1,3-Dipolar cycloaddition of isatin-derived azomethine ylides with 2*H*-azirines: stereoselective synthesis of 1,3-diazaspiro[bicyclo[3.1.0]hexane]oxindoles

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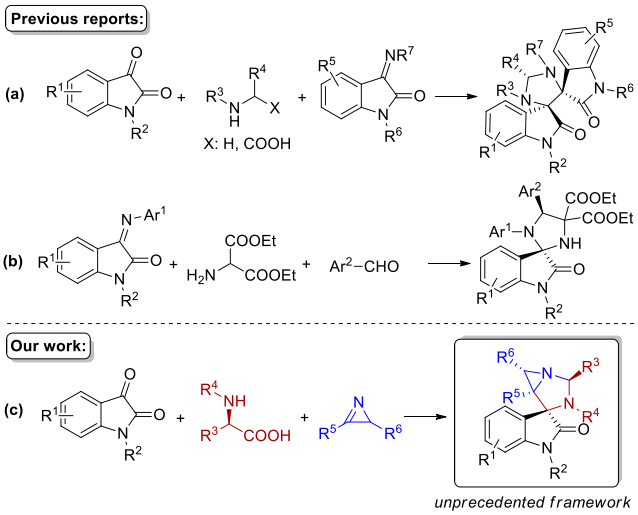
Introduction

Spiroheterocycles containing oxindole scaffold are regarded as a growing field of interest due to their highly pronounced biological and pharmaceutical activity,[1] particularly the spiro-oxindolopyrrolidine framework, which constitutes the core unit of numerous alkaloids and pharmaceutics.[2]

Among the known synthetic strategies,[3] the 1,3-dipolar cycloaddition (1,3-DC) of isatin-derived azomethine ylides with dipolarophiles has been proved to be the main tool for the construction of spirocyclic oxindoles.[4] In terms of dipolarophiles, a considerable amount of alkenes[5] and alkynes[6] have been subjected to 1,3-DC leading to the formation of various spiro-oxindolopyrrolidines and -pyrrolines. In contrast, the assembly of analogous spiro-oxindoloimidazolidines by the utilization of imines as dipolarophiles is scarcely explored.[7-9] Additionally, the few reported efforts mainly focus on the synthesis of dispirooxindole derivatives, exploiting the reaction of an electron-deficient isatin-derived ketimine with an azomethine ylide generated from isatin and amines/α-aminoacids (Scheme 1a).[7] Other approaches involve a different route for the *in situ* formation of the azomethine ylide, employing diazooxindoles, amines and aldehydes as starting materials.[8] An alternative protocol, established recently by Shi's group, relies on the three-component reaction of isatin-derived imines, amino-ester and aldehydes *via* phosphoric acid catalyzed 1,3-DC and enables the construction of the spiro-oxindoloimidazolidine scaffold with a different regiochemical outcome (Scheme 1b).[9]

Although the scope of 1,3-DC in the synthesis of spirocyclic oxindoles has been broadened by various dipolarophiles, to the best of our knowledge, the utilization of 2*H*-azirines as dipolarophiles in cycloaddition reactions of isatin-derived azomethine ylides have not been studied yet.



Scheme 1. Synthesis of spiro-oxindoloimidazolidines

As a continuation of our interest in constructing aziridine-based heterocycles,[ref] we report here the first synthesis of 1,3-diazaspiro[bicyclo[3.1.0]hexane]oxindole framework through the one-pot three-component reaction of isatins, α-amino acids and 2*H*-azirines in a diastereo- and regioselective manner (Scheme 1c).

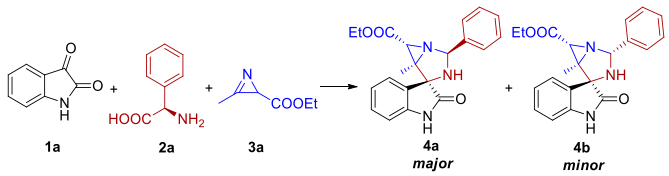
Results and discussion

At the outset of the study, the feasibility of the azirine-based 1,3-DC was investigated by performing the model three component reaction of isatin (**1a**), D-(-)-2-phenylglycine (**2a**) and (±)-ethyl 3-methyl-2*H*-azirine-2-carboxylate (**3a**) in polar solvents at room temperature (Table 1, entries 1–5). To our delight, the cycloaddition proceeded smoothly in DMSO and led to desired *endo*-

cycloadducts **4a** and **4b**, as racemic diastereomers, in acceptable HPLC yield and high diastereoselectivity (92:8 dr) (Table 1, entry 5). The structures of diastereomers **4a** and **4b** were unambiguously confirmed by NMR spectroscopy and X-ray diffraction of single crystals (See Supporting Information). To further optimize the reaction conditions, a broader range of anhydrous solvents were screened at elevated temperature (Table 1, entries 6–16). Generally, the formation of the desired cycloadducts was favored in polar protic and -aprotic solvents (Table 1, entries 6–8, 11 and 16), while nonpolar solvents were not tolerated. In terms of the combined yield, ethanol and DMSO were proved to be the best media (71% and 73% HPLC yield, respectively) (Table 1, entries 7 and 16), however, higher diastereoselectivity (92:8 dr) was achieved in DMSO. Modification of the concentration resulted in inferior or similar yields, but interestingly had no impact on the diastereomeric ratio (Table 1, entries 17–21).

Therefore, we found that the model reaction in DMSO (0.25 M for **1a**) at 60 °C after 8 hour could deliver the product **4a** and **4b** in high HPLC yield of 72% and with maintained diastereoselectivity of 92:8 dr (Table1, entry 19).

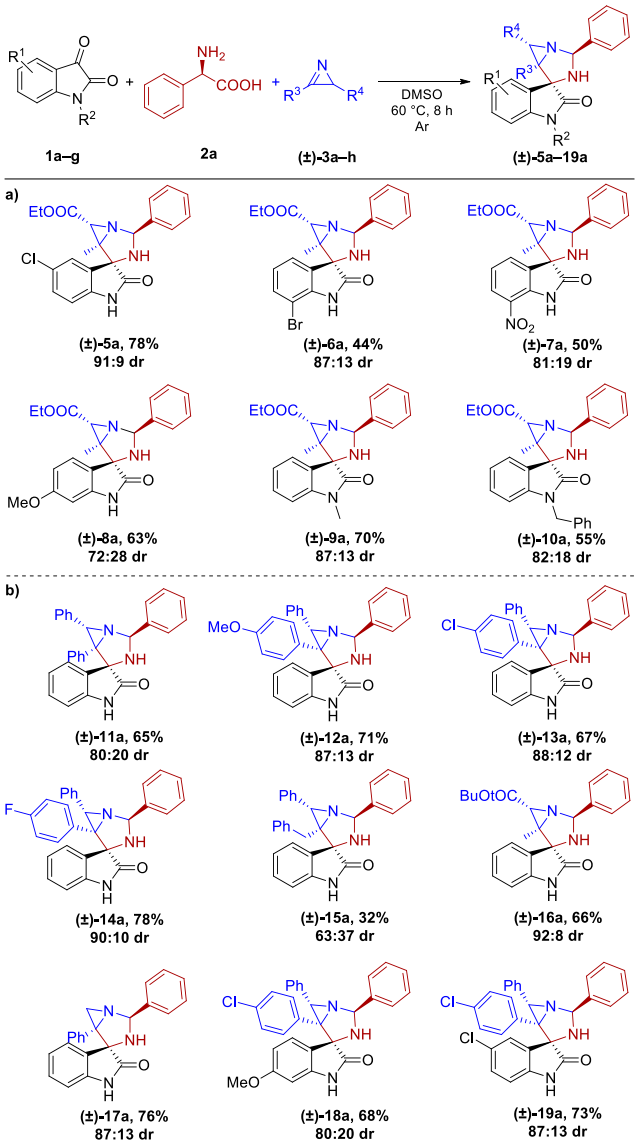
Table 1. Optimization of the reaction conditions.



Entry[a]	Solvent	Temp. (°C)	Time (h)	Conv. (%)	Yield (%)[b]	dr[c]
1	MeOH	rt	36	91	44	87:13
2	EtOH	rt	36	81	9	85:15
3	TFE	rt	36	83	10	62:38
4	DMF	rt	36	84	11	90:10
5	DMSO	rt	36	93	54 (47)[d]	92:8
6	MeOH	60	36	98	53	84:16
7	EtOH	60	36	98	71	82:18
8	IPA	60	36	90	49	74:26
9	tBuOH	60	36	85	13	59:41
10	MeCN	60	36	84	4	74:26
11	DMF	60	36	97	37	90:10
12	THF	60	36	83	2	52:48
13	Toluene	60	36	-	-	-
14	$CHCl_3$	60	36	82	2	52:48
15	TFE	60	36	94	31	53:47
16	DMSO	60	36	100	73	92:8
17	DMSO[e]	60	8	100	51	92:8
18	DMSO[f]	60	8	100	61	92:8
19	**DMSO**	**60**	**8**	**100**	**72 (65)[d]**	**92:8**
20	DMSO[g]	60	8	100	68	92:8
21	DMSO[h]	60	8	100	69	92:8

[a]Reaction conditions: isatin (0.25 mmol), D-(-)-2-phenylglycine (0.3 mmol), 2*H*-azirine (0.25 mmol), 1 mL anhydrous solvent, argon atmosphere. [b]Combined yield of **4a** and **4b**. Determined by HPLC analysis. [c]The diastereomeric ratio (dr) was determined by HPLC analysis. Both diastereomers were calibrated. [d]Isolated yield of **4a** in parenthesis. [e]0.25 mL anhydr. solvent was applied. [f]0.5 mL anhydr. solvent was applied. [g]2 mL anhydr. solvent was applied. [h]4 mL anhydr. solvent was applied.

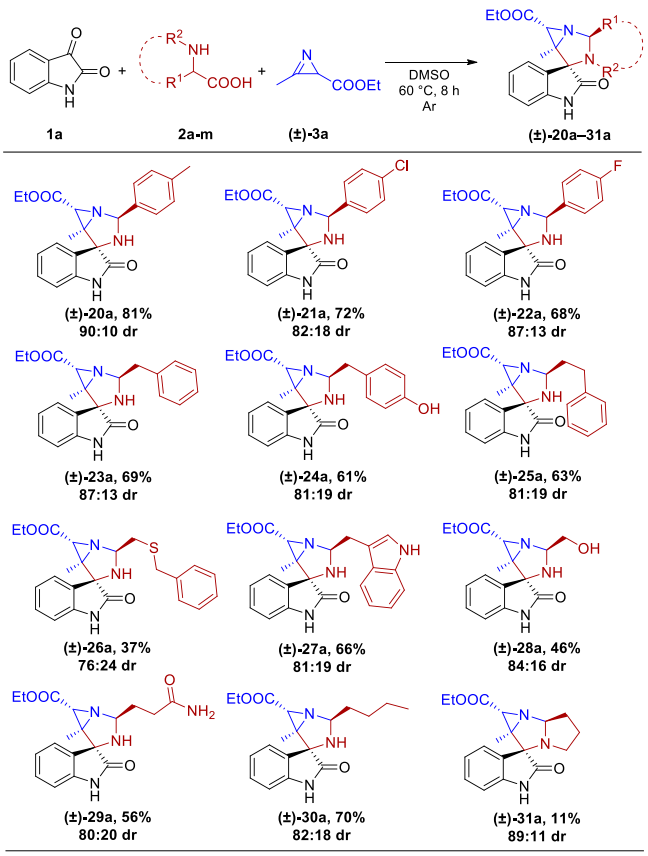
At first, with the optimized conditions in hand, the generality of the 1,3-DC with respect to the isatin component was examined, using phenylglycine **2a** and azirine **3a** as inputs. Gratifyingly, electron-rich and electron-deficient isatins were both tolerated well, providing the major diastereomers **5a–10a** in 44–78% isolated yields (Scheme 2a). Remarkable substituent effect was not observed, however, the presence of electron withdrawing groups (Br and NO_2) at C-7 position or the application of *N*-benzylisatin resulted in lower yields (**6a**, **7a** and **10a)**. Subsequently, the azirine scope of the 1,3-DC was investigated, employing isatin (**1a**) and phenylglycine **2a** as precursors of the azomethine ylide (Scheme 2b, **11a–17a**). Pleasingly, 2,3-diphenylazirines furnished the corresponding products **11a**–**14a** in good yields and dr as well, regardless of the electronic nature of the benzene ring. Interestingly, 2*H*-azirine bearing benzyl group at the R^3 position resulted in diminished diastereoselectivity (**15a**, 63:37 dr). The facilitated formation of the minor diastereomer might be explained by π-π interaction between the benzyl moiety and the phenyl group of the azomethine ylide. On the other hand, the sterical properties of the R^4 substituent had negligible impact on the stereochemical outcome of the 1,3-DC (**16a** and **17b**).



Reaction conditions: isatin (0.5 mmol), D-(-)-2-phenylglycine (0.6 mmol), 2*H*-azirine (0.5 mmol), 2 mL anhydrous DMSO, argon atmosphere, 60 °C, 8 h. The dr was determined by LC-MS analysis.

Scheme 2. Scope of isatins and *2H*-azirines.

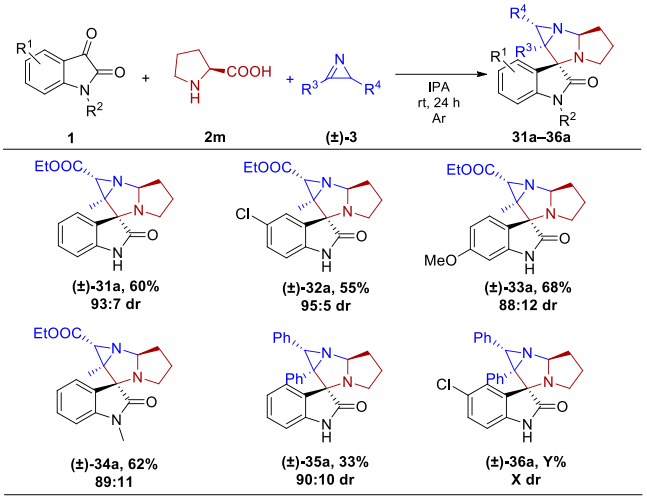
Further exploration of the substrate scope was focused on the α-aminoacid component (Scheme 3). The reaction of isatin (**1a**), azirine **3a** and phenylglycines possessing electron-donating (Me) or electron-withdrawing (Cl, F) substituents at *para* position proceeded smoothly under the optimal reaction conditions and delivered the expected spirooxindoles **20a**–**22a** in good isolated yields and dr (Scheme 3). Lengthening of the R^1 side chain by methylene group had no significant influence on the diastereoselectivity and the efficiency of the 1,3-DC (Scheme 3, **23a**–**25a**). To our delight, trifunctional α-aminoacids, such as *S*-benzylcysteine, tryptophan, serine and glutamine were also compatible with the reaction (Scheme 3, **26a**–**29a**) Although aliphatic norleucine was readily transformed to cycloadduct **30a** in 70% isolated yield, proline was surprisingly barely tolerated (**31a**, 11%).



Reaction conditions: isatin (0.5 mmol), amino acid (0.6 mmol), 2*H*-azirine (0.5 mmol), 2 mL anhydrous DMSO, argon atmosphere, 60 °C, 8 h. The dr was determined by LC-MS analysis.

Since the pyrrolidine scaffold is a key structure in drug discovery, the optimal reaction conditions for the formation of **31a** was reinvestigated (See Supporting Information). In dry isopropanol at room temperature, the desired product **31a** could be obtained in an improved yield of 60% (Scheme 4). Afterwards, further cycloadducts were synthesized in moderate to good yields and high diastereoselectivites, demonstrating the general performance of the proline-involved 1,3-DC under the reoptimized conditions (Scheme 4, **32a**–**36a**).

Scheme 3. Scope of amino acids.

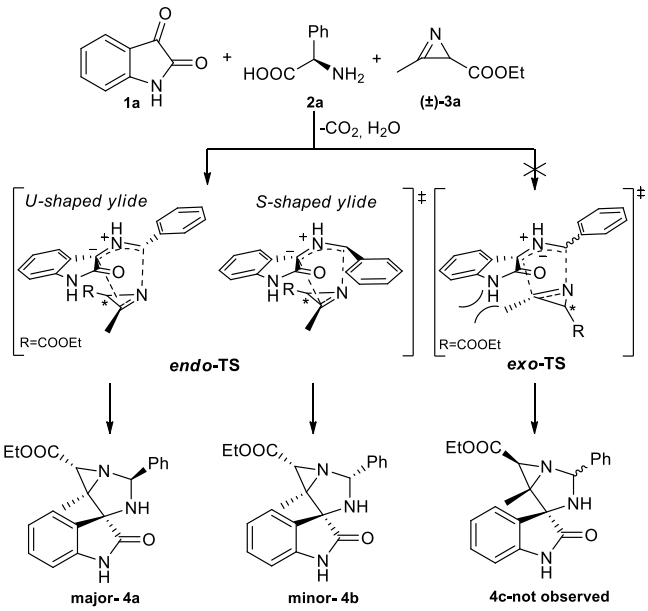


Reaction conditions: isatin (0.5 mmol), L-proline (0.6 mmol), 2*H*-azirine (1.5 mmol), 8 mL anhydrous IPA, argon atmosphere, rt, 24 h. The dr was determined by LC-MS analysis.

Scheme 4. Three-component reactions involving L-proline under reoptimized reaction conditions.

Based on the above experimental and analytical results, plausible reaction pathways are proposed (Scheme 5). Initially, azomethine ylide is generated from **1a** and **2a** *via* a condensation/lactonization/decarboxylation sequence. Although the subsequent regioselective 1,3-dipolar cycloaddition with 2*H*-azirine **3a** can occur through both *endo*- and *exo*-TS, no evidence was found for exocyclic products. The exclusive formation of the *endo*-cycloadducts **4a** and **4b** might be explained by the sterical repulsion emerged in *exo*-TS between the methyl substituent of the azirine and the benzene ring of the oxindole moiety. Since the S-shaped conformation of the azomethine ylide is more favored against the U-shaped,[X] the *endo*-selective 1,3-DC leads to the predominant formation of diastereomer **4a**.

In summary, we have succesfully developed a one-pot, three component reaction for the synthesis of a novel aziridine-fused spiro[imidazolidine-4,3'-oxindole] framework through 1,3-dipolar cycloaddition of 2*H*-azirines with azomethine ylides generated from isatins and α-amino acids. The protocol tolerates a wide range of substrates and enables the facile construction of highly diverse 1,3-diazaspiro[bicyclo[3.1.0]hexane]oxindoles in complete regio- and high diastereoselectivities in isolated yields up to 81%.



Scheme 5. Proposed reaction mechanism for 1,3-DC.