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Iron-catalyzed C–O bond functionalization of butyrolactam derivatives with various N-/C-nucleophiles†

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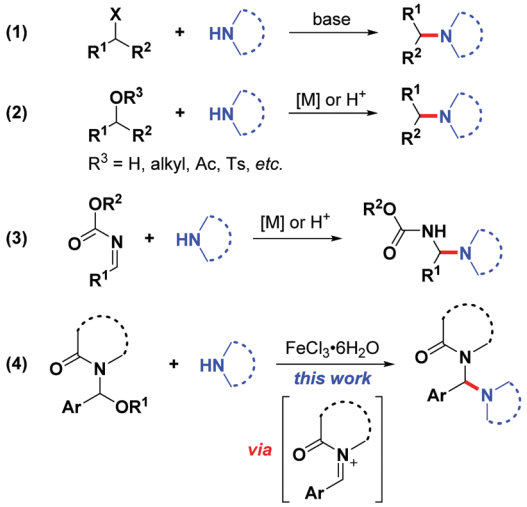
An efficient iron-catalyzed C–O bond functionalization of butyrolactam derivatives with various N-/C-nucleophiles to enable the synthesis of pharmaceutically important butyrolactam derivatives has been developed here. The versatility of the present methodology is demonstrated for direct amination and carbonation by using a variety of sulfonamides, amines, amides, indoles, and 1,3-dicarbonyl compounds under mild conditions. The reaction also showed a wide substrate scope and synthetic simplicity. Additionally, only alcohol was produced as the by-product in all cases.

Introduction

Amination is a direct and powerful strategy for the construction of new C–N bonds, which feature in the synthesis of various pharmaceuticals and fine chemicals.[1] Generally, this transformation is performed with pre-activating agents, which are problematic due to over alkylation and the production of stoichiometric amounts of waste (Scheme 1, **1**).[2] Recently, considerable achievements towards the direct catalytic amination of alcohols have been made (Scheme 1, **2**).[3] However, this transition metal-catalyzed hydrogen autotransfer process suffered from several limitations such as extra additives, harsh reaction conditions, metal residue and narrow substrate scope.[4] On the other hand, while most of the subclasses of stabilized carbenium ions (from benzyl,[5] allyl alcohols,[6] benzylic ethers[7] and acetates[8] *etc.*) have gained prominence for *N*-alkylation, similar reactions using *N*-acyliminium ions remain less explored (Scheme 1, **3**). In addition, previous works focus on the reaction of intra- or intermolecular *N*-acyliminium ions (α-amidoalkylation),[9] which results in the formation of new C–C bonds; however, dealing with coupling with N-centered nucleophiles which leads to the construction of C–N bonds will be challenging.[10,11]

Butyrolactam has been found to be a privileged structural unit in the field of natural products and other biologically active molecules.[12] Considering the wide applications of nitrogen-containing intermediates, especially of *gem*-diamino derivatives[12c,d,e,f,13] (Fig. 1), in drug design and discovery, the exploration of new methods for the incorporation of this important heterocyclic core into *N*,*N*-aminals has become highly desirable, and the typical structure can be depicted as compound **I**. However, existing approaches (Curtius or Hofmann-type rearrangements)[13b,14] to aminal products of this type significantly lack efficiency (multistep and low overall yield). Although Brønsted acid[15] or transition-metal[16] catalyzed amidation of *N*-acylimines is known (Scheme 1, **4**), the substrate scope of imines is limited to carboxylic acid derivatives, and related works are rarely reported to date. To the best of our knowledge, the general intermolecular catalytic addition of N-/C-nucleophiles to *N*-acyliminium ions has rarely been reported.



Scheme 1 Methods for the amination.

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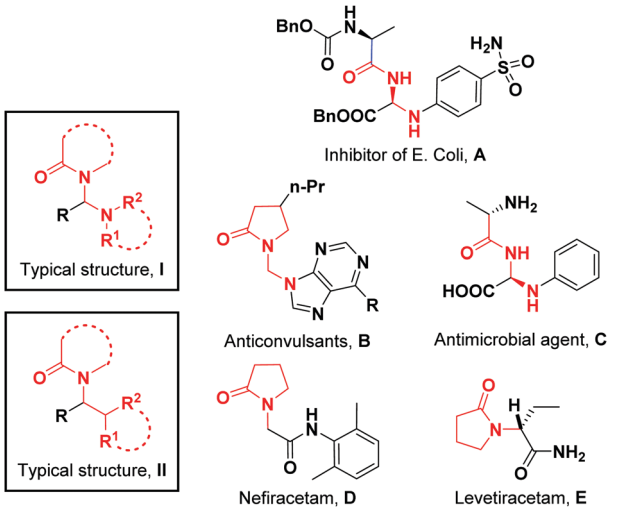


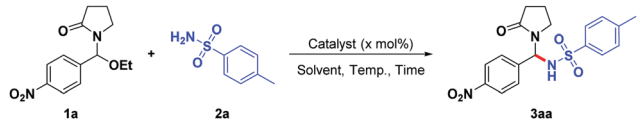
Fig. 1 Butyrolactam containing drugs and pharmaceutically relevant molecules.

Herein, we report a simple, chromatography-free, and efficient iron-catalyzed amination or carbonation of *N*-acyliminium ions *via* benzylic C(sp^3)–O activation of functionalized butyrolactam derivatives for the convenient construction of *gem*-diamino derivatives or other butyrolactam derivatives under simple iron-catalyzed reaction conditions.

Results and discussion

Initially, butyrolactam derivative **1a** was used as the electrophilic precursor with sulfonamide **2a** (a unique pharmacophore)[17] in the reaction, to access the *gem*-diamine compounds. $In(OTf)_3$ gave the best result after screening different metal triflate-based catalysts[9c,e,11d,g] and afforded **3aa** in moderate yield (64%) (Table 1, entries 1–4). As expected, no reaction occurred in the absence of a catalyst, even after 48 h (entry 5). Other Lewis acids and Brønsted acids could also activate the benzylic C(sp^3)–O bond of **1a** (entries 6–9). Among them, $FeCl_3{\cdot}6H_2O$ was the most suitable to promote this amidoalkylation process, affording the desired product **3aa** in 73% yield (entry 6). When other iron salts including $Fe(acac)_3$, $FeSO_4{\cdot}7H_2O$, $FeCl_2$, and $Fe(NO_3)_3{\cdot}9H_2O$ were used, no better results were obtained (entries 10–13). Thus, $FeCl_3{\cdot}6H_2O$ was selected as the optimal catalyst for the reaction, not only because it offers practical advantages from economic and environmental standpoints, but also due to its low biotoxicity. Additionally, changing CH_2Cl_2 to other solvents, such as toluene, CH_3NO_2, MeCN, and EtOH, just led to decreased yields (entries 15–18). *N*-Acyliminium ions generated in these cases were less prone to amination than decomposition; thus, by-product 4-nitrobenzaldehyde was also detected. To our satisfaction, the yield remarkably increased with an attempt to increase the catalyst loading from 5 mol% to 10 mol%, and the final product could be easily isolated in 85% yield by simple filtration without column chromatography (entry 19, in 1 mL of DCM). Additionally, a relatively lower yield (70%) was obtained when the reaction temperature was decreased to 30 °C (entry 20).

Table 1 Optimization of the reaction conditions[a]



1a 2a 3aa

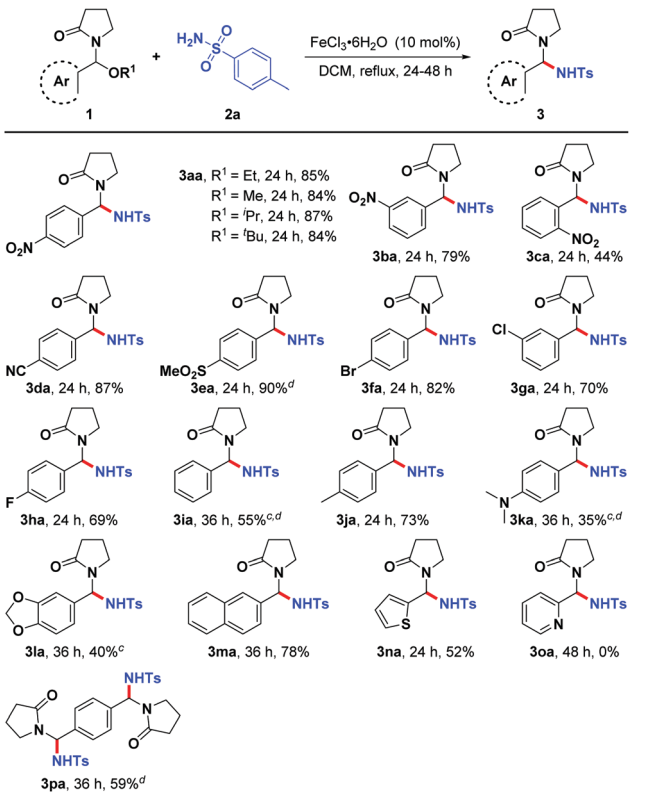
Entry	Catalyst (*x* mol%)	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	$Cu(OTf)_2$ (5)	CH_2Cl_2	Reflux	24	44
2	$In(OTf)_3$ (5)	CH_2Cl_2	Reflux	24	64
3	$Zn(OTf)_2$ (5)	CH_2Cl_2	Reflux	24	<10
4	AgOTf (5)	CH_2Cl_2	Reflux	24	50
5	—	CH_2Cl_2	Reflux	48	0
6	$FeCl_3{\cdot}6H_2O$ (5)	CH_2Cl_2	Reflux	24	73
7	I_2 (5)	CH_2Cl_2	Reflux	24	54
8	$NaHSO_4$ (5)	CH_2Cl_2	Reflux	24	59
9	HCl (5)	CH_2Cl_2	Reflux	24	45[c]
10	$Fe(acac)_3$ (5)	CH_2Cl_2	Reflux	24	<10
11	$FeSO_4{\cdot}7H_2O$ (5)	CH_2Cl_2	Reflux	24	67
12	$FeCl_2$ (5)	CH_2Cl_2	Reflux	24	57
13	$Fe(NO_3)_3{\cdot}9H_2O$ (5)	CH_2Cl_2	Reflux	24	70
14	$FeCl_3{\cdot}6H_2O$ (5)	CH_2Cl_2	Reflux	24	72
15	$FeCl_3{\cdot}6H_2O$ (5)	Tol.	Reflux	24	59
16	$FeCl_3{\cdot}6H_2O$ (5)	CH_3NO_2	Reflux	24	Trace
17	$FeCl_3{\cdot}6H_2O$ (5)	MeCN	Reflux	24	38
18	$FeCl_3{\cdot}6H_2O$ (5)	EtOH	Reflux	24	Trace
19	$FeCl_3{\cdot}6H_2O$ (10)	CH_2Cl_2	Reflux	24	88 (85)[de]
20	$FeCl_3{\cdot}6H_2O$ (10)	CH_2Cl_2	30	24	70

[a] Reaction conditions: **1a** (1 mmol) and 4-methylbenzenesulfonamide **2a** (1.2 mmol) in 2 mL of solvent. [b] Isolated yield. [c] HCl (37 wt%). [d] Yield of **3aa** was obtained using simple filtration. [e] In DCM (1 mL).

With the optimal reaction conditions in hand, we continued to examine the scope of the reaction by using various *N*-acyliminium ion precursors. As listed in Table 2, the influence of leaving groups on *N*,*O*-acetal **1a** was first investigated. Besides ethoxy aminal derivative, methoxy-, isopropoxy-, and *tert*-butoxy-substituted partners have also been proved to be suitable substrates in the reaction, respectively (Table 2, **3aa**). To our delight, functional groups on the aromatic ring such as nitro (**3aa–3ca**), cyano (**3da**), methylsulfonyl (**3ea**), halogens (**3fa–3ha**) and methyl (**3ja**) were compatible with the mild reaction conditions, giving the desired butyrolactam derivatives **3aa–3ja** in moderate to excellent yields (44–90%). However, the ortho steric hindrance had dramatic detrimental effects on the transformation (**3ca**, 44%). It was found that the substrates with strong electron-donating groups obviously reduced the reactivity presumably owing to the low stabilities of these starting materials under acidic conditions (**3ka–3la**, 35–40% yields). In the meantime, the corresponding aldehydes (by-products) were observed in our system. Other aromatic motifs, such as naphthalene-2-yl (**1m**) and thiophen-2-yl (**1n**), could be facilely incorporated into the skeletons of the γ-butyrolactam-based compound in 78% and 52% yield, respectively (**3ma** and **3na**). However, heterocyclic substrate **1o** was totally inert under the identical conditions, which may be due to the relatively strong basicity arising from the pyridine part (**3oa**). Furthermore, the double functionalization of substrate **1p** also worked well, giving rise to the desired amination product **3pa** in 59% yield.

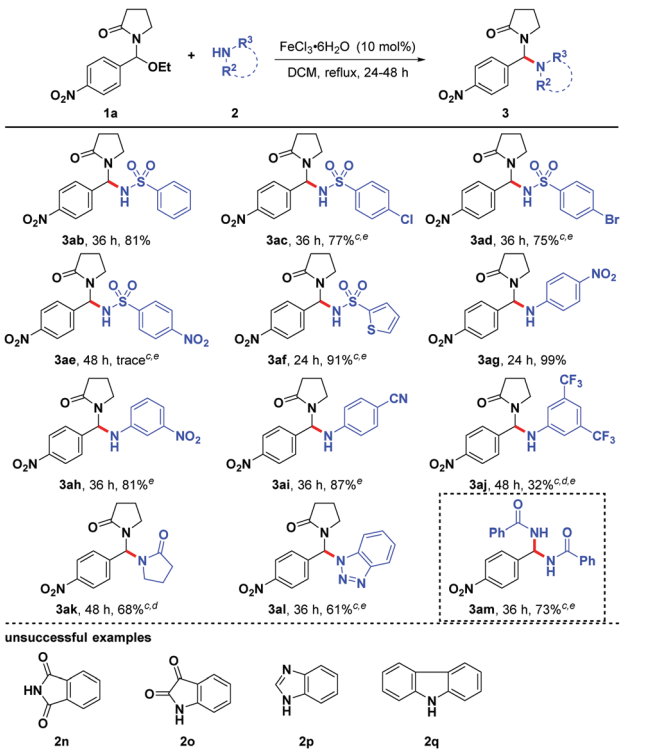
To gain further insights into this novel iron-promoted amination of *N*-acyliminium species, a series of N-sources

Table 2 Substrate scope of butyrolactam derivatives[ab]



[a] Reaction conditions: **1** (1 mmol) and 4-methylbenzenesulfonamide **2a** (1.2 mmol) in DCM (1 mL) at 40 °C for 24–48 h. [b] Yield of pure products obtained using simple filtration. [c] Isolated yield using column chromatography. [d] 2 mmol-scale reaction.

Table 3 Substrate scope of various N-nucleophiles[ab]

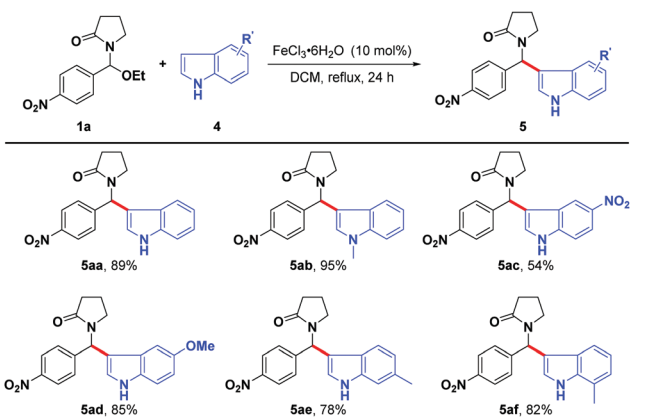


[a] Reaction conditions: **1a** (1.2 mmol) and N-source **2** (1 mmol) in DCM (1 mL) at 40 °C for 24–48 h. [b] Yield of pure products obtained using simple filtration. [c] 1.2 equiv. of N-nucleophile was used. [d] Isolated yield using column chromatography. [e] 2 mmol-scale reaction.

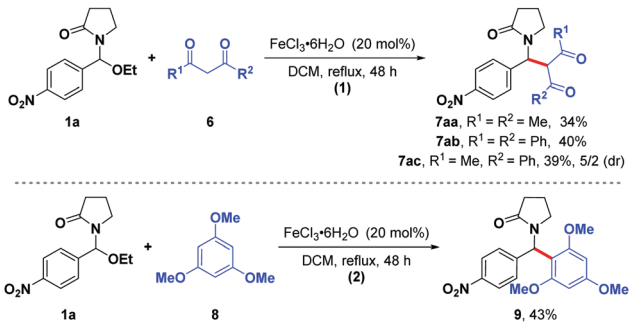
including sulfonamides, aromatic amines, amides and other N-heterocyclic compounds were explored and the results are summarized in Table 3. It was found that the reactions of sulfonamides with **1a** proceeded smoothly to produce the corresponding products with up to 81% yields (**3ab–3ad**). However, electron-poor **2e** was not a suitable substrate because the electronic effect might have a dramatic detrimental influence on product formation (**3ae**). In addition, a synthetically useful heterocycle **2f**[18] also participated in the reaction to give the corresponding amination product **3af** in 91% yield. Similarly, arylamines (**2g–i**) showed good reactivities and CF_3-containing **2j** was also tolerated under the standard conditions (**3ag–3aj**, 32–99% yields). Cyclic amide **2k** was also found to be a good candidate, furnishing bis-pyrrolidin-2-one product **3ak** in 68% yield. By contrast, benzamide (**2m**) was unusual in this regard, only *N*,*N*′-((4-nitrophenyl)methylene)dibenzamide **3am** was obtained unexpectedly. Especially noteworthy was that 1*H*-benzo[*d*][1,2,3]triazole (**2l**) could also react well to give butyrolactam derivative **3al**[12c,d] in 61% yield. Further examination also revealed that other heterocyclic compounds **2n–2q** were reluctant to participant in the reactions.

Interestingly, a C3-alkylated product **5aa** was formed in 89% yield when indole (**4a**) was introduced into the reaction. Next, we set out to study the scope of this C–O bond cleavage protocol with respect to structurally varied indoles **4**, and the results are listed in Table 4. Generally, indoles containing different substituents of varying electronic character and steric hindrance on the indole moieties smoothly reacted with 1-(ethoxy(4-nitrophenyl)methyl)pyrrolidin-2-one (**1a**) to deliver the expected products **5ab–5af** in 54%–95% yields (the typical structure can be depicted as compound **II** in Fig. 1).

Table 4 Substrate scope of various indoles[a]



[a] Reaction conditions: **1a** (1.2 mmol) and indole **4** (1 mmol) in DCM (1 mL) at 40 °C for 24 h; isolated yield using column chromatography.



Scheme 2 Testing 1,3-dicarbonyl compounds and 1,3,5-trimethoxybenzene.

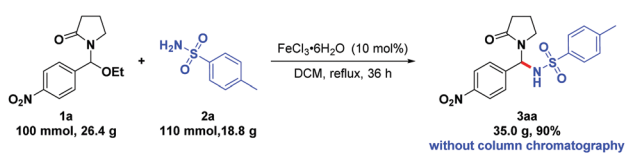
The present method could also accomplish the coupling of *N*,*O*-acetal **1a** with 1,3-dicarbonyl compounds **6** to give the corresponding products **7aa–7ac** in 34–40% yields under slightly modified reaction conditions (Scheme 2, **1**). Furthermore, 1,3,5-trimethoxybenzene (**8**) was also a suitable substrate for the present reaction, leading to product **9** in 43% yield (Scheme 2, **2**). In addition, a large-scale (100 mol) synthesis of **3aa** (35.0 g, 90% yield) was also successfully performed based on the present optimized protocol (Scheme 3).

To gain insights into the putative mechanism of the above reaction, a radical trapping experiment was performed (Scheme 4). When the model reaction was treated with radical scavengers of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, 2 equiv.) under standard reaction conditions, the product **3aa** was obtained in 82% yield. This result suggested that a radical-type mechanism could be ruled out.

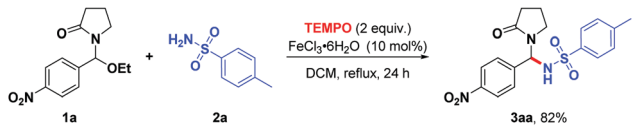
On the basis of the control experiment and a literature survey,[5–11] a proposed mechanism is depicted in Scheme 5. Initially, the coordination of butyrolactam derivative **1** with iron catalyst followed by C–O bond cleavage gives the *N*-acyliminium ion **B** and Fe^{III}-OR^1 species. Subsequently, the intermediate **B** reacts with nucleophiles to produce intermediate **C**. Finally, the catalytic cycle closes with a proton transfer process between intermediate **C** and Fe^{III}-OR^1 species and generation of product, alcohol (HOR^1), and iron catalyst.

Conclusions

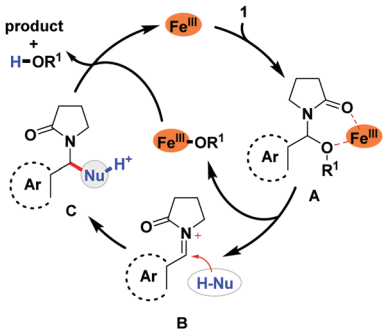
In conclusion, a novel, efficient, and chromatography-free Fe-catalyzed amination of *N*-acyliminium species *via* benzylic C(sp^3)–O activation of functionalized butyrolactam derivatives has been developed. This method provides extremely inexpensive and mild access to various *gem*-diamino equivalents in moderate to excellent yields, which are important structural



Scheme 3 Large-scale direct amination of butyrolactam derivative **1a**.



Scheme 4 Radical trapping experiment.



Scheme 5 Proposed reaction mechanism.

units in biologically active molecules. Extension of the method to other kinds of C-nucleophiles also improved the synthetic potentials of the present method in the context of diversity-oriented synthesis. Moreover, this C–N/C–C bond formation reaction is highly efficient and practical since it works under simple reaction conditions in which the products can even be obtained using simple filtration without the need for organic extraction or column chromatography. Rewardingly, the usage of *N*-acyliminium ions as *N*-alkylating agents complements amination approaches and makes headway in catalytic *N*-acyliminium ion chemistry.

Experimental

General procedures for the iron-catalyzed C–O bond functionalization of butyrolactam derivatives with N-/C-nucleophiles

A solution of butyrolactam derivative **1** (1.2 mmol), N-/C-nucleophile (1.0 mmol), and $FeCl_3{\cdot}6H_2O$ (16 mg, 0.1 mmol) in DCM (1.0 mL) was stirred under air at 40 °C for 24–48 h. Upon completion of the reaction (detected using TLC), the free-flowing solid was filtered and washed with ethyl acetate/petroleum ether (1 : 4) to afford the desired products as pale white solids. The product thus obtained was recrystallized from ethanol or ethyl acetate to get pure compounds as white crystals. Once the final product can't be separated by filtration, the solvent of the resulting mixture was removed with the aid of a rotary evaporator, and the pure product was obtained after purification of the residue using column chromatography (silica gel, ethyl acetate/petroleum ether).

General procedure for the large-scale synthesis

1a (100 mmol, 26.4 g), 4-methylbenzenesulfonamide **2a** (110 mmol, 18.8 g), and $FeCl_3{\cdot}6H_2O$ (1.62 g, 10 mmol) in 100 mL

of CH_2Cl_2 was stirred at 40 °C for 36 h. The free-flowing solid was filtered and washed with ethyl acetate/petroleum ether (1 : 4) to afford the desired product as a pale white solid (35.0 g, 90% isolated yield).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo and M. Tada, *Chem. Rev.*, 2008, **108**, 3795; (*b*) T. Lu, Z. Lu, Z.-X. Ma, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2013, **113**, 4862; (*c*) S.-Z. Song, Y.-N. Meng, Q. Li and W.-T. Wei, *Adv. Synth. Catal.*, 2020, **362**, 2120.

2 (*a*) B. M. Trost, *Science*, 1991, **254**, 1471; (*b*) S. L. Buchwald, C. Mauger, G. Mignani and U. Scholz, *Adv. Synth. Catal.*, 2006, **348**, 23; (*c*) K. Suzuki, Y. Hori and T. Kobayashi, *Adv. Synth. Catal.*, 2008, **350**, 652; (*d*) T. R. Long, P. K. Maity, T. B. Samarakoon and P. R. Hanson, *Org. Lett.*, 2010, **12**, 2904; (*e*) T. Xie, G.-Q. Wang, Y.-W. Wang, W. Rao, H. Xu, S. Li, Z.-L. Shen and X.-Q. Chu, *iScience*, 2020, **23**, 101259; (*f*) X.-Q. Chu, T. Xie, Y.-W. Wang, X.-R. Li, W. Rao, H. Xu and Z.-L. Shen, *Chem. Commun.*, 2020, **56**, 8699.

3 For selected reviews and examples see: (*a*) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555; (*b*) G. Guillena, D. Ramon and M. Yus, *Chem. Rev.*, 2010, **110**, 1611; (*c*) T. R. M. Rauws and B. U. W. Maes, *Chem. Soc. Rev.*, 2012, **41**, 2463; (*d*) F. Shi, M. K. Tse, S. Zhou, M.-M. Pohl, J. Radnik, S. Huebner, K. Jaehnisch, A. Brueckner and M. Beller, *J. Am. Chem. Soc.*, 2009, **131**, 1775.

4 (*a*) T. Suzuki, *Chem. Rev.*, 2011, **111**, 1825; (*b*) S. Michlik and R. Kempe, *Chem. – Eur. J.*, 2010, **16**, 13193; (*c*) A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *J. Org. Chem.*, 2011, **76**, 2328; (*d*) X. C. Yu, C. Z. Liu, L. Jiang and Q. Xu, *Org. Lett.*, 2011, **13**, 6184; (*e*) E. L. Zhang, H. W. Tian, S. D. Xu, X. C. Yu and Q. Xu, *Org. Lett.*, 2013, **15**, 2704.

5 (*a*) V. Terrasson, S. Marque, M. Georgy, J.-M. Campagne and D. Prima, *Adv. Synth. Catal.*, 2006, **348**, 2063; (*b*) K. Motokura, N. Nakagiri, T. Mizugaki, K. Ebitani and K. Kaneda, *J. Org. Chem.*, 2007, **72**, 6006; (*c*) G.-W. Wang, Y.-B. Shen and X.-L. Wu, *Eur. J. Org. Chem.*, 2008, 4367; (*d*) S. Haubenreissera and M. Niggemann, *Adv. Synth. Catal.*, 2011, **353**, 469; (*e*) B. G. Das, R. Nallagonda and P. Ghorai, *J. Org. Chem.*, 2012, **77**, 5577.

6 (*a*) F. Ozawa, H. Okamoto, S. Kawagishi, S. Yamamoto, T. Minami and M. Yoshifuji, *J. Am. Chem. Soc.*, 2002, **124**, 10968; (*b*) H. Qin, N. Yamagiwa, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2007, **46**, 409; (*c*) Y. Lu, X. Fu, H. Chen, X. Du, X. Jia and Y. Liu, *Adv. Synth. Catal.*, 2009, **351**, 1517; (*d*) H. Yamamoto, E. Ho, K. Namba, H. Imagawa and M. Nishizawa, *Chem. – Eur. J.*, 2010, **16**, 11271; (*e*) T. Ohshima, Y. Nakahara, J. Ipposhi, Y. Miyamotob and K. Mashima, *Chem. Commun.*, 2011, **47**, 8322.

7 X. Fan, L.-A. Fu, N. Li, H. Lv, X.-M. Cui and Y. Qi, *Org. Biomol. Chem.*, 2013, **11**, 2147.

8 (*a*) P. Rubenbauer and T. Bach, *Adv. Synth. Catal.*, 2008, **350**, 1125; (*b*) D. A. Powell and G. Pelletier, *Tetrahedron Lett.*, 2008, **49**, 2495; (*c*) M. Feuerstein, D. Laurenti, H. Doucet and M. Santelli, *Tetrahedron Lett.*, 2001, **42**, 2313; (*d*) H.-P. Deng, Y. Wei and M. Shi, *Eur. J. Org. Chem.*, 2011, 1956.

9 For selected reviews and examples see: (*a*) W. N. Speckamp and M. J. Moolenaar, *Tetrahedron*, 2000, **56**, 3817; (*b*) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi and C. A. Maryanoff, *Chem. Rev.*, 2004, **104**, 1431; (*c*) S. S. Kinderman, M. M. T. Wekking, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra and F. P. J. T. Rutjes, *J. Org. Chem.*, 2005, **70**, 5519; (*d*) I. T. Raheem, P. S. Thiara, E. A. Peterson and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2007, **129**, 13404; (*e*) F. Pin, S. Comesse, B. Garrigues, Š. Marchalin and A. Daïch, *J. Org. Chem.*, 2007, **72**, 1181; (*f*) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Ttevitt and D. J. Dixon, *J. Am. Chem. Soc.*, 2009, **131**, 10796; (*g*) U. Martínez-Estibalez, A. Gómez-SanJuan, O. García-Calvo, E. Aranzamendi, E. Lete and N. Sotomayor, *Eur. J. Org. Chem.*, 2011, 3610.

10 (*a*) D. S. Carter and D. L. Van Vranken, *J. Org. Chem.*, 1999, **64**, 8537; (*b*) S. Gunawan and C. Hulme, *Tetrahedron Lett.*, 2013, **54**, 4467; (*c*) A. La Venia, B. Lemrova and V. Krchnak, *ACS Comb. Sci.*, 2013, **15**, 59.

11 (*a*) T. Tsuchimoto, Y. Ozawa, R. Negoro, E. Shirakawa and Y. Kawakami, *Angew. Chem., Int. Ed.*, 2004, **43**, 4231; (*b*) G. Mentink, J. H. van Maarseveen and H. Hiemstra, *Org. Lett.*, 2002, **4**, 3497; (*c*) R. B. Othman, T. Bousquet, M. Othman and V. Dalla, *Org. Lett.*, 2005, **7**, 5335; (*d*) R. B. Othman, R. Affani, M. Tranchant, S. Antoniotti, V. Dalla and E. Duach, *Angew. Chem., Int. Ed.*, 2009, **48**, 1; (*e*) E. Shirakawa, N. Uchiyama and T. Hayashi, *J. Org. Chem.*, 2011, **76**, 25; (*f*) M.-M. Sun, T.-S. Zhang and W.-L. Bao, *J. Org. Chem.*, 2013, **78**, 8155; (*g*) H.-Y. Xu, S.-Y. Wang, R. Jiang, X.-P. Xu, X.-Q. Chu and S.-J. Ji, *Tetrahedron*, 2012, **68**, 8340; (*h*) X.-Q. Chu, S.-Y. Wang and S.-J. Ji, *RSC Adv.*, 2013, **3**, 8380; (*i*) X.-Q. Chu, X.-P. Xu and S.-J. Ji, *Chem. – Eur. J.*, 2016, **22**, 14181; (*j*) S.-W. Zhao, S.-Z. Cai, M.-L. Wang, W. Rao, H. Xu, L. Zhang, X.-Q. Chu and Z.-L. Shen, *Adv. Synth. Catal.*, 2020, **362**, 3388; (*k*) X.-Q. Chu, W.-B. Cao, X.-P. Xu and S.-J. Ji, *J. Org. Chem.*, 2017, **82**, 1145; (*l*) X.-Q. Chu, Y. Zi, H. Meng, X.-P. Xu and S.-J. Ji, *Org. Biomol. Chem.*, 2014, **12**, 4243.

12 (*a*) S. Akiyama, T. Niki, T. Utsunomiya, J. Watanabe, M. Nishioka, H. Suzuki, F. Hayasaka and K. Yamagishi,

EP1020447, 2000; (*b*) J. Gobert, C. Giurgea, J.-P. Geerts and G. Bodson, EP1020447, 1985; (*c*) B. Kenda, Y. Quesnel, A. Ates, P. Michel, L. Turet and J. Mercier, WO2006128693, 2006; (*d*) B. Kenda, P. Michel and Y. Quesnel, WO2005054188, 2005; (*e*) J. Gobert, J.-P. Geerts and G. Bodson, EP0162036, 1985; (*f*) R. J. Schmiesing and R. J. Murray, US5334720, 1994; (*g*) A. H. Gouliaev and A. Senning, *Brain Res. Rev.*, 1994, **19**, 180; (*h*) G. Ramachandran, N. S. Karthikeyan, P. Giridharan and K. I. Sathiyanarayanan, *Org. Biomol. Chem.*, 2012, **10**, 5343.

13 (*a*) Y. Nishimura, in *Studies in Natural Products Chemistry*, ed. A. ur-Rahman, Elsevier, Amsterdam, 1995, vol. 16, p. 75; (*b*) M. D. Fletcher and M. M. Campbell, *Chem. Rev.*, 1998, **98**, 763; (*c*) W. D. Kingsbury, J. C. Boehm, D. Perry and C. Gilvary, *Proc. Natl. Acad. Sci. U. S. A.*, 1984, **81**, 4573; (*d*) S. Y. Hwang, D. A. Berges, J. J. Taggart and C. Gilvarg, *J. Med. Chem.*, 1989, **32**, 694; (*e*) Y. Nishimura, E. Shitara, H. Adachi, M. Toyoshima, M. Nakajima, Y. Okami and T. Takeuchi, *J. Org. Chem.*, 2000, **65**, 2; (*f*) E. R. Lepper, S. W. Ng, M. Gutschow, M. Weiss, S. Hauschildt, T. K. Hecker, F. A. Luzzio, K. Eger and W. D. Figg, *J. Med. Chem.*, 2004, **47**, 2219.

14 (*a*) M. Goodman and M. Chorev, *Acc. Chem. Res.*, 1979, **12**, 1; (*b*) M. Chorev and M. Goodman, *Acc. Chem. Res.*, 1993, **26**, 266; (*c*) M. Chorev, C. G. Willson and M. Goodman, *J. Am. Chem. Soc.*, 1977, **99**, 8075; (*d*) P. Moutevelis-Minakakis and I. J. Photaki, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2277; (*e*) A. R. Katritzky, L. Urogdi and A. Mayence, *J. Org. Chem.*, 1990, **55**, 2206; (*f*) M. Zhao, H. K. Kleinman and M. Mokotoff, *J. Pept. Res.*, 1997, **49**, 240.

15 (*a*) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang and J. C. Antilla, *J. Am. Chem. Soc.*, 2005, **127**, 15696; (*b*) Y. Liang, E. B. Rowland, G. B. Rowland, J. A. Perman and J. C. Antilla, *Chem. Commun.*, 2007, 4477; (*c*) X. Cheng, S. Vellalath, R. Goddard and B. List, *J. Am. Chem. Soc.*, 2008, **130**, 15786.

16 S.-J. Zhu, J. Dong, S.-M. Fu, H.-F. Jiang and W. Zeng, *Org. Lett.*, 2011, **13**, 4914.

17 (*a*) J. Barker and M. Kilner, *Coord. Chem. Rev.*, 1994, **133**, 219; (*b*) M. Y. Lee, M. H. Kim, J. Kim, S. H. Kim, B. T. Kim, I. H. Jeong, S. Chang, S. H. Kim and S. Y. Chang, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 541; (*c*) W. Vernier, W. Chong, D. Rewolinski, S. Greasley, T. Pauly, M. Shaw, D. Dinh, R. A. Ferre, S. Nukui, M. Ornelas and E. Reyner, *Bioorg. Med. Chem.*, 2010, **18**, 3307; (*d*) M. S. AlSaid, M. M. Ghorab, M. S. AlDosari and M. M. Hamed, *Eur. J. Med. Chem.*, 2011, **46**, 201.

18 (*a*) A. S. Gonzlez, R. G. Arrays and J. C. Carretero, *Org. Lett.*, 2006, **8**, 2977; (*b*) H. Morimoto, G. Lu, N. Aoyama, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2007, **129**, 9588.

