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Transition-metal-free regioselective synthesis of spiro-oxazolidines through [3 + 2] annulation reactions of azadienes with haloalcohols†

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The transition-metal-free regioselective [3 + 2] annulation of azadienes with haloalcohols for the preparation of highly functionalized spiro-oxazolidines is experimentally simple and proceeds under mild conditions. The metal-free protocols have more significance than the metal-catalyzed ones when the toxicity associated with the metal catalyst is considered. This transformation features a broad substrate scope, good yields, and excellent regioselectivity. Moreover, large-scale synthesis and representative transformations of spiro-oxazolidines were carried out to provide additional evidence on the practicality of this approach.

Introduction

Spirocyclic skeletons are privileged structural moieties in many biologically active natural products owing to their inherent three-dimensional architecture.[1] Among the useful classes of oxygen- and nitrogen-based heterocycles, oxazolidine is a significant motif present in various natural products and pharmaceuticals (as shown in Fig. 1), and it is used as a chiral auxiliary and chiral ligand in diverse asymmetric transformations.[2,3] In particular, spiro-oxazolidines, with heteroatom-substituted quaternary stereocenters, are valuable building blocks to construct medicinally relevant compounds.[4]

Since the existence of heteroatoms can bring new synthetic and biological values, the focus has recently been shifted to utilizing azadienes (**1** and **4**) to prepare heterocycles containing multi-heteroatoms.[5] Azadiene contains exocyclic alkylidene and an imine unit, which acts as a four-atom synthon in various Michael additions and subsequent cascade reactions, delivering diverse cyclic compounds through [4 + *n*] cycloaddition reactions due to the driving force for aromatization.[6] Recently, Zhao's group reported [4 + 3] annulation through 1,4 addition of α-bromohydroxamates to azadienes to access benzofuran-fused seven-membered heterocycles (Scheme 1a).[7] In contrast to well-developed [4 + *n*] cyclizations through 1,4-addition, which are applicable only for the synthesis of aromatized heterocycles, these azadienes can also serve as two-atom synthons to undergo [2 + *n*] annulation to synthesize spirocyclic motifs.[8] Very recently, Liu's group developed a methodology for the synthesis of spirocyclopentanone through [3 + 2] cycloaddition of cyclopropanes with azadienes (Scheme 1b).[9] Except a few reports, the synthesis of spiro-oxazolidine scaffolds has not been developed yet.[10] The 1,2-addition reactions are comparatively less developed; Trost's group have recently demonstrated Pd-catalyzed [3 + 2] spiroannulation from azadienes and vinyl epoxides (Scheme 1c).[11] These reported methods involved noble metal-

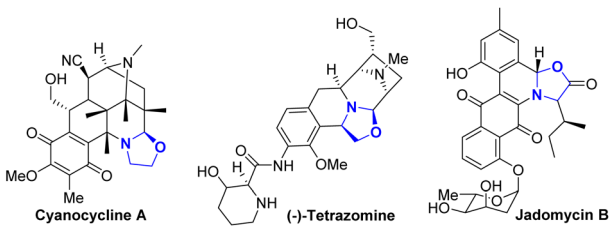

Fig. 1 Representative examples of bioactive oxazolidine scaffolds.

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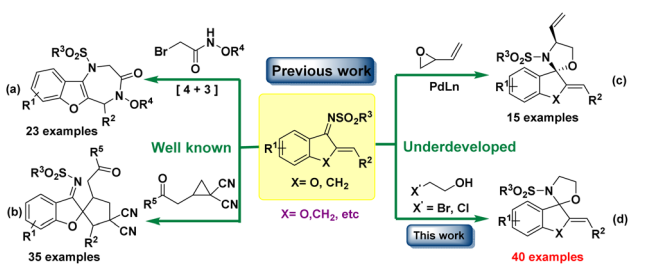


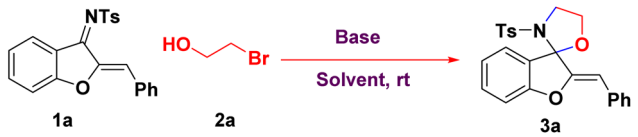
Scheme 1 Annulation reactions of azadienes with various reaction partners.

catalyzed protocol, high cost, multistep cascade reactions, drastic reaction conditions, and limited substrate scope, adding to their drawbacks. The quest to explore alternatives to transition metal catalysts is mainly attributed to the toxicity inherent in such systems, especially when it comes to synthesizing heterocycles of biological relevance. Hence, protocols that proceed under transition-metal-free conditions are always desirable among the scientific community.[12]

However, to our knowledge, the regioselective transition-metal-free [3 + 2] spiroannulation of azadienes has not been studied yet. Therefore, it is highly desirable to synthesize spiro-oxazolidines under transition-metal-free and ambient reaction conditions. Herein, we describe the development of an approach for the regioselective synthesis of spiro-oxazolidines under ambient reaction conditions.

Recently, haloalcohols (Br, Cl, and I) and their homologs were explored and developed as Michael donors for [3 + 2]/[4 + 2] annulation reactions with various Michael acceptors for the synthesis of an important class of heterocyclic compounds.[13] Based on this background and as a continuation of our interest in bioactive-fused polycyclic structure synthesis,[14] we carried out [3 + 2] annulation of azadienes with haloalcohols under milder reaction conditions to obtain the corresponding spiro-oxazolidines, which are constituents of various natural products and pharmaceuticals (Scheme 1d).

Table 1 Optimization of reaction conditions for the synthesis of spiro-oxazolidine derivatives[a]



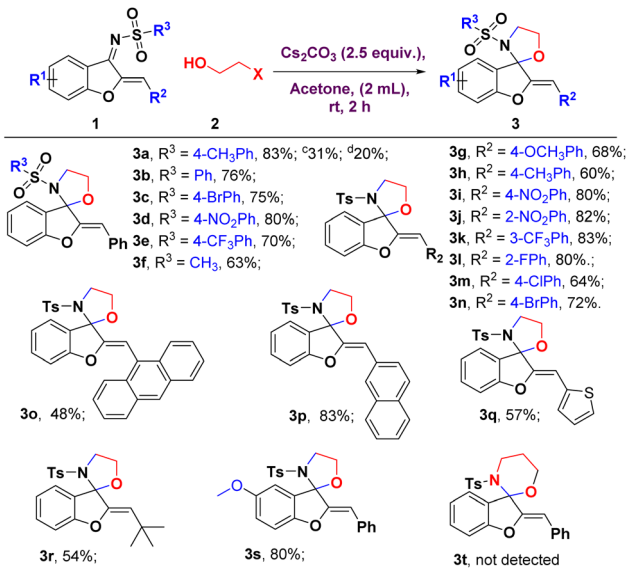
Sr. no.	2a (equiv.)	Base	Solvent	Time (h)	Yield[b] (%)
1	1.5	DBU	MeCN	3	28
2	1.5	K_3PO_4	MeCN	6	78
3	1.5	K_2CO_3	MeCN	12	52
4	1.5	Et_3N	MeCN	12	Trace
5	1.5	NaH	MeCN	12	40
6	1.5	Cs_2CO_3	MeCN	3	81
7	1.5	*t*-BuOK	MeCN	12	40
8	1.5	Cs_2CO_3	1,4-Dioxane	12	10
9	1.5	Cs_2CO_3	DMF	6	72
10	1.5	Cs_2CO_3	DMSO	12	Trace
11	1.5	Cs_2CO_3	THF	12	5
12	1.5	Cs_2CO_3	DCM	12	nr
13	1.5	Cs_2CO_3	Toluene	12	nr
14	1.5	Cs_2CO_3	EtOAc	2	30
15	**1.5**	**Cs_2CO_3**	**Acetone**	**2**	**83**
16	1	Cs_2CO_3	Acetone	2	75
17	2	Cs_2CO_3	Acetone	2	83
18[c]	1.5	Cs_2CO_3	Acetone	2	73
19[d]	1.5	Cs_2CO_3	Acetone	2	81

[a] All reactions were performed with **1a** (0.27 mmol, 1.0 equiv.), **2a** (0.40 mmol, 1.5 equiv.), and base (0.67 mmol, 2.5 equiv.) in solvent (2.0 mL) at room temperature (rt) under N_2. [b] Isolated yields. [c] Cs_2CO_3 (0.53 mmol, 2.0 equiv.). [d] Cs_2CO_3 (0.80 mmol, 3.0 equiv.), nr = no reaction.

Results and discussion

The investigation started by evaluating the reaction of benzofuran-derived azadienes **1a** (1.0 equiv.), and 2-bromoethanol **2a** (1.5 equiv.) with, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.5 equiv.) as a base in MeCN at room temperature (*i.e.*, 25 °C) for 3 h, and the desired (*Z*)-2-benzylidene-3′-tosyl-2*H*-spiro[benzofuran-3,2′-oxazolidine] product **3a** was generated in 28% yield (Table 1; entry 1). After extensive screening of various bases such as K_3PO_4, K_2CO_3, Et_3N, NaH, Cs_2CO_3, and *t*-BuOK, surprisingly it was found that Cs_2CO_3 provided the highest 81% yield in 3 h (entries 2–7). Similarly, organic solvents were also studied, namely 1,4-dioxane, DMF, DMSO, THF, dichloromethane (DCM), toluene, ethyl acetate (EtOAc), and acetone; among the studied solvents, acetone (83%, yield) proved to be the best (entries 8–15). Furthermore, variation in the stoichiometry of 2-bromoethanol did not show promising results (entries 16 and 17). A lower yield was observed when the base loading decreased or increased (entries; 18 and 19).

After optimizing the reaction conditions, we began exploring the scope of the [3 + 2] annulation reaction (Scheme 2). When various *N*-protecting groups such as *N*-SO_2Ph, *N*-SO_2PhBr, *N*-Ns, *N*-SO_2PhCF_3, and *N*-Ms containing azadienes were used as substrates, the corresponding target products **3b–3f** were obtained in good yields (63–76%). We observed that spirocyclization was facilitated by 2-chloroethanol and 2-iodoethanol provided the product with lower yields (20–31%). Various substitutions at *ortho*, *meta*, and *para* positions on the phenyl of azadienes provided products in good to high yields (**3g–3n**). The



Scheme 2 Substrate scope for the synthesis of spiro-oxazolidine derivatives.[a,b] [a]All reactions were performed with **1** (0.27 mmol, 1.0 equiv.), **2** (0.40 mmol, 1.5 equiv.), and Cs_2CO_3 (0.67 mmol, 2.5 equiv.) in 2.0 mL acetone at room temperature for 2 h. [b]Isolated yields. [c]2-Chloroethanol and *t*-BuOK. [d]2-Iodoethanol and *t*-BuOK.

electron-withdrawing groups 4-NO_2 and 3-CF_3, on azadienes, gave superior yield (**3i–3k**, 80–83%) to electron-donating groups 4-OMe and 4-Me (**3g–3h**, 60–68%). Further, the mono-substituted halogens (–F, –Cl, and –Br) on the phenyl ring were well tolerated to produce corresponding products **3l–3n** in good to excellent yields (64–80%), which offers new possibilities for the cross-coupling type of manipulations. The sterically hindered 9-anthryl and 2-naphthyl substituted azadienes delivered products **3o–3p** in 48% and 83% yields, respectively. The azadiene bearing a heterocyclic 2-thiophenyl group was converted into the expected product **3q** in 57% yield. The reaction also extended to *t*-butyl substituents on the azadiene yielding product **3r** in 54% yield. Furthermore, the azadiene-bearing substituent at the benzofuryl ring was readily converted to afford the corresponding product **3s** in high yields (80%). Unfortunately, the reaction of azadienes with 3-bromopropan-1-ol did not give our desired products (**3t**) under optimized reaction conditions.

Further, we expanded this methodology to indanone-derived azadienes **4** and 2-bromoethanol **2a** as model substrates under standard reaction conditions. As shown in Table 2, in the presence of Cs_2CO_3 in acetone at room temperature, the desired product (*Z*)-2-benzylidene-3′-tosyl-2,3-dihydrospiro[indene-1,2′-oxazolidine] **5a** was obtained in 61% yield after 3 h (Table 2, entry 1). Replacing Cs_2CO_3 with inorganic bases such as K_3PO_4, K_2CO_3, NaH, and organic bases DBU, Et_3N, and *t*-BuOK effectively mediated this strategy except K_2CO_3 and Et_3N, while Cs_2CO_3 was the optimal one (entries 2–7). The yields were significantly reduced when we performed the reaction in other solvents, namely MeCN, 1,4-dioxane, DMF, DMSO, THF, DCM, toluene, and EtOAc (entries 11–15); among the studied solvents, MeCN (63%, yield) proved to be the best.

Table 2 Optimization of reaction conditions for the synthesis of spiro-oxazolidine derivatives[a]

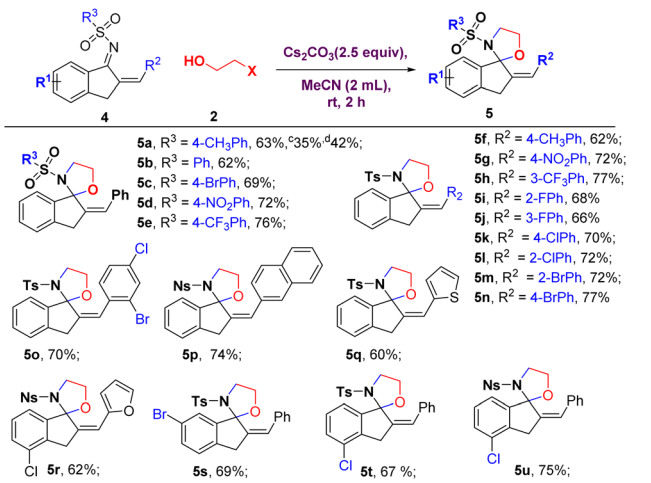
Sr. no.	Base	Solvent	Time (h)	Yield[b] (%)
1	Cs_2CO_3	Acetone	3	61
2	K_3PO_4	Acetone	3	59
3	K_2CO_3	Acetone	12	nr
4	Et_3N	Acetone	12	nr
5	NaH	Acetone	3	45
6	DBU	Acetone	3	21
7	*t*-BuOK	Acetone	5	59
8	**Cs_2CO_3**	**MeCN**	**2**	**63**
9	Cs_2CO_3	1,4-Dioxane	3	53
10	Cs_2CO_3	DMF	6	43
11	Cs_2CO_3	DMSO	12	nr
12	Cs_2CO_3	THF	6	Trace
13	Cs_2CO_3	DCM	12	nr
15	Cs_2CO_3	Toluene	12	nr
16	Cs_2CO_3	EtOAc	6	29

[a] All reactions were performed with **4a** (0.27 mmol, 1.0 equiv.), **2a** (0.40 mmol, 1.5 equiv.), and base (0.67 mmol, 2.5 equiv.) in solvent (2.0 mL) at room temperature (rt) under N_2. [b] Isolated yields. nr = no reaction.

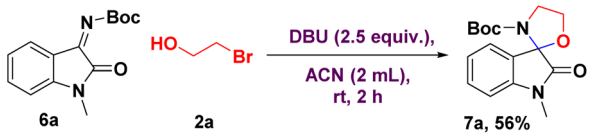
The substrate scope was subsequently investigated with the optimal reaction conditions in hand (Table 2, entry 8). As shown in Scheme 3, various *N*-protecting groups containing azadienes converted into the desired products **5b–5e** in moderate to good yields (62–76%). In our substrate scope generalization studies, 2-chloroethanol and 2-iodoethanol provided products with good yields (35–42%). An examination of the substituent effects on the phenyl ring of azadiene showed that electron-withdrawing (–NO_2, –CF_3, **5g**, **5h**, 72–77%) groups were superior to electron-donating (–CH_3, **5f**, 62%) groups. Mono- and di-substituted halogens (–F, –Cl, and –Br) were well tolerated to produce corresponding products **5i–5o** in good to high yields (66–77%). Azadiene bearing 2-thiophenyl, 2-naphthyl, and 2-furanyl groups were converted into the corresponding products **5p–5r** (60–74%). Halogen-substituted indanyl ring afforded the corresponding products **5s–5u** in good yields (67–75%).

With the optimized reaction conditions, we explored its generality for isatin-derived *N*-Boc ketimine **6a** with 2-bromoethanol **2a** (Scheme 4). It is worth noting that isatin-derived *N*-Boc ketimine (**6a**) also tolerated the [3 + 2] annulation reaction and gave the corresponding oxospiro[indoline-3,2′-oxazolidine] **7a** in good yield (56%). This provides an alternative to the convenient assembly of spiro-oxazolidines from another perspective.

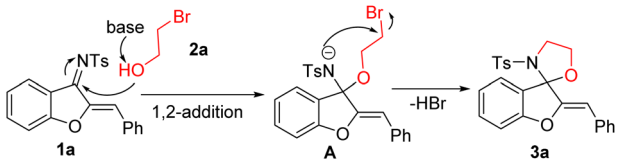
Based on literature reports, a plausible reaction mechanism has been proposed to explain the cascade 1,2-addition followed by the spiro-cyclization that leads to the formation of product (Scheme 5). Initially, the base abstracts the alcoholic proton of **2a**, and then *in situ* generated oxoanion attacks on imine of azadiene **1a** *via* direct addition to deliver intermediate A. Then, displacement of bromine takes place to form the desired product (**3a**).



Scheme 3 Substrate scope for the synthesis of spiro-oxazolidine derivatives.[a,b] [a]All reactions were performed with **4** (0.27 mmol, 1.0 equiv.), **2** (0.40 mmol, 1.5 equiv.), and base (0.67 mmol, 2.5 equiv.) in solvent (2.0 mL) at room temperature (rt) under N_2. [b]Isolated yields. [c]2-Chloroethanol and K_3PO_4. [d]2-Iodoethanol and Cs_2CO_3.

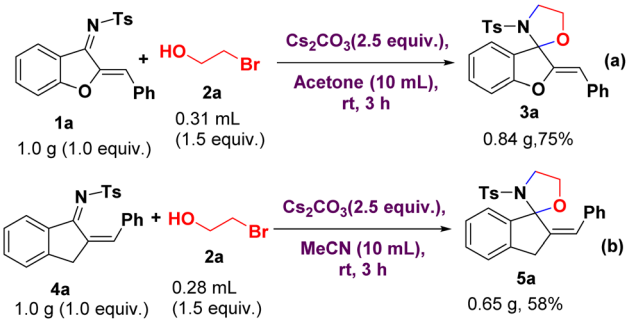


Scheme 4 Synthesis of spiro-oxazolidines derivatives from isatin-derived ketimines.

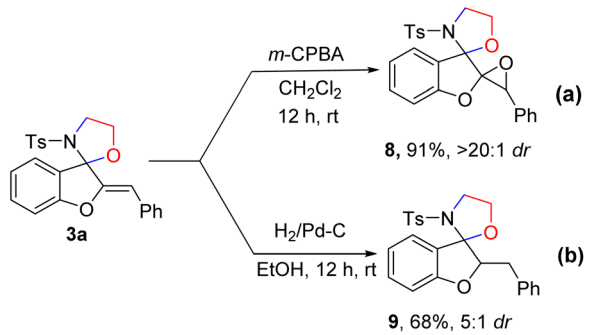


Scheme 5 Plausible reaction mechanism for the synthesis of spiro-oxazolidines.

To demonstrate the synthetic potential of this transformation, we investigated the scaled-up preparation of **3a** and **5a** under the standard reaction conditions (Scheme 6a and b). The reaction of 1.0 g of **1a** and **4a** proceeded smoothly, to deliver products **3a** and **5a** with yields of 75% and 58% in 3 h, respectively. Furthermore, to investigate the potential utility and enrich the spirocyclic compound's molecular complexity, we carried out the derivatization of the product **3a** (Scheme 7). When *m*-CPBA was used for the epoxidation of **3a** in DCM, epoxide **8** was obtained with excellent yields and diastereoselectivity (91%, >20 : 1 dr) in 12 h (Scheme 7a). Various epoxides are valuable building blocks in chemical synthesis and such structural motifs are present in biologically active molecules.[15] Hydrogenation of **3a** readily generated product **9** in good yields with moderate diastereoselectivity (Scheme 7b).



Scheme 6 Gram-scale synthesis.



Scheme 7 Synthetic transformation of product **3a**.

Conclusions

In summary, we have developed a highly regioselective and chemoselective [3 + 2] spiroannulative transformation of aza-dienes. The reaction was carried out in one pot without transition metals and under mild reaction conditions. This method demonstrated good substrate generality, and was successfully applied to large-scale synthesis. Product derivations further confirmed the applicability of this method. However, this feeding sequence-controlled divergent reaction was limited to a special type of substrate.

Data availability

The data supporting this study are available in the published article and its ESI.†

Conflicts of interest

There are no conflicts to declare.

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