Benzylic fluorination induced by N–F bond activation of Selectfluor® with a solvent-dependent selectivity switch

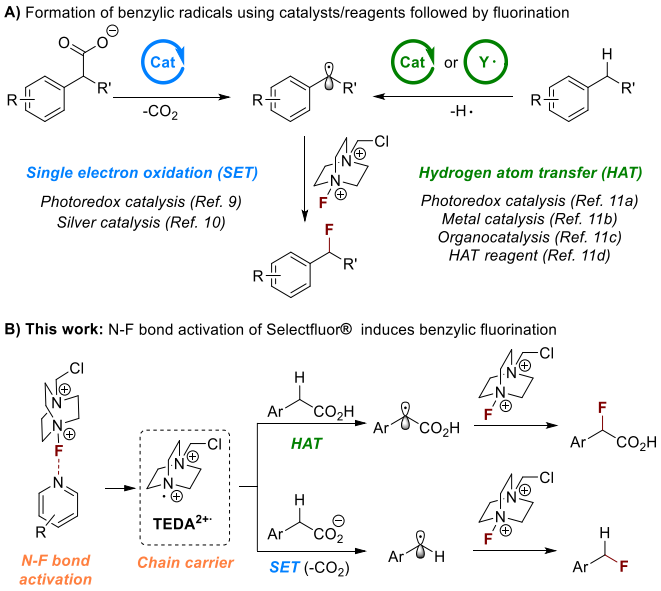
Amiera Madani,[a] [b] Lucia Anghileri,[a] [b] Matthias Heydenreich,[c] Heiko M. Möller[c] and Bartholomäus Pieber*[a]

[a] Amiera Madani, Lucia Anghileri, Bartholomäus Pieber
Department of Biomolecular Systems
Max-Planck-Institute of Colloids and Interfaces
Am Mühlenberg 1, 14476 Potsdam (Germany)
E-mail: bartholomaeus.pieber@mpikg.mpg.de
[b] Amiera Madani, Lucia Anghileri
Department of Chemistry and Biochemistry
Freie Universität Berlin
Arnimallee 22, 14195 Berlin (Germany)
[c] M. Heydenreich, H. M. Möller
Institute of Chemistry/Analytical Chemistry
University of Potsdam
Karl-Liebknecht-Strasse 24–25, 14476 Potsdam (Germany)

Supporting information for this article is given via a link at the end of the document.

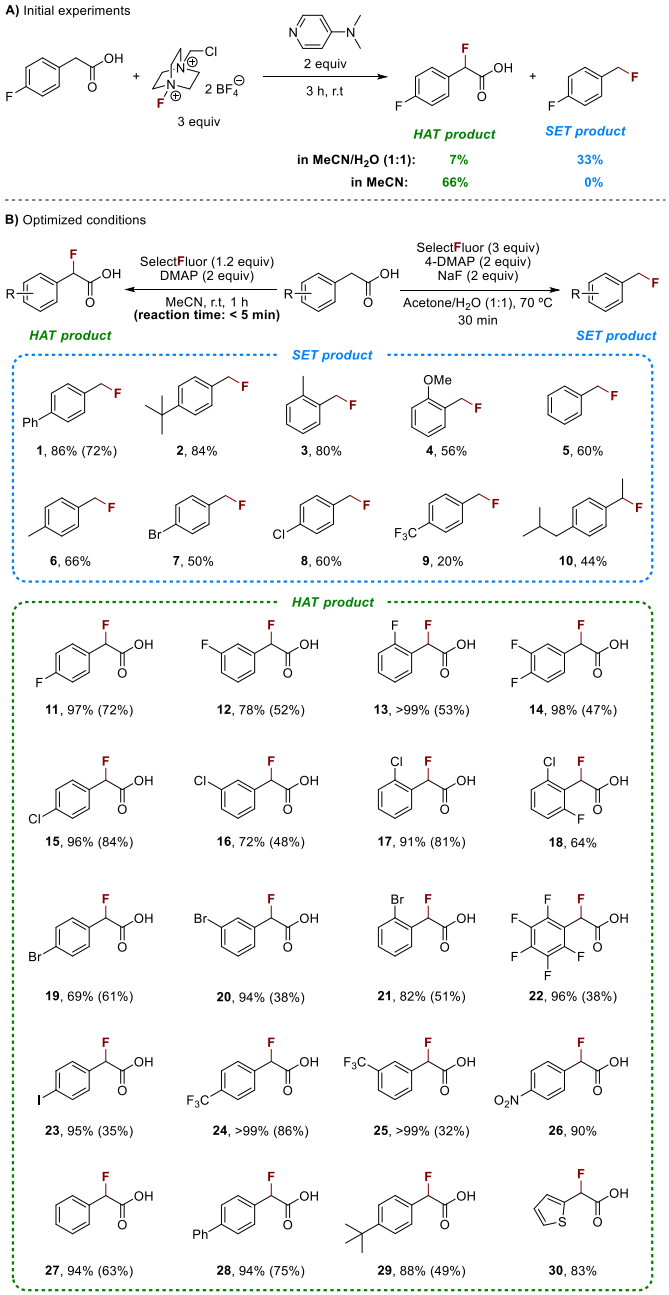
Abstract: We present a divergent radical strategy for the fluorination of phenylacetic acid derivatives through N–F bond activation of Selectfluor® with 4-(dimethylamino)pyridine. Comprehensive reaction investigation revealed the critical role of reaction media on selectivity. In presence of water, decarboxylative fluorination through a single electron oxidation is dominant. Non-aqueous conditions result in the clean formation of α-fluoro-α-arylcarboxylic acids through hydrogen atom transfer.

Fluorination increases the lipophilicity and metabolic stability of organic molecules, resulting in improved active pharmaceutical ingredients and agrochemicals.[1] Position emission tomography (PET) of [^{18}F]-labelled radiopharmaceuticals is important to study biochemical pathways and physiological processes.[2] Consequently, the development of efficient and selective protocols to construct C–F bonds is desirable.[3] Nucleophilic and electrophilic fluorination dominate the field, but radical fluorinations recently gained significant momentum due to two reasons.[3] First, the limitation to hazardous radical fluorine sources, such as XeF_2 and F_2 was overcome by the discovery that electrophilic N–F reagents transfer fluorine atoms to carbon-centered radicals.[4] Second, the increasing interest in synthetic radical chemistry resulted in attractive methods to generate C-centered radicals using dedicated catalysts and reagents.[5]
The formation of benzylic C(sp^3)-F bonds using 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane-1,4-diium ditetrafluoroborate (Selectfluor®)[6] is among the most studied C–F bond formations that proceed via a radical mechanism.[3-4, 7] These transformations are promising tools to modify drug candidates for preventing undesired benzylic oxidation by cytochrome P450 oxidases.[8] Common strategies are decarboxylative fluorinations that use photo-[9] or silver catalysts to induce single electron transfer (SET) oxidation,[10] and the direct fluorination of benzylic C(sp^3)-H bonds using catalysts or reagents that enable hydrogen atom transfer (HAT) (Scheme 1, A).[11] A dedicated catalyst or reagent is regularly used to generate initially the key benzylic radical, which ultimately undergoes F-atom transfer with Selectfluor® to yield the desired product. Catalyst-free benzylic fluorination of aza-heterocycles was reported to proceed through the formation of a charge transfer (CT) complex through N–F bonding between *N*-heterocyclic substrates and Selectfluor®. This induces a stepwise electron/proton transfer or a concerted proton-coupled electron transfer process.[12] Nitrogen-fluorine halogen bonding between Selectfluor® and pyridine additives was also reported to facilitate silver-catalyzed radical fluorinations, but no product was observed in the absence of the metal catalyst.[13]
We envisioned that strategic N–F bond activation of Selectfluor® could serve as a tool to generate *N*-(chloromethyl)triethylenediamine radical dication (TEDA$^{2+\cdot}$), a potent single electron oxidant and hydrogen atom transfer reagent.[14] This would access an operationally simple and divergent strategy for the generation of benzylic carbon-centered radicals that could ultimately engage with Selectfluor® to form C–F bonds. Here we present that this mechanistic blueprint can be indeed applied to achieve the direct fluorination of benzylic C(sp^3)-H bonds via a HAT mechanism and the decarboxylative formation of benzylic C(sp^3)-F bonds through a SET process (Scheme 1, B).



Scheme 1. Benzylic C(sp^3)-F bond formation using Selectfluor® through radical intermediates.

We started our investigations by studying if a combination of Selectfluor® and 4-(dimethylamino)pyridine (DMAP) triggers decarboxylative C–F bond formation or direct fluorination of benzylic C(sp^3)–H bonds. We chose 2-(4-fluorophenyl)acetic acid as model substrate that serves as an ideal probe for both mechanistic scenarios (Scheme 2, A). To our delight, we indeed observed a mixture of both fluorination products at room temperature with good selectivity towards the decarboxylative SET product in an acetonitrile/water mixture. Under non-aqueous conditions, the HAT product was formed selectively.

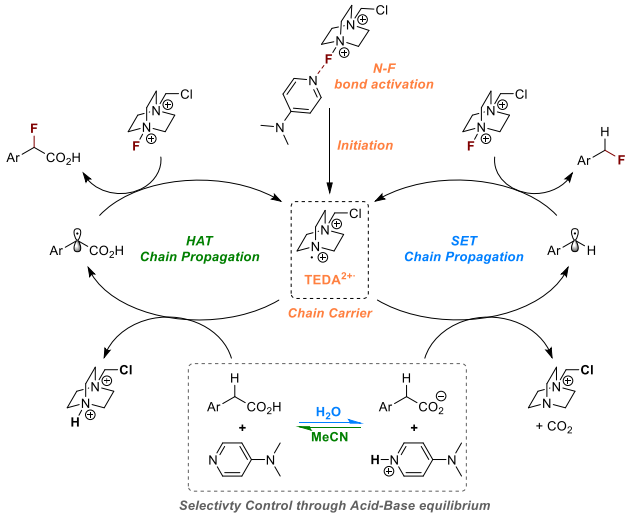


Scheme 2. Initial results and scope of the benzylic C(sp^3)-F bond formation using Selectfluor® and DMAP. Yields were determined by ^{1}H-NMR using dimethyl maleate as internal standard. Isolated yields are in parentheses.

After considerable experimentation (see SI), we found that the decarboxylative fluorination works best in acetone:water (1:1) using two equivalents of DMAP and excess of Selectfluor® (3 equiv) (Scheme 2, B). Further, the addition of sodium fluoride (2 equiv) and elevated temperatures (70°C) where beneficial to convert a series of phenylacetic acid derivatives to the corresponding, volatile SET products (**1-10**) within 30 min in moderate to good NMR-yields. Unreacted starting material was observed in many cases and no major side-product could be identified (see SI).

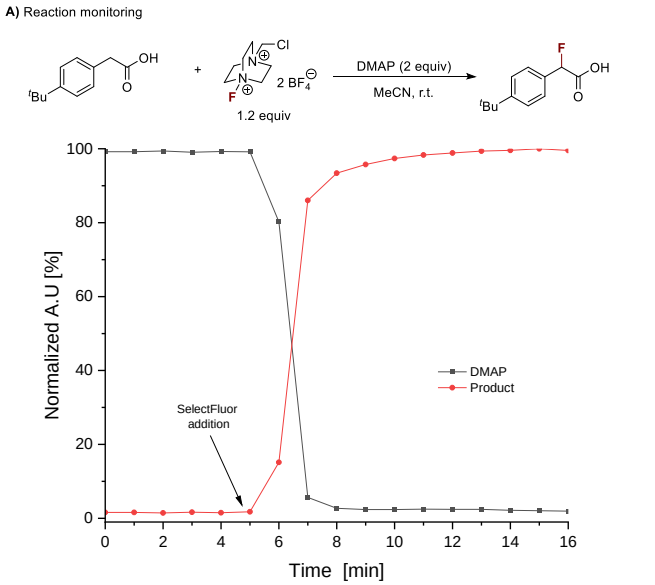
A combination of two equivalents DMAP and 1.2 equivalents Selectfluor® in acetonitrile produced the HAT products (**11-30**) at room temperature in good to excellent NMR-yields (Scheme 2, B). Phenylacetic acid derivatives with electron-rich and electron-deficient substituents were cleanly converted to the respective α-fluoro-α-arylacetic acids, which supports a HAT mechanism. Small amounts of unreacted starting material were detected in all cases, which were difficult to separate by column chromatography and resulted in modest isolated yields in certain cases. Reaction time of one hour was used due to practical reasons, but detailed investigations revealed that the fluorination occurs in less than five minutes (Table S14 & S15). Interestingly, the carboxylic acid functionality is crucial for the HAT protocol. No reaction was observed using other functional groups, such as ketones, amides, boronic acid esters or boronates (see SI). This can be rationalized by an activation of the C−H bond towards electrophilic hydrogen atom abstracting species by the carboxylate.[15]

We propose that a mixture of DMAP and Selectfluor® spontaneously produces $TEDA^{2+\cdot}$, which acts as a chain carrier for the SET and HAT process (Scheme 3). The radical chain is efficient for the HAT route (1.2 equiv Selectfluor® under optimized conditions), whereas the SET pathway seems to suffer from a significant amount of undesired termination events (3 equiv Selectfluor® under optimized condition). The switch between the SET and HAT pathway is a consequence of different pK_a values of phenylacetic acids and DMAP under the applied conditions. The organic base deprotonates the carboxylic acid in an aqueous environment enabling single electron oxidation of the carboxylate by $TEDA^{2+\cdot}$. SET oxidation triggers decarboxlation to produce a C-centered radical that ultimately reacts with Selectfluor® to yield the desired product and $TEDA^{2+\cdot}$. Phenylacetic acid derivatives have low acidity in aprotic polar solvents (pK_a of phenylacetic acid in $MeNO_2$ = >19).[16] The pK_a of the conjugated acid of pyridine derivatives in MeCN is lower.[17] As a result, the amount of carboxylate under these conditions is low. This reduces the chances for decarboxylative SET and HAT becomes the dominant pathway.

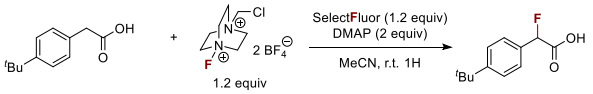


Scheme 3. Proposed mechanism for the formation of benzylic C(sp^3)-F bonds via the activation of Selectfluor® using DMAP.

The simple preparation of α-fluoro-α-arylcarboxylic acids through the HAT approach is particularly interesting, because the current approach to synthesize such scaffolds requires formation of a silyl ketene acetal using a strong base, followed by treatment with Selectfluor®.[10c, 18] The HAT fluorination protocol is not sensitive to air or moisture, works with bench-stable reagents and produces the desired products in up to quantitative yields. This operational simplicity is promising for the synthesis of [^{18}F]-labelled radiopharmaceuticals using [^{18}F]-Selectfluor®.[19] In particular, the short reaction times are ideally suited for such applications, due to the short half-lives of [^{18}F]-radionuclides (110 min).[19] Monitoring the fluorination of 4-*tert*-butylphenylacetic acid using in situ FTIR spectroscopy showed that the reaction forms the HAT product instantaneously once Selectfluor® is added to a solution of DMAP and the substrate in MeCN (Figure 1, A).



B) "Delayed addition" experiments



Entry	Compound added delayed[a]	Conversion [%][b]	Yield [%][c]
1	Substrate	n.d.	n.d.
2	SelectFluor	>98	>98
3	DMAP	88	88

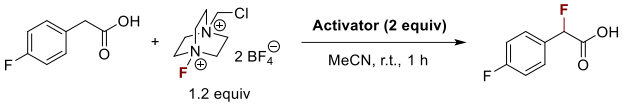
Reaction conditions: 4-*tert*-butylphenylacetic acid (0.3 mmol), Selectfluor (0.36 mmol), 4-DMAP (0.6 mmol), MeCN (1.5 mL), r.t, 1 h. [a]This ingredient was added to the reaction mixture after 30 min [b]Conversion of 4-fluorophenylacetic acid determined by ^{1}H-NMR using dimethyl maleate as an internal standard. [c]NMR yield determined by ^{1}H-NMR using dimethyl maleate as an internal standard.

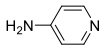
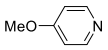
Figure 1. Practical aspects of the HAT protocol. (A) Reaction monitoring using in situ FTIR spectroscopy. (B) Delayed addition experiments.

Fast consumption of the fluorination reagent was also monitored in absence of the substrate (Figure S5). This indicates that the fluorine source and the organic base form a reactive, labile species that leads to productive fluorination, or, if no substrate is present in the reaction mixture, to degradation products. ^{1}H-NMR experiments using Teflon inserts showed the formation of a DMAP·HF adduct upon mixing DMAP and Selectfluor® along with several unidentified compounds that are likely *N*-fluorinated DMAP derivatives.[20] We carried out a series of "delayed-addition" experiments to clarify if the order of reagent addition is crucial for successful fluorination (Figure 1, B). When Selectfluor® and DMAP were mixed in MeCN and the substrate was added after 30 min, no reaction was observed. Premixing the substrate with Selectfluor® or DMAP is possible.

Finally, we sought to study if the N–F bond activation principle can be expanded to other electrophilic fluorine sources and if the electronics of the activator play a role. A reaction employing *N*-fluorobenzenesulfonimide (NFSI) is possible, but significantly lower conversions were obtained under otherwise identical conditions, whereas 1-fluoropyridinium tetrafluoroborate did not result in any fluorination product. This underlines the importance of TEDA$^{2+\cdot}$ as chain carrier.[14] Exchanging DMAP with pyridine derivatives that contain electron donating substituents, such as 4-aminopyridine or 4-methoxypyridine, reduced the efficacy of this reaction (Table 1). Modest conversions were obtained with pyridine underlining that a strong Lewis basicity is key for the generation of TEDA$^{2+\cdot}$.

Table 1. Influence of Lewis basicity on N-F bond activation of Selectfluor®.[a]



Entry	Activator	Conversion [%][b]	Yield [%][c]
1		97	97
2		82	82
3		66	66
4		9	9

[a]Reaction conditions: 4-fluorophenylacetic acid (0.3 mmol), Selectfluor (0.36 mmol), 4-DMAP (0.6 mmol), MeCN (1.5 mL), r.t, 4 h. [b]Conversion of 4-fluorophenylacetic acid determined by ^{1}H-NMR using dimethyl maleate as an internal standard. [c]NMR yield determined by ^{1}H-NMR using dimethyl maleate as an internal standard.

In summary, we developed a new strategy for the formation of benzylic C(sp^3)-F bonds via the formation of TEDA$^{2+\cdot}$ from Selectfluor® and 4-(dimethylamino)pyridine. Controlling the pK_a of phenylacetic acid derivatives via the reaction media enables switching between a SET and a HAT mechanism to produce different products. Under aqueous conditions a decarboxylative fluorination was observed, whereas non-aqueous conditions allow for direct fluorination of benzylic C(sp^3)-H bonds. This enables a facile and clean formation of α-fluoro-α-arylacetic acids within a few minutes at room temperature.

Acknowledgements

We gratefully acknowledge the Max Planck Society for generous financial support. A.M. and B.P. acknowledge the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy−EXC 2008/1 (UniSysCat)−390540038 for financial support. L.A. and B.P. acknowledge the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) for financial support (PI 1635/2-19). B.P. acknowledges financial support by a Liebig Fellowship from the German Chemical Industry Fund (Fonds der Chemischen Industrie, FCI). We thank our colleague John J. Molloy for fruitful scientific discussions.

Keywords: Radical fluorination • N–F bond activation • charge transfer • Decarboxylative fluorination • Hydrogen atom transfer

[1] a) N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822-5880; b) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315-8359; c) D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071-1081; d) T. Fujiwara, D. O'Hagan, *J. Fluorine Chem.* **2014**, *167*, 16-29.

[2] A. F. Brooks, J. J. Topczewski, N. Ichiishi, M. S. Sanford, P. J. H. Scott, *Chem. Sci.* **2014**, *5*, 4545-4553.

[3] P. A. Champagne, J. Desroches, J. D. Hamel, M. Vandamme, J. F. Paquin, *Chem. Rev.* **2015**, *115*, 9073-9174.

[4] C. Chatalova-Sazepin, R. Hemelaere, J.-F. Paquin, G. M. Sammis, *Synthesis* **2015**, *47*, 2554-2569.

[5] S. Crespi, M. Fagnoni, *Chem. Rev.* **2020**, *120*, 9790-9833.

[6] P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent, C.-H. Wong, *Angew. Chem. Int. Ed.* **2005**, *44*, 192-212.

[7] a) G. Tarantino, C. Hammond, *Green Chem.* **2020**, *22*, 5195-5209; b) R. Szpera, D. F. J. Moseley, L. B. Smith, A. J. Sterling, V. Gouverneur, *Angew. Chem. Int. Ed.* **2019**, *58*, 14824-14848; c) B. Lantaño, A. Postigo, *Org. Biomol. Chem.* **2017**, *15*, 9954-9973; d) P. Xiao, X. Pannecoucke, J.-P. Bouillon, S. Couve-Bonnaire, *Chem. Soc. Rev.* **2021**, *50*, 6094-6151.

[8] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320-330.

[9] a) S. Ventre, F. R. Petronijevic, D. W. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 5654-5657; b) X. Wu, C. Meng, X. Yuan, X. Jia, X. Qian, J. Ye, *Chem. Commun.* **2015**, *51*, 11864-11867; c) G. Tarantino, C. Hammond, *ACS Catal.* **2018**, *8*, 10321-10330; d) B. Pieber, M. Shalom, M. Antonietti, P. H. Seeberger, K. Gilmore, *Angew. Chem. Int. Ed.* **2018**, *57*, 9976-9979.

[10] a) T. V. Nguyen, V. T. Pham, T. V. T. Nguyen, N. T. S. Phan, T. Truong, *J. Catal.* **2018**, *360*, 270-276; b) Z. Wang, C.-Y. Guo, C. Yang, J.-P. Chen, *J. Am. Chem. Soc.* **2019**, *141*, 5617-5622; c) S. Mizuta, I. S. R. Stenhagen, M. O'Duill, J. Wolstenhulme, A. K. Kirjavainen, S. J. Forsback, M. Tredwell, G. Sandford, P. R. Moore, M. Huiban, S. K. Luthra, J. Passchier, O. Solin, V. Gouverneur, *Org. Lett.* **2013**, *15*, 2648-2651.

[11] a) J.-B. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 17494-17500; b) P. Xu, S. Guo, L. Wang, P. Tang, *Angew. Chem. Int. Ed.* **2014**, *53*, 5955-5958; c) Y. Amaoka, M. Nagatomo, M. Inoue, *Org. Lett.* **2013**, *15*, 2160-2163; d) A. M. Hua, D. N. Mai, R. Martinez, R. D. Baxter, *Org. Lett.* **2017**, *19*, 2949-2952; e) J.-j. Ma, W.-b. Yi, G.-p. Lu, C. Cai, *Org. Biomol. Chem.* **2015**, *13*, 2890-2894.

[12] K. E. Danahy, J. C. Cooper, J. F. Van Humbeck, *Angew. Chem. Int. Ed.* **2018**, *57*, 5134-5138.

[13] A. M. Hua, S. L. Bidwell, S. I. Baker, H. P. Hratchian, R. D. Baxter, *ACS Catal.* **2019**, *9*, 3322-3326.

[14] F. J. Aguilar Troyano, K. Merkens, A. Gómez-Suárez, *Asian J. Org. Chem.* **2020**, *9*, 992-1007.

[15] L. M. Pipitone, G. Carboni, D. Sorrentino, M. Galeotti, M. Salamone, M. Bietti, *Org. Lett.* **2018**, *20*, 808-811.

[16] X. Subirats, S. P. Porras, M. Rosés, E. Kenndler, *J Chromatogr A* **2005**, *1079*, 246-253.

[17] S. Tshepelevitsh, A. Kütt, M. Lõkov, I. Kaljurand, J. Saame, A. Heering, P. G. Plieger, R. Vianello, I. Leito, *Eur. J. Org. Chem.* **2019**, *2019*, 6735-6748.

[18] a) F. Zhang, J. Z. Song, *Tetrahedron Lett.* **2006**, *47*, 7641-7644; b) H. Wang, C.-F. Liu, Z. Song, M. Yuan, Y. A. Ho, O. Gutierrez, M. J. Koh, *ACS Catal.* **2020**, *10*, 4451-4459.

[19] H. Teare, E. G. Robins, A. Kirjavainen, S. Forsback, G. Sandford, O. Solin, S. K. Luthra, V. Gouverneur, *Angew. Chem. Int. Ed.* **2010**, *49*, 6821-6824.

[20] M. S. Chauhan, G. D. Yadav, F. Hussain, S. Singh, *Catal. Sci. Technol.* **2014**, *4*, 3945-3952.