Phosphine-catalyzed highly diastereoselective [3 + 2] cyclization of isatin derived electron-deficient alkenes with α-allenic esters†

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A novel phosphine-catalyzed highly diastereoselective [3 + 2] cycloaddition of isatin derived α,β-unsaturated ketones with α-allenic ester has been developed.

Phosphine-catalyzed [3 + 2] or [4 + 2] cyclization reactions of allenoates have been proven to be powerful synthetic tools in the rapid formation of cyclic molecular complexity.[1–3] The synthetic utility of these cycloaddition reactions has been largely demonstrated by the preparation of biologically active natural products and pharmaceutically interesting substances.[1k] With the aim of exploring new phosphine-catalyzed cyclization reaction of allenoates, herein, we wish to report a novel phosphine-catalyzed highly diastereoselective [3 + 2] cycloaddition of isatin derived α,β-unsaturated ketones with α-allenic ester. The reaction affords the functionalized spirocyclic oxindolic cyclopentanes, which are the core structures in a variety of natural alkaloid derivatives,[4,5] in good to excellent yields with high regioselectivities and diastereoselectivities.

Initially, employing (*E*)-1-benzyl-3-(2-oxopropylidene)indolin-2-one **1a** (1.0 equiv.) and ethyl 2,3-pentadienoate **2a** (2.0 equiv.) as the substrates, the reaction was conducted in the presence of 20 mol% PBu_3 in toluene at room temperature, affording the [3 + 2] cycloaddition product **3a** in 76% total yield as a diastereoisomeric mixture of (*cis*, *trans*)-**3a** and (*trans*, *trans*)-**3a** with a ratio of 4 : 1 (Table S1, entry 1, see ESI†).[6] It should be mentioned here that this [3 + 2] cycloaddition reaction is highly regioselective because no other regioisomers were detected. Subsequently, the solvent effects and catalysts were investigated for this reaction, and the results are summarized in Table S1 (ESI†). As depicted in Table S1 (ESI†), the employed solvent had a significant influence on the reaction outcome in which toluene and *n*-Bu_2O were suitable solvents for the reaction to give **3a** in good yields, presumably due to that the substrates have good solubility in *n*-Bu_2O (Table S1, entries 1 and 2, ESI†). However, the solvents such as ^{t}BuOMe, dichloromethane (DCM), Et_2O, and tetrahydrofuran (THF) retarded the reaction rate and reduced the yields of **3a** (Table S1, entries 3–6, ESI†). The reaction in MeCN or DMF led to the complex product mixtures (Table S1, entries 7 and 8, ESI†). Subsequently, we tested other alkyl phosphines such as PMe_3 or P^tBu_3 in this reaction, but it was found that they could not catalyze this reaction under the standard conditions (Table S1, entries 9 and 10, ESI†). Decreasing the catalyst loading to 10 mol% slowed down the reaction rate, affording the product **3a** in lower yield (Table S1, entry 11, ESI†). Based on these experimental results, the best reaction condition has been identified to carry out this reaction using PBu_3 (20 mol%) as the catalyst at room temperature.

Next, we examined the performance of commonly used phosphines with aromatic substituents for this reaction, and the results are summarized in Table S2 (See ESI†). Interestingly, using the phosphines with aromatic substituents could catalyze this reaction under the identified optimal conditions, affording the same product **3a** in similar yield, however, the major product is the diastereoisomer (*trans*, *trans*)-**3a**. Phosphine with more aromatic substituents led to higher diastereoselectivities (Table S2, entries 1–3, ESI†). $P(MeO)Ph_2$ did not catalyze this reaction (Table S2, entry 4, ESI†). Furthermore, we examined the aryl phosphines having electron-donating groups or with electron-withdrawing groups on their benzene rings (Table S2, entries 5–7, ESI†). It turned out that aryl phosphine $P(4\text{-}FC_6H_4)_3$ which has an electron-withdrawing group on the benzene ring gave the best diastereoselectivity (Table S2, entry 7, ESI†). Subsequently, using $P(4\text{-}FC_6H_4)_3$ as the catalyst, we screened the solvent again (Table S2, entries 8–13, ESI†). It was found that dioxane was the most suitable solvent for this reaction, affording the product **3a** in 73% yield with excellent diastereoselectivity (Table S2, entry 13, ESI†).

Having identified the optimal reaction conditions, we next set out to examine the scope and limitations of this [3 + 2] cycloaddition reaction catalyzed by PBu_3 using various isatin derivatives **1** with different substituents on the benzene rings, and the results are summarized in Table 1. As shown in Table 1, whether the electron-withdrawing or electron-donating group at 4-, 5- or 6-position of the benzene ring of *N*-benzyl isatins **1** was employed, the reactions proceeded smoothly to give the corresponding products **3** in good total yields (up to 90%) with diastereoisomer (*cis*, *trans*)-**3** as the major products along with modest to excellent diastereoselectivities (Table 1, entries 1–7). The major diastereoisomer was unequivocally assigned as (*cis, trans*)-configuration by X-ray diffraction of the major product of **3q** (see ESI†). It is worthy noting that the substrates having a substituent at 4-position of the benzene ring afforded the product **3** with excellent diastereoselectivities (*cis*, *trans*) : (*trans*, *trans*) > 20 : 1 (Table 1, entries 2 and 3). Varying R^1 from the methyl group to the phenyl group still afforded the corresponding product **3j** in 70% yield, but, along

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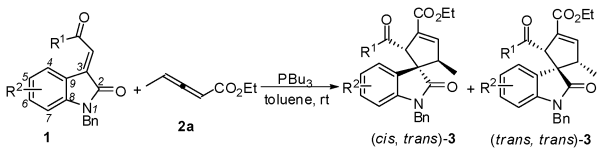
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all compounds and X-ray crystal data of **1n**, **3j**, **3q**. See DOI: 10.1039/c0cc04289g

Table 1 Scope of the reactions catalyzed by PBu_3[a]



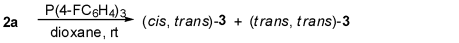
Entry	No	R^1	R^2	Yield[b] (%)	(*cis*, *trans*) : (*trans*, *trans*)[c]
1	**1a**	Me	H	**3a**, 76	4 : 1
2	**1b**	Me	4-Br	**3b**, 89	> 20 : 1
3	**1c**	Me	4-Cl	**3c**, 90	> 20 : 1
4	**1d**	Me	5-Br	**3d**, 74	7 : 1
5	**1f**	Me	5-F	**3f**, 76	4 : 1
6	**1g**	Me	5-Me	**3g**, 85	4 : 1
7	**1h**	Me	6-Br	**3h**, 70	4 : 1
8	**1j**	Ph	H	**3j**, 70	2 : 1
9[d]	**1q**	Me	H	**3q**, 91	3 : 1

[a] The reaction was carried out on a 0.1 mmol scale with 20 mol% catalyst under Ar in toluene (1.0 ml) at rt for 8 h, and the ratio of **1/2** was 1.0/2.0. [b] Isolated yield. [c] The diastereomeric ratio of (*cis*, *trans*)/(*trans*, *trans*) was determined by ^{1}H NMR spectroscopic data. [d] The benzyl group was replaced by 9-anthrylmethyl group.

with reduced diastereoselectivity (*cis*, *trans*) : (*trans*, *trans*) = 2 : 1 (Table 1, entry 8). Changing the N-substituent from the benzyl group to the 9-anthrylmethyl group gave the corresponding product **3q** in high yield along with slightly reduced diastereoselectivity (Table 1, entry 9).

We subsequently examined the scope and limitations of this [3 + 2] cycloaddition reaction catalyzed by $P(4\text{-}FC_6H_4)_3$ using various isatin derivatives **1** with different substituents on the benzene rings, and the results are summarized in Table 2. As shown in Table 2, whether the electron-withdrawing or electron-donating group at 4-, 5-, 6- or 7-position of the benzene ring of *N*-benzyl isatins **1** was employed, the reactions

Table 2 Scope of the reactions catalyzed by $P(4\text{-}FC_6H_4)_3$[a]



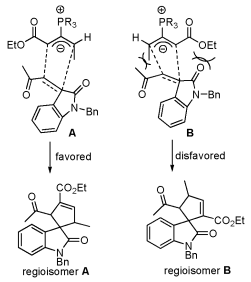
Entry	No	R^1	R^2	Yield[b] (%)	(*cis*, *trans*) : (*trans*, *trans*)[c]
1	**1a**	Me	H	**3a**, 73	< 1 : 20
2	**1b**	Me	4-Br	**3b**, 40	20 : 1
3	**1c**	Me	4-Cl	**3c**, 40	20 : 1
4	**1d**	Me	5-Br	**3d**, 74	1 : 11
5	**1e**	Me	5-F	**3e**, 78	1 : 14
6	**1f**	Me	5-Me	**3f**, 75	< 1 : 20
7	**1g**	Me	6-Br	**3g**, 78	1 : 20
8	**1h**	Me	7-Br	**3h**, 92	< 1 : 20
9	**1i**	Me	7-CF_3	**3i**, 60	< 1 : 20
10	**1j**	Ph	H	**3j**, 70	< 1 : 20
11	—	Ph	4-Br	—[d]	—
12	—	Ph	4-Cl	—[d]	—
13	**1k**	Ph	5-Br	**3k**, 82	< 1 : 20
14	**1l**	Ph	5-F	**3l**, > 99	< 1 : 20
15	**1m**	Ph	5-Me	**3m**, 82	< 1 : 20
16	**1n**	Ph	6-Br	**3n**, > 99	< 1 : 20
17	**1o**	Ph	7-Br	**3o**, 80	< 1 : 20
18	**1p**	Ph	7-CF_3	**3p**, 93	< 1 : 20

[a] The reaction was carried out on a 0.1 mmol scale with 20 mol% catalyst under Ar in dioxane (1.0 ml) at rt for 8 h, and the ratio of **1/2** was 1.0/2.5. [b] Isolated yield. [c] The diastereomeric ratio of (*cis*, *trans*)/(*trans*, *trans*) was determined by ^{1}H NMR spectroscopic data. [d] No reaction occurred.

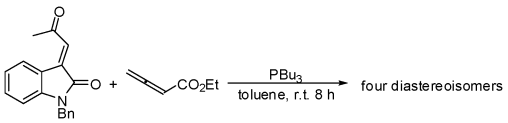
proceeded smoothly to give **3** in modest to good total yields (up to 92%) with excellent diastereoselectivities (Table 2, entries 1–9). In contrast to aforementioned reactions catalyzed by PBu_3, the reactions catalyzed by $P(4\text{-}FC_6H_4)_3$ mainly afforded the diastereoisomers (*trans*, *trans*)-**3** as the major products, which was unequivocally assigned by X-ray diffraction of the major product of **3j** (see ESI†), except for the substrates having a substituent at the 4-position of the benzene ring, which still gave (*cis*, *trans*) diastereoisomers as the major products, presumably due to the steric effect (Table 2, entries 2 and 3). Varying R^1 from the methyl group to the phenyl group still afforded the corresponding product **3j** in 70% yield with excellent diastereoselectivity (*cis*, *trans*) : (*trans*, *trans*) < 1 : 20 (Table 2, entry 10). Unfortunately, when R^1 = Ph and the substituent is at the 4-position of the benzene ring of *N*-benzyl isatins **1**, these substrates could not undergo this phosphine-catalyzed [3 + 2] cycloaddition reaction (Table 2, entries 11 and 12). When R^1 = Ph and the substituent is at the 5-, 6- or 7-position of the benzene ring of *N*-benzyl isatins **1**, these substrates could undergo this reaction smoothly, affording the corresponding products in good to excellent yields (up to > 99%) with excellent diastereoselectivities (*cis*, *trans*) : (*trans*, *trans*) < 1 : 20 (Table 2, entries 13–18).

The regiochemical outcome of this reaction may be rationalized as depicted in Scheme 1. Based on steric considerations, this [3 + 2] cycloaddition reaction can take place *via* the transition state **A**, which would be expected to be favored over the more sterically demanding transition state **B**. Thus, we obtained regioisomer **A** as our product.

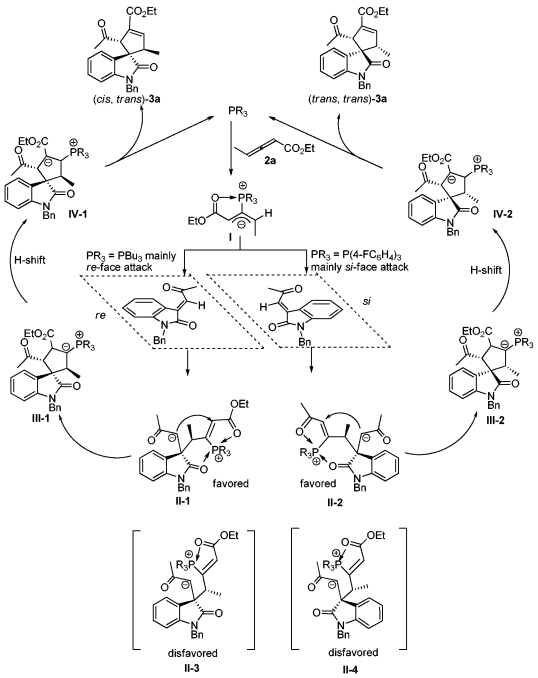
On the basis of the above results and commonly accepted mechanism for phosphine-catalyzed [3 + 2] cycloaddition reaction,[7] a plausible mechanism for the PBu_3- or $P(4\text{-}FC_6H_4)_3$-catalyzed [3 + 2] cycloaddition reaction between isatin derived α,β-unsaturated ketones with α-allenic ester is proposed in Scheme 3. The catalyst phosphine as a nucleophile reacts with ethyl 2,3-pentadienoate **2a** to produce the zwitterionic intermediate **I**, which subsequently undergoes a Michael addition to generate the intermediate **II-1** or **II-2** through attacking the activated olefin *via* the *re*-face or *si*-face. The intermediates **II-1** and **II-2** may be more favored than the intermediates **II-3** and **II-4** due to the internal coordination of oxygen to phosphorus atom,[8] resulting in that the methyl group and the carbonyl group on the isatin ring always possess the *trans*-position in the final product. Presumably, due to the steric reasons, the intermediate **I** is more favored to attack the activated olefin *via* the *re*-face if the catalyst is PBu_3; the intermediate **I** is more favored to attack the activated olefin *via*



Scheme 1 Rational explanation of the regioselectivity.



Scheme 2 PBu_3-catalyzed reaction using 2,3-butadienoate as the substrate.



Scheme 3 A plausible mechanism.

the *si*-face if the catalyst is $P(4\text{-}FC_6H_4)_3$, which leads to a different major product with a different spiro-configuration. The intermediates **II-1** and **II-2** undergo the ring-closing reaction to generate intermediates **III-1** and **III-2**, respectively, which can be converted to intermediates **IV-1** and **IV-2** *via* a H-shift. Releasing the phosphine, the products are finally furnished.

A control experiment has been carried out using 2,3-butadienoate as the substrate under the standard conditions as shown in Scheme 2. However, four diastereoisomers were given along with the ratio of 1/0.2/1/0.4, indicating that the methyl group on ethyl 2,3-pentadienoate is a key factor to affect the regioselectivity (see ESI† for details).

In conclusion, we have found and developed a novel phosphine-catalyzed highly diastereoselective [3 + 2] cycloaddition of isatin derived α,β-unsaturated ketones with α-allenic ester, affording the functionalized spirocyclic products in good to excellent yields, with high regioselectivities and diastereoselectivities. The phosphine catalyst affects the final product and was proven to be critical for controlling the diastereoselectivity. Efforts are in progress to elucidate further mechanistic details of these reactions and to understand their scope and limitations.

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6 The stereochemistry is specified by the orientation of the functional groups which have higher priority at the C1-, C2-, C3-positions of five-membered rings. In the case of (*cis*, *trans*)-**3a**, two carbonyl groups at the C1 and C2 positions are on the same side, which is defined as *cis*; one carbonyl group at the C1 position and one methyl group at the C3 position are on the opposite side, which is defined as *trans*.

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