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One-Pot Synthesis of Fluorinated Pyrimidine Derivatives from Aldehydes by Photocatalytic α-Perfluoroalkenylation

Yu-Jun Zhu[a] and Constantin Czekelius*[a]

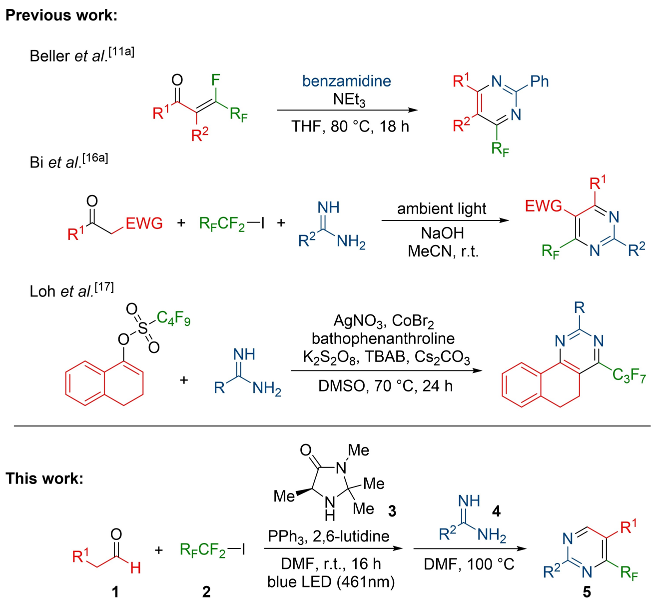
Dedicated to Prof. Thomas J. J. Müller on the occasion of his 60th birthday.

A straightforward, operationally simple and inexpensive one-pot synthesis of substituted 4-perfluoroalkyl-pyrimidine derivatives is reported. Employing triphenylphosphine as a photocatalyst and an additional imidazolidinone organocatalyst, aldehydes undergo α-perfluoroalkenylation giving highly electron-deficient enals, which form the heterocycle upon condensation with a guanidinium salt. The method tolerates many functional groups and gives the corresponding products in up to 84% yield over both steps.

Introduction

Pyrimidine and its derivatives are a privileged structural motif among nitrogen-containing heterocycles. They are present in many bioactive molecules such as the nucleotides and play a key function in life science and material chemistry.[1] Their straight-forward synthesis and electronic modification is therefore of utmost importance for pharmacological research, the agrochemical industry and for luminescent materials such as heat shock protein 90 (HSP 90) inhibitors, acaricides, or novel fluorescence dyes.[2]

The introduction of fluorine atoms or fluoroalkyl groups into the heteroaromatic scaffold has a unique impact on its chemical and physical properties such as solubility, lipophilicity, metabolic stability, and chemical reactivity which can be exploited for the optimization of the corresponding application.[3] During the past decades numerous efficient methods were developed based on perfluoroalkylated metal complexes,[4] transition metal catalysts[5] or on radical-type perfluoroalkylations. Herein, alkenes[6] including their boron-derivatives,[7] alkynes,[8] enamines,[9] enol ethers,[5b–d,10] carbonyl compounds[11] and related carbanions[12] were transformed to the corresponding perfluorinated alkene,[13] ketone,[11c,14] and peroxide[15] intermediates which were used as building blocks for further cyclizations (Scheme 1). In addition to these protocols, several catalytic multicomponent cyclizations of amidines, fluoroalkyl halides and styrenes or ketone derivatives[16] as well as a desulfonylative/defluorinative fragment-recombination[17] were also separately reported by the groups of Loh, Ma, and Bi. However, there is little precedence for analogous transformations involving aldehydes instead of ketones as often the robust reaction conditions are not compatible with this more delicate substrate class. Examples for their direct synthesis through perfluoroalkylation are also quite limited.[5a,9b,10c,d,f,12b]



Scheme 1. Synthesis of perfluoroalkylated pyrimidine derivatives.

In previous work, our group established an operationally simple photocatalytic α-perfluoroalkenylation of aldehydes under mild conditions in ambient atmosphere.[18] By irradiation of blue light, a perfluoroalkyl radical generated from the *in situ* formed electron donor-acceptor complex[19] with triphenylphosphine presumably reacts with the enamine which is derived from the aldehyde and the imidazolidinone organocatalyst in a parallel catalytic cycle[11a,20] giving the tetrasubstituted, perfluorinated enal upon base-mediated HF elimination.

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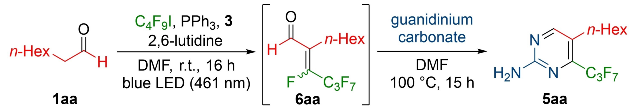
Inspired by this straight-forward synthesis and giving the interesting potential to employ these enals as synthesis intermediates[18b] we present in this work a one-pot protocol for the transformation of aldehydes directly into the corresponding 5-substitued 4-perfluoroalkyl-pyrimidines as a convenient and effective application of our photocatalytic perfluoroalkenylation methodology.

Results and Discussion

Initial investigations started to identify suitable reaction conditions for the cyclization of β-fluoro-β-fluoroalkyl-enals with guanidinium salts. Following the procedure of our prior work 2-(perfluorobutylidene)octanal (**6aa**) was prepared as a test substrate.[18] This enal and guanidine carbonate (5 equiv) were heated in DMF and the reaction was monitored by ^{19}F NMR (Table 1, entries 1–5).

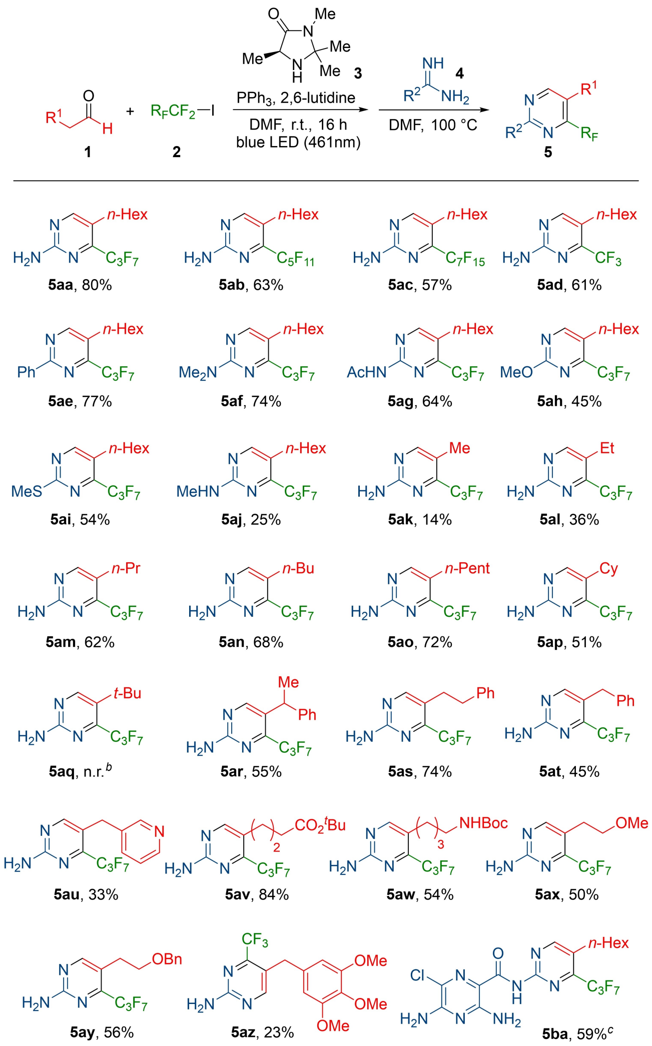
Delightfully, a clean transformation and 67% conversion were observed within 15 h at 100 °C (Table 1, entry 1). Surprisingly, even better conversions were found when imidazolidinone, 2,6-lutidine and triphenylphosphine, which are integral components in the photocatalytic perfluoroalkenylation, were individually tested as additives (entries 2–4). The enal was almost completely converted into the product under these conditions, which suggested that a one-pot transformation is in fact feasible (entry 5). When 6 equivalents of guanidine carbonate were added directly to the reaction mixture of the

Table 1. Screening of reaction conditions for the one-pot synthesis of perfluoroalkylated pyrimidine **5aa** from *n*-octanal.

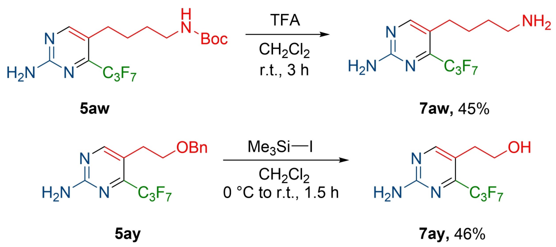


entry	enal	additive	guanidine [equiv]	conversion[a] [%]
1	neat	none	5	67
2	neat	Imidazolidinone (20 mol%) only	5	97
3	neat	2,6-lutidine (1.2 equiv) only	5	99
4	neat	PPh$_3$ (10 mol%) only	5	93
5	neat	all	5	>99
6	photoreaction mixture		6	93
7	photoreaction mixture		4	>99
8	photoreaction mixture		3	>99
9	photoreaction mixture		2	89
10[b]	photoreaction mixture		3	91
11[c]	photoreaction mixture		3	n.d.[e]
12[d]	photoreaction mixture		3	n.d.[e]
13[f]	photoreaction mixture		3	47
14[g]	photoreaction mixture		3	22

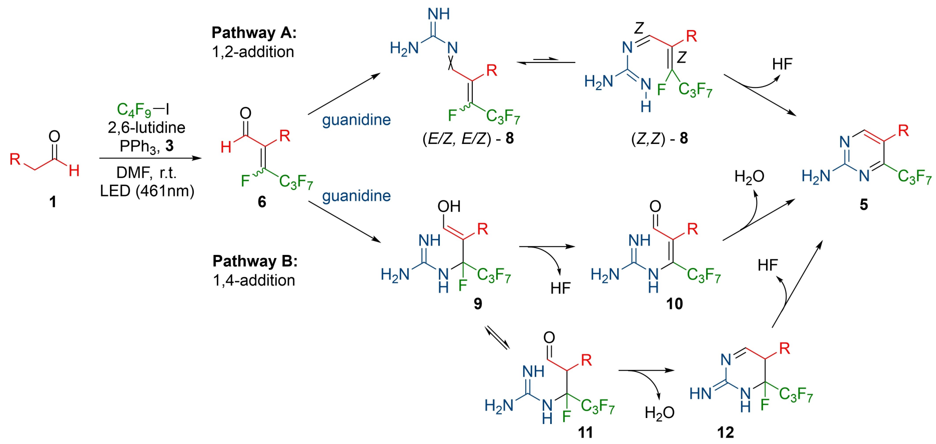
[a] Conversions were determined by ^{19}F NMR using PhCF$_3$ as internal standard. [b] The reaction time was 7 h. [c] With guanidinium chloride as additive. [d] With guanidinium nitrate as additive. [e] n.d. = product **5aa** was not found after the one-pot transformation. [f] The reaction was run at 50 °C. [g] The reaction was run at room temperature.



Scheme 2. One-pot synthesis of 5-substituted 4-perfluoroalkyl-pyrimidines.[a] [a] Reaction conditions: **1** (0.76 mmol), R$_F$CF$_2$I (1.6 mmol), imidazolidinone **3** (0.18 mmol), PPh$_3$ (0.084 mmol) and 2,6-lutidine (1.0 mmol) in 0.5 mL DMF at r.t. for 16 h under irradiation of blue light (461 nm). Then, addition of guanidine carbonate (1.14 mmol) or guanidine derivatives (2.28 mmol) together with Na$_2$CO$_3$ (3.42 mmol) in 7 mL DMF at 100 °C for 15 h. Isolated yields are given. [b] n.r. = No reaction, the corresponding enal was not found in the photocatalytic step of the transformation. [c] For details, see Supporting Information.



Scheme 3. Deprotection of 2-aminopyrimidine derivatives.



Scheme 4. Mechanistic pathways for the one-pot synthesis of 4-perfluoroalkyl-pyrimidines.

photoreaction containing the fluorinated enal, the aminopyrimidine was formed efficiently. Decreasing the amount of guanidine salt to three equivalents did not impair conversion and the product was isolated in 80% yield. However, further reduction to two equivalents resulted in a significantly lower conversion (entries 6–9). Unlike guanidine carbonate, the corresponding hydrochloride and nitrate salts failed to give the desired products (entries 11 and 12). When the reaction was run at lower temperatures, low conversion was found and another set of perfluoropropyl signals was visible in the crude ^{19}F NMR spectrum. These are presumably related to the first condensation intermediate, which could not be isolated and structurally elucidated, however (entries 13 and 14).

With the optimized reaction conditions in hand, the substrate scope was investigated (Scheme 2). We found that a series of perfluoroiodoalkanes was proven suitable for this one-pot synthesis afffording the desired products **5 aa**–**5 ad** in good yields. Varying the guanidine reaction partner, we found that the carbonate anion played an important role on the reaction outcome. With excess amounts of Na_2CO_3 as additive, a series of substituted and unsubstituted guanidine derivatives, amidines and carbamimidates gave pyrimidines **5 ae**–**5 aj** efficiently. Amiloride,[21] a widely used clinic potassium-retaining diuretic and natriuretic, was also successfully transformed into perfluoroalkylated pyrimidine derivative **5 ba** in 59% yield through this one-pot method.

As illustrated in Scheme 2, a variety of branched and unbranched aldehydes was applied in this one-pot method. In most cases, the corresponding 2-amino-4-perfluoroalkyl-pyrimidines were successfully isolated in yields up to 80%. It should be highlighted that the one-pot approach offers the advantage that also short-chain aldehydes can be transformed into the pyrimidine products, i.e. **5 ag** and **5 am**, in good yields although their corresponding 2-perfluoroalkylidene derivatives defied isolation in the past due to their high volatility. Only for sterically highly demanding substrates such as 3,3-dimethylbutanal, the method reaches its limits since the photocatalytic alkenylation did not provide the corresponding enal.

Aromatic and heteroaromatic aldehydes afforded the desired products **5 as**–**5 au**, but the electron-deficient side chain might hamper the reaction and both **5 at** and **5 au** were formed in lower yields compared with **5 as**. Esters and ketones were already shown to be well-suited for a chemoselective perfluoroalkenylation.[18] However, only the *tert*-butyl ester gave 2-amino-pyrimidine **5 av** in high yields. Presumably, the smaller alkyl groups in methyl or ethyl esters might not be able to prevent the nucleophilic attack of the carbonyl moiety by the guanidine. Protected alcohols and amines were compatible with this one-pot synthesis as well, providing the desired products in 50–56% yield. As expected, nitriles or bromides led to decomposition only.

The deprotection of hydroxy- and amino-functionalized 2-aminopyrimidines **5 ay** and **5 aw** was straight-forward giving the corresponding alcohol **7 ay** and amine **7 aw**, which can be used in further transformations (Scheme 3). Pyrimidine **5 az**, incorporating a very electron-rich aromatic moiety, which is known for its antifungals activity,[22] was also obtained by this simple one-pot protocol in 23% yield. In a semi-preparative scale experiment with C_4F_9I using 1 mmol of *n*-octanal, a yield of 80% was found matching the small-scale reaction.

The mechanism of the developed multi-step transformation can proceed via different pathways (Scheme 4). After the *in situ* generation of enal **6**, it could undergo a 1,2-addition to give condensation product **8**, which upon intramolecular cyclization gives the desired products **5**. However, this requires the four double bond isomers of **8** to be efficiently isomerized to the most reactive *Z,Z*-stereoisomer, presumably with the help of a nucleophilic catalyst such as guanidine in an addition/elimination sequence. In a parallel pathway, enal **6** first undergoes 1,4-addition to give enol **9**. Elimination of HF from this renders the vinylogous formamide **10** from which the target product **5** is accessible through condensation. Alternatively, **11**, the tautomer of **9**, could also undergo condensation to the unsaturated heterocycle **12** and then form the final product after HF elimination and aromatization. The specific role of the carbonate anion we observed may be associated with the ion interaction which has been reported by Hunger *et al.* in 2013 allowing for efficient proton transfer during the nucleophilic attack of the guanidine on the activated carbonyl group.[23] Initial investigations with respect to the described transformation did not allow for the identification of the predominant pathway yet and will the subject of a future study.

Conclusions

In conclusion, a straightforward and operationally friendly one-pot synthesis transforming aldehydes into the corresponding 4-perfluoroalkyl-pyrimidines was developed. As a rare example of a cyclization of tetrasubstituted and highly electron-deficient enals and a practical application of our previously reported photocatalytic perfluoroalkenylation, this protocol provides a series of highly functionalized pyrimidines in up to 84% yield. The enals produced from the photocatalytic α-perfluoroalkenylation were used directly without further isolation, allowing the application of those aldehydes generating highly volatile intermediates. In addition, upscaling and the successful synthesis of bioactive molecules showed that this method is expected to find further application in pharmaceutical research and development.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Photocatalysis · Aldehydes · One-pot synthesis · Fluorinated heterocycles · Pyrimidines

[1] a) L. M. De Coen, T. S. A. Heugebaert, D. García, C. V. Stevens, *Chem. Rev.* **2016**, *116*, 80–139; b) R. Komatsu, H. Sasabe, J. Kido, *J. Photon. Energy* **2018**, *8*, doi: 10.1117/1.JPE.8.032108; c) J. Zhuang, S. Ma, *ChemMedChem* **2020**, *15*, 1875–1886.

[2] a) Y. K. Chen, E. W. Co, P. Guntupalli, J. D. Lawson, W. R. L. Notz, J. A. Stafford, T.-N. Huong-Thu, Oxime derivatives as HSP90 inhibitors. *WO 2009097578A1*, **2009**; b) Y.-C. Wu, H.-J. Li, L. Liu, D. Wang, H.-Z. Yang, Y.-J. Chen, *J. Fluoresc.* **2008**, *18*, 357–363; c) Q. Wang, H. Song, Q. Wang, *Chin. Chem. Lett.* **2022**, *33*, 626–642.

[3] a) J. C. Biffinger, H. W. Kim, S. G. DiMagno, *ChemBioChem* **2004**, *5*, 622–627; b) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; c) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319; d) R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496–3508; e) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264; f) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359.

[4] a) D. J. Burton, S. W. Hansen, *J. Am. Chem. Soc.* **1986**, *108*, 4229–4230; b) P. Moreau, N. Naji, A. Commeyras, *J. Fluor. Chem.* **1987**, *34*, 421–441; c) C. Portella, B. Dondy, *Tetrahedron Lett.* **1991**, *32*, 83–86; d) B. Dondy, C. Portella, *J. Org. Chem.* **1993**, *58*, 6671–6674.

[5] a) Q.-L. Zhou, Y.-Z. Huang, *J. Fluor. Chem.* **1988**, *39*, 323–327; b) K. Sato, M. Higashinagata, T. Yuki, A. Tarui, M. Omote, I. Kumadaki, A. Ando, *J. Fluor. Chem.* **2008**, *129*, 51–55; c) K. Sato, S. Yamazoe, Y. Akashi, T. Hamano, A. Miyamoto, S. Sugiyama, A. Tarui, M. Omote, I. Kumadaki, A. Ando, *J. Fluor. Chem.* **2010**, *131*, 86–90; d) N. Kamigata, K. Udodaira, T. Shimizu, *Phosphorus, Sulphur, Silicon* **1997**, *129*, 155–168; e) Q. Li, S.-N. Zhao, G. Li, Y. He, X.-J. Zhao, *Eur. J. Org. Chem.* **2024**, *27*, e202400447; f) T. Zhang, Y. Zhang, Z. Li, B. Wu, Q. Shen, *Org. Chem. Front.* **2024**, *11*, 3924–3928.

[6] a) M. Yoshida, M. Ohkoshi, N. Aoki, Y. Ohnuma, M. Iyoda, *Tetrahedron Lett.* **1999**, *40*, 5731–5734; b) M. Yoshida, M. Ohkoshi, M. Iyoda, *Chem. Lett.* **2000**, *7*, 804–805; c) M. Yoshida, M. Ohkoshi, T. Murao, H. Matsuyama, M. Iyoda, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1833–1842; d) Y.-b. Wu, G.-p. Lu, T. Yuan, Z.-b. Xu, L. Wan, C. Cai, *Chem. Commun.* **2016**, *52*, 13668–13670; e) E. Shi, J. Liu, C. Liu, Y. Shao, H. Wang, Y. Lv, M. Ji, X. Bao, X. Wan, *J. Org. Chem.* **2016**, *81*, 5878–5885; f) Y. Cheng, C. Mück-Lichtenfeld, A. Studer, *J. Am. Chem. Soc.* **2018**, *140*, 6221–6225.

[7] a) C. Gerleve, M. Kischkewitz, A. Studer, *Angew. Chem. Int. Ed.* **2018**, *57*, 2441–2444; b) Y.-J. Li, D.-G. Liu, J.-H. Ren, T.-J. Gong, Y. Fu, *J. Org. Chem.* **2023**, *88*, 4325–4333.

[8] T. Umemoto, Y. Kuriu, O. Miyano, *Tetrahedron Lett.* **1982**, *23*, 3579–3582.

[9] a) D. Cantacuzéne, R. Dorme, *Tetrahedron Lett.* **1975**, *25*, 2031–2034; b) D. Cantacuzéne, C. Wakselman, D. Régine, *J. Chem. Soc., Perkin Trans I.* **1977**, *12*, 1365–1371; c) I. Rico, D. Cantacuzéne, C. Wakselman, *Tetrahedron Lett.* **1981**, *22*, 3405–3408.

[10] a) T. Umemoto, Y. Kuriu, S.-c. Nakayama, O. Miyano, *Tetrahedron Lett.* **1982**, *23*, 1471–1474; b) G. Wen-Zheng, Y.-M. Wu, W.-Y. Huang, *Chin. J. Chem.* **1991**, *9*, 527–535; c) K. Miura, Y. Takeyama, K. Oshima, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542–1553; d) W.-Y. Huang, Y.-M. Wu, *Chin. J. Chem.* **1992**, *10*, 373–378; e) S. Valdersnes, L. K. Sydnes, *Eur. J. Org. Chem.* **2009**, *2009* 5816–5831; f) S. Peng, K. G. Moloy, *J. Fluor. Chem.* **2017**, *201*, 7–10; g) Y. Li, J. Liu, S. Zhao, X. Du, M. Guo, W. Zhao, X. Tang, G. Wang, *Org. Lett.* **2018**, *20*, 917–920.

[11] a) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877; b) H. Huo, X. Huang, X. Shen, K. Harms, E. Meggers, *Synlett* **2016**, *27*, 749–753; c) F. Ye, S. Zhang, Z. Wei, F. Weniger, A. Spannenberg, C. Taeschler, S. Ellinger, H. Jiao, H. Neumann, M. Beller, *Eur. J. Org. Chem.* **2020**, *2020*, 70–81; d) G. Liu, H. Shen, Z. Wang, *Org. Lett.* **2024**, *26*, 1863–1867.

[12] a) T. Umemoto, Y. Gotoh, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 439–445; b) W.-Y. Huang, L. Lü, *Chin. J. Chem.* **1991**, *9*, 174–180.

[13] a) K.-W. Chi, G. G. Furin, Y. V. Gatilov, I. Y. Bagryanskay, E. L. Zhuzhgov, *J. Fluor. Chem.* **2000**, *103*, 105–115; b) G. G. Furin, Y. V. Gatilov, I. Y. Bagryanskay, E. L. Zhuzhgov, *Russ. Chem. Bull., Int. Ed.* **2001**, *50*, 476–479.

[14] a) D. V. Sevenard, O. G. Khomutov, O. V. Koryakova, V. V. Sattarova, M. I. Kodess, J. Stelten, I. Loop, E. Lork, K. I. Pashkevich, G.-V. Röschenthaler, *Synthesis* **2000**, *2000*, 1738–1748; b) F. Chanteau, R. Plantier-Royon, C. Portella, *Synlett* **2004**, *2004*, 512–516; c) F. Chanteau, B. Didier, B. Dondy, P. Doussot, R. Plantier-Royon, C. Portella, *Eur. J. Org. Chem.* **2004**, 1444–1454; d) A. Kotljarov, R. A. Irgashev, V. O. Iaroshenko, D. V. Sevenard, V. Y. Sosnovskikh, *Synthesis* **2009**, *2009*, 3233–3242; e) M. V. Goryaeva, Y. V. Burgart, M. A. Ezhikova, M. I. Kodess, V. I. Saloutin, *Beilstein J. Org. Chem.* **2015**, *11*, 385–391; f) Q.-D. Wang, Y.-W. Wang, T. Xie, Y.-Y. Cui, M. Ma, Z.-L. Shen, X.-Q. Chu, *J. Org. Chem.* **2021**, *86*, 8236–8247.

[15] a) Y. Ma, Y. Chen, L. Lv, Z. Li, *Adv. Synth. Catal.* **2021**, *363*, 3233–3239; b) Y. Ma, L. Lv, Z. Li, *J. Org. Chem.* **2022**, *87*, 1564–1573.

[16] a) R. Wang, W. Guan, Z.-B. Han, F. Liang, T. Suga, X. Bi, H. Nishide, *Org. Lett.* **2017**, *19*, 2358–2361; b) X.-Q. Chu, B.-Q. Cheng, Y.-W. Zhang, D. Ge, Z.-L. Shen, T.-P. Loh, *Chem. Commun.* **2018**, *54*, 2615–2618; c) X.-Q. Chu, T. Xie, L. Li, D. Ge, Z.-L. Shen, T.-P. Loh, *Org. Lett.* **2018**, *20*, 2749–2752; d) P. Zhao, L. Wang, X. Guo, J. Chen, Y. Liu, L. Wang, Y. Ma, *Org. Lett.* **2023**, *25*, 3314–3318.

[17] T. Xie, Y.-W. Zhang, L.-L. Liu, Z.-L. Shen, T.-P. Loh, X.-Q. Chu, *Chem. Commun.* **2018**, *54*, 12722–12725.

Research Article
doi.org/10.1002/ejoc.202500047

[18] a) C. Wulkesch, C. Czekelius, *J. Org. Chem.* **2021**, *86*, 7425–7438; b) L. Bunnemann, C. Wulkesch, V. C. Voigt, C. Czekelius, *Molecules* **2024**, *29*, 5034.
[19] a) L. Helmecke, M. Spittler, K. Baumgarten, C. Czekelius, *Org. Lett.* **2019**, *21*, 7823–7827; b) M. Bracker, L. Helmecke, M. Kleinschmidt, C. Czekelius, C. M. Marian, *Molecules* **2020**, *25*, 1606.
[20] M. Neumann, S. Füldner, B. König, K. Zeitler, *Angew. Chem. Int. Ed.* **2011**, *50*, 951–954.
[21] Q. Sun, P. Sever, *JRASS* **2020**, *21*, 1–9.
[22] H. Berber, M. Soufyane, M. Santillana-Hayat, C. Mirand, *Tetrahedron Lett.* **2002**, *43*, 9233–9235.
[23] J. Hunger, R. Neueder, R. Buchner, A. Apelblat, *J. Phys. Chem. B* **2013**, *117*, 615–622.
[24] a) T. Deng, W. Mazumdar, Y. Yoshinaga, P. B. Patel, D. Malo, T. Malo, D. J. Wink, T. G. Driver, *J. Am. Chem. Soc.* **2021**, *143*, 19149–19159; b) K. E. Borbas, C. Ruzié, J. Lindsey, *Org. Lett.* **2008**, *10*, 1931–1934; c) T. Lee, J. B. Jones, *J. Am. Chem. Soc.* **1996**, *118*, 502–508; d) E. Zeiler, V. S. Korotkov, K. Lorenz-Baath, T. Böttcher, S. A. Sieber, *Bioorg. Med. Chem.* **2012**, *20*, 583–591; e) S. Duan, X. Yang, Z. Yang, Y. Liu, Q. Shi, Z. Yang, H. Wu, Y. Han, Y. Wang, H. Shen, Z. Huang, X.-H. Dong, Z. Zhang, *Macromolecules* **2021**, *54*, 10830–10837; f) S. E. Denmark, L. R. Marcin, *J. Org. Chem.* **1995**, *60*, 3221–3235; g) E. Y. Osei-Twum, D. McCallion, A. S. Nazran, R. Panicucci, P. A. Risbood, J. Warkentin, *J. Org. Chem.* **1984**, *49*, 336–342; h) Q. He, L. Cao, Y. Wei, G. R. Dake, *Chem. Eur. J.* **2022**, *28*, e202201328; i) B. Meka, S. R. Ravada, M. M. K. Kumar, K. P. Nagasree, T. Golakoti, *Bioorg. Chem.* **2018**, *80*, 408–421; j) B. Rajagopal, Y.-Y. Chen, C.-C. Chen, X.-Y. Liu, H.-R. Wang, P.-C. Lin, *J. Org. Chem.* **2014**, *79*, 1254–1264; k) P. Bey, M. Jung, 2-Halomethyl derivatives of 2-amino acids. *US4743691*, **1988**.

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