Tetrahedron 69 (2013) 7019–7025

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Lewis acid catalyzed formation of 3-amino-3-carboxy-tetrahydroquinoline derivatives via tandem 1,5-hydride transfer/cyclization process

Wen-Yong Han [a,c], Jian Zuo [a,c], Zhi-Jun Wu [b], Xiao-Mei Zhang [a], Wei-Cheng Yuan [a,*]

[a] National Engineering Research Center of Chiral Drugs, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China
[b] Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China
[c] University of Chinese Academy of Sciences, Beijing 100049, China

ARTICLE INFO

Article history:
Received 21 April 2013
Received in revised form 29 May 2013
Accepted 13 June 2013
Available online 21 June 2013

Keywords:
Lewis acid
1,5-Hydride transfer
Tetrahydroquinolines
Spirocyclic skeleton
(*Z*)-Alkylidene azlactone

ABSTRACT

A $Sc(OTf)_3$-catalyzed intramolecular tandem 1,5-hydride transfer/cyclization process to construct 3-amino-3-carboxy-tetrahydroquinoline derivatives has been developed. The methodology gives access to a range of relatively complex tetrahydroquinolines (tetracyclic and pentacyclic heterocycles bearing spirocyclic skeleton and two stereogenic centers) in good to excellent yields with diastereoselectivities ranging from 57:43 to 73:27. The synthetic utility of the method was also demonstrated by an efficient ring opening derivatization reaction.

1. Introduction

Tetrahydroquinoline scaffolds belong to an important class of heterocycles and are found in a number of naturally occurring and biologically active compounds (Fig. 1).[1] Some tetrahydroquinoline compounds are useful building blocks for the synthesis of many pharmaceutical and agrochemical reagents, as well as for the total synthesis of some natural products.[1,2] In accord with the importance, there have been a lot of interests in the development of synthetic methodologies to access various tetrahydroquinoline compounds. In this regard, diverse tetrahydroquinoline derivatives have been designed and prepared with metal-based and organocatalytic strategies.[3] Despite that important progress in the field of the synthesis of diverse tetrahydroquinoline derivatives has been made, to the best of our knowledge, the construction of a class of promising tetrahydroquinoline compounds, which possess a 3-amino-3-carboxy-tetrahydroquinoline scaffold and can be characterized as a kind of cyclic α-quaternary α-amino acids,[4] remains unexplored so far. Given the fact that different class of tetrahydroquinoline skeletons may show promise as certain biologically relevant compounds, hence, the development of elegant and efficient protocol for preparing 3-amino-3-carboxy-tetrahydroquinoline compounds is highly desirable.

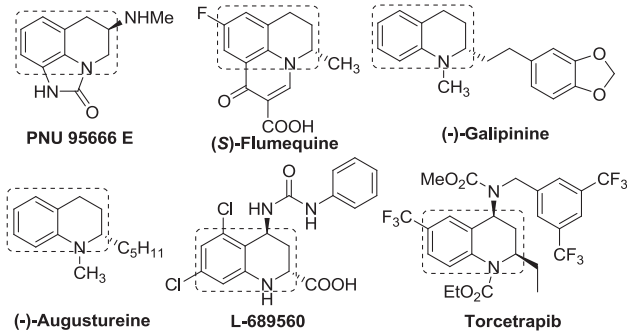


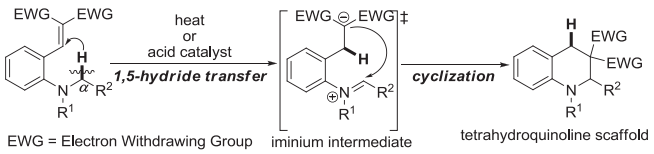
Fig. 1. Some biologically active compounds containing a tetrahydroquinoline skeleton.

The functionalization of sp^3 C–H bond via intramolecular tandem 1,5-hydride transfer/cyclization process represents an important topic in synthetic organic chemistry.[5] As shown in Scheme 1, in that process, the C–H bond α to the nitrogen atom is firstly cleaved via a 1,5-hydride shift to form an iminium intermediate, and then

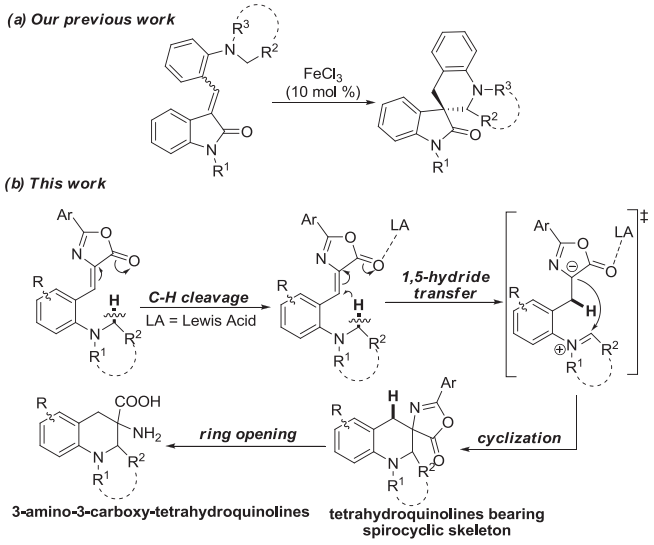
* Corresponding author. E-mail addresses: yuanwc@cioc.ac.cn, yuanweicheng@126.com (W.-C. Yuan).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.06.047

undergoes a cyclization reaction to afford tetrahydroquinoline scaffold. Much effort has been devoted to this tandem transformation by applying it for the construction of various tetrahydroquinoline derivatives.[6] We recently reported an efficient $FeCl_3$-catalyzed stereoselective intramolecular 1,5-hydride transfer/cyclization reaction for generating structurally diverse spirooxindole tetrahydroquinolines (Scheme 2 (a)).[7] Enlightened by the related literature[5,6] and the fact that alkylidene azlactones belong to a type of highly reactive Michael acceptors,[8] we reasoned that with appropriate alkylidene azlactone derivatives as substrates and certain Lewis acids as catalysts via a 1,5-hydride transfer and subsequent cyclization, the reaction should offer the possibility to access a new family of tetrahydroquinoline derivatives bearing spirocyclic skeleton, which could be further transformed to 3-amino-3-carboxy-tetrahydroquinoline compounds (Scheme 2 (b)). In parallel with our efforts to develop new catalytic system for the synthesis of heterocyclic compounds,[7,9] herein, we present the results of our endeavors on this subject.



Scheme 1. The functionalization of sp^3 C–H bond via 1,5-hydride transfer/cyclization process.

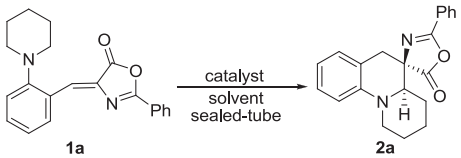


Scheme 2. (a) Intramolecular tandem 1,5-hydride transfer/cyclization process for the synthesis of spirooxindole tetrahydroquinolines. (b) Strategy for the synthesis of 3-amino-3-carboxy-tetrahydroquinolines with intramolecular tandem 1,5-hydride transfer/cyclization process.

2. Results and discussion

To test our hypothesis, we decided to initiate our study by using (*Z*)-alkylidene azlactone **1a**[10] as a model substrate for screening of the reaction conditions (Table 1). A control experiment revealed that the planed 1,5-hydride transfer/cyclization process could take place in mesitylene without any catalyst, but a harsh condition high to 190 °C in sealed-tube was needed. Even so, the expected product **2a** could be isolated in only 32% yield with diastereoselective ratio (dr) of 62:38 after 24 h (Table 1, entry 1). However, to our delight, adding 20 mol % $Sc(OTf)_3$ into the reaction system, we were able to isolate the product **2a** in 85% yield with 65:35 dr after 3 h (Table 1, entry 2). After further examination to some other Lewis acids, it was observed that $Mg(ClO_4)_2$, $Zn(OTf)_2$, CuOTf, $NiCl_2$, $FeCl_3$, $Ni(OAc)_2$, $Cu(OTf)_2$, and $AgNO_3$ were inferior to $Sc(OTf)_3$ for the conversion (Table 1, entries 3–10). These results reveal that, to a large extent, the tolerance of the Lewis acids to the high temperature and the acidity of the Lewis acids play a dramatic effect on the reactivity. Afterward, we investigated the influence of the solvent, mesitylene proved to be the best choice as reaction medium for the 1,5-hydride transfer/cyclization process (Table 1, entry 2 vs entries 11–13). And then, the catalyst loading was tested, conducting the experiment with 5 mol % and 10 mol % catalyst loading, respectively, it was found that the reactions showed analogous diastereoselectivity and reactivity (Table 1, entries 14 and 15). Ultimately, increasing the catalyst loading to 30 mol % allowed the full conversion of the starting material within 1 h, giving the product **2a** in 90% yield with 69:31 dr (Table 1, entry 16).

Table 1
Screening of reaction conditions[a]



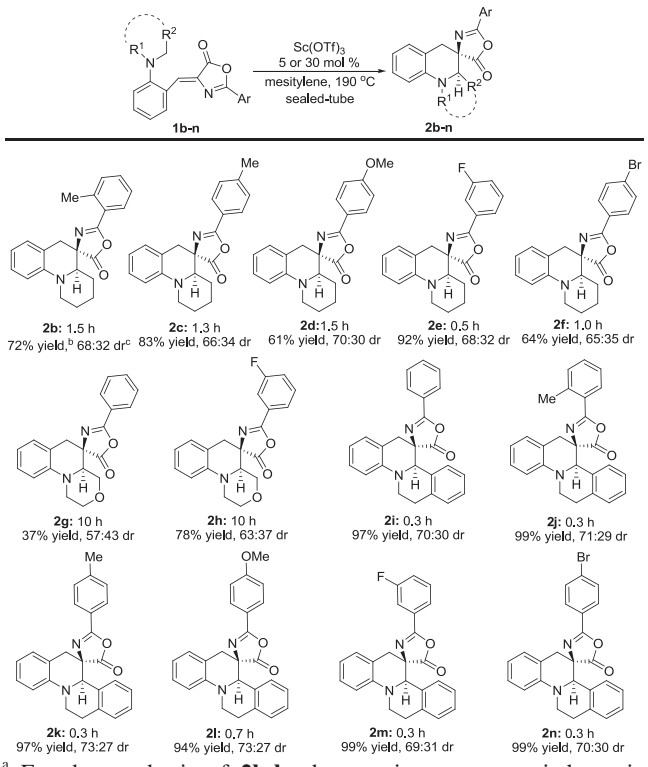
Entry	Solvent	Catalyst	Time (h)	Dr[b]	Yield (%)[c]
1	Mesitylene		24	62:38	32
2	Mesitylene	$Sc(OTf)_3$	3	65:35	85
3	Mesitylene	$Mg(ClO_4)_2$	5	60:40	25
4	Mesitylene	$Zn(OTf)_2$	5	65:35	26
5	Mesitylene	CuOTf	5	69:31	18
6	Mesitylene	$NiCl_2$	5	63:37	38
7	Mesitylene	$FeCl_3$	5	59:41	71
8	Mesitylene	$Ni(OAc)_2$	5	nd[d]	<10
9	Mesitylene	$Cu(OTf)_2$	5	nd	<10
10	Mesitylene	$AgNO_3$	5	55:45	76
11	DCE	$Sc(OTf)_3$	24	nd	<10[e]
12	Toluene	$Sc(OTf)_3$	24	nd	<10[f]
13	CH_3CN	$Sc(OTf)_3$	24	nd	Trace[e]
14	Mesitylene	$Sc(OTf)_3$	5	66:34	82[g]
15	Mesitylene	$Sc(OTf)_3$	5	66:34	83[h]
16	Mesitylene	$Sc(OTf)_3$	1	69:31	90[i]

[a] Unless otherwise specified, all reactions were carried out in sealed-tube with **1a** (0.1 mmol) and 20 mol % catalyst in 2.0 mL of specified solvent at 190 °C for the stated time.
[b] Determined by ^1H NMR.
[c] Isolated yield of diastereomeric mixture.
[d] Not determined.
[e] Run at 100 °C.
[f] Run at 150 °C.
[g] 5 mol % of $Sc(OTf)_3$ was used.
[h] 10 mol % of $Sc(OTf)_3$ was used.
[i] 30 mol % of $Sc(OTf)_3$ was used. DCE=1,2-dichloroethane.

Having identified a useful set of reaction conditions, we next examined the reaction scope by subjecting various (*Z*)-alkylidene azlactones **1b**–**n**[10] to the $Sc(OTf)_3$-catalyzed intramolecular 1,5-hydride transfer/cyclization process. The results are summarized in Table 2, generally, the expected 3-amino-3-carboxy-tetrahydroquinoline derivatives **2b**–**n** bearing spirocyclic skeleton were able to be obtained in moderate to excellent yields (37–99%) with diastereoselectivities ranging from 57:43 to 73:27. For the piperidine derived substrates **1b**–**f**, it was found that the reaction proceeded smoothly, leading to the expected heterocyclic products **2b**–**f** with good results independently of the substitution pattern on the Ar group. Nevertheless, under the same reaction conditions, the related morpholine derived substrates **1g**–**h** required a relatively prolonged reaction time for delivering the corresponding 3-amino-3-carboxy-tetrahydroquinoline derivatives **2g** and **2h**.

Gratifyingly, perhaps due to the superior hydride donor capability of benzylic over aliphatic secondary C–H bond, the tetrahydroisoquinoline derivatives **1i**–**n** more easily underwent the intramolecular 1,5-hydride transfer/cyclization reaction than those piperidine and morpholine derived substrates, giving the corresponding products **2i**–**n** in almost quantitative yields after shorter reaction time with only 5 mol % $Sc(OTf)_3$. Additionally, we also surveyed the reactivity of the corresponding pyrrolidine derived substrates. Unfortunately, the reaction was very complicated as monitored by thin layer chromatography (TLC) analysis and no desired product was obtained. We surmised that the failure of this reaction was probably caused by the harsh reaction temperature. However, when we tried to perform the reaction at 100 °C with corresponding pyrrolidine-based substrate, the reaction still did not take place. Nevertheless, we also found that the starting materials, which incorporate acyclic amines, such as corresponding *N*-methyl-1-phenylmethanamine-based substrate, were not able to tolerate the reaction conditions and could not give the expected products (data not shown).

Table 2
$Sc(OTf)_3$-catalyzed intramolecular 1,5-hydride transfer/cyclization process of **1**[a]

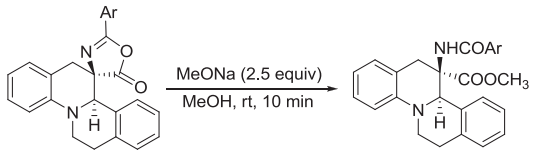


[a] For the synthesis of **2b-h**, the reactions were carried out in sealed-tube under argon atmosphere with **1** (0.2 mmol) and 30 mol % $Sc(OTf)_3$ in 4.0 mL mesitylene at 190 °C for the specified time; for the synthesis of **2i-n**, the reactions were carried out in sealed-tube under argon atmosphere with **1** (0.2 mmol) and 5 mol % $Sc(OTf)_3$ in 4.0 mL mesitylene at 190 °C for the specified time.

[b] Isolated yield of diastereomeric mixture, the same note applies to all of the other products.

[c] Determined by ^1H NMR, the same note applies to all of the other products.

With a library of relatively complex products **2a**–**n** (tetracyclic and pentacyclic heterocycles bearing spirocyclic skeleton and two stereogenic centers) in hand, the synthetic utility of the methodology was further demonstrated by the transformations of some products into the relevant ring opening compounds (Scheme 3). We chose products **2i**, **2k**, and **2n** as the research subjects regardless of the substitution pattern on the Ar group. Upon the treatment of these products with sodium methoxide in methanol at room temperature for 10 min, respectively, we could readily obtain the corresponding ring opening compounds **3i**, **3k**, and **3n** in quantitative yield and almost no change in diastereoselectivity (Scheme 3). It is worth noting that these ring opening compounds possess a special 3-amino-3-carboxy-tetrahydroquinoline scaffold, particularly bearing amino and carboxyl two potential points for structural diversification as a prelude to library synthesis.



Scheme 3. Transformation of the products **2i**, **2k**, and **2n** to corresponding ring opening compounds.

Finally, considering the fact that no reaction occurred at the stereogenic center in **2n** during its transformation into compound **3n** (Scheme 3), we reasoned that the compounds **2n** and **3n** should possess the same relative configuration. For the isomers **A**, as shown in the left of Fig. 2, there is a trans relationship between the H_a and the amide group, it should no NOE effect between the H_a and the H_c of amide group. On the other hand, for the isomers **B**, as shown in the right of Fig. 2, there is a cis relationship between the H_b and the amide group and it should give the NOE effect between the H_b and the H_c of amide group. Consequently, based on the NOE experiments the stereochemistry for the major and minor diastereoisomers of **3n** is able to be determined[11] As shown in Fig. 2, the major diastereoisomers of **3n** were assigned as isomers **A** and the minor diastereoisomers of **3n** were assigned as isomers **B**. Thereby, the relative configuration of product **2n** should be able to be determined with logical deduction. Assuming via a common reaction pathway in the construction of compounds **2a**–**n**, the stereochemistry of these 3-amino-3-carboxy-tetrahydroquinoline products in this work was assigned by analogy.

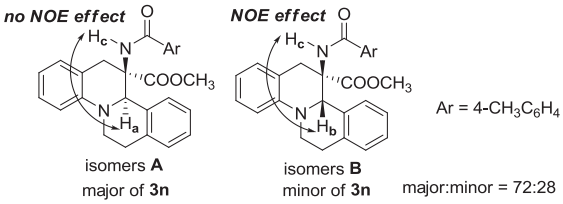


Fig. 2. The stereochemistry analysis of the products.

3. Conclusion

In conclusion, we have developed a $Sc(OTf)_3$-catalyzed intramolecular tandem 1,5-hydride transfer/cyclization reaction for the construction of a range of 3-amino-3-carboxy-tetrahydroquinoline derivatives. This protocol could afford the tetracyclic and pentacyclic tetrahydroquinoline products, containing a spirocyclic skeleton and two stereogenic centers, in good to excellent yields with diastereoselectivities ranging from 57:43 to 73:27. Additionally, we revealed that these relatively complex products could be readily transformed to cyclic α-quaternary α-amino acid analogous, and

the relative configurations of the products were tentatively determined by NOE experiments and derivatization. The method described here provides an efficient access to 3-amino-3-carboxytetrahydroquinoline frameworks, which are valuable for medicinal and pharmaceutical chemistry.

4. Experimental section

4.1. General

Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. ^{1}H NMR chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard. Data were reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet, br=broad, br s=broad singlet), coupling constants (Hertz), and integration. ^{13}C NMR chemical shifts were reported in ppm (δ) from tetramethylsilane (TMS) with the solvent resonance as the internal standard. Melting points were recorded on a Buchi Melting Point B-545 unit.

4.2. Representative procedure for the synthesis of (*Z*)-alkylidene azlactones

To a solution of 2-fluorobenzaldehyde (4.96 g, 40 mmol) and K_2CO_3 (6.36 g, 46 mmol) in DMF (40 mL) was added piperidine (4.56 mL, 46 mmol). The resulting reaction mixture was heated under reflux until complete consumption of 2-fluorobenzaldehyde. The reaction mixture was allowed to cool to room temperature, diluted with water, and extracted with ethyl acetate. The combined organic extracts were washed with a saturated NH_4C1 solution and concentrated under reduced pressure. The product 2-(piperidin-1-yl)benzaldehyde was utilized for next step without purification.

Glycine (5.0 g, 66.7 mmol) was dissolved in 50 mL of 10% NaOH solution. BzCl (10.79 mL, 93.0 mmol) was added to the solution and stirred vigorously for 30 min. Crushed ice (60 g) was added to the solution and then concentrated HCl was added dropwise until the mixture was acidified (pH 2–3). The precipitate was filtrated and washed with distilled water until neutrality. The product 2-benzamidoacetic acid was obtained after drying in vacuum.

A mixture of 2-(piperidin-1-yl)benzaldehyde (0.946 g, 5 mmol) and 2-benzamidoacetic acid (0.896 g, 5 mmol) was heated in 95 °C with the addition of NaOAc (2.5 mmol) and Ac_2O (5 mmol). After completion of the reaction, 2 mL ethanol was added to the mixture and was stirred for 10 h at room temperature. The solid was filtered off, washed with water, and ice-cold ethanol. The crude product was recrystallized from toluene to give the corresponding (*Z*)-alkylidene azlactones **1a** (Note: For the preparation of compounds **1b**–**n**, the corresponding crude products were recrystallized from ethanol to give the desired products **1b**–**n**).

*4.2.1. (Z)-2-Phenyl-4-(2-(piperidin-1-yl)benzylidene) oxazol-5(4H)-one (**1a**).* Orange solid, yield 50%; mp 146.0–147.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.61–1.65 (m, 2H), 1.77–1.84 (m, 4H), 2.95–2.98 (m, 4H), 7.07 (d, *J*=8.1 Hz, 1H), 7.15 (t, *J*=7.5 Hz, 1H), 7.39 (t, *J*=7.5 Hz, 1H), 7.49–7.61 (m, 3H), 7.76 (s, 1H), 8.17 (d, *J*=7.5 Hz, 2H), 8.68 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 24.1, 26.3, 55.0, 118.9, 122.5, 125.8, 127.2, 128.1, 128.8, 129.2, 132.0, 132.1, 132.9, 133.0, 155.9, 162.6, 168.0. HRMS (ESI-TOF) calcd for $C_{21}H_{21}N_2O_2$ $[M+H]^+$: 333.1598; found: 333.1599.

*4.2.2. (Z)-4-(2-(Piperidin-1-yl)benzylidene)-2-o-tolyloxazol-5(4H)-one (**1b**).* Red solid, yield 31%; mp 128.1–129.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.63 (d, *J*=5.1 Hz, 2H), 1.78–1.85 (m, 4H), 2.83 (s, 3H), 2.97 (t, *J*=5.1 Hz, 4H), 7.06–7.16 (m, 2H), 7.26–7.48 (m, 4H), 7.77 (s, 1H), 8.08 (d, *J*=7.8 Hz, 1H), 8.67 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 22.8, 24.1, 26.3, 55.0, 118.9, 122.5, 124.2, 126.1, 127.2, 128.8, 130.1, 131.9, 132.0, 132.1, 132.2, 132.7, 140.4, 155.9, 162.7, 167.9. HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_2$ $[M+H]^+$: 347.1754; found: 347.1748.

*4.2.3. (Z)-4-(2-(Piperidin-1-yl)benzylidene)-2-p-tolyloxazol-5(4H)-one (**1c**).* Yellow solid, yield 61%; mp 172.9–174.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.63 (t, *J*=5.4, 2H), 1.76–1.84 (m, 4H), 2.45 (s, 3H), 2.96 (t, *J*=5.4 Hz, 4H), 7.06 (d, *J*=8.1 Hz, 1H), 7.14 (t, *J*=7.5 Hz, 1H), 7.30–7.41 (m, 3H), 7.72 (s, 1H), 8.05 (d, *J*=8.1 Hz, 2H), 8.67 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 21.8, 24.1, 26.3, 55.0, 118.9, 122.5, 123.0, 127.2, 128.1, 128.5, 129.6, 131.8, 132.2, 132.9, 143.9, 155.7, 162.8, 168.2. HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_2$ $[M+H]^+$: 347.1754; found: 347.1753.

*4.2.4. (Z)-2-(4-Methoxyphenyl)-4-(2-(piperidin-1-yl)benzylidene) oxazol-5(4H)-one (**1d**).* Yellow solid, yield 31%; mp 161.8–162.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.60–1.66 (m, 2H), 1.76–1.83 (m, 4H), 2.95 (t, *J*=5.1 Hz, 4H), 3.89 (s, 3H), 6.99–7.07 (m, 3H), 7.14–7.37 (m, 2H), 7.68 (s, 1H), 8.11 (dd, J_1=1.8 Hz, J_2=6.9 Hz, 2H), 8.66 (dd, J_1=1.5 Hz, J_2=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 24.1, 26.3, 54.9, 55.5, 114.3, 118.1, 118.8, 122.4, 127.3, 127.6, 130.1, 131.6, 132.3, 132.8, 155.6, 162.5, 163.5, 168.3. HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_3$ $[M+H]^+$: 363.1703; found: 363.1703.

*4.2.5. (Z)-2-(3-Fluorophenyl)-4-(2-(piperidin-1-yl)benzylidene) oxazol-5(4H)-one (**1e**).* Orange solid, yield 46%; mp 151.2–152.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.62 (d, *J*=5.1, 2H), 1.76–1.81 (m, 4H), 2.96 (t, *J*=5.1 Hz, 4H), 7.07 (d, *J*=8.1 Hz, 1H), 7.16 (d, *J*=7.5 Hz, 1H), 7.27 (t, *J*=5.4 Hz, 1H), 7.37–7.40 (m, 1H), 7.47–7.50 (m, 1H), 7.78 (s, 1H), 7.85 (d, *J*=9.3 Hz, 1H), 7.94 (d, *J*=7.8 Hz, 1H), 8.63 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 24.1, 26.3, 55.1, 114.8 (d, *J*=23.8 Hz, 1C), 119.0, 120.0 (d, *J*=21.3 Hz, 1C), 122.5, 123.9 (d, *J*=3.1 Hz, 1C), 126.9, 128.0 (d, *J*=8.4 Hz, 1C), 130.2, 130.6 (d, *J*=7.9 Hz, 1C), 131.6, 132.3, 133.1, 156.0, 161.4, 164.3, 164.4 (d, *J*=491.4 Hz, 1C). HRMS (ESI-TOF) calcd for $C_{21}H_{20}FN_2O_2$ $[M+H]^+$: 351.1503; found: 351.1510.

*4.2.6. (Z)-2-(4-Bromophenyl)-4-(2-(piperidin-1-yl)benzylidene) oxazol-5(4H)-one (**1f**).* Orange solid, yield 35%; mp 163.6–165.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.62 (d, *J*=5.7, 2H), 1.79 (t, *J*=4.8, 4H), 2.96 (t, *J*=5.1, 4H), 7.06 (d, *J*=8.1 Hz, 1H), 7.14 (t, *J*=7.5 Hz, 1H), 7.40 (t, *J*=7.5 Hz, 1H), 7.65 (d, *J*=8.4 Hz, 2H), 7.76 (s, 1H), 8.01 (d, *J*=8.4, 2H), 8.62 (d, *J*=7.8, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 24.1, 26.3, 55.0, 118.9, 122.5, 124.7, 127.0, 127.9, 129.4, 129.8, 131.7, 132.1, 132.2, 133.0, 156.0, 161.8, 167.7. HRMS (ESI-TOF) calcd for $C_{21}H_{20}BrN_2O_2$ $[M+H]^+$: 411.0703; found: 411.0696.

*4.2.7. (Z)-4-(2-Morpholinobenzylidene)-2-phenyloxazol-5(4H)-one (**1g**).* Yellow solid, yield 43%; mp 187.6–189.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.00 (s, 4H), 3.92 (s, 4H), 7.09 (d, *J*=7.8 Hz, 1H), 7.21 (t, *J*=7.5 Hz, 1H), 7.43 (t, *J*=7.2 Hz, 1H), 7.49–7.60 (m, 3H), 7.75 (m, 1H), 8.16 (d, *J*=6.0 Hz, 2H), 8.69 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 53.7, 67.0, 118.8, 123.5, 125.6, 127.2, 128.1, 128.2, 128.8, 132.1, 132.6, 133.1, 133.2, 154.1, 163.1, 167.8. HRMS (ESI-TOF) calcd for $C_{20}H_{19}N_2O_3$ $[M+H]^+$: 335.1390; found: 335.1384.

*4.2.8. (Z)-2-(3-Fluorophenyl)-4-(2-morpholinobenzylidene) oxazol-5(4H)-one (**1h**).* Yellow solid, yield 45%; mp 165.2–166.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.00 (t, *J*=4.2 Hz, 4H), 3.92 (t, *J*=4.2 Hz, 4H), 7.10 (d, *J*=8.1 Hz, 1H), 7.19–7.29 (m, 2H), 7.41–7.50 (m, 2H), 7.78 (s, 1H), 7.84 (d, *J*=9.0 Hz, 1H), 7.93 (d, *J*=7.8 Hz, 1H), 8.65 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 53.8, 67.0, 114.9 (d, *J*=23.8 Hz, 1C), 118.9, 120.1 (d, *J*=21.3 Hz, 1C), 123.5, 123.9 (d, *J*=3.0 Hz, 1C), 127.1, 127.8 (d, *J*=47.7 Hz, 1C), 129.0, 130.6 (d, *J*=7.9 Hz, 1C), 132.2, 132.4, 133.2, 154.3, 161.9 (d, *J*=3.6 Hz, 1C), 162.7

(d, *J*=246.2 Hz, 1C), 167.4. HRMS (ESI-TOF) calcd for $C_{20}H_{18}FN_2O_3$ $[M+H]^+$: 353.1296; found: 353.1297.

*4.2.9. (Z)-4-(2-(3,4-Dihydroisoquinolin-2(1H)-yl)benzylidene)-2-phenyloxazol-5(4H)-one (**1i**).* Yellow solid, yield 50%; mp 161.6–162.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.08 (t, *J*=5.7 Hz, 2H), 3.35 (t, *J*=5.7 Hz, 2H), 4.30 (s, 2H), 7.12–7.26 (m, 6H), 7.42 (d, *J*=6.6 Hz, 1H), 7.51–7.61 (m, 3H), 7.78 (s, 1H), 8.20 (d, *J*=7.2 Hz, 2H), 8.73 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 29.2, 53.3, 54.1, 119.1, 123.0, 125.8, 126.0, 126.3, 126.4, 127.2, 128.2, 128.8, 128.9, 129.1, 132.0, 132.4, 133.1, 133.2, 134.3, 134.4, 154.2, 162.9, 167.9. HRMS (ESI-TOF) calcd for $C_{25}H_{21}N_2O_2$ $[M+H]^+$: 381.1598; found: 381.1602.

*4.2.10. (Z)-4-(2-(3,4-Dihydroisoquinolin-2(1H)-yl)benzylidene)-2-o-tolyloxazol-5(4H)-one (**1j**).* Yellow solid, yield 34%; mp 151.0–152.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.85 (s, 3H), 3.10 (t, *J*=5.4 Hz, 2H), 3.36 (t, *J*=5.7 Hz, 2H), 4.30 (s, 2H), 7.11–7.26 (m, 6H), 7.33–7.50 (m, 4H), 7.80 (s, 1H), 8.10 (d, *J*=7.8 Hz, 1H), 8.73 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 22.8, 29.2, 53.3, 54.0, 119.1, 122.9, 124.2, 125.9, 126.1, 126.3, 126.4, 127.2, 128.4, 129.0, 130.2, 131.9, 132.1, 132.3, 132.5, 132.9, 134.3, 140.5, 154.2, 163.1, 167.7. HRMS (ESI-TOF) calcd for $C_{26}H_{23}N_2O_2$ $[M+H]^+$: 395.1754; found: 395.1746.

*4.2.11. (Z)-4-(2-(3,4-Dihydroisoquinolin-2(1H)-yl)benzylidene)-2-p-tolyloxazol-5(4H)-one (**1k**).* Yellow solid, yield 42%; mp 190.0–191.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.47 (s, 3H), 3.09 (d, *J*=5.1 Hz, 2H), 3.34 (t, *J*=5.4 Hz, 2H), 4.30 (s, 2H), 7.12–7.28 (m, 6H), 7.34 (t, *J*=7.8 Hz, 2H), 7.43 (t, *J*=7.5 Hz, 1H), 7.75 (s, 1H), 8.08 (d, *J*=7.8 Hz, 2H), 8.74 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 21.8, 29.2, 53.2, 54.0, 119.0, 122.9, 125.9, 126.3, 126.4, 127.2, 128.0, 128.2, 129.0, 129.6, 131.8, 132.5, 133.1, 134.3, 144.0, 154.1, 163.0, 168.0. HRMS (ESI-TOF) calcd for $C_{26}H_{23}N_2O_2$ $[M+H]^+$: 395.1754; found: 395.1749.

*4.2.12. (Z)-4-(2-(3,4-Dihydroisoquinolin-2(1H)-yl)benzylidene)-2-(4-methoxyphenyl)oxazol-5(4H)-one (**1l**).* Yellow solid, yield 35%; mp 192.0–193.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.08 (t, *J*=5.1 Hz, 2H), 3.34 (t, *J*=5.7 Hz, 2H), 3.90 (s, 3H), 4.29 (s, 2H), 7.02 (d, *J*=8.7 Hz, 2H), 7.10–7.26 (m, 6H), 7.41 (t, *J*=7.8 Hz, 1H), 7.70 (s, 1H), 8.13 (d, *J*=8.7 Hz, 2H), 8.72 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 29.2, 53.2, 54.0, 55.5, 114.4, 114.5, 118.0, 119.0, 122.9, 125.9, 126.3, 126.4, 127.1, 127.4, 129.0, 130.2, 131.6, 132.7, 133.0, 134.3, 154.0, 162.8, 163.6, 168.1. HRMS (ESI-TOF) calcd for $C_{26}H_{23}N_2O_3$ $[M+H]^+$: 411.1703; found: 411.1688.

*4.2.13. (Z)-4-(2-(3,4-Dihydroisoquinolin-2(1H)-yl)benzylidene)-2-(3-fluorophenyl)oxazol-5(4H)-one (**1m**).* Yellow solid, yield 29%; mp 168.5–169.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.08 (d, *J*=4.5 Hz, 2H), 3.33 (d, *J*=5.1 Hz, 2H), 4.29 (s, 2H), 7.12–7.33 (m, 7H), 7.41–7.54 (m, 2H), 7.80 (s, 1H), 7.87 (d, *J*=8.7 Hz, 1H), 7.96 (d, *J*=7.5 Hz, 1H), 8.70 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 29.2, 53.4, 54.0, 114.8 (d, *J*=24.4 Hz, 1C), 119.1, 120.1 (d, *J*=21.2 Hz, 1C), 123.0, 123.9 (d, *J*=2.9 Hz, 1C), 126.0, 126.3 (d, *J*=12.1 Hz, 1C), 126.9, 127.9 (d, *J*=8.5 Hz, 1C), 129.0, 129.7, 130.6 (d, *J*=7.9 Hz, 1C), 132.0, 132.2, 133.2, 134.2 (d, *J*=3.4 Hz, 1C), 154.4, 161.8, 162.7 (d, *J*=246.1 Hz, 1C), 167.4. HRMS (ESI-TOF) calcd for $C_{25}H_{20}FN_2O_2$ $[M+H]^+$: 399.1503; found: 399.1499.

*4.2.14. (Z)-2-(4-Bromophenyl)-4-(2-(3,4-dihydroisoquinolin-2(1H)-yl)benzylidene)oxazol-5(4H)-one (**1n**).* Yellow solid, yield 51%; mp 170.0–171.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.08 (t, *J*=5.1 Hz, 2H), 3.34 (t, *J*=5.7 Hz, 2H), 4.29 (s, 2H), 7.10–7.26 (m, 6H), 7.43 (t, *J*=7.5 Hz, 1H), 7.66 (d, *J*=8.4 Hz, 2H), 7.79 (s, 1H), 8.03 (d, *J*=8.5 Hz, 2H), 8.69 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 29.2, 53.4, 54.0, 119.1, 122.9, 124.6, 126.0, 126.3, 126.4, 127.0, 128.1, 129.0, 129.3, 129.4, 132.0, 132.1, 132.2, 133.2, 134.2, 134.3, 154.3, 162.1, 167.5. HRMS (ESI-TOF) calcd for $C_{25}H_{20}BrN_2O_2$ $[M+H]^+$: 459.0703; found: 459.0701.

4.3. General experimental procedure for the tandem 1,5-hydride transfer/cyclization process

A mixture of the substrate **1** (0.2 mmol) and $Sc(OTf)_3$ (0.06 mmol for **1a**–**h**, 0.01 mmol for **1i**–**n**) in 4.0 mL freshly distilled mesitylene was heated to 190 °C in a sealed-tube under argon atmosphere until the TLC analysis showed the completion of the reaction. The mixture was then cooled to room temperature after which it was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate to give the corresponding product **2**.

*4.3.1. 2-Phenyl-1′,2′,3′,4′,4a′,6′-hexahydro-5H-spiro[oxazole-4,5′-pyrido[1,2-a]quinolin]-5-one (**2a**).* Colorless oil, yield 90%; 69:31 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 1.30–1.45 (m, 2H), 1.60–1.85 (m, 4H), 2.80–2.88 (m, 1.7H), 3.07 (s, 0.3H), 3.33–3.50 (m, 2H), 4.13–4.17 (m, 1H), 6.75–6.80 (m, 1H), 6.99–7.04 (m, 2H), 7.21–7.26 (m, 1H), 7.44–7.58 (m, 3H), 8.05–8.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 23.4, 23.7, 24.6, 25.1, 26.6, 26.9, 35.7, 37.2, 48.5, 48.8, 60.2, 60.7, 69.1, 70.6, 113.1, 113.7, 118.0, 118.1, 118.2, 119.4, 125.4, 125.6, 127.7, 127.8, 127.9, 128.2, 128.4, 128.5, 128.7, 129.3, 129.4, 132.7, 132.8, 144.9, 145.0, 161.0, 161.1, 175.8, 179.0. HRMS (ESI-TOF) calcd for $C_{21}H_{21}N_2O_2$ $[M+H]^+$: 333.1598; found: 333.1607.

*4.3.2. 2-o-Tolyl-1′,2′,3′,4′,4a′,6′-hexahydro-5H-spiro[oxazole-4,5′-pyrido[1,2-a]quinolin]-5-one (**2b**).* Colorless oil, yield 72%; 69:31 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 1.40–1.44 (m, 2H), 1.64–1.85 (m, 4H), 2.57 (s, 2H), 2.66 (s, 1H), 2.81–3.03 (m, 2H), 3.35–3.45 (m, 2H), 4.10–4.14 (m, 1H), 6.72–6.76 (m, 1H), 6.96–7.00 (m, 2H), 7.18–7.20 (m, 1H), 7.24–7.33 (m, 2H), 7.39–7.44 (m, 1H), 7.85–7.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 21.9, 22.1, 23.6, 23.8, 24.9, 25.1, 26.9, 27.0, 36.1, 37.2, 48.5, 48.8, 60.2, 60.6, 69.3, 70.5, 113.1, 113.5, 118.0, 118.1, 119.4, 124.9, 125.8, 126.0, 127.7, 127.9, 129.3, 129.4, 130.0, 130.1, 131.5, 131.7, 131.8, 131.9, 139.4, 139.6, 145.1, 145.2, 161.5, 161.6, 175.9, 179.2. HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_2$ $[M+H]^+$: 347.1754; found: 347.1763.

*4.3.3. 2-p-Tolyl-1′,2′,3′,4′,4a′,6′-hexahydro-5H-spiro[oxazole-4,5′-pyrido[1,2-a]quinolin]-5-one (**2c**).* Colorless oil, yield 83%; 66:34 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 1.39–1.42 (m, 2H), 1.69–1.80 (m, 4H), 2.42–2.45 (m, 3H), 2.78–2.86 (m, 2H), 3.32–3.37 (m, 1.3H), 3.42–3.48 (m, 0.7H), 4.12–4.16 (m, 1H), 6.73–6.78 (m, 1H), 6.98–7.03 (m, 2H), 7.17–7.32 (m, 3H), 7.92–7.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 21.6, 21.7, 23.4, 23.8, 24.7, 25.1, 26.7, 26.9, 35.8, 37.3, 48.5, 48.9, 60.3, 60.7, 69.0, 70.5, 113.1, 113.8, 118.1, 118.2, 119.5, 122.7, 122.8, 127.7, 127.9, 128.0, 128.3, 129.2, 129.3, 129.4, 129.5, 143.5, 143.6, 145.0, 145.1, 161.1, 176.0, 179.3. HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_2$ $[M+H]^+$: 347.1754; found: 347.1757.

*4.3.4. 2-(4-Methoxyphenyl)-1′,2′,3′,4′,4a′,6′-hexahydro-5H-spiro[oxazole-4,5′-pyrido[1,2-a]quinolin]-5-one (**2d**).* Colorless oil, yield 61%; 70:30 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 1.38–1.44 (m, 2H), 1.56–1.80 (m, 4H), 2.77–2.85 (m, 2H), 3.31–3.34 (m, 1.4H), 3.35–3.46 (m, 0.6H), 3.86 (s, 2H), 3.88 (s, 1H), 4.11–4.15 (m, 1H), 6.72–6.77 (m, 1H), 6.92–7.02 (m, 4H), 7.16–7.18 (m, 1H), 7.96–8.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 23.4, 23.8, 24.7, 25.2, 26.7, 26.9, 35.9, 37.4, 48.6, 48.9, 55.3, 55.4, 60.4, 60.8, 68.9, 70.5, 113.1, 113.8, 113.9, 114.1, 117.8, 117.9, 118.1, 118.2, 119.6, 127.6, 127.8, 129.1, 129.3, 129.4, 129.9, 130.2, 145.0, 145.1, 160.7, 161.0, 163.1, 163.2, 176.1, 179.3. HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_3$ $[M+H]^+$: 363.1703; found: 363.1706.

*4.3.5. 2-(3-Fluorophenyl)-1′,2′,3′,4′,4a′,6′-hexahydro-5H-spiro[oxazole-4,5′-pyrido[1,2-a]quinolin]-5-one (**2e**).* Colorless oil, yield

92%; 68:32 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 1.28–1.44 (m, 2H), 1.58–1.85 (m, 4H), 2.80–2.87 (m, 1.7H), 3.07 (s, 0.3H), 3.30–3.49 (m, 2H), 4.12–4.16 (m, 1H), 6.74–6.79 (m, 1H), 6.98–7.03 (m, 2H), 7.18–7.29 (m, 2H), 7.43–7.47 (m, 1H), 7.74–7.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 23.4, 23.8, 24.6, 25.1, 26.6, 26.9, 35.6, 37.2, 48.5, 48.9, 60.3, 60.7, 69.4, 70.8, 113.1, 113.8, 115.0, 115.1, 115.4, 118.1, 118.3, 119.2, 119.7, 120.0, 124.0, 124.1, 127.8, 128.0, 129.3, 129.4, 130.3, 130.4, 130.5, 144.9, 145.0, 160.1, 160.9, 164.1, 164.2, 175.5, 178.6. HRMS (ESI-TOF) calcd for $C_{21}H_{20}FN_2O_2$ $[M+H]^+$: 351.1503; found: 351.1508.

*4.3.6. 2-(4-Bromophenyl)-1′,2′,3′,4′,4a′,6′-hexahydro-5H-spiro[oxazole-4,5′-pyrido[1,2-a]quinolin]-5-one (**2f**).* Colorless oil, yield 64%; 65:35 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 1.33–1.38 (m, 2H), 1.55–1.83 (m, 4H), 2.77–2.85 (m, 2H), 3.28–3.35 (m, 1.3H), 3.28–3.47 (m, 0.7H), 4.11–4.15 (m, 1H), 6.72–6.77 (m, 1H), 6.97–7.02 (m, 2H), 7.16–7.21 (m, 1H), 7.58–7.64 (m, 2H), 7.87–7.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 23.4, 23.8, 24.5, 25.1, 26.6, 27.0, 35.6, 37.2, 48.5, 48.9, 60.3, 60.7, 69.3, 70.8, 113.1, 113.8, 117.9, 118.1, 118.3, 119.3, 124.4, 124.5, 127.7, 127.8, 127.9, 129.3, 129.4, 129.7, 131.9, 132.1, 144.9, 145.0, 160.4, 175.6, 178.7. HRMS (ESI-TOF) calcd for $C_{21}H_{20}BrN_2O_2$ $[M+H]^+$: 411.0703; found: 411.0690.

*4.3.7. 2′-Phenyl-2,4,4a,6-tetrahydro-1H,5′H-spiro[[1,4] oxazino[4,3-a]quinoline-5,4′-oxazol]-5′-one (**2g**).* Colorless oil, yield 37%; 57:43 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 2.83–3.06 (m, 2H), 3.25–3.37 (m, 1H), 3.43–3.48 (m, 2H), 3.73–3.79 (m, 2.6H), 3.97–3.79 (m, 1.4H), 6.82–6.83 (m, 1H), 6.93–6.95 (m, 1H), 7.01–7.03 (m, 1H), 7.22–7.26 (m, 1H), 7.47–7.61 (m, 3H), 8.02–8.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 36.3, 37.7, 46.3, 46.9, 58.0, 58.1, 66.6, 66.8, 67.0, 67.3, 68.2, 112.4, 113.0, 118.1, 119.2, 119.3, 119.4, 125.3, 125.4, 127.9, 128.0, 128.1, 128.4, 128.7, 128.9, 129.5, 129.6, 133.0, 133.1, 144.4, 144.7, 161.5, 161.9, 175.0, 178.3. HRMS (ESI-TOF) calcd for $C_{20}H_{19}N_2O_3$ $[M+H]^+$: 335.1390; found: 335.1392.

*4.3.8. 2′-(3-Fluorophenyl)-2,4,4a,6-tetrahydro-1H,5′H-spiro[[1,4]oxazino[4,3-a]quinoline-5,4′-oxazol]-5′-one (**2h**).* Colorless oil, yield 78%; 63:37 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 2.83–3.06 (m, 2H), 3.25–3.36 (m, 1H), 3.44–3.59 (m, 2H), 3.73–3.79 (m, 2.6H), 3.99 (s, 1.4H), 6.83–6.84 (m, 1H), 6.94–6.96 (m, 1H), 7.02–7.04 (m, 1H), 7.23–7.46 (m, 3H), 7.72–7.75 (m, 1H), 7.80–7.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 36.1, 37.6, 46.2, 46.8, 57.9, 58.0, 66.7, 66.9, 67.1, 68.3, 112.4, 113.0, 115.1, 115.4, 119.3, 119.4, 120.0, 120.2, 123.8, 123.9, 124.0, 124.1, 127.9, 128.0, 129.4, 129.6, 130.4, 130.5, 130.6, 144.3, 144.5, 160.9, 161.0, 164.2, 164.3, 174.5, 177.8. HRMS (ESI-TOF) calcd for $C_{20}H_{18}FN_2O_3$ $[M+H]^+$: 353.1296; found: 353.1298.

*4.3.9. 2′-Phenyl-6,7,11b,13-tetrahydro-5′H-spiro[isoquinolino [2,1-a]quinoline-12,4′-oxazol]-5′-one (**2i**).* Colorless oil, yield 97%; 70:30 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 2.67–2.72 (m, 1H), 3.02–3.08 (m, 0.8H), 3.22–3.28 (m, 1.5H), 3.40–3.44 (m, 0.7H), 3.54–3.80 (m, 1H), 3.98–4.02 (m, 1H), 4.81 (s, 0.3H), 4.86 (s, 0.7H), 6.83–7.03 (m, 3H), 7.13–7.23 (m, 5H), 7.28–7.48 (m, 3H), 7.77 (d, J=7.5 Hz, 1.4H), 7.93 (d, J=7.5 Hz, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 29.9, 30.2, 36.1, 37.2, 42.9, 45.6, 62.2, 62.7, 71.2, 73.0, 112.5, 114.6, 117.7, 118.2, 124.8, 126.3, 127.3, 127.4, 127.6, 127.7, 127.8, 128.4, 128.5, 128.7, 128.8, 129.2, 129.3, 132.4, 132.6, 137.4, 146.0, 146.5, 160.4, 176.5, 179.5. HRMS (ESI-TOF) calcd for $C_{25}H_{21}N_2O_2$ $[M+H]^+$: 381.1598; found: 381.1585.

*4.3.10. 2′-o-Tolyl-6,7,11b,13-tetrahydro-5′H-spiro [isoquinolino[2,1-a]quinoline-12,4′-oxazol]-5′-one (**2j**).* Colorless oil, yield 99%; 71:29 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 2.24 (s, 2.1H), 2.58 (s, 0.9H), 2.69–2.74 (m, 1H), 3.04–3.10 (m, 0.7H), 3.18–3.28 (m, 2.3H), 3.39–3.80 (m, 1H), 3.99–4.02 (m, 1H), 4.83 (s, 0.3H), 4.88 (s, 0.7H), 6.85–6.93 (m, 2H), 7.11–7.34 (m, 9H), 7.55 (d, J=7.5 Hz, 0.7H), 7.71 (d, J=7.5 Hz, 0.3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 21.1, 21.8, 29.9, 30.2, 36.4, 37.3, 43.0, 45.2, 62.0, 62.5, 71.1, 73.2, 112.6, 114.5, 117.8, 125.6, 125.8, 126.3, 127.2, 127.3, 127.4, 127.5, 127.6, 128.0, 128.8, 129.0, 129.6, 129.7, 131.2, 131.4, 131.5, 137.5, 138.8, 146.0, 161.0, 161.3, 176.6, 179.8. HRMS (ESI-TOF) calcd for $C_{26}H_{23}N_2O_2$ $[M+H]^+$: 395.1754; found: 395.1729.

*4.3.11. 2′-p-Tolyl-6,7,11b,13-tetrahydro-5′H-spiro [isoquinolino[2,1-a]quinoline-12,4′-oxazol]-5′-one (**2k**).* Colorless oil, yield 97%; 73:27 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 2.37 (s, 2.1H), 2.45 (s, 0.9H), 2.67–2.72 (m, 1H), 3.01–3.07 (m, 0.8H), 3.22–3.25 (m, 1.5H), 3.28–3.29 (m, 0.7H), 3.40–4.02 (m, 2H), 4.80 (s, 0.3H), 4.84 (s, 0.7H), 6.82–6.85 (m, 1H), 6.90–7.02 (m, 2H), 7.12–7.30 (m, 7H), 7.66 (d, J=8.1 Hz, 1.4H), 7.82 (d, J=8.1 Hz, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 21.5, 21.6, 29.9, 30.2, 36.1, 37.2, 42.9, 45.6, 62.1, 62.6, 71.1, 72.9, 112.5, 114.5, 117.7, 118.2, 118.9, 122.6, 124.8, 126.2, 127.3, 127.4, 127.6, 127.7, 127.8, 128.3, 128.8, 129.1, 129.2, 129.4, 131.3, 137.4, 143.1, 143.3, 146.0, 160.4, 176.7, 179.6. HRMS (ESI-TOF) calcd for $C_{26}H_{23}N_2O_2$ $[M+H]^+$: 395.1754; found: 395.1731.

*4.3.12. 2′-(4-Methoxyphenyl)-6,7,11b,13-tetrahydro-5′H-spiro [isoquinolino[2,1-a]quinoline-12,4′-oxazol]-5′-one (**2l**).* Colorless oil, yield 94%; 73:27 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 2.66–2.71 (m, 1H), 3.00–3.06 (m, 0.7H), 3.24–3.78 (m, 3.3H), 3.81 (s, 2.1H), 3.87 (s, 0.9H), 3.99–4.01 (m, 1H), 4.77 (s, 0.3H), 4.82 (s, 0.71H), 6.81–7.02 (m, 8H), 7.11–7.27 (m, 2H), 7.70 (d, J=8.7 Hz, 1.4H), 7.89 (d, J=8.7 Hz, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 30.1, 30.2, 36.2, 37.2, 42.9, 45.6, 55.2, 55.3, 62.1, 62.6, 71.1, 72.8, 112.4, 113.9, 114.1, 114.5, 117.6, 118.2, 118.9, 126.2, 127.2, 127.3, 127.6, 127.7, 127.8, 128.3, 128.8, 129.2, 129.3, 129.4, 129.6, 137.5, 146.0, 146.5, 160.0, 162.8, 163.0, 176.8, 179.7. HRMS (ESI-TOF) calcd for $C_{26}H_{23}N_2O_3$ $[M+H]^+$: 411.1703; found: 411.1694.

*4.3.13. 2′-(3-Fluorophenyl)-6,7,11b,13-tetrahydro-5′H-spiro [isoquinolino[2,1-a]quinoline-12,4′-oxazol]-5′-one (**2m**).* Colorless oil, yield 99%; 69:31 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 2.68–2.73 (m, 1H), 3.02–3.08 (m, 0.7H), 3.16–3.28 (m, 1.6H), 3.42–3.43 (m, 0.7H), 3.54–3.80 (m, 1H), 3.98–4.02 (m, 1H), 4.81 (s, 0.3H), 4.86 (s, 0.7H), 6.82–6.85 (m, 1H), 6.90–7.28 (m, 9H), 7.33–7.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 29.9, 30.2, 36.0, 37.1, 42.9, 45.6, 62.3, 62.7, 71.3, 73.2, 112.6, 114.6, 114.7, 117.8, 118.3, 123.3, 123.4, 124.8, 126.4, 127.4, 127.5, 127.7, 127.8, 127.9, 128.5, 128.9, 129.2, 129.3, 130.4, 137.4, 145.9, 146.4, 160.8, 164.1, 164.2, 176.1, 179.1. HRMS (ESI-TOF) calcd for $C_{25}H_{20}FN_2O_2$ $[M+H]^+$: 399.1503; found: 399.1501.

*4.3.14. 2′-(4-Bromophenyl)-6,7,11b,13-tetrahydro-5′H-spiro [isoquinolino[2,1-a]quinoline-12,4′-oxazol]-5′-one (**2n**).* Colorless oil, yield 99%; 70:30 dr; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 2.66–2.71 (m, 1H), 3.01–3.07 (m, 0.7H), 3.15–3.25 (m, 1.6H), 3.41–3.42 (m, 0.7H), 3.52–3.78 (m, 1H), 3.98–4.01 (m, 1H), 4.79 (s, 0.3H), 4.84 (s, 0.7H), 6.81–6.82 (m, 1H), 6.89–7.26 (m, 7H), 7.50 (d, J=8.7 Hz, 1.4H), 7.59–7.62 (m, 2H), 7.75 (d, J=8.7 Hz, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 29.8, 30.1, 35.9, 37.0, 42.9, 45.5, 62.2, 62.6, 71.2, 73.1, 112.6, 114.5, 117.8, 118.2, 118.7, 124.8, 126.3, 127.4, 127.5, 127.7, 127.8, 128.4, 128.8, 128.9, 129.0, 129.1, 129.2, 131.9, 132.0, 137.3, 145.8, 146.3, 159.6, 159.7, 176.1, 179.1. HRMS (ESI-TOF) calcd for $C_{25}H_{20}BrN_2O_2$ $[M+H]^+$: 459.0703; found: 459.0688.

4.4. Experimental procedure for the transformation of 2i, 2k, and 2n to the corresponding ring opening compounds

A solution of compound **2i**, **2k** or **2m** (0.2 mmol) in MeOH (3 mL) was stirred at 0 °C for 3 min, then MeONa (0.5 mmol) was added, respectively. The mixture was allowed to warm to room temperature and stirred for 10 min. After cooling to 0 °C, the reaction was

quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. The residue was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate to give the corresponding product (**3i**, **3k** or **3m**).

*4.4.1. Methyl 12-benzamido-7,11b,12,13-tetrahydro-6H-isoquinolino [2,1-a]quinoline-12-carboxylate (**3i**).* White foam, yield 95%; 75:25 dr; mp 76.1–77.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 2.71–2.77 (m, 0.2H), 3.06–3.10 (m, 0.8H), 3.19–3.26 (m, 2H), 3.57–3.61 (m, 3H), 3.83–4.03 (m, 2H), 4.09–4.12 (m, 1H), 4.69 (s, 0.8H), 4.96 (s, 0.2H), 6.83–6.90 (m, 3H), 7.05–7.22 (m, 5H), 7.27–7.39 (m, 4H), 7.43–7.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 26.4, 31.2, 31.8, 35.5, 42.0, 45.7, 52.2, 52.9, 59.8, 61.9, 62.8, 63.5, 111.8, 113.6, 119.2, 122.0, 126.1, 126.3, 126.6, 126.8, 126.9, 127.0, 127.8, 127.9, 128.5, 128.8, 130.2, 130.3, 131.4, 131.5, 131.6, 135.3, 143.2, 144.8, 166.5, 167.2, 171.9, 172.5. HRMS (ESI-TOF) calcd for $C_{26}H_{24}N_2NaO_3$ $[M+Na]^+$: 435.1679; found: 435.1725.

*4.4.2. Methyl 12-(4-methylbenzamido)-7,11b,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinoline-12-carboxylate (**3k**).* White solid, yield 97%; 72:28 dr; mp 95.3–96.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 2.34 (s, 2.2H), 2.37 (s, 0.8H), 2.71–2.77 (m, 0.3H), 3.03–3.07 (m, 0.7H), 3.17–3.24 (m, 2H), 3.56 (s, 0.7H), 3.59 (s, 2.3H), 3.81–4.09 (m, 3H), 4.67 (s, 0.7H), 4.94 (s, 0.3H), 6.76–7.05 (m, 4H), 7.14–7.30 (m, 6H), 7.47 (d, J=8.1 Hz, 1.4H), 7.57 (d, J=8.1 Hz, 0.6H), 7.65 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 21.3, 21.4, 26.3, 31.1, 31.8, 35.5, 41.9, 45.6, 52.2, 52.9, 59.6, 61.8, 62.7, 63.4, 111.8, 113.6, 119.1, 119.4, 122.0, 126.0, 126.3, 126.6, 126.8, 126.9, 127.0, 127.3, 127.8, 127.9, 128.8, 129.1, 129.4, 130.2, 130.3, 135.3, 141.9, 144.8, 166.4, 167.1, 171.9, 172.6. HRMS (ESI-TOF) calcd for $C_{27}H_{26}N_2NaO_3$ $[M+Na]^+$: 449.1836; found: 449.1859.

*4.4.3. Methyl 12-(4-bromobenzamido)-7,11b,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinoline-12-carboxylate (**3n**).* White solid, yield 95%; 70:30 dr; mp 105.0–106.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (major+minor) (ppm): 2.71–3.22 (m, 3H), 3.53 (s, 0.9H), 3.60 (s, 2.1H), 3.78–4.07 (m, 3H), 4.67 (s, 0.7H), 4.94 (s, 0.3H), 6.73–6.89 (m, 3H), 7.02–7.30 (m, 5H), 7.39–7.51 (m, 4H), 7.66 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 26.2, 31.2, 31.5, 35.4, 41.9, 45.7, 52.3, 53.0, 59.6, 61.8, 62.9, 63.4, 111.8, 113.8, 119.3, 121.8, 125.1, 126.1, 126.4, 126.7, 127.1, 127.4, 127.8, 127.9, 128.4, 128.6, 128.8, 129.5, 130.3, 131.4, 131.7, 135.2, 142.9, 144.7, 165.5, 166.3, 171.6, 172.4. HRMS (ESI-TOF) calcd for $C_{26}H_{23}BrN_2NaO_3$ $[M+Na]^+$: 513.0784; found: 513.0790.

Acknowledgements

We are grateful for financial support from National Basic Research Program of China (973 Program) (2010CB833300), and Western Light Talent Culture Project, and Sichuan Youth Science and Technology Foundation.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.06.047.

References and notes

1. For selected reviews, see: (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070; (b) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787–828; (c) Sridharan, V.; Suryavanshi, P. A.; Menendez, J. C. *Chem. Rev.* **2011**, *111*, 7157–7259.
2. For selected examples, see: (a) Tsushima, K.; Osumi, T.; Matsuo, N.; Itaya, N. *Agric. Biol. Chem.* **1989**, *53*, 2529–2530; (b) Wallace, O. B.; Lauwers, K. S.; Jones, S. A.; Dodge, J. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1907–1910; (c) Yang, P. Y.; Zhou, Y. G. *Tetrahedron: Asymmetry* **2004**, *15*, 1145–1149; (d) Morehouse, L. A.; Sugarman, E. D.; Bourassa, P.-A.; Sang, T. M.; Zimetti, F.; Gao, F.; Rothblat, G. H.; Milici, A. J. *J. Lipid Res.* **2007**, *48*, 1263–1272; (e) Guinó, M.; Phua, P. H.; Caille, J. C.; Hii, K. K. *J. Org. Chem.* **2007**, *72*, 6290–6293; (f) Rano, T. A.; Sieber-McMaster, E.; Pelton, P. D.; Yang, M.; Demarest, K. T.; Kuo, G.-H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2456–2460; (g) Rano, T. A.; Kuo, G.-H. *Org. Lett.* **2009**, *11*, 2812–2815.
3. For selected examples, see: (a) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536–10537; (b) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 759–762; (c) Wang, C.; Li, C.; Wu, X.; Pettman, A.; Xiao, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6524–6528; (d) Wang, D.-S.; Zhou, Y.-G. *Tetrahedron Lett.* **2010**, *51*, 3014–3017; (e) Xie, M.-S.; Chen, X.-H.; Zhu, Y.; Gao, B.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3799–3802; (f) Jia, Z.-X.; Luo, Y.-C.; Xu, P.-F. *Org. Lett.* **2011**, *13*, 832–835; (g) Wang, T.; Zhuo, L.-G.; Li, Z.; Chen, F.; Ding, Z.; He, Y.; Fan, Q.-H.; Xiang, J.; Yu, Z.-X.; Chan, A. S. C. *J. Am. Chem. Soc.* **2011**, *133*, 9878–9891; (h) Shi, F.; Xing, G.-J.; Tao, Z.-L.; Luo, S.-W.; Tu, S.-J.; Gong, L.-Z. *J. Org. Chem.* **2012**, *77*, 6970–6979.
4. For selected reviews concerning cyclic α-quaternary α-amino acids, see: (a) Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629–8659; (b) Undheim, K. *Amino Acids* **2008**, *34*, 357–402; (c) Cativiela, C.; Ordóñez, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1–63.
5. For selected reviews, see: (a) Davies, H. M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422–6425; (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238; (c) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424; (d) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335–344.
6. For selected examples on the intramolecular 1,5-hydride transfer/cyclization process, see: (a) Zhang, C.; Kanta De, C.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416–417; (b) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129–132; (c) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226–13227; (d) Shikanai, D.; Murase, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2009**, *131*, 3166–3167; (e) Pahadi, N. K.; Paley, M.; Jana, R.; Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16626–16627; (f) Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 1798–1799; (g) Haibach, M. C.; Deb, I.; Kanta De, C.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 2100–2103; (h) Zhang, C.; Das, D.; Seidel, D. *Chem. Sci.* **2011**, *2*, 233–236; (i) Mori, K.; Sueoka, S.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 2424–2426; (j) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 6166–6169; (k) Cao, W.; Liu, X.; Wang, W.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 600–603; (l) Zhang, L.; Chen, L.; Lv, J.; Cheng, J.-P.; Luo, S. *Chem.—Asian J.* **2012**, *7*, 2569–2576; (m) Chen, L.; Zhang, L.; Lv, J.; Cheng, J.-P.; Luo, S. *Chem.—Eur. J.* **2012**, *18*, 8891–8895.
7. Han, Y.-Y.; Han, W.-Y.; Hou, X.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 4054–4057.
8. For selected examples on the catalytic asymmetric transformation based on azlactones, see: (a) Weber, M.; Jautze, S.; Frey, W.; Peters, R. *J. Am. Chem. Soc.* **2010**, *132*, 12222–12225; (b) Trost, B. M.; Morris, P. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 6167–6170; (c) Steurer, M.; Jensen, K. L.; Worgull, D.; Jørgensen, K. A. *Chem.—Eur. J.* **2012**, *18*, 76–79; (d) Wang, D.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, 2764–2766; (e) Weber, M.; Jautze, S.; Frey, W.; Peters, R. *Chem.—Eur. J.* **2012**, *18*, 14792–14804.
9. (a) Liao, Y.-H.; Liu, X.-L.; Wu, Z.-J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2010**, *12*, 2896–2899; (b) Chen, W.-B.; Wu, Z.-J.; Pei, Q.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2010**, *12*, 3132–3135; (c) Liu, X.-L.; Liao, Y.-H.; Wu, Z.-J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2010**, *75*, 4872–4875; (d) Chen, W.-B.; Wu, Z.-J.; Hu, J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2011**, *13*, 2472–2475; (e) Liu, X.-L.; Wu, Z.-J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2011**, *76*, 4008–4017; (f) Han, Y.-Y.; Wu, Z.-J.; Chen, W.-B.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2011**, *13*, 5064–5067; (g) Han, Y.-Y.; Chen, W.-B.; Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 490–493.
10. The representative procedure for the synthesis of (*Z*)-alkylidene azlactones **1** was depicted in Experimental section.
11. For details of the NOE experiments, see Supplementary data.