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Communication

C–H Amination

Hexafluoro-2-propanol Promotes *para*-Selective C–H Amination of Free Anilines with Azodicarboxylates

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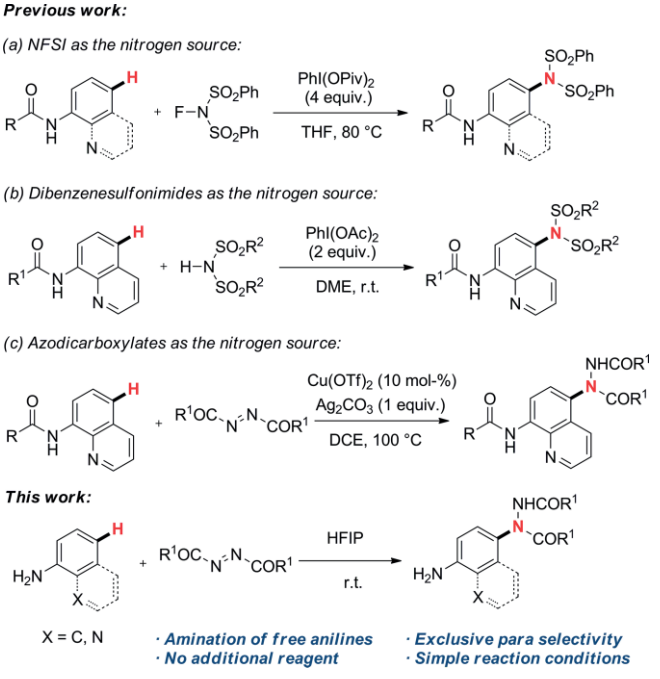
Abstract: An effective, mild, and clean method for the C–H amination of free anilines with azodicarboxylates in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) without the need for any additional catalysts or reagents was developed. The reaction was found to be highly regioselective and provided a series of *p*-aminophenylhydrazine derivatives in excellent yields. Moreover, compatibility with a free amino group makes this protocol an attractive strategy in synthetic chemistry.

Introduction

The direct C–H amination of arenes is an important strategy to streamline the discovery and preparation of functional molecules. In the past decades, with the rapid development of transition-metal-catalyzed C–H activation, significant advances have been made in the direct C–H amination of arenes,[1] and specifically, high regioselectivity can be achieved.[2] However, the C–H amination of free anilines still remains a great challenge owing to the high nucleophilicity of the free amino group, which leads to the formation of salts in acidic media that can chelate metal catalysts.[3] Thus, *N*-protected anilines are usually employed to avoid the formation of byproducts. In particular, the direct amination of the C–H bond at the *ortho* position of *N*-protected anilines has been relatively well studied.[2h,4] In contrast, methods for the *meta*- and *para*-selective C–H amination of *N*-protected anilines are considerably less developed. Only a handful of examples have been reported in recent years. The strategy of directing the C–H amination to the *meta* position of *N*-protected anilines was recently developed for the first time by Yu and co-workers.[2g] Besides, in 2011, Zhang and co-workers described the first Pd-catalyzed *para*-selective C–H amination of anilides by using *N*-fluorobenzenesulfonimide (NFSI) as a source of nitrogen.[2h] Recently, the metal-free hypervalent iodine reagent mediated oxidative *para*-selective C–H amination of 8-aminoquinolines and anilides with NFSI was reported by Li and co-workers (Scheme 1a).[5] Almost at the same time, Xu and co-workers developed a method for the C–H bond amidation of 8-amidoquinolines at the C5 position by using dibenzenesulfonimide as the nitrogen source.[6] Moreover, a similar process was reported with readily available azodicarboxylates (Scheme 1c).[7] However, the introduction and subsequent removal of protecting groups not only requires additional operations but also significantly decreases functional-group compatibility. Undoubtedly, the most attractive and ideal route is the direct C–H amination of free anilines.



Scheme 1. *para*-Selective amination of *N*-protected anilines. DME = 1,2-dimethoxyethane, Tf = trifluoromethylsulfonyl, DCE = 1,2-dichloroethane.

To the best of our knowledge, there is only one report on the C–H amination of free anilines with azodicarboxylates.[8] However, this method suffers from the utilization of a large amount of catalyst ($LiClO_4$) and a low yield (30 %). Herein, we report the direct *para*-selective C–H amination of free anilines with azodicarboxylates as a source of nitrogen promoted by 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP).

Results and Discussion

Owing to the electron-withdrawing character of fluoroalkyl groups, fluorinated alcohols such as trifluoroethanol (TFE) and

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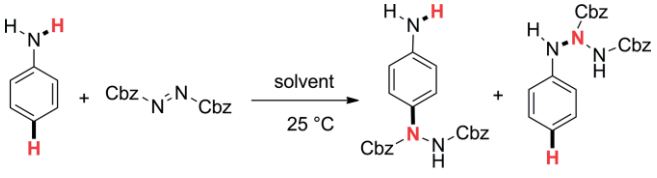
HFIP exhibit unique features in organic synthesis.[9] Therefore, a number of remarkable reactions have been studied in these solvents.[10]

In our initial study, the C–H amination of aniline (**1a**) with azodicarboxylate **2a** (Cbz = benzyloxycarbonyl) was chosen as the model system to optimize the reaction conditions (Table 1). We first examined the reaction in pure HFIP solvent, and the mixture was stirred at 25 °C for 2 h. Product **3aa** was isolated in 94 % yield, and only a trace amount of triazane **4aa** was detected (Table 1, Entry 1). An increase of the concentration of the substrate led to the formation of byproducts (Table 1, Entry 2). We then tested HFIP as an additive with other solvents (Table 1, Entries 3–8). In dichloromethane, with 9.5–2.0 equiv. of HFIP (Table 1, Entries 3–5), marked decreases in the selectivity and yield of **3aa** were observed. Moderate results were obtained with 9.5 equiv. of HFIP in water or toluene (Table 1, Entries 6 and 7). In THF, the yield of and selectivity to **3aa** were greatly diminished owing to H-bond association, which inhibited the H-bonding effect of HFIP (Table 1, Entry 8).[11] Other fluorinated solvents such as TFE and perfluoro-2-methylpropan-2-ol (PFTB) were not effective (Table 1, Entries 9 and 10). In EtOH, both a low yield and low selectivity were observed (Table 1, Entry 11). These different results showed very well that the H-bonding ability of HFIP is essential for a good outcome in the C–H amination reaction.

Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3aa** **4aa**

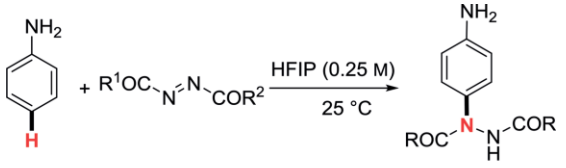
Entry	Solvent	Time [h]	Yield[b] [%] 3aa	4aa
1	HFIP (0.25 M)	2	96 (94[c])	trace
2	HFIP (9.5 equiv.)	2	92	5
3	CH_2Cl_2/HFIP (3:1)	2	81	14
4	CH_2Cl_2/HFIP (6.7:1)	4	60	32
5	CH_2Cl_2/HFIP (17.2:1)	6	45	42
6	H_2O/HFIP (3:1)	4	62	31
7	toluene/HFIP (3:1)	2	76	18
8	THF/HFIP (3:1)	2	24	48
9	CF_3CH_2OH	2	59	28
10	$(CF_3)_3COH$	0.75	54	43
11	EtOH	5	20	56

[a] Conditions: **1a** (0.5 mmol) and **2a** (0.55 mmol, 1.1 equiv.) were dissolved in solvent (0.25 M). [b] Yield determined by NMR spectroscopy by using nitromethane as an internal standard. [c] Yield of isolated product.

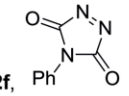
With the optimized reaction conditions in hand (Table 1, Entry 1), we next investigated other azodicarboxylates with the free aniline (Table 2).

Azodicarboxylates **2b**–**d** reacted smoothly with aniline to afford the corresponding hydrazides **3ab**–**ad** in excellent yields. However, upon using azodicarboxylate **2e**, the reaction proceeded badly and led to the corresponding product **3ae** in only 34 % yield. This low yield could be explained by decomposition

Table 2. Amination of aniline with different azodicarboxylates.[a]

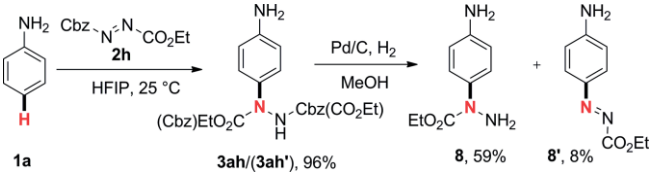


1a **2a–2g** **3aa–3ag**

Entry	Azodicarboxylate	t [h]	Product	Yield[b] [%]
1	**2a** ($R^1 = R^2$ = OBn)	2	**3aa**	94
2[c]	**2b** ($R^1 = R^2$ = OEt)	2	**3ab**	88
3[d]	**2c** ($R^1 = R^2$ = O*i*Pr)	2	**3ac**	90
4	**2d** ($R^1 = R^2$ = OCH_2CCl_3)	2	**3ad**	94
5	**2e** ($R^1 = R^2$ = O*t*Bu)	2	**3ae**	34
6	 **2f**, Ph	2	**3ag**	57
7	**2g** (R = 1-piperidinyl)	16	**3ah**	n.r.

[a] Conditions: **1a** (0.5 mmol) and **2a** (0.55 mmol, 1.1 equiv.) were dissolved in HFIP (0.25 M). [b] Yield of isolated product. [c] Triazane **4ab** was formed in 9 % yield. [d] Triazane **4ac** was formed in 8 % yield.

in HFIP, which is slightly acidic (pK_a = 9.3).[12] Moreover, hydrazide **3ag** was obtained from cyclic azodicarboxylate **2f** in moderate yield. Unfortunately, azodicarboxylate **2g** was not suitable for this reaction. Upon treatment of aniline with asymmetric azodicarboxylate **2h**, a mixture of hydrazides **3ah**/**3ah′** was obtained. The ratio was analyzed after hydrogenolysis of the benzyloxycarbonyl group. Products **8**/**8′** were obtained in a 7.6:1.0 ratio. The regioselective attack can be explained by the fact that the steric demand of the nitrogen atom bearing the CO_2Et group is lower than that of the nitrogen atom bearing the Cbz group (Scheme 2).



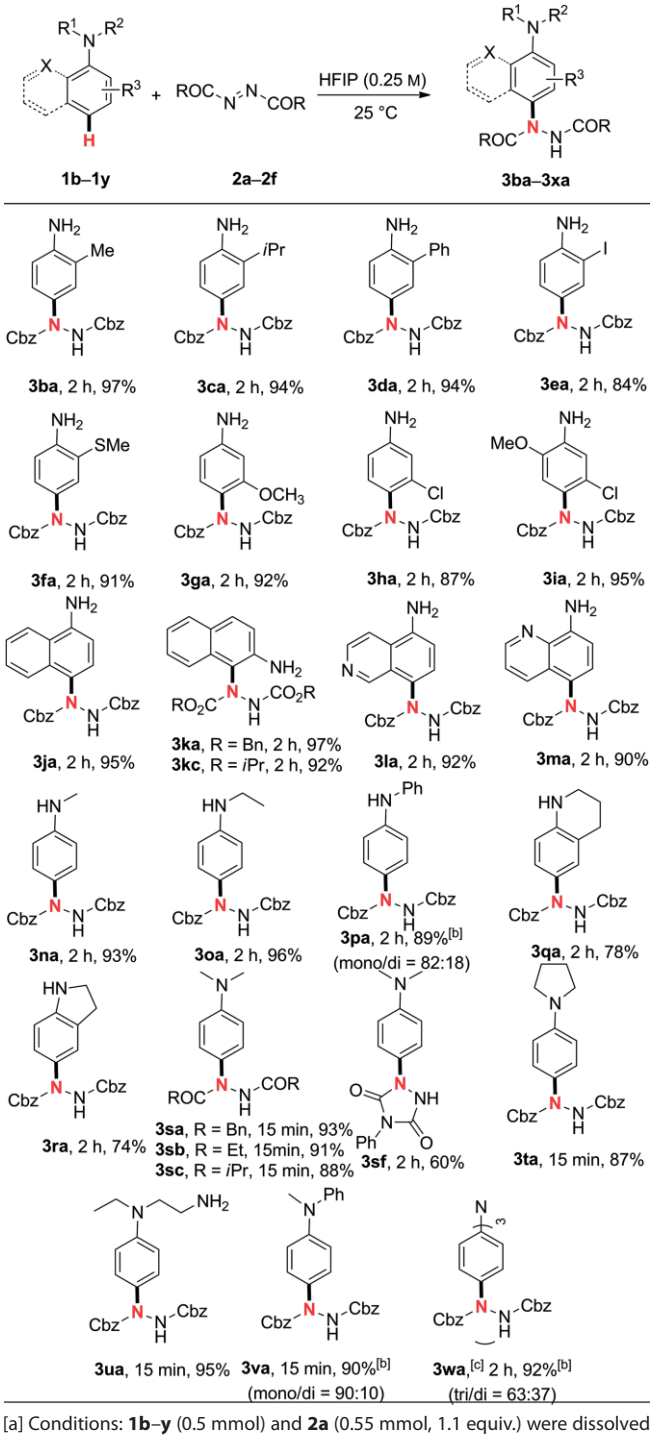
Scheme 2. Amination of aniline with an asymmetric azodicarboxylate.

We then turned our attention to the scope of the aniline derivatives (Table 3). Primary anilines **1b**–**i** substituted at either the *ortho* or *meta* position or at both positions reacted with azodicarboxylate **2a** smoothly to generate the desired products **3ba**–**ia** in excellent yields. Notably, the nucleophilicity of electron-poor anilines such as 2-nitroaniline is low, and no reaction occurred. Naphthylamines **1j**–**k** were also applicable in this reaction and provided products **3ja**–**kc** in very good yields. Notably, quinolineamines **1l** and **1m** also showed good reactivity and gave **3la** and **3ma** in yields of 92 and 90 %, respectively. Then, secondary anilines **1n**–**r**, including tetrahydroquinoline (**1q**) and indoline (**1r**), were treated with azodicarboxylate **2a** under the optimized conditions, and they all afforded the corresponding products **3na**–**ra** in good to moderate yields. From tertiary anilines **1s**–**w**, the amination reaction was faster than that with primary anilines and regioselective. Dimethylaniline

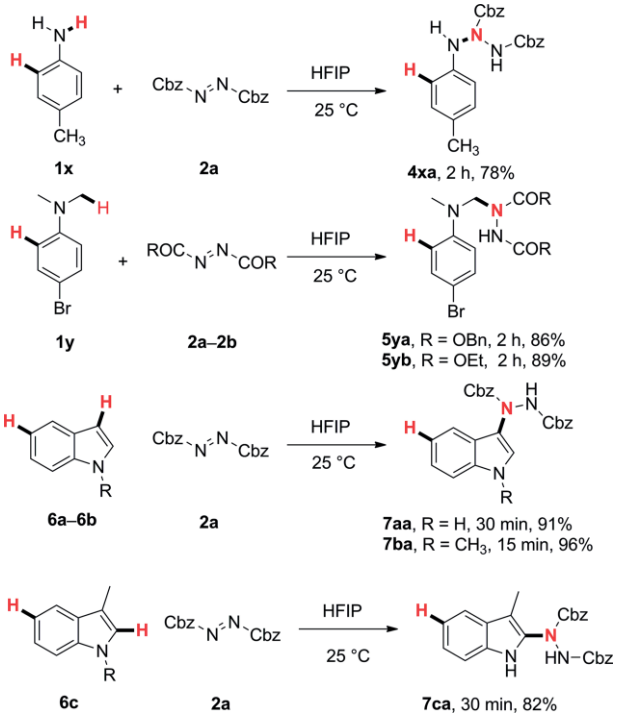
(**1s**) reacted with azodicarboxylates **2a**–**c** and **2f** to provide hydrazides **3sa**–**sc** in excellent yields (88–93 %). *N*-Phenylpyrrolidine (**1t**), *N*-(2-aminoethyl)-*N*-ethylaniline (**1u**), and *N*-methyl-*N*-phenylaniline (**1v**) reacted efficiently to afford only the *para*-hydrazido derivatives in yields of 87, 95, and 90 %, respectively. Notably, the free alkylamino group in **1u** did not interfere with the reaction owing to its deactivation through the hydrogen bond formed with HFIP.[13] Upon treatment of triphenylamine (**1w**) with azodicarboxylate **2a** (3.3 equiv.), a mixture of tri- and disubstituted products (ratio 63:37) was isolated in 92 % yield.

Furthermore, we were interested in the C–H reactivity at different positions (Scheme 3). For aniline **1x** substituted in the *para* position, only the expected triazane **4xa** was isolated in 78 % yield. However, if the *para* position of *N*,*N*-dimethylaniline (**1y**) was substituted, products **5ya** and **5yb** were selectively obtained in good yields instead of the expected *ortho*-substituted compounds. The mechanism could involve rearrangement of an ylide.[14] Representatively, in the case of indole (**6a**) and *N*-methylindole (**6b**), the usual C3-amination products **7aa** and **7ba** were isolated as the sole products in excellent yields. Moreover, if indole **6c** was substituted at the C3 position, C2-amination product **7ca** was selectively obtained in good yield.

Table 3. The amination of azodicarboxylate with different anilines.[a]



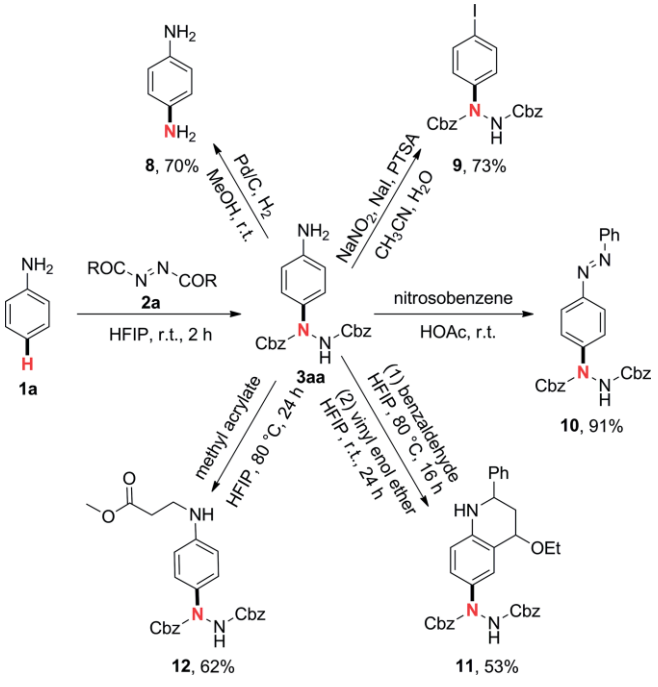
[a] Conditions: **1b**–**y** (0.5 mmol) and **2a** (0.55 mmol, 1.1 equiv.) were dissolved in solvent (0.25 M), and the mixture was stirred at 25 °C for the specified period unless otherwise noted; yields of the isolated products are given. [b] The major product is shown. [c] **2a** (3.3 equiv.).



Scheme 3. Selective amination reaction of different C–H bonds.

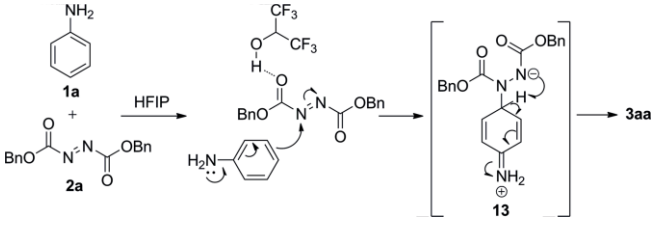
To illustrate the high synthetic potential of the new hydrazide primary anilines, different reactions were performed (Scheme 4). For example, hydrazide product **3aa** could be straightforwardly transformed into *p*-phenylenediamine (**8**) in 70 % yield by removal of the Cbz group and cleavage of the N–N bond in a single step.[7] One of the advantages to have a free amine in reactions is the possibility to remove or use it in other transformations.[15] By means of the well-known Sandmeyer reaction, diazotization of **3aa** with $NaNO_2$ followed by treatment with NaI produced 4-iodophenylhydrazine (**9**) in 73 % yield.[15a] Moreover, azo aromatic compound **10** could be obtained from compound **3aa** with nitrobenzene in acetic acid at room temperature in 91 % yield.[15b] Besides, from product **3aa**, a [4+2] aza-Diels–Alder cycloaddition[15c] could be realized in one pot in HFIP after the addition of benzaldehyde followed by ethyl vinyl ether. The corresponding tetrahydroquinoline **11**

was obtained in a reasonable yield of 57 % over three steps. Always in one pot, a Michael addition[15d] was performed with methyl acrylate to afford the monoalkylated product **12** in moderate yield.



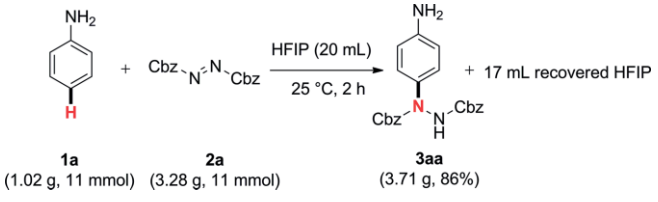
Scheme 4. Synthetic utilities of this reaction. PTSA = *para*-toluenesulfonic acid.

On the basis of previous literature reports[9e,10c,10e,16] and our studies,[13,15d] a plausible H-bond activation of the azodicarboxylate by HFIP is proposed (Scheme 5). Then, nucleophilic attack of aniline (**1a**) on **2a** generates intermediate **13**, which subsequently undergoes hydrogen transfer to afford the expected product **3aa**. Owing to HFIP–azodicarboxylate association, aniline can only react in its *para* position, which is sterically less hindered than the *ortho* position.



Scheme 5. Proposed mechanism.

A gram-scale reaction was also evaluated (Scheme 6). The *para*-selective amination of **1a** with **2a** was performed on an 11.0 mmol scale in 20 mL of HFIP for 2 h. Not only was the desired product **3aa** obtained smoothly in 86 % yield, but also 17 mL of HFIP was recovered after distillation directly from the reaction.



Scheme 6. Gram-scale reaction.

Conclusions

We developed an effective, mild, and clean method for C–H amination between azodicarboxylate derivatives and a wide range of anilines in 1,1,1,3,3,3-hexafluoro-2-propanol. The desired products were formed smoothly at room temperature without any additional catalyst or reagent in short times. This reaction was highly regioselective, provided *para*-substituted anilines, and was shown to have a broad substrate scope. The compatibility of a free amino group in this procedure is of high synthetic value. Besides, because of its low boiling point (b.p. 59 °C) and low viscosity, HFIP can be easily recovered and reused.

Experimental Section

General Procedure: Azodicarboxylate **2a** (0.55 mmol, 1.1 equiv.) was added to a stirred solution of aniline (**1a**; 0.5 mmol) in HFIP (2 mL) at 25 °C. The mixture was stirred at this temperature for 2 h. Upon completion of the reaction (TLC monitoring), the mixture was concentrated under reduce pressure to give a crude product. Then, the crude product was purified by column chromatography (silica gel; cyclohexane/diethyl ether, 2:1) to afford **3aa** as a white solid.

Acknowledgments

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Keywords: C–H activation · Amination · Regioselectivity · Azodicarboxylates · Fluorine

[1] a) D. N. Zalatan, J. D. Bois, *Org. Process Res. Dev.* **2009**, *292*, 347–378; b) T. G. Driver, *Org. Biomol. Chem.* **2010**, *8*, 3831–3846; c) J. D. Bois, *Org. Process Res. Dev.* **2011**, *15*, 758–762; d) J. L. Roizen, M. E. Harvey, J. D. Bois, *Acc. Chem. Res.* **2012**, *45*, 911; e) M. L. Louillat, F. W. Patureau, *Chem. Soc. Rev.* **2014**, *43*, 901–910; f) K. Shin, H. Kim, S. Chang, *Acc. Chem. Res.* **2015**, *48*, 1040–1052; g) G. He, B. Wang, W. A. Nack, G. Chen, *Acc. Chem. Res.* **2016**, *49*, 635–645; h) J. Jiao, K. Murakami, K. Itami, *ACS Catal.* **2016**, *6*, 610–633; i) X. Dong, Q. Liu, Y. Dong, H. Liu, *Chem. Eur. J.* **2017**, *23*, 2481–2511; j) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247–9301.

[2] a) R.-J. Tang, C.-P. Luo, L. Yang, C.-J. Li, *Adv. Synth. Catal.* **2013**, *355*, 869–873; b) H. J. Kim, M. J. Ajitha, Y. Lee, J. Ryu, H. Kim, Y. Lee, Y. Jung, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 1132–1140; c) T. Matsubara, S. Asako, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2014**, *136*, 646–649; d) D. Zhu, G. Yang, J. He, L. Chu, G. Chen, W. Gong, K. Chen, M. D. Eastgate, J. Q. Yu, *Angew. Chem. Int. Ed.* **2015**, *54*, 2497–2500; *Angew. Chem.* **2015**, *127*, 2527–2530; e) X.-H. Hu, X.-F. Yang, T.-P. Loh, *ACS Catal.* **2016**, *6*, 5930–5934; f) Z. Dong, G. Dong, *J. Am. Chem. Soc.* **2013**, *135*, 18350–18353; g) P. Wang, G. C. Li, P. Jain, M. E. Farmer, J. He, P. X. Shen, J. Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14092–14099; h) K. Sun, Y. Li, T. Xiong, J. Zhang, Q. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 1694–1697; i) B. Berzina, I. Sokolovs, E. Suna, *ACS Catal.* **2015**, *5*, 7008–7014.

[3] a) J. S. Arnold, H. M. Nguyen, *J. Am. Chem. Soc.* **2012**, *134*, 8380–8383; b) X. Li, X. Li, N. Jiao, *J. Am. Chem. Soc.* **2015**, *137*, 9246–9249; c) M. S. Mayo, X. Yu, X. Zhou, X. Feng, Y. Yamamoto, M. Bao, *Org. Lett.* **2014**, *16*,

764–767; d) Z. Zhang, C. Miao, C. Xia, W. Sun, *Org. Lett.* **2016**, *18*, 1522–1525; e) M.-N. Zhao, L. Yu, R.-R. Hui, Z.-H. Ren, Y.-Y. Wang, Y.-Y. Wang, Z.-H. Guan, *ACS Catal.* **2016**, *6*, 3473–3477.

[4] a) K.-H. Ng, A. S. C. Chan, W.-Y. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 12862–12864; b) X. Jia, J. Han, *J. Org. Chem.* **2014**, *79*, 4180–4185; c) Q. Li, S. Y. Zhang, G. He, Z. Ai, W. A. Nack, G. Chen, *Org. Lett.* **2014**, *16*, 1764–1767; d) H. Wang, Y. Yu, X. Hong, Q. Tan, B. Xu, *J. Org. Chem.* **2014**, *79*, 3279–3288.

[5] Y. Wang, Y. Wang, Z. Guo, Q. Zhang, D. Li, *Asian J. Org. Chem.* **2016**, *5*, 1438–1441.

[6] D. Ji, X. He, Y. Xu, Z. XU, W. Liu, Q. Zhu, Y. Xu, *Org. Lett.* **2016**, *18*, 4478–4481.

[7] H. Sahoo, M. K. Reddy, I. Ramakrishna, M. Baidya, *Chem. Eur. J.* **2016**, *22*, 1592–1596.

[8] W. J. Kinart, C. M. Kinart, R. Oszczeda, Q. T. Tran, *Catal. Lett.* **2005**, *103*, 185–189.

[9] a) C. Reichardt, *Chem. Rev.* **1994**, *94*, 2319–2358; b) A. Berkessel, J. A. Adrio, D. Hüttenhain, J. M. Neudörfl, *J. Am. Chem. Soc.* **2006**, *128*, 8421–8426; c) A. Börner, I. Shuklov, N. Dubrovina, *Synthesis* **2007**, 2925–2943; d) C. Laurence, J. Legros, P. Nicolet, D. Vuluga, A. Chantzis, D. Jacquemin, *J. Phys. Chem. B* **2014**, *118*, 7594–7608; e) S. Gennen, M. Alves, R. Mereau, T. Tassaing, B. Gilbert, C. Detrembleur, C. Jerome, B. Grignard, *ChemSusChem* **2015**, *8*, 1845–1849; f) S. Khaksar, *J. Fluorine Chem.* **2015**, *172*, 51–61; g) C. Laurence, J. Legros, A. Chantzis, A. Planchat, D. Jacquemin, *J. Phys. Chem. B* **2015**, *119*, 3174–3184; h) B. Crousse, J. P. Bégué, D. Bonnet-Delpon, *Synlett* **2004**, 18.

[10] a) P. A. Champagne, Y. Benhassine, J. Desroches, J. F. Paquin, *Angew. Chem. Int. Ed.* **2014**, *53*, 13835–13839; *Angew. Chem.* **2014**, *126*, 14055–14059; b) G. X. Li, J. Qu, *Chem. Commun.* **2010**, *46*, 2653–2655; c) H. F. Motiwala, R. H. Vekariya, J. Aube, *Org. Lett.* **2015**, *17*, 5484–5487; d) P. Trillo, A. Baeza, C. Najera, *J. Org. Chem.* **2012**, *77*, 7344–7354; e) R. H. Vekariya, J. Aube, *Org. Lett.* **2016**, *18*, 3534–3537; f) V. D. Vukovic, E. Richmond, E. Wolf, J. Moran, *Angew. Chem. Int. Ed.* **2017**, *56*, 3085–3089; *Angew. Chem.* **2017**, *129*, 3131–3135; g) N. Weisner, M. G. Khaledi, *Green Chem.* **2016**, *18*, 681–685.

[11] See ref.[9b]

[12] J. Choy, S. Jaime-Figueroa, L. Jiang, P. Wagner, *Synth. Commun.* **2008**, *38*, 3840–3853.

[13] a) K. De, J. Legros, B. Crousse, D. Bonnet-Delpon, *Tetrahedron* **2008**, *64*, 10497–10500; b) A. Di Salvo, M. David, B. Crousse, D. Bonnet-Delpon, *Adv. Synth. Catal.* **2006**, *348*, 118–124.

[14] E. Fahr, H. Lind, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 372–384; *Angew. Chem.* **1966**, *78*, 376–388. The reaction occurred in the dark and under argon.

[15] a) E. Krasnokutskaya, N. Semenischeva, V. Filimonov, P. Knochel, *Synthesis* **2007**, 81–84; b) Y. Lian, J. R. Hummel, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2013**, *135*, 12548–12551; c) M. V. Spanedda, V. D. Hoang, B. Crousse, D. Bonnet-Delpon, J.-P. Begue, *Tetrahedron Lett.* **2003**, *44*, 217–219; d) K. De, J. Legros, B. Crousse, D. Bonnet-Delpon, *J. Org. Chem.* **2009**, *74*, 6260–6265.

[16] M. O. Ratnikov, V. V. Tumanov, W. A. Smit, *Angew. Chem. Int. Ed.* **2008**, *47*, 9739–9742; *Angew. Chem.* **2008**, *120*, 9885–9888.

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