



Cite this: *Chem. Commun.*, 2023, 59, 14411

Received 18th September 2023,  
Accepted 12th November 2023

DOI: 10.1039/d3cc04597h

rsc.li/chemcomm

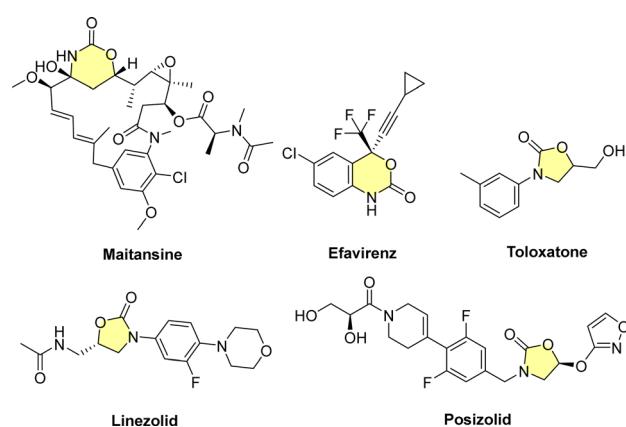
**Utilizing CO<sub>2</sub> as a one-carbon building block in the preparation of high-value chemical entities is a cornerstone of modern organic synthesis. Herein, we exemplify this strategy through a mild, one-pot methodology that gives rapid access to N-heteroaryl substituted 6-, 8- and 9-membered carbamates via CO<sub>2</sub> fixation.**

The United Nations launched seventeen “Sustainable Development Goals (SDGs)” in 2015. The 7th SDG is dedicated to affordable, renewable, efficient and clean energy.<sup>1</sup> In addition, the EU has set targets of at least 55% cuts in greenhouse gas emissions (from 1990 levels), a 32% share for renewable energy and 32.5% improvement in energy efficiency under the European Green Deal scheme.<sup>2</sup> To achieve these goals attaining self-sufficiency in sustainable energy and raw materials, scaling up renewable carbon and circular carbon feedstocks are of note. A net-zero carbon future for synthetic methodology has to be the governing paradigm; thus, development of C<sub>1</sub> chemistry is a key challenge.<sup>3</sup>

Employing carbon dioxide as a building block has gained a prominent place in C<sub>1</sub> chemistry, especially in recent years; on one hand it is a waste that has to be minimized,<sup>4</sup> on the other it is an inexpensive and abundant C<sub>1</sub>-building block.<sup>5–13</sup> However, CO<sub>2</sub> valorization still remains problematic due to its thermodynamic stability and chemical inertness; therefore, highly reactive or sensitive substrates in combination with harsh conditions are needed in many cases. Catalysed coupling of CO<sub>2</sub> with epoxides and aziridines towards polycarbonates/polycarbamates<sup>14</sup> and cyclic carbonates/carbamates<sup>15,16</sup> and photocatalyzed electrophilic addition of CO<sub>2</sub> to enones,<sup>17</sup> represent some of the most recent methodologies using CO<sub>2</sub> as a

feedstock. Cyclic carbamates belong to a particular class of heterocycles where C<sub>1</sub> chemistry based on CO<sub>2</sub> fixation has been extensively employed in order to replace traditional methods that employed the highly toxic phosgene gas and CO.<sup>18,19</sup> These entities, in particular, the *N*-aryl five- or six-membered cyclic carbamates (namely, oxazolidinones and oxazinanones – NAOs), have attracted considerable attention from synthetic chemists not only because they are extremely useful building blocks,<sup>20–22</sup> but also due to the fact that they have been widely utilized as therapeutic agents; there are anti-cancer, antiviral and anti-inflammatory NAOs.<sup>23,24</sup> Most importantly, NAOs have proved highly efficient as broad spectrum Gram-positive antibiotics (Fig. 1).<sup>25</sup> In addition, due to the high significance of medium-size N-heterocycles we still need more tools in our arsenal for their efficient and sustainable construction.<sup>26–29</sup>

The direct fixation of CO<sub>2</sub> in the synthesis of NAOs requires prefunctionalized, highly reactive substrates, *i.e.* propargyl amines<sup>30,31</sup> or *N*-aziridines,<sup>32–34</sup> amino alcohols<sup>35,36</sup> and epoxy amines,<sup>37–39</sup> even in solvent-free procedures.<sup>40</sup> Three-component



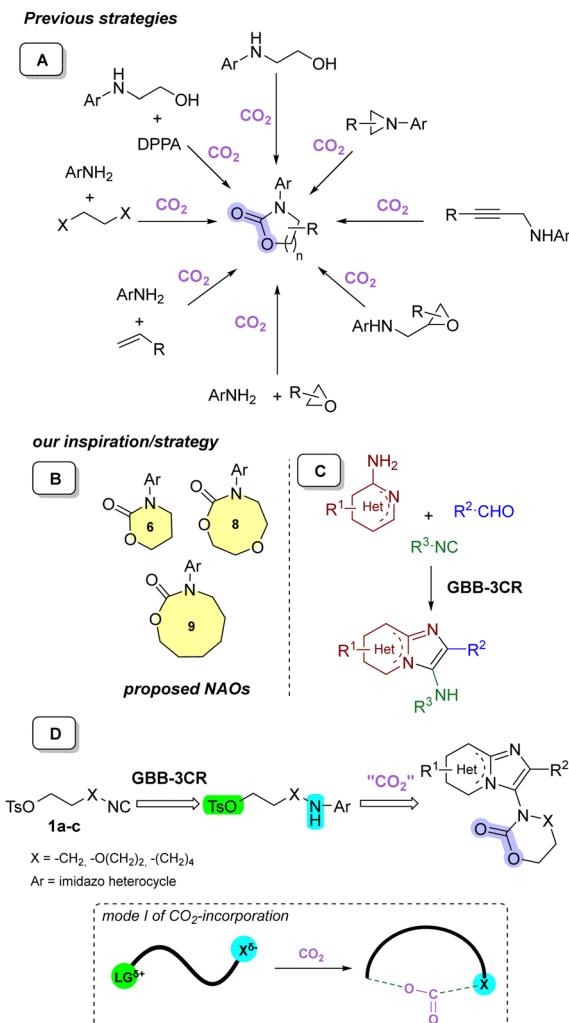
**Fig. 1** Presence of 5- and 6-membered cyclic carbamates in a wide range of therapeutic agents. Maitansine is utilized in antibody–drug conjugates; efavirenz is an antiretroviral drug; toloxatone was an antidepressant; linezolid and posizolid are antibiotics.

<sup>a</sup> Department of Chemistry, University of Crete, Voutes, 70013, Heraklion, Greece.  
E-mail: knocho@uoc.gr

<sup>b</sup> Department of Materials Science & Technology, University of Crete, Voutes, 70013, Heraklion, Greece

† Electronic supplementary information (ESI) available: General procedures, characterization data for products (NMR and MS) and crystallographic data. CCDC 2294775–2294778. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3cc04597h>





**Scheme 1** (A) Representative synthetic strategies accessing NAOs; (B) proposed access to 6-, 8- and 9-membered NAOs using our procedure; (C) the archetypal MCR utilized; (D) employment of three different isocyano alkyl tosylates in the GBB-3CR to yield both the targeted aryl substitution and the suitable intermediate for the  $\text{CO}_2$  fixation substrate (mode I).

reactions involving  $\text{CO}_2$ /haloalkane/anilines,<sup>41,42</sup>  $\text{CO}_2$ /epoxide/anilines<sup>43</sup> and  $\text{CO}_2$ /alkene/anilines<sup>44</sup> have also been reported (Scheme 1A).<sup>45</sup> The main issues with these synthetic processes, which can be divided into three modes of action,<sup>11</sup> are the relatively limited substrate scope; the scarcity of examples bearing aryl groups, especially heteroaryls, the frequent employment of high pressure  $\text{CO}_2$  (>10 bar) and the use of metal catalysts/organocatalysts.<sup>46–48</sup>

In order to overcome these issues, we envisioned providing access to a variety of unprecedented *N*-aryl substituted oxazinanes *via* an efficient and straightforward synthetic pathway. Moreover, to the best of our knowledge some of our target scaffolds, such as the 9-membered *N*-aryl substituted oxazinonanes and the 8-membered *N*-aryl substituted dioxazocanones, are currently unknown entities (Scheme 1B). The Groebke–Blackburn–Bienaymé three component reaction (GBB-3CR)<sup>49–51</sup> was chosen for two main reasons beyond its versatility with three points of

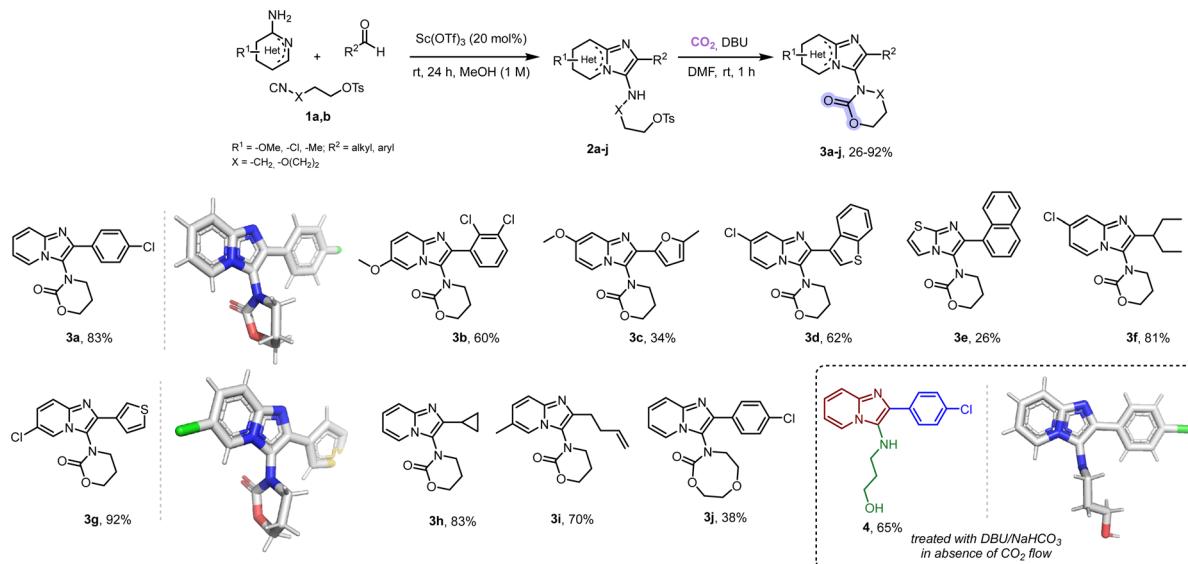
diversification and the ease with which it can be performed (Scheme 1C). First of all, it would give access to a variety of imidazo[1,2-*a*]-heterocycles, including, the privileged scaffold imidazo[1,2-*a*]pyridine, a well-known moiety in many marketed drugs, such as zolpidem, minodronic acid, *etc.*<sup>52</sup> Secondly, we hypothesized that our recently developed isocyano alkyl tosylates **1a–c** in a GBB-3CR<sup>53</sup> can constitute an excellent mode I-substrate<sup>11</sup> with a nucleophilic center ( $\text{X}^{\delta-}$ , highlighted in cyan), which triggers the  $\text{CO}_2$  incorporation, combined with an electrophilic site ( $\text{LG}^{\delta+}$ , highlighted in green) (Scheme 1D).

Hence, after quite some experimentation (Table S1, ESI†), we found that treatment of the GBB-derivatives **2a–j** (used without purification) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and under  $\text{CO}_2$  flow (1 atm) in DMF at room temperature led to the targeted carbamates **3a–j** in only 1 hour with good to very good yields of the desired products (Scheme 2). The substrate scope is indeed broad; aliphatic and (hetero)aromatic aldehydes, various substituted 2-amino pyridines and thiazoles with different isocyano alkyl tosylates **1a,b** all afforded the corresponding carbamates **3** (Schemes 2 and 3). We were also able to access the unprecedented 8-membered dioxazocanone **3j**. Notably, substrates with groups such as cyclopropyl units and double bonds yielded the corresponding carbamates **3h** and **3i**, respectively, in high yields without any side reactions being observed (see mechanism, ESI† Scheme S1). The reaction is scalable, as it was performed on a 5 mmol scale without any issues or a substantial difference in yield. The single crystal structures of **3a** and **3g** reveal a T-shape orientation of the imidazopyridine scaffold with the carbamate. Carbon dioxide fixation was also examined in the absence of any base, however, unreacted starting material was recovered. In addition, when the GBB-3CR adduct **2a** was treated with either DBU or even with carbonates like  $\text{NaHCO}_3$  in the absence of carbon dioxide flow, deprotection of the tosyl group yielding compound **4** was seen. Probably, there is a  $\text{OTs}^{\delta-}$  exchange towards an intermediate carbonate with its subsequent basic hydrolysis to the corresponding alcohol.<sup>54,55</sup>

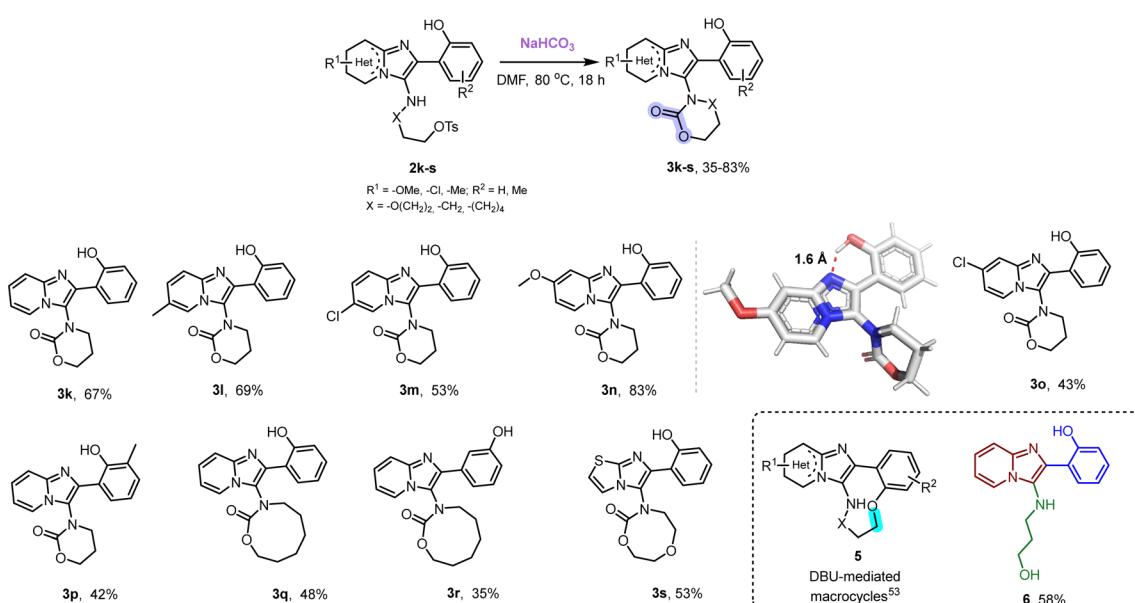
Carbonate salts as  $\text{C}_1$  feedstocks instead of carbon dioxide have rarely been applied to the synthesis of oxazolidinones and especially to the case of oxazinanones.<sup>56–59</sup> Very interestingly, when we employed a salicyl aldehyde as our oxo-component in the GBB-3CR, we noticed that just treatment with  $\text{NaHCO}_3$  in the absence of any metal-catalyst or metal-additive afforded the carbamates **3k–s** in high yields (Scheme 3).

The reaction is also working at rt with slightly worst yields and conversion. *ortho*- and *meta*-substituted salicyl aldehydes yielded the corresponding products; dependent on the chain size of the isocyano alkyl tosylates (**1a–c**), different ring sizes of carbamates were formed including six-membered rings and the difficult to access eight- and nine-membered rings.<sup>60</sup> The single crystal structure of **3n** features not only the T-shape orientation, but also an intramolecular hydrogen bond N–H of 1.6 Å, rigidifying the scaffold. Using an alternative base, such as  $\text{Et}_3\text{N}$ , which does not include a carbonate moiety, led to the deprotection of the tosyl group to yield the corresponding alcohol **6** (see mechanism, ESI† Scheme S2). Treatment with





**Scheme 2** The synthesis of substituted 6- and 8-membered carbamates through a one-pot process. The yields referred to are overall yields after two steps. X-ray structures of **3a** (CCDC 2294778†) and **3g** (CCDC 2294775†) were obtained. Deprotection of the GBB adduct **2a** gave the corresponding alcohol **4**, shown with its single crystal structure (CCDC 2294777†).



**Scheme 3** The synthesis of substituted 6-, 8- and 9-membered carbamates in the presence of substituted salicyl aldehydes in a one-pot process. The yields referred to are overall yields after two steps. X-ray structure of **3n** (CCDC 2294776†) was obtained.

DBU gave rise to medium-sized macrocycles.<sup>53</sup> After treatment of the GBB-3CR adducts without the phenolic group, such as **2a-j**, with NaHCO<sub>3</sub>, we observed deprotection of -OTs group and formation of **4** instead of re-fixing of CO<sub>2</sub> (Scheme 2).

Taking advantage of the structural features of the GBB-3CR scaffolds, we were able to construct a library of 19 diverse N-heteroaryl substituted carbamates with different ring sizes *via* fixing CO<sub>2</sub>. The substrate scope is broad and the C<sub>1</sub> feedstock proceeds either through base-catalyzed reaction under a CO<sub>2</sub> flow (1 atm) or by employing a carbonate salt in the presence of

salicyl aldehydes. The procedures occur rapidly in a one-pot fashion under mild reaction conditions without any metal-catalyst or metal-additive. Single crystal structures reveal the structural conformation of the unprecedented carbamate products.

C. G. N. conceptualized and directed the project. M. F., P. K. A and I. V. performed the syntheses and collected the analytical data. A. P and C. S. determined the single crystal X-ray structures. C. G. N. and M. F. contributed to the manuscript writing. The research project (to C. G. N) was supported by the Hellenic

Foundation for Research and Innovation (H. F. R. I.) under the “2nd Call for H. F. R. I. Research Projects to support Post-Doctoral Researchers” (Project Number: 0911) and Empeirikon Idryma. We acknowledge the mass spectrometry facility of the University of Crete and we would like sincerely thank Dr Tamsyn Montagnon for her valuable remarks.

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- United Nations Department of Economic and Social Affairs (UNDESA) and the Secretariat of the United Nations Framework Convention on Climate Change (UNFCCC), 2022.
- C. Fetting, *The European Green Deal*, 2020.
- X.-F. Wu, P. J. Dyson and B. A. Arndtsen, *J. Org. Chem.*, 2023, **88**, 4891–4893.
- W. Lamb and G. Grassi, *Emissions Gap Report 2022*, 2022.
- S. Dabral and T. Schaub, *Adv. Synth. Catal.*, 2019, **361**, 223–246.
- Q. Liu, L. Wu, R. Jackstell and M. Beller, *Nat. Commun.*, 2015, **6**, 5933.
- T. Sakakura, J.-C. Choi and H. Yasuda, *Chem. Rev.*, 2007, **107**, 2365–2387.
- M. Mikkelsen, M. Jørgensen and F. C. Krebs, *Energy Environ. Sci.*, 2010, **3**, 43–81.
- A. Pinaka and G. C. Vougioukalakis, *Coord. Chem. Rev.*, 2015, **288**, 69–97.
- M. Aresta, A. Dibenedetto and A. Angelini, *Chem. Rev.*, 2014, **114**, 1709–1742.
- S. Wang and C. Xi, *Chem. Soc. Rev.*, 2019, **48**, 382–404.
- S. Pradhan, S. Roy, B. Sahoo and I. Chatterjee, *Chem. – Eur. J.*, 2021, **27**, 2254–2269.
- W. Wang, D. Li, S. Zou and C. Xi, *J. Org. Chem.*, 2023, **88**, 5007–5014.
- T. Kessaratiwon, T. Theerathanagorn, D. Crespy and V. D’Elia, *J. Org. Chem.*, 2023, **88**, 4894–4924.
- T. Fujihara and Y. Tsuji, *Front. Chem.*, 2019, **7**, 1–8.
- H. Koizumi, K. Takeuchi, K. Matsumoto, N. Fukaya, K. Sato, M. Uchida, S. Matsumoto, S. Hamura, J. Hirota, M. Nakashige and J.-C. Choi, *J. Org. Chem.*, 2023, **88**, 5015–5024.
- S. Okumura, K. Torii and Y. Uozumi, *Org. Lett.*, 2023, **25**, 5226–5230.
- L. Cotarca and H. Eckert, *Phosgenations: A Handbook*, 2005.
- M. E. Dyen and D. Swern, *Chem. Rev.*, 1967, **67**, 197–246.
- P. Adams and F. A. Baron, *Chem. Rev.*, 1965, **65**, 567–602.
- S. G. Davies, A. C. Garner, P. M. Roberts, A. D. Smith, M. J. Sweet and J. E. Thomson, *Org. Biomol. Chem.*, 2006, **4**, 2753–2768.
- C. R. McElroy, F. Aricò, F. Benetollo and P. Tundo, *Pure Appl. Chem.*, 2011, **84**, 707–719.
- P. Prasher, T. Mall and M. Sharma, *Drug Dev. Res.*, 2023, **84**, 397–405.
- G. F. S. Fernandes, C. B. Scarim, S.-H. Kim, J. Wu and D. Castagnolo, *RSC Med. Chem.*, 2023, **14**, 823–847.
- T. A. Mukhtar and G. D. Wright, *Chem. Rev.*, 2005, **105**, 529–542.
- F. Hu, X. Li, Z. Ding, L. Wang, C. Ge, L. Xu and S.-S. Li, *ACS Catal.*, 2022, **12**, 943–952.
- G. Bai, F. Dong, L. Xu, Y. Liu, L. Wang and S.-S. Li, *Org. Lett.*, 2019, **21**, 6225–6230.
- S.-S. Li, L. Zhou, L. Wang, H. Zhao, L. Yu and J. Xiao, *Org. Lett.*, 2018, **20**, 138–141.
- X. Ma, X. Zhang, J. M. Awad, G. Xie, W. Qiu and W. Zhang, *Green Chem.*, 2019, **21**, 4489–4494.
- M. Yoshida, Y. Komatsuzaki and M. Ihara, *Org. Lett.*, 2008, **10**, 2083–2086.
- J. Hu, J. Ma, Q. Zhu, Z. Zhang, C. Wu and B. Han, *Angew. Chem., Int. Ed.*, 2015, **54**, 5399–5403.
- A. W. Miller and S. T. Nguyen, *Org. Lett.*, 2004, **6**, 2301–2304.
- D. Adhikari, A. W. Miller, M.-H. Baik and S. T. Nguyen, *Chem. Sci.*, 2015, **6**, 1293–1300.
- P. Sonzini, C. Damiano, D. Intrieri, G. Manca and E. Gallo, *Adv. Synth. Catal.*, 2020, **362**, 2961–2969.
- T. Niemi, I. Fernández, B. Steadman, J. K. Mannisto and T. Repo, *Chem. Commun.*, 2018, **54**, 3166–3169.
- J. Paz, C. Pérez-Balado, B. Iglesias and L. Muñoz, *J. Org. Chem.*, 2010, **75**, 3037–3046.
- J. Rintjema, R. Epping, G. Fiorani, E. Martín, E. C. Escudero-Adán and A. W. Kleij, *Angew. Chem., Int. Ed.*, 2016, **55**, 3972–3976.
- Y. Lee, J. Choi and H. Kim, *Org. Lett.*, 2018, **20**, 5036–5039.
- Y. Toda, M. Shishido, T. Aoki, K. Sukegawa and H. Suga, *Chem. Commun.*, 2021, **57**, 6672–6675.
- S. Arshadi, A. Banaei, S. Ebrahimiasl, A. Monfared and E. Vessally, *RSC Adv.*, 2019, **9**, 19465–19482.
- T. Niemi, J. E. Pereira-Buceta, I. Fernández, O.-M. Hiltunen, V. Salo, S. Rautiainen, M. T. Räisänen and T. Repo, *Chem. – Eur. J.*, 2016, **22**, 10355–10359.
- C. Mei, Y. Zhao, Q. Chen, C. Cao, G. Pang and Y. Shi, *ChemCatChem*, 2018, **10**, 3057–3068.
- B. Wang, E. H. M. Elageed, D. Zhang, S. Yang, S. Wu, G. Zhang and G. Gao, *ChemCatChem*, 2014, **6**, 278–283.
- L. Feng, X. Li, C. Xu and S. M. Sadeghzadeh, *Catal. Lett.*, 2020, **150**, 1729–1740.
- L. Wang, C. Qi, W. Xiong and H. Jiang, *Chin. J. Catal.*, 2022, **43**, 1598–1617.
- J. Ye, L. Song, W. Zhou, T. Ju, Z. Yin, S. Yan, Z. Zhang, J. Li and D. Yu, *Angew. Chem., Int. Ed.*, 2016, **55**, 10022–10026.
- Z. Zhang, J. Ye, D. Wu, Y. Zhou and D. Yu, *Chem. – Asian J.*, 2018, **13**, 2292–2306.
- J.-H. Ye, T. Ju, H. Huang, L.-L. Liao and D.-G. Yu, *Acc. Chem. Res.*, 2021, **54**, 2518–2531.
- K. Groebke, L. Weber and F. Mehlin, *Synlett*, 1998, 661–663.
- C. Blackburn, B. Guan, P. Fleming, K. Shiosaki and S. Tsai, *Tetrahedron Lett.*, 1998, **39**, 3635–3638.
- H. Bienaymé and K. Bouzid, *Angew. Chem., Int. Ed.*, 1998, **37**, 2234–2237.
- A. Boltjes and A. Dömling, *Eur. J. Org. Chem.*, 2019, 7007–7049.
- M. Fragkiadakis, P. Anastasiou, M. Zingiridis, M. E. Triantafyllou-Rundell, A. Reyes Romero, C. C. Stoumpos and C. G. Neochoritis, *J. Org. Chem.*, 2023, **88**, 12709–12715.
- Y. R. Jorapur and D. Y. Chi, *J. Org. Chem.*, 2005, **70**, 10774–10777.
- S. B. Singh, D. E. Kaelin, J. Wu, L. Miesel, C. M. Tan, P. T. Meinke, D. Olsen, A. Lagrutta, P. Bradley, J. Lu, S. Patel, K. W. Rickert, R. F. Smith, S. Soisson, C. Wei, H. Fukuda, R. Kishii, M. Takei and Y. Fukuda, *ACS Med. Chem. Lett.*, 2014, **5**, 609–614.
- P. D. G. Greenwood and J. Waser, *Eur. J. Org. Chem.*, 2019, 5183–5186.
- H. Jin, Y. Yang, J. Jia, B. Yue, B. Lang and J. Weng, *RSC Adv.*, 2014, **4**, 26990–26992.
- Y. Osa, Y. Hikima, Y. Sato, K. Takino, Y. Ida, S. Hirono and H. Nagase, *J. Org. Chem.*, 2005, **70**, 5737–5740.
- L. Fehr, L. Sewald, R. Huber and M. Kaiser, *Eur. J. Org. Chem.*, 2023, e202300135.
- T. Huber, R. E. Wildermuth and T. Magauer, *Chem. – Eur. J.*, 2018, **24**, 12107–12120.

