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Tributylphosphine promoted domino reaction for efficient construction of spiro[cyclohexane-1,3'-indoline] and spiro[indoline-3,2'-furan-3',3''-indoline]

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Abstract

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

Keywords

tributylphosphine; spiroxindole; isatin; spiro[cyclohexane-1,3'-indoline]; spiro[indoline-3,2'-furan-3',3''-indoline].

Introduction

The spirooxindole is one of the most privileged heterocyclic rings, which not only exists in many naturally occurring substances, but also is featured in many medicinally relevant compounds with wide biological applications such antiviral, antibacterial and anti-cancer activities [1-9]. The remarkable pharmacological activity and unique molecular architecture have made spirooxindole and their derivatives to be the high attractive synthetic targets. As a consequence, many elegant synthetic procedures have been developed for the preparation of the diverse carbocyclic and heterocyclic spirooxindoles [10-16].

In recent years, nucleophilic tertiary phosphine catalyzed reaction has been emerged as one of the most powerful tools for the construction of diverse carbocyclic and heterocyclic systems [17-24]. In the conventional phosphine-catalyzed reactions, the initial nucleophilic attack of tertiary phosphines to electron-deficient alkenes or alkynes to give zwitterionic intermediates, which in turn reacted with various electrophiles containing C=O, C=C and C=N scaffold to give versatile five-membered carbo- and heterocycles [25-34]. The superior catalytic ability of tertiary phosphines was primarily attributable to their excellent nucleophility as a nucleophile trigger and decent cleaving ability as a leaving group in the catalytic process [35-43]. The tertiary phosphine catalyzed reaction have been widely used to construct diverse spirooxindole systems by using readily available isatins and 3-methyleneoxindoles as key substrates [44-51]. 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 spirooxindols [52-58]. In continuation of our aim to explore elegant domino reactions for spiro compounds [59-64] and in order to demonstrate the potential synthetic values of the nucleophilic phosphine

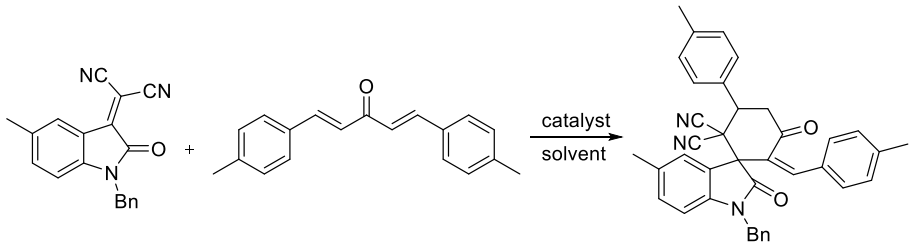
catalyzed annulation reaction, herein we wish to report tributylphosphine catalyzed reaction of isatylidene malononitriles and bis-chalcones for synthesis of functionalized various spiro[cyclohexane-1,3'-indolines] and the related reactions.

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 could not catalyzed this reaction (Entries 1-2 in Table 1). Additionally, no reaction was observed when triphenylphosphine was used as catalyst (Entry 3). When tri(n-butyl)phosphine was used, the reaction in the solvent of methylene dichloride , chloroform and toluene at room temperature gave the expected functionalized spiro[cyclohexane-1,3'-indoline] **3a** in lower 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 higher nucleophilic catalytic ability than that of triphenylphos. It should be pointed out that the synthesis of polysubstituted cyclohexanones was reported by tri(n-butyl)phosphine catalyzed reaction of 1,4-dien-3-ones with 2-aryl 1,1-dicyanoalkenes.[9b] Then, the yield of **3a** increased to 40%, 65% and 75%, respectively by increasing the reaction temperature to 50 ^{o}C (Entries 7-9 in Table 1). Therefore, chloroform is the suitable solvent. The reaction in chloroform at 65 ^{o}C in six hours afforded the product **3a** in 84% (Entry 10). Prolonging the reaction time, the yield of **3a** could not be increased furtherly (Entries 11-12). At last, when 10% equivalent tri(n-butyl)phosphine was used, the yield of **3a** decreased to 65% yield. When 50% equivalent tri(n-butyl)phosphine was used, the yield of **3a** still maintained in 82% yield. Thus, the best reaction conditions were obtained by carrying out the reaction in

chloroform at 65 °C for six hours in the presence of 20% equivalent tri(n-butyl)phosphine as catalyst.

Table 1 Optimization of reaction conditions[a]



3a

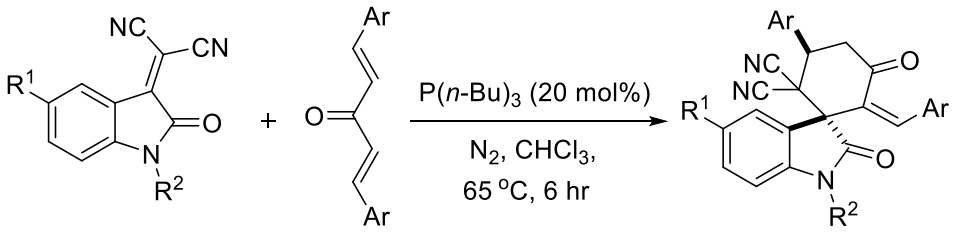
Entry	Catalyst	Solvent	Temp/°C	Time/h	Yield (%)[b]
1	DABCO	$CHCl_3$	r.t.	24	-
2	DMAP	$CHCl_3$	r.t.	24	-
3	PPh_3	$CHCl_3$	r.t.	24	-
4	PBu_3	CH_2Cl_2	r.t.	24	30
5	PBu_3	PhMe	r.t.	24	35
6	PBu_3	$CHCl_3$	r.t.	24	45
4	PBu_3	CH_2Cl_2	50	24	40
5	PBu_3	PhMe	50	24	65
6	PBu_3	$CHCl_3$	50	24	75
7	**PBu_3**	**$CHCl_3$**	**65**	**6**	**84**
8	PBu_3	$CHCl_3$	65	12	82
9	PBu_3	$CHCl_3$	65	24	80
10	PBu_3[c]	$CHCl_3$	65	24	65
11	PBu_3[d]	$CHCl_3$	65	6	82

a. Reaction conditions: isatylidene malononitrile (0.5 mmol), bis-chalcone (0.6 mmol), catalyst (20% equiv.), solvent (10 mL), N_2 atmosphere; b. Isolated yields; c. PBu_3 (10% equiv) was used; d. PBu_3 (50% equiv) was used.

With the best reaction conditions in hand, the scope of the reaction was developed by using various substrates. The results are summarized in Table 2. It can be found that all reactions proceeded smoothly to give the expected spiro[cyclohexane-1,3'-indolines] **3a-3w** in moderate to good yields. The isatylidene malononitriles with different substituents at 5-position and 1-position can be successfully employed in the

reaction. The bis-chalcones with electron-donating groups gave the 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], two diastereoisomers might be formed in the obtained products. The ^{1}H NMR spectra clearly indicated that the obtained products contain two diastereoisomers with the ratio in the range of 3:1 to 5:1. Thus, it is disappointed to find that diastereselectivity of this reaction was not very good. Because the polarity of the two diastereoisomers were very similar, it is very difficult to separate them as pure compounds by column chromatography. For convenience, the only pure major diastereoisomers of the spiro compounds **3a-3w** were successfully isolated and were fully characterized. For comparison, the major isomers **3f**, **3o** and minor isomers **3f'**, **3o'** were also successfully separated as pure compounds and were fully characterized, respectively In order to determine the relative configuration of the spiro compounds, the single crystal structures of the major isomers **3l** (Fig. 1) and **3s** (Fig. 2) was determined by X-Ray diffraction method. From the two figures, it can be seen that the aryl group exist on 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.

Table 2 Reaction of isatylidene malononitriles and bis-chalcones[a]



3a-3w

Entry	Compd	R^1	R^2	Ar	Yield (%)[b]	dr[c]
1	**3a**	CH_3	Bn	*p*-$CH_3C_6H_4$	84	4:1

2	**3b**	CH_3	Bn	*p*-*t*-BuC_6H_4	80	4:1
3	**3c**	CH_3	Bn	C_6H_5	80	4:1
4	**3d**	CH_3	Bn	*p*-ClC_6H_4	70	5:1
5	**3e**	CH_3	Bn	*p*-BrC_6H_4	75	5:1
6	**3f**	CH_3	CH_3	*p*-*t*-BuC_6H_4	55	3:1
7	**3g**	CH_3	H	*p*-$CH_3C_6H_4$	60	3:1
8	**3h**	CH_3	H	*p*-*t*-BuC_6H_4	65	3:1
9	**3i**	CH_3	*n*-Bu	*p*-BrC_6H_4	65	5:1
10	**3j**	CH_3	*n*-Bu	*p*-$CH_3C_6H_4$	68	4:1
11	**3k**	CH_3	*n*-Bu	*p*-*t*-BuC_6H_4	70	5:1
12	**3l**	Cl	Bn	*p*-$CH_3C_6H_4$	65	5:1
13	**3m**	Cl	Bn	*p*-*t*-BuC_6H_4	72	5:1
14	**3n**	Cl	Bn	*p*-*i*-PrC_6H_4	70	4:1
15	**3o**	Cl	*n*-Bu	*p*-$CH_3C_6H_4$	50	5:1
16	**3p**	F	Bn	*p*-$CH_3C_6H_4$	53	4:1
17	**3q**	F	Bn	*p*-*i*-PrC_6H_4	72	4:1
18	**3r**	H	H	*p*-$CH_3C_6H_4$	56	6:1
19	**3s**	H	Bn	*p*-$CH_3C_6H_4$	72	4:1
20	**3t**	H	Bn	*p*-*i*-PrC_6H_4	68	5:1
21	**3u**	H	Bn	C_6H_5	52	4:1
22	**3v**	H	Bn	*p*-ClC_6H_4	45	4:1
23	**3w**	H	Bn	*p*-BrC_6H_4	50	5:1

a. Reaction conditions: isatylidene malononitrile (0.5 mmol), bis-chalcone (0.6 mmol), P(*n*-Bu)$_3$ (20% equiv), $CHCl_3$ (10.0 mL), N_2 atmosphere; b. Isolated yields. c. The dr ratio was determined by ^{1}H NMR spectra.

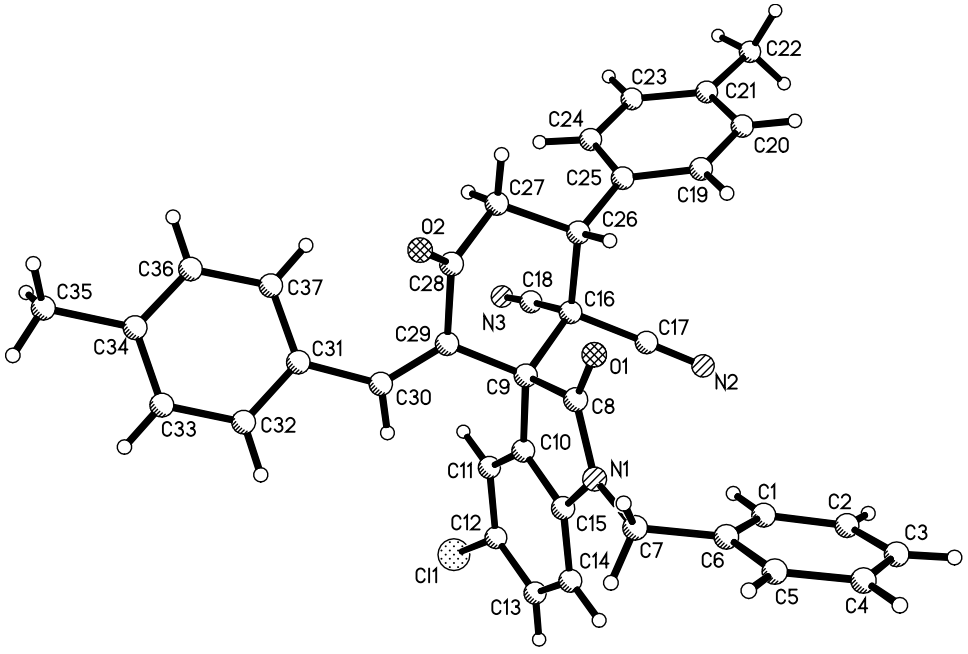


Figure 1 Single crystal structure of the compound **3l**

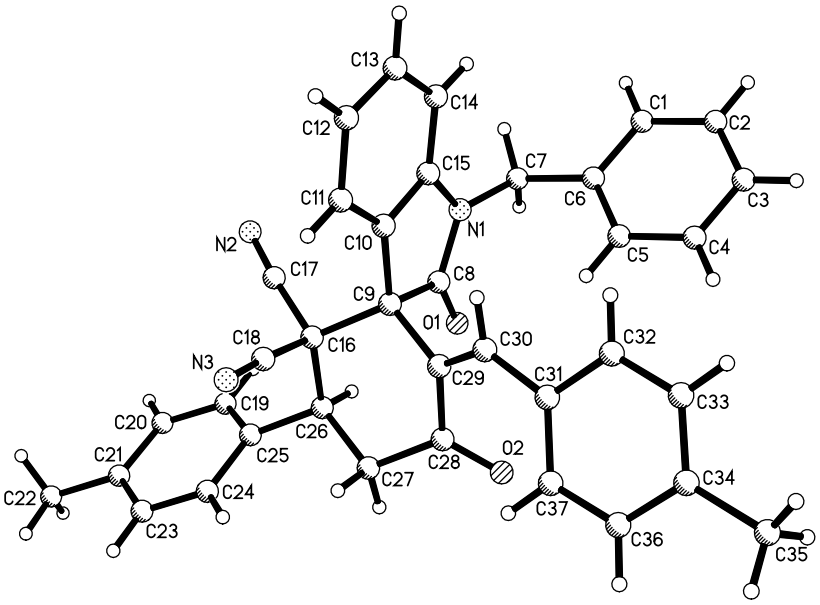
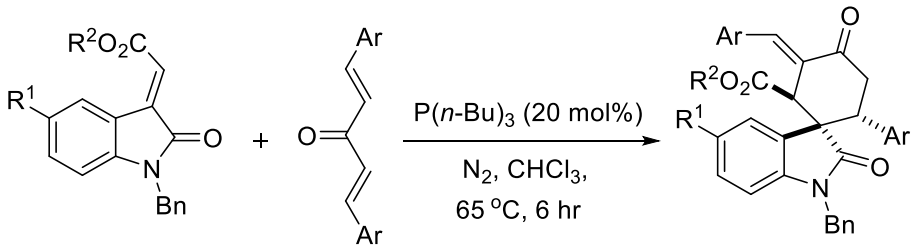


Figure 2 Single crystal structure of the compound **3s**

In order to develop the scope of this reaction, 3-(ethoxycarbonylmethylene)oxindoles **4** were also employed in the reaction. We were pleased to find that catalyzed reaction proceeded smoothly in the presence of excess amount of tri(n-butyl)phosphine under similar reaction conditions. The results are summarized in Table 3. Because there are three chiral carbon atoms in the molecule, several diastereoisomers might be formed in the reaction. The spiro[cyclohexane-1,3'-indolines] **5a-5e** can be successfully obtained in moderate to good yields. The single crystal structure of the compound **5a** was determined by X-Ray diffraction method (Fig. 3). It can be found the ethoxycarbonyl group and the phenyl group of oxindole moiety remained the *trans*-position as that 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 3-possition in the newly formed cyclohexyl ring, while it exists on the 6-position in the above obtained spiro compounds **3**. This result clearly indicated that these two reactions have the opposite regioselectivity.

Another kind of readily available 1,3-dipolarophile, 3-phenacylidenoxindole, was also tested in the reaction. However, it was found that the C=C bond in 3-phenacylidenoxindole was directly reduced to give the corresponding saturated 3-(2-oxo-2-phenylethyl)indolin-2-one. The similar reduction reaction of 3-phenacylidenoxindoles by trialkylphosphine have been previously reported in the literature [65].

Table 3 Reaction of 3-(ethoxycarbonylmethylene)oxindoles and bis-chalcones[a]



5a-5e

Entry	Compd	R^1	R^2	Ar	Yield (%)[b]
1	**5a**	Cl	Et	*p*-$CH_3C_6H_4$	60
2	**5b**	Cl	Et	*p*-$CH_3OC_6H_4$	57
3	**5c**	Cl	Me	*p*-$CH_3C_6H_4$	42
4	**5d**	Cl	Me	*p*-*i*-PrC_6H_4	58
5	**5e**	H	Et	*p*-$CH_3C_6H_4$	56

a. Reaction conditions: 3-methyleneoxindole (0.5 mmol), bis-chalcone (0.6 mmol), P(*n*-Bu)$_3$ (2.0 equiv), $CHCl_3$ (10.0 mL), N_2 atmosphere; b. Isolated yields.

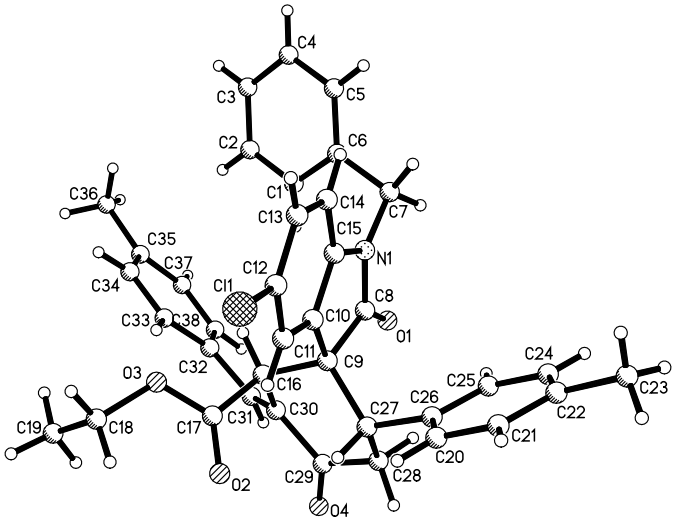
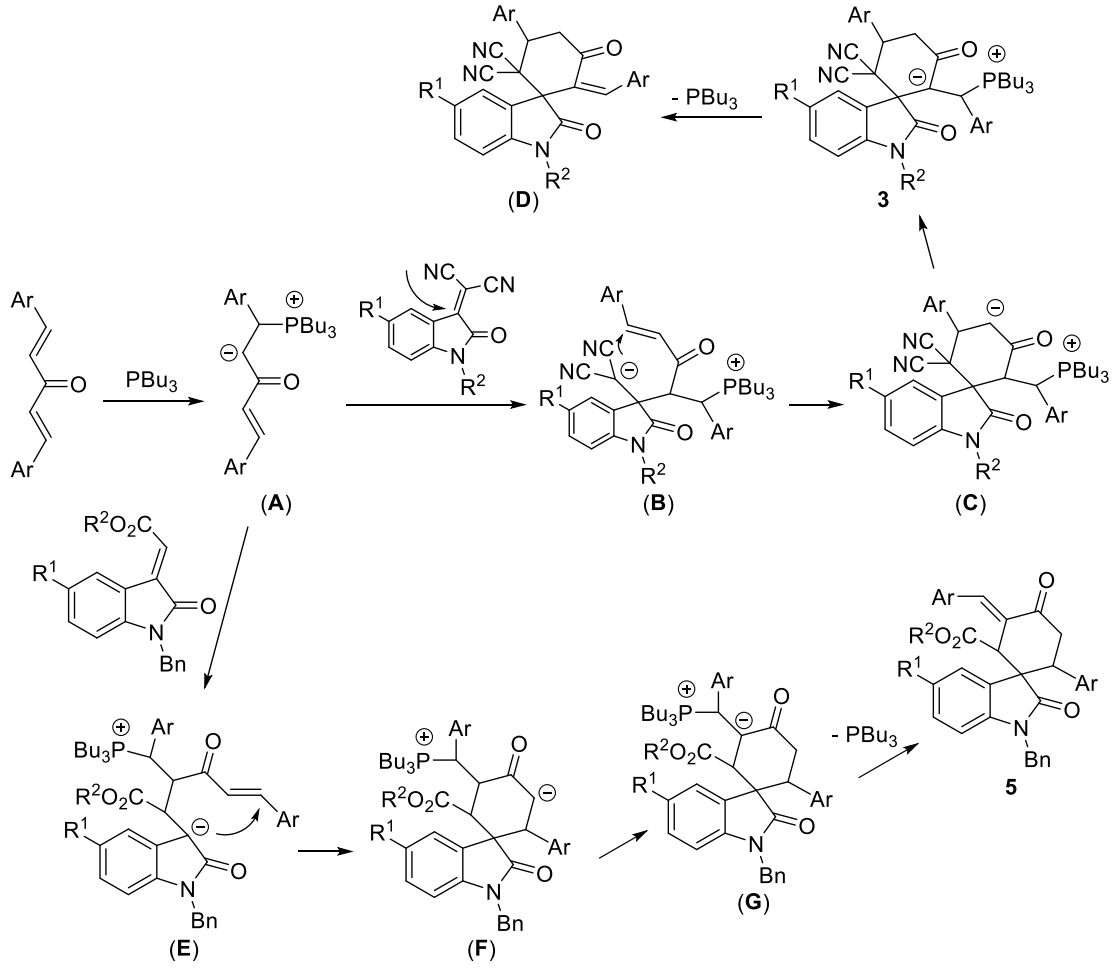


Figure 3 Single crystal structure of the compound **5a**



Scheme 1 Proposed reaction mechanism for the compounds **3** and **5**

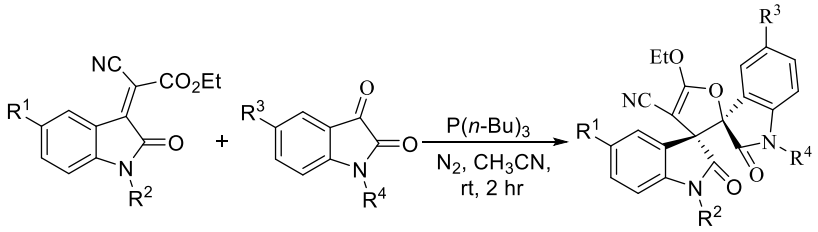
For explaining the formation of the two kinds of spiro[cyclohexane-1,3'-indolines] **3** and **5**, a plausible reaction mechanism was proposed in **Scheme 1** on the basis of the previously reported works and the obtained results. Firstly, the nucleophilic addition of tributylphosphine to the bis-chalcone gave the active zwitterionic species (**A**). Secondly, the Michael addition of the zwitterionic species (**A**) to isatylidene malononitrile at 3-position of the oxindole scaffold resulted in a adduct (**B**). Thirdly, the intramolecular addition of the carbanion to the enone afforded the cyclic intermediate (**C**), which in turn converted to the intermediate (**D**) by a transfer of negative charge. At last, the spiro compound **3** was formed by elimination of the tributylphosphine. When 3-(ethoxycarbonylmethylene)oxindole **4** was employed in the reaction, the nucleophilic

addition of the zwitterion (**A**) to it at the exocyclic position gave the adduct (**E**), which in turn proceeded 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 ziwtterion to the isatylidene malononitrile **2** and 3-(ethoxycarbonylmethylene)oxindole **4** resulted in the different regioselectivity in the formation of the spiro compounds **3** and **5**.

For further demonstrating the synthetic values of this reaction, 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, our attention was converted to examine this unprecedented reaction of isatins with ethyl isatylidene cyanoacetates. At last we found that the tri(n-butyl)phosphine catalyzed reaction of ethyl isatylidene cyanoacetates **6a** and isatin **7a** always resulted in unexpected spiro[indoline-3,2'-furan-3',3''-indoline] **8** as major product. The loading of tri(n-butyl)phosphine played an important rule for the formation of the two products. Thus, this reaction is not a simple catalyst reaction and tri(b-butyl)phosphine acted not only as a catalyst. When 2.0 equiv. of $P(n\text{-}Bu)_3$ was used, the reaction gave the spiro compound **8a** in 71% yield. Under the optimized reaction conditions, the scope of the reaction was developed by using various substituted ethyl isatylidene cyanoacetate and isatins. The results are summarized in **Table 3**. All reactions proceeded smoothly to give the expected spiro[indoline-3,2'-furan-3',3''-indolines] **8a-8m** in moderate to good yields. The substituents on the isatylidene cyanoacetate have marginal effect on the yields, while the electron-donating methyl groups on isatins gave higher yields than that of the electron-withdrawing chloro, fluoro groups. The structures of the spiro compounds **8a-8m** were fully characterized by IR, HRMS, ^{1}H and ^{13}C NMR spectra.

The single crystal structure of the compound **8a** (Fig. 3) was determined by X-ray diffraction method. From the Fig. 3, it can be seen that the two moieties of oxindole exist on the *trans*-configuration. Therefore, this reaction showed very high diastereoselectivity.

Table 3 Reaction of ethyl isatylidene cyanoacetates and isatins[a]



8a-8m

Entry	Compd	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	*n*-Bu	CH_3	Bn	76
7	**8g**	Cl	*n*-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

a. Reaction conditions: isatin (0.3 mmol), isatylidene cyanoacetate (0.3 mmol), P(*n*-Bu)$_3$ (0.6 mmol), MeCN (5.0 mL), N_2 atmosphere; b. Isolated yields.

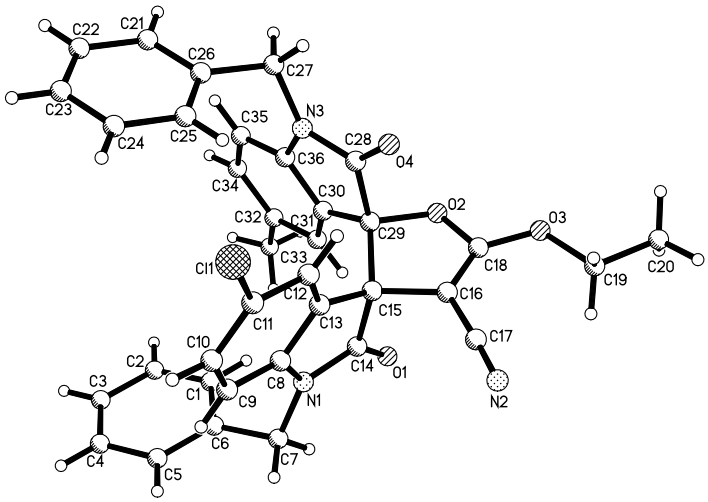
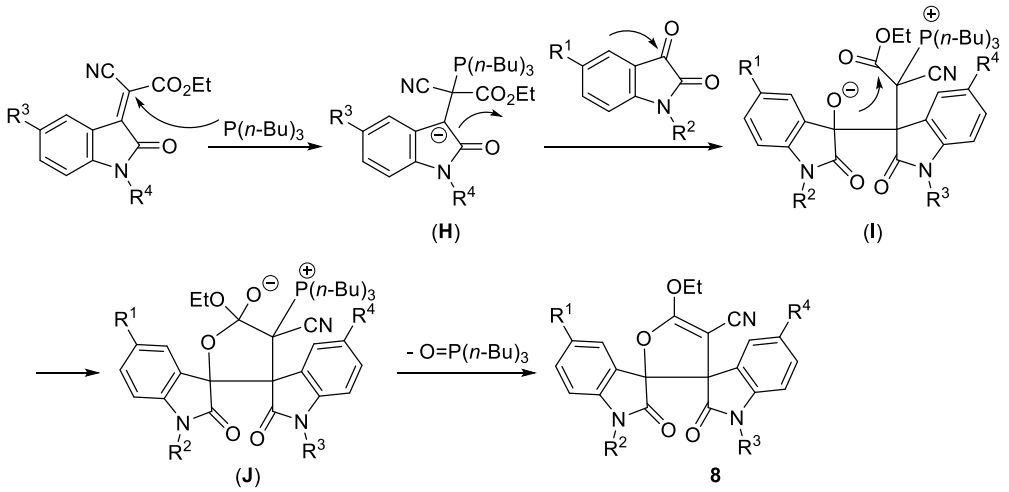


Figure 4 Single crystal strutures of the compound **8a**

For the explaining the fprmation of the dispiro compounds **8**, a plausiblke reaction mechanism was also proposed in **Scheme 2**. At first, the nucelophilic addition of tributylphosphine to isatylidene cyanoacetate gave a zwitterionic salt (**H**). Secondly, the addiiton of the carbanion to the carbonyl group of the isatin afforded the adduct (**I**). Then, the intramolecular attack of alkoxide to the carbonyl group in ester moiety produced the cyclic intermediate (**J**). At last, the dispiro compound **8** was foremd by elimination of tributylphosphine oxide.



Scheme 2 Proposed formation mechanism for the dispiro compound **8**

Conclusion

In summary, we have investigated tri(n-butyl)phosphine catalyzed annulation reaction 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, tributylphosphine domino promoted reaction of isatins and ethyl isatylidene cyanoacetates selectively gave spiro[indoline-3,2'-furan-3',3''-indolines] in satisfactory yields. The relative configuration of the complex spirooxindoles were confirmed by determination of several single crystal structures. The plausible reaction mechanism was also rationally proposed. This reaction has the advantages of using readily available substrates, simple operation, good yields and molecular diversity, which enable it might be found potential applications in the heterocyclic and medicinal chemistry.

Experimental

1. General procedure for the preparation of the spiro[cyclohexane-1,3'-indolines] 3a-3w: In an atmosphere of nitrogen, isatylidene malononitrile (0.5 mmol) and bis-chalcone (0.6 mmol) was dissolved in chloroform (10.0 mL) in Schlenk bottle. The tributylphosphine (20% equiv) was added by syringe. The solution was stirred at 60 ^{o}C for six hours. After removing the solvent at reduced pressure, the residue was subjected to column chromatography with a petroleum ether and ethyl acetate (V/V = 15:1) as eluent to give the pure product **3a-3m** 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%, m.p. 213-215 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) 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, CH_2), 5.02 (d, *J* = 13.2 Hz, 1H, CH_2), 4.86 (d, *J* = 15.0 Hz, 1H, CH_2), 3.46 (t, *J* = 13.8 Hz, 1H, CH), 3.08 (d, *J* = 15.6 Hz, 1H, CH_2), 2.40 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.34 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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) υ: 3727, 3405, 3029, 2921, 2863, 2317, 1911, 1709, 1609, 1501, 1443, 1362, 1295, 1185, 1049, 1022, 959, 920, 820, 732 cm^{-1}; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{38}H_{31}NaN_3O_2$ ($[M+Na]^+$): 584.2314, found: 584.2306.

2. General procedure for the preparation of the spiro[cyclohexane-1,3'-indolines] 5a-5e: In an atmosphere of nitrogen, 3-(ethoxycarbonylmethyl)oxindoles (0.5 mmol) and bis-chalcone (0.6 mmol) was dissolved in chloroform (10.0 mL) Schlenk bottle. The tributylphosphine (1.0 mmol) was added by syringe. The solution was stirred at 60 ^oC for six hours. After removing the solvent at reduced pressure, the residue was subjected to column chromatography with a petroleum ether and ethyl acetate (V/V = 15:1) as eluent to give the pure product **5a-5e** for analysis.

***rel*-Ethyl (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%, m.p. 221-223 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_2), 4.57 (d, *J* = 15.6 Hz, 1H, CH_2), 4.52-4.47 (m, 1H, CH_2), 4.36-4.24 (m, 2H, OCH_2), 3.94 (s, 1H, CH), 3.80-3.72 (m, 1H, CH), 3.00-2.94 (m, 1H, CH_2), 2.37 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 1.30 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 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) υ: 3723, 3412, 2933, 2871, 2324, 1925, 1817, 1703, 1604, 1474, 1442, 1339, 1172, 1091, 1010, 904, 824, 716 cm^{-1}; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{38}H_{34}ClNaNO_4$ ($[M+Na]^+$): 626.2069, found: 626.2066.

3. General procedure for the preparation of the spiro[cyclohexane-1,3'-indolines] 8a-8m: In an atmosphere of nitrogen, isatylidene cyanoacetate (0.3 mmol) and isatins (0.3 mmol) was dissolved in acetonitrile (10.0 mL). The tributylphosphine (0.6 mmol) was added by syringe. 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 a petroleum ether and ethyl acetate (V/V = 15:1) as eluent to give the pure product **8a-8m** for analysis.

***rel*-(3*R*,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%, m.p. 175-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_2), 5.07 (d, *J* = 16.0 Hz, 1H, CH_2), 4.65 (q, *J* = 7.2 Hz, 2H, CH_2), 4.35-4.30 (m, 2H, CH_2), 2.12 (s, 3H, CH_3), 1.54 (t, *J* = 7.2 Hz, 3H, CH_3).^{13}C NMR (100 MHz, $CDCl_3$) 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) υ: 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}; MS (*m*/*z*): HRMS (ESI) Calcd. for $C_{36}H_{28}NaClN_3O_4$ ($[M+Na]^+$): 624.1666, found: 624.1660.

Supporting Information

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

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References

1. Williams, R. M. and Cox, R. *J. Acc. Chem. Res.* **2003**, *36*, 127-139.
2. Dounay, A. B. and Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945-2963.
3. Santos, M. *Tetrahedron* **2014**, *70*, 9735-9757.
4. Yu, D. Q. and Liu, H. M. *Eur. J. Med. Chem.* **2015**, *97*, 673-698.
5. Ye, N.; Chen, H. Y.; Wold, E. A.; Shi, P. Y. and Zhou, J. *ACS Infec. Dis.* **2016**, *2*, 382-392.
6. Kotha, S. B.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, *2*, 165-193.
7. B. M. Trost, and M. K. Brennan, *Synthesis* **2009**, *18*, 3003-3025.
8. Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165-5181.
9. Singh, G. S. and Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104-6155.
10. Liu, Y. Y.; Wang, H. and Wan, J. P. *Asian J. Org. Chem.* **2013**, ***2***, 374-386.
11. Cao, Z. Y.; Wang, Y. H.; Zeng, X. P.; Zhou, J. *Tetrahedron* ***2***014, *70*, 2406-2415.
12. Cheng, D. Q.; Ishihara, Y.; Tan, B.; Barbas, C. B. *ACS Catalysis* **2014***, 4,* 743-762.
13. Pavlovska, T. L.; Redkin, R. G.; Lipson, V. V.; Atamanuk, D. V. *Mol. Divers.* **2016**, *20*, 299-344.
14. Bencivenni, G.; Wu, L. Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M. P.;

Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed. Engl*. **2009**, *48*, 7200-7203.
15. Chen, G. S.; Fang, Y. B.; Ren, Z.; Tian, X.; Liu, Y. L. *Organic Chemistry Frontiers* **2021**, *8*, 3820-3828.
16. Balha, M.; Mondal, B.; Pan, S. C. *Org. Biomol. Chem*. **2019**, *17*, 6557-6561.
17. Zhang, C. and Lu, X. *J. Org. Chem.* **1995**, *60*, 2906-2908.
18. Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535-544.
19. Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035-1050.
20. Wei, Y. and Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005-1018.
21. Guo, H. C.; Fan, Y. C.; Sun, Z. H. *Chem. Rev.* **2018**, *118*, 10049-10293.
22. Ye, L. W.; Zhou, J.; Tang, Y., *Chem. Soc. Rev.* **2008**, *37*, 1140-1152.
23. Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102-3116.
24. Zhou, R.; Liu, R. F.; Li, R. F.; He, Z. J. *Chin. J. Org. Chem.* **2014**, *34*, 2385-2405.
25. Xie, P.; Huang, Y. *Org. Biomol. Chem.* **2015**, *13*, 8578-8595.
26. Zhou R., He, Z. J. *Eur. J. Org. Chem.* **2016**, *11*, 1937-1954.
27. Wei, Y.; Shi, M. *Org. Chem. Front.* **2017**, *4*, 1876-1890.
28. Karanam, P.; Reddy, G. M.; Koppolu, S. R.; Lin, W. *Tetrahedron Lett.* **2018**, *59*, 59-76.
29. Tan, B.; Candeias, N. R.; Barbas, C. F. *J. Am. Chem. Soc.* **2011**, *133*, 4672-4675.
30. Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 7837-7841.
31. Zhang, X. C.; Cao, S. H.; Shi, M. *Org. Lett.* **2011**, *13*, 1142-1145.
32. Deng, H.; Wei, Y.; Shi M. *Org. Lett.* **2011**, *13*, 3348-3351.
33. Zhang, X.; Cao, S.; Wei, Y.; Shi, M. *Chem. Commun.* **2011**, *47*, 1548-1550.
34. Mei, L. Y.; Wei, Y.; Xu, Q.; Shi, M. *Organometallics* **2013**, *32*, 3544-3556.
35. Cai, L. C.; Zhang, B.; Wu, G. P.; Song, H. B.; He, Z. J. *Chem. Commun.* **2011**, *47*, 1045-1047.
36. Zhou, R.; Wang, J.F.; Tian, J. J.; He Z. J. *Org. Biomol. Chem.* **2012**, *10*, 773-781.
37. Zhou, R.; Yang, C. J.; Liu, Y. Y.; Li, R. F.; He, Z. J. *J. Org. Chem.* **2014**, *79*, 10709-10715.
38. Qin, Z. F.; Liu, W.; Wang, D. Y.; He, Z. J. *J. Org. Chem.* **2016**, *81*, 4690-4700.
39. Yang, C. J.; Chen, X. Y.; Tang, T.; He, Z. J. *Org. Lett.* **2016**, *18*, 1486-1489.
40. Zhu, C. Z.; Sun, Y. L.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2017**, *359*, 1263-1270.
41. Ramachary, D. B.; Prabhakar Reddy, T.; Suresh Kumar, A. *Org. Biomol. Chem.* **2017**, *15*, 9785-9789.
42. Zhang, J.; Wu, H. H.; Zhang, J. *Org. Lett.* **2017**, *19*, 6080-6083.

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.
44. Zhang, X. C.; Cao, S. H.; Wei, Y.; Shi, M. *Chem. Commun*. **2011**, *47*, 1548-1550.
45. Wang, Y.; Liu, L.; Zhang, T.; Zhong, N. J.; Wang, D.; Chen, Y. J. *J. Org. Chem.* **2012**, *77*, 4143-4147.
46. Catherine, G.; Maxime, G.; Jean-Christophe, C.; Laurent, S.; Pascal, R.; Arnaud, V.; Angela, M. *J. Org. Chem.* **2013**, *78*, 1488-1496.
47. Hu, C. C.; Zhang, Q. L.; Huang, Y. *Chem. Asian J.* **2013**, *8*, 1981-1984.
48. Zhang, J. Y.; Cheng, C.; Wang, D.; Miao, Z. W. *J. Org. Chem.* **2017**, *82*,10121-10128.
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.
50. Hu, F. L.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2014**, *356*, 736-742
51. He, T. T.; Peng, L.; Li, S.; Hu, F. L.; Xie, C. D.; Huang, S. L.; Jia, S. Q.; Qin, W. L.; Yan, H. L. *Org. Lett.* **2020**, *22*, 6966-6971.
52. Han, Y., Sheng, Y. J.; Yan, C. G. *Org. Lett.* **2014**, *16*, 2654-2657.
53. Gong, H.; Sun, J.; Yan, C. G. *Synthesis* **2014**, *46*, 2327-2332.
54. Han, Y.; Qi, W. J.; Shen, Y. J.; Yan, C. G. *Tetrahedron Lett*. **2015**, *56*, 5196-5198.
55. Qi, W. J.; Han, Y.; Yan, C. G. *Tetrahedron* **2016**, *72,* 5057-5063.
56. Liu, C. Z.; Han, Y.; Qi, W. J.; Yan, C. G. *Heterocyclic Commun.* **2016**, *22*, 301-306.
57. Qi, W. J.; Han, Y.; Liu, C. Z.; Yan, C. G. *Chin. Chem. Lett.* **2017**, 28, 442-445.
58. Han, Y.; Zheng, H.; Zhang, Y. Y.; Yan, C. G.; *Chin. Chem. Lett.* **2020**, *31*, 1337-1341.
59. Sun, J.; Zhang, Y.; Shi, R. G. *Org. Biomol. Chem.* **2019**, *17*, 3978-3983.
60. Ye, R.; Yan, C. G. *Eur. J. Org. Chem.* **2019**, 5882-5886.
61. Cao, J.; Yang, F.; Sun, J.; Huang, Y.; Yan, C. G. *J. Org. Chem*. **2019**, *86*, 622-635.
62. Pan, L. N.; Sun, J., Shi R. G.; Yan, C. G. *Org. Chem. Front.* **2020**, *7*, 3202-3208.
63. Zhan, S. C.; Sun, J.; Liu, R. Z.; Yan, C. G. *Org. Biomol. Chem.* **2020**, *18*, 163-168.
64. Liu, D.; Cao, J.; Sun, J.; Liu, R. Z.; Yan, C. G. *Org. Lett.* **2020**, *22*, 8931-8936.
65. Cao, S. H.; Zhang, X. C.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2011**, 2668-2672.