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Organocatalytic Remote Asymmetric Inverse-Electron-Demand Oxa-Diels−Alder Reaction of Allyl Ketones with Isatin-Derived Unsaturated Keto Esters

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Abstract. A remote cascade asymmetric inverse-electron-demand oxa-Diels−Alder reaction of allyl ketones with isatin-derived *β,γ*-unsaturated *α*-keto esters has been developed in the presence of a chiral bifunctional squaramide catalyst. Taking advantage of the secondary amide activating group, a series of enantioenriched 3,4'-pyranyl spirooxindole derivatives bearing three contiguous chiral centers were attained in high yields (84 to >99%) with excellent enantioselectivity (96−99% *ee*). Moreover, the gram-scale synthesis and the construction of 1-benzazepine scaffold by the product were also demonstrated.

Keywords: Asymmetric catalysis; Benzazepines; Inverse-electron-demand oxa-Diels−Alder reaction; Spirooxindoles; Squaramide

Introduction

Spirooxindoles are intriguing synthetic targets in organic and medicinal chemistry owing to their wide spectrum of biological and pharmacological activities.[1] In particular, 3,4'-pyranyl spirooxindoles with multiple stereocenters have been proven to be a privileged skeleton in a variety of natural products and pharmaceutical molecules that possess important biological activities, such as p38α inhibitor,[2b] antibacterial agent[2c] and trigolutes A–D[2a,d] (Figure 1). Accordingly, considerable efforts have been devoted to exploit highly efficient methods for the construction of diverse 3,4'-pyranyl spirooxindole scaffolds,[3] especially in an asymmetric manner.[4–6] However, the great majority of the reported protocols mainly focus on Michael/cyclization of dicyano alkylidene oxindoles[4] and Michael/hemiketalization of isatin-derived *β,γ*-unsaturated *α*-keto esters.[5] By contrast, the novel and elegant strategies for enantioselective synthesis of 3,4'-pyranyl spirooxindoles remain limited as yet and some of these methods are associated with limitations of low synthetic efficiency and stereoselectivity.[6] In this context, it is strongly desired to develop simple and practical synthetic methodologies for the efficient construction of enantioenriched 3,4'-pyranyl spirooxindole scaffolds, yet an extreme challenge.

Isatin-derived *β,γ*-unsaturated *α*-keto esters possessing multiple reactive sites have been successfully developed as efficient synthons to construct 3,4'-pyranyl spirooxindole frameworks. Currently, in the existing modes of reaction, [5] the exo unsaturated C–C double bond and C–O double bond participated in the bond forming reactions, leading to the construction of 3,4'-pyranyl spirooxindole structures. Specifically, the isatin-derived *β,γ*-unsaturated *α*-keto esters were served as C3 synthon by reaction with bisnucleophiles (Nu–Nu) to facilitate the synthesis of 3,4'-pyranyl spirooxindoles (Scheme 1a). Although these substantial advances have been achieved, the novel reaction modes of isatin-derived *β,γ*-unsaturated *α*-keto esters have not been developed and there is still some room to explore them in depth.

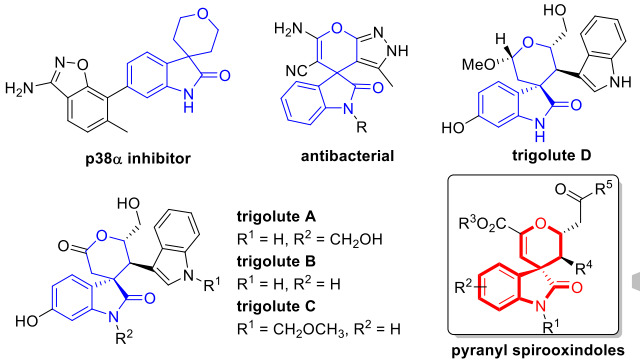

Figure 1. Representative examples of biologically active pyranyl spirooxindoles.

On the other hand, catalytic asymmetric inverse-electron-demand hetero-Diels−Alder (IEDHDA) reactions have emerged as a powerful strategy for accessing optically active six-membered heterocycles especially pyran frameworks, which are a fertile source of pharmacologically active scaffolds

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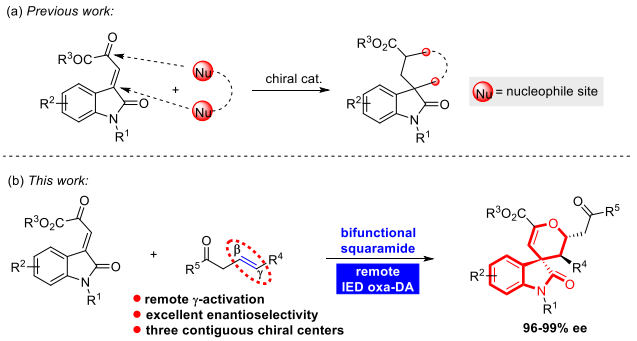
andnaturally occurring molecules.[7] On this account, a vast number of the asymmetric IEDHDA reactions have been investigated and various efficient creative substrates or intermediates possessing IEDHDA reactive activity, such as ketenes,[8] dienamines,[9] aldehydes,[10] enamines,[11] enolates,[12] and enol ethers[13] have been extensively exploited to deliver various chiral six-membered heterocycles. Recently, the allyl ketones which widely applied to α- or γ-selective Michael additions or aldol reactions,[14] have been successfully utilized in a remote asymmetric inverse-electron-demand (IED) oxa-Diels–Alder reaction for construction of pyran skeletons.[15] Nowadays, the development of asymmetric remote activation via organocatalysis is still a challenging research topic in the area of organic synthesis because of the long distance from the activated site (γ- or η-site) to the chiral center of the catalyst.



Scheme 1 Strategies for the construction of 3,4'-pyranyl sprioxindole scaffolds

Based on this background, as a part of our ongoing study on bifunctional squaramide organocatalytic asymmetric cascade strategy on the construction of spirooxindole scaffolds, we report the remote asymmetric IED oxa-Diels–Alder reaction of allyl ketones with isatin-derived β,γ-unsaturated α-keto esters, which could afford a series of highly functionalized 3,4'-pyranyl spirooxindoles with three contiguous chiral carbon centers by using a chiral squaramide catalyst (Scheme 1b).

Results and Discussion

Initially, we chose isatin-derived β,γ-unsaturated α-keto ester **1a** and phenyl allyl ketone **2a** as the model substrates in the presence of 5 mol % quinine-derived squaramide **C1** to test the feasibility. To our delight, the reaction proceeded efficiently to afford the desired β,γ-regioselective IED oxa-DA cycloadduct **3aa** in excellent yield (93%) and enantioselectivity (95% *ee*), albeit with good diastereoselectivity (16:1 *dr*), when the dichloromethane (DCM) was used as solvent at room temperature within 2 minutes (Table 1, entry 1). To further improve the stereoselectivity, a series of bifunctional squaramide catalysts **C2**–**C9** (Figure 2) were subsequently investigated, and the results are outlined in Table 1. A similar result was acquired with catalyst **C3**, while catalysts **C2**, **C5** and **C7** gave

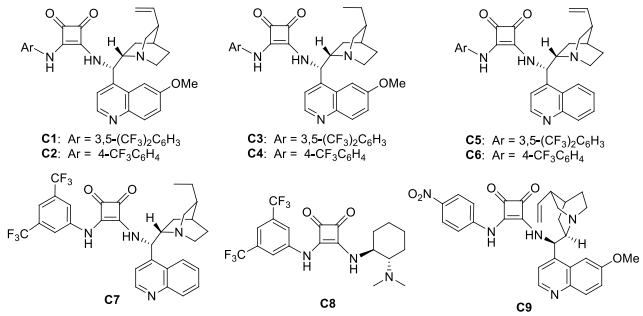
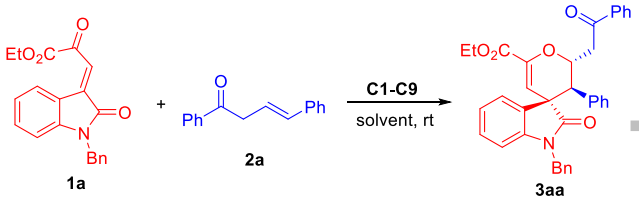


Figure 2 Screened bifunctional squaramide catalysts.

Table 1. Screening of organocatalysts and optimization of the reaction conditions [a]



Entry	Solvent	Cat.	Time [min]	Yield[b] [%]	dr[c]	ee[d] [%]
1	CH_2Cl_2	C1	2	93	16:1	95
2	CH_2Cl_2	C2	2	94	7:1	95
3	CH_2Cl_2	C3	2	91	16:1	94
4	CH_2Cl_2	C4	2	96	>20:1	96
5	CH_2Cl_2	C5	2	90	9:1	94
6	CH_2Cl_2	C6	2	96	19:1	95
7	CH_2Cl_2	C7	2	92	10:1	92
8	CH_2Cl_2	C8	2	93	5:1	71
9	CH_2Cl_2	C9	2	94	10:1	-94
10	$CHCl_3$	C4	5	95	9:1	88
11	DCE	C4	5	97	4:1	87
12	PhMe	C4	5	94	7:1	89
13	CH_3CN	C4	25	91	5:1	60
14	THF	C4	20	96	5.3:1	76
15[e]	CH_2Cl_2	C4	5	96	19:1	95
16[f]	CH_2Cl_2	C4	2	95	8:1	95
17[g]	CH_2Cl_2	C4	15	96	>20:1	99
18[h]	CH_2Cl_2	C4	15	95	>20:1	99

[a] Unless otherwise specified, reactions were carried out with **1a** (0.1 mmol), **2a** (0.12 mmol), and catalyst (5 mol %) in solvent (1.0 mL) at room temperature.
[b] Isolated yields.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by chiral HPLC analysis.
[e] 2.5 mol % catalyst was used.
[f] 10 mol % catalyst was used.
[g] The reaction was performed at 0 °C.
[h] The reaction was performed at −20 °C.

worse reaction outcomes affording product **3aa** with lowerdiastereoselectivities (Table 1, entries 2, 5 and 7). The diastereoselectivity could be improved to 19:1 in the presence of catalyst **C6** (Table 1, entry 6). However, cyclohexanediamine-derived squaramide

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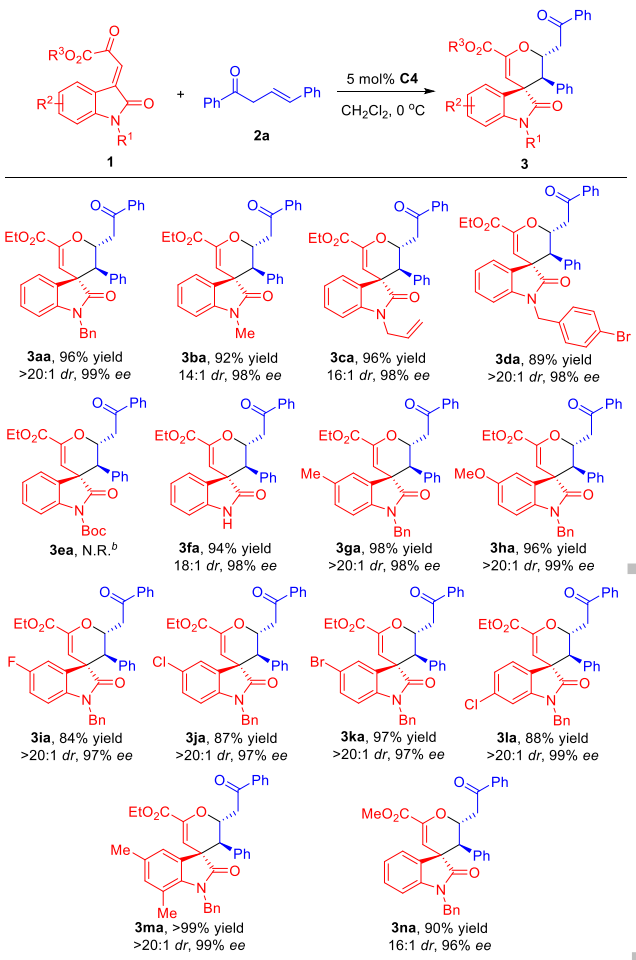
catalyst **C8** furnished **3aa** with a significantly decreased stereoselctivity (5:1 *dr*, 71% *ee*). The pseudo-enantiomer catalyst **C9** led to maintained yield and enantioselectivity, but slightly decreased diastereoselectivity (Table 1, entry 9). Among these cinchona alkaloid-derived squaramides, squaramide **C4** gave the best result affording product **3aa** in 96% yield with excellent diastereo- and enantioselectivity (>20:1 *dr*, 96% *ee*, Table 1, entry 4). Moreover, several thiourea catalysts were also screened and the diastereoselectivity declined significantly albeit with higher enantioselectivity (for details, see the Supporting Information). Accordingly, catalyst **C4** was evaluated as the optimal catalyst for further studies. A survey of the solvent effect showed the reaction media had a tremendous impact on the reaction activity and efficiency. Among chloroform, 1,2-dichloroethane (DCE), toluene, tetrahydrofuran (THF) and acetonitrile, DCM remained the suitable solvent (Table 1, entries 10−14). Subsequently, no improvements were obtained when we tested the effect of catalyst loading with increasing to 10 mol % and reducing to 2.5 mol % respectively (Table 1, entries 15 and 16). Striving as much as possible to further improve the enantioselectivity, lower reaction temperature was evaluated. To our delight, an improvement in enantioselectivity (99% *ee*) was achieved when the temperature was lowered to 0 °C (Table 1, entry 17). Further reducing the temperature to −20 °C, the outcome was unchanged.

With the optimum reaction conditions established, we then commenced to probe the substrate scope and limitation of this reaction. As summarized in Table 2, a variety of isatin-derived *β,γ*-unsaturated *α*-keto esters **1** with different *N*-protected groups were firstly tested under the optimized conditions. It was found that the diastereoselectivity slightly declined when the *N*-protected groups of isatin-derived *β,γ*-unsaturated *α*-keto esters were alkyl substituents or without the substituent (Table 2, **3ba**, **3ca** and **3fa**). There was no reaction for the *N*-Boc protected substrate **1e**, probably due to the electronic equalization of unsaturated bond. Subsequently, various isatin-derived *β,γ*-unsaturated *α*-keto esters **1** with halogens and electron-donating substituents at the 5-, 6-, or 5,7-position on the oxindole ring also participated in the reaction, and the reaction could facilely afford their corresponding products **3ga**−**3ma** in high yields (84 to >99%) with excellent stereoselectivities (>20:1 *dr*, 97−99% *ee*). Besides, isatin-derived *β,γ*-unsaturated *α*-keto ester **1n** was also well tolerated and gave the desired product **3na** in high yield (90%) and excellent enantioselectivity (96% *ee*), but slightly decreased diasteroselectivity (16:1 *dr*).

Table 2. Substrate scope of isatin-derived *β,γ*-unsaturated *α*-keto esters **1b–1n**.[a]

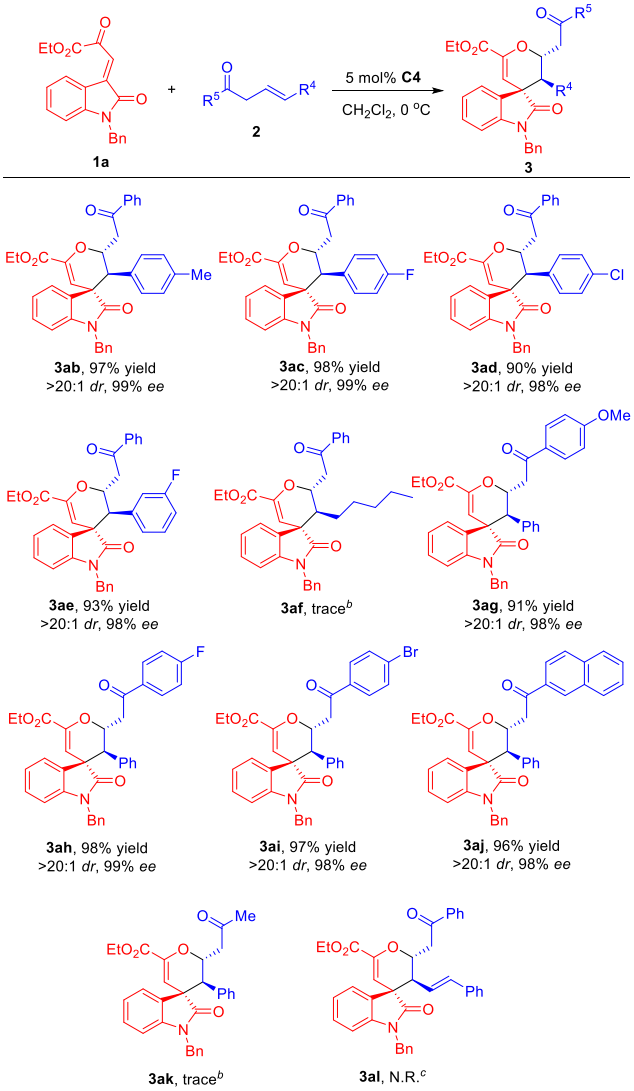


[a] Reaction conditions: **1** (0.10 mmol), **2a** (0.12 mmol), and catalyst **C4** (5 mol %) in CH_2Cl_2 (1.0 mL) were stirred at 0 ℃ for 15 min. The *dr* and *ee* values were determined by ^{1}H NMR and HPLC anslysis, respectively.
[b] No reaction

To further explore the generality of this reaction, structurally diverse allyl ketones **2** were examined under the standard conditions by reacting with **1a**. As shown in Table 3, it appeared that the reaction could proceed smoothly to generate the corresponding products **3** in high yields (90−98%) with consistently excellent stereoselectivities (>20:1 *dr*, 98−99% *ee*) in almost all case, regardless of the electronic and steric properties of the substituents. Methyl, methoxy, fluoro, chloro, and bromo substituents on the phenyl ring in **2b**−**2e** and **2g**−**2i,** were all compatible in this IED oxa-Diels−Alder, affording the corresponding products in high levels of yield and stereoselectivity. Also, **2j** with a sterically bulky 2-naphthalene moiety worked well to give the 3,4'-pyranyl spirooxindole **3aj** in high yield (96%) with excellent diastereo- and enantioselectivitie (>20:1 *dr*, 98% *ee*). As a scope limiting issue, when the substituent R^4 or R^5 was alkyl, only trace reaction was observed in spite of extending reaction time to 48 h, indicating the lower reactivity of substrates **2f** and **2k**. We attempted to synthesize the allyl ketones with a vinyl phenyl substitution and could only successfully synthesize (3*E*,5*E*)-1,6-diphenylhexa-3,5-dien-1-one **2l** with R^4 as a vinyl

phenyl group. However, the substrate was unable to react with **1a**. The stereoscopic configuration of this reaction product **3ai** was unambiguously identified on the basis of single-crystal X-ray diffraction analysis as (2'*R*, 3*S*, 3'*S*) (Figure 3).[16] And the stereochemistry of the other products was tentatively assigned by analogy to **3ai**.

Table 3. Substrate scope of allyl ketones **2b–2k**.[a]



[a] Reaction conditions: **1a** (0.10 mmol), **2** (0.12 mmol), and catalyst **C4** (5 mol %) in CH_2Cl_2 (1.0 mL) were stirred at 0 ℃ for 15 min. The *dr* and *ee* values were determined by ^{1}H NMR and HPLC anslysis, respectively.
[b] Reaction performed for 48 h.
[c] No reaction occurred.

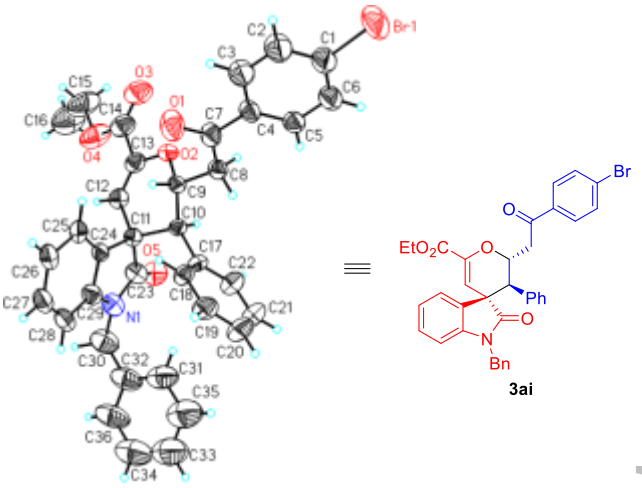


Figure 3. X-ray structure of **3ai** (another two symmetric molecules and one ethyl acetate molecule are omitted for clarity).

To demonstrate the potential utility of the above methodology, a gram-scale reaction of **1f** and **2a** was carried out under the standard conditions. As exemplified in Scheme 2a, the desired 3,4'-pyranyl spirooxindole **3fa** could be obtained in 93% yield with 18:1 *dr* and 99% *ee*, which indicated this present strategy shows promising prospects for mass production. Remarkably, an elegant derivatization of **3fa** into 1-benzazepine **5fa** was developed because of the prevalent presence of 1-benzazepine motifs in various biologically active molecules.[17] As illustrated in Scheme 2b, the *N*-unprotected spirocyclic oxindole **3fa** could be easily transferred to Boc-protected spirocyclic oxindole **4fa** in 90% yield. Inspired by previous studies on the further transformations of spirooxindoles,[6c,18] the structurally complex enantioenriched 1-benzazepine derivative **5fa** with bridge ring could be facilely delivered in 98% yield with 18:1 *dr* and 97% *ee* by treatment of isolated **4fa** with conc. HCl in MeOH at 80 ℃ (for details, see the Supporting Information). And then in the presence of AcOH and 4-bromophenylhydrazine hydrochloride under reflux reactions, **5fa** could be conveniently transformed into **6fa** in moderate yield (Scheme 2c).

In addition, to further validate the synthetic utility of this protocol, the 3,4'-pyranyl spirooxindole **3aa** was reduced to corresponding product **6aa** by treating with $NaBH_4$ in MeOH at 0 ℃. Without further purification, the **6aa** reacted with *p*-toluenesulfonic acid ($TsOH\cdot H_2O$) in toluene at 80 ℃, and the 6:1 *E*/*Z* geometric isomer **7aa** was obtained in 64% yield for the two steps without sacrifice of the enantioselectivity (Scheme 2d). Unfortunately, the expected transesterification product **7aa'** was not observed (for details, see the Supporting Information).

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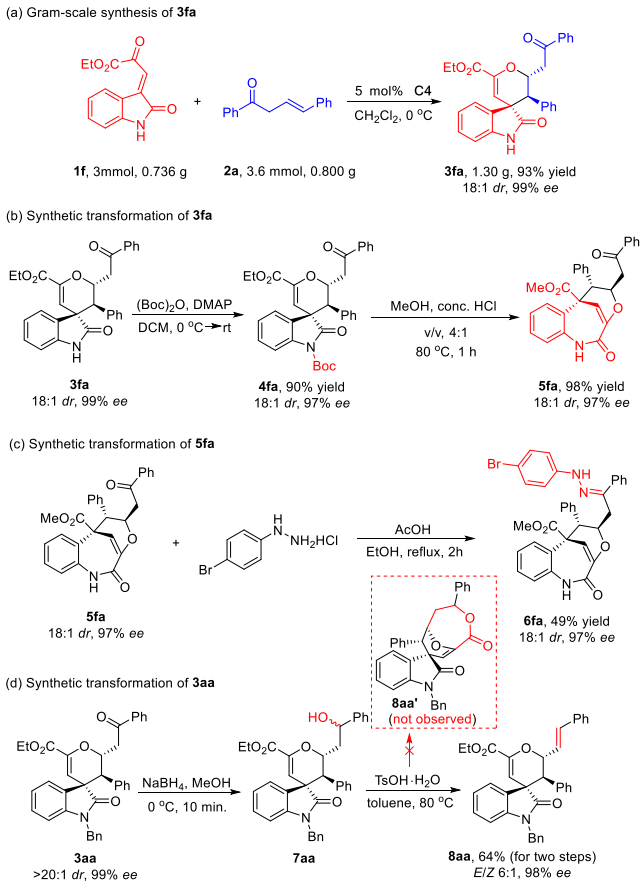
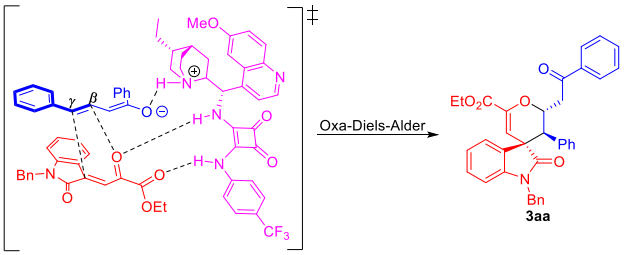


Scheme 2 Further investigation of the potential utility of the reaction.

Finally, on the basis of the absolute configuration of the major isomer **3aa** and the literature reports,[5a,19] a plausible transition-state model was tentatively proposed to account for the stereoselectivity. As depicted in Scheme 3, the substrates are synergistically activated by the squaramide **C4** through the deprotonation of allyl ketone **2a** to form dienolate by the tertiary amine moiety and the activation of isatin-derived *β,γ*-unsaturated *α*-keto esters **1a** by double hydrogen bonds from the amide N−H. And immediately, the generated dienolate interacts *in situ* with the oriented oxindole keto ester, which undergoes the IED oxa-Diels−Alder sequence to generate the product **3aa**.



Scheme 3. Proposed transition state for the reaction.

Conclusion

In conclusion, we have successfully developed a highly efficient method to synthesize chiral 3,4'-pyranyl spirooxindoles via remote cascade asymmetric inverse-electron-demand oxa-Diels−Alder reactions of allyl ketones with isatin-derived *β,γ*-unsaturated *α*-keto esters. By using bifunctional squaramide catalyst, a series of structurally diverse 3,4'-pyranyl spirooxindoles could be obtained in high yields (up to >99%) with excellent stereoselectivities (up to >20:1 *dr*, 99% *ee*). In addition, the potential utility of this methodology has been demonstrated by gram-scale synthesis and further transformations. Remarkably, the bioactive 1-benzazepine motif has been facilely construted by derivatization reaction.

Experimental Section

General Methods

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Column chromatography was performed with silica gel (200-300 mesh). Melting points were determined with an XT-4 melting-point apparatus and are uncorrected. ^{1}H NMR spectra were measured with Bruker Ascend 400 MHz spectrometer in $CDCl_3$, chemical shifts were reported in *δ* (ppm) units relative to tetramethylsilane (TMS) as the internal standard. ^{13}C NMR spectra were measured at 100 MHz (Bruker Ascend 400 MHz spectrometer), chemical shifts were reported in ppm relative to TMS with the solvent resonance as internal standard ($CDCl_3$ at 77.00 ppm). ^{19}F NMR spectra were measured at 377 MHz (Bruker Ascend 400 MHz spectrometer). Proton coupling patterns are described as broad (br) singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). High resolution mass spectra were measured with an Agilent 6520 Accurate-Mass-Q-TOF MS system equipped with an electrospray ionization (ESI) source. Enantiomeric excesses were determined by chiral HPLC analysis using an Agilent 1200 LC instrument with a Daicel Chiralpak IA, IC or AD-H column.

The isatin-derived *β,γ*-unsaturated *α*-keto esters **1a**−**1n** were prepared according to the reported literature procedures.[5] The allyl ketones **2a**−**2h**, **2j** and **2k** were prepared according to the reported literature procedures.[15,20]

Synthesis of allyl ketone 2i

To a solution of 1-(4-bromophenyl)ethan-1-one **S1** (989.9 mg, 5.0 mmol, 1.0 equiv.) and phenyl acetylene **S2** (510.7 mg, 5.0 mmol, 1.0 equiv.) in DMSO (12.5 mL) was added KOH (303.1 mg, 5.5 mmol, 1.1 equiv.). The resulting solution was stirred at 100 °C for 1 h. The reaction mixture was cooled to room temperature, and the reaction was diluted with H_2O (12.5 mL), neutralized with saturated aqueous NH_4Cl and extracted with ethyl acetate (4×12.5

mL). The organic extract was washed with H_2O (3×10 mL), brine (10 mL) and dried with anhydrous $NaSO_4$. After removal of ethyl acetate, the product was purified by flash chromatography (petroleum ether/ethyl acetate, v:v = 30:1) to afford **2i** as a white solid (783.1 mg, 52% yield).

General procedure for the enantioselective synthesis of compounds 3

Isatin-derived *β,γ*-unsaturated *α*-keto esters **1** (0.10 mmol), allyl ketones **2** (0.12 mmol), and **C4** (2.8 mg, 0.005 mmol) were dissolved in CH_2Cl_2 (1.0 mL), and the mixture was stirred at 0 ℃ for 15 minutes. After completion of the reaction, the reaction mixture was concentrated and directly purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1 to 3:1) to afford the pure products **3** as solid.

Synthesis of compound 3fa on a preparative scale

Isatin-derived *β,γ*-unsaturated *α*-keto ester **1f** (98.1 mg, 0.4 mmol, 1.0 equiv.), allyl ketone **2a** (106.7 mg, 0.48 mmol, 1.2 equiv.), and **C4** (11.2 mg, 0.02 mmol) were dissolved in CH_2Cl_2 (4.0 mL), and the mixture was stirred at 0 ℃ for 45 minutes. After completion of the reaction, the reaction mixture was concentrated and directly purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1 to 2:1) to afford the pure product **3fa** as a white solid.

Synthesis of compound 4fa

A mixture of spirooxindole **3fa** (140.9 mg, 0.3 mmol, 1.0 equiv.) and DMAP (3.7 mg, 0.03 mmol, 0.1 equiv.) in DCM (2.0 mL) was cooled in an ice-bath with stirring and a solution of $(Boc)_2O$ (78.6 mg, 0.36 mmol, 1.2 equiv.) in DCM (0.5 mL) was added slowly. The solution was stirred another 2 h at room temperature. The reaction was evaporated under reduced pressure and directly purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1 to 3:1) to afford the pure product **4fa** as a light yellow solid.

Synthesis of compound 5fa

A glass vial equipped with a magnetic stirring bar was charged with **4fa** (56.8 mg, 0.10 mmol) in a mixture solvent (1.5 mL, v/v, MeOH: con. HCl = 4:1), and refluxed at 80 ℃ for 1 hour. After the reaction was completed, the reaction mixture was evaporated under reduced pressure and directly purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1 to 1:1) to afford the pure product **5fa** as a light yellow solid.

Synthesis of compound 6fa

A glass vial equipped with a magnetic stirring bar was charged with **5fa** (45.3 mg, 0.10 mmol) and 4-bromophenylhydrazine hydrochloride in ethanol (1.0 mL), and two drops of acetic acid was added. The reaction mixture was boiled under reflux for 2 hours. After the reaction was completed, the reaction mixture was evaporated under reduced pressure and directly purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford the pure product **6fa** as a light yellow solid.

Synthesis of compound 8aa

A glass vial equipped with a magnetic stirring bar was charged with **3aa** (55.8 mg, 0.10 mmol, 1.0 equiv.) in methanol (1.0 mL) at 0 ℃. Then $NaBH_4$ (7.6 mg, 0.20 mmol, 2.0 equiv.) was added at the same temperature for 10 minutes. After full conversion of the first step, extraction, dry, concentration was followed, $TsOH·H_2O$ (19.0 mg, 0.10 mmol, 1.0 equiv.) and toluene (1.0 mL) were added into crude product **7aa**. And then stirred at 80 ℃ for a further 1 h, after the reaction was completed, the reaction mixture was evaporated under reduced pressure and directly purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 6:1 to 4:1) to afford the 6:1 *E*/*Z* geometric isomers **8aa** as a white solid.

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FULL PAPER

Organocatalytic Remote Asymmetric Inverse-Electron-Demand Oxa-Diels−Alder Reaction of Allyl Ketones with Isatin-Derived Unsaturated Keto Esters

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