z.; Zhang, L.; Dong, C.; Su, X.; Li, H.; Tang, W.; Xu, L.; Fan, Q. *RSC Adv.* **2013**, *3*, 1025. (d) Jiang, P.; Li, F.; Xu, Y.; Liu, Q.; Wang, J.; Ding, H.; Yu, R.; Wang, Q. *Org. Lett.* **2015**, *17*, 5918.
- (3) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem. Int. Ed.* **2009**, *48*, 1830.
- (4) alkenylations: (a) Rauf, W.; Thompson, A. L.; Brown, J. M. *Chem. Commun.* **2009**, *45*, 3874. (b) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 1972. (c) Wang, L.; Liu, S.; Li, Z.; Yu, Y. *Org. Lett.* **2011**, *13*, 6137. (d) Willwacher, J.; Rakshit, S.; Glorius, F. *Org. Biomol. Chem.* **2011**, *9*, 4736. (d) Jiang, P.; Xu, Y.; Sun, F.; Liu, X.; Li, F.; Yu, R.; Li, Y.; Wang, Q. *Org. Lett.* **2016**, *18*, 1426.
- (5) Cyclizations (a) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066. (b) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 1338. (c) Kathiravan, S.; Nicholls, I. A. *Chem. Commun.* **2014**, *50*, 14964. (d) Manna, M. K.; Hossian, A.; Jana, R. *Org. Lett.* **2015**, *17*, 672.
- (6) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero,

- S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (e) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; *Chem. Rev.* **2016**, *116*, 422.
- (7) For reviews on trifluoromethylations: (a) Kirk, K. L. *Org. Proc. Res. & Dev.* **2008**, *12*, 305. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (c) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (d) Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2476. (e) Barata-Vallejo, S.; Postigo, A. *Coord. Chem. Rev.* **2013**, *257*, 3051. (f) Merino, E.; Nevado, C. *Chem. Soc. Rev.* **2014**, *43*, 6598. (g) Zhang, C. *Org. Biomol. Chem.* **2014**, *12*, 6580. (h) Barata-Vallejo, S.; Lantaño, B.; Postigo, A. *Chem. Eur. J.* **2014**, *20*, 16806. (i) Lantaño, B.; Torviso, M. R.; Bonesi, S. M.; Barata-Vallejo, S.; Postigo, A. *Coord. Chem. Rev.* **2015**, *258*, 76. (j) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650. (k) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683. (l) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. (m) Alonso, C.; de Marigorta, E. M.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847. Recent papers on trifluoromethylation: (n) Zhang, L.-S.; Chen, K.; Chen, G.; Li, B.-J.; Luo, S.; Guo, Q.-Y.; Wei, J.B.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 10-13. (o) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298. (p) Miura, M.; Feng, C.-G.; Ma, S. Yu, J.-Q. *Org. Lett.* **2013**, *15*, 5258. (q) Liu, H.; Gu, Z.; Jiang, X. *Adv. Synth. Catal.* **2013**, *355*, 617. (r) Wang, X.; Truesdale, L.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648. (s) Cai, S.; Chen, C.; Suna, Z.; Xi, C.; *Chem. Commun.* **2013**, *49*, 4552. (t) Shang, M.; Sun, S.-Z.; Wang, H.-L.; Laforteza, B. N.; Dai, H.-X.; Yu J.-Q. *Angew. Chem. Int. Ed.* **2014**, *53*, 10439. (u) Hu, L.; Chen, X.; Gui, Q.; Tan, Z.; Zhu, G. *Chem. Commun.* **2016**, *52*, 6845. (v) Natte, K.; Jagadeesh, R. V.; He, L.; Rabeah, J.; Chen, J.; Taeschler, C.; Ellinger, S.; Zaragoza, F.; Neumann, H.; Brückner, A.; Beller, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 2782.
- (8) (a) Zhao, Y.; Hu, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 1033. (b) Liang, A.; Li, X.; Liu, D.; Li, J.; Zou, D.; Wu, Y.; Wu, (c) Zhang, X.; Yang, C. *Adv. Synth. Catal.* **2015**, *357*, 2721. (d) Leng, F.; Wang, Y.; Li, H.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Chem. Commun.* **2013**, *49*, 10697. (e) Wu, G.; Deng, Y.;

- Wu, C.; Wang, X.; Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2014**, 21, 4477. (f) Ohtsuka, Y.; Yamakawa, T. *J. Fluor. Chem.* **2016**, 185, 96.
- (9) (a) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, 53, 2477. (b) Zhang, H.; Chen, P.; Liu, G. *Angew. Chem. Int. Ed.* **2014**, 53, 10174.
- (10) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herlé, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, 492, 95.
- (11) Sikka, P.; Sahu, J. K.; Mishra, A. K.; Hashim, S. R. *Med. Chem.* **2015**, 5, 479.
- (12) (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, 96, 1123; (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, 102, 2523; (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, 108, 5299. (d) Merritt E.A.; Olofsson B. *Angew. Chem. Int. Ed.* **2009**, 48, 9052. (e) V. V. Zhdankin, *Hypervalent Iodine Chemistry*, Wiley, Chichester **2014**. (f) Olofsson, B., *Top. Curr. Chem.* **2016**, 373, 135; (g) Aradi, K.; Tóth, B. L.; Tolnai, G. L.; Novák, Z., *Synlett* **2016**, 27, 1456.
- (13) (a) Tolnai, G. L.; Székely, A.; Makó, Z.; Gáti, T.; Daru, J.; Bihari, T.; Stirling, A.; Novák, Z. *Chem. Commun.* **2015**, 51, 4488. (b) Tóth, B. L.; Kovács, Sz.; Sályi, G.; Novák, Z. *Angew. Chem. Int. Ed.* **2016**, 56, 1988.
- (14) See the details in the SI.
- (15) (a) Bonney, K. J.; F. Schoenebeck, *Chem. Soc. Rev.* **2014**, 43, 6609. (b) Paton, R. S.; Brown, J. M. *Angew. Chem. Int. Ed.* **2012** 51, 10448. (c) Haines, B. E; Berry, J. F.; Yu, J.-Q.; Musaev, D. G. *ACS Catal.* **2015**, 6, 829. (d) Canty, A. J.; Ariafield, A.; Sanford, M. S.; Yates, B. F. *Organomet.* **2013**, 32, 544. (e) Cook, A. K.; Sanford, M. S. *J. Am. Chem. Soc.* **2015**, 137, 3109.
- (16) Solubility of Pd(OTFA)₂ is much better than Pd(OAc)₂ in DCM.
- (17) The resting state of the iodonium salt is the dissociated, ionic form and the iodonium cation attacks the activated reactants. See SI for further details.
- (18) N. R. Deprez, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, 131, 11234-11241
- (19) A. J. Hickman, M. S. Sanford, *ACS Catal.* **2011**, 1, 170 –174.

- (20) Crystallographic data for the crystal structure of **5** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 1486264
- (21) Macrae, C. F.; Edgington, P.R.; McCabe, P.; Pidcock E.; Shields, G. P.; Taylor, R.; Towler M.; van de Streek, J. *J. Appl. Cryst.* **2006**, *39*, 453.