Formal [4+1] Annulation of Cyclopropyl Amides and Water Mediated by Lewis Acid: A Novel Entry to γ-Butyrolactones

Dingyuan Zhang, Rui Zhang,* Yongjiu Liang, Dewen Dong*

Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022, P. R. of China
Fax +86(431)85262676; E-mail: ariel@ciac.jl.cn; E-mail: dwdong@ciac.jl.cn

Received 10.02.2012; Accepted after revision: 28.03.2012

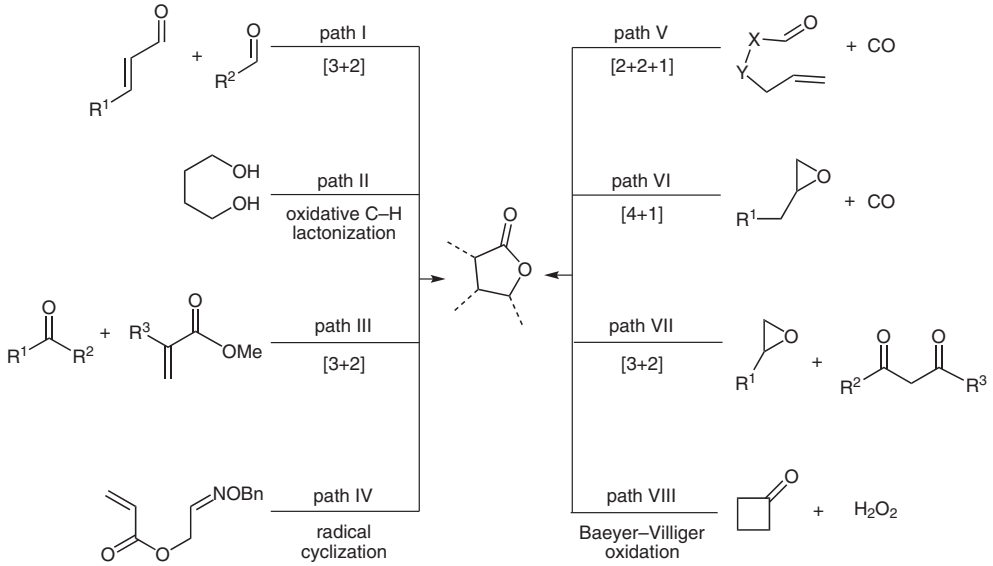
Abstract: An efficient one-pot synthesis of substituted γ-butyrolactones from cyclopropyl amides mediated by the Lewis acid $SnCl_4 \cdot 5H_2O$ is reported. A mechanism involving a tandem ring-opening reaction and intramolecular cyclization reaction is proposed.

Key words: γ-lactones, cyclopropyl amides, Lewis acids, synthetic methods, water

The γ-butyrolactone motif makes up the core structure of numerous bioactive compounds that display broad pharmacological and biological profiles including antifungal, antiinflammatory, antihelmitic, antitumor, antibiotic, antiviral, and cytostatic properties.[1,2] A variety of synthetic methods for γ-butyrolactones are available, including N-heterocyclic carbene chemistry (path I, Scheme 1),[3] direct oxidative C–H lactonization (path II),[4] SmI_2-mediated reductive coupling reaction (path III),[5] radical addition cyclization reaction (path IV),[6] formal [2+2+1] cycloaddition (path V),[7] epoxide carbonylation (path VI),[8] cyclization of epoxides with 1,3-dicarbonyl compounds (path VII),[9] and Baeyer–Villiger oxidation (path VIII).[10] Each of these approaches represents an important advance toward the objective of a general method for the synthesis of γ-butyrolactones. Nevertheless, to match the increasing scientific and practical demands, it is still of great importance to develop simple and efficient approaches to the construction of γ-butyrolactone derivatives, especially those with wide applicability to achieve more elaborate and flexible substitution patterns.

The utility of cyclopropanes in organic synthesis has been recognized. This is, in part due to their ready accessibility and good reactivity, which originates from the inherent ring strain that can lead to a variety of ring-opening or ring-enlargement reactions under the influence of a wide range of chemicals including electrophiles, nucleophiles, and radicals.[11,12] Indeed, the groups of Reissig and Reiser reported the synthesis of γ-butyrolactones from cyclopropanes.[13,14] In a present paper, we investigated the reaction of primary cyclopropyl amides, and provided an alternative synthesis of substituted γ-butyrolactones. Herein, we wish to report our experimental results and present a plausible mechanism for the ring-opening/recyclization.

In our recent work, we developed a one-pot synthesis of halogenated pyridin-2(1*H*)-ones from 1-carbamoyl-1-acyl cyclopropanes under Vilsmeier conditions,[15a] and the divergent synthesis of fully substituted 1*H*-pyrazoles[15b]



Scheme 1 General synthetic strategies available to access γ-butyrolactones

SYNTHESIS 2012, 44, 1679–1685
Advanced online publication: 08.05.2012
DOI: 10.1055/s-0031-1290971; Art ID: SS-2012-H0134-OP

and pyrazolin-5-one *N*-oxides[15c] from the oximes of 1-acyl-1-carbamoyl cyclopropanes in the presence of Vilsmeier reagent ($POCl_3$/DMF) and hypervalent iodine reagent (PIFA), respectively.

Very recently, we achieved a novel synthesis of cyclopropyl amides through the application of the iodoform reaction in water.[16] In connection with these studies, and because of our continued interest in the synthesis of carbo- and heterocycles,[17] we synthesized a series of cyclopropyl amides to examine their behavior toward Lewis acids. Thus, the reaction of *N*-phenylcyclopropane-1,1-dicarboxamide (**1a**) and $SnCl_4 \cdot 5H_2O$ (1.0 equiv) was first attempted in toluene at room temperature, but no reaction occurred as indicated by TLC. When **1a** and $SnCl_4 \cdot 5H_2O$ (1.0 equiv) were heated in toluene at reflux for 12 hours, the reaction proceeded and furnished a product (in 48% yield) that was characterized as 2-oxo-*N*-phenyl-tetrahydrofuran-3-carboxamide (**2a**) on the basis of its spectroscopic and analytical data (Table 1, entry 1).

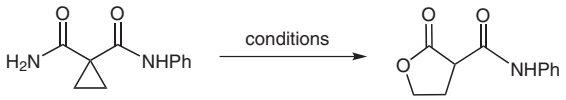
Optimization of the reaction conditions, including reaction temperature, solvent, and Lewis acid, was then undertaken. When **1a** was treated with $SnCl_4 \cdot 5H_2O$ (1.0 equiv) in either acetonitrile at reflux or in DMF at 110 °C, no reaction was observed (Table 1, entries 2 and 3). Subjecting **1a** and $SnCl_4 \cdot 5H_2O$ (2.0 equiv) to acetic acid at 110 °C afforded **2a** in 82% yield (Table 1, entry 4).

In the case of the reaction of **1a** and $SnCl_4 \cdot 5H_2O$ (2.0 equiv) in toluene at reflux, **2a** could be obtained in 88% yield (Table 1, entry 5). It is worth noting that when the reaction of **1a** was conducted with a Lewis acid, such as $SnCl_4$, $TiCl_4$, $FeCl_3$ or $BF_3 \cdot OEt_2$, in anhydrous toluene, no desired product **2a** was detected (Table 1, entries 6–9). These results revealed that the presence of water in the reaction system was necessary for the ring-opening/cyclization process, which was further demonstrated by other reactions of **1a** in the presence of either hydrated Lewis acid, such as $FeCl_3 \cdot 6H_2O$, $FeCl_2 \cdot 4H_2O$, or $CuCl_2 \cdot 2H_2O$ (Table 1, entries 10–12), or Lewis acid in a wet reaction medium (Table 1, entry 13).

Having established the optimal conditions for the synthesis of γ-butyrolactones, we intended to determine its scope with respect to the amide motif. Thus, a series of cyclopropyl amides **1b**–**h** were subjected to $SnCl_4 \cdot 5H_2O$ under identical conditions to those used with **2a** (Table 1, entry 5); the results are summarized in Table 2. It was observed that all the reactions proceeded smoothly to afford the corresponding γ-butyrolactones **2b**–**h** in good yields (Table 2, entries 2–8).

The versatility of this γ-butyrolactone synthesis was also evaluated by using 1-benzoylcyclopropane-carboxamide **1i** (Table 2, entry 9). In the case of cyclopropyl amide **1j**, which bears a 2-substituted methyl group (*cis*-**1j** was used),[18] the reaction proceeded to give γ-butyrolactone **2j**

Table 1 Optimization of the Reaction Conditions for the Synthesis of **2a**

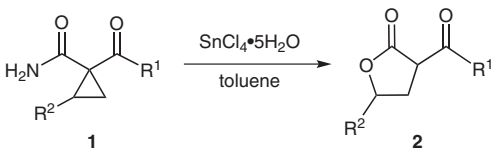


1a **2a**

Entry	Lewis acid	Equiv	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	$SnCl_4 \cdot 5H_2O$	1.0	toluene	reflux	12	48
2	$SnCl_4 \cdot 5H_2O$	1.0	MeCN	reflux	12	n.r.
3	$SnCl_4 \cdot 5H_2O$	1.0	DMF	110	12	n.r.
4	$SnCl_4 \cdot 5H_2O$	2.0	AcOH	110	3	82
5	$SnCl_4 \cdot 5H_2O$	2.0	toluene	reflux	2	88
6	$SnCl_4$	2.0	toluene[b]	reflux	12	n.r.
7	$TiCl_4$	2.0	toluene[b]	reflux	12	n.r.
8	$FeCl_3$	2.0	toluene[b]	reflux	12	n.r.
9	$BF_3 \cdot Et_2O$	2.0	toluene[b]	reflux	12	n.r.
10	$FeCl_3 \cdot 6H_2O$	2.0	toluene	reflux	5	81
11	$FeCl_2 \cdot 4H_2O$	2.0	toluene	reflux	10	74
12	$CuCl_2 \cdot 2H_2O$	2.0	toluene	reflux	8	53
13	$BF_3 \cdot Et_2O$	2.0	toluene[c]	reflux	2	81

[a] Isolated yield of **2a**.
[b] Anhydrous toluene was employed.
[c] H_2O (2.0 equiv) was added.

Table 2 The Synthesis of γ-Butyrolactones **2**[a]



Entry	1	R^1	R^2	2	Yield (%)[b]
1	**1a**	PhNH	H	**2a**	88
2	**1b**	4-MeC_6H_4NH	H	**2b**	80
3	**1c**	4-$MeOC_6H_4NH$	H	**2c**	82
4	**1d**	4-ClC_6H_4NH	H	**2d**	79
5	**1e**	2-MeC_6H_4NH	H	**2e**	71
6	**1f**	2-$MeOC_6H_4NH$	H	**2f**	67
7	**1g**	2-ClC_6H_4NH	H	**2g**	65
8	**1h**	2,4-$Me_2C_6H_3NH$	H	**2h**	83
9	**1i**	Ph	H	**2i**	81
10	**1j**[c]	PhNH	Me	**2j**	84[d]

[a] Reaction conditions: **1** (1.0 mmol), $SnCl_4 \cdot 5H_2O$ (2.0 mmol), toluene (10 mL), reflux, 1.0–4.5 h.
[b] Isolated yield.
[c] *cis*-**1j** was used.
[d] Overall yield for diastereoisomers **2j**; dr = 3:2 (determined by ^1H NMR analysis).

in a highly regioselective manner and the γ-butyrolactone product was exclusively obtained with the methyl group at the γ-position (Table 2, entry 10). Such a high degree of regioselective ring-opening could result from the push–pull effect of the methyl group (the donor) and two carbonyl groups (the acceptor).[19] In addition, **2j** was obtained as inseparable diastereoisomers with a ratio of 3:2 according to ^1H NMR spectroscopic analysis.[20] In the ^1H NMR spectra of **2j**, the *cis*-isomer displayed four peaks at δ = 2.36, 2.75, 3.70 and 4.68 ppm, and a singlet peak at δ = 9.16 ppm, which were assigned to the β-H, β-H, α-H and γ-H of the γ-butyrolactone ring, and the proton of its amide group, respectively, whereas *trans*-**2j** displayed four peaks at δ = 2.16, 3.00, 3.70, 4.83 ppm, and a singlet peak at δ = 8.72 ppm, respectively.

It is worth mentioning that the structure of **2d** was elucidated by means of an X-ray single crystal analysis (Figure 1) and confirmed by its spectroscopic and analytical data. Therefore, we have provided a facile and convenient synthesis of γ-butyrolactone of type **2**. Indeed, γ-butyrolactones **2** have several interesting characteristics stemming from the presence of the amide and ester moieties that should render them very useful for further synthetic transformations.

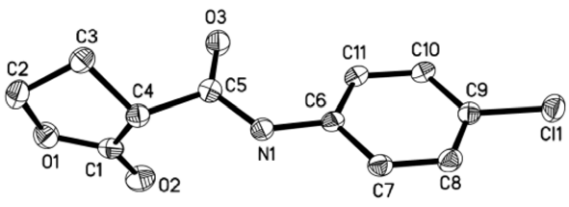
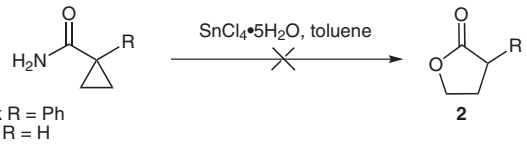


Figure 1 ORTEP drawing of **2d**

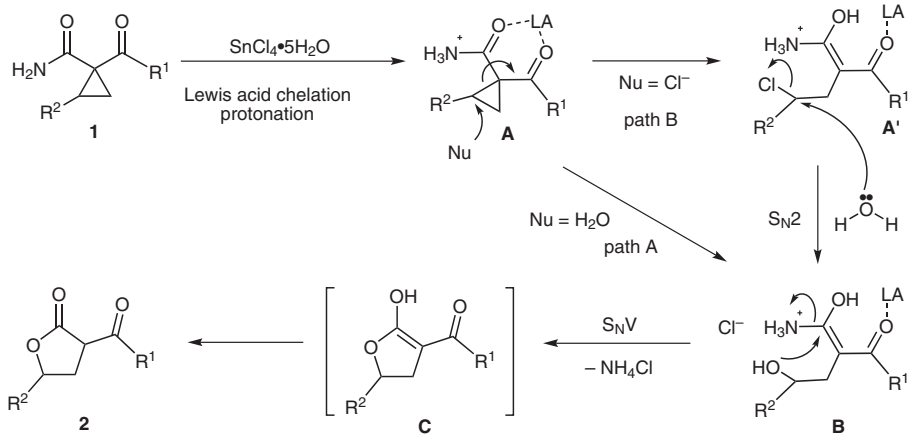
To examine the scope and limitation of the γ-butyrolactone synthetic protocol, 1-phenylcyclopropyl amide **1k** and cyclopropyl amide **1l** were prepared. However, no reaction was observed when **1k** or **1l** were subjected to the identical condition used for synthesis of **2a** (Scheme 2). The results suggested that the activation by the second carbonyl group adjacent to the cyclopropane ring of **1** is crucial for its ring-opening/cyclization transformation.



Scheme 2 Reaction of cyclopropyl amides **1k** and **1l**

The ring-opening or ring-enlargement reactions of cyclopropanes in the presence of various Lewis acids has been widely investigated.[11–14,19] Based on these literature reports and on the results presented above, a plausible mechanism for the synthesis of γ-butyrolactones **2** was proposed and is depicted in Scheme 3. Cyclopropyl amide **1** is activated by chelation to a Lewis acid with two carbonyl oxygen atoms.[21] The reaction then follows two possible modes of ring-opening: (a) the chelated **A** is attacked by H_2O to give intermediate **B** through a regioselective ring-opening process (path A), or (b) chelated **A** is attacked by a chloride nucleophile to form **A′**, followed by an S_N2 process with H_2O to afford intermediate **B** (path B).[13,14,22] Sequential intramolecular oxa-Michael addition and elimination reaction of ammonium chloride (S_NV reaction) then generates intermediate **C**, which is finally converted into γ-butyrolactones **2**.

The formal [4C+1O] annulation encouraged us to explore the reaction of cyclopropyl amides **1** with other nucleophiles. Thus, cyclopropyl amide **1a** was treated with sulfur nucleophile, $Na_2S \cdot 9H_2O$ (1.5 equiv), in the presence of $SnCl_4 \cdot 5H_2O$ (2.0 equiv) in toluene heated to reflux. After workup and purification by column chromatography, the reaction furnished two products, one was γ-butyrolactone **2a**, and the second was characterized as γ-thiolactone **3a** on the basis of its spectral and analytical data (Table 3, entry 1). In the same fashion, selected cyclopropyl amides **1** $SnCl_4 \cdot 5H_2O$, and $Na_2S \cdot 9H_2O$ were heated in toluene to reflux to afford the corresponding γ-thiolactones **3** in good to moderate yields (Table 3 , entries 2–5). Thus, we have provided a facile one-pot synthesis of substituted γ-thiolactone of type **3** via a formal [4C+1S] annulation reaction. Actually, γ-thiolactone derivatives represent another important class of thiaheterocycles that impart a diverse range of useful bioactivities and are widely used as key in-

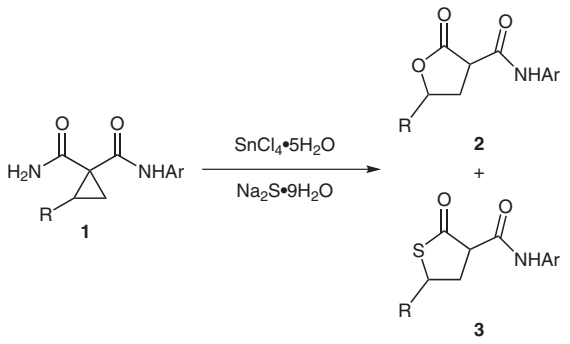


Scheme 3 Plausible mechanism for the synthesis of γ-butyrolactones **2** from cyclopropyl amides **1**

termediates in the preparation of natural products and related structures.[23]

In summary, a novel and efficient synthesis of γ-butyrolactones **2** has been developed from readily available cyclopropyl amides **1** mediated by the Lewis acid $SnCl_4·5H_2O$. The approach involves a formal [4C+1O] annulation process, namely tandem regioselective ring-opening and intramolecular cyclization reactions. The high regioselectivity, simplicity of execution, ready availability of substrates, and, importantly, the potential of the products, make this novel protocol very attractive. Further work on the utilization and extensions to the scope of the protocol are under investigation in our laboratory.

Table 3 Synthesis of γ-Thiolactones from Cyclopropyl Amides[a]



Entry	1	Ar	R	3	Yield (%)[b]	2	Yield (%)[b]
1	**1a**	PhNH	H	**3a**	64	**2a**	27
2	**1b**	4-MeC_6H_4NH	H	**3b**	52	**2b**	41
3	**1e**	2-MeC_6H_4NH	H	**3e**	74	**2e**	23
4	**1g**	2-ClC_6H_4NH	H	**3g**	70	**2g**	24
5	**1j**[c]	PhNH	Me	**3j**	63[d]	**2j**	28

[a] Reaction conditions: **1** (1.0 mmol), $SnCl_4·5H_2O$ (2.0 mmol), $Na_2S·9H_2O$ (1.5 mmol), in toluene (10 mL), 1.0–12.0 h, reflux.
[b] Isolated yield.
[c] *cis*-**1j** was used.
[d] Overall yield for diastereoisomers **3j**; dr = 5:3 (determined by ^1H NMR analysis).

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^1H NMR spectra were recorded at 300 or 400 MHz with TMS as internal standard at 25 °C on a Varian Inova-400 (or Bruker-300) spectrometer, and ^{13}C NMR spectra were recorded at 100 or 150 MHz at 25 °C on a Varian Inova-400 (or Bruker-600) spectrometer. IR spectra (KBr) were recorded on a Shimadzu FTIR-8400S spectrophotometer in the range of 400–4000 cm^{-1}. MALDI-TOF MS analysis was recorded on a Bruker Daltonics Autoflex III Smartbeam, and ESI MS analysis was recorded on an Acquity UPLC Quattro Premier XE. Petroleum ether (PE) used was the fraction boiling in the range 60–90 °C. Elemental analyses were carried out on a Perkin-Elmer PE-2400 analyzer.

Substituted γ-Butyrolactones 2; Typical Procedure
To a 50 mL round-bottomed flask was added **1a** (1.0 mmol), $SnCl_4·5H_2O$ (2.0 mmol), and toluene (10.0 mL). The mixture was heated at reflux for 1 h, then cooled to r.t. The mixture was neutralized with sat. aq $NaHCO_3$ (2 × 20 mL), extracted with CH_2Cl_2 (3 × 20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by short flash silica gel column chromatography (EtOAc–PE, 1:3) to give compound **2a**.

2-Oxo-*N*-phenyl-tetrahydrofuran-3-carboxamide (2a)
Yield: 181 mg (88%); white solid; mp 140–141 °C.

IR (KBr, neat): 3251, 3089, 2933, 1755, 1645, 1608, 1554, 1448, 1382, 1151, 1010, 952, 759, 688 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.54–2.64 (m, 1 H), 2.76–2.88 (m, 1 H), 3.61 (t, *J* = 9.5 Hz, 1 H), 4.32–4.40 (m, 1 H), 4.45–4.52 (m, 1 H), 7.13 (t, *J* = 7.5 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.54 (d, *J* = 8.0 Hz, 2 H), 8.93 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 45.8, 67.6, 119.9 (2C), 124.7, 128.9 (2C), 137.2, 163.2, 175.7.

MS: *m/z* $[M + 1]^+$ calcd for $C_{11}H_{12}NO_3^+$: 206.0; found 206.0.

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83; Found: C, 64.26; H, 5.47; N, 6.88.

2-Oxo-*N*-(*p*-tolyl)tetrahydrofuran-3-carboxamide (2b)
Yield: 175 mg (80%); yellow solid; mp 125–126 °C.

IR (KBr, neat): 3247, 3044, 2918, 1760, 1670, 1546, 1377, 1157, 1012, 821 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 2.56–2.67 (m, 1 H), 2.76–2.89 (m, 1 H), 3.61 (t, *J* = 10.0 Hz, 1 H), 4.33–4.41 (m, 1 H), 4.45–4.53 (m, 1 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.43 (d, *J* = 8.5 Hz, 2 H), 8.84 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 24.5, 45.7, 67.6, 120.0 (2C), 129.5 (2C), 134.4, 134.7, 162.8, 175.8.

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39; Found: C, 65.57; H, 6.17; N, 6.35.

_N_-(4-Methoxyphenyl)-2-oxotetrahydrofuran-3-carboxamide (2c)
Yield: 193 mg (82%); yellow solid; mp 108–109 °C.

IR (KBr, neat): 3234, 3049, 2921, 2837, 1757, 1645, 1510, 1384, 1242, 1155, 1012, 956, 800 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.55–2.67 (m, 1 H), 2.75–2.86 (m, 1 H), 3.60 (t, *J* = 9.0 Hz, 1 H), 3.80 (s, 3 H), 4.33–4.41 (m, 1 H), 4.46–4.52 (m, 1 H), 6.87 (d, *J* = 8.0 Hz, 2 H), 7.45 (d, *J* = 9.0 Hz, 2 H), 8.81 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 45.6, 55.4, 67.6, 114.0 (2C), 121.7 (2C), 130.3, 156.5, 163.0, 175.8.

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95; Found: C, 61.48; H, 5.53; N, 5.87.

_N_-(4-Chlorophenyl)-2-oxotetrahydrofuran-3-carboxamide (2d)
Yield: 189 mg (79%); white solid; mp 131–132 °C.

IR (KBr, neat): 3344, 3130, 2916, 1747, 1693, 1606, 1544, 1494, 1379, 1159, 1012, 952, 837 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.57–2.69 (m, 1 H), 2.75–2.88 (m, 1 H), 3.62 (t, *J* = 9.5 Hz, 1 H), 4.34–4.42 (m, 1 H), 4.47–4.54 (m, 1 H), 7.29 (d, *J* = 8.5 Hz, 2 H), 7.50 (d, *J* = 9.0 Hz, 1 H), 8.99 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 45.8, 67.6, 121.1 (2C), 129.0 (2C), 129.7, 135.8, 163.1, 175.8.

Anal. Calcd for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.84; Found: C, 55.26; H, 4.15; N, 5.77.

Crystal data for **2d**: CCDC 823715; $C_{11}H_{10}ClNO_3$; white; *M* = 239.66; orthorhombic; space group P2(1)2(1)2(1); *a* = 5.294 (3), *b* = 10.197 (5), *c* = 19.812 (10) Å; *V* = 1069.5 (10) Å^3; α = 90.00°, β = 90.00°, γ = 90.00°; *Z* = 4; *T* = 300 K; F_{000} = 500.0; R_1 = 0.0479; wR_2 = 0.1131. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax: +44(1223)336033; or deposit@ccdc.cam.ac.uk.

2-Oxo-_N_-(_o_-tolyl)tetrahydrofuran-3-carboxamide (2e)
Yield: 156 mg (71%); white solid; mp 125–126 °C.

IR (KBr, neat): 3298, 2991, 1762, 1654, 1541, 1172, 1016, 958, 761 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 2.59–2.70 (m, 1 H), 2.77–2.90 (m, 1 H), 3.67 (t, *J* = 9.5 Hz, 1 H), 4.34–4.43 (m, 1 H), 4.47–4.54 (m, 1 H), 7.08 (t, *J* = 7.0 Hz, 1 H), 7.21 (t, *J* = 8.0 Hz, 2 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 8.93 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 24.5, 45.6, 67.6, 122.0, 125.1, 126.7, 128.7, 130.5, 135.3, 162.9, 176.1.

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39; Found: C, 65.59; H, 6.03; N, 6.56.

_N_-(2-Methoxyphenyl)-2-oxotetrahydrofuran-3-carboxamide (2f)
Yield: 158 mg (67%); yellowish solid; mp 123–124 °C.

IR (KBr, neat): 3319, 2979, 2881, 1772, 1677, 1529, 1251, 1180, 1020, 756 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54–2.66 (m, 1 H), 2.78–2.91 (m, 1 H), 3.64 (t, *J* = 9.0 Hz, 1 H), 3.91 (s, 3 H), 4.33–4.41 (m, 1 H), 4.45–4.52 (m, 1 H), 6.88–6.98 (m, 2 H), 7.04–7.11 (m, 1 H), 8.28–8.32 (m, 1 H), 9.38 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 46.1, 55.8, 67.5, 110.2, 119.8, 120.8, 124.3, 127.1, 148.4, 162.8, 175.3.

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95; Found: C, 61.48; H, 5.63; N, 5.79.

_N_-(2-Chlorophenyl)-2-oxotetrahydrofuran-3-carboxamide (2g)
Yield: 156 mg (65%); white solid; mp 111–112 °C.

IR (KBr, neat): 3261, 2974, 1762, 1679, 1541, 1184, 1035, 752 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.59–2.70 (m, 1 H), 2.77–2.90 (m, 1 H), 3.70 (t, *J* = 9.5 Hz, 1 H), 4.35–4.43 (m, 1 H), 4.47–4.54 (m, 1 H), 7.05–7.10 (m, 1 H), 7.25–7.31 (m, 1 H), 7.38–7.41 (m, 1 H), 8.30–8.33 (m, 1 H), 9.49 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 45.9, 67.4, 121.7, 123.6, 125.1, 127.5, 129.3, 134.2, 163.2, 175.3.

Anal. Calcd for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.84; Found: C, 55.06; H, 4.30; N, 5.89.

_N_-(2,4-Dimethylphenyl)-2-oxotetrahydrofuran-3-carboxamide (2h)
Yield: 194 mg (83%); yellowish solid; mp 121–122 °C.

IR (KBr, neat): 3224, 3022, 2920, 1770, 1641, 1537, 1161, 1014, 956, 800, 680 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 2.29 (s, 3 H), 2.57–2.69 (m, 1 H), 2.76–2.89 (m, 1 H), 3.65 (t, *J* = 9.5 Hz, 1 H), 4.33–4.42 (m, 1 H), 4.46–4.52 (m, 1 H), 7.00 (s, 1 H), 7.01 (d, *J* = 6.0 Hz, 1 H), 7.74 (d, *J* = 8.5 Hz, 1 H), 8.81 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 20.7, 24.5, 45.5, 67.5, 122.3, 127.1, 129.0, 131.1, 132.6, 134.9, 163.1, 176.0.

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00; Found: C, 66.76; H, 6.53; N, 6.13.

3-Benzoyldihydrofuran-2(3*H*)-one (2i)
Yield: 154 mg (81%); yellowish solid; mp 48–50 °C.

IR (KBr, neat): 3446, 1772, 1680, 1450, 1257, 1153, 761 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46–2.58 (m, 1 H), 2.82–2.94 (m, 1 H), 4.40–4.48 (m, 1 H), 4.50–4.60 (m, 2 H), 7.52 (t, *J* = 7.5 Hz, 2 H), 7.64 (t, *J* = 7.0 Hz, 1 H), 8.09 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 26.0, 48.0, 67.8, 128.8 (2C), 129.5 (2C), 134.1, 135.3, 172.8, 193.0.

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30; Found: C, 69.23; H, 5.44.

5-Methyl-2-oxo-_N_-phenyl-tetrahydrofuran-3-carboxamide (2j-1)
Yield: 184 mg (84%); yellowish solid; mp 105–107 °C.

IR (KBr, neat): 3273, 3138, 1666, 1553, 1447, 1367, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 6.0 Hz, 3 H), 2.28–2.39 (m, 1 H), 2.71–2.81 (m, 1 H), 3.67–3.74 (m, 1 H), 4.63–4.74 (m, 1 H), 7.13 (t, *J* = 7.0 Hz, 1 H), 7.33 (t, *J* = 7.0 Hz, 2 H), 7.52–7.57 (m, 2 H), 9.16 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.6, 32.9, 49.1, 75.7, 119.2 (2C), 123.7, 128.8 (2C), 138.5, 165.7, 173.8.

5-Methyl-2-oxo-_N_-phenyl-tetrahydrofuran-3-carboxamide (2j-2)
Yield: 184 mg (84%); yellowish solid; mp 105–107 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 6.0 Hz, 3 H), 2.11–2.21 (m, 1 H), 2.97–3.06 (m, 1 H), 3.67–3.74 (m, 1 H), 4.76–4.86 (m, 1 H), 7.13 (t, *J* = 7.0 Hz, 1 H), 7.33 (t, *J* = 7.0 Hz, 2 H), 7.52–7.57 (m, 2 H), 8.72 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.9, 33.3, 48.1, 76.5, 119.2 (2C), 123.7, 128.8 (2C), 138.6, 165.7, 173.8.

Substituted γ-Thiolactones 3; Typical Procedure

To a 50 mL round-bottomed flask was added **1a** (1.0 mmol), $SnCl_4·5H_2O$ (2.0 mmol), $Na_2S·9H_2O$ (1.5 mmol), and toluene (10.0 mL). The mixture was heated at reflux for 2 h, then cooled to r.t. The mixture was neutralized with sat. aq $NaHCO_3$, then extracted with CH_2Cl_2 (3 × 20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by short flash silica gel column chromatography (EtOAc–petroleum ether, 1:4) to give compound **3a**.

2-Oxo-*N*-phenyl-tetrahydrothiophene-3-carboxamide (3a)

Yield: 142 mg (64%); yellowish solid; mp 141–142 °C.

IR (KBr, neat): 3225, 3040, 1681, 1664, 1639, 1541, 1363, 1310, 1041, 816 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.63–2.86 (m, 2 H), 3.33–3.42 (m, 1 H), 3.45–3.56 (m, 2 H), 7.13 (t, *J* =7.5 Hz, 1 H), 7.33 (t, *J* = 7.0 Hz, 2 H), 7.53 (d, *J* = 7.5 Hz, 2 H), 8.62 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4, 30.8, 57.4, 119.9 (2C), 124.6, 128.9 (2C), 137.3, 163.2, 207.7.

Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33; Found: C, 59.58; H, 5.06; N, 6.38.

2-Oxo-*N*-*p*-tolyl-tetrahydrothiophene-3-carboxamide (3b)

Yield: 122 mg (52%); yellowish solid; mp 160–161 °C.

IR (KBr, neat): 3285, 1697, 1653, 1541, 1356, 1047, 926, 758 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 2.64–2.68 (m, 1 H), 2.76–2.80 (m, 1 H), 3.35–3.38 (m, 1 H), 3.46–3.53 (m, 2 H), 7.12 (d, *J* = 7.0 Hz, 2 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 8.49 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.9, 28.5, 30.8, 57.3, 120.1 (2C), 129.5 (2C), 134.3, 134.8, 162.8, 207.9.

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95; Found: C, 61.51; H, 5.49; N, 5.89.

2-Oxo-*N*-*o*-tolyl-tetrahydrothiophene-3-carboxamide (3e)

Yield: 174 mg (74%); yellowish solid; mp 149–151 °C.

IR (KBr, neat): 3306, 1695, 1662, 1591, 1541, 1443, 746 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 2.70–2.71 (m, 1 H), 2.79–2.81 (m, 1 H), 3.38–3.40 (m, 1 H), 3.46–3.49 (m, 1 H), 3.56–3.60 (m, 1 H), 7.07 (d, *J* = 8.0 Hz, 1 H), 7.18 (t, *J* = 8.0 Hz, 2 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 8.58 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 17.7, 28.5, 30.8, 57.3, 122.1, 125.1, 126.7, 128.7, 130.5, 135.4, 163.0, 208.2.

MS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{13}NO_2SNa$: 258.0; found: 258.0.

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95; Found: C, 61.53; H, 5.52; N, 5.91.

***N*-(2-Chlorophenyl)-2-oxo-tetrahydrothiophene-3-carboxamide (3g)**

Yield: 179 mg (70%); yellowish solid; mp 114–116 °C.

IR (KBr, neat): 3229, 3034, 1691, 1641, 1543, 1360, 1034, 866, 754 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.68–2.72 (m, 1 H), 2.80–2.82 (m, 1 H), 3.36–3.41 (m, 1 H), 3.47–3.50 (m, 1 H), 3.59–3.62 (m, 1 H), 7.06 (t, *J* = 7.0 Hz, 1 H), 7.26 (t, *J* = 7.0 Hz, 1 H), 7.38 (d, *J* = 7.0 Hz, 1 H), 8.31 (d, *J* = 7.0 Hz, 1 H), 9.15 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 28.4, 30.8, 57.6, 121.7, 123.6, 125.0, 127.5, 129.3, 134.3, 163.3, 207.1.

Anal. Calcd for $C_{11}H_{10}ClNO_2S$: C, 51.66; H, 3.94; N, 5.48; Found: C, 51.48; H, 4.02; N, 5.43.

5-Methyl-2-oxo-*N*-phenyl-tetrahydrothiophene-3-carboxamide (3j-1)

Yield: 148 mg (63%); yellowish solid; mp 124–126 °C.

IR (KBr, neat): 3404, 3157, 1693, 1656, 1404, 1313, 812, 582 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 9.5 Hz, 3 H), 2.12–2.19 (m, 1 H), 2.95–3.01 (m, 1 H), 3.63–3.69 (m, 1 H), 4.10–4.15 (m, 1 H), 7.10 (t, *J* = 6.0 Hz, 1 H), 7.32 (t, *J* = 8.5 Hz, 2 H), 7.52 (d, *J* = 8.5 Hz, 2 H), 8.34 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 36.4, 43.8, 58.8, 119.9, 124.5, 128.9, 137.3, 162.8, 207.4.

5-Methyl-2-oxo-*N*-phenyl-tetrahydrothiophene-3-carboxamide (3j-2)

Yield: 148 mg (63%); yellowish solid; mp 124–126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 9.5 Hz, 3 H), 2.30–2.33 (m, 1 H), 2.81–2.85 (m, 1 H), 3.63–3.69 (m, 1 H), 3.84–3.87 (m, 1 H), 7.01 (t, *J* = 6.0 Hz, 1 H), 7.32 (t, *J* = 8.5 Hz, 2 H), 7.52 (d, *J* = 8.5 Hz, 2 H), 8.93 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 37.3, 41.7, 59.0, 120.1, 124.6, 128.9, 137.3, 163.6, 207.4.

Acknowledgment

Financial support of this research by the National Natural Science Foundation of China (51073150 and 21172211) and 'Hundred Talents Program' of the Chinese Academy of Sciences is greatly acknowledged.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Primary Data for this article are available online at http://www.thieme-connect.com/ejournals/toc/synthesis and can be cited using the following DOI: 10.4125/pd0028th.

References

(1) (a) Pilli, R.; Rosso, G.; De Oliveira, M.; Cordell, G. In *The Alkaloids: Chemistry and Biology*; Vol. 62; Academic Press: New York, **2005**, 77–173. (b) Connolly, J.; Hill, R. *Dictionary of Terpenoids*; Vol. 1; Chapman and Hall: London, **1991**, 476–541. (c) Koch, S.; Chamberlin, A. *Enantiomerically Pure γ-Butyrolactones in Natural Products Synthesis*; Atta-ur-Rahman; Elsevier Science: Amsterdam, **1995**, 687–725. (d) Ogliaruso, M.; Wolfe, J. In *Synthesis of Lactones and Lactams*; John Wiley & Sons: New York, **1993**.

(2) (a) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1869. (b) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285. (c) Gil, S.; Parra, M.; Rodriguez, P.; Segura, J. *Mini-Rev. Org. Chem.* **2009**, *6*, 345. (d) Kitson, R.; Millemaggi, A.; Taylor, R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9426. (e) Amancha, P. K.; Liu, H. J.; Ly, T. W.; Shia, K. S. *Eur. J. Org. Chem.* **2010**, 3473.

(3) (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (b) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507. (c) Ye, W.; Cai, G.; Zhuang, Z.; Jia, X.; Zhai, H. *Org. Lett.* **2005**, *7*, 3769.

(4) (a) Dohi, T.; Takenaga, N.; Goto, A.; Maruyama, A.; Kita, Y. *Org. Lett.* **2007**, *9*, 3129. (b) Ito, M.; Osaku, A.; Shiibashi, A.; Ikariya, T. *Org. Lett.* **2007**, *9*, 1821.

(5) (a) Wang, W.; Xu, M.; Lei, X.; Lin, G. *Org. Lett.* **2000**, *2*, 3773. (b) Xu, M.; Wang, W.; Lin, G. *Org. Lett.* **2000**, *2*, 2229.
(6) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071.
(7) Mandal, S.; Amin, S.; Crowe, W. *J. Am. Chem. Soc.* **2001**, *123*, 6457.
(8) Schmidt, J.; Lobkovsky, E.; Coates, G. *J. Am. Chem. Soc.* **2005**, *127*, 11426.
(9) Guan, J.; Zhen, Z.; Zou, Y.; Yue, Z.; Jiang, P.; Li, Y.; Wu, Y. *Tetrahedron* **2011**, *67*, 860.
(10) Xu, S.; Wang, Z.; Zhang, X.; Zhang, X.; Ding, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 2840.
(11) For reviews on cyclopropanes, see: (a) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (b) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597. (c) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493. (d) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603.
(12) For selected examples of ring-opening or ring-enlargement reactions of cyclopropanes, see: (a) Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F.; Spiga, M. *Org. Lett.* **2005**, *7*, 4565. (b) Ogoshi, S.; Nagata, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 5350. (c) Liu, L.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 5348. (d) Patel, N. C.; Schwarz, J. B.; Islam, K.; Miller, W.; Tran, T. P.; Wei, Y. *Synth. Commun.* **2011**, *41*, 2209. (e) Novikov, R. A.; Korolev, V. A.; Timofeev, V. P.; Tomilov, Y. V. *Tetrahedron Lett.* **2011**, *52*, 4996. (f) Chagarovskiy, A. O.; Ivaonva, O. A.; Rakhmankulov, E. R.; Budynina, E. M.; Trushkov, I. V.; Melnikov, M. Y. *Adv. Synth. Catal.* **2010**, *352*, 3179.
(13) Brückner, C.; Reissig, H.-U. *J. Org. Chem.* **1988**, *53*, 2440.
(14) (a) Böhm, C.; Schinnerl, M.; Bubert, C.; Zabel, M.; Labahn, T.; Parisini, E.; Reiser, O. *Eur. J. Org. Chem.* **2000**, 2955. (b) Böhm, C.; Reiser, O. *Org. Lett.* **2001**, *3*, 1315. (c) Nosse, B.; Chhor, R. B.; Jeong, W. B.; Böhm, C.; Reiser, O. *Org. Lett.* **2003**, *5*, 941. (d) Chhor, R. B.; Nosse, B.; Sörgel, S.; Böhm, C.; Seitz, M.; Reiser, O. *Chem.–Eur. J.* **2003**, *9*, 260. (e) Kalidindi, S.; Jeong, W. B.; Schall, A.; Bandichhor, R.; Nosse, B.; Reiser, O. *Angew. Chem. Int. Ed.* **2007**, *46*, 6361. (f) Macabeo, A. P. G.; Kreuzer, A.; Reiser, O. *Org. Biomol. Chem.* **2011**, *9*, 3146.
(15) (a) Pan, W.; Dong, D.; Wang, K.; Zhang, J.; Wu, R.; Xiang, D.; Liu, Q. *Org. Lett.* **2007**, *9*, 2421. (b) Wang, K.; Xiang, D.; Liu, J.; Pan, W.; Dong, D. *Org. Lett.* **2008**, *10*, 1691. (c) Wang, K.; Fu, X.; Liu, J.; Liang, Y.; Dong, D. *Org. Lett.* **2009**, *11*, 1015.
(16) Zhang, D.; Zhang, R.; Xiang, D.; Zhang, N.; Liang, Y.; Dong, D. *Synthesis* **2012**, 705.
(17) For our recent work, see: (a) Xiang, D.; Wang, K.; Liang, Y.; Zhou, G.; Dong, D. *Org. Lett.* **2008**, *10*, 345. (b) Huang, J.; Liang, Y.; Pan, W.; Yang, Y.; Dong, D. *Org. Lett.* **2007**, *9*, 5345. (c) Zhang, R.; Zhang, D.; Liang, Y.; Zhou, G.; Dong, D. *J. Org. Chem.* **2011**, *76*, 2880. (d) Xiang, D.; Yang, Y.; Zhang, R.; Liang, Y.; Pan, W.; Huang, J.; Dong, D. *J. Org. Chem.* **2007**, *72*, 8593. (e) Zhang, R.; Liang, Y.; Zhou, G.; Wang, K.; Dong, D. *J. Org. Chem.* **2008**, *73*, 8089. (f) Wang, Y.; Xin, X.; Liang, Y.; Lin, Y.; Duan, H.; Dong, D. *Adv. Synth. Catal.* **2009**, *351*, 2217. (g) Zhang, R.; Zhang, D.; Guo, Y.; Zhou, G.; Jiang, Z.; Dong, D. *J. Org. Chem.* **2008**, *73*, 9504. (h) Ouyang, Y.; Dong, D.; Yu, H.; Liang, Y.; Liu, Q. *Adv. Synth. Catal.* **2006**, *348*, 206. (i) Dong, D.; Bi, X.; Liu, Q.; Cong, F. *Chem. Commun.* **2005**, 3580. (j) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578.
(18) The relative configuration of *cis*-**1j** was determined by NOESY analysis, see Zhang et al.[16]
(19) For reviews on donor-acceptor-substituted cyclopropanes and their reactivity, see: (a) Reissig, H.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Yu, M.; Pagenkopf, B. *Tetrahedron* **2005**, *61*, 321. (c) De Simone, F.; Waser, J. *Synthesis* **2009**, 3353. (d) Schneider, T.; Werz, D. *Org. Lett.* **2011**, *13*, 1848.
(20) The relative configurations of diastereoisomers *cis*-**2j** and *trans*-**2j** were determined by NOESY analysis, see the Supporting Information.
(21) For Lewis acid chelation, see: (a) Pohlhaus, P.; Johnson, J. *J. Am. Chem. Soc.* **2005**, *127*, 16014. (b) Yamazaki, S.; Ohmitsu, K.; Ohi, K.; Otsubo, T.; Moriyama, K. *Org. Lett.* **2005**, *7*, 759. (c) Parsons, A.; Smith, A.; Neel, A.; Johnson, J. *J. Am. Chem. Soc.* **2010**, *132*, 9688. (d) Smith, A.; Slade, M.; Johnson, J. *Org. Lett.* **2011**, *13*, 1996.
(22) For ring-opening of cyclopropanes, see: (a) Yang, Y.; Shi, M. *Eur. J. Org. Chem.* **2006**, 5394. (b) Yang, Y.; Shi, M. *Org. Lett.* **2006**, *8*, 1709. (c) Yang, Y.; Shi, M. *J. Org. Chem.* **2005**, *70*, 10082. (d) Shi, M.; Tang, X.; Yang, Y. *J. Org. Chem.* **2008**, *73*, 5311.
(23) (a) Sasaki, H.; Oishi, H.; Hayashi, T.; Matsuura, I.; Ando, K.; Sawada, M. *J. Antibiot.* **1982**, *35*, 396. (b) Dal Negro, R.; Visconti, M.; Micheletto, C.; Tognella, S. *Pulm. Pharmacol. Ther.* **2008**, *21*, 304. (c) Farid, N.; Smith, R.; Gillespie, T.; Rash, T.; Blair, P.; Kurihara, A.; Goldberg, M. *Drug Metab. Dispos.* **2007**, *35*, 1096.