C–H Functionalization

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Synthesis of *gem*-Difluoro Olefins through C–H Functionalization and β-fluoride Elimination Reactions

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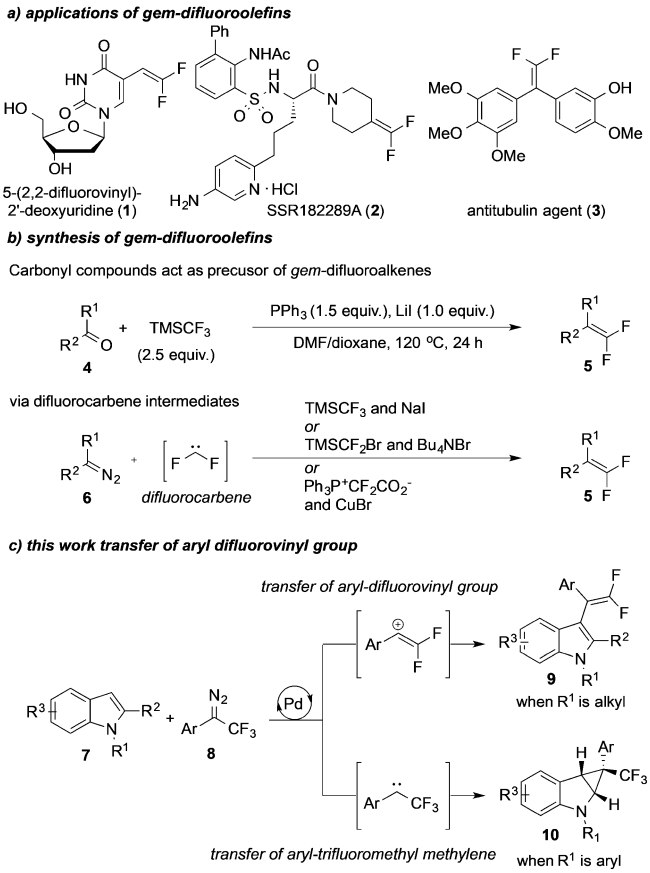
Abstract: *A palladium catalyzed C–H functionalization and consecutive β-fluoride elimination reaction between indole heterocycles and fluorinated diazoalkanes is reported. This approach provides for the first time a facile method for the rapid synthesis of gem-difluoro olefins using fluorinated diazoalkanes under mild reaction conditions. Cyclopropanation products were obtained when N-arylated rather than N-alkylated indoles were applied in this reaction. Mechanistic studies reveal the importance of the β-fluoride elimination step in this transformation. This method presents a new concept for the simple and direct transfer of a 1-aryl-(2,2-difluorovinyl) group to access gem-difluoro olefins.*

Gem-difluoro olefins are a unique structural motif with important applications ranging from drugs to materials. This fascinating group features unique properties that affect the metabolic stability and lipophilicity of organic molecules.[1,2] The strong electronegative nature of fluorine and the chemical reactivity of the *gem*-difluorovinyl moiety renders *gem*-difluoro olefins formidable electrophiles that can act as irreversible inhibitors of thymidylate synthase or other enzymes, and small molecules such as 5-(2,2-difluorovinyl)-2′-deoxyuridine (**1**) play an important role in the development of new antiviral agents.[3] Further prominent applications of *gem*-difluoro olefins include the orally active thrombin inhibitor SSR182289A (**2**), antitubulin agents (**3**), and amino acids derivatives (Scheme 1 a).[1c,4] In organic synthesis, *gem*-difluoro olefines are important intermediates with applications, for example, in carbonylation or carboxylation reaction of one of its C–F bonds.[5]

The efficient synthesis of *gem*-difluoro olefines has thus received broad attention in the past decades. Carbonyl compounds are traditional precursors for *gem*-difluoro olefination reactions, including the Wittig,[6] Horner–Wadsworth–Emmons,[7] and Julia-Kocienski reaction.[8] However, these traditional methods that apply carbonyl groups as a precursor to *gem*-difluoro olefines are limited in application due to strongly basic reaction conditions and limitations in the substrate scope.[6–8] More recently, difluorocarbene was found to be an efficient precursor to synthesize *gem*-difluoro olefins from aryldiazoacetates (Scheme 1 b).[9–11] There are few examples on the application of fluorinated diazoalkanes as a precursor of a CF_2 moiety, although recently, Wang and coworkers reported the *gem*-difluorovinylation of organoboronic acids with 2,2,2-trifluoro diazoethane following elimination of HF under strongly basic and forcing conditions at elevated temperature (100 °C).[12]



Scheme 1. a) Applications of *gem*-difluoro olefins in medicinal chemistry. b) Synthesis methods for *gem*-difluoro olefins. c) Pd-catalyzed reaction of fluorinated diazoalkanes with indole heterocycles.

Intrigued by these findings, we envisioned the introduction of a (2,2-difluorovinyl)-benzene group onto indole heterocycles[13] and electron-rich aromatic systems through carbene transfer of fluorinated diazoalkanes under mild reaction conditions (Scheme 1 c). A reaction sequence comprising C–H functionalization and subsequent β-fluoride elimination[14] should enable the direct one-step synthesis of analogues of antitubulin agents (**3**). Fluorinated diazoalkanes

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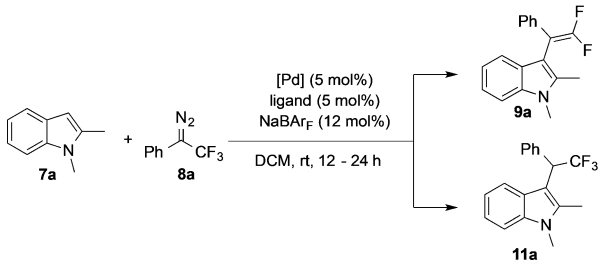
are important reagents for the introduction of trifluoromethyl or difluoromethyl groups into small organic molecules,[15] however applications of this important group of diazoalkanes in C–H functionalization reactions are scarce. Molander and Ryu studied the reaction of 2,2,2-trifluoro diazoethane with indole heterocycles, yet no reaction product was observed.[16] Osipov and co-workers investigated trifluoro diazoproponiate, but high reaction temperatures were needed for the activation of this stabilized diazoester.[17]

We hypothesized that phenyl(trifluoromethyl) diazomethane (**8a**) could be applied as a source of the (2,2-difluorovinyl)-benzene moiety and we thus investigated its reaction with 1,2-dimethyl indole (**7a**) and different Pd^{II} catalysts using $NaBAr_F$ as an additive and *rac*-BINAP as the ligand in DCM solvent. All of the Pd^{II} precursors investigated gave a mixture of the *gem*-difluoro olefin **9a** and carbene-insertion product **11a**.[18] Experiments using Cu^{I} catalysts proved inferior in terms of both selectivity and reactivity compared to Pd^{II}.[18] The highest **9a**/**11a** ratio was obtained using $Pd(OAc)_2$, and we next studied the influence of reaction parameters such as ligand, solvent, and temperature. Monodentate phosphine ligands gave only poor yield and selectivity.[18] By contrast, bidentate phosphine ligands play an important role in the selectivity and yield of this reaction, and when using a dppbe ligand, the *gem*-difluoro olefin product was obtained in 92% yield with good selectivity (Table 1, entry 6, **9a**; **11a** = 13:1). Weakly coordinating $NaBAr_F$ is crucial for this transformation since acetate might deactivate the Pd catalyst; without $NaBAr_F$, no reaction was observed (Table 1, entry 7). A control experiment using a Pd^0 complex revealed no formation of the reaction product, which emphasizes the importance of a Pd^{II} catalyst in this transformation (Table 1, entry 8).

Having established conditions to selectively conduct the introduction of a 1-aryl-(2,2-difluorovinyl) group onto 1,2-dimethyl indole, we next investigated the substrate scope of this transformation and studied different indole heterocycles (Scheme 2). Different aliphatic substituents, including terminal olefins, proved compatible with the reaction conditions, and in all cases, the *gem*-difluoro olefin product was obtained in very good to excellent yield of isolated product, even on gram-scale (**9a**–**9j**; for the gram-scale experiment, see **9d**). No byproduct arising from cyclopropanation was observed when using substrates bearing an olefinic substituent (**9g**, **9h**). Next, different substitution patterns of the aryl trifluoro diazoethane reaction partner (**8b**–**f**) were studied, all of which selectively gave the desired *gem*-difluoro olefin product in high yield of isolated product (**9k**–**9o**).

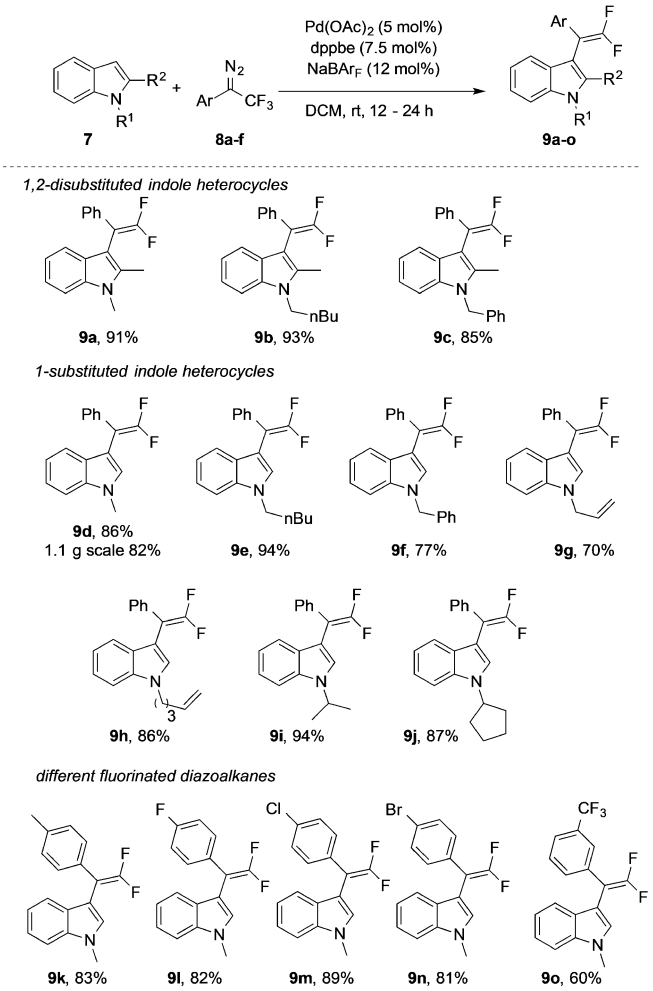
Next, we studied the influence of the substitution pattern of the parent indole heterocycle. Different halogen or electron-donating substituents were well tolerated at the 5-, 6-, and 7-positions of the indole heterocycle, and introduction

Table 1: Optimization of the *gem*-difluoro olefination reaction.



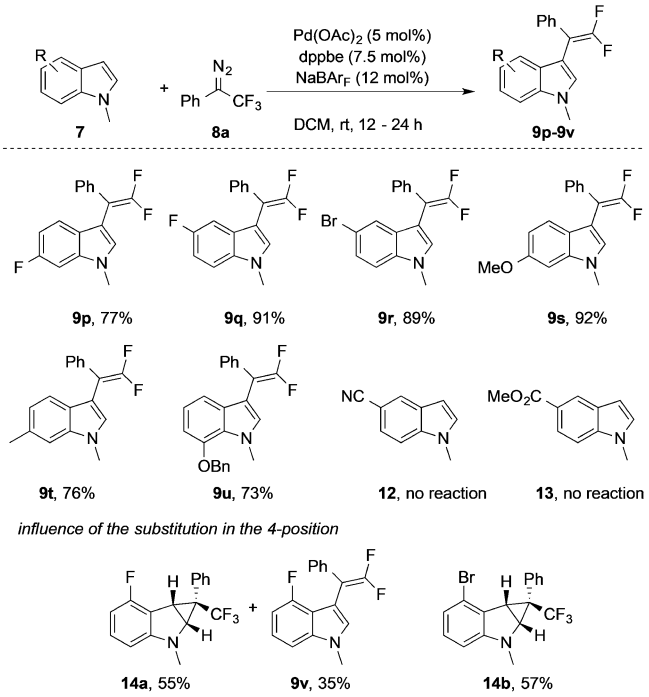
Entry[a]	[Pd]	Ligand	Solvent	Yield% (**9a**/**11a**)
1	$Pd(OAc)_2$	BINAP	DCM	55:18
2	$Pd(OAc)_2$	dcype	DCM	59:8
3	$Pd(OAc)_2$	dppe	DCM	83:8
4	$Pd(OAc)_2$	dppb	DCM	42:5
5	$Pd(OAc)_2$	dppbe	DCM	91:9
6[b]	$Pd(OAc)_2$	dppbe	DCM	92:7
7[c]	$Pd(OAc)_2$	dppbe	DCM	n.r.
8	$Pd(dba)_2$	dppbe	DCM	n.r.

[a] Reaction condition: 0.2 mmol **7a**, 0.3 mmol **8a**, 5 mol% Pd^{II} catalysts, 12.0 mol% NaBArF and 5.0 mol% Ligand were dissolved in 2.5 mL DCM under N_2 atmosphere and at room temperature. The yield and selectivity were determined by ^{1}H-NMR of the reaction crude. [b] 7.5 mol% Ligand was added. [c] reaction without NaBArF. n.r. = no reaction, dcype = 1,2-*bis*(dicyclohexylphoshino)ethane, dppe = 1,2-*bis*-(diphenylphoshino)ethane, dppb = 1,4-*bis*(diphenylphoshino)butane, dppbe = 1,2-*bis*(diphenylphoshino)benzene.



Scheme 2. Substrate scope with different N-alkyl indole and fluorinated diazoalkanes.

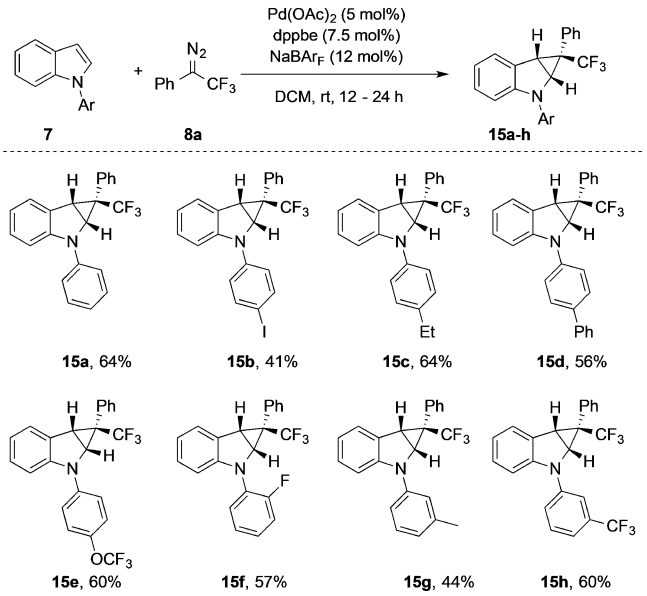
of the 1-aryl-(2,2-difluorovinyl) group into the 3-position occurred with high efficiency (Scheme 3, **9p**–**9v**). When studying electron-withdrawing substituents, no reaction occurred under the standard conditions, which might be related



Scheme 3. Reaction of different core-substituted indole heterocycles.

to missing nucleophilicity of the indole heterocycle (Scheme 3, **12**–**13**). The introduction of a substituent at the 4-position had a marked effect on the C–H functionalization. In the case of 4-fluoro-1-methyl indole, both cyclopropanation and C–H functionalization of the heterocycle occurred (Scheme 3, **14a** and **9v**). When increasing the steric bulk using a bromo substituent, selective cyclopropanation reaction occurred (Scheme 3, **14b**), which additionally allows the introduction of a trifluoromethyl cyclopropane under otherwise identical reaction conditions.

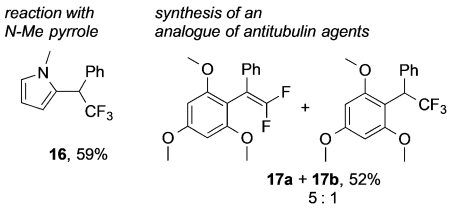
Intrigued by this selectivity switch, we decided to study the influence of the N-protecting group to identify conditions suitable for cyclopropanation. No reaction was observed for *N*-Boc- or *N*-pivaloyl-protected indole (for details, see the Supporting Information). When switching to a simple phenyl protecting group, a complete switch in chemoselectivity was observed, and the cyclopropane product **15a** was obtained under identical reaction conditions as the sole reaction product, which might be rationalized by lower nucleophilicity of the N-aryl indole heterocycles. We next studied different N-aryl-protected indole derivatives and selectively obtained the cyclopropanation product in moderate yield (Scheme 4, **15a**–**h**). Different halogens or a strongly electron-withdrawing substituent like the trifluoromethoxy group are tolerated. Notably, the 4-iodophenyl-substituted indole **15b** was obtained in moderate yield without the competing side reaction of oxidative insertion of the Pd complex into the C–I bond. This observation indicates that the active Pd



Scheme 4. Cyclopropanation reaction with N-aryl indole heterocycles.

catalyst in this reaction might rather be a Pd^{II} complex than a Pd^{0} complex.

We then studied the reaction of electron-rich aromatic substrates. *N*-Methyl pyrrole underwent C–H functionalization at the C-2 position in moderate yield to give the trifluoromethylated reaction product (Scheme 5, **16**). By



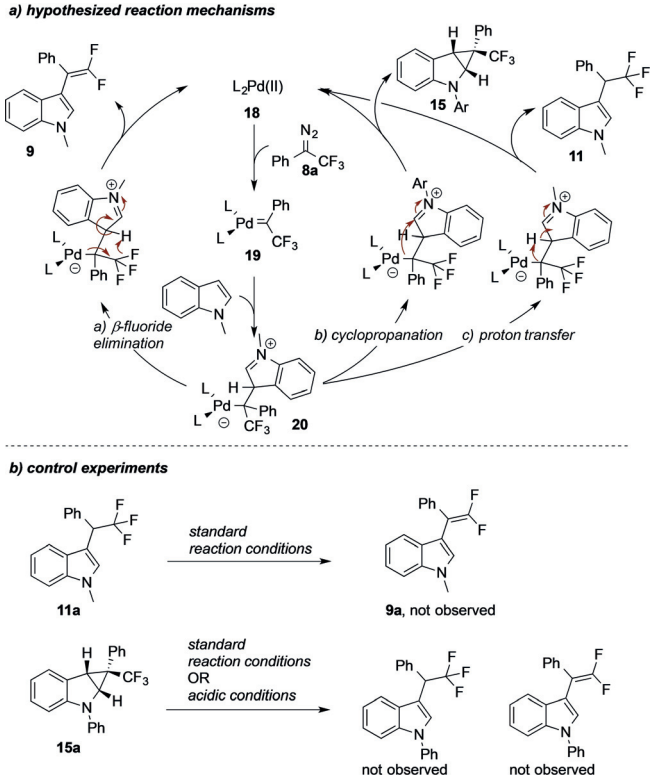
Scheme 5. Reaction of electron-rich aromatic compounds under the optimized reaction conditions and application in the synthesis of an analogue of antitubulin agents.

contrast, benzofuran, benzothiophene, *N*-methyl indazole, *N*-methyl-azaindole, unprotected indole, and dimethyl aniline did not react under the present conditions and only decomposition of the diazoalkane was observed.[18]

Finally, we planned the synthesis of an analogue of *gem*-difluorinated antitubulin agents by introducing a 1-aryl-(2,2-difluorovinyl) group onto an electron-rich benzene ring. For this purpose, we studied the reaction of 1,3,5-trimethoxybenzene with phenyl trifluoro diazoethane. Gratifyingly, the product was isolated with good chemoselectivity in moderate yield as a mixture of both *gem*-difluoro olefin and trifluoromethylated product (Scheme 5, **17a** and **17b**).

From a mechanism perspective, we hypothesize that a Pd^{II} catalyst (**18**) undergoes initial formation of a Pd-carbene complex (**19**; for the reactivity of a Pd^{0} complex, see also Table 1, entry 8).[18,19] Subsequent nucleophilic addition of indole generates **20**, which undergoes β-fluoride elimination to yield the *gem*-difluoro olefin **9**. Alternatively, a 1,2-proton

shift with concomitant release of the Pd^{II} complex gives access to the trifluoromethylated reaction product **11**. Control reactions with the trifluoromethylated reaction product **11a** revealed no formation of **9a**, thus underpinning the importance of the β-fluoride elimination pathway (Scheme 6b).



Scheme 6. a) Proposed reaction mechanism. b) Control experiments.

Finally, the cyclopropane product can be obtained through cleavage of the Pd^{II} complex followed by cyclization (Scheme 6a). In a control reaction on the stability of the cyclopropane **15a**, we observed ring opening neither under the standard reaction conditions nor when stirring over silica gel overnight (Scheme 6b).

In summary, we herein report a Pd-catalyzed reaction of fluorinated diazoalkanes with indole heterocycles. By careful choice of ligand and reaction conditions, trifluoromethyl-substituted diazoalkanes react in an efficient C–H functionalization reaction and allow the formal introduction of a 1-aryl-(2,2-difluorovinyl) group onto indole heterocycles and electron-rich aromatic systems even on gram scale. This approach enables the direct synthesis of important *gem*-difluoro olefins in one synthetic step involving a β-fluoride elimination as the key synthetic step.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbene transfer · C–H functionalization · fluorine · *gem*-difluoro olefins · palladium

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Angew. Chem. **2020**, *132*, 5620–5624

[1] a) P. J. Brothers, W. R. Roper, *Chem. Rev.* **1988**, *88*, 1293–1326; b) W. R. Moore, G. L. Schatzman, E. T. Jarvi, R. S. Gross, J. R. J. McCarthy, *J. Am. Chem. Soc.* **1992**, *114*, 360–361; c) J.-M. Altenburger, G. Y. Lassalle, M. Matrougui, D. Galtier, J.-C. Jetha, Z. Bocsker, C. N. Berry, C. Lunven, J. Lorrain, J.-P. Herault, P. Schaeffer, S. E. O'Connor, J.-M. Herbert, *Bioorg. Med. Chem.* **2004**, *12*, 1713–1730; d) M. A. Rogawski, *Epilepsy Res.* **2006**, *69*, 273–275; e) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.

[2] a) K. Uneyama, *Hydrogen Bonding in Organofluorine Compounds in Organofluorine Chemistry*, Blackwell Publishing, Oxford, **2006**; b) C. Ni, J. Hu, *Synthesis* **2014**, *46*, 842–963; c) *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, West Sussex, **2009**.

[3] a) M. Bobek, I. Kavai, E. De Clercq, *J. Med. Chem.* **1987**, *30*, 1494–1497; b) Y.-C. C. Cheng, B. A. Domin, R. A. Sharma, M. Bobek, *Antimicrob. Agents Chemother.* **1976**, *10*, 119–122; c) J. Reefschlager, D. Barwolff, P. Langen, *Acta Virol.* **1984**, *28*, 282–286.

[4] a) Y. Pan, J. Qiu, R. B. Sliverman, *J. Med. Chem.* **2003**, *46*, 5292–5293; b) S. Messaoudi, B. Treguier, A. Hamze, J.-F. Peyrat, J. R. De Losada, J.-M. Liu, J. Biognon, J. Wdzieczak-Bakala, S. Thoret, J. Dubois, J.-D. Brion, M. Alami, *J. Med. Chem.* **2009**, *52*, 4538–4542; c) K. Fujii, Y. Nakamoto, K. Hatano, Y. Kanetsuki, JP 2006016331, **2006**.

[5] a) J. Liu, J. Yang, F. Ferretti, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2019**, *58*, 4690–4694; *Angew. Chem.* **2019**, *131*, 4738–4742; b) L. Yang, W.-W. Ji, E. Lin, J.-L. Li, W.-X. Fan, Q. Li, H. Wang, *Org. Lett.* **2018**, *20*, 1924–1927; c) L.-F. Jiang, B.-T. Ren, B. Li, G.-Y. Zhang, Y. Peng, Z.-Y. Guan, Q.-H. Deng, *J. Org. Chem.* **2019**, *84*, 6557–6564; d) S.-S. Yan, D.-S. Wu, J.-H. Ye, L. Gong, X. Zeng, C.-K. Ran, Y.-Y Gui, J. Li, D.-G. Yu, *ACS Catal.* **2019**, *9*, 6987–6992; e) F.-T. Gao, Z. Fang, R.-R. Su, P.-X. Rui, X.-G. Hu, *Org. Biomol. Chem.* **2018**, *16*, 9211–9217.

[6] a) J. Zheng, J. Cai, J.-H. Lin, Y. Guo, J.-C. Xiao, *Chem. Commun.* **2013**, *49*, 7513–7515; b) I. Nowak, M. Robins, *Org. Lett.* **2005**, *7*, 721–724; c) J. Zheng, J.-H. Lin, J. Cai, Y. Guo, J.-C. Xiao, *Chem. Eur. J.* **2013**, *19*, 15261–15266; d) D. J. Burton, Z.-Y. Yang, W. Qiu, *Chem. Rev.* **1996**, *96*, 1641–1643.

[7] S. R. Piettre, L. Cabanas, *Tetrahedron Lett.* **1996**, *37*, 5881–5884.

[8] a) Y. Zhao, W. Huang, L. Zhu, J. Hu, *Org. Lett.* **2010**, *12*, 1444–1447; b) B. Gao, Y. Zhao, M. Hu, C. Ni, J. Hu, *Chem. Eur. J.* **2014**, *20*, 7803–7810; c) B. Gao, Y. Zhao, J. Hu, *J. Org. Chem. Front.* **2015**, *2*, 163–168.

[9] a) M. Hu, C. Ni, L. Li, Y. Han, J. Hu, *J. Am. Chem. Soc.* **2015**, *137*, 14496–14501; b) M. Hu, Z. He, B. Gao, C. Ni, J. Hu, *J. Am. Chem. Soc.* **2013**, *135*, 17302–17305.

[10] J. Zheng, J.-H. Lin, L.-Y. Yu, Y. Wei, X. Zheng, J.-C. Xiao, *Org. Lett.* **2015**, *17*, 6150–6153.

[11] Z. Zhang, W. Yu, C. Wu, C. Wang, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2016**, *55*, 273–277; *Angew. Chem.* **2016**, *128*, 281–285.

[12] G. Wu, Y. Deng, C. Wu, X. Wang, Y. Zhang, J. Wang, *Eur. J. Org. Chem.* **2014**, 4477–4481.

[13] Selected articles: a) K. J. Hock, A. Knorrscheidt, R. Hommelsheim, J. Ho, M. J. Weissenborn, R. M. Koenigs, *Angew. Chem.*

Int. Ed. **2019**, *58*, 3630 – 3634; *Angew. Chem.* **2019**, *131*, 3669 – 3673; b) Z. Wang, G. Xu, S. Tang, Y. Shao, J. Sun, *Org. Lett.* **2019**, *21*, 8488 – 8491; c) P. K. Dutta, J. Chauhan, M. K. Ravva, S. Sen, *Org. Lett.* **2019**, *21*, 2025 – 2029; d) M. Delgado-Rebollo, A. Prieto, P. J. Perez, *ChemCatChem* **2014**, *6*, 2047 – 2052; e) V. Arredondo, S. C. Hiew, E. S. Gutman, I. D. U. A. Premachandra, D. van Vranken, *Angew. Chem. Int. Ed.* **2017**, *56*, 4156 – 4159; *Angew. Chem.* **2017**, *129*, 4220 – 4223.

[14] Selected articles: a) V. T. Tran, J. A. Gurak Jr, K. S. Yang, K. M. Engle, *Nat. Chem.* **2018**, *10*, 1126 – 1133; b) T. Ichitsuka, T. Fujita, T. Arita, J. Ichikawa, *Angew. Chem. Int. Ed.* **2014**, *53*, 7564 – 7568; *Angew. Chem.* **2014**, *126*, 7694 – 7698; c) H. Zhao, A. Ariafard, Z. Lin, *Organometallics* **2006**, *25*, 812 – 819; d) Z. Zhang, W. Yu, Q. Zhou, T. Li, Y. Zhang, J. Wang, *Chin. J. Chem.* **2016**, *34*, 473 – 476; e) Z. Zhang, Q. Zhou, W. Yu, T. Li, G. Wu, Y. Zhang, J. Wang, *Org. Lett.* **2015**, *17*, 2474 – 2477; f) R. T. Thornbury, F. Dean Toste, *Angew. Chem. Int. Ed.* **2016**, *55*, 11629 – 11632; *Angew. Chem.* **2016**, *128*, 11801 – 11804.

[15] a) A review: L. Mertens, R. M. Koenigs, *Org. Biomol. Chem.* **2016**, *14*, 10547 – 10556; For selected references: b) R. Hommelsheim, Y. Guo, Z. Yang, C. Empel, R. M. Koenigs, *Angew. Chem. Int. Ed.* **2019**, *58*, 1203 – 1207; *Angew. Chem.* **2019**, *131*, 1216 – 1220; c) U. P. N. Tran, R. Hommelsheim, Z. Yang, C. Empel, K. Hock, T. V. Nguyen, R. Koenigs, *Chem. Eur. J.* **2019**, https://doi.org/10.1002/chem.201904680; d) G. A. Molander, L. N. Cavalcanti, *Org. Lett.* **2013**, *15*, 3166 – 3169; e) K. J. Hock, L. Mertens, F. K. Metze, C. Schmittmann, R. M. Koenigs, *Green Chem.* **2017**, *19*, 905 – 909; f) F. G. Adly, M. G. Gardiner, A. Ghanem, *Chem. Eur. J.* **2016**, *22*, 3447 – 3461; g) X. Lv, Z. Kang, D. Xing, W. Hu, *Org. Lett.* **2018**, *20*, 4843 – 4847; h) B. Ye, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 7896 – 7899; *Angew. Chem.* **2014**, *126*, 8030 – 8033.

[16] G. A. Molander, D. Ryu, *Angew. Chem. Int. Ed.* **2014**, *53*, 14181 – 14185; *Angew. Chem.* **2014**, *126*, 14405 – 14409.

[17] I. E. Tsyshchuk, D. V. Vorobyeva, A. S. Peregudov, S. N. Osipov, *Eur. J. Org. Chem.* **2014**, 2480 – 2486.

[18] For details, see the Supporting Information.

[19] a) Y. V. Tomilov, A. B. Kostitsyn, E. V. Shulishov, O. M. Nefedov, *Synthesis* **1990**, 246 – 248; b) B. F. Straub, *J. Am. Chem. Soc.* **2002**, *124*, 14195 – 14201.

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