Three-Component Condensation for the Construction of Novel Spirooxindoles

Fei Ji, Mu Sun, Mei-fang Lv, Wen-bin Yi, Chun Cai*

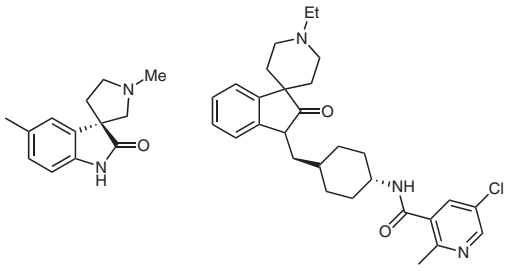
Chemical Engineering College, Nanjing University of Science and Technology, Nanjing 210094, P. R. of China
Fax +86(25)84315030; E-mail: c.cai@mail.njust.edu.cn

Received: 13.11.2012; Accepted after revision: 05.12.2012

Abstract: A new route for the synthesis of novel spirooxindoles from isocyanides, dialkyl acetylenedicarboxylates, and N-substituted isatylidene derivatives through [3+2] cycloaddition has been developed. This method has several advantages, such as high regioselectivity, high yields, readily available starting materials, and one-pot operations. The synthetic alkyne-containing spirooxindoles could also be used in the selective synthesis of triazole-containing spirocyclic compounds using a copper azide–alkyne cycloaddition (CuAAC) reaction.

Key words: multicomponent reaction, spirooxindoles, [3+2] cycloaddition, CuAAC reaction, triazoles

Spirooxindoles are attractive targets in organic synthesis because of their high pronounced biological activity as well as their wide utility as synthetic intermediates for alkaloids, medical candidates, and clinical pharmaceuticals (Figure 1).[1] Research focused on the synthesis of these compounds is, therefore, of interest in organic synthesis, and numerous successful examples of the synthesis of diversely structured spirooxindoles have been recorded in recent years.[2]



horsfiline CRF receptor antagonists

Figure 1 Alkaloids, medical candidates, and clinical pharmaceuticals containing the spirooxindole skeleton

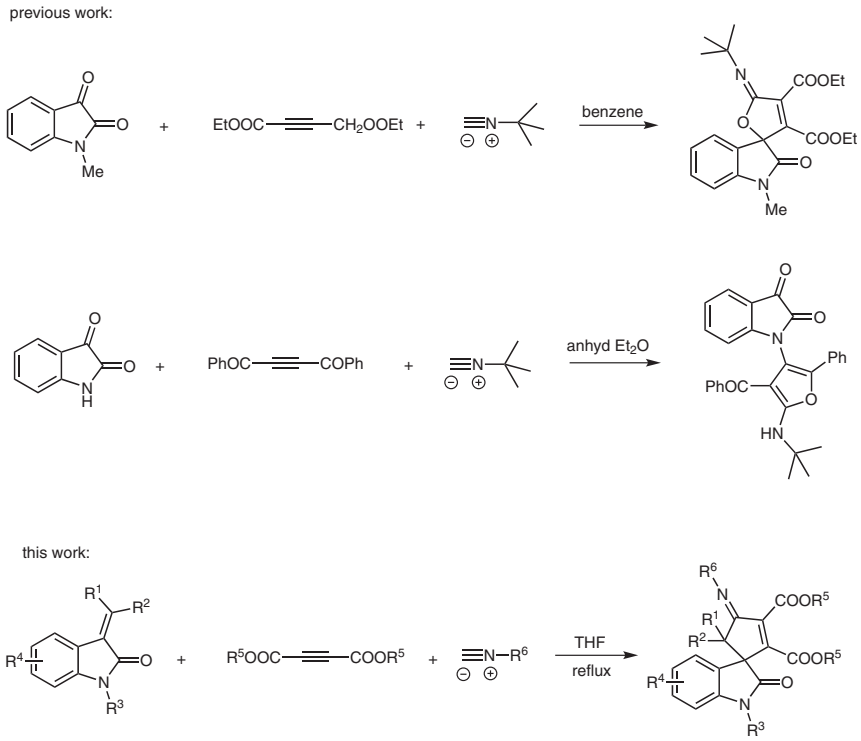
Multicomponent reactions (MCRs) are one of the most powerful and significant tools in organic synthesis. They are widely utilized to generate high levels of diversity, because they allow more than two building blocks to be combined in a practical, time-saving, and one-pot operation, affording complex structures by simultaneous formation of two or more bonds.[3] Multicomponent reactions between nucleophiles and activated alkynes have received much attention from organic chemists, particular for heterocyclic synthesis.[4] Of special interest in this area are reactions between isocyanides and activated alkynes. It has been shown that the addition of isocyanides to electron-withdrawing alkynes, such as dialkyl acetylenedicarboxylates, generates zwitterionic intermediates. The active intermediates could be trapped by a third component, e.g. aldehydes,[5] amides,[6] oximes,[7] carboxylic acids,[8] and active methylene-containing compounds,[9] to form heterocycles. Recently, multicomponent reactions involving isatin derivatives, dialkyl acetylenedicarboxylates, and isocyanides have attracted the interest of many researchers. In 2003, Esmaeili and co-workers reported that the treatment of isocyanides and dialkyl acetylenedicarboxylates with N-substituted isatin derivatives led to the efficient synthesis of novel γ-spiro-iminolactones (Scheme 1).[10] Later, Sabbaghan and co-workers used N-unsubstituted isatins to obtain 1-(3-furyl)-1*H*-indole-2,3-diones in excellent yields (Scheme 1).[11]

In views of these previous results, we envisaged that a novel multicomponent reaction based on the above [3+2] cycloaddition could be accessed if N-substituted isatylidenes were employed as substrates instead of isatin derivatives. To our satisfaction, we found that three-component condensation of N-substituted isatylidenes, dialkyl acetylenedicarboxylates, and isocyanides proceeded smoothly, giving the desired products in excellent yields (Scheme 1).

Initial studies focused on the optimization of the three-component reaction of N-substituted isatylidenes (R^1 = R^2 = CN) (0.5 mmol), diethyl acetylenedicarboxylate (0.6 mmol), and *tert*-butyl isocyanide (0.6 mmol) for the synthesis of **1** as a model reaction. Various solvents and temperatures were considered (Table 1). It was found that tetrahydrofuran was the best choice of solvent (cf. entries 1–7 with 8–10) and that higher temperatures could increase the yield efficiently (cf. entry 10 with 8 and 9). At the same time, this reaction did not require a catalyst and proceeded to give **1** in high yield.

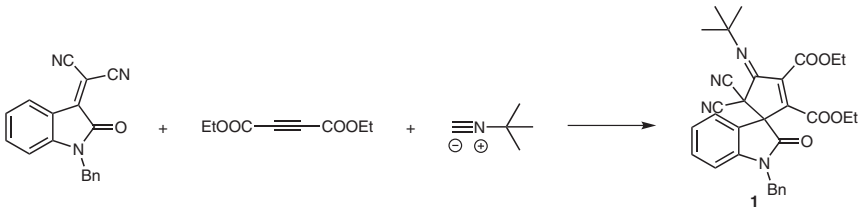
Under the optimized conditions, a variety of N-substituted isatylidenes, dialkyl acetylenedicarboxylates, and isocyanides were employed to evaluate the substrate scope of the reaction. All of the spirooxindoles **2**–**14** were obtained in good yields (Scheme 2). As anticipated, these reactions proceeded very cleanly under reflux in tetrahydrofuran. All of the compounds described in this paper are novel.

SYNTHESIS 2013, 45, 0375–0381
Advanced online publication: 21.12.2012
DOI: 10.1055/s-0032-1316836; Art ID: SS-2012-F0884-OP



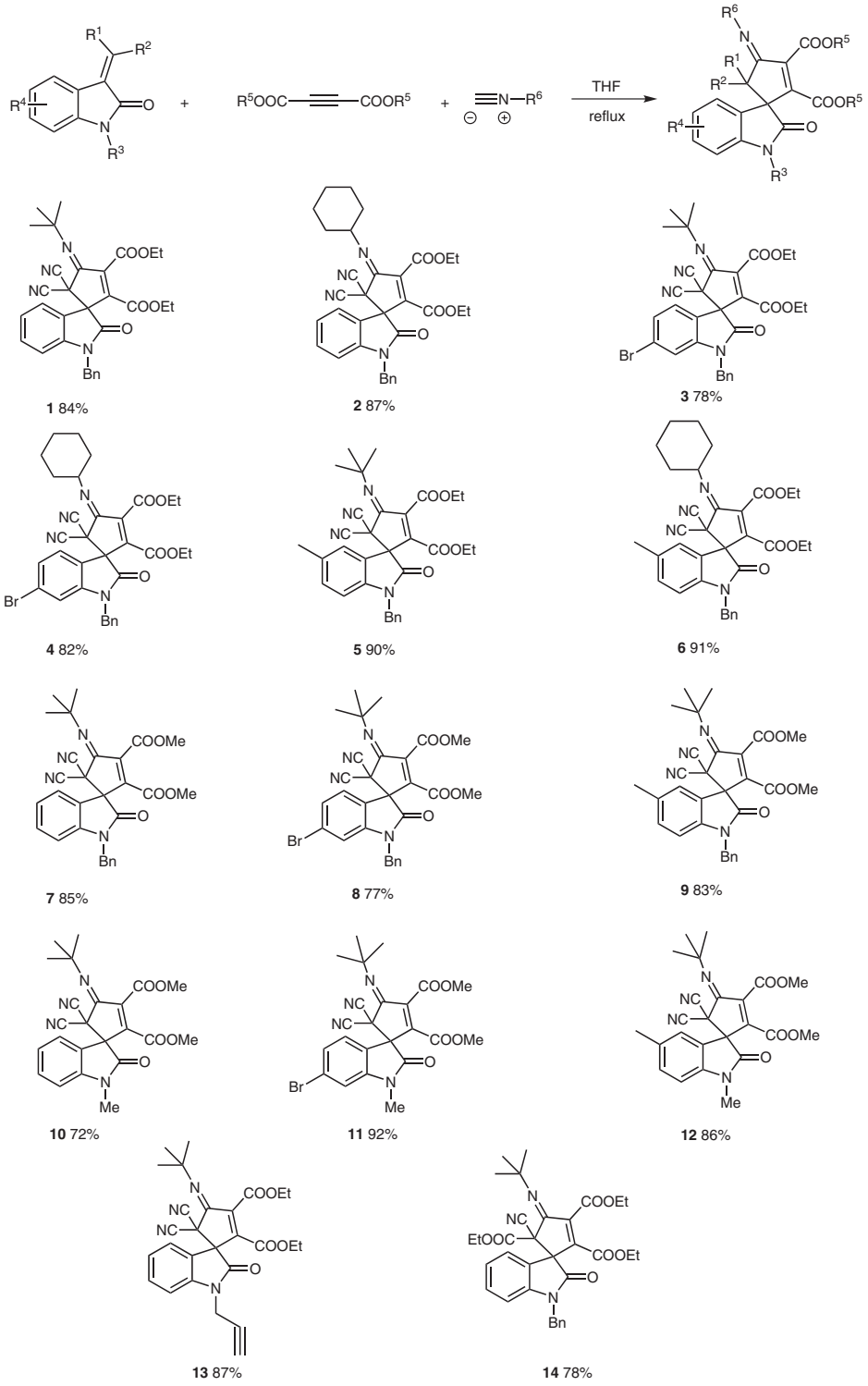
Scheme 1 Comparison of previous work with ours

Table 1 Effect of Solvents and Temperature on the Reaction[a]



Entry	Solvent	Temp (°C)	Yield[b] (%)
1	EtOH	78	45
2	CH_2Cl_2	40	56
3	toluene	108	40
4	EtOAc	77	30
5	Et_2O	34	45
6	H_2O	100	–[c]
7	PEG400–H_2O	80	–[c]
8	THF	25	62
9	THF	45	78
10	THF	65	84

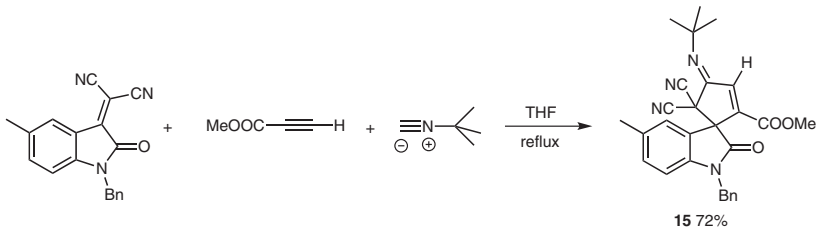
[a] Reaction conditions: benzyl isatylidene (0.5 mmol), diethyl acetylenedicarboxylate (0.6 mmol), *tert*-butyl isocyanide (0.6 mmol), solvent (2 mL), 24 h, sealed tube.
[b] Isolated yield.
[c] No reaction.



Scheme 2 Synthesized spirooxindoles

To examine the regioselectivity of this [3+2] cycloaddition, methyl propiolate was employed as an unsymmetrical alkyne, the yield and regioselectivity of the resultant product **15** were very good (Scheme 3).

The structures of the new spirooxindoles were fully characterized by mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy, and elemental analysis. The structure of **7** was also confirmed by single-crystal X-ray analysis (Figure 2).



Scheme 3 Regioselectively synthesized spirooxindole

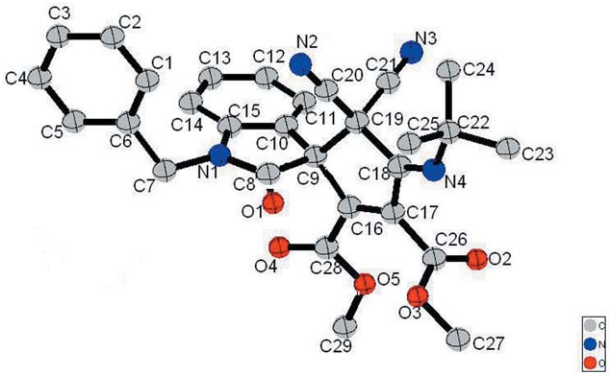


Figure 2 Single-crystal X-ray analysis of **7**

On the basis of the well-established chemistry of isocyanides,[12] it is conceivable that the initial event is the formation of zwitterionic species **A** from isocyanides and dialkyl acetylenedicarboxylates. The zwitterionic species **A** can add to the electrophilic C=C bond of **B** resulting in the formation of **C**, which then undergoes cyclization to deliver the final product **D**. Although less likely, the possibility of concerted 1,3-dipolar cycloaddition cannot be dismissed at the present time (Scheme 4).

In addition, triazoles also show some special biological activity.[13] The significant biological activity of spirooxindoles and triazoles emphasized the need to develop efficient synthetic strategies to access these scaffolds and increase the structural diversity for drug discovery and medicinal chemistry programs. Thus, we tried to explore the feasibility of the synthesis of triazole-containing spirooxindoles. With the help of the copper-catalyzed azide–alkyne cycloaddition (CuAAC),[14] the synthetic alkyne-containing spirooxindoles **13** reacted with an azide to provide triazole-containing spirooxindoles **16** and **17** in high yields (Figure 3).

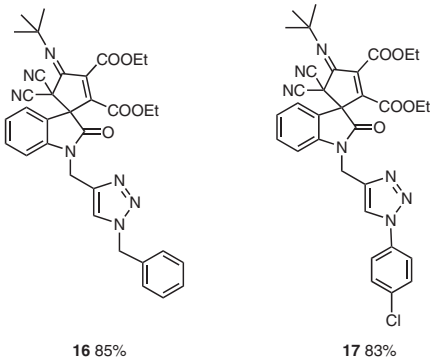
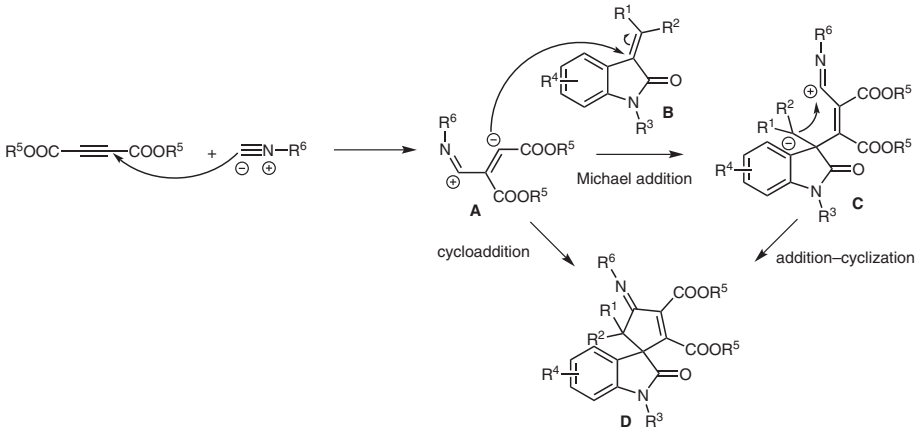


Figure 3 Triazole-containing spirooxindoles synthesized

In conclusion, an efficient, atom-economic, environmentally friendly, and highly regioselective method for the preparation of the novel spirooxindoles using readily available starting materials in tetrahydrofuran is reported. The prominent advantages of this method are operational simplicity, good yields, no catalyst, and the easy workup procedure employed. In addition, the further functional-



Scheme 4 Possible mechanism for the formation of spirooxindoles

ization of novel spirooxindoles with the CuAAC reaction also provided efficient methods to prepare libraries of enriched spirocyclic compounds.

All materials were obtained from commercial suppliers and used without further purification. All melting points are uncorrected. Mass spectra were taken on Shimadzu LCMS-2020. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz in $CDCl_3$, respectively, and referenced to internal TMS. Elemental analyses were performed on a Yanagimoto MT3CHN recorder.

Dimethyl 1′-Benzyl-4-(*tert*-butylimino)-5,5-dicyano-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (7); Typical Procedure

To a soln of benzyl isatylidene (0.5 mmol, 1 equiv) and dimethyl acetylenedicarboxylate (0.6 mmol, 1.2 equiv) in THF (2.5 ml) in a sealed tube, *tert*-butyl isocyanide (0.6 mmol, 1.2 equiv) was added. The mixture was stirred under reflux for 24 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel) to give **7**.

Diethyl 1′-Benzyl-4-(*tert*-butylimino)-5,5-dicyano-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (1)

White solid; yield: 0.225 g (84%); mp 170–172 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (m, 3 H), 1.39 (m, 3 H), 1.54 (s, 9 H), 3.87 (m, 1 H), 4.08 (m, 1 H), 4.40 (m, 2 H), 5.03 (m, 2 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 7.16 (m, 1 H), 7.31 (m, 1 H), 7.37 (m, 3 H), 7.44 (d, *J* = 18.5 Hz, 2 H), 7.49 (d, *J* = 7.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.35, 12.99, 29.25, 44.14, 58.91, 61.23, 61.50, 109.36, 110.61, 121.90, 122.66, 124.74, 126.64, 127.08, 127.91, 130.41, 133.54, 142.91, 144.33, 159.34, 161.11, 169.52.

MS (ESI): *m*/*z* = 539 [M + H].

Anal. Calcd for $C_{31}H_{30}N_4O_5$: C, 69.13; H, 5.61; N, 10.40. Found: C, 69.04; H, 5.81; N, 10.20.

Diethyl 1′-Benzyl-5,5-dicyano-4-(cyclohexylimino)-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (2)

White solid; yield: 0.245 g (87%); mp 150–152 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.76 (m, 1 H), 0.87 (m, 2 H), 1.26 (m, 1 H), 1.36 (m, 5 H), 1.62 (m, 3 H), 1.81 (m, 4 H), 3.85 (m, 1 H), 4.04 (m, 2 H), 4.40 (m, 2 H), 4.98 (m, 2 H), 6.85 (d, *J* = 16.0 Hz, 1 H), 7.11 (m, 1 H), 7.33 (m, 1 H), 7.37 (m, 4 H), 7.40 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.38, 12.83, 13.06, 22.59, 22.92, 24.29, 31.30, 31.98, 32.45, 38.86, 39.03, 39.20, 40.09, 44.06, 61.33, 61.51, 61.77, 62.19, 62.88, 109.38, 122.32, 122.57, 122.70, 124.55, 126.65, 127.10, 127.92, 130.51, 133.53, 140.46, 142.66, 144.37, 148.83, 158.97, 160.33, 169.14, 169.08.

MS (ESI): *m*/*z* = 565 [M + H].

Anal. Calcd for $C_{33}H_{32}N_4O_5$: C, 70.20; H, 5.71; N, 9.92. Found: C, 70.10; H, 5.52; N, 9.86.

Diethyl 1′-Benzyl-6′-bromo-4-(*tert*-butylimino)-5,5-dicyano-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (3)

White solid; yield: 0.240 g (78%); mp 118–120 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (m, 3 H), 1.39 (m, 3 H), 1.54 (s, 9 H), 3.93 (m, 1 H), 4.11 (m, 1 H), 4.40 (m, 2 H), 5.02 (m, 2 H), 7.14 (s, 1 H), 7.36 (m, 7 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.46, 13.02, 29.25, 44.23, 59.06, 61.52, 61.60, 110.50, 112.84, 120.80, 124.54, 125.64, 125.89, 126.57, 127.32, 128.07, 132.96, 143.95, 144.16, 159.23, 160.94, 169.46.

MS (ESI): *m*/*z* = 617 [M + H].

Anal. Calcd for $C_{31}H_{29}BrN_4O_5$: C, 60.30; H, 4.73; N, 9.07. Found: C, 60.21; H, 4.56; N, 9.28.

Diethyl 1′-Benzyl-6′-bromo-5,5-dicyano-4-(cyclohexylimino)-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (4)

White solid; yield: 0.263 g (82%); mp 142–144 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (m, 1 H), 1.01 (m, 2 H), 1.42 (m, 6 H), 1.65 (m, 3 H), 1.86 (m, 4 H), 3.97 (m, 1 H), 4.14 (m, 2 H), 4.83 (m, 2 H), 5.06 (m, 2 H), 7.02 (s, 1 H), 7.34 (m, 7 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.51, 12.86, 13.10, 22.60, 22.93, 24.33, 31.32, 32.01, 32.48, 39.83, 44.24, 61.58, 61.87, 62.25, 63.04, 109.22, 109.69, 110.45, 112.83, 120.75, 121.31, 124.60, 125.55, 125.74, 126.00, 126.62, 127.34, 128.10, 133.00, 136.12, 139.73, 143.98, 144.64, 148.54, 150.11, 158.98, 160.20, 161.42, 169.09, 169.62.

MS (ESI): *m*/*z* = 643 [M + H].

Anal. Calcd for $C_{33}H_{31}BrN_4O_5$: C, 61.59; H, 4.86; N, 8.71. Found: C, 61.78; H, 4.96; N, 8.52.

Diethyl 1′-Benzyl-4-(*tert*-butylimino)-5,5-dicyano-5′-methyl-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (5)

White solid; yield: 0.249 g (90%); mp 151–153 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (m, 3 H), 1.37 (m, 3 H), 1.52 (s, 9 H), 2.32 (s, 3 H), 3.86 (m, 1 H), 4.07 (m, 1 H), 4.38 (m, 2 H), 4.98 (m, 2 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 7.14 (m, 1 H), 7.33 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.35, 12.96, 20.07, 29.22, 44.09, 58.82, 61.22, 61.50, 109.14, 110.63, 110.72, 121.80, 125.30, 126.59, 127.00, 127.85, 130.74, 132.49, 133.63, 140.44, 144.50, 159.38, 161.16, 169.42.

MS (ESI): *m*/*z* = 553 [M + H].

Anal. Calcd for $C_{32}H_{32}N_4O_5$: C, 69.55; H, 5.84; N, 10.14. Found: C, 69.36; H, 5.64; N, 10.34.

Diethyl 1′-Benzyl-5,5-dicyano-4-(cyclohexylimino)-5′-methyl-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (6)

White solid; yield: 0.263 g (91%); mp 115–117 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (m, 1 H), 0.94 (m, 2 H), 1.42 (m, 6 H), 1.67 (m, 2 H), 1.85 (m, 5 H), 2.33 (s, 3 H), 3.91 (m, 1 H), 4.09 (m, 2 H), 4.43 (m, 2 H), 5.04 (m, 2 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 7.17 (m, 2 H), 7.35 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.34, 12.44, 12.86, 13.09, 20.07, 22.63, 22.97, 24.35, 31.34, 32.00, 32.48, 40.19, 44.09, 61.33, 61.51, 61.77, 62.17, 62.87, 109.15, 109.40, 109.51, 121.75, 122.37, 125.21, 125.47, 126.67, 127.05, 127.90, 130.84, 132.40, 133.70, 135.85, 140.25, 140.41, 144.60, 149.01, 150.59, 159.09, 160.45, 161.62, 169.11, 169.65.

MS (ESI): *m*/*z* = 579 [M + H].

Anal. Calcd for $C_{34}H_{34}N_4O_5$: C, 70.57; H, 5.92; N, 9.68. Found: C, 70.38; H, 5.71; N, 9.89.

Dimethyl 1′-Benzyl-4-(*tert*-butylimino)-5,5-dicyano-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (7)

White solid; yield: 0.217 g (85%); mp 128–130 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.54 (s, 9 H), 3.51 (s, 3 H), 3.93 (s, 3 H), 5.04 (m, 2 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 7.16 (m, 1 H), 7.39 (m, 7 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.24, 44.10, 52.00, 52.09, 59.00, 109.50, 110.54, 121.66, 122.72, 124.57, 126.59, 127.07, 127.92, 130.54, 133.54, 142.78, 144.24, 159.83, 161.51, 169.37.

MS (ESI): *m*/*z* = 511 [M + H].

Anal. Calcd for $C_{29}H_{26}N_4O_5$: C, 68.22; H, 5.13; N, 10.97. Found: C, 68.11; H, 5.32; N, 10.78.

Dimethyl 1′-Benzyl-6′-bromo-4-(*tert*-butylimino)-5,5-dicyano-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (8)
White solid; yield: 0.226 g (77%); mp 135–137 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.54 (s, 9 H), 3.56 (s, 3 H), 3.93 (s, 3 H), 5.00 (m, 2 H), 7.03 (s, 1 H), 7.34 (m, 7 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.23, 44.22, 52.19, 59.15, 110.40, 112.96, 120.55, 124.67, 125.74, 126.53, 127.31, 128.08, 132.95, 143.80, 144.02, 159.72, 161.33, 169.32.

MS (ESI): *m*/*z* = 589 [M + H].

Anal. Calcd for $C_{29}H_{25}BrN_4O_5$: C, 59.09; H, 4.28; N, 9.51. Found: C, 59.20; H, 4.42; N, 9.72.

Dimethyl 1′-Benzyl-4-(*tert*-butylimino)-5,5-dicyano-5′-methyl-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (9)
White solid; yield: 0.217 g (83%); mp 128–130 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.54 (s, 9 H), 2.34 (s, 3 H), 3.52 (s, 3 H), 3.93 (s, 3 H), 5.02 (m, 2 H), 6.76 (d, *J* = 8.5 Hz, 1 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 7.26 (s, 1 H), 7.31 (m, 1 H), 7.36 (m, 2 H), 7.39 (d, *J* = 19.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.13, 29.24, 44.07, 52.01, 52.08, 58.94, 109.24, 110.58, 121.61, 125.17, 126.58, 127.00, 127.88, 130.90, 132.53, 133.68, 140.33, 144.40, 159.89, 161.57, 169.29.

MS (ESI): *m*/*z* = 525 [M + H].

Anal. Calcd for $C_{30}H_{28}N_4O_5$: C, 68.69; H, 5.38; N, 10.68. Found: C, 68.50; H, 5.18; N, 10.77.

Dimethyl 4-(*tert*-Butylimino)-5,5-dicyano-1′-methyl-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (10)
White solid; yield: 0.157 g (72%); mp 138–140 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.52 (s, 9 H), 3.35 (s, 3 H), 3.60 (s, 3 H), 3.91 (s, 3 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 7.19 (m, 1 H), 7.43 (d, *J* = 7.5 Hz, 1 H), 7.50 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.37, 29.23, 52.09, 58.98, 108.40, 110.31, 110.56, 121.66, 122.71, 124.44, 130.68, 143.55, 144.28, 159.82, 161.48, 169.17.

MS (ESI): *m*/*z* = 435 [M + H].

Anal. Calcd for $C_{23}H_{22}N_4O_5$: C, 63.59; H, 5.10; N, 12.90. Found: C, 63.34; H, 5.22; N, 12.79.

Dimethyl 6′-Bromo-4-(*tert*-butylimino)-5,5-dicyano-1′-methyl-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (11)
White solid; yield: 0.235 g (92%); mp 180–182 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.53 (s, 9 H), 3.34 (s, 3 H), 3.64 (s, 3 H), 3.91 (s, 3 H), 7.18 (d, *J* = 1.5 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 7.33 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.51, 29.23, 52.09, 52.25, 59.14, 110.11, 110.42, 112.06, 120.54, 124.78, 125.64, 143.80, 144.76, 159.72, 161.29, 169.11.

MS (ESI): *m*/*z* = 513 [M + H].

Anal. Calcd for $C_{23}H_{21}BrN_4O_5$: C, 53.81; H, 4.12; N, 10.91. Found: C, 53.98; H, 4.01; N, 10.98.

Dimethyl 4-(*tert*-Butylimino)-5,5-dicyano-1′,5′-dimethyl-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (12)
White solid; yield: 0.193 g (86%); mp 185–187 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.53 (s, 9 H), 2.38 (s, 3 H), 3.34 (s, 3 H), 3.62 (s, 3 H), 3.92 (s, 3 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 7.23 (s, 1 H), 7.29 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.16, 26.37, 29.24, 52.01, 52.07, 58.94, 108.08, 110.34, 110.59, 121.64, 125.10, 130.97, 132.49, 141.15, 144.38, 159.86, 161.54, 169.11.

MS (ESI): *m*/*z* = 449 [M + H].

Anal. Calcd for $C_{24}H_{24}N_4O_5$: C, 64.28; H, 5.39; N, 12.49. Found: C, 64.19; H, 5.52; N, 12.28.

Diethyl 4-(*tert*-Butylimino)-5,5-dicyano-2′-oxo-1′-(prop-2-ynyl)-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (13)
White solid; yield: 0.212 g (87%); mp 122–124 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (m, 3 H), 1.38 (m, 3 H), 1.53 (s, 9 H), 2.33 (d, *J* = 1.5 Hz, 1 H), 3.98 (m, 1 H), 4.09 (m, 1 H), 4.40 (m, 2 H), 4.55 (d, *J* = 17.5 Hz, 1 H), 4.80 (d, *J* = 17.5 Hz, 1 H), 7.23 (m, 2 H), 7.48 (d, *J* = 7.5 Hz, 1 H), 7.52 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.46, 12.97, 27.22, 29.24, 58.96, 61.32, 61.53, 61.91, 72.29, 74.62, 109.31, 110.20, 110.49, 121.85, 123.03, 124.70, 130.50, 141.72, 144.16, 159.17, 161.00, 168.57.

MS (ESI): *m*/*z* = 487 [M + H].

Anal. Calcd for $C_{27}H_{26}N_4O_5$: C, 66.65; H, 5.39; N, 11.52. Found: C, 66.56; H, 5.47; N, 11.36.

Triethyl 1′-Benzyl-4-(*tert*-butylimino)-5-cyano-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3,5-tricarboxylate (14)
White solid; yield: 0.228 g (78%); mp 142–144 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (m, 3 H), 1.04 (m, 3 H), 1.39 (m, 3 H), 1.44 (s, 9 H), 3.83 (m, 2 H), 4.08 (m, 2 H), 4.40 (m, 2 H), 4.94 (d, *J* = 16.0 Hz, 1 H), 5.12 (d, *J* = 15.5 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.90 (m, 1 H), 7.05 (d, *J* = 7.5 Hz, 1 H), 7.28 (m, 2 H), 7.36 (m, 2 H), 7.46 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.37, 12.49, 13.19, 28.86, 43.93, 57.99, 60.69, 60.78, 62.69, 108.94, 114.81, 121.66, 123.47, 123.95, 126.68, 126.84, 127.79, 129.57, 134.03, 143.19, 149.66, 159.94, 161.86, 162.62, 171.47.

MS (ESI): *m*/*z* = 586 [M + H].

Anal. Calcd for $C_{33}H_{35}N_3O_7$: C, 67.68; H, 6.02; N, 7.17. Found: C, 67.48; H, 5.87; N, 7.25.

Methyl (*E*)-1′-Benzyl-4-(*tert*-butylimino)-5,5-dicyano-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2-carboxylate (15)
Purple solid; yield: 0.168 g (72%); mp 154–156 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50 (s, 9 H), 2.34 (s, 3 H), 3.62 (s, 3 H), 4.99 (d, *J* = 15.5 Hz, 1 H), 5.07 (d, *J* = 15.5 Hz, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 7.19 (s, 1 H), 7.30 (m, 1 H), 7.37 (m, 2 H), 7.43 (d, *J* = 7.5 Hz, 2 H), 7.51 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.20, 29.64, 44.00, 50.97, 51.94, 58.69, 59.33, 109.19, 110.51, 111.32, 122.36, 124.99, 126.53, 126.97, 127.91, 130.60, 131.53, 132.31, 133.74, 140.24, 146.71, 154.54, 160.80, 169.77.

MS (ESI): *m*/*z* = 467 [M + H].

Anal. Calcd for $C_{28}H_{26}N_4O_3$: C, 72.09; H, 5.62; N, 12.01. Found: C, 72.15; H, 5.54; N, 12.17.

Diethyl 1′-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-4-(*tert*-butylimino)-5,5-dicyano-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (16); Typical Procedure
A soln of spirooxindole **13** (0.5 mmol), CuI (0.1 mmol), Et_3N (0.5 mmol), and azide (0.5 mmol) were stirred at 40 °C for 24 h. When the reaction was complete, the mixtures were concentrated to dry-

ness under reduced pressure. The crude products were isolated by flash column chromatography (silica gel).

White solid; yield: 0.263 g (85%); mp 118–120 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (m, 3 H), 1.37 (m, 3 H), 1.52 (s. 9 H), 3.75 (m, 1 H), 3.98 (m, 1 H), 4.38 (m, 2 H), 5.02 (d, *J* = 15.5 Hz, 1 H), 5.21 (d, *J* = 16.0 Hz, 1 H), 5.41 (d, *J* = 15.0 Hz, 1 H), 5.51 (d, *J* = 15.0 Hz, 1 H), 7.17 (m, 1 H), 7.24 (m, 3 H), 7.34 (m, 3 H), 7.44 (m, 2 H), 7.66 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.32, 13.00, 29.23, 35.71, 53.34, 58.92, 61.26, 61.55, 109.73, 110.45, 110.67, 121.59, 122.23, 122.88, 124.62, 127.18, 127.76, 128.08, 130.69, 133.27, 141.02, 142.16, 144.26, 159.27, 161.01, 169.14.

MS (ESI): *m*/*z* = 620 [M + H].

Anal. Calcd for $C_{34}H_{33}N_7O_5$: C, 65.90; H, 5.37; N, 15.82. Found: C, 65.75; H, 5.54; N, 15.87.

Diethyl 4-(*tert*-Butylimino)-1′-[(1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl]-5,5-dicyano-2′-oxo-1′,2′-dihydrospiro[cyclopent-2-ene-1,3′-indole]-2,3-dicarboxylate (17)
White solid; yield: 0.265 g (83%); mp 128–130 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (m, 3 H), 1.39 (m, 3 H), 1.54 (s, 9 H), 3.94 (m, 1 H), 4.05 (m, 1 H), 4.40 (m, 2 H), 5.08 (d, *J* = 16.0 Hz, 1 H), 5.38 (d, *J* = 16.0 Hz, 1 H), 7.20 (m, 2 H), 7.47 (m, 4 H), 7.65 (m, 2 H), 8.19 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.41, 13.02, 29.25, 35.66, 58.99, 61.44, 61.61, 109.54, 110.37, 110.98, 120.35, 120.52, 121.55, 123.08, 124.81, 128.91, 130.81, 133.62, 134.34, 141.72, 141.98, 144.15, 159.44, 160.97, 169.27.

MS (ESI): *m*/*z* = 640 [M + H].

Anal. Calcd for $C_{33}H_{30}ClN_7O_5$: C, 61.92; H, 4.72; N, 15.32. Found: C, 61.76; H, 4.54; N, 15.47.

Acknowledgment

We thank financial supported by NUST research funding (2011ZDJH07). We also acknowledge the Analysis and Testing Center of Nanjing University of Science and Technology for NMR analysis of this work.

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/pd0036th.

References

(1) (a) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748.
(2) (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (c) Chen, X. H.; Wei, Q.; Xiao, H.; Luo, S. W.; Gong, L. Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (d) Bencivenni, G.; Wu, L. Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M. P.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 7200. (e) Wei, Q.; Gong, L. Z. *Org. Lett.* **2010**, *12*, 1008. (f) Shintani, R.; Hayashi, S. Y.; Murakami, M.; Takeda, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3754. (g) Castaldi, M. P.; Troast, D. M.; Porco, J. A. *Org. Lett.* **2009**, *11*, 3362.
(3) For reviews on domino reactions, see: (a) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6234. (b) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.
(4) (a) Oakes, T. R.; David, H. G.; Nagel, F. J. *J. Am. Chem. Soc.* **1969**, *91*, 4761. (b) Takizawa, T.; Obata, N.; Suzuki, Y.; Yanagida, T. *Tetrahedron Lett.* **1969**, *10*, 3407. (c) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 810. (d) Yavari, I.; Maghsoodlou, M. T. *J. Chem. Res., Synop.* **1998**, 386.
(5) (a) Reddy, B. V. S.; Reddy, A. M.; Somashekar, D.; Yadav, J. S.; Sridhar, B. *Synthesis* **2010**, 2571. (b) Terzidis, M. A.; Stephanidou-Stephanatou, J.; Tsoleridis, C. A. *J. Org. Chem.* **2010**, *75*, 1948.
(6) (a) Shaabani, A.; Sarvary, A.; Ghasemi, S.; Rezayan, A. H.; Ghadari, R.; Ng, S. W. *Green Chem.* **2011**, *13*, 582. (b) Adib, M.; Sayahi, M. H.; Nosrati, M.; Zhu, L. G. *Tetrahedron Lett.* **2007**, *48*, 4195. (c) Yavari, I.; Alizadeh, A.; Anary-Abbasinejad, M.; Bijanzadeh, H. R. *Tetrahedron* **2003**, *59*, 6083.
(7) (a) Alizadeh, A.; Rostamnia, S. *Synthesis* **2008**, 57. (b) Baharfar, R.; Jaafari, L.; Azimi, R. *Chin. Chem. Lett.* **2011**, *22*, 943.
(8) (a) Alizadeh, A.; Oskueyan, Q.; Rostamnia, S.; Ghanbari-Niaki, A.; Mohebbi, A. R. *Synthesis* **2008**, 2929. (b) Alizadeh, A.; Rostamnia, S.; Zhu, L. G. *Synthesis* **2008**, 1788. (c) Alizadeh, A.; Rostamnia, S.; Zhu, L. G. *Tetrahedron* **2006**, *62*, 5641. (d) Alizadeh, A.; Rostamnia, S.; Hu, M. L. *Synlett* **2006**, 1592. (e) Azuaje, J.; Coelho, A.; Maatougui, A. E.; Blanco, J. M.; Sotelo, E. *ACS Comb. Sci.* **2011**, *13*, 89.
(9) (a) Shaabani, A.; Sarvary, A.; Rezayan, A. H.; Keshipour, S. *Tetrahedron* **2009**, *65*, 3492. (b) Shaabani, A.; Ghadari, R.; Sarvary, A.; Rezayan, A. H. *J. Org. Chem.* **2009**, *74*, 4372.
(10) Esmaeili, A. A.; Darbanian, M. *Tetrahedron* **2003**, *59*, 5545.
(11) Yavari, I.; Hossaini, Z.; Sabbaghan, M. *Monatsh. Chem.* **2007**, *138*, 107.
(12) (a) Esmaeili, A. A.; Moradi, A.; Habibi, A. *Synlett* **2011**, 2307. (b) Nair, V.; Menon, R. S.; Beneesh, P. B.; Sreekumar, V.; Bindu, S. *Org. Lett.* **2004**, *6*, 767. (c) Shaabani, A.; Rezayan, A. H.; Rahmati, A.; Sarvary, A. *Synlett* **2007**, 1458.
(13) (a) Pibiri, I.; Buscemi, S. *Curr. Bioact. Compd.* **2010**, *6*, 208. (b) Tripathi, R. P.; Yadav, A. K.; Ajay, A.; Bisht, S. S.; Chaturvedi, V.; Sinha, S. K. *Eur. J. Med. Chem.* **2010**, *45*, 142. (c) Siddiqui, N.; Ahsan, W.; Alam, M. S.; Ali, R.; Jain, S.; Azad, B.; Akhtar, J. *Int. J. Pharm. Sci. Rev. Res.* **2011**, *8*, 161.
(14) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (c) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (d) Niu, T. F.; Gu, L.; Yi, W. B.; Cai, C. *ACS Comb. Sci.* **2012**, *14*, 309. (e) MacDonald, J. P.; Badillo, J. J.; Arevalo, G. E.; Silva-García, A.; Franz, A. K. *ACS Comb. Sci.* **2012**, *14*, 285.