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Organocatalytic domino sequence to asymmetrically access spirocyclic oxindole-α-methylene-γ-lactams

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ABSTRACT

An asymmetric allylic alkylation-lactamization domino sequence of 3-aminooxindoles with Morita-Baylis-Hillman carbonates catalyzed by quinidine derivative (*β-ICD*) was developed. And a series of chiral spirocyclic oxindole-α-methylene-γ-lactams have been facilely prepared in good yields and stereoselectivities. This developed protocol would broaden the utilization of Morita-Baylis-Hillman carbonates in asymmetric construction of spirocyclic oxindoles.

1. Introduction

Spirocyclic oxindoles are widely present in an array of natural products and pharmaceuticals as a major class of optically active privileged scaffolds [1]. Up to now, enormous efforts have been made to construct spirocyclic oxindoles with structural complexity and diversity [2]. On the other hand, α-methylene-γ-butyrolactams are important building blocks in organic synthesis, many of which possess significant biological activities, including anticancer and anti-inflammatory effects [3]. Consequently, diversity-driven studies for medicinal studies on the biologically related scaffolds render it highly attractive and demanding to assemble the spirocyclic oxindole-α-methylene-γ-lactam, which might fully take advantage of the synergistic effects of both spirocycilc oxindoles and α-methylene-γ-butyrolactam scaffolds.

In recent years, a set of asymmetric synthetic strategies to rapid construction of spirooxindole scaffold merging with γ-lactam have been established [4]. One major method relies on α,β-unsaturated aldehydes [4g,5] or 2-bromoenals [4d,6] which are susceptible to the attack by *N*-heterocyclic carbene (NHC) to form α,β-unsaturated acyl azoliums and subsequently react with various 3-aminooxindoles or oxindole imines to afford spirocyclic oxindole-γ-lactams (Scheme 1(a)). In 2012, Jiao's [5b] and Chi's [5a] groups disclosed that NHC-catalyzed [3 + 2] annulation of α,β-unsaturated aldehydes with oxindole imines successfully delivered a range of spirocyclic oxindole-γ-lactams. Thereafter, NHC-catalyzed [3 + 2] annulation of 2-bromoenals with 3-aminooxindoles was also reported [4d,6]. Besides, another major synthetic pathway was based on 3-isothiocyanato oxindoles as nucleophiles (Scheme 1(b)) [4e,7]. Despite these impressive advances, developing new efficient method to access diversified spirocyclic oxindole-γ-lactams is still extremely attractive and urgent, allowing us to broadly exploit their medicinal potentials.

Morita-Baylis-Hillman adduct derivatives (MBHADs), as versatile synthons, offer a wide array of synthetic opportunities in asymmetric synthesis, especially in organocatalysis [8]. Essentially, they are prone to being attacked by various nucleophiles to facilely realize diverse functionalizations [9]. Nevertheless, we noticed that using Morita-Baylis-Hillman carbonate as Michael acceptors for the synthesis of spirocyclic oxindole has been rarely exploited. Wang's group reported an organocatalytic asymmetric domino reaction of MBHADs and 3-hydroxyoxindoles promoted by quinidine [10].

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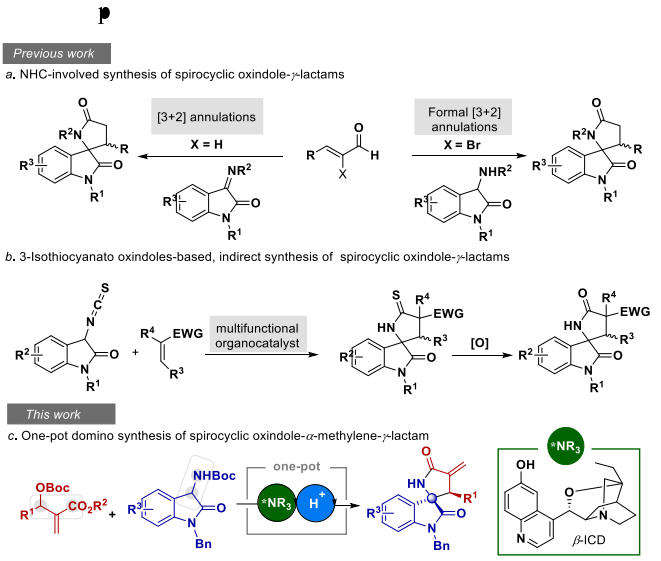


Scheme 1. Synthetic Profiles for Spirocyclic Oxindole-γ-Lactams.

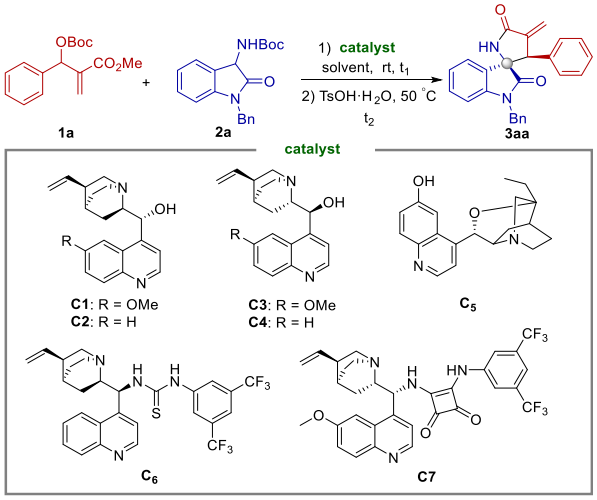
However, considering the significant difference in the reactivities between *N* and *O* atoms, also, 3-aminooxindoles are expected to serve as competent reaction partners [11]. Driven by our continued efforts in the construction of spirooxindoles [12,13], we speculated that a newly designed domino sequence by using 3-aminooindoles with MBH carbonates could proceed an allylic alkylation-cyclization process to rapidly assemble spirocyclic oxindole-α-methylene-γ-lactams. Despite an achiral metal-catalyzed stepwise protocol has been reported by Yoda and co-workers [4h], asymmetric approach to access optically active spirocyclic oxindole-α-methylene-γ-lactams still remains a synthetic challenge. Herein, we developed a new asymmetric organocatalytic domino reaction between 3-aminooxindoles and MBHADs catalyzed by quinidine derivative (β-ICD), enabling a facile access to enantiopure spirooxindoles bearing α-methylene-γ-butyrolactam moieties (Scheme 1(c)).

2. Results and discussion

2.1. Optimization of the reaction conditions

In order to verify our speculation, we initiated our studies on a reaction of MBH carbonate **1a** and 3-aminooxindole **2a** by using a series of cinchona alkaloid derivatives as the catalyst in toluene (Table 1). It is worth mentioning that a one-pot process was designed to realize the domino sequence by sequentially proceeding the organocatalytic allylic alkylation and acid-promoted lactamization and deprotection. Various readily available alkaloids including quinine, quinidine, cinchonine, cinchonidine and β-isocupreidine (β-ICD) were tested to catalyze this reaction as shown in Table 1 (entries 1–5). To our delight, upon using β-ICD (**C5**) as catalysts, the target product **3aa** was successfully achieved in high yield with excellent diastereoselectivity and good enantioselectivity (Table 1, entry 5). Except for **C4**, the other alkaloids (**C1**, **C2**, & **C3**) were able to effectively promote the reaction to deliver the target product, albeit with lower enantiomeric ratios (er) in a slightly longer reaction time. However, two cinchona-derived bifunctional organocatalysts (**C6** & **C7**) were unable to afford the desired product (Table 1, entries 6–7). Besides, cinchona alkaloids $(DHQD)_2PYR$ and $(DHQD)_2PHAL$ have been tested, but giving inferior results (Table 1, entries 8–9). Using **C5** as the optimal

Table 1
Optimization of reaction Conditions[a].



entry	Solvent	cat.	t_1/t_2 (h)	yield(%)[b]	dr[c]	er[d]
1	$PhCH_3$	**C1**	23/5	79	>20:1	67.0:32.0
2	$PhCH_3$	**C2**	23/5	76	>20:1	61.0:39.0
3	$PhCH_3$	**C3**	23/5	97	>20:1	87.0:13.0
4	$PhCH_3$	**C4**	23/5	trace	–	–
5	$PhCH_3$	**C5**	17/6	96	>20:1	89.0:11.0
6	$PhCH_3$	**C6**	23/5	trace	–	–
7	$PhCH_3$	**C7**	23/5	trace	–	–
8	$PhCH_3$	$(DHQD)_2PYR$	23/5	32	>20:1	77.0:23.0
9	$PhCH_3$	$(DHQD)_2PHAL$	23/5	53	>20:1	87.5:12.5
10	PhC_2H_5	**C5**	13/6	72	>20:1	91.0:9.0
11	o-xylene	**C5**	13/6	96	>20:1	87.5:12.5
12	CH_2Cl_2	**C5**	13/4	91	>20:1	79.0:21.0
13	DMC	**C5**	13/4	97	>20:1	86.0:14.0
14	THF	**C5**	13/10	90	>20:1	83.5:16.5
15	DMF	**C5**	17/6	trace	–	–
16	$PhCF_3$	**C5**	13/5	86	>20:1	93.5:6.5
17	C_6F_6	**C5**	12/5	96	>20:1	94.5:5.5
18[e]	**C_6F_6**	**C5**	**15/5**	**97**	**>20:1**	**95.0:5.0**
19[f]	C_6F_6	**C5**	24/5	87	>20:1	93.0:7.0

[a] Unless otherwise noted, all reactions were carried out using **1a** (0.20 mmol, 2.0 equiv), **2a** (0.10 mmol, 1.0 equiv), and catalyst (0.02 mmol, 20 mol %) in solvent (0.5 mL) and stirred at room temperature for the specified time (t_1). After that, $TsOH·H_2O$ (0.15 mmol, 1.5 equiv) was added to the mixture and then heated at 50 °C for the specified time (t_2). TLC was used to monitor the reaction progress, and time t_1 and t_2 were given based on the consumption of starting material **2a** and the formation of product **3aa**, respectively.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.
[d] Determined by HPLC on a chiral stationary phase.
[e] Reaction was carried out in C_6F_6 (0.25 mL) with **C5** (0.01 mmol, 10 mol%) as catalyst.
[f] Reaction was carried out in C_6F_6 (0.10 mL) with **C5** (0.01 mmol, 10 mol%) as catalyst.

catalyst, a series of solvents were then screened, where similar results were achieved except DMF (Table 1, entries 10–16). Interestingly, upon using perfluorobenzene (C_6F_6) as the solvent, an obvious improvement in enantioselectivity was observed (Table 1, entry 17), which might be attributed to its π-π interaction or electrostatic interaction with substrates or catalysts [14]. Subsequently, using C_6F_6 as an additive rather than a solvent was also examined (See Supporting Information, Table S2), and it was found that the er value was enhanced when increasing the amount of C_6F_6 in ethylbenzene as the solvent, but still worse than the results by using C_6F_6 as the solvent. Encouraged by these promising results, we then investigated the amount of C_6F_6 and the catalyst loading.

To our delight, in the presence of 10 mol% catalyst **C5**, **3aa** was ultimately obtained in excellent yield (97%) with excellent stereoselectivity (>20:1 dr, 95.0:5.0 er) (Table 1, entry 18).

2.2. Scope and limitations of substrates

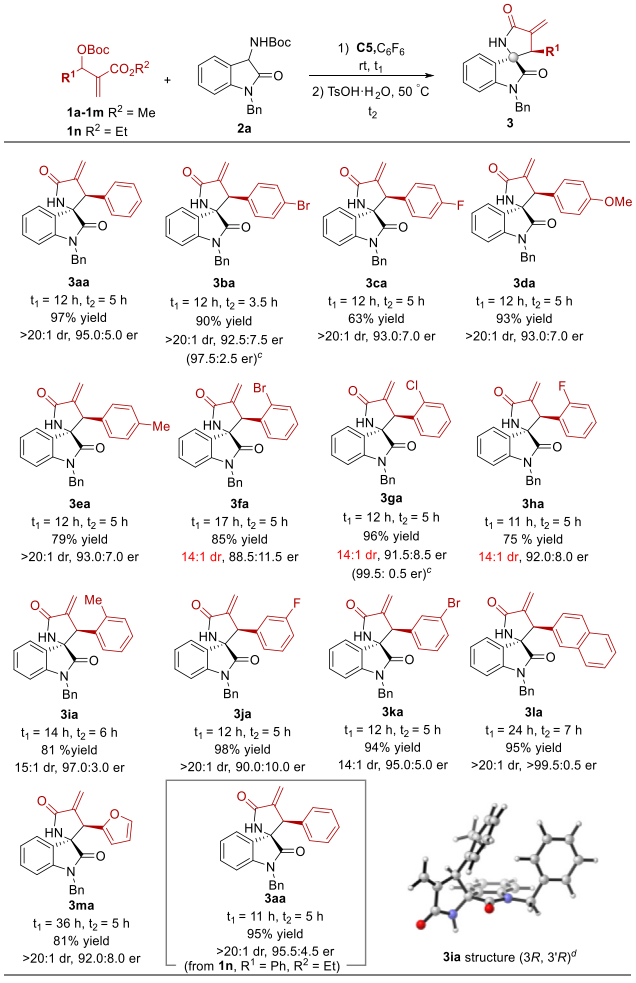
After obtaining the optimal conditions in hand, we turned our attention to investigate the functional group tolerance (Scheme 2). Initially, various MBH carbonates (Scheme 2, **1a-1n**) with different substituents were evaluated under the standard conditions. The results showed that electron-donating or electron-withdrawing groups on different positions of the phenyl ring were found suitable for this reaction (Scheme 2, **3aa**-**3ka**). However, introducing a fluoro group onto the para- or ortho-position of the phenyl ring would obviously decrease the corresponding yield (Scheme 2, **3ca** & **3ha**), presumably due to the strong electron-withdrawing effect of fluorine atom. Besides, the corresponding products were obtained in good yields with good enantioselectivities and excellent diastereoselectivities. Encouragingly, spirocyclic lactam product **3la** was also obtained in excellent yield and enantioselectivity (>99.5:0.5 er), upon using MBH carbonate bearing a naphthyl ring, though an elongated reaction time was required. In addition, the furyl-substituted MBH carbonate displayed satisfactory reactivity, giving the product **3ma** in 81% yield with 92.0:8.0 er. Alkyl substituted MBH carbonate **1o** was prepared and subjected to the optimal reaction conditions, but the desired product and the plausible adduct formed in the first step were unable to be observed (see Supporting Information). To be noted, the enantioselectivity was also perfectly maintained by replacing methyl group with ethyl group (Scheme 2, **3aa**, bottom).

[a]Unless otherwise noted, reaction was carried out using **1a** (0.10 mmol, 1.0 equiv), **2** (0.20 mmol, 2.0 equiv), and catalyst **C5** (0.01 mmol, 10 mol%) in C_6F_6 (0.25 mL) and stirred at room temperature for the specified time (t_1). After that, TsOH·H_2O (0.15 mmol, 1.5 equiv) was added to the mixture and then heated at 50 °C for the specified time (t_2). [b]Isolated yields, dr value was determined by ^{1}H NMR analysis, er value was determined by HPLC on a chiral stationary phase. [c]After single run of recrystallization. [d]Structure and stereochemistry were confirmed by X-ray analysis and circular dichroism spectroscopy.

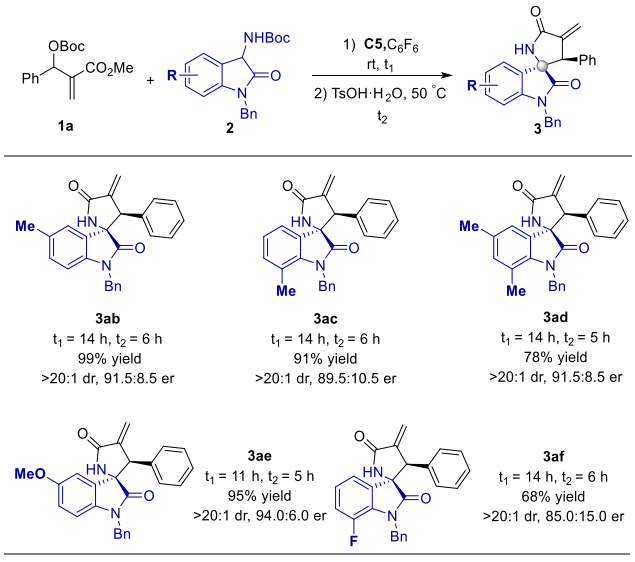
The absolute configuration was successfully confirmed by X-ray crystallography and circular dichroism spectroscopy (See details in Supporting Information). The crystallography data of racemic mixtures demonstrate that the plausible configurations should be (3*R*, 3′*R*) or (3*S*, 3′*S*). To figure out the dominant enantiomer in this asymmetric reaction, the CD spectrum of **3ia** was also determined. As shown in Fig. S1 (See Supporting Information), the comparison between experimental and predicted CD spectra suggests that the dominant configuration of the product **3ia** can be assigned to be (3*R*, 3′*R*) (Supporting Information. Fig. S2). These results can be also supported by Wang's work [10], in which the absolute configuration of similar spirooxindoles bearing α-methylene-γ-butyrolactone motifs was confirmed to be (C3R, C3′R) by X-ray analysis.

Subsequently, various substituted 3-aminooxindoles (**2b-2f**) were also examined in the protocol. The results are listed in Scheme 3. It was found that electron-donating substituents on the phenyl ring of 3-aminooxindole were well tolerated, giving the corresponding products **3ab-3ae** in good to excellent yields with excellent diastereoselectivities and good enantioselectivities. The presence of a fluoro group severely affected the yield, and the desired product **3af** was furnished in moderate yield, albeit with comparable stereoselectivity. However, the stereoselectivity was markedly sabotaged upon replacing Bn with Me, which might be attributed to the change of steric effect (see Supporting Information).

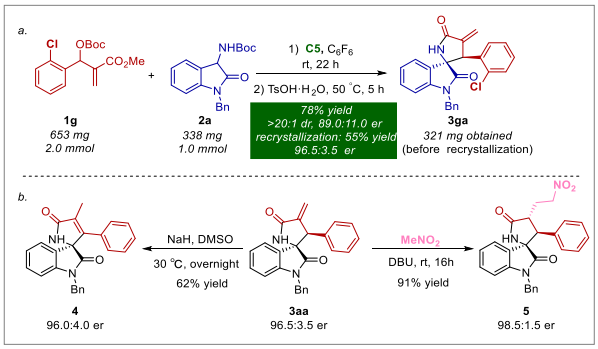
[a]Unless otherwise noted, reaction was carried out using **1a** (0.10 mmol, 1.0 equiv), **2** (0.20 mmol, 2.0 equiv), and catalyst **C5**



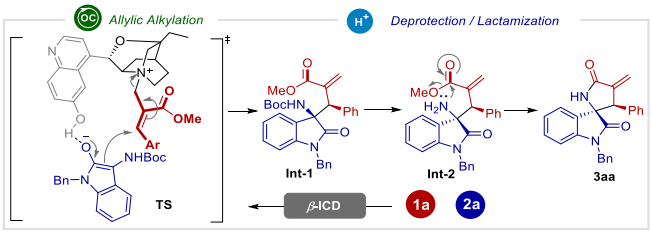
Scheme 2. Scope of Morita-Baylis-Hillman Carbonates **1**[a,b].



Scheme 3. Scope of 3-Aminooxindoles **2**[a,b].



Scheme 4. Scale-up Experiment and Transformation of the Spirooxindole Compound.



Scheme 5. Plausible Mechanism.

(0.01 mmol, 10 mol%) in C_6F_6 (0.25 mL) and stirred at room temperature for the specified time (t_1). After that, $TsOH·H_2O$ (0.15 mmol, 1.5 equiv) was added to the mixture and then heated at 50 °C for the specified time (t_2). [b]Isolated yields, dr value was determined by ^1H NMR analysis, er value was determined by HPLC on a chiral stationary phase.

To further testify the scalability of this protocol, a scale-up experiment of **1g** and **2a** was performed as shown in Scheme 4a. Satisfyingly, the corresponding product **3ga** was obtained in 78% yield with 89.0:11.0 er and >20:1 dr, while the enantiopurity of **3ga** was improved to 96.5:3.5 er through a single run of recrystallization. To demonstrate the synthetic utility of the resulting spirocyclic oxindole, the transformations of product **3aa** (96.5:3.5 er) were conducted (Scheme 4b). Pleasingly, the double-bond shifting product **4** can be effectively obtained in a moderate yield (62%) without eroding enantioselectivity (96.0:4.0 er) in the presence of NaH. Further experiments showed that compound **3aa** could undergo Michael addition with nitromethane in the presence of DBU, successfully delivering the corresponding derivate **5** in an excellent yield (91%) and enantioselectivity (98.5:1.5 er).

On the basis of our experimental results and the absolute configuration of the product **3**, a possible reaction mechanism is tentatively proposed in Scheme 5. Initially, a SN_2' attack of cinchona alkaloids (β-ICD) on the MBHAD **1a** followed by an intermolecular Michael addition of the enolized **2a** gives the asymmetric allylic alkylation product **Int-1.** Subsequently, acid-promoted deprotection and lactamization would facilely afford the desired spirooxindole **3aa** (Scheme 5).

3. Conclusion

In conclusion, we have established an organocatalytic protocol of 3-aminooxindole with Morita-Baylis-Hillman carbonates to assemble novel chiral spirocyclic oxindole-α-methylene-γ-lactam skeleton. In this protocol, the asymmetric allylic alkylation-lactamization domino sequence was effectively realized by employing β-ICD as the catalyst in perfluorobenzene. The resulting spirocyclic oxindole-α-methylene-γ-lactams were obtained in good to excellent yields with excellent diastereoselectivitie and good enantioselectivities. Moreover, this strategy would broaden the library of spirooxindole heterocycles, paving the way to the diversity-driven investigation on the biological activities of difficultly accessible heterocycles.

4. Experimental section

Unless otherwise noted, all solvents and reagents were purchased from commercial suppliers and used without further purification. Flash chromatography was carried out on silica gel (200–300 mesh). ^1H NMR spectra were recorded at 400 MHz. The chemical shifts were recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal standard. Data were reported as follows: chemical shift, multiplicity (s, single; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constants (Hz), integration. ^{13}C NMR data were collected at 100 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the tetramethylsilane with the solvent resonance as an internal standard. Infrared spectra (IR) were measured by FT-IR apparatus. ECD spectra was recorded with JASCO J-815 spectrometer. High resolution mass spectroscopy (HRMS) was recorded on TOF MS ES + Mass spectrometer and acetonitrile was used to dissolve the sample. MBH Carbonates **1a-1n** were prepared according to the reported protocols [15], and 3-aminooxindole derivatives **2** were prepared according to the literature procedure with minor modifications [4h].

4.1. General procedures

4.1.1. General procedures for the synthesis of 3-aminooxindoles *2*

To a suspension of 3-(hydroxyimino)-1-methylindolin-2-ones [16] (2 mmol, 1 equiv.) in methanol (4 mL) was added Pd/C (10% palladium on carbon) (10 wt%). The mixture was stirred under a hydrogen atmosphere at room temperature for 10 h. Thereafter, the vessel was evacuated and backfilled with Ar three times. Then di-tert-butyl dicarbonate (2.2 mmol, 1.2 equiv.) was added and the reaction mixture was stirred at room temperature for additional 4–9 h. After completion of the reaction (confirmed by TLC analysis), Pd/C was removed by filtration. The obtained filtrate was concentrated to dryness and the resulting residue was purified by flash column chromatography (EA/PE = 1/4) on silica gel to yield the crude substrates. Finally, the corresponding products can be further purified through recrystallization over hexanes and CH_2Cl_2. The data of the known compounds **2** were consistent with the previously reports [17]. Characterization data of new compounds **2c**, **2d** and **2f** are provided herein.

4.1.2. General experimental procedure for the synthesis of spirocyclic lactams *3*

To a solution of MBH carbonates **1** (0.2 mmol, 2.0 equiv.) and 3-aminooxindoles **2** (0.1 mmol, 1.0 equiv.) in hexafluorobenzene (C_6F_6) was added β-ICD (0.01 mmol, 10 mol%). The reaction mixture was stirred at room temperature until the TLC analysis showed the complete consumption of starting materials **2** (11–36 h). Subsequently, 1.5 equiv. of $TsOH·H_2O$ was added and stirred at 50 °C (preheated). After the completion of the reaction, the resulting residue was purified by column chromatography (EA/PE = 2/3) to afford the corresponding chiral spirocyclic oxindole-α-methyl-γ-lactams **3**.

4.1.3. General procedures for the synthesis of *4*

A suspension of compound **3aa** (38 mg, 1.0 mmol) in dry DMSO (1.0 mL) with vigorous stirring was cooled to 0 °C, then sodium

hydride was added (4 mg, 0.2 mmol) under argon atmosphere. The mixture was stirred at 30 °C for overnight and quenched with 1.0 mL water under 0 °C. The mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EA/PE = 2/3) to give the desired compound **4** (62%, 96.0:4.0 er).

4.1.4. General procedures for the synthesis of **5**

The reaction was performed according a reported literature [18]. To a solution of compound **3aa** (38 mg, 0.1 mmol) in anhydrous nitromethane (0.332 mL, 6.2 mmol) was added DBU (3 μL, 0.02 mmol). The mixture was stirred at rt. for 16 h. The solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography on silica gel (EA/PE = 2/3) to give the desired compound **5** (91%, 98.5:1.5 er).

4.2. Characterization data of compound **2**,**3aa-3ma**, **3 ab-3af**, **4** and **5**

3-Aminooxindole ***(2c)***. White solid (684 mg, yield 97%) from 533 mg of 1-benzyl-3-(hydroxyimino)-7-methylindolin-2-one which was prepared according the literature without purified [3] m.p. 212–213 °C; IR (neat) *ν* 3362, 1728, 1503, 1159, 923, 726, 594 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ* 7.31–7.28 (m, 2H), 7.25–7.18 (m, 4H), 6.94–6.93 (m, 2H), 5.47 (*br* s, 1H), 5.27–5.16 (m, 3H), 2.23 (s, 3H) 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) *δ* 175.8, 155.7, 140.8, 137.4, 133.0, 128.9, 127.7, 127.2, 125.8, 123.0, 122.3, 120.0, 80.5, 53.4, 45.4, 28.3, 18.7; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{24}N_2NaO_3^+$ 375.1679, found 375.1679.

3-Aminooxindole ***(2d)***. White solid (667 mg, yield 91%) from 561 mg of 1-benzyl-3-(hydroxyimino)-5,7-dimethylindolin-2-one which was prepared according the literature without purified [3] m.p. 206–207 °C; IR (neat) *ν* 3352, 1727, 1516, 1339, 1159, 920, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32–7.29 (m, 2H), 7.25–7.17 (m, 3H), 7.09 (s, 1H), 6.77 (s, 1H), 5.20–5.16 (m, 4H), 2.26 (s, 3H), 2.20 (s, 3H), 1.48 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 175.6, 155.7, 138.3, 137.4, 133.5, 132.6, 128.8, 127.7, 127.2, 125.8, 123.1, 119.7, 80.6, 53.5, 45.3, 28.3, 20.7, 18.5; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{22}H_{26}N_2NaO_3^+$ 389.1836, found 389.1831.

3-Aminooxindole ***(2f)***. White solid (606 mg, yield 85%) from 541 mg of 1-benzyl-7-fluoro-3-(hydroxyimino)indolin-2-one which was prepared according the literature without purified [3] m.p. 72–73 °C; IR (neat) *ν* 3346, 2976, 1707, 1352, 1158, 959, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ* 7.39–7.37 (m, 2H), 7.32–7.27 (m, 3H), 7.23–7.14 (m, 1H), 6.98–6.96 (m, 2H), 5.29 (*br* s, 1H), 5.15–4.97 (m, 3H), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) *δ* 174.3, 155.5, 147.4 (d, $J_{C\text{-}F}$ = 244.4 Hz), 136.7, 129.8, 129.4 (d, $J_{C\text{-}F}$ = 8.6 Hz), 128.6, 127.7, 123.6 (d, $J_{C\text{-}F}$ = 6.2 Hz), 120.3, 117.3 (d, $J_{C\text{-}F}$ = 19.5 Hz), 80.8, 53.9, 45.8, 28.2; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{20}H_{21}FN_2NaO_3^+$ 379.1428, found 379.1442.

Spirocyclic lactam ***(3aa)***. White solid (37 mg, yield 97%) from 34 mg of **2a**, *er* 95.0:5.0; White solid (36 mg, yield 95%) from 34 mg of **2a** (replacing methyl group with ethyl group), *er* 95.5:4.5; $[\alpha]_D^{20}$ = −16.5 (c = 0.05 in CH_2Cl_2); m.p. 138–139 °C; IR (neat) *ν* 3220, 1712, 1611, 1354, 1174, 736, 455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ* 7.55 (d, *J* = 6.6 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.23–7.11 (m, 5H), 7.08–7.01 (m, 5H), 6.41 (d, *J* = 7.6 Hz 1H), 6.35 (d, *J* = 7.2 Hz, 2H), 6.29 (d, *J* = 3.2 Hz, 1H), 5.35 (d, *J* = 2.4 Hz, 1H), 4.96 (d, *J* = 16.0 Hz, 1H), 4.47 (s, 1H), 4.13 (d, *J* = 16.0 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) *δ* 174.9, 171.1, 143.3, 140.3, 134.7, 133.3, 130.4, 130.0, 128.6, 128.3, 127.3, 127.2, 126.4, 123.7, 123.4, 118.1, 109.8, 67.9, 57.4, 44.0; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{20}N_2NaO_2^+$ 403.1417, found 403.1397; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 15.6 min (major), 18.2 min (minor).

Spirocyclic lactam ***(3ba)***. White solid (42 mg, yield 90%) from 34 mg of **2a**; *er* 92.5:7.5; $[\alpha]_D^{20}$ = −44.9 (c = 0.05 in CH_2Cl_2); m.p. 247–248 °C; IR (neat) *ν* 3165, 1706, 1611, 1172, 1009, 729, 496 cm^{-1}; ^1H NMR (d_6-DMSO, 400 MHz) *δ* 8.89 (s, 1H), 7.79 (dd, *J* = 8.8, 0.8 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.32–7.28 (m, 1H), 7.25–7.19 (m, 4H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.56 (dd, *J* = 7.2, 0.8 Hz, 2H), 6.12 (d, *J* = 3.6 Hz 1H), 5.23 (d, *J* = 2.8 Hz, 1H), 4.91 (d, *J* = 12.0 Hz, 1H), 4.75 (t, *J* = 3.2 Hz, 1H), 4.43 (d, *J* = 16.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (d_6-DMSO, 100 MHz) *δ* 175.2, 170.1, 143.3, 142.5, 135.7, 133.7, 132.3, 131.9, 130.5, 128.8, 127.7, 127.5, 126.8, 124.9, 123.6, 122.0, 115.7109.8, 67.6, 55.4, 55.1, 43.2; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{19}BrN_2NaO_2^+$ 481.0522, found 481.0498; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 21.0 min (minor), 24.0 min (major).

Spirocyclic lactam ***(3ca)***. White solid (25 mg, yield 63%) from 34 mg of **2a**; *er* 93.0:7.0; $[\alpha]_D^{20}$ = +15.0 (c = 0.05 in CH_2Cl_2); m.p. 201–202 °C; IR (neat) *ν* 3196, 1698, 1612, 1342, 1171, 755, 455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ* 7.55 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.24–7.10 (m, 5H), 7.03–6.99 (m, 2H), 6.90 (t, *J* = 8.8 Hz, 2H), 6.73 (s, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 6.44 (d, *J* = 7.2 Hz, 2H), 6.34 (d, *J* = 3.6 Hz, 1H), 5.35 (d, *J* = 2.8 Hz, 1H), 4.98 (d, *J* = 16.0 Hz, 1H), 4.46 (t, *J* = 3.2 Hz, 1H), 4.16 (d, *J* = 16.0 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) *δ* 172.76 (d, $J_{C\text{-}F}$ = 387.4 Hz), 162.78 (d, $J_{C\text{-}F}$ = 247.4 Hz), 143.3, 140.3, 134.6, 131.7 (d, $J_{C\text{-}F}$ = 8.1 Hz), 129.1 (d, $J_{C\text{-}F}$ = 3.2 Hz), 128.6, 127.5, 127.0, 126.5, 123.6 (d, $J_{C\text{-}F}$ = 24.3 Hz), 118.1, 115.6 (d, $J_{C\text{-}F}$ = 21.4 Hz), 109.7, 67.8, 56.6, 44.0; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{19}FN_2NaO_2^+$ 421.1323, found 421.1307; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 17.5 min (major), 20.1 min (minor).

Spirocyclic lactam ***(3da)***. White solid (38 mg, yield 93%) from 34 mg of **2a**; *er* 93.0:7.0; $[\alpha]_D^{20}$ = −24.9 (c = 0.05 in CH_2Cl_2); m.p. 234–235 °C; IR (neat) *ν* 3350, 1716, 1609, 1360, 1173, 762, 545 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ* 7.54 (d, *J* = 6.8 Hz, 1H), 7.20–7.13 (m, 3H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 3H), 6.44 (d, *J* = 7.2 Hz, 1H), 6.37 (d, *J* = 7.2 Hz, 2H), 6.32 (d, *J* = 3.2 Hz, 1H), 5.37 (d, *J* = 2.4 Hz, 1H), 5.05 (d, *J* = 15.6 Hz, 1H), 4.45 (t, *J* = 3.2 Hz, 1H), 4.13 (d, *J* = 16.0 Hz, 1H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) *δ* 174.9, 171.2, 159.6, 143.3, 140.6, 134.6, 131.1, 130.4, 128.5, 127.33, 127.26, 126.5, 125.1, 123.8, 123.4, 118.0, 114.0, 109.7, 68.0, 56.8, 55.1, 44.0; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{26}H_{22}N_2NaO_3^+$ 433.1523, found 433.1520; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 21.0 min (minor), 22.5 min (major).

Spirocyclic lactam ***(3ea)***. White solid (31 mg, yield 79%) from 34 mg of **2a**; *er* 93.0:7.0; $[\alpha]_D^{20}$ = −23.4 (c = 0.05 in CH_2Cl_2); m.p. 240–241 °C; IR (neat) *ν* 3172, 1701, 1612, 1345, 1172, 817, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, *J* = 6.8 Hz, 1H), 7.21–7.13 (m, 3H), 7.09–7.02 (m, 4H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.43–6.40 (m, 3H), 6.35 (d, *J* = 3.2 Hz, 1H), 6.29 (s, 1H), 5.38 (d, *J* = 2.4 Hz, 1H), 5.02 (d, *J* = 15.9 Hz, 1H), 4.46 (s, 1H), 4.13 (d, *J* = 16.0 Hz, 1H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) *δ* 174.9, 170.9, 143.3, 140.3, 138.0, 134.6, 130.4, 130.2, 129.9, 129.3, 128.5, 127.3, 127.2, 126.5, 123.7, 123.4, 118.1, 109.7, 67.9, 57.2, 44.0, 21.3; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{26}H_{22}N_2NaO_2^+$ 417.1573, found 417.1567; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 17.7 min (major), 19.1 min (minor).

Spirocyclic lactam ***(3fa)***. White solid (39 mg, yield 85%) from 34 mg of **2a**; *er* 88.5:11.5; $[\alpha]_D^{20}$ = +55.1 (c = 0.05 in CH_2Cl_2); m.p. 165–166 °C; IR (neat) *ν* 3060, 1705, 1613, 1465, 1343, 1753, 552 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56 (d, *J* = 6.8 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.22–7.08 (m, 7H), 6.52–6.48 (m, 3H), 6.35–6.34 (m, 2H), 5.24–2.22 (m, 2H), 5.50 (d, *J* = 16.0 Hz, 1H), 4.19 (d, *J* = 16.0 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) *δ* 174.8, 143.0, 134.8, 134.1, 132.7, 130.4, 129.7, 128.6, 127.7, 127.3, 127.1, 126.5, 126.3, 125.2, 123.3, 118.6, 109.6, 67.5, 54.3, 44.1; HRMS (TOF-ESI) m/z $[M + Na]^+$

calcd for $C_{25}H_{19}BrN_2NaO_2^+$ 481.0522, found 481.0522; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 14.6 min (major), 21.0 min (minor).

Spirocyclic lactam (**3ga**). White solid (40 mg, yield 96%) from 34 mg of **2a**; *er* 91.5:8.5; $[\alpha]_D^{20}$ = −30.1 (c = 0.05 in CH_2Cl_2); m.p. 217−218 °C; IR (neat) ν 3187, 1700, 1489, 1343, 1173, 822, 690 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.85 (s, 1H), 7.74 (d, J = 6.8 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.27−7.23 (m, 1H), 7.19−7.13 (m, 4H), 6.97 (d, J = 8.4 Hz, 2H), 6.60 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 6.8 Hz, 2H), 6.07 (d, J = 3.6 Hz, 1H), 5.18 (d, J = 2.8 Hz, 1H), 4.85 (d, J = 16.0 Hz, 1H), 4.72 (t, J = 2.8 Hz, 1H), 4.38 (d, J = 16.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 100 MHz) δ 175.2, 170.2, 143.2, 142.6, 135.7, 133.4, 133.3, 132.0, 130.5, 128.9, 128.7, 127.64, 127.56, 126.8, 125.0, 123.6, 115.7, 109.7, 67.7, 55.0, 43.1; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{19}ClN_2NaO_2^+$ 437.1027, found 437.1017; HPLC analysis (CHIRALCEL IG, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 32.2 min (major), 34.9 min (minor).

Spirocyclic lactam (**3ha**). White solid (30 mg, yield 75%) from 34 mg of **2a**; *er* 92.0:8.0; $[\alpha]_D^{20}$ = −17.4 (c = 0.05 in CH_2Cl_2); m.p. 188−189 °C; IR (neat) ν 3189, 1710, 1462, 1175, 797, 733, 550 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.53 (q, J = 7.2 Hz, 2H), 7.31−7.27 (m, 1H), 7.19−7.06 (m, 6H), 6.89−6.84 (m, 2H), 6.47 (d, J = 7.6 Hz, 3H), 6.31 (d, J = 3.2 Hz, 1H), 5.30 (d, J = 2.4 Hz, 1H), 5.02−4.95 (m, 2H), 4.19 (d, J = 16.0 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 174.8, 170.7, 163.0, 160.6, 142.9, 140.2, 134.8, 131.7 (d, $J_{C\text{-}F}$ = 2.9 Hz), 130.3, 129.7 (d, $J_{C\text{-}F}$ = 8.4 Hz), 128.6, 127.3, 127.0, 126.5, 124.5 (d, $J_{C\text{-}F}$ = 3.5 Hz), 124.3, 123.5, 120.9 (d, $J_{C\text{-}F}$ = 13.3 Hz), 117.9, 115.0 (d, $J_{C\text{-}F}$ = 22.5 Hz), 109.6, 67.3, 48.3, 44.0; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{19}FN_2NaO_2^+$ 421.1323, found 421.1300; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 14.2 min (major), 18.3 min (minor).

Spirocyclic lactam (**3ia**). White solid (32 mg, yield 81%) from 34 mg of **2a**; *er* 97.0:3.0 $[\alpha]_D^{20}$ = +15.1 (c = 0.05 in CH_2Cl_2); m.p. 271−272 °C; IR (neat) ν 3175, 2919, 1707, 1341, 945, 752, 487 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, J = 7.2 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.23−7.12 (m, 5H), 7.09−7.03 (m, 3H), 6.62 (s, 1H), 6.42 (d, J = 7.6 Hz, 1H), 6.36−6.31 (m, 3H), 5.24 (d, J = 2.4 Hz, 1H), 5.05 (d, J = 16.0 Hz, 1H), 4.85 (t, J = 2.8 Hz, 1H), 4.10 (d, J = 15.9 Hz, 1H), 1.62 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 175.2, 171.0, 143.2, 141.9, 138.2, 134.7, 132.4, 130.9, 130.4, 130.2, 128.7, 128.1, 128.0, 127.2, 126.5, 126.4, 124.0, 123.3, 118.3, 109.8, 67.9, 52.6, 44.1, 19.4; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{26}H_{22}N_2NaO_2^+$ 417.1573, found 417.1555; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 12.0 min (major), 15.6 min (minor).

Spirocyclic lactam (**3ja**). White solid (39 mg, yield 98%) from 34 mg of **2a**; *er* 90.0:10.0; $[\alpha]_D^{20}$ = +15.1 (c = 0.05 in CH_2Cl_2); m.p. 225−226 °C; IR (neat) ν 2919, 1699, 1462, 1175, 936, 755, 621 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.54 (d, J = 7.2 Hz, 1H), 7.22−7.10 (m, 6H), 6.99 (t, J = 8.0 Hz, 1H), 6.80−6.75 (m, 3H), 6.50−6.49 (m, 3H), 6.33 (s, 1H), 5.36 (s, 1H), 4.95 (d, J = 15.9 Hz, 1H), 4.46 (s, 1H), 4.19 (d, J = 16.0 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 174.7, 170.8, 162.6 (d, $J_{C\text{-}F}$ = 246.8 Hz), 143.3, 139.9, 135.9 (d, $J_{C\text{-}F}$ = 7.5 Hz), 134.7, 130.6, 130.0 (d, $J_{C\text{-}F}$ = 8.1 Hz), 128.6, 127.4, 127.0, 126.5, 125.7, 123.7, 123.6, 118.4, 116.8 (d, $J_{C\text{-}F}$ = 22.1 Hz), 115.4 (d, $J_{C\text{-}F}$ = 21.0 Hz). 109.8, 67.7, 56.8, 44.0; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{19}FN_2NaO_2^+$ 421.1323, found 421.1334; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 16.5 min (major), 17.7 min (minor).

Spirocyclic lactam (**3ka**). White solid (43 mg, yield 94%) from 34 mg of **2a**; *er* 93.5:6.5; $[\alpha]_D^{20}$ = +11.7 (c = 0.05 in CH_2Cl_2); m.p. 194−195 °C; IR (neat) ν 3193, 1704, 1612, 1347, 1173, 758, 553 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.55−7.52 (m, 1H), 7.44−7.42 (m, 1H), 7.23 (dd, J = 6.4, 1.2 Hz, 1H), 7.20−7.13 (m, 5H), 7.07 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.50 (t, J = 6.4 Hz, 4H), 6.37−6.35 (m, 1H), 5.38 (d, J = 3.2 Hz, 1H), 4.98 (d, J = 16.0 Hz, 1H), 4.43 (t, J = 3.2 Hz, 1H), 4.18 (d, J = 16.0 Hz, 1H); $^{13}C\{^1H\}$ ($CDCl_3$, 100 MHz) δ 174.6, 170.6, 143.2, 139.6, 135.7, 134.6, 132.8, 131.6, 130.7, 130.2, 128.7, 128.6, 127.5, 126.8, 126.5, 123.7, 123.6, 122.5, 118.5, 109.9, 67.6, 56.8, 44.1 HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{19}BrN_2NaO_2^+$ 481.0522, found 481.0523; HPLC analysis (CHIRALCEL IG, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 36.0 min (minor), 43.9 min (major).

Spirocyclic lactam (**3la**). White solid (41 mg, yield 95%) from 34 mg of 2a; *er* 99.5:0.5; $[\alpha]_D^{20}$ = +27.3 (c = 0.05 in CH_2Cl_2); m.p. 242−243 °C; IR (neat) ν 3193, 1700, 1612, 1341, 1173, 755, 478 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.84−7.79 (m, 2 H), 7.75−7.72 (m, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.33−7.29 (m, 1H), 7.24−7.17 (m, 2H), 7.14−7.09 (m, 1H), 7.04−7.00 (m, 2H), 6.87 (t, J = 7.6 Hz, 2H), 6.77 (s, 1H), 6.43 (d, J = 3.2 Hz, 1H), 6.17 (d, J = 8.0 Hz, 1H), 6.01 (d, J = 7.6 Hz, 1H), 5.43 (t, J = 3.2 Hz, 1H), 5.36 (d, J = 2.8 Hz, 1H), 4.83 (d, J = 16.0 Hz, 1H), 3.98 (d, J = 16.0 Hz, 1H) $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 175.0, 170.9, 143.3, 141.7, 134.3, 133.6, 132.6, 130.44, 130.40, 128.9, 128.7, 128.3, 128.1, 127.0, 125.9, 125.7, 125.6, 125.5, 123.7, 123.4, 121.9, 119.2, 109.9, 68.1, 51.2, 43.9; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{29}H_{22}N_2NaO_2^+$ 453.1573, found 453.1563; HPLC analysis (CHIRALCEL OD-H, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 20.7 min (major), 44.9 min (minor).

Spirocyclic lactam (**3ma**). White solid (30 mg, yield 81%) from 34 mg of **2a**; *er* 92.0:8.0; $[\alpha]_D^{20}$ = +27.3 (c = 0.05 in CH_2Cl_2); m.p. 196−197 °C; IR (neat) ν 3263, 1711, 1611, 1347, 1174, 735, 547 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (d, J = 7.2 Hz, 1H), 7.23−7.21 (m, 5H), 7.14 (t, J = 7.2 Hz, 1H), 6.90−6.83 (m, 2H), 6.59 (d, J = 8.0 Hz, 1H), 6.44 (s, 1H), 6.33−6.30 (m, 2H), 6.25 (d, J = 2.8 Hz, 1H), 5.51 (d, J = 2.4 Hz, 1H), 5.00 (d, J = 15.9 Hz, 1H), 4.63 (s, 1H), 4.36 (d, J = 15.9 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 174.5, 170.1, 148.7, 143.2, 142.6, 138.4, 134.9, 130.5, 128.7, 127.5, 127.2, 127.1, 123.8, 123.5, 118.6, 110.7, 109.9, 109.7, 66.5, 50.6, 44.1; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{23}H_{18}N_2NaO_3^+$ 393.1210, found 393.1202; HPLC analysis (CHIRALCEL IG, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 33.7 min (major), 48.4 min (minor).

Spirocyclic lactam (**3 ab**). White solid (39 mg, yield 99%) from 35 mg of **2b**; *er* 91.5:8.5; $[\alpha]_D^{20}$ = −29.4 (c = 0.05 in CH_2Cl_2); m.p. 262−263 °C; IR (neat) ν 3267, 1979, 1712, 1495, 1159, 922, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.27 (m, 3H), 7.10−6.97 (m, 7H), 6.66 (s, 1H), 6.47−6.23 (m, 4H), 5.37 (s, 1H), 4.94 (d, J = 15.6 Hz, 1H), 4.47 (s, 1H), 4.11 (d, J = 15.6 Hz, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 174.9, 171.0, 140.9, 140.4, 134.8, 133.5, 133.1, 130.7, 130.0, 128.6, 128.3, 127.3, 127.2, 126.5, 124.4, 118.0, 109.5, 68.0, 57.4, 44.0, 21.2; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{26}H_{22}N_2NaO_2^+$ 417.1573, found 417.1556; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 11.3 min (major), 17.1 min (minor).

Spirocyclic lactam (**3ac**). White solid (36 mg, yield 91%) from 35 mg of 2c; *er* 89.5: 10.5; $[\alpha]_D^{20}$ = +24.7 (c = 0.05 in CH_2Cl_2); m.p. 236−237 °C; IR (neat) ν 2919, 1703, 1447, 1183, 1025, 732, 482 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, J = 6.8 Hz, 1H), 7.35 (t, J = 7.2 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.12−7.00 (m, 7H), 6.45 (s, 1H), 6.34 (d, J = 3.2 Hz, 1H), 6.22 (d, J = 7.2 Hz, 2H), 5.37 (d, J = 3.2 Hz, 1H), 5.12 (d, J = 17.2 Hz, 1H), 4.53−4.83 (m, 2H), 2.02 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 175.8, 170.9, 141.5, 140.4, 136.8, 134.4, 133.4, 130.2, 128.7, 128.6, 128.4, 128.0, 126.7, 125.0, 123.5, 121.8, 120.4, 118.0, 67.2, 57.7, 45.2, 18.5; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{26}H_{22}N_2NaO_2^+$ 417.1573, found 417.1557; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 13.5 min (major), 15.2 min (minor).

Spirocyclic lactam (**3ad**). White solid (32 mg, yield 78%) from 37 mg of **2d**; *er* 91.5:8.5; $[\alpha]_D^{20}$ = +14.2 (c = 0.05 in CH_2Cl_2); m.p. 252−253 °C; IR (neat) ν 2856, 1984, 1706, 1448, 1153, 929, 747 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.83 (s, 1H), 7.44 (s, 1H), 7.40−7.36

(m, 1H), 7.27 (t, J = 8.0 Hz, 2H), 7.14–7.06 (m, 3H), 7.04–6.97 (m, 2H), 6.84 (s, 1H), 6.29 (d, J = 5.6 Hz, 2H), 6.06 (s, 1H), 5.16 (s, 1H), 4.92 (d, J = 17.2 Hz, 1H), 4.67–4.61 (m, 2H), 2.31 (s, 3H), 1.91 (s, 3H); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 100 MHz) δ 176.3, 170.3, 142.9, 139.0, 137.7, 134.4, 134.3, 132.6, 130.2, 129.0, 128.9, 128.8, 128.6, 127.0, 125.4, 123.4, 119.6, 115.4, 67.4, 56.4, 44.5, 20.9, 18.1; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{27}H_{24}N_2NaO_2^+$ 431.1730, found 431.1712; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 10.5 min (major), 13.7 min (minor).

Spirocyclic lactam ***(3ae)***. White solid (39 mg, yield 95%) from 37 mg of **3e**; *er* 94.0:6.0; $[\alpha]_D^{20}$ = −31.7 (c = 0.05 in CH_2Cl_2); m.p. 210–211 °C; IR (neat) ν 3322, 1982, 1700, 1458, 1177, 940, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33 (t, J = 7.2 Hz, 1H), 7.21–7.05 (m, 8H), 6.80 (s, 1H|), 6.69 (d, J = 8.4 Hz, 1H), 6.35–6.30 (m, 4H), 5.37 (d, J = 2.0 Hz, 1H), 4.93 (d, J = 16.0 Hz, 1H), 4.45 (s, 1H), 4.10 (d, J = 16.0 Hz, 1H), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 174.7, 171.1, 156.5, 140.3, 136.5, 134.8, 133.4, 130.0, 128.6, 128.3, 127.2, 126.5, 118.0, 114.8, 110.6, 110.3, 68.3, 57.5, 55.9, 44.1; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{26}H_{22}N_2NaO_3^+$ 433.1523, found 433.1507; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 16.0 min (major), 26.6 min (minor).

Spirocyclic lactam ***(3af)***. White solid (27 mg, yield 68%) from 36 mg of **3f**; *er* 85.0:15.0; $[\alpha]_D^{20}$ = −15.0 (c = 0.05 in CH_2Cl_2); m.p. 230–231 °C; IR (neat) ν 2920, 1716, 1484, 1188, 971, 694, 459 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.29 (m, 3H), 7.22 (t, J = 7.2 Hz, 2H), 7.14–7.00 (m, 6H), 6.56–6.36 (m, 4H), 5.40 (s, 1H), 4.87 (d, J = 15.6 Hz, 1H), 4.47–4.42 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 174.5, 170.8, 147.2 (d, $J_{C\text{-}F}$ = 246.8 Hz), 139.7, 135.9, 132.9, 130.3, 129.9, 128.7, 128.6, 128.4, 127.1, 126.5, 124.2 (d, $J_{C\text{-}F}$ = 6.3 Hz), 119.7, 118.7, 118.6 (d, $J_{C\text{-}F}$ = 23.9 Hz), 118.5, 67.8, 57.6, 45.4; HRMS (TOF-ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{19}FN_2NaO_2^+$ 421.1323, found 421.1309; HPLC analysis (CHIRALCEL IA, hexane/*i*-PrOH = 80/20, 0.8 mL/min, UV 254 nm) t_R = 13.9 min (major), 18.2 min (minor).

Spirocyclic lactam ***(4)***. White solid (24 mg, yield 62%) from 38 mg of **3aa**; *er* 96.0:4.0; $[\alpha]_D^{20}$ = −32.2 (c = 0.05 in CH_2Cl_2); m.p. 252–253 °C; IR (neat) ν 3357, 2920, 1707, 1079, 798, 691, 450 cm^{-1}; ^1H NMR (d_6-DMSO, 400 MHz) δ 8.95 (s, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.29–7.18 (m, 7H), 7.07 (t, J = 7.2 Hz, 1H), 6.97 (d, J = 7.2 Hz, 2H), 6.87 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 7.2 Hz, 2H), 4.97 (d, J = 16.0 Hz, 1H), 4.77 (d, J = 16.0 Hz, 1H), 1.86 (s, 3H); $^{13}C\{^1H\}$ NMR (d_6-DMSO, 100 MHz) δ 174.1, 173.4, 150.1, 143.5, 135.8, 132.6, 132.0, 130.5, 129.3, 129.00, 128.97, 128.1, 127.8, 127.3, 126.0, 124.6, 123.7, 110.4, 70.1, 43.7, 10.2; HRMS (TOF-ESI) m/z $[M + K]^+$ calcd for $C_{25}H_{20}KN_2O_2^+$ 419.1156, found 419.1187; HPLC analysis (CHIRALCEL IG, hexane/*i*-PrOH = 70/30, 1.0 mL/min, UV 254 nm) t_R = 21.8 min (major), 29.2 min (minor).

Spirocyclic lactam ***(5)***. White solid (40 mg, yield 91%) from 38 mg of **3aa**; *er* 98.5:1.5; $[\alpha]_D^{20}$ = −22.8 (c = 0.05 in CH_2Cl_2); m.p. 236–237 °C; IR (neat) ν 3379, 1709, 1363, 1175, 987, 748, 591 cm^{-1}; ^1H NMR (d_6-DMSO, 400 MHz) δ 8.58 (s, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.33 (t, J = 7.2 Hz, 1H), 7.24–7.13 (m, 5H), 7.08 (t, J = 7.6 Hz, 2H), 6.94 (d, J = 7.6 Hz, 2H), 6.52 (d, J = 7.6 Hz, 1H), 6.47 (d, J = 7.3 Hz, 2H), 4.80–4.72 (m, 2H), 4.65 (ddd, J = 14.5, 8.3, 6.7 Hz, 1H), 4.37 (d, J = 16.0 Hz, 1H), 3.85 (d, J = 12.4 Hz, 1H), 3.57 (ddd, J = 12.2, 7.8, 6.2 Hz, 1H), 2.39–2.30 (m, 1H), 2.07–1.99 (m, 1H); $^{13}C\{^1H\}$ NMR (d_6-DMSO, 100 MHz) δ 177.8, 175.8, 143.3, 135.6, 134.0, 130.3, 128.87, 128.85, 128.7, 128.6, 128.0, 127.4, 126.7, 124.7, 123.4, 109.7, 73.2, 67.5, 56.8, 43.0, 27.4; HRMS (TOF-ESI) m/z $[M + K]^+$ calcd for $C_{26}H_{23}KN_3O_4^+$ 480.1320, found 480.1353; HPLC analysis (CHIRALCEL IG, hexane/*i*-PrOH = 80/30, 1.0 mL/min, UV 254 nm) t_R = 28.1 min (major), 49.6 min (minor).

Declaration of competing interest

The authors declare no competing financial interest.

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Appendix A. Supplementary data

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References

[1] (a) C.V. Galliford, K.A. Scheidt, Angew. Chem. Int. Ed. 46 (2007) 8748–8758;
(b) M. Rottmann, C. McNamara, B.K. Yeung, M.C. Lee, B. Zou, B. Russell, P. Seitz, D.M. Plouffe, N.V. Dharia, J. Tan, S.B. Cohen, K.R. Spencer, G.E. Gonzalez-Paez, S.B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E.K. Schmitt, H.P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T.H. Keller, D.A. Fidock, E.A. Winzeler, T.T. Diagana, Science 329 (2010) 1175–1180;
(c) V.V. Vintonyak, K. Warburg, H. Kruse, S. Grimme, K. Hubel, D. Rauh, H. Waldmann, Angew. Chem. Int. Ed. 49 (2010) 5902–5905;
(d) B.K. Yeung, B. Zou, M. Rottmann, S.B. Lakshminarayana, S.H. Ang, S.Y. Leong, J. Tan, J. Wong, S. Keller-Maerki, C. Fischli, A. Goh, E.K. Schmitt, P. Krastel, E. Francotte, K. Kuhen, D. Plouffe, K. Henson, T. Wagner, E.A. Winzeler, F. Petersen, R. Brun, V. Dartois, T.T. Diagana, T.H. Keller, J. Med. Chem. 53 (2010) 5155–5164;
(e) Y. Zhao, L. Liu, W. Sun, J. Lu, D. McEachern, X. Li, S. Yu, D. Bernard, P. Ochsenbein, V. Ferey, J.C. Carry, J.R. Deschamps, D. Sun, S. Wang, J. Am. Chem. Soc. 135 (2013) 7223–7234;
(f) A. Aguilar, W. Sun, L. Liu, J. Lu, D. McEachern, D. Bernard, J.R. Deschamps, S. Wang, J. Med. Chem. 57 (2014) 10486–10498;
(g) A. Kumar, G. Gupta, A.K. Bishnoi, R. Saxena, K.S. Saini, R. Konwar, S. Kumar, A. Dwivedi, Bioorg. Med. Chem. 23 (2015) 839–848;
(h) B. Yu, D.Q. Yu, H.M. Liu, Eur. J. Med. Chem. 97 (2015) 673–698;
(i) B. Yu, Z. Yu, P.P. Qi, D.Q. Yu, H.M. Liu, Eur. J. Med. Chem. 95 (2015) 35–40.
[2] (a) N.R. Ball-Jones, J.J. Badillo, A.K. Franz, Org. Biomol. Chem. 10 (2012) 5165–5181;
(b) G.S. Singh, Z.Y. Desta, Chem. Rev. 112 (2012) 6104–6155;
(c) L. Hong, R. Wang, Adv. Synth. Catal. 355 (2013) 1023–1052;
(d) Y.L. Liu, X. Wang, Y.L. Zhao, F. Zhu, X.P. Zeng, L. Chen, C.H. Wang, X.L. Zhao, J. Zhou. *Angew. Chem. Int. Ed.* 52 (2013) 13735–13739;
(e) D. Cheng, Y. Ishihara, B. Tan, C.F. Barbas, ACS Catal. 4 (2014) 743–762;
(f) X.P. Yin, X.P. Zeng, Y.L. Liu, F.M. Liao, J.S. Yu, F. Zhou, J. Zhou. *Angew. Chem. Int. Ed.* 53 (2014) 13740–13745;
(g) W. Tang, D. Du, Chem. Rec. 16 (2016) 1489–1500;
(h) Z.Y. Cao, F. Zhou, J. Zhou, Acc. Chem. Res. 51 (2018) 1443–1454;
(i) G.J. Mei, F. Shi, Chem. Commun. 54 (2018) 6607–6621;
(j) L.-L. Zhang, J.-W. Zhang, S.-H. Xiang, Z. Guo, B. Tan, Chin. J. Chem. 36 (2018) 1182–1186;
(k) Y.H. Wang, J.S. Tian, P.W. Tan, Q. Cao, X.X. Zhang, Z.Y. Cao, F. Zhou, X. Wang, J. Zhou. *Angew. Chem. Int. Ed.* 59 (2020) 1634–1643.
[3] (a) H. Krawczyk, Ł. Albrecht, J. Wojciechowski, W.M. Wolf, U. Krajewska, M. Różalski, Tetrahedron 64 (2008) 6307–6314;
(b) A.S.-Y. Lee, Y.-T. Chang, Tetrahedron Lett. 51 (2010) 3800–3802;
(c) H.L. Teng, F.L. Luo, H.Y. Tao, C.J. Wang, Org. Lett. 13 (2011) 5600–5603;
(d) A. Janecka, A. Wyrebska, K. Gach, J. Fichna, T. Janecki, Drug Discov. Today 17 (2012) 561–572;
(e) W. Delong, W. Lanying, W. Yongling, S. Shuang, F. Juntao, Z. Xing, Eur. J. Med. Chem. 130 (2017) 286–307.
[4] (a) B.D. Cui, J. Zuo, J.Q. Zhao, M.Q. Zhou, Z.J. Wu, X.M. Zhang, W.C. Yuan, J. Org. Chem. 79 (2014) 5305–5314;
(b) F. Tan, L.Q. Lu, Q.Q. Yang, W. Guo, Q. Bian, J.R. Chen, W.J. Xiao, Chem. Eur J. 20 (2014) 3415–3420;
(c) L. Chen, Z.J. Wu, M.L. Zhang, D.F. Yue, X.M. Zhang, X.Y. Xu, W.C. Yuan, J. Org. Chem. 80 (2015) 12668–12675;
(d) K.Q. Chen, Y. Li, C.L. Zhang, D.Q. Sun, S. Ye, Org. Biomol. Chem. 14 (2016) 2007–2014;
(e) F. Tan, W. Xiao, G. Zeng, *Chin. J. Org. Chem.* 37 (2017) 824;
(f) P. Yang, X. Wang, F. Chen, Z.B. Zhang, C. Chen, L. Peng, L.X. Wang, J. Org. Chem. 82 (2017) 3908–3916;
(g) X.Y. Chen, J.W. Xiong, Q. Liu, S. Li, H. Sheng, C. von Essen, K. Rissanen, D. Enders, Angew. Chem. Int. Ed. 57 (2018) 300–304;
(h) T. Sengoku, D. Hayashi, M. Takahashi, H. Yoda, Eur. J. Org Chem. (2018) 1813–1820.
[5] (a) H. Lv, B. Tiwari, J. Mo, C. Xing, Y.R. Chi, Org. Lett. 14 (2012) 5412–5415;
(b) B. Zhang, P. Feng, L.H. Sun, Y. Cui, S. Ye, N. Jiao, Chem. Eur J. 18 (2012) 9198–9203.
[6] D. Jiang, S. Dong, W. Tang, T. Lu, D. Du, J. Org. Chem. 80 (2015) 11593–11597.
[7] (a) Q. Chen, J. Liang, S. Wang, D. Wang, R. Wang, Chem. Commun. 49 (2013)

1657–1659;
(b) W.Y. Han, S.W. Li, Z.J. Wu, X.M. Zhang, W.C. Yuan, Chem. Eur J. 19 (2013) 5551–5556;
(c) X.L. Liu, W.Y. Han, X.M. Zhang, W.C. Yuan, Org. Lett. 15 (2013) 1246–1249;
(d) H. Wu, L.L. Zhang, Z.Q. Tian, Y.D. Huang, Y.M. Wang, Chem. Eur J. 19 (2013) 1747–1753;
(e) R. Chowdhury, M. Kumar, S.K. Ghosh, Org. Biomol. Chem. 14 (2016) 11250–11260;
(f) L. Liu, B.-L. Zhao, D.-M. Du, Eur. J. Org Chem. 2016 (2016) 4711–4718;
(g) N. Lin, X.-w. Long, Q. Chen, W.-r. Zhu, B.-c. Wang, K.-b. Chen, C.-w. Jiang, J. Weng, G. Lu, Tetrahedron 74 (2018) 3734–3741;
(h) W.-R. Zhu, Q. Chen, N. Lin, K.-B. Chen, Z.-W. Zhang, G. Fang, J. Weng, G. Lu, Org. Chem. Front. 5 (2018) 1375–1380.

[8] (a) D. Basavaiah, A.J. Rao, T. Satyanarayana, Chem. Rev. 103 (2003) 811–892;
(b) K. Jiang, J. Peng, H.L. Cui, Y.C. Chen, Chem. Commun. (2009) 3955–3957;
(c) T.Y. Liu, M. Xie, Y.C. Chen, Chem. Soc. Rev. 41 (2012) 4101–4112;
(d) P. Xie, Y. Huang, Org. Biomol. Chem. 13 (2015) 8578–8595;
(e) N.J. Zhong, Y.Z. Wang, L. Cheng, D. Wang, L. Liu, Org. Biomol. Chem. 16 (2018) 5214–5227.

[9] (a) I. Namboothiri, D. Nair, T. Kumar, Synlett 27 (2016) 2425–2442;
(b) Y. Zheng, J. Wang, P.J. Xia, Q.L. Zhao, J.A. Xiao, H.Y. Xiang, X.Q. Chen, H. Yang, J. Org. Chem. 82 (2017) 12202–12208.

[10] Q.L. Wang, L. Peng, F.Y. Wang, M.L. Zhang, L.N. Jia, F. Tian, X.Y. Xu, L.X. Wang, Chem. Commun. 49 (2013) 9422–9424.

[11] (a) B. Cui, Y. Chen, J. Shan, L. Qin, C. Yuan, Y. Wang, W. Han, N. Wan, Y. Chen, Org. Biomol. Chem. 15 (2017) 8518–8522;
(b) C.-W. Lei, C.-B. Zhang, Z.-H. Wang, K.-X. Xie, J.-Q. Zhao, M.-Q. Zhou, X.-M. Zhang, X.-Y. Xu, W.-C. Yuan, Org. Chem. Front. 7 (2020) 499–506.

[12] J.W. Ren, Q.L. Zhao, J.A. Xiao, P.J. Xia, H.Y. Xiang, X.Q. Chen, H. Yang, Chem. Eur J. 25 (2019) 4673–4677.

[13] J.W. Ren, L. Zheng, Z.P. Ye, Z.X. Deng, Z.Z. Xie, J.A. Xiao, F.W. Zhu, H.Y. Xiang, X.Q. Chen, H. Yang, Org. Lett. 21 (2019) 2166–2170.

[14] (a) A. Grandbois, S.K. Collins, Chem. Eur J. 14 (2008) 9323–9329;
(b) A. Lattanzi, C. De Fusco, A. Russo, A. Poater, L. Cavallo, Chem. Commun. 48 (2012) 1650–1652.

[15] D.J.V.C. van Steenis, T. Marcelli, M. Lutz, A.L. Spek, J.H. van Maarseveen, H. Hiemstra, Adv. Synth. Catal. 349 (2007) 281–286.

[16] J. Chen, B.Q. Huang, Z.Q. Wang, X.J. Zhang, M. Yan, Org. Lett. 21 (2019) 9742–9746.

[17] T. Emura, T. Esaki, K. Tachibana, M. Shimizu, J. Org. Chem. 71 (2006) 8559–8564.

[18] A.P. Jadhav, V.U. Bhaskara Rao, P. Singh, R.G. Gonnade, R.P. Singh, Chem. Commun. 51 (2015) 13941–13944.