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Base-Catalyzed Diastereoselective Construction of Spiro-epoxyoxindoles by the Darzens Reaction of 3-Chlorooxindoles with Aryl Aldehydes under Solvent-free Grinding

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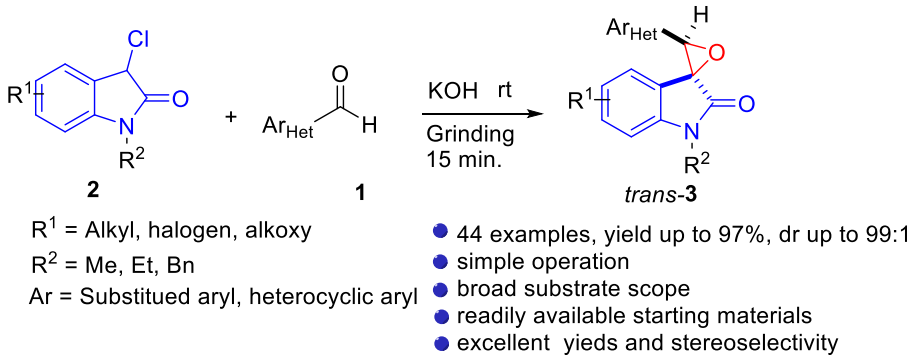

Abstract A highly efficient, diastereoselective strategy for the synthesis of aryl-substituted spiro-epoxyoxindole derivatives by a Darzens-type reaction of α-chlorooxindoles with aryl aldehydes in the presence of bases under solvent-free grinding conditions has been developed. The process features with easy work-up, mild reaction condition, high to excellent diastereoselectivitie and yields as well as environmental compatibility.

Key words spiro-epoxyoxindoles, α-chlorooxindoles, Darzens-type reaction aldehydes, grinding, solvent-free,

Introduction

Spirocyclic oxindoles have been recognized as a privileged class of heterocyclic motifs due to their common occurence in natural products and clinical pharmaceuticals.[1-6] Amongst them, spiro-epoxyoxindoles, which feature an epoxide ring fused to C-3 position of oxindole core, have been identified not only as privileged frameworks with significant biological activities such as antifungal,

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antitubercular, anti-Fusarium oxysporum and anticancer activities (Fig.1),[7-12]but also as very valuable intermediates containing the smallest spiro-fusion epoxide ring for readily undergoing versatile chemical transformations, owing to its inherent ring strain.[13-21]As a result of their intriguing structures, stereochemical complexity and biological activity, considerable efforts have been devoted to the construction of spiro-epoxyoxindole frameworks over the past decade. Till now, various powerful strategies have

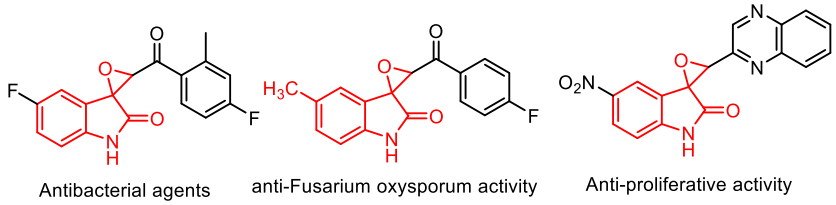
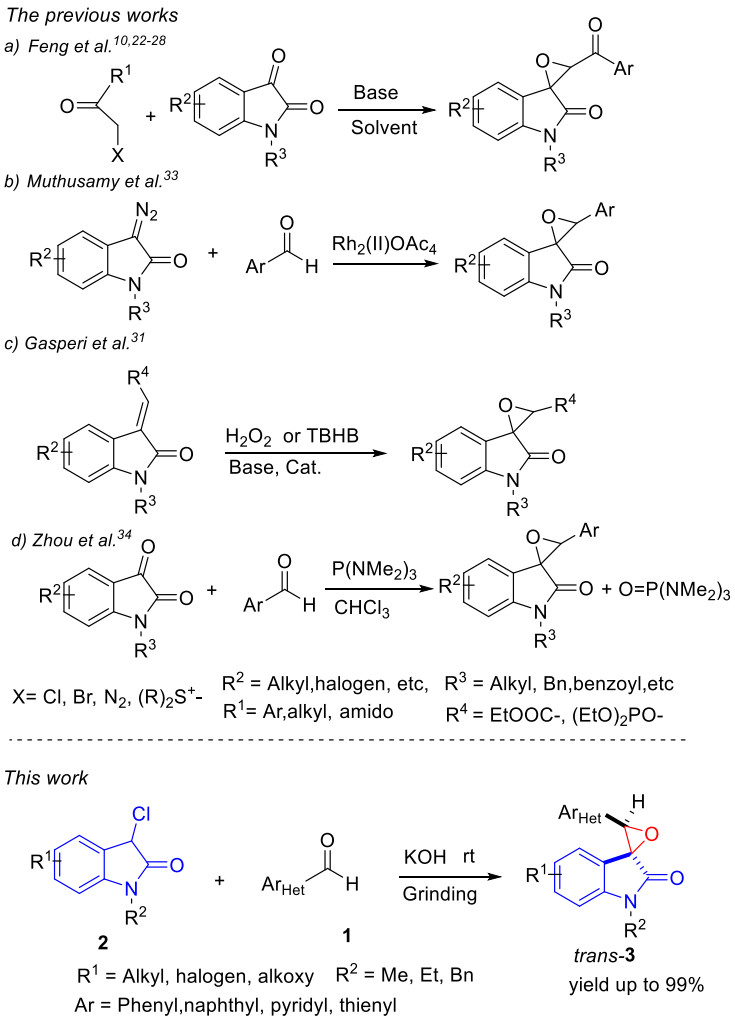


Figure 1. Representative biologically active spiro-epoxyoxindoles

been developed to access these skeletons, generally including a number of common and useful reactions such as Darzens reaction of α-halo/diazo/sulfonium ylide carbonyl compounds with isatins,[22,10,23-28] Corey-Chaykovsky epoxidation of isatin,[29] catalyzed epoxidation of the 3-alkenyl oxindole(Scheme1**)**.[30,31,7,15,11,32]Among these methods, the Darzens-Type reaction between α-halo or sulfonium ylide carbonyl compounds and isatins is still very important methods to prepare benzoyl-substituted spiro-epoxyoxindoles. In contrast, aryl-substituted spiro-epoxyoxindoles, as an important member of the group of spiro-epoxyoxindole derivatives, have scarcely been reported. So far, to the best of our knowledge there are only three reports on the synthesis of aryl-substituted spiro-epoxyoxindole. In 2004, Muthusamy's group[33]described the rhodium(II)-catalyzed epoxidation of 3-diazooxindoles with aryl aldehydes, and only ten cases were obtained with moderate yields (Scheme1**)**. Recently, Zhou and co-workers [34]reported the $P(NMe_2)_3$-mediated reductive epoxidation of isatins with aldehydes, affording aryl-substituted spiro-epoxyoxindoles with 43-89% yields and good steroselectivity (Scheme1**)**. Very recently, Jin's group[30] established a visible-light-induced aerobic epoxidation of 3-benzylideneindolin-2-ones with a meso-tetraphenylporphyrin (TPP) photosensitizer, giving the corresponding epoxides in excellent *trans*-steroselectivity. In the above methods, transition-metal-catalyzed insertion of 3-diazooxindoles is a very powerful organic transformation, but preparation, isolation, and storage of these α-diazocompounds is problematic due in large part to their instability and hazardous nature. While these epoxidations of 3-benzylideneindolin-2-one heavily depend on the use of transition metals or stoichiometric amounts of chemical oxidants such as organic and inorganic peroxides, the result for giving rise to safety, environmental and economic concerns. Furthermore, $P(NMe_2)_3$-mediated reductive epoxidation system required the use of stoichiometric amount of trivalent phosphine reagent ($P(NMe_2)_3$), and the formation of stoichiometric hexamethylphosphorous triamide waste from the Kukhtin−Ramirez adduct not only complicates purification of the product but also reduces the atom economy. Therefore, further exploration of other types of synthons to enrich the aryl-substituted spiro-epoxyoxindole chemistry is still of great importance, especially Darzens-Type reaction from readily available and bench stable starting materials under oxidant-free conditions (Scheme1**)**.



Scheme 1. Previous and proposed works

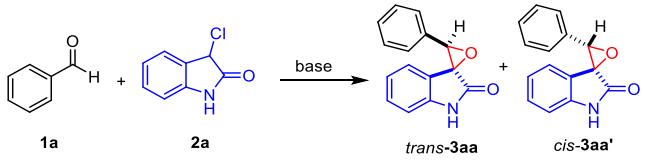
3-Halooxindoles,which feature with the dual nucleophilicity and eletrophilicity at the C-3 position, have emerged as a new versatile synthon in many elegant annulation reactions to date, giving various highly substituted spirocyclic oxindoles.[35-43] We imagined that the use of 3-halooxindoles for Darzens-Type reaction with diverse aromatic aldehydes would provide a straightforward approach to access aryl-substituted spiro-epoxyoxindoles. Inspired by the significant research in this area, and as a part of our long-standing research on the development of new methodologies for the synthesis and applications of 3-halooxindoles and spirocyclic oxindoles.[44-46]We herein wish to report our study on a Darzens-Type condensation reaction of aromatic aldehydes with 3-chlorooxindoles under the solvent-free grinding conditions. This strategy provides facile access to aryl-substituted spiro-epoxyoxindole compounds with high to excellent diastereoselectivities and yields.

Results and Discussion

Initially, to optimize the reaction conditions a representative reaction of 3-chlorooxindole **2a** and benzaldehyde **1a** that could presumably afford the spiro-epoxyoxindole **3aa** was performed under various conditions (Table 1). To begin with, based on Darzens common reaction condition, the above model substrates were refluxed in ethanol in the presence of 10 mol % KOH, and monitored

by TLC intermittently. Gratifyingly, after 4h of continuous reflux the reaction attained completion and gave the desired 3'-phenylspiro[indoline-3,2'-oxiran]-2-one **3aa** in 88% yield with diastereoselective ratio of 92:8 (Table 1, entry 1). In contrast, the above reaction took 6 h for only

Table 1. Screening of the Reaction Conditions



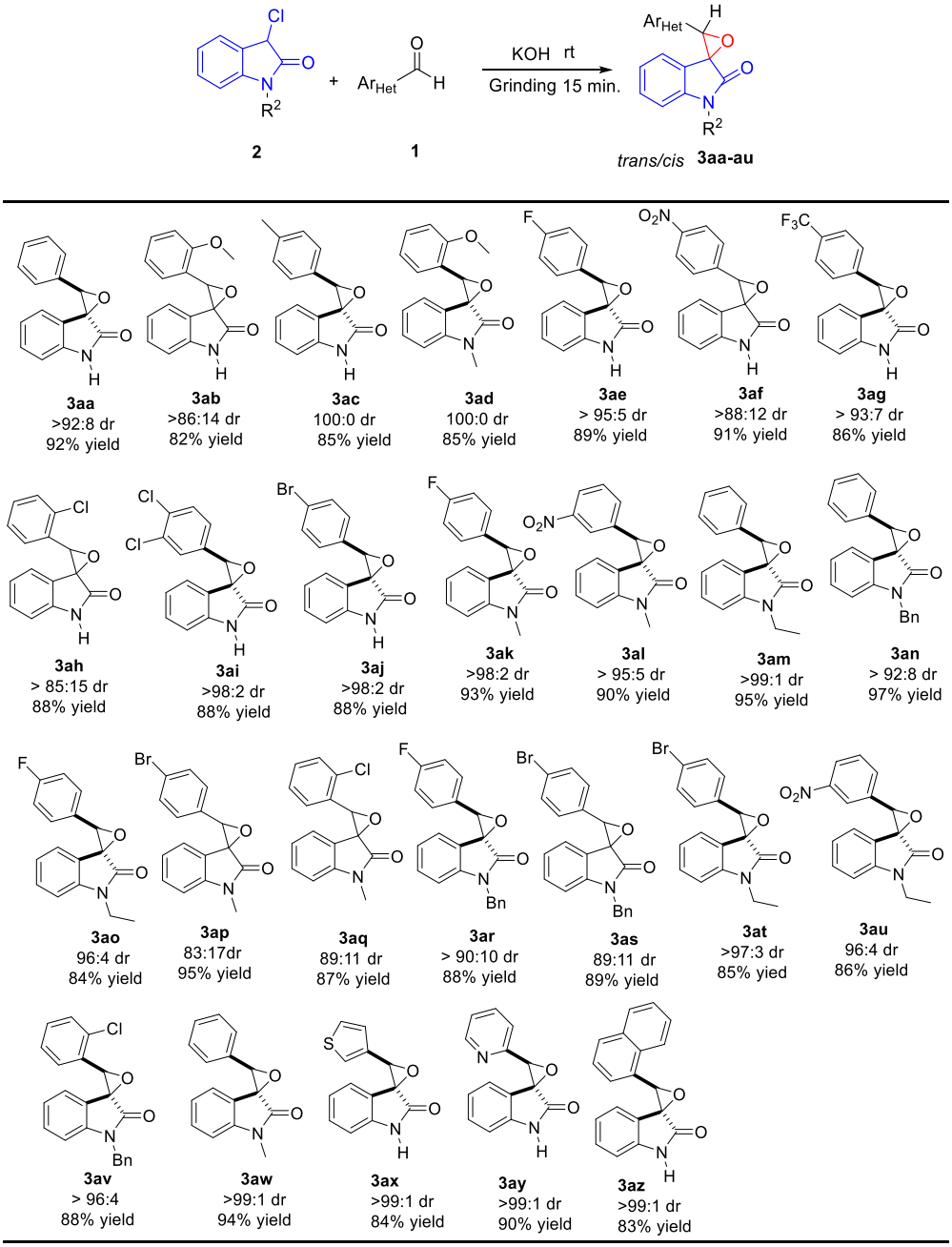
Entry	Catalyst	Solvent	T (°C)	Time (h)	Yield[c] (%)	dr[c]
1	KOH	EtOH	reflux	4	88	92:8
2	KOH	EtOH	rt	6	70	92:8
3	KOH	MeOH	reflux	4	77	86:14
4	KOH	MeOH	rt	4	68	83:17
5	KOH	MeCN	reflux	4	68	86:14
6	KOH	THF	reflux	6	66	87:13
7	KOH	CH_2Cl_2	reflux	6	72	83:17
8	KOH	DCE	reflux	6	78	89:11
9	KOH	—	grinding	0.25	92	92:8
10	NaOH	—	grinding	0.25	82	90:10
11	K_2CO_3	—	grinding	0.25	70	94:6
12	Na_2CO_3	—	grinding	0.25	75	99:1
13	$CsCO_3$	—	grinding	0.25	79	93:7
14	DBU	—	grinding	0.25	77	92:8
15	DABCO	—	grinding	0.25	74	93:7
16	$NaOA_C$	—	grinding	0.25	73	98:2
17	LiOH	—	grinding	0.25	85	91:9
18	Li_2CO_3	—	grinding	0.25	80	93:7

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.64ml, 0.6mmol), **2a** (0.6mmol) and 10 mol % catalyst in the specified condition for the indicated time.[b]Isolated yields.[c]dr determined by ^{1}H NMR of crude reaction mixture. — Solvent-free condition.

70 % completion at room temperature (Table 1, entry 2). With a view to increase the yield, other solvents were also further explored for this reaction, including MeOH, MeCN, THF, CH_2Cl_2 and DEC under room temperature as well as reflux, but they did not give better results (entries 3–8). From the above screen results, it is evident that refluxing the reactants in ethanol was the optimum condition (Table 1, entry 1). However, inspired by solvent-free reactions, we focused on investigating the reaction under the solvent-free grinding method. To our surprise, the reaction provided **3aa** in 92% yield with diastereoselective ratio of 92:8 after 15 min (Table 1, entry 9). This preliminary result implied that the solvent-free grinding method gave superior yields in less time in comparison to other conditions (Table 1). Subsequently, a series of bases including inorganic bases such as NaOH, LiOH, K_2CO_3, $NaCO_3$, $CsCO_3$, Li_2CO_3 and NaOAc (entries 10-13, 16-18) and organic bases including DBU and DABCO were screened (entries 14-15), but no better results were also achieved (Table 1, entries 11−15). Thus, these conditions listed in entry 9 were set as the optimal reaction conditions for the generation of product **3**.

Having established the optimal conditions, we set out to explore the generality of this base-catalyzed solvent-free grinding method. As summarized in Scheme 2, this reaction displayed good

Scheme 2. Substrate scope of various aromatic aldehydes[b]



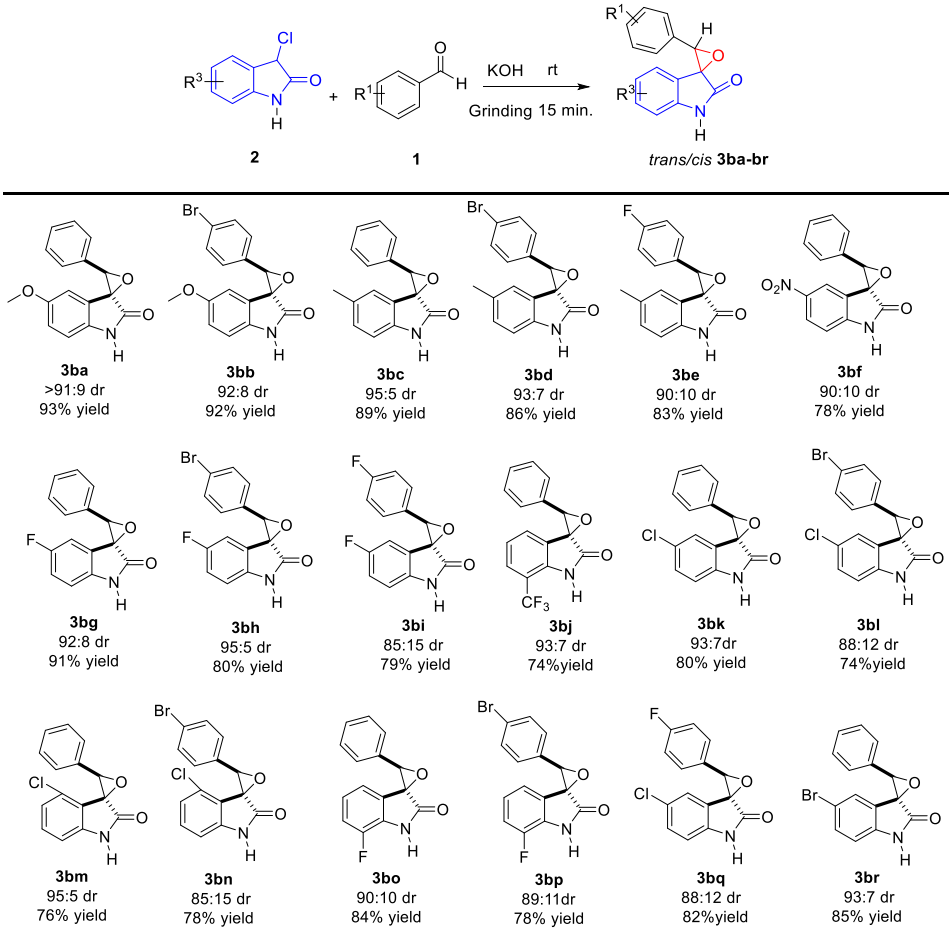
[a]The dr value was determined by ^{1}H NMR. [b]The reactions were carried out with **1** (0.6 mmol), 2 (0.6 mmol), KOH (0.06 mmol) in a mortar and ground continuously for 15 min. [c]Isolated yield.

functional group compatibility. Benzaldehydes bearing different electron-donating substituents such as MeO, Me had little influence on the reactivity and stereoselectivity regardless of the substituent position of the aromatic ring (*ortho* or *para*) and protected/unprotected N atoms, giving the corresponding products **3ab**−**ad** in excellent yields and diastereoselective ratios of 86:14−100:0 dr. Meanwhile, electron-withdrawing groups on the phenyl ring such as NO_2, CF_3, F, Cl, Br were also compatible with the developed protocol, affording their respective products **3ae-al**, **3ao-av** with very satisfying results. We also examined different N-substituted 3-chlorooxindoles **2**, it was found

that N-benzyl, ethyl and methyl protected 3-chlorooxindoles **2** seemingly have no influence on the reactivity and stereoselectivity. Furthermore, these standard reaction conditions also were applied to the Darzens condensation of heterocyclic and polycyclic aromatic aldehydes such as 3-thiophene aldehyde, 2-pyridinecarboxaldehyde, α-naphthaldehyde with 3-chlorooxindoles **2**, affording the corresponding products **3ax-az** in high yields (83−90%) with excellent stereoselectivities (>99:1 dr) (Scheme 2). It was disappointing that aromatic ketones such as acetyl benzene failed to give condensation products.

To explore further the scope of the substrate scope, we focused on a variety of substituted 3-chlorooxindoles **2** (Scheme 3). Generally, 3-chlorooxindoles could smoothly react with aldehydes **1** after installing an electron-donating group into the oxindole skeleton, delivering the corresponding products **3ba**−**be** in high yields (83−93%) with excellent stereoselectivities (90:10−92:8 dr).

Scheme 3. Substrate scope of various substituted 3-chlorooxindoles[b]



[a]The dr value was determined by ^{1}H NMR. [b]The reactions were carried out with **1** (0.6 mmol), 2 (0.6 mmol), KOH (0.06 mmol) in a mortar and ground continuously for 15 min. [c]Isolated yield.

Similarly, the substrates attaching an electron-withdrawing group to the aromatic ring of the oxindoles also showed good reactivities, affording products **3bf**−**br** with excellent diastereoselectivities but moderate yields. Notably, all of these N-unprotected 3-chlorooxindoles can be suitable for the transformation, generating corresponding products **3**.

The structures of all products **3** were assigned based on ^{1}H, ^{13}C NMR and HRMS analysis, and

by diagnosis of singlets at δ = 5.25–4.61 in their ^{1}H NMR spectra, which revealed the formation of the corresponding spiro-epoxide ring at the 3-position of oxindole structural motifs. The ^{13}C NMR and DEPT-135 analyses show a quaternary carbon at approximate 61.0 ppm for oxindole-3-carbon. High resolution mass spectrum also indicated the required molecular ion peak. The relative configuration of products **3bh** was determined to be *trans*-form by single-crystal X-ray analysis (Figure 2).[47]Assuming that they go through a common reaction pathway, the relative configurations of the other products were established by analogy. It was disappointing that the products **3ad**,**3af**, **3ag**, **3ai**, **3ao**, **3ar** gave a quite complex NMR spectrum of substantial peak doubling owing to the close values of R_f of two diastereoisomers, and it appeared to be impossible to isolate the other one by column chromatography.

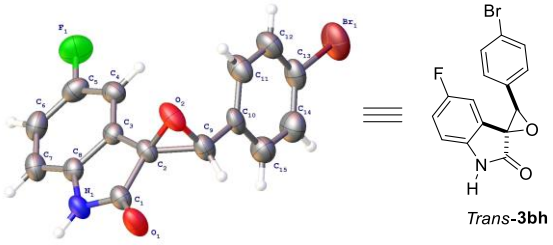
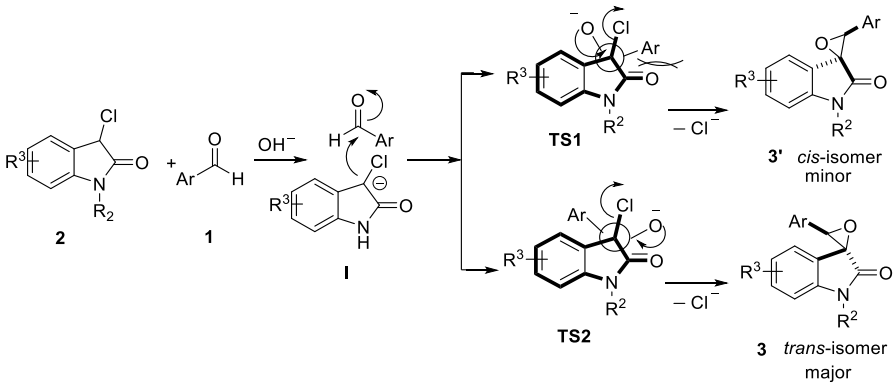


Figure 2. X-ray crystal structure of **3bh**

Based on our experimental results and previous literature reports,[48,28,49] a proposed probable mechanism was outlined and is shown in Scheme 4. The reaction starts with the generation of the carbanion intermediate **I** at 3-position of α-chlorooxindoles in the presence of base, which simultaneously attacks the carbonyl carbon of aldehydes to the form transition-state intermediate TS, which presumably exists in two transient states: *cis*-form **TS1** and *trans*-form **TS2**. the *trans*-form is more stable than the *cis*-form because it experiences less steric hindrance, electrostatic repulsions and a possible π–π stacking interaction between the aryl groups, and it becomes the preferential intermediate. Subsequently, the chlorine leaving group is replaced by the oxygen atom, forming spiro-oxirane frameworks in the preferential *trans*-form configuration.



Scheme 4. Proposed reaction mechanism

Conclusion

In summary, we have developed a highly diastereoselective synthesis of aryl-substituted spiro-epoxyoxindole derivatives applying a Darzens-type reaction to α-chlorooxindoles with aryl aldehydes in the presence of bases under solvent-free grinding conditions. The present methodology shows good functional group tolerance, excellent yields and diastereoselectivities. The ready availability of the starting materials, solvent-free grinding reaction conditions and practical nature

of the process should make this reaction valuable in synthetic chemistry.

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