


 Cite this: *Chem. Commun.*, 2023, 59, 2497

 Received 3rd January 2023,  
 Accepted 30th January 2023

DOI: 10.1039/d3cc00046j

rsc.li/chemcomm

## Transient imine as a directing group for the Pd-catalyzed anomeric C(sp<sup>3</sup>)-H arylation of 3-aminosugars†

 Juba Ghouilem,<sup>a</sup> Sokna Bazzi,<sup>a</sup> Nicolas Grimblat,<sup>id</sup><sup>b</sup> Pascal Retailleau,<sup>c</sup>  
 Vincent Gandon<sup>id</sup><sup>bd</sup> and Samir Messaoudi<sup>id</sup><sup>\*a</sup>

The first example of Pd(II)-catalyzed anomeric arylation of 3-aminosugars is reported by using an L,X-type transient directing group (TDG) approach combined with an external 2-pyridone ligand. The released free amine was *in situ* transformed into an azide function, which was then exploited in a CuAAC to increase the molecular complexity and prepare a variety of complex substituted C3-triazolo C-glycosides in good yields.

The aryl C-glycoside motif, which is found in many natural products and drug candidates, has attracted tremendous attention in medicinal chemistry and drug discovery.<sup>1</sup> These glycomimetics often feature enhanced resilience to enzymatic and hydrolytic cleavage under biological conditions compared to their O/N-glycoside congeners.<sup>2</sup> In particular, aryl C-glycosides bearing a nitrogen atom at the C3 position of the sugar moiety (e.g. 3-amino or 3-triazolo C-glycosides) are one of the most important families of C-glycosides found in natural bioactive compounds.<sup>3</sup> These glycosides have emerged as a privileged class with diverse potential applications (Fig. 1).

Classical methods for the synthesis of aryl C-glycosides have largely relied on the use of metal-catalyzed cross-coupling strategies involving the use of stoichiometric organometallic coupling partners.<sup>3f-h</sup> The persistent need from drug discovery programs to elaborate complex aryl C-glycosides has led to pioneering developments in the field of C-H functionalization.<sup>4</sup> This approach, which avoids the preactivation of the coupling

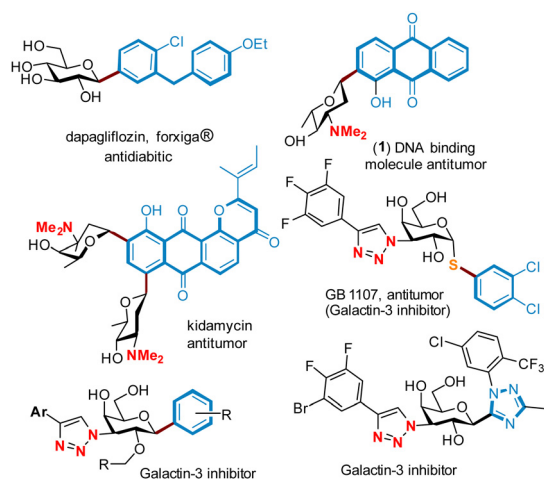


Fig. 1 Aryl C-glycoside-based bioactive molecules.

partners, has led to new paradigms for the synthesis of aryl C-glycosides. In this context, several groups have reported elegant methods by applying metal-catalyzed activation of C(sp<sup>2</sup>)-H bonds. However, methods involving a direct activation of the less reactive C(sp<sup>3</sup>)-H bonds of the sugar partners are rare.<sup>5</sup> Thus far, precise structural design and selective modification of glycosides remain challenging tasks. Recently, Ackermann's group<sup>5e</sup> and our group<sup>5d</sup> reported independently two studies in which the anomeric, as well as C-3 positions of the sugar moieties, were functionalized selectively through a Pd-catalyzed C(sp<sup>3</sup>)-H activation reaction (Scheme 1A and B). Nevertheless, these strategies require synthetic steps to prepare the activated sugar substrate and remove the directing group. To address this issue, we sought to develop a transient imine directing group approach<sup>6</sup> for the Pd-catalyzed anomeric C(sp<sup>3</sup>)-H arylation of 3-aminosugars to access aryl C-glycosides in an expedient way (Scheme 1C).

We hypothesized that the stereoselective introduction of the aryl moiety could be accomplished through a C(sp<sup>3</sup>) arylation of the *in situ* generated axial imine intermediate (A, Fig. 2) as an

<sup>a</sup> Université Paris-Saclay, CNRS, BioCIS, 92290, Châtenay-Malabry, France.

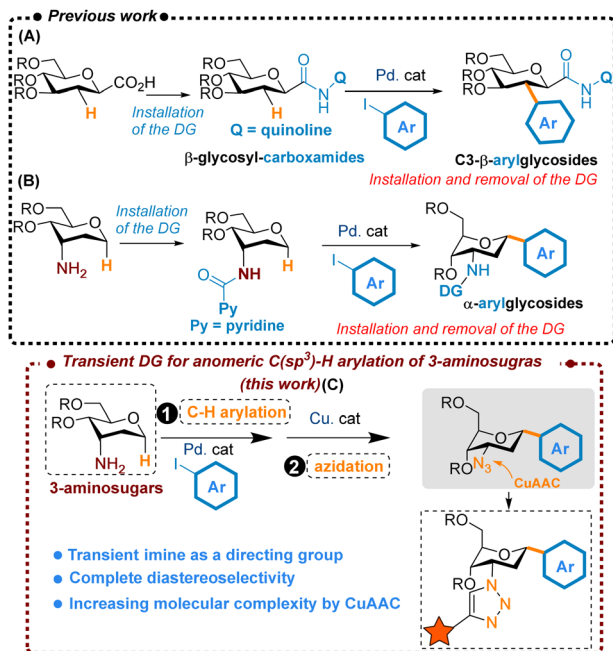
E-mail: samir.messaoudi@universite-paris-saclay.fr; Tel: +(33) 0146835887

<sup>b</sup> Laboratoire de Chimie Moléculaire (LCM), CNRS UMR 9168, Ecole Polytechnique, Institut Polytechnique de Paris, route de Saclay, Palaiseau 91120, France

<sup>c</sup> Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Saclay, avenue de la terrasse, Gif-sur-Yvette 91198, France

<sup>d</sup> Université Paris-Saclay, CNRS, ICMO, 91405, Orsay cedex, France

 † Electronic supplementary information (ESI) available: General experimental procedures for the starting materials and <sup>1</sup>H and <sup>13</sup>C spectra for all new compounds. CCDC 2225278 and 2225279. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3cc00046j>

Scheme 1 Strategies to access aryl C-glycosides.

L,X-type transient directing group, to direct the palladium(II) catalyst selectively to the  $\alpha$ -anomeric C(sp<sup>3</sup>)-H bond through a bidentate coordinating mechanism (intermediates **B** and **C**). Before testing the coupling experimentally, a computational study of the key CMD step was performed at the M06//6-311++G(d,p)/SDD level of theory in order to evaluate the free energy demand. It was found that when the axial imine pyridol directing group was used ( $R = \text{Ac}$ ), the CMD transition state (CMD-TS) that gives rise to the  $\alpha$ -configuration necessitates a barrier of 19.71 kcal mol<sup>-1</sup> (Fig. 2), which is comparable to our previous reported study with the use of a classical directing group strategy.<sup>5d</sup>

We anticipated at this stage that the final C-aryl glycosides bearing a free amine will be extremely polar and tricky to purify,

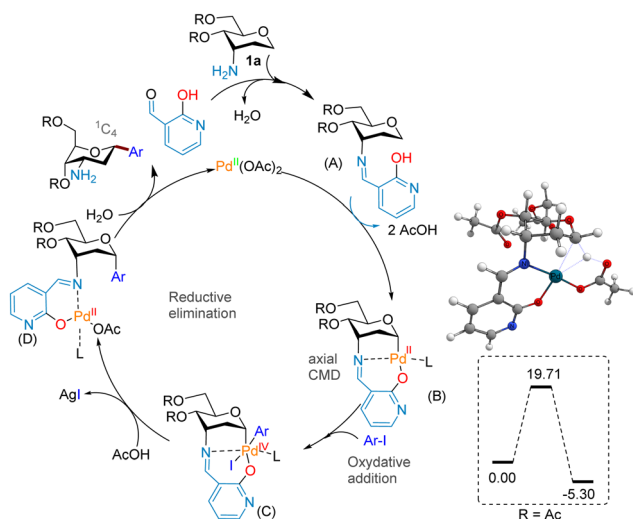


Fig. 2 Proposed mechanism and DFT calculations.

Table 1 Survey of the conditions for the anomeric arylation of **1a-c** with **2a**<sup>a</sup>

4-iodotoluene **2a** (3 equiv)

$\text{Pd}(\text{OAc})_2$  (10 mol%), TDG (50 mol%), L (50 mol%)  
CuSO<sub>4</sub> · H<sub>2</sub>O (xx mol%), K<sub>2</sub>CO<sub>3</sub> (xx equiv)  
MeOH, RT, 4 h  
[Ag] (2 equiv), H<sub>2</sub>O (10 equiv), HFIP/AcOH (19:1) 0.1M, 16h, 90 °C  
HCl N-SO<sub>2</sub>N<sub>3</sub>

**1a** ( $R = \text{Bn}$ )  
**1b** ( $R = \text{Ac}$ )  
**1c** ( $R = \text{benzylidene}$ ) (1 equiv)

1. C-H arylation; 2. azidation

3a

TDGs

TDG1, TDG2, TDG3, TDG4, TDG5

Ligands

L1, L2, L3, L4, L5, L6, L7, L8

Entry	TDG	Ligand	[Pd]	[Ox]	Yield <sup>b</sup> (%)
1	TDG1	L1	Pd(OAc) <sub>2</sub>	AgTFA	27
2	TDG2	L1	Pd(OAc) <sub>2</sub>	AgTFA	0
3	TDG3	L1	Pd(OAc) <sub>2</sub>	AgTFA	23
4	TDG4	L1	Pd(OAc) <sub>2</sub>	AgTFA	32
5	TDG5	L1	Pd(OAc) <sub>2</sub>	AgTFA	0
6	TDG4	L2	Pd(OAc) <sub>2</sub>	AgTFA	34
7	TDG4	L3	Pd(OAc) <sub>2</sub>	AgTFA	41
8	TDG4	L4	Pd(OAc) <sub>2</sub>	AgTFA	43
9	TDG4	L5	Pd(OAc) <sub>2</sub>	AgTFA	42
10	TDG4	L6	Pd(OAc) <sub>2</sub>	AgTFA	37
11	TDG4	L7	Pd(OAc) <sub>2</sub>	AgTFA	51
12	TDG4	L8	Pd(OAc) <sub>2</sub>	AgTFA	40
13	TDG4	—	Pd(OAc) <sub>2</sub>	AgTFA	27
14	TDG4	L7	Pd(OAc) <sub>2</sub>	Cu(TFA) <sub>2</sub>	28
15	TDG4	L7	Pd(OAc) <sub>2</sub>	AgOAc	0
16	TDG4	L7	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> O	0
17	TDG4	L7	Pd(OAc) <sub>2</sub>	AgOMs	0
18	TDG4	L7	PdCl <sub>2</sub>	AgTFA	20
19	TDG4	L7	Pd(OAc) <sub>2</sub> /Pd(TFA) <sub>2</sub>	AgTFA	42
20	TDG4	L7	Pd(OAc) <sub>2</sub>	AgTFA	51 <sup>c</sup>

<sup>a</sup> Reactions were conducted with substrate **1a-c** (0.4 mmol), **2a** (1.2 mmol), Pd. cat. (10 mol%), TDG (50 mol%), L (50 mol%), Ag-source (2 equiv.), and H<sub>2</sub>O (10 equiv.) in a mixture of HFIP:AcOH (19:1) [0.1 M] at 90 °C for 16 h. <sup>b</sup> Yield of isolated product **3a**. <sup>c</sup> 30 min heating under microwave irradiation.

so to ease their isolation and analysis, we envisioned transforming the released free amine products without purification into azides. The later could then undergo a CuAAC process to increase the molecular complexity and prepare a variety of complex substituted C3-triazolo C-glycosides. This approach is conceptually attractive in terms of diversifying the C-aryl glycoside pharmacophore, aiming to identify novel scaffolds of biological interest.

To initiate this study, we selected O-protected 3-amino sugars **1a-c** and 4-iodotoluene **2a** as models. To facilitate isolation and purification of the desired C3-azido C-glycosides and reduce the generation of waste, we decided to examine both transformations in a one-pot manner as depicted in Table 1: (i) the Pd-catalyzed C(sp<sup>3</sup>) activation directed by the *in situ* generated transient imine group and (ii) the Cu-catalyzed azidation



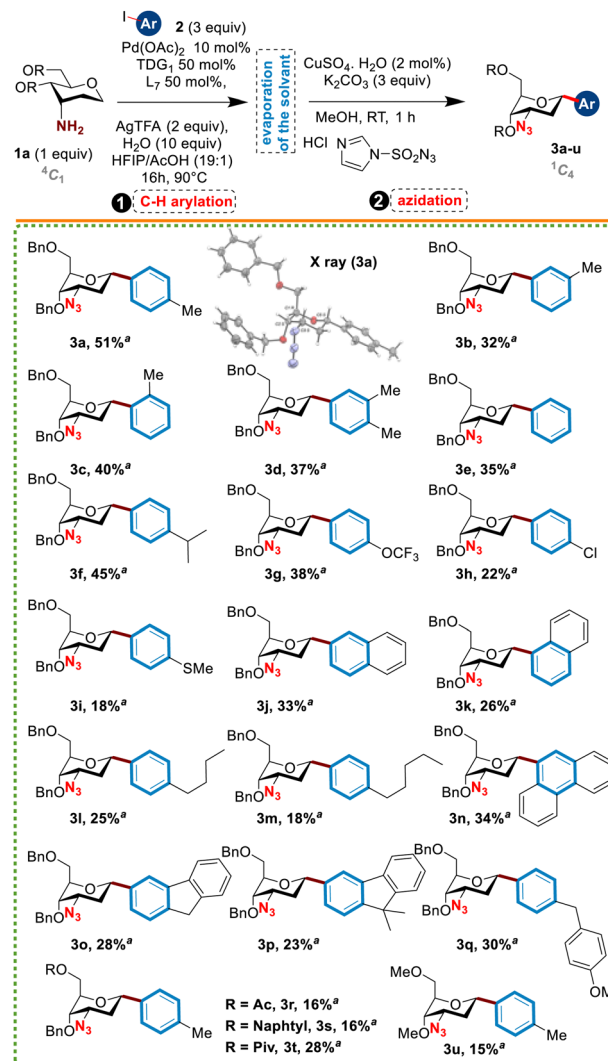
of the released free amine. Representative results are summarized in Table 1.

In preliminary experiments, the C(sp<sup>3</sup>)-arylation was examined first by using Pd(OAc)<sub>2</sub> as a catalyst (10 mol%), TDG1 (50 mol%), L1 (50 mol%) as a ligand, AgTFA (2 equiv.) and H<sub>2</sub>O (10 equiv.) in a mixture of HFIP/AcOH (19:1 ratio, 0.1 M) at 110 °C for 16 h. The reaction mixture was monitored by LCMS and once the disappearance of the starting material was observed and the formation of the 3-amino *C*-tolyl glycoside intermediate was detected, the diazo-transfer reagent imidazole-1-sulfonyl azide<sup>7</sup> (3 equiv.), CuSO<sub>4</sub>·H<sub>2</sub>O (10 mol%) and K<sub>2</sub>CO<sub>3</sub> (3 equiv.), was added to the mixture which was stirred for two additional hours at RT. Under these conditions, no desired product was detected by LCMS analysis when both starting substrates **1b** and **1c** in which the hydroxyl functions were protected by acetyl or benzylidene groups, were used (Table 1). However, the use of *O*-benzylated sugar **1a** led to the formation of the desired C3-azido *C*-aryl glycoside in a modest 27% yield for the two steps (entry 1). X-ray analysis clearly showed the  $\alpha$ -configuration of the aryl group and the <sup>1</sup>C<sub>4</sub> conformation of the sugar nucleus, demonstrating the high diastereoselectivity of this reaction. This first set of results clearly demonstrated that the choice of the protecting group of the sugar moiety plays a pivotal role in this reaction.

It is worth noting that all our attempts to isolate the 3-amino *C*-tolyl glycoside intermediate [**3a-NH2**] were not an easy task and revealed that this aryl *C*-glycoside displays unexpected photo-physical properties. Precisely, no absorbance at ~240 nm and at ~360 nm wavelength was detected despite the presence of three aromatic nuclei (ESI<sup>†</sup>). This issue renders the monitoring of the reaction by LCMS or TLC much more complicated, thus prompting us to continue our study by using the initial approach involving the *in situ* transformation of the amino group to an azide.

Knowing that the azidation step works quantitatively, we screened several parameters (Pd-catalyst, TDG, ligand, base, solvent, temperature, and reaction time, Table 1) to increase the yield of the first steps. The screening of various transient directing groups revealed that TDG3 and TDG4 display the same reactivity as TDG1 (23% and 32% yields, respectively) while quinoline benzaldehyde TDG2 or TDG5 were completely unreactive. A characteristic aspect of the developed method lies in the pyridone ligands used for this coupling. 5-Nitro-pyridone L2 was firstly examined, resulting in a similar yield as with 5-CF<sub>3</sub> pyridone L1 (34% vs. 32% yields). Substitution of the C3 position of the pyridine with electron-withdrawing groups further improved the yield up to 51% (L3–L7), except for L6, which produced **3a** in a yield similar to L1. Not surprisingly, only a 25% yield of **3a** was obtained when the reaction was performed without ligand. Various other parameters were examined (Pd-catalyst, source of Ag, other oxidants, reaction temperature) but without success to improve the yield. Finally, we found that the arylation/azidation occurred smoothly with 51% yield when using Pd(OAc)<sub>2</sub> as a catalyst (10 mol%), TDG4 (50 mol%), L7 as the ligand (50 mol%), AgTFA (2 equiv.), and H<sub>2</sub>O (10 equiv.) as an additive in a mixture of HFIP:AcOH (19:1) at 90 °C for 16 h (entry 11). Interestingly, the reaction time was reduced to only 30 min when the coupling was performed

Table 2 Scope of the coupling of **1a** with various aryl iodides **2** followed by the azidation<sup>a</sup>

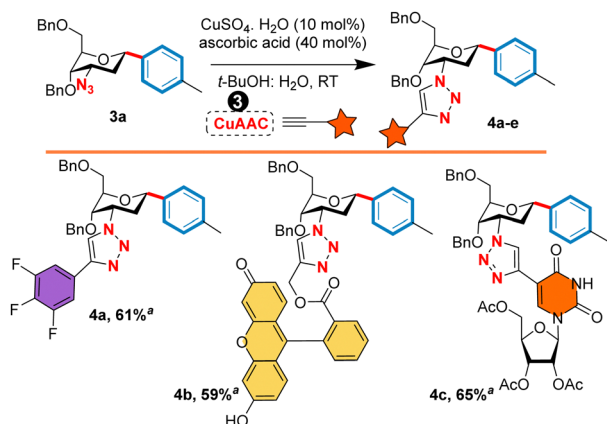


<sup>a</sup> Reactions were performed in a flame dried re-sealable tube using sugar **1a** (0.4 mmol), ArI (1.2 mmol), Pd(OAc)<sub>2</sub> (10 mol%), TDG (50 mol%), L (50 mol%), AgTFA (2 equiv.), and H<sub>2</sub>O (10 equiv.) in a mixture of HFIP:AcOH (19:1) [0.1 M] at 90 °C for 16 h. <sup>a</sup> Yield of isolated product.

under microwave irradiation (entry 20). Of note, the use of a Pd-catalyst and TDG was necessary to achieve this transformation since no reaction took place when the coupling was conducted in their absence.

Motivated by these results, we next explored the scope of this new anomeric arylation procedure of **1a** with aryl iodides. At first, we were pleased to see that various aryl iodides bearing diverse functions such as -OMe, -Me, -SMe, -Cl, -OCF<sub>3</sub>, and -alkyl chain (butyl or pentyl) reacted smoothly with **1a** to afford the desired aryl *C*-glycosides **3a-w** in moderate to good yields and exclusive  $\alpha$ -anomeric stereoselectivity (Table 2). Surprisingly, the presence of an *ortho* substituent at the aromatic ring of the coupling partner did not affect the reaction process, as compound **3c** was obtained in a satisfactory yield. Moreover, bulky polycyclic aromatic partners such as fluorene and phenanthrene





**Scheme 2** Reactions were performed in a flame dried re-sealable tube using **3a** (0.4 mmol), alkyne (0.4 mmol), CuSO<sub>4</sub>·H<sub>2</sub>O (0.04 mmol, 10 mol%), ascorbic acid (40 mol%) in t-BuOH:H<sub>2</sub>O (2:1) 0.1 M at RT. <sup>a</sup> Yield of isolated product.

were also tolerated under these conditions (compounds **3n-p**). Finally, the synthetic utility of this methodology was demonstrated by the synthesis of the C-glycoside **3q** as an analog of the dapagliflozin drug (FORXIGAs) used to treat type 2 diabetes (Fig. 1). Although the yields remained modest due to the unreacted anomeric C–H bond of sugars of type **1a**, this constitutes the first example of intermolecular C(sp<sup>3</sup>)–H functionalization using a transient directing group.

It is worth noting that the role of protecting groups turned out to be crucial for this reaction, particularly the primary alcohol at the C6 position of the sugar. Low yields were obtained when acetyl and naphthyl groups were used instead of benzyl one (compounds **3r** and **3s**); however, the pivalyl group seems to be better (compound **3t**, 28% yield). Furthermore, switching from benzyl- to methoxyl-protecting groups led to the desired compound **3u** in only a 15% yield.

Another important application of this method is the orthogonal preparation of a series of complex 3-triazolo-aryl C-glycosides through the simple copper-catalyzed azide-alkyne cycloaddition (CuAAC reaction).<sup>8</sup> Different motifs were introduced at the azide function such as the trifluorinated benzene **4a**, which can be considered as a direct analog of GB1107 (Fig. 1).

In addition, other triazolo aryl C-glycosides bearing biologically valuable functions such as a fluorescein glycoconjugate **4b**, as well as the uridine-glycoconjugate **4c** were synthesized in 59% and 65% yields, respectively (Scheme 2).

In conclusion, we report the first example of intermolecular anomeric C(sp<sup>3</sup>)–H functionalization using a transient directing group. This approach obviates the need for installation and removal of the directing group and furnishes in one pot manner a diverse collection of synthetically valuable 3-azido aryl C-glycosides with excellent  $\alpha$ -selectivity. Moreover, the azide function allowed us to increase the structural complexity of this series of glycosides through a CuAAC reaction. Notably,

the facile nature of this reaction has successfully been applied to the synthesis of various substituted triazolo aryl C-glycosides.

The authors acknowledge the support of this project by CNRS, Universite Paris-Saclay and the ANR SelfSuCHI (ANR-18-CE07-0012).

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- (a) J. Štambaský, M. Hocek and P. Kočovský, *Chem. Rev.*, 2009, **109**, 6729; (b) E. De Clercq, *J. Med. Chem.*, 2016, **59**, 2301; (c) Y. Yang and B. Yu, *Chem. Rev.*, 2017, **117**, 12281; (d) K. Kitamura, Y. Ando, T. Matsumoto and K. Suzuki, *Chem. Rev.*, 2018, **118**, 1495; (e) É. Bokor, S. Kun, D. Goyard, M. Tóth, J.-P. Praly, S. Vidal and L. Somsák, *Chem. Rev.*, 2017, **117**(3), 1687; (f) C.-F. Liu, *Molecules*, 2022, **27**, 7439.
- (a) R. Duval and C. Duplais, *Nat. Prod. Rep.*, 2017, **34**, 161; (b) C. Jaramillo and S. Knapp, *Synthesis*, 1994, 1; (c) K. Kitamura, U. Ando, T. Matsumoto and K. Suzuki, *Angew. Chem., Int. Ed.*, 2014, **53**, 1258.
- (a) T. Cañeque, F. Gomes, T. Thi Mai, G. Maestri, M. Malacria and R. Rodriguez, *Nat. Chem.*, 2015, **7**, 744; (b) Y. Chang, L. Xing, Q. Sun, S. Liang, T. Liu, X. Zhang, T. Zhu, B. A. Pfeifer, Q. Che and G. Zhang, *J. Nat. Prod.*, 2020, **83**, 2749; (c) G. D. A. Martin, L. T. Tan, P. R. Jensen, R. E. Dimayuga, C. R. Fairchild, C. Raventos-Suarez and W. Fenical, *J. Nat. Prod.*, 2007, **70**, 1406; (d) H. Huang, T. Yang, X. Ren, J. Liu, Y. Song, A. Sun, J. Ma, B. Wang, Y. Zhang and C. Huang, *J. Nat. Prod.*, 2012, **75**, 202; Y. Song, G. Liu, J. Li, H. Huang, X. Zhang, H. Zhang and J. Ju, *Mar. Drugs*, 2015, **13**, 1304; (e) K. Toshima, H. Ouchi, Y. Okazaki, T. Kano, M. Moriguchi, A. Asai and S. Matsumura, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2748; (f) K. Toshima, Y. Maeda, H. Ouchi, A. Asaib and S. Matsumura, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2163; (g) C. Liu, W. Wang, B. J. A. Elsworth and A. Regueiroren, WO/2021/242982, 2021; (h) C. Liu, P. Rao Jalagam, J. Feng, W. Wang, T. Raja, M. Reddy Sura, R. K. V. L. P. Manepalli, B. Reddy Alipedi, S. Medavarapu, S. K. Nair, V. Muthalagu, R. Natesan, A. Gupta, B. Beno, M. Panda, K. Ghosh, J. K. Shukla, H. Sale, P. Haldar, N. Kalidindi, D. Shah, D. Patel, A. Mathur, B. A. Ellsworth, D. Cheng and A. Regueiro-Ren, *J. Med. Chem.*, 2022, **65**, 11084.
- J. Ghouilem, M. de Robichon, F. Le Bideau, A. Ferry and S. Messaoudi, *Chem. – Eur. J.*, 2021, **27**, 491.
- (a) N. Probst, G. Grelier, N. Ghermani, V. Gandon, M. Alami and S. Messaoudi, *Org. Lett.*, 2017, **19**, 5038; (b) N. Probst, G. Grelier, S. Dohaoui, M. Alami, V. Gandon and S. Messaoudi, *ACS Catal.*, 2018, **8**, 7781; (c) J. Ghouilem, R. Franco, P. Retailleau, M. Alami, V. Gandon and S. Messaoudi, *Chem. Commun.*, 2020, **56**, 1715; (d) J. Ghouilem, C. Tran, N. Grimblat, P. Retailleau, M. Alami, V. Gandon and S. Messaoudi, *ACS Catal.*, 2021, **11**, 1818; (e) J. Wu, A. Kopp and L. Ackermann, *Angew. Chem., Int. Ed.*, 2022, **61**, e202114993.
- For recent reviews, see: (a) J. I. Higham and J. A. Bull, *Org. Biomol. Chem.*, 2020, **18**, 7291; (b) M. I. Lapuh, S. Mazeh and T. Besset, *ACS Catal.*, 2020, **10**, 12898; (c) C. Jacob, B. U. W. Maes and G. Evans, *Chem. – Eur. J.*, 2021, **27**, 13899; (d) P. Gandeepan and L. Ackermann, *Chemistry*, 2018, **4**, 199.
- (a) S. P. Green, K. M. Wheelhouse, A. D. Payne, J. P. Hallett, P. W. Miller and J. A. Bull, *Org. Process Res. Dev.*, 2020, **24**, 67; (b) A. Vasella, C. Witzig, J.-L. Chiara and M. Martin-Lomas, *Helv. Chim. Acta*, 1991, **74**, 2073; (c) P. B. Alper, S.-C. Hung and C.-H. Wong, *Tetrahedron Lett.*, 1996, **37**, 6029; (d) P. T. Nyffeler, C.-H. Liang, K. M. Koeller and C.-H. Wong, *J. Am. Chem. Soc.*, 2002, **124**, 10773.
- (a) N. Nebra and J. García-Álvarez, *Molecules*, 2020, **25**, 2015; (b) E. Haldon, M. C. Nicasio and P. J. Pérez, *Org. Biomol. Chem.*, 2015, **13**, 9528–9550; (c) D. H. Hilko, L. F. Bornaghi and S.-A. Poulsen, *J. Org. Chem.*, 2018, **83**, 11944; (d) G. G. Crisp and B. L. Flynn, *J. Org. Chem.*, 1993, **58**, 6614; (e) K. Peterson, R. Kumar, O. Stenström, P. Verma, P. R. Verma, M. Hakansson, B. Kahl-Knutsson, F. Zetterberg, H. Leffler, M. Akke, D. T. Logan and U. J. Nilsson, *J. Med. Chem.*, 2018, **61**(3), 1164.

