



Tri(*n*-butyl)phosphine-promoted domino reaction for the efficient construction of spiro[cyclohexane-1,3'-indolines] and spiro[indoline-3,2'-furan-3',3''-indolines]

Hui Zheng, Ying Han^{*}, Jing Sun and Chao-Guo Yan^{*}

Full Research Paper

Open Access

Address:
College of Chemistry and Chemical Engineering, Yangzhou
University, Yangzhou 225002, China

Email:
Ying Han^{*} - hanying@yzu.edu.cn; Chao-Guo Yan^{*} -
cgyan@yzu.edu.cn

^{*} Corresponding author

Keywords:
isatin; spiro[cyclohexane-1,3'-indoline];
spiro[indoline-3,2'-furan-3',3''-indoline]; spirooxindole;
tri(*n*-butyl)phosphine

Beilstein J. Org. Chem. **2022**, *18*, 669–679.
<https://doi.org/10.3762/bjoc.18.68>

Received: 21 April 2022

Accepted: 02 June 2022

Published: 14 June 2022

Associate Editor: D. Spring

© 2022 Zheng et al.; licensee Beilstein-Institut.
License and terms: see end of document.

Abstract

The tri(*n*-butyl)phosphine-catalyzed reaction of isatylidene malononitriles and bis-chalcones in chloroform at 65 °C afforded functionalized spiro[cyclohexane-1,3'-indolines] in good yields and with good diastereoselectivity. On the other hand, the tri(*n*-butyl)phosphine-catalyzed reaction of 3-(ethoxycarbonylmethylene)oxindoles and bis-chalcones gave functionalized spiro[cyclohexane-1,3'-indolines] with different regioselectivity. Additionally, the tri(*n*-butyl)phosphine-promoted domino annulation reaction of isatins and ethyl isatylidene cyanoacetates produced spiro[indoline-3,2'-furan-3',3''-indolines] in satisfactory yields.

Introduction

Spirooxindole is a privileged heterocyclic core existing in many natural products and medicinally relevant compounds. A variety of spirooxindole derivatives has been identified with a broad range of biological activities [1-5]. On the other hand, spirooxindoles can be constructed by introduction of various carbocyclic and heterocyclic units, which made them suitable for chemistry and many potential applications [6-9]. The development of unique spirooxindole systems and efficient synthetic methods for these compounds have attracted continual interests in many fields. A literature survey indicated that many convenient and atom-economic synthetic protocols have been de-

veloped for the synthesis of diverse spirooxindoles in recent years [10-16].

Nucleophilic tertiary phosphine-catalyzed reactions were successfully applied for the construction of diverse carbocyclic systems [17-24]. In these reactions, the tertiary phosphine firstly adds to electron-deficient alkenes, alkynes, and allenes to give active ionic intermediates. Then, the in situ-generated ionic intermediates further react with various reagents to give versatile cyclic compounds with recovery of the tertiary phosphine [25-34]. The superior catalytic ability of tertiary phosphines

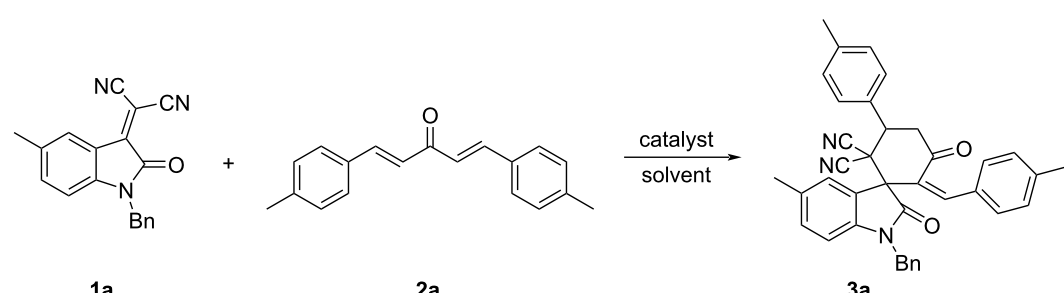
was primarily attributed to their excellent nucleophilicity as a nucleophile trigger and decent cleaving ability as a leaving group in the catalytic process [35-43]. The tertiary phosphine-catalyzed reactions have been widely applied to construct diverse spirooxindole systems by using readily available isatins and 3-methyleneoxindoles as key substrates [44-52]. In this respect, we have also developed several domino reactions by employing tertiary phosphine addition to electron-deficient alkynes as key protocol for the construction of diverse polycyclic spirooxindoles [53-59]. In continuation of our aim to explore elegant domino reactions for spiro compounds [60-66] and in order to demonstrate the potential synthetic value of the nucleophilic phosphine-catalyzed annulation reaction, herein we wish to report the tri(*n*-butyl)phosphine-catalyzed reaction of isatylidene malononitriles and bis-chalcones for the synthesis of functionalized various spiro[cyclohexane-1,3'-indolines] and related reactions.

Results and Discussion

Initially, the reaction conditions were optimized by using isatylidene malononitrile **1a** and bis-chalcone **2a** as standard

reaction. Tertiary amines such as DMAP and DABCO did not catalyze this reaction (entries 1 and 2 in Table 1). Additionally, no reaction was observed when triphenylphosphine was used as catalyst (Table 1, entry 3). However, in the presence of tri(*n*-butyl)phosphine, the reaction in methylene dichloride, chloroform, and toluene at room temperature gave the expected functionalized spiro[cyclohexane-1,3'-indoline] **3a** albeit with low yields (entries 4–6 in Table 1). The spiro[cyclohexane-1,3'-indoline] **3a** was clearly produced by a tri(*n*-butyl)phosphine-catalyzed formal [4 + 2] cycloaddition reaction. This result showed that tri(*n*-butyl)phosphine has a higher nucleophilic catalytic ability than triphenylphosphine. It should be pointed out that the synthesis of polysubstituted cyclohexanones was reported by a tri(*n*-butyl)phosphine-catalyzed reaction of 1,4-dien-3-ones with 2-aryl-1,1-dicyanoalkenes [36]. At higher temperature (50 °C), the yield of the product **3a** increased to 40% (in CH₂Cl₂), 65% (in toluene), and to 75% (in chloroform), respectively, in a Schlenk flask (entries 7–9 in Table 1). Therefore, chloroform was selected as the suitable solvent. The reaction in chloroform at 65 °C for six hours afforded the product **3a** in 84% yield (entry 10, Table 1). By prolonging the reaction

Table 1: Optimization of reaction conditions.^a



Entry	Catalyst	Solvent	Temp [°C]	Time [h]	Yield [%] ^b
1	DABCO	CHCl ₃	rt	24	–
2	DMAP	CHCl ₃	rt	24	–
3	PPh ₃	CHCl ₃	rt	24	–
4	P(<i>n</i> -Bu) ₃	CH ₂ Cl ₂	rt	24	30
5	P(<i>n</i> -Bu) ₃	PhMe	rt	24	35
6	P(<i>n</i> -Bu) ₃	CHCl ₃	rt	24	45
7	P(<i>n</i> -Bu) ₃	CH ₂ Cl ₂	50	24	40
8	P(<i>n</i> -Bu) ₃	PhMe	50	24	65
9	P(<i>n</i> -Bu) ₃	CHCl ₃	50	24	75
10	P(<i>n</i> -Bu) ₃	CHCl₃	65	6	84
11	P(<i>n</i> -Bu) ₃	CHCl ₃	65	12	82
12	P(<i>n</i> -Bu) ₃	CHCl ₃	65	24	80
13	P(<i>n</i> -Bu) ₃ ^c	CHCl ₃	65	24	65
14	P(<i>n</i> -Bu) ₃ ^d	CHCl ₃	65	6	82

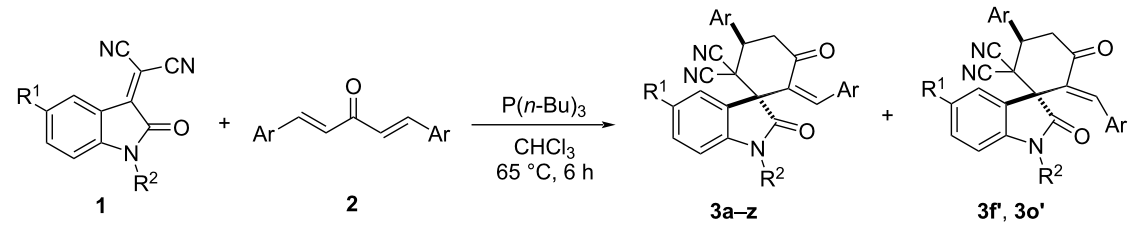
^aReaction conditions: isatylidene malononitrile (0.5 mmol), bis-chalcone (0.6 mmol), catalyst (20% equiv), solvent (10 mL), N₂ atmosphere in Schlenk tube; ^bisolated yields of the mixed diastereoisomers; ^cPBu₃ (10% equiv) was used; ^dPBu₃ (50% equiv) was used.

time, the yield of **3a** did not increase further (entries 11 and 12, Table 1). At last, when 10% equiv tri(*n*-butyl)phosphine were used, the yield of product **3a** decreased to 65% (entry 13, Table 1), whereas 50% equiv tri(*n*-butyl)phosphine did not improve the yield of **3a** (82% yield, entry 14, Table 1). It should be pointed out that the total yield of the mixed two isomers was calculated in Table 1. Thus, the best results were obtained by carrying out the reaction in chloroform at 65 °C for six hours in the presence of 20% equiv tri(*n*-butyl)phosphine as catalyst.

With the best reaction conditions in hand, the scope of the reaction was developed by using various substrates and the results

are summarized in Table 2. It was found that all reactions proceeded smoothly to give the expected spiro[cyclohexane-1,3'-indolines] **3a–z** in moderate to good yields. The isatylidene malononitriles with different substituents at the C5-position and C1-position can be successfully employed in the reaction. The reaction with bis-chalcones with electron-donating groups gave slightly higher yields of the products than that of bis-chalcones with electron-withdrawing groups. Because there are two chiral carbon atoms in the spiro[cyclohexane-1,3'-indolines] and the *Z/E*-configuration of the exocyclic C–C double bonds, several diastereoisomers might be formed in the obtained products. The ¹H NMR spectra clearly indicated that the obtained products

Table 2: Reaction of isatylidene malononitriles and bis-chalcones.^a



Entry	Compound	R ¹	R ²	Ar	Yield [%] ^b	<i>Z/E</i> ^c
1	3a	CH ₃	Bn	<i>p</i> -CH ₃ C ₆ H ₄	67	4:1
2	3b	CH ₃	Bn	<i>p</i> - <i>t</i> -BuC ₆ H ₄	64	4:1
3	3c	CH ₃	Bn	C ₆ H ₅	64	4:1
4	3d	CH ₃	Bn	<i>p</i> -ClC ₆ H ₄	58	5:1
5	3e	CH ₃	Bn	<i>p</i> -BrC ₆ H ₄	62	5:1
6	3f (3f') ^d	CH ₃	CH ₃	<i>p</i> - <i>t</i> -BuC ₆ H ₄	42 (14)	3:1
7	3g	CH ₃	H	<i>p</i> -CH ₃ C ₆ H ₄	45	3:1
8	3h	CH ₃	H	<i>p</i> - <i>t</i> -BuC ₆ H ₄	49	3:1
9	3i	CH ₃	<i>n</i> -Bu	<i>p</i> -BrC ₆ H ₄	54	5:1
10	3j	CH ₃	<i>n</i> -Bu	<i>p</i> -CH ₃ C ₆ H ₄	54	4:1
11	3k	CH ₃	<i>n</i> -Bu	<i>p</i> - <i>t</i> -BuC ₆ H ₄	58	5:1
12	3l	Cl	Bn	<i>p</i> -CH ₃ C ₆ H ₄	54	5:1
13	3m	Cl	Bn	<i>p</i> - <i>t</i> -BuC ₆ H ₄	60	5:1
14	3n	Cl	Bn	<i>p</i> - <i>i</i> PrC ₆ H ₄	56	4:1
15	3o (3o') ^d	Cl	<i>n</i> -Bu	<i>p</i> -CH ₃ C ₆ H ₄	42 (8)	5:1
16	3p	F	Bn	<i>p</i> -CH ₃ C ₆ H ₄	53	4:1
17	3q	F	Bn	<i>p</i> - <i>i</i> PrC ₆ H ₄	58	4:1
18	3r	H	H	<i>p</i> -CH ₃ C ₆ H ₄	48	6:1
19	3s	H	Bn	<i>p</i> -CH ₃ C ₆ H ₄	58	4:1
20	3t	H	Bn	<i>p</i> - <i>i</i> PrC ₆ H ₄	57	5:1
21	3u	H	Bn	C ₆ H ₅	42	4:1
22	3v	H	Bn	<i>p</i> -ClC ₆ H ₄	45	4:1
23	3w	H	Bn	<i>p</i> -BrC ₆ H ₄	47	5:1
24	3x	CH ₃	CH ₃	2-thiophenyl	52	trace
25	3y	Cl	CH ₃	2-thiophenyl	45	trace
26	3z	H	Bn	2-thiophenyl	53	trace

^aReaction conditions: isatylidene malononitrile (0.5 mmol), bis-chalcone (0.6 mmol), P(*n*-Bu)₃ (20% equiv), CHCl₃ (10.0 mL), N₂ atmosphere;

^bisolated yields; ^cthe *Z/E* ratio was determined by ¹H NMR spectroscopy; ^dthe minor isomers **3f'** and **3o'** were isolated.

contain two isomers with ratios in the range of 3:1 to 6:1. Thus, it was disappointing to find that the diastereoselectivity of this reaction was not very good. Because the polarity of the two diastereoisomers were very similar, it was very difficult to isolate them as pure compounds by column chromatography. For convenience, only the pure major diastereoisomers of the spiro compounds **3a–w** were successfully isolated and fully characterized, which also caused the isolated yields of the products slightly decreased. For comparison, the minor isomers **3f'** and

3o' were also successfully separated and obtained as pure compounds and were fully characterized, respectively. Additionally, 1,5-di(thiophen-2-yl)penta-1,4-dien-3-one was also successfully employed in the reaction. The major isomers of the corresponding spiro compounds **3x** and **3y** were predominately produced in moderate yields. In order to determine the relative configuration of the spiro compounds, the single crystal structures of the major isomers **3l** (Figure 1), **3s** (Figure 2), and **3f'** (Figure 3) were determined by X-ray diffraction analysis. As

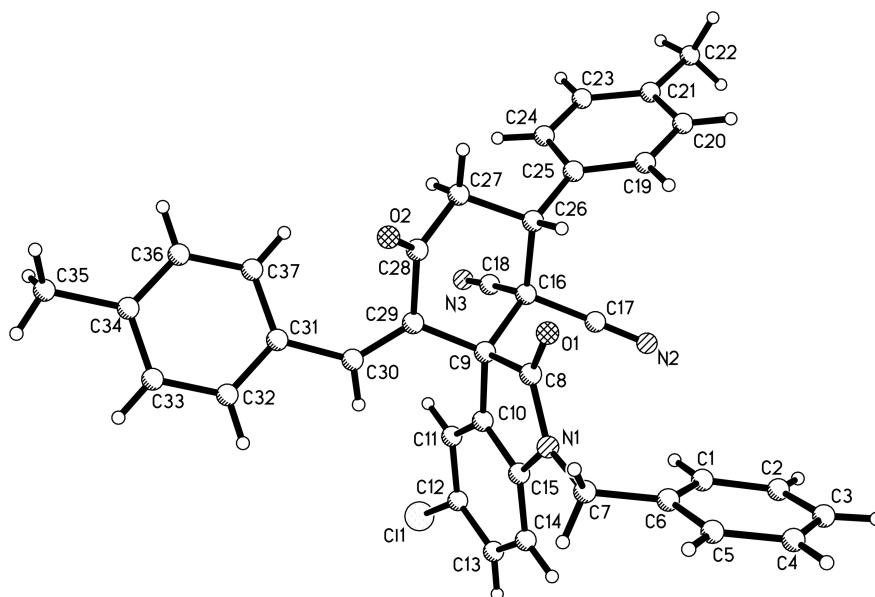


Figure 1: Single crystal structure of compound **3l**.

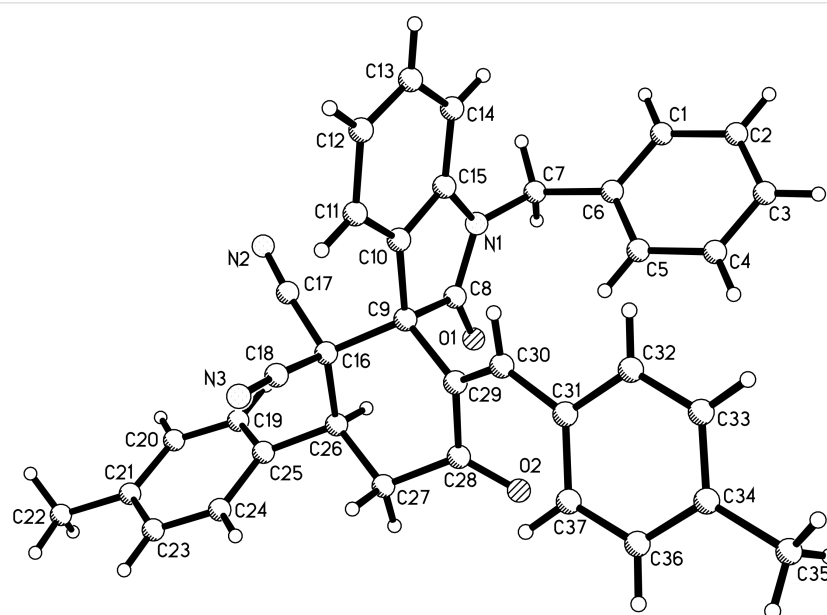


Figure 2: Single crystal structure of compound **3s**.

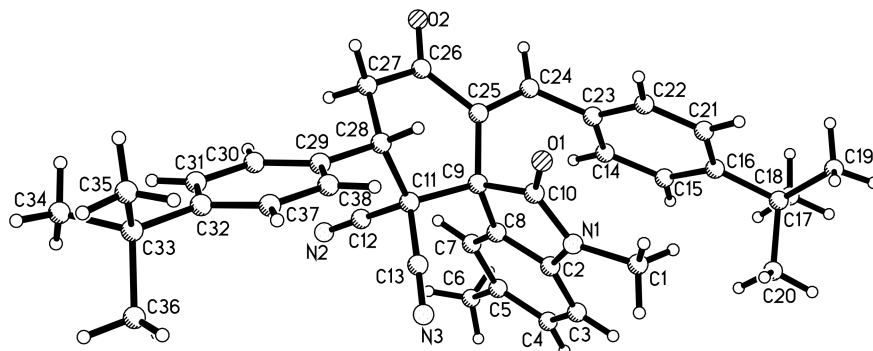


Figure 3: Single crystal structure of compound **3f**.

can be seen from Figure 1 and Figure 2, the aryl group exists in the *trans*-position of the carbonyl group of the oxindole scaffold in the newly formed cyclohexyl ring. On the other hand, the aryl group exist on the *cis*-position of the carbonyl group on the exocyclic C=C bond (*Z*-configuration). Thus, it can be concluded that the major isomers **3a–z** have this kind of the relative configuration. In Figure 3, the aryl group and the carbonyl group of the oxindole scaffold also exist on *trans*-position in the newly formed cyclohexyl ring, while an *E*-configuration was observed for the exocyclic C=C double bond. Therefore, the major and minor isomers were actually attributable to the *Z/E*-configuration of the C=C bond, not to the *cis/trans*-positions in the newly formed cyclohexyl ring.

In order to expand the scope of this reaction, 3-(ethoxycarbonylmethylene)oxindoles **4** were also employed in the reaction with bis-chalcones **2**. We were pleased to find that the reaction proceeded smoothly in the presence of an excess amount of

tri(*n*-butyl)phosphine under similar reaction conditions and the results are summarized in Table 3. Because there are three chiral carbon atoms in the molecule, several diastereoisomers can be formed in the reaction. The spiro[cyclohexane-1,3'-indolines] **5a–e** were obtained in moderate to good yields. The single crystal structure of compound **5a** was determined by X-ray diffraction method (Figure 4). It can be found that the ethoxycarbonyl group and the phenyl group of the oxindole moiety remained in the *trans*-position as in the starting 3-(ethoxycarbonylmethylene)oxindole. The aryl group and the carbonyl group exist on *trans*-position in the newly formed cyclohexyl ring. It should be pointed out that the exocyclic benzylidene group exists on the C3-position in the newly formed cyclohexyl ring, while it exists on the C6-position in the above obtained spiro compounds **3a–z**.

This result clearly indicated that these two reactions have the opposite regioselectivity. Another kind of readily available 1,3-

Table 3: Reaction of 3-(ethoxycarbonylmethylene)oxindoles and bis-chalcones.^a

Entry	Compound	R ¹	R ²	Ar	Yield (%) ^b
1	5a	Cl	Et	<i>p</i> -CH ₃ C ₆ H ₄	60
2	5b	Cl	Et	<i>p</i> -CH ₃ OC ₆ H ₄	57
3	5c	Cl	Me	<i>p</i> -CH ₃ C ₆ H ₄	42
4	5d	Cl	Me	<i>p</i> -iPrC ₆ H ₄	58
5	5e	H	Et	<i>p</i> -CH ₃ C ₆ H ₄	56

^aReaction conditions: 3-(ethoxycarbonylmethylene)oxindole (0.5 mmol), bis-chalcone (0.6 mmol), P(*n*-Bu)₃ (1.0 mmol), CHCl₃ (10.0 mL), N₂ atmosphere; ^bisolated yields.

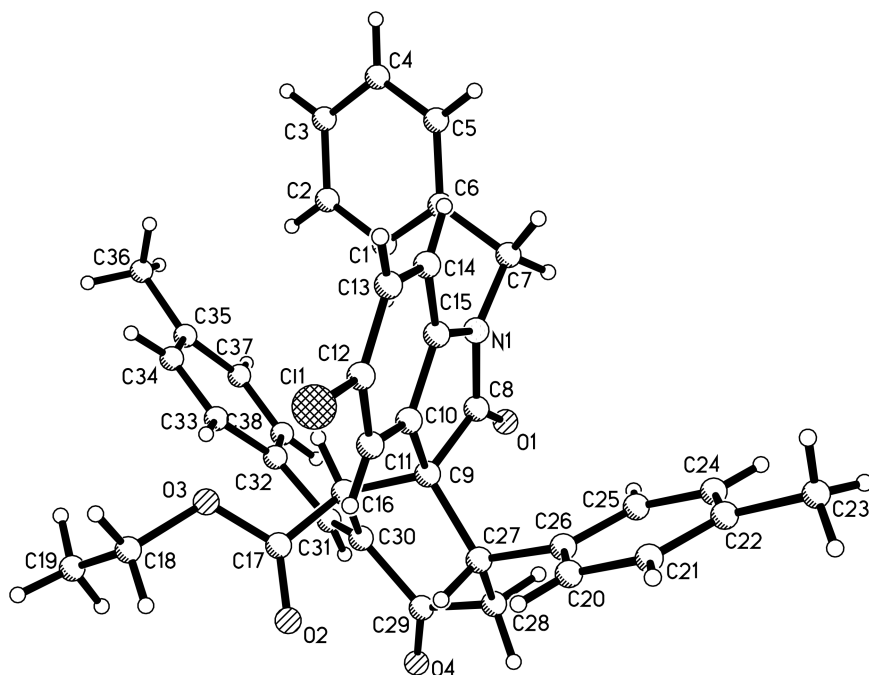


Figure 4: Single crystal structure of compound 5a.

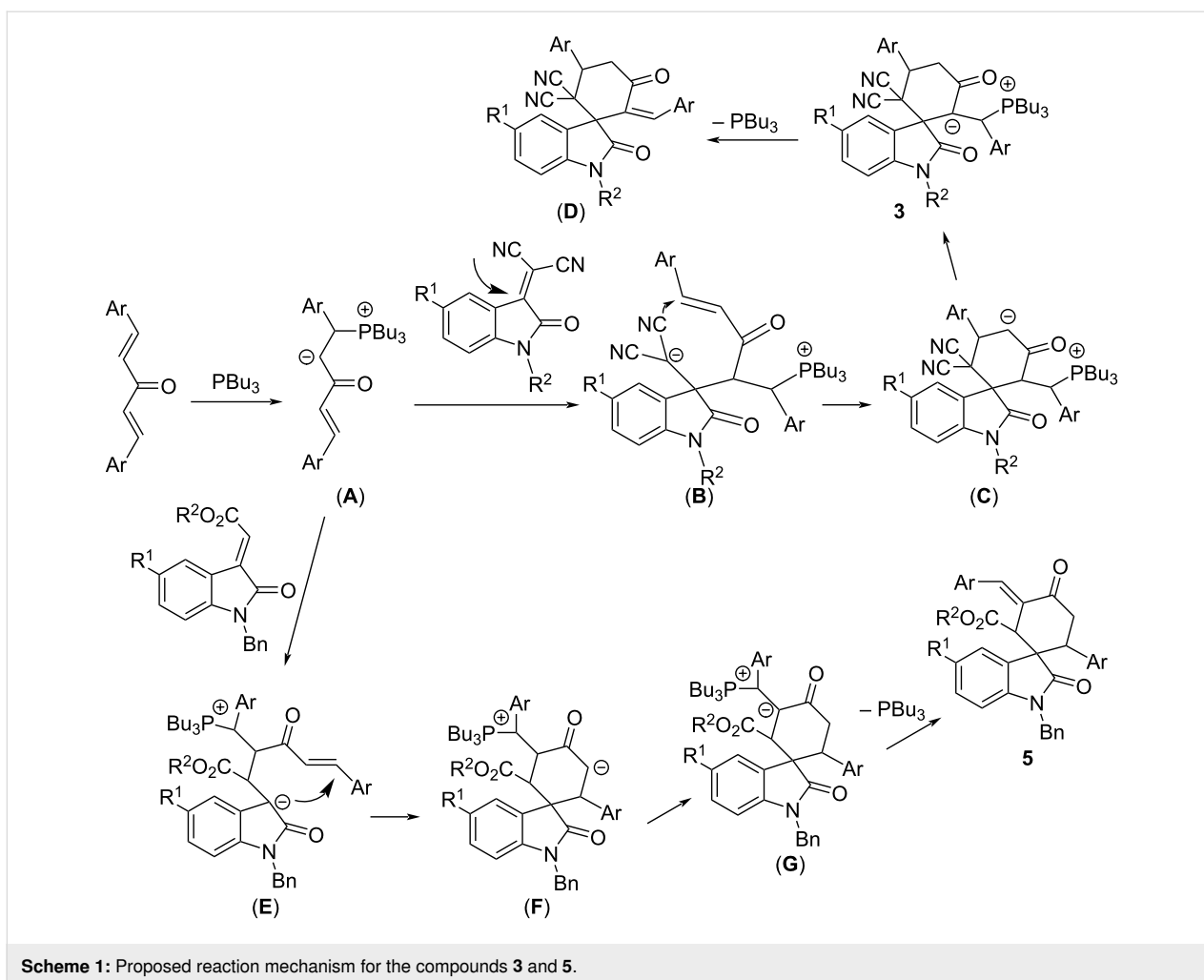
dipolarophile, 3-phenacylidinoxindole, was also tested in the reaction. However, it was found that the C=C bond in 3-phenacylidinoxindole was directly reduced to give the corresponding saturated 3-(2-oxo-2-phenylethyl)indolin-2-one. A similar reduction reaction of 3-phenacylidinoxindoles by trialkylphosphine has been previously reported in the literature [65].

For explaining the formation of the two kinds of spiro[cyclohexane-1,3'-indolines] **3** and **5**, a plausible reaction mechanism has been proposed (Scheme 1) on the basis of previously reported works and the obtained results from this work. Firstly, the nucleophilic addition of tributylphosphine to the bis-chalcone gives the active zwitterionic species (**A**). Secondly, the Michael addition of the zwitterionic species (**A**) to isatylidene malononitrile at the C3-position of the oxindole scaffold results in adduct (**B**). Thirdly, the intramolecular addition of the carbanion to the enone affords the cyclic intermediate (**C**), which in turn converts into the intermediate (**D**) by transfer of a negative charge. Finally, the spiro compound **3** is formed by elimination of tributylphosphine. When 3-(ethoxycarbonylmethylene)oxindole **4** is employed in the reaction, the nucleophilic addition of the zwitterion (**A**) to this compound takes place at the exocyclic position giving the adduct (**E**), which in turn proceeds with the intermediates (**F**) and (**G**) according to the above mentioned similar processes to give the spiro compound **5**. The different addition direction of the zwitterion **A** to the isatylidene malononitrile **2** and 3-(ethoxycarbonylmethylene)oxindole **4**

results in the different regioselectivity in the formation of the spiro compounds **3** and **5**.

For further demonstrate the synthetic value of this procedure, ethyl isatylidene cyanoacetates **6** were also employed in the reaction. However, the reaction did not proceed to give the expected spiro[cyclohexane-1,3'-indoline], while a new spiro[indoline-3,2'-furan-3',3''-indoline] was obtained, which was clearly constructed from the annulation reaction of isatin with ethyl isatylidene cyanoacetate.

Therefore, we turned our attention to the examination of this unprecedented reaction of isatins with ethyl isatylidene cyanoacetates. At last, we successfully found that tri(*n*-butyl)phosphine promoted the reaction of ethyl isatylidene cyanoacetate **6a** and isatin **7a** always resulted in spiro[indoline-3,2'-furan-3',3''-indoline] **8a** as the major product. The loading of tri(*n*-butyl)phosphine played an important role for the formation of the products. When 2.0 equiv of P(*n*-Bu)₃ were used, the reaction gave the spiro compound **8a** in 71% yield. Thus, this reaction is not a simple catalytic reaction and tri(*n*-butyl)phosphine acted not only as a catalyst. It was also noticed that when triphenylphosphine was used instead of tri(*n*-butyl)phosphine, the expected product was not obtained. Under the optimized reaction conditions, we next investigated the scope of the reaction by using various substituted ethyl isatylidene cyanoacetates and isatins and the results are summarized in Table 4. All reactions proceeded smoothly to give the expected spiro[indoline-3,2'-



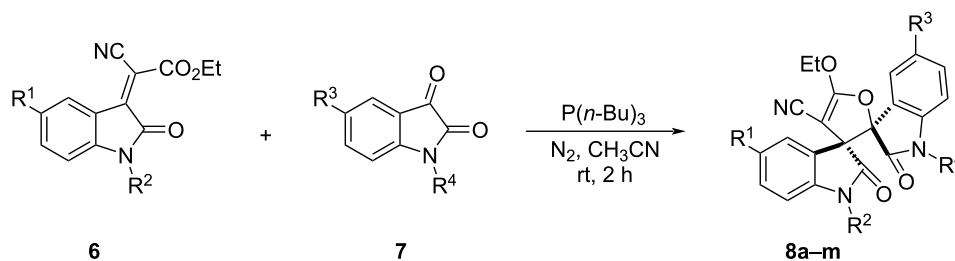
furan-3',3''-indolines] **8a–m** in moderate to good yields. The substituents on the isatylidene cyanoacetates had only a marginal effect on the yields, while the presence of electron-donating methyl groups in the isatins gave higher yields than electron-withdrawing groups such as chloro and fluoro substituents. The structures of the spiro compounds **8a–m** were fully characterized by their IR, HRMS, ^1H and ^{13}C NMR spectra. In addition, the single crystal structure of compound **8a** (Figure 5) was determined by X-ray diffraction analysis. From Figure 5, it can be seen that the two oxindole moieties exist on the *trans*-configuration. Therefore, this reaction showed very high diastereoselectivity.

To explain the formation of the dispiro compounds **8**, a plausible reaction mechanism has been proposed and is shown in Scheme 2. At first, the nucleophilic addition of tributylphosphine to isatylidene cyanoacetate gives a zwitterionic salt (**H**). Secondly, the addition of the carbanion to the carbonyl group of the isatin affords the adduct (**I**). Then, the intramolecular attack of the alkoxide to the carbonyl group in the ester moiety

produces the cyclic intermediate (**J**). Finally, the dispiro compound **8** is formed by elimination of tri(*n*-butyl)phosphine oxide.

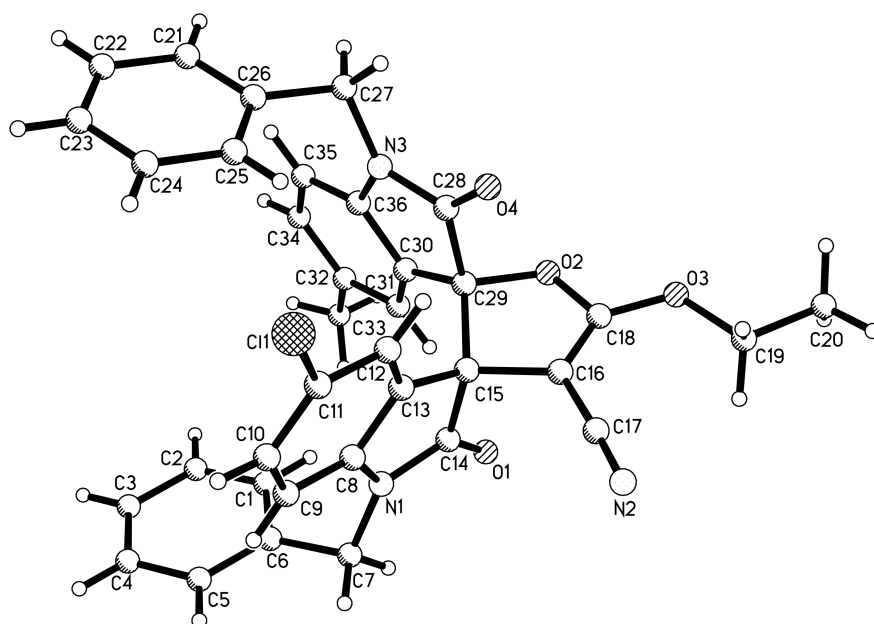
Conclusion

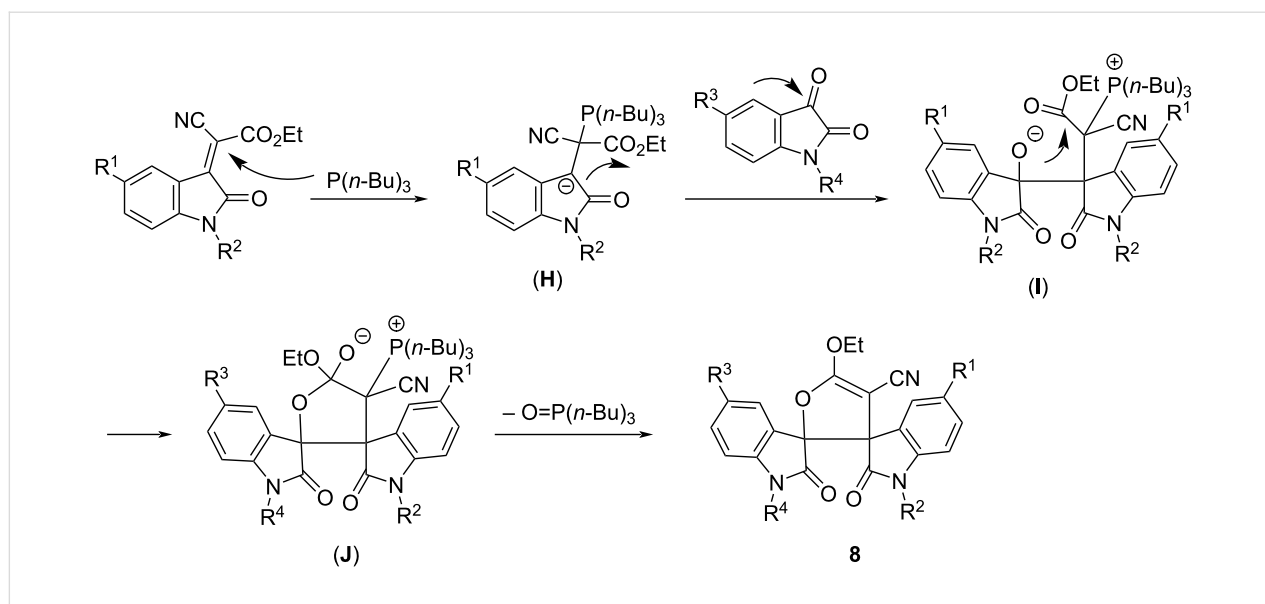
In summary, we have investigated tri(*n*-butyl)phosphine-catalyzed annulation reactions of bis-chalcones with isatylidene malononitriles or 3-(ethoxycarbonylmethylene)oxindoles for the efficient construction of two kinds of spiro[cyclohexane-1,3'-indolines] in good yields and with good diastereoselectivity. Additionally, tri(*n*-butyl)phosphine promoted the domino reaction of isatins and ethyl isatylidene cyanoacetates to give selectively spiro[indoline-3,2'-furan-3',3''-indolines] in satisfactory yields. The relative configuration of the complex spiro-oxindoles was confirmed by determination of several single crystal structures. Also, plausible reaction mechanisms have been proposed. This reaction has the advantages of using readily available substrates, simple operation, good yields, and molecular diversity, which enable it to find potential applications in heterocyclic and medicinal chemistry.

Table 4: Reaction of ethyl isatylidene cyanoacetates and isatins.^a

Entry	Compound	R ¹	R ²	R ³	R ⁴	Yield (%) ^b
1	8a	Cl	Bn	CH ₃	Bn	71
2	8b	Cl	Bn	CH ₃	H	70
3	8c	Cl	Bn	Cl	Bn	57
4	8d	Cl	Bn	F	Bn	56
5	8e	Cl	Bn	H	Bn	54
6	8f	Cl	<i>n</i> -Bu	CH ₃	Bn	76
7	8g	Cl	<i>n</i> -Bu	CH ₃	H	73
8	8h	F	Bn	CH ₃	Bn	69
9	8i	F	Bn	Cl	Bn	47
10	8j	F	Bn	F	Bn	35
11	8k	CH ₃	CH ₃	CH ₃	Bn	77
12	8l	H	Bn	CH ₃	Bn	83
13	8m	H	Bn	CH ₃	CH ₃	62

^aReaction conditions: isatin (0.3 mmol), isatylidene cyanoacetate (0.3 mmol), $P(n\text{-Bu})_3$ (0.6 mmol), MeCN (5.0 mL), N_2 atmosphere; ^bisolated yields.

**Figure 5:** Single crystal structure of compound **8a**.



Scheme 2: Proposed mechanism for the formation of dispiro compounds **8**.

Experimental

1. General procedure for the preparation of the spiro[cyclohexane-1,3'-indolines] 3a–w: In an atmosphere of nitrogen, isatylidene malononitrile (0.5 mmol) and bis-chalcone (0.6 mmol) were dissolved in chloroform (10.0 mL) in a Schlenk bottle. Then, tri(*n*-butyl)phosphine (20% equiv) was added by syringe and the solution was stirred at 65 °C for six hours. After removing the solvent at reduced pressure, the residue was subjected to column chromatography with petroleum ether/ethyl acetate 15:1 (v/v) as eluent to give the pure product **3a–m** for analysis.

rel-(1*R*,3*R*)-1'-Benzyl-5'-methyl-6-((*Z*)-4-methylbenzylidene)-2',5-dioxo-3-(*p*-tolyl)spiro[cyclohexane-1,3'-indoline]-2,2-dicarbonitrile (3a): white solid, 84% yield; mp 213–215 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.70 (s, 1H, ArH), 7.43 (s, 2H, ArH), 7.33 (s, 4H, ArH), 7.29 (s, 1H, ArH), 7.25–7.22 (m, 4H, ArH), 7.19–7.18 (m, 1H, ArH), 7.13–7.11 (m, 2H, ArH), 6.76–6.75 (m, 1H, ArH), 6.63 (s, 1H, CH), 5.07 (d, *J* = 15.6 Hz, 1H, CH₂), 5.02 (d, *J* = 13.2 Hz, 1H, CH₂), 4.86 (d, *J* = 15.0 Hz, 1H, CH₂), 3.46 (t, *J* = 13.8 Hz, 1H, CH), 3.08 (d, *J* = 15.6 Hz, 1H, CH₂), 2.40 (s, 3H, CH₃), 2.38 (s, 3H, CH₃), 2.34 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 196.9, 171.7, 140.7, 140.4, 139.8, 139.6, 134.4, 134.0, 131.9, 131.6, 130.8, 130.1, 129.8, 129.3, 129.1, 129.0, 128.9, 128.0, 127.1, 127.0, 123.0, 112.3, 110.9, 60.3, 49.0, 44.6, 44.4, 42.6, 21.4, 21.2; IR (KBr) ν: 3727, 3405, 3029, 2921, 2863, 2317, 1911, 1709, 1609, 1501, 1443, 1362, 1295, 1185, 1049, 1022, 959, 920, 820, 732 cm⁻¹; HRMS–ESI (*m/z*): [M + Na]⁺ calcd for C₃₈H₃₁NaN₃O₂, 584.2314; found, 584.2306.

2. General procedure for the preparation of the spiro[cyclohexane-1,3'-indolines] 5a–e: In an atmosphere of nitrogen, 3-(ethoxycarbonylmethyl)oxindole (0.5 mmol) and bis-chalcone (0.6 mmol) were dissolved in chloroform (10.0 mL) in a Schlenk bottle. Then, tri(*n*-butyl)phosphine (1.0 mmol) was added by syringe and the solution was stirred at 65 °C for six hours. After removing the solvent at reduced pressure, the residue was subjected to column chromatography with petroleum ether/ethyl acetate 15:1 (v/v) as eluent to give the pure product **5a–e** for analysis.

Ethyl rel-(1*S*,2*S*,6*R*)-1'-benzyl-5'-chloro-3-((*Z*)-4-methylbenzylidene)-2',5-dioxo-6-(*p*-tolyl)spiro[cyclohexane-1,3'-indoline]-2-carboxylate (5a): white solid, 60% yield; mp 221–223 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.67 (s, 1H, ArH), 7.29 (d, *J* = 7.6 Hz, 2H, ArH), 7.21–7.14 (m, 4H, ArH), 7.07 (t, *J* = 7.6 Hz, 2H, ArH), 7.01 (d, *J* = 8.4 Hz, 1H, ArH), 6.91 (d, *J* = 8.0 Hz, 2H, ArH), 6.84 (d, *J* = 8.0 Hz, 2H, ArH), 6.77 (d, *J* = 7.6 Hz, 2H, ArH), 6.34 (d, *J* = 8.4 Hz, 1H, CH), 4.70 (d, *J* = 16.0 Hz, 1H, CH₂), 4.57 (d, *J* = 15.6 Hz, 1H, CH₂), 4.52–4.47 (m, 1H, CH₂), 4.36–4.24 (m, 2H, OCH₂), 3.94 (s, 1H, CH), 3.80–3.72 (m, 1H, CH), 3.00–2.94 (m, 1H, CH₂), 2.37 (s, 3H, CH₃), 2.20 (s, 3H, CH₃), 1.30 (t, *J* = 7.2 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 200.0, 175.1, 170.6, 140.6, 139.0, 138.8, 136.8, 135.0, 134.8, 131.6, 131.2, 130.1, 129.8, 129.3, 129.0, 128.6, 128.5, 127.5, 127.4, 127.1, 124.5, 110.2, 61.8, 53.0, 50.7, 43.4, 42.5, 42.0, 21.4, 21.0, 14.1; IR (KBr) ν: 3723, 3412, 2933, 2871, 2324, 1925, 1817, 1703, 1604, 1474, 1442, 1339, 1172, 1091, 1010, 904, 824, 716 cm⁻¹; HRMS–ESI (*m/z*): [M + Na]⁺ calcd for C₃₈H₃₄ClNaO₄, 626.2069; found, 626.2066.

3. General procedure for the preparation of the spiro[cyclohexane-1,3'-indolines] 8a–m: In an atmosphere of nitrogen, isatylidene cyanoacetate (0.3 mmol) and isatin (0.3 mmol) were dissolved in acetonitrile (10.0 mL). Then, tri(*n*-butyl)phosphine (0.6 mmol) was added by syringe and the solution was stirred at room temperature for two hours. After removing the solvent at reduced pressure, the residue was subjected to column chromatography with petroleum ether/ethyl acetate 15:1 (v/v) as eluent to give the pure products **8a–m** for analysis.

rel-(3R,3'R)-1,1''-Dibenzyl-5''-chloro-5'-ethoxy-5-methyl-2,2''-dioxodispiro[indoline-3,2'-furan-3',3''-indoline]-4'-carbonitrile (8a): white solid, 71% yield; mp 175–177 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.64 (s, 1H, ArH), 7.53 (s, 1H, ArH), 7.18–7.08 (m, 5H, ArH), 7.03 (t, *J* = 6.8 Hz, 3H, ArH), 6.71 (d, *J* = 7.6 Hz, 2H, ArH), 6.54 (d, *J* = 7.2 Hz, 2H, ArH), 6.39 (d, *J* = 8.0 Hz, 1H, ArH), 6.34 (d, *J* = 8.4 Hz, 1H, ArH), 5.17 (d, *J* = 16.4 Hz, 1H, CH₂), 5.07 (d, *J* = 16.0 Hz, 1H, CH₂), 4.65 (q, *J* = 7.2 Hz, 2H, CH₂), 4.35–4.30 (m, 2H, CH₂), 2.12 (s, 3H, CH₃), 1.54 (t, *J* = 7.2 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 174.0, 173.1, 170.9, 142.4, 141.5, 134.2, 134.2, 133.6, 132.2, 130.4, 129.2, 128.8, 128.7, 128.6, 127.7, 127.6, 127.4, 126.4, 126.0, 124.0, 120.7, 114.2, 110.4, 109.6, 89.0, 69.1, 62.8, 60.1, 43.9, 20.9, 14.7; IR (KBr) ν: 3467, 3063, 3035, 2990, 2919, 2205, 1739, 1706, 1632, 1602, 1496, 1454, 1434, 1408, 1381, 1361, 1333, 1293, 1258, 1215, 1199, 1186, 1167, 1133, 1089, 1070, 1026, 997, 962, 933, 911, 895, 875, 836, 818, 776, 747 cm⁻¹; HRMS–ESI (*m/z*): [M + Na]⁺ calcd for C₃₆H₂₈NaClN₃O₄, 624.1666; found, 624.1660.

Supporting Information

Characterization data and ¹H NMR, ¹³C NMR, HRMS spectra of the compounds are available. The crystallographic data of the compounds **3l** (CCDC 2166451), **3s** (CCDC 2166452), **3f'** (CCDC 2173182), **5a** (CCDC 2166453), **8a** (CCDC 2166454) have been deposited at the Cambridge Crystallographic Database Center (<http://www.ccdc.cam.ac.uk>).

Supporting Information File 1

Characterization data and copies of NMR and HRMS spectra.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-68-S1.pdf>]

Funding

This work was financially supported by the National Natural Science Foundation of China (Nos. 21572196, 21871227).

ORCID® iDs

Chao-Guo Yan - <https://orcid.org/0000-0002-2777-9582>

Preprint

A non-peer-reviewed version of this article has been previously published as a preprint: <https://doi.org/10.3762/bxiv.2022.26.v1>

References

- Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127–139. doi:10.1021/ar020229e
- Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2964. doi:10.1021/cr020039h
- Santos, M. M. M. *Tetrahedron* **2014**, *70*, 9735–9757. doi:10.1016/j.tet.2014.08.005
- Yu, B.; Yu, D.-Q.; Liu, H.-M. *Eur. J. Med. Chem.* **2015**, *97*, 673–698. doi:10.1016/j.ejmech.2014.06.056
- Ye, N.; Chen, H.; Wold, E. A.; Shi, P.-Y.; Zhou, J. *ACS Infect. Dis.* **2016**, *2*, 382–392. doi:10.1021/acsinfecdis.6b00041
- Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165–193. doi:10.1055/s-0028-1083300
- Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003–3025. doi:10.1055/s-0029-1216975
- Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165–5181. doi:10.1039/c2ob25184a
- Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104–6155. doi:10.1021/cr300135y
- Liu, Y.; Wang, H.; Wan, J. *Asian J. Org. Chem.* **2013**, *2*, 374–386. doi:10.1002/ajoc.201200180
- Cao, Z.-Y.; Wang, Y.-H.; Zeng, X.-P.; Zhou, J. *Tetrahedron Lett.* **2014**, *55*, 2571–2584. doi:10.1016/j.tetlet.2014.01.084
- Cheng, D.; Ishihara, Y.; Tan, B.; Barbas, C. F., III. *ACS Catal.* **2014**, *4*, 743–762. doi:10.1021/cs401172r
- Pavlovskaya, T. L.; Redkin, R. G.; Lipson, V. V.; Atamanuk, D. V. *Mol. Diversity* **2016**, *20*, 299–344. doi:10.1007/s11030-015-9629-8
- Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaoli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200–7203. doi:10.1002/anie.200903192
- Chen, G.-S.; Fang, Y.-B.; Ren, Z.; Tian, X.; Liu, Y.-L. *Org. Chem. Front.* **2021**, *8*, 3820–3828. doi:10.1039/d1qo00575h
- Balha, M.; Mondal, B.; Pan, S. C. *Org. Biomol. Chem.* **2019**, *17*, 6557–6561. doi:10.1039/c9ob01199d
- Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906–2908. doi:10.1021/jo00114a048
- Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535–544. doi:10.1021/ar000253x
- Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050. doi:10.1002/adsc.200404087
- Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005–1018. doi:10.1021/ar900271g
- Guo, H.; Fan, Y. C.; Sun, Z.; Wu, Y.; Kwon, O. *Chem. Rev.* **2018**, *118*, 10049–10293. doi:10.1021/acs.chemrev.8b00081
- Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140–1152. doi:10.1039/b717758e
- Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102–3116. doi:10.1039/b816700c
- Zhou, R.; Liu, R.; Li, R.; He, Z. *Chin. J. Org. Chem.* **2014**, *34*, 2385–2405. doi:10.6023/cjoc201406049

25. Xie, P.; Huang, Y. *Org. Biomol. Chem.* **2015**, *13*, 8578–8595. doi:10.1039/c5ob00865d
26. Zhou, R.; He, Z. *Eur. J. Org. Chem.* **2016**, 1937–1954. doi:10.1002/ejoc.201501585
27. Wei, Y.; Shi, M. *Org. Chem. Front.* **2017**, *4*, 1876–1890. doi:10.1039/c7qo00285h
28. Karanam, P.; Reddy, G. M.; Koppolu, S. R.; Lin, W. *Tetrahedron Lett.* **2018**, *59*, 59–76. doi:10.1016/j.tetlet.2017.11.051
29. Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672–4675. doi:10.1021/ja110147w
30. Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837–7841. doi:10.1002/anie.201102094
31. Zhang, X.-C.; Cao, S.-H.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 1142–1145. doi:10.1021/ol1031798
32. Deng, H.-P.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 3348–3351. doi:10.1021/ol201094f
33. Gu, J.; Xiao, B.-X.; Chen, Y.-R.; Li, Q.-Z.; Ouyang, Q.; Du, W.; Chen, Y.-C. *Org. Lett.* **2018**, *20*, 2088–2091. doi:10.1021/acs.orglett.8b00649
34. Mei, L.-y.; Wei, Y.; Xu, Q.; Shi, M. *Organometallics* **2013**, *32*, 3544–3556. doi:10.1021/om400473p
35. Cai, L.; Zhang, B.; Wu, G.; Song, H.; He, Z. *Chem. Commun.* **2011**, *47*, 1045–1047. doi:10.1039/c0cc02817g
36. Zhou, R.; Wang, J.; Tian, J.; He, Z. *Org. Biomol. Chem.* **2012**, *10*, 773–781. doi:10.1039/c1ob06187a
37. Zhou, R.; Yang, C.; Liu, Y.; Li, R.; He, Z. *J. Org. Chem.* **2014**, *79*, 10709–10715. doi:10.1021/jo502106c
38. Qin, Z.; Liu, W.; Wang, D.; He, Z. *J. Org. Chem.* **2016**, *81*, 4690–4700. doi:10.1021/acs.joc.6b00596
39. Yang, C.; Chen, X.; Tang, T.; He, Z. *Org. Lett.* **2016**, *18*, 1486–1489. doi:10.1021/acs.orglett.6b00456
40. Zhu, C.-Z.; Sun, Y.-L.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2017**, *359*, 1263–1270. doi:10.1002/adsc.201700031
41. Ramachary, D. B.; Prabhakar Reddy, T.; Suresh Kumar, A. *Org. Biomol. Chem.* **2017**, *15*, 9785–9789. doi:10.1039/c7ob02424j
42. Zhang, J.; Wu, H.-H.; Zhang, J. *Org. Lett.* **2017**, *19*, 6080–6083. doi:10.1021/acs.orglett.7b02895
43. Wang, C.; Gao, Z.; Zhou, L.; Wang, Q.; Wu, Y.; Yuan, C.; Liao, J.; Xiao, Y.; Guo, H. *Chem. Commun.* **2018**, *54*, 279–282. doi:10.1039/c7cc08380g
44. Zhang, X.-C.; Cao, S.-H.; Wei, Y.; Shi, M. *Chem. Commun.* **2011**, *47*, 1548–1550. doi:10.1039/c0cc04289g
45. Wang, Y.; Liu, L.; Zhang, T.; Zhong, N.-J.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2012**, *77*, 4143–4147. doi:10.1021/jo3002535
46. Gomez, C.; Gicquel, M.; Carry, J.-C.; Schio, L.; Retailleau, P.; Voiturier, A.; Marinetti, A. *J. Org. Chem.* **2013**, *78*, 1488–1496. doi:10.1021/jo302460d
47. Hu, C.; Zhang, Q.; Huang, Y. *Chem. – Asian J.* **2013**, *8*, 1981–1984. doi:10.1002/asia.201300650
48. Zhang, J.; Cheng, C.; Wang, D.; Miao, Z. *J. Org. Chem.* **2017**, *82*, 10121–10128. doi:10.1021/acs.joc.7b01582
49. Chen, L.-J.; Yu, J.-H.; He, B.; Xie, J.-W.; Liu, Y.-X.; Zhu, W.-D. *J. Org. Chem.* **2020**, *85*, 7793–7802. doi:10.1021/acs.joc.0c00418
50. Hu, F.-L.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2014**, *356*, 736–742. doi:10.1002/adsc.201301070
51. Xiao, B.-X.; Jiang, B.; Song, X.; Du, W.; Chen, Y.-C. *Chem. Commun.* **2019**, *55*, 3097–3100. doi:10.1039/c9cc00386j
52. He, T.; Peng, L.; Li, S.; Hu, F.; Xie, C.; Huang, S.; Jia, S.; Qin, W.; Yan, H. *Org. Lett.* **2020**, *22*, 6966–6971. doi:10.1021/acs.orglett.0c02519
53. Han, Y.; Sheng, Y.-J.; Yan, C.-G. *Org. Lett.* **2014**, *16*, 2654–2657. doi:10.1021/ol5008394
54. Gong, H.; Sun, J.; Yan, C. G. *Synthesis* **2014**, *46*, 2327–2332. doi:10.1055/s-0033-1339120
55. Han, Y.; Qi, W.-J.; Shen, Y.-J.; Yan, C.-G. *Tetrahedron Lett.* **2015**, *56*, 5196–5198. doi:10.1016/j.tetlet.2015.07.071
56. Qi, W.-J.; Han, Y.; Yan, C.-G. *Tetrahedron* **2016**, *72*, 5057–5063. doi:10.1016/j.tet.2016.06.020
57. Liu, C.-Z.; Han, Y.; Qi, W.-J.; Yan, C.-G. *Heterocycl. Commun.* **2016**, *22*, 301–306. doi:10.1515/hc-2016-0123
58. Qi, W.-J.; Han, Y.; Liu, C.-Z.; Yan, C.-G. *Chin. Chem. Lett.* **2017**, *28*, 442–445. doi:10.1016/j.ccllet.2016.09.014
59. Han, Y.; Zheng, H.; Zhang, Y.-Y.; Yan, C.-G. *Chin. Chem. Lett.* **2020**, *31*, 1337–1341. doi:10.1016/j.ccllet.2019.10.042
60. Sun, J.; Zhang, Y.; Shi, R.-G.; Yan, C.-G. *Org. Biomol. Chem.* **2019**, *17*, 3978–3983. doi:10.1039/c9ob00166b
61. Ye, R.; Yan, C.-G. *Eur. J. Org. Chem.* **2019**, 5882–5886. doi:10.1002/ejoc.201900955
62. Cao, J.; Yang, F.; Sun, J.; Huang, Y.; Yan, C.-G. *J. Org. Chem.* **2019**, *84*, 622–635. doi:10.1021/acs.joc.8b02457
63. Pan, L.-N.; Sun, J.; Shi, R.-G.; Yan, C.-G. *Org. Chem. Front.* **2020**, *7*, 3202–3208. doi:10.1039/d0qo00845a
64. Zhan, S.-C.; Sun, J.; Liu, R.-Z.; Yan, C.-G. *Org. Biomol. Chem.* **2020**, *18*, 163–168. doi:10.1039/c9ob02013f
65. Liu, D.; Cao, J.; Sun, J.; Liu, R.-Z.; Yan, C.-G. *Org. Lett.* **2020**, *22*, 8931–8936. doi:10.1021/acs.orglett.0c03331
66. Cao, S.-H.; Zhang, X.-C.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2011**, 2668–2672. doi:10.1002/ejoc.201100017

License and Terms

This is an open access article licensed under the terms of the Beilstein-Institut Open Access License Agreement (<https://www.beilstein-journals.org/bjoc/terms>), which is identical to the Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0>). The reuse of material under this license requires that the author(s), source and license are credited. Third-party material in this article could be subject to other licenses (typically indicated in the credit line), and in this case, users are required to obtain permission from the license holder to reuse the material.

The definitive version of this article is the electronic one which can be found at:
<https://doi.org/10.3762/bjoc.18.68>