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Modular synthesis of congested $\beta^{2,2}$-amino acids *via* the merger of photocatalysis and oxidative functionalisations†

Khadijah Anwar,[a] Luca Capaldo,[b] Ting Wan,[b] Timothy Noël[b] and Adrián Gómez-Suárez*[a]

A two-step protocol for the modular synthesis of β^2- and α-quaternary $\beta^{2,2}$-amino acid derivatives is reported. The key steps are a photocatalytic hydroalkylation reaction, followed by an oxidative functionalisation to access *N*-protected β-amino acids, esters, and amides. This strategy can be effectively scaled up *via* continuous-flow technology.

β-Amino acids are key components in a wide range of biologically active molecules.[1] Their incorporation into peptides results in strong modifications to the peptide secondary structure, leading to an increased resistance to proteases and peptidases.[1c,d] Compared to the more abundant α-amino acids, the addition of another C–C bond in β-amino acids provides new opportunities to modify the substituent pattern on the C2 and C3 positions. This leads to an extra level of complexity and depending on this, it is possible to have β^2-, $\beta^{2,2}$-, β^3-, or $\beta^{2,3}$-amino acids. Among them, the β^2- and β^3-variants are the most prominent in the life sciences, which is reflected by the numerous methodologies available to access them.[2] The less explored α-quaternary $\beta^{2,2}$-amino acids have been shown to be particularly effective at affecting peptide conformation by inducing the formation of more rigid secondary structures, enhancing stability towards proteolytic degradation.[1a] In addition, they can be used as intermediates to access pharmaceutically relevant structures such as β-lactams, γ-amino alcohols, or azetidines. The synthetic challenges associated with the construction of quaternary centres means there are few methods available for the preparation of $\beta^{2,2}$-amino acids, hampering the exploration of their biological properties. Therefore, the development of new approaches to access α-quaternary β^2-amino acids is important to unlock their full potential.

Current approaches primarily proceed *via* two-electron disconnections (Fig. 1). These include multi-step sequences, such as alkylation followed by Curtius rearrangement,[3] nitrile reductions,[4] reductive aminations;[5,6] or the Arndt–Eistert homologation.[7] The most common way to prepare β-amino acids is through Mannich addition reactions, which are limited to certain reactive electrophiles (*e.g.*, iminium species such as Vilsmeier–Hack type reagents), or the use of unsubstituted, or very specifically substituted, enolate equivalents as nucleophiles.[8,9] As a consequence, there are major restrictions in the type of substituents which can be incorporated into the final product, limiting these approaches to the synthesis of β^2-, β^3- and $\beta^{2,3}$-amino acid derivatives. In contrast to these processes governed by ionic intermediates, radical reactions can enable a more facile construction of quaternary centres. The comparatively high energy of radicals can be used to overcome kinetic barriers associated with steric hindrance, which may be more difficult to accomplish with a two-electron approach. This has been extensively demonstrated, for example, in the application of radical-based strategies for the synthesis of complex natural products bearing quaternary centres.[10]

With this in mind, we have designed a modular strategy to access α-quaternary $\beta^{2,2}$-amino acid analogues from readily available feedstocks using radical chemistry.[11] The proposed approach proceeds in a two-step sequence (Fig. 1B): (**1**) light-mediated Giese-type reaction[12] between alkylidenemalononitriles (**A**)[13,14] – readily synthesised *via* Knoevenagel condensation –[15] and α-amino acids,[16] and (**2**) oxidation of the resulting β-quaternary malononitriles[17] (**B**) to access the targeted $\beta^{2,2}$-amino acid analogues (**C**).

Optimisation of the light-mediated Giese-type reaction to access malononitrile derivatives **B** revealed that the best conditions were: irradiation (blue LEDs, 2 × 32 W, λ_{max} = 440 nm) of a mixture of alkylidenemalononitrile **A** (1.0 equiv.) and Cbz-glycine (2.0 equiv.) in the presence of Ir[(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (**Ir-F**, 0.5 mol%) and *sym*-collidine (2.0 equiv.), in 1,4-dioxane (0.2 M) at 60 °C.[18] This was followed by aerobic oxidation (O_2 balloon) of malononitrile **B** with Cs_2CO_3 (2.0 equiv.), and EtOH (10.0 equiv.) as nucleophile for 24 h, affording the targeted $\beta^{2,2}$-amino esters in optimal yields.[17,18]

[a] *Organic Chemistry, Bergische Universität Wuppertal, Gaußstr. 20, 42119, Wuppertal, Germany. E-mail: gomezsuarez@uni-wuppertal.de*
[b] *Flow Chemistry Group, Van't Hoff Institute for Molecular Sciences (HIMS), University of Amsterdam, Science Park 904, Amsterdam 1098 XH, The Netherlands*

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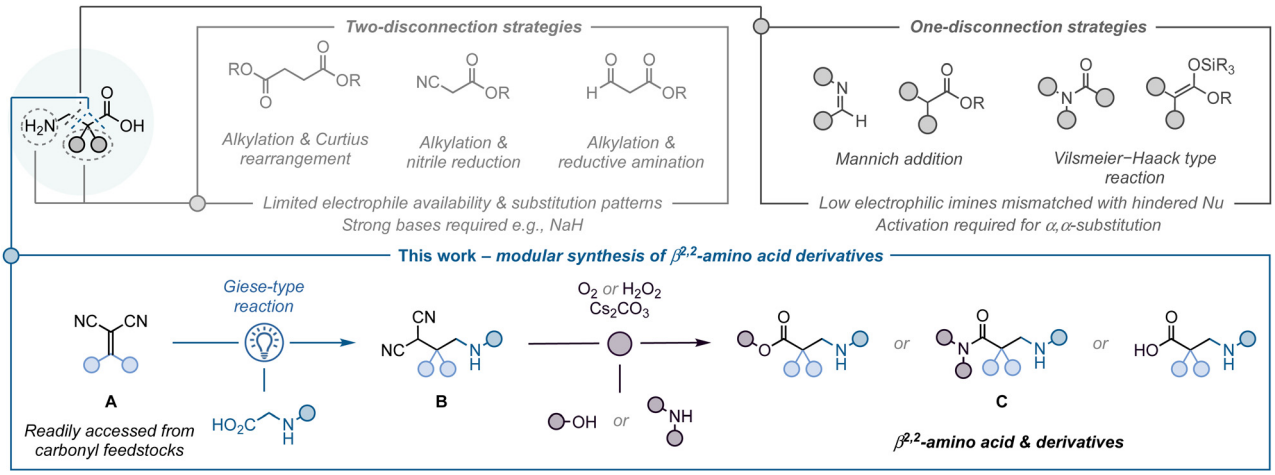
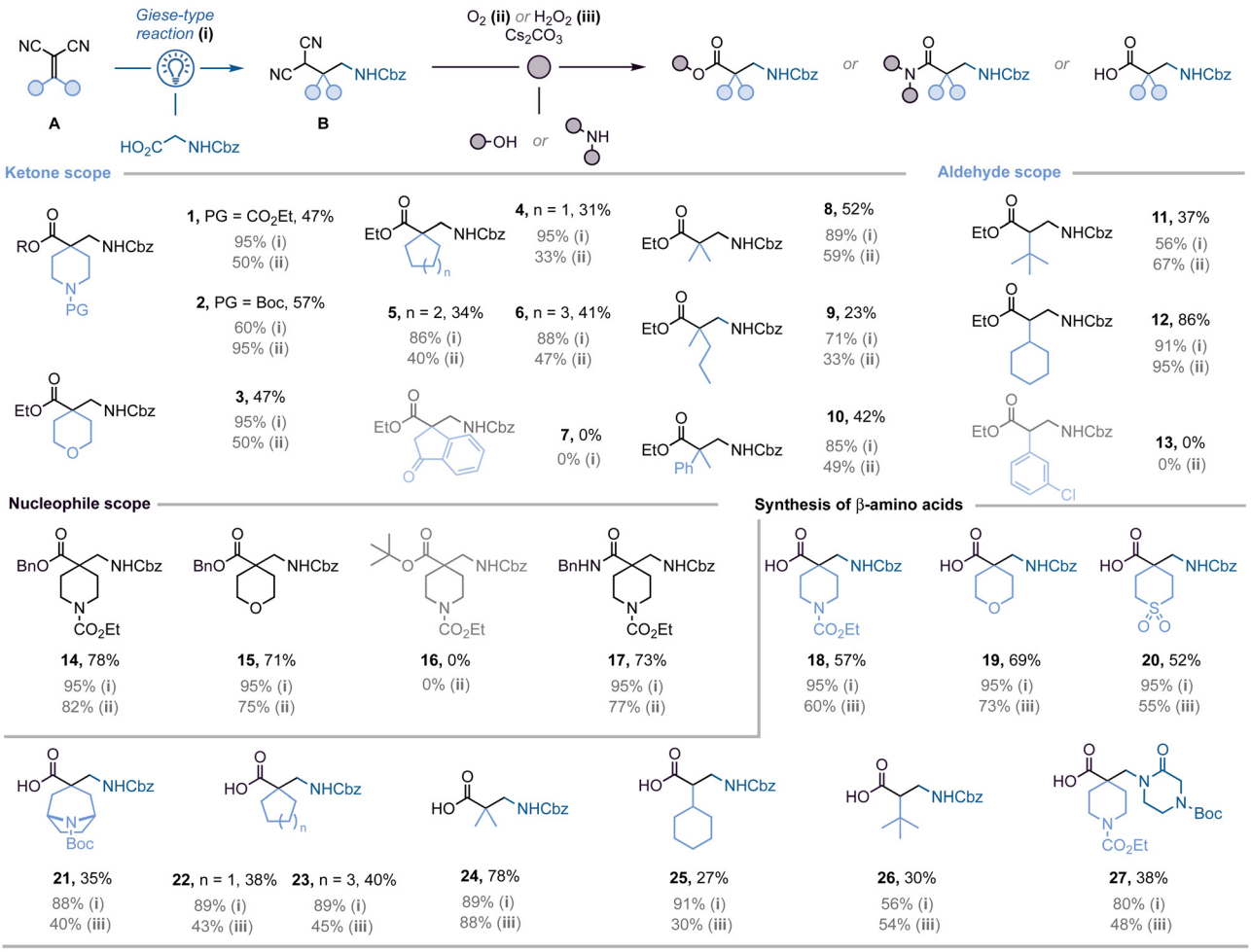


Fig. 1 Access to quaternary β^2-amino esters – state-of-the-art *vs.* our strategy.

With the optimised conditions in hand, we explored the scope and limitations of this strategy (Scheme 1). Aliphatic heterocycles are well-tolerated, as shown by the successful preparation of quaternary β^2-amino esters bearing piperidine (**1–2**), and tetrahydropyran (**3**) motifs (two-step yields: 47%, 57%, and 47%, respectively). Modification of the size of the ring



Reaction conditions: (i) **A** (1.0 equiv.), Cbz-glycine (2.0 equiv.), *sym*-collidine (2.0 equiv.), **Ir-F** (0.5 mol%), 1,4-dioxane (0.2 M), 60 °C, 16 h, blue LEDs (λ_{max} = 440 nm). (ii) **B** (1.0 equiv.), nucleophile (2.0–10.0 equiv.), Cs_2CO_3 (2.0 equiv.), O_2 (1.0 bar), RT, 24 h. (iii) **B** (1.0 equiv.), H_2O_2 (35% wt%, 10.0 equiv.), Cs_2CO_3 (2.0 equiv.), CH_3CN (0.1 M), RT, 16 h.

Scheme 1 Scope & limitations of the methodology. Giese reactions carried out in 0.5–1.0 mmol scale, oxidative functionalisations in 0.2 mmol scale.

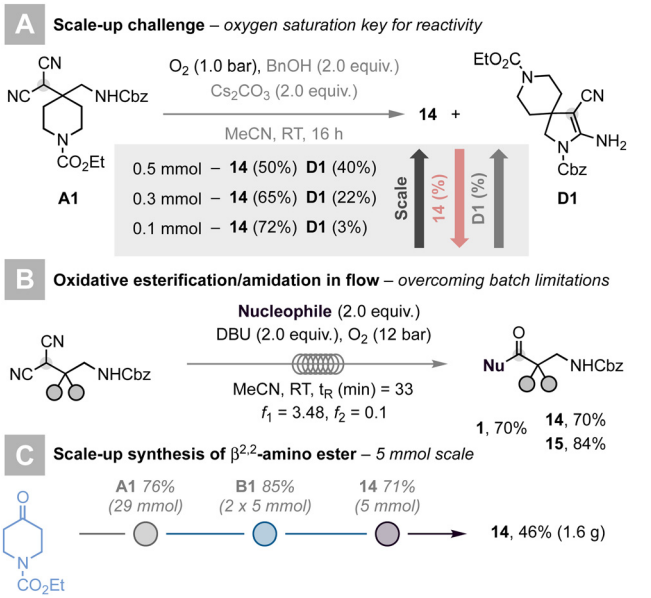
system at the α-position is achievable, as exemplified by the incorporation of cyclopentane (**4**), cyclohexane (**5**), and cycloheptane (**6**) motifs (31%, 34%, and 41% yield, respectively). The Giese-type reaction was unsuccessful when employing dihydroindenone-derived alkylidene malononitrile (**7**). This might be due to the increased steric hindrance afforded by the dihydroindenone-core, making the key radical addition step more difficult. Additionally, the methodology is not restricted to cyclic ketones, as shown by the synthesis of $\beta^{2,2}$-amino esters bearing acyclic substituents (**8–10**). Monosubstituted β^2-amino esters can also be obtained when using aldehydes in the Knoevenagel condensation step. The use of sterically demanding *tert*-butyl (**11**) and cyclohexyl (**12**) substituents led to the desired products in high yields, however benzylidene malononitriles gave complex mixtures of products (**13**, not isolated). Moreover, while the use of benzyl alcohol instead of EtOH allowed for the preparation of the corresponding benzyl esters **14** and **15** in good yields (78% and 71%, respectively), the corresponding *tert*-butyl ester (**16**) could not be isolated; probably due to the increased steric hindrance afforded by the *tert*-butyl group. Finally, the use of benzyl amine afforded the corresponding amide (**17**) in good yields after two steps (73%).

To expand the practicality of the method, *N*-protected β-amino acids were prepared directly using H_2O_2 as the oxidant (**18–23**).[19,20] Both acyclic ketones (**24**), as well as aldehydes (**25–26**), can be used to access the corresponding β-amino acids. In addition, the modularity of our strategy was further highlighted by replacing Cbz-glycine by an unnatural amino acid bearing a piperazinone core in the first step, thus enabling the synthesis of highly polar β^2-amino acid **27** in 38% yield.

Attempts to scale up the reaction were frustrated by the competitive formation of spirocyclic compound **D1** (Scheme 2A).[21] We hypothesised that due to poor solubility of oxygen in organic solvents, the formation of ester **14** was hampered, thus favouring the pathway leading to **D1**. We reasoned that the selective formation of the targeted β^2-amino ester should be achieved by increasing the O_2 content in solution. In batch, this calls for high O_2 pressures, increasing safety hazards, and limiting the applicability of our methodology; flow technology stands as an ideal solution to this challenge.

In recent years, flow chemistry[22] has emerged as a powerful technology to handle gas/liquid reaction mixtures. The possibility to control pressure using cheap back-pressure regulators (BPRs) and the advantages offered by Taylor recirculation for improved mass-transfer have changed paradigms in this field.[23] Flow chemistry has proven incredibly beneficial to perform oxidation reactions using molecular oxygen as a simple, green, and mild oxidant.[24] Other advantages of flow chemistry include shorter reaction times, enhanced heat-transfer, straightforward scalability, and improved safety standards and reproducibility.

Thus, we decided to tackle the challenges outlined above and scale our protocol up by adopting continuous-flow conditions. After a short re-optimisation of reaction conditions, which led to the replacement of insoluble carbonates with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in the role of the base to avoid possible clogging issues, we succeeded in translating



Scheme 2 Scale-up synthesis of quaternary β^2-amino esters.

our reaction from batch to flow.[18] A feed containing the malononitrile, DBU, and the nucleophile was merged with an O_2 feed *via* a PEEK T-mixer. The resulting slug-flow was pressurised at 12 bar by means of an adjustable BPR and pumped through a PFA coil (perfluoroalkoxy, V = 25 mL, ID: 2 mm) kept at 50 °C. A residence time (t_R) of 33 min was required to ensure reproducible access to β^2-amino esters. This new process proved effective to access ester **1**, **14**, and **15** in high yields (Scheme 2B). The use of this continuous-flow process, in combination with the readily scalable batch reactions to access alkylidenemalononitrile **A1** and α-quaternary malononitrile **B1**, enabled the synthesis of β^2-amino ester **14** in 46% yield (1.6 g) after three steps (Scheme 2C).

In summary, we have developed a modular two-step strategy for the synthesis of α-quaternary β-amino acid derivatives from readily available ketones, malononitrile, and α-amino acids. The method tolerates the introduction of (hetero)cyclic and acyclic substituents, both aliphatic and aromatic, at the β-position and allows for the synthesis of monosubstituted β^2-amino acids when aldehydes are employed instead of ketones. Moreover, by tuning the last step of the strategy, it is possible to selectively access β-amino esters, β-amino amides, or *N*-protected β-amino acids. Finally, to overcome limitations associated with mass transfer in the scale-up of the oxidative esterification step, we have developed a continuous-flow process that enables reproducible and scalable access to α-quaternary $\beta^{2,2}$-amino esters in gram scale.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) G. Lelais and D. Seebach, *Biopolymers*, 2004, **76**, 206–243; (*b*) P. Spiteller and F. von Nussbaum, *Enantioselective Synthesis of* β-*Amino Acids*, 2005, pp. 19–91; (*c*) C. Cabrele, T. A. Martinek, O. Reiser and L. Berlicki, *J. Med. Chem.*, 2014, **57**, 9718–9739; (*d*) M. P. Del Borgo, K. Kulkarni and M. I. Aguilar, *Curr. Pharm. Des.*, 2017, **23**, 3772–3785; (*e*) U. Bąchor and M. Mączyński, *Molecules*, 2021, **26**, 438.
2 (*a*) D. Seebach, A. K. Beck, S. Capone, G. Deniau, U. Grošelj and E. Zass, *Synthesis*, 2009, 1–32; (*b*) V. Chhiba, M. Bode, K. Mathiba and D. Brady, *Cascade Biocatalysis*, 2014, pp. 297–314.
3 J. J. W. Duan, L. Chen, Z. Lu, B. Jiang, N. Asakawa, J. E. Sheppeck, R.-Q. Liu, M. B. Covington, W. Pitts, S.-H. Kim and C. P. Decicco, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 266–271.
4 (*a*) C. Cativiela, M. D. Diaz-de-Villegas and J. A. Galvez, *J. Org. Chem.*, 1994, **59**, 2497–2505; (*b*) T. Hansen, T. Alst, M. Havelkova and M. B. Strøm, *J. Med. Chem.*, 2010, **53**, 595–606; (*c*) M. H. Paulsen, M. Engqvist, D. Ausbacher, M. B. Strøm and A. Bayer, *Org. Biomol. Chem.*, 2016, **14**, 7570–7578.
5 D. Lin, G. Deng, J. Wang, X. Ding, H. Jiang and H. Liu, *J. Org. Chem.*, 2010, **75**, 1717–1722.
6 For alternative two-step approaches see: (*a*) J.-S. Yu, H. Noda and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2018, **57**, 818–822; (*b*) P. Tovillas, C. D. Navo, P. Oroz, A. Avenoza, F. Corzana, M. M. Zurbano, G. Jimenez-Oses, J. H. Busto and J. M. Peregrina, *J. Org. Chem.*, 2022, **87**, 8730–8743.
7 D. Seebach, M. Overhand, F. N. M. Kühnle, B. Martinoni, L. Oberer, U. Hommel and H. Widmer, *Helv. Chim. Acta*, 1996, **79**, 913–941.
8 (*a*) N. S. Chowdari, J. T. Suri and C. F. Barbas, *Org. Lett.*, 2004, **6**, 2507–2510; (*b*) T. Akiyama, Y. Saitoh, H. Morita and K. Fuchibe, *Adv. Syn. Catal.*, 2005, **347**, 1523–1526; (*c*) A. Hasegawa, Y. Naganawa, M. Fushimi, K. Ishihara and H. Yamamoto, *Org. Lett.*, 2006, **8**, 3175–3178; (*d*) A. Ting, S. Lou and S. E. Schaus, *Org. Lett.*, 2006, **8**, 2003–2006; (*e*) A. L. Tillman, J. Ye and D. J. Dixon, *Chem. Commun.*, 2006, 1191–1193, DOI: 10.1039/B515725K; (*f*) R. Moumné, B. Denise, A. Parlier, S. Lavielle, H. Rudler and P. Karoyan, *Tetrahedron Lett.*, 2007, **48**, 8277–8280.
9 A. Romanens and G. Bélanger, *Org. Lett.*, 2015, **17**, 322–325.
10 (*a*) M. J. Schnermann and L. E. Overman, *Angew. Chem., Int. Ed.*, 2012, **51**, 9576–9580; (*b*) C. R. Jamison and L. E. Overman, *Acc. Chem. Res.*, 2016, **49**, 1578–1586; (*c*) Y. Slutskyy, C. R. Jamison, G. L. Lackner, D. S. Muller, A. P. Dieskau, N. L. Untiedt and L. E. Overman, *J. Org. Chem.*, 2016, **81**, 7029–7035; (*d*) J. Li, F. Li, E. King-Smith and H. Renata, *Nat. Chem.*, 2020, **12**, 173–179; (*e*) Z. Xin, H. Wang, H. He and S. Gao, *Tetrahedron Lett.*, 2021, **71**, 153029.
11 (*a*) H. Jia and T. Ritter, *Angew. Chem., Int. Ed.*, 2022, **61**, e202208978; (*b*) N. Tanaka, J. L. Zhu, O. L. Valencia, C. R. Schull and K. A. Scheidt, *J. Am. Chem. Soc.*, 2023, **145**, 24486–24492.
12 A. L. Gant Kanegusuku and J. L. Roizen, *Angew. Chem., Int. Ed.*, 2021, **60**, 21116–21149.
13 (*a*) H.-L. Cui and Y.-C. Chen, *Chem. Commun.*, 2009, 4479–4486; (*b*) B. Farajpour and A. Alizadeh, *Org. Biomol. Chem.*, 2022, **20**, 8366–8394.
14 Examples of radical additions to alkylidenemalononitriles: (*a*) R. A. Holton, A. D. Williams and R. M. Kennedy, *J. Org. Chem.*, 2002, **51**, 5480–5482; (*b*) Z. Tu, C. Lin, Y. Jang, Y.-J. Jang, S. Ko, H. Fang, J.-T. Liu and C.-F. Yao, *Tetrahedron Lett.*, 2006, **47**, 6133–6137; (*c*) D. Dondi, D. Ravelli, M. Fagnoni, M. Mella, A. Molinari, A. Maldotti and A. Albini, *Chem. – Eur. J.*, 2009, **15**, 7949–7957; (*d*) X. Z. Fan, J. W. Rong, H. L. Wu, Q. Zhou, H. P. Deng, J. D. Tan, C. W. Xue, L. Z. Wu, H. R. Tao and J. Wu, *Angew. Chem., Int. Ed.*, 2018, **57**, 8514–8518; (*e*) L. Li, L. Fang, W. Wu and J. Zhu, *Org. Lett.*, 2020, **22**, 5401–5406; (*f*) D. Kuwana, Y. Komori, M. Nagatomo and M. Inoue, *J. Org. Chem.*, 2022, **87**, 730–736.
15 K. van Beurden, S. de Koning, D. Molendijk and J. van Schijndel, *Green Chem. Lett. Rev.*, 2020, **13**, 349–364.
16 (*a*) L. Chu, C. Ohta, Z. Zuo and D. W. MacMillan, *J. Am. Chem. Soc.*, 2014, **136**, 10886–10889; (*b*) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle and D. W. MacMillan, *Science*, 2014, **345**, 437–440; (*c*) Z. Zuo and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2014, **136**, 5257–5260; (*d*) S. B. Lang, K. M. O'Nele and J. A. Tunge, *J. Am. Chem. Soc.*, 2014, **136**, 13606–13609; (*e*) Y. Yin, Y. Dai, H. Jia, J. Li, L. Bu, B. Qiao, X. Zhao and Z. Jiang, *J. Am. Chem. Soc.*, 2018, **140**, 6083–6087; (*f*) T. Shao, X. Ban and Z. Jiang, *Chem. Rec.*, 2023, **23**, e202300122.
17 (*a*) J. Li, M. J. Lear and Y. Hayashi, *Angew. Chem., Int. Ed.*, 2016, **55**, 9060–9064; (*b*) Y. Hayashi, J. Li, H. Asano and D. Sakamoto, *Eur. J. Org. Chem.*, 2018, 675–677.
18 See ESI† for further details.
19 Y. Sun, Z. Qiao, D. Li, J. Ni, J. Wang, P. Wang, N. Song and M. Li, *Org. Lett.*, 2022, **24**, 7944–7949.
20 For compound **20**, 4-thianone was used as the starting ketone.
21 K. Anwar, F. J. A. Troyano, A. H. Abazid, O. El Yarroudi, I. Funes-Ardoiz and A. Gomez-Suarez, *Org. Lett.*, 2023, **25**, 3216–3221.
22 (*a*) M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chem. Rev.*, 2017, **117**, 11796–11893; (*b*) B. Gutmann and C. O. Kappe, *J. Flow Chem.*, 2017, **7**, 65–71; (*c*) M. Baumann, T. S. Moody, M. Smyth and S. Wharry, *Org. Process Res. Dev.*, 2020, **24**, 1802–1813; (*d*) L. Capaldo, Z. Wen and T. Noël, *Chem. Sci.*, 2023, **14**, 4230–4247.
23 (*a*) G. Laudadio, S. Govaerts, Y. Wang, D. Ravelli, H. F. Koolman, M. Fagnoni, S. W. Djuric and T. Noël, *Angew. Chem., Int. Ed.*, 2018, **57**, 4078–4082; (*b*) F. Raymenants, T. M. Masson, J. Sanjosé-Orduna and T. Noël, *Angew. Chem., Int. Ed.*, 2023, **62**, e202308563.
24 (*a*) A. Gavriilidis, A. Constantinou, K. Hellgardt, K. K. Hii, G. J. Hutchings, G. L. Brett, S. Kuhn and S. P. Marsden, *Reaction Chem. Eng.*, 2016, **1**, 595–612; (*b*) H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque and T. Noël, *Chem. Soc. Rev.*, 2016, **45**, 83–117; (*c*) C. A. Hone and C. O. Kappe, *Top. Curr. Chem.*, 2018, **377**, 2.