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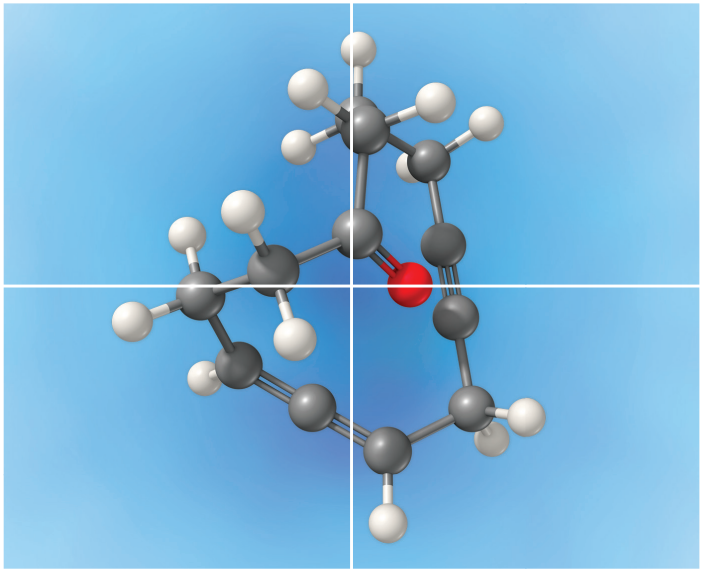

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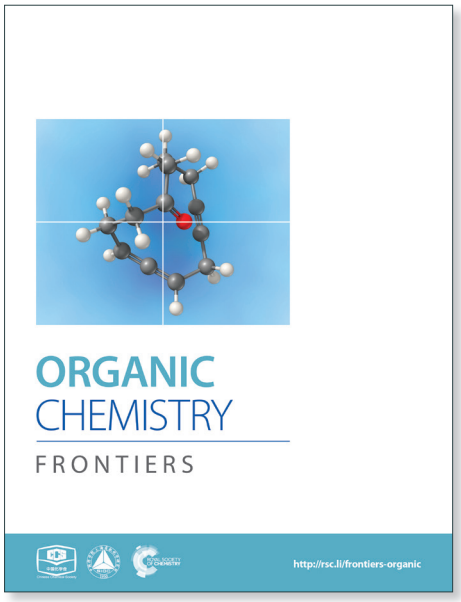

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ARTICLE

Diastereoselective synthesis of cyclopentanone-fused spirooxindoles by N-heterocyclic carbene-catalyzed homoenolate annulation with isatilidenes†

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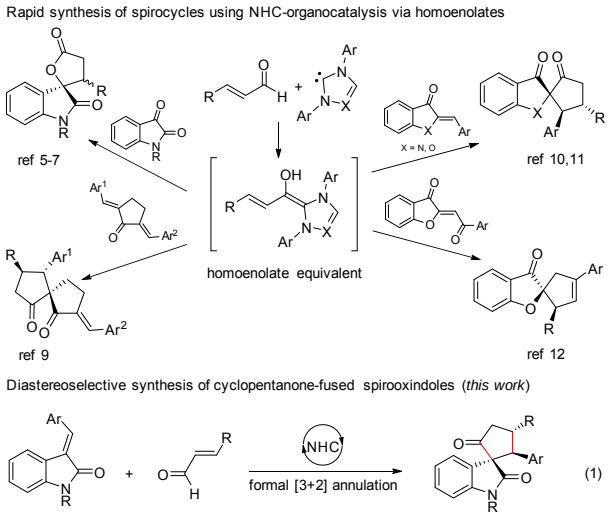
N-Heterocyclic carbene (NHC)-catalyzed formal [3+2] annulation of α,β-unsaturated aldehydes with *N*-substituted isatilidenes resulting in the diastereoselective synthesis of cyclopentanone-fused spirooxindoles is demonstrated. Mechanistically, the reaction proceeds via the generation of homoenolate equivalent intermediates from NHC and enals, which on interception with isatilidenes afford spiro-heterocyclic compound bearing an all-carbon quaternary spiro-center in moderate to good yield and and generally with high diatereoselectivity. Moreover, functionalization of the spirooxindoles as well as the initial studies on the enantioselective version of this reaction are presented.

Introduction

N-heterocyclic carbenes (NHCs)-based organocatalysis have been widely explored for the umpolung of aldehydes resulting in a variety of unique organic transformations.[1] Ever since the seminal discovery independently by Glorius[2] and Bode[3] in 2004 on NHC-induced generation of homoenolate equivalents from α,β-unsaturated aldehydes followed by the formal [3+2] annulation with aldehydes leading to γ-butyrolactones, the NHC-homoenolate concept has been utilized for the construction of several acyclic compounds, carbocycles, heterocycles, and even spiroheterocycles.[4] In 2006, Nair and co-workers demonstrated the NHC-catalyzed homoenolate formal [3+2] annulation with 1,2-dicarbonyl compounds for the synthesis of spiro γ-butyrolactones (Scheme 1).[5] Interestingly, the enantioselective version of the spirooxindole γ-butyrolactone synthesis was disclosed by Ye and co-workers[6] using chiral NHCs and later by Scheidt and co-workers using a cooperative NHC/Lewis acid strategy.[7] Moreover, the enantioselective synthesis of spirooxindole γ-butyrolactams by NHC-catalyzed homoenolate annulation with isatin-derived ketimines was disclosed by Chi and co-workers.[8]

The stereoselective and formal [3+2] annulation route to spirocyclopentanones by the NHC-catalyzed reaction of enals with cyclic dienones was demonstrated by the Nair group in 2008.[9] Moreover, highly enantioselective formal [3+2] annulation reaction of enals with azaaurones/aurones leading to the synthesis of spiroheterocycles was recently disclosed by the Glorius group[10] and Zhao group.[11] Very recently, NHC-catalyzed reaction of enals with benzoylidene benzofuran 3-ones (aurone analogs) resulting in the synthesis of cyclopentene-fused spirobenzofuran 3-ones was uncovered by the Nair group.[12] Furthermore, the enantioselective [4+3] annulation reaction of NHC-bound homoenolate equivalents with *o*-quinone methides to access 2-benzoxopinones was developed independently by Ye group[13] and Scheidt group.[14]



Scheme 1. NHC-catalyzed routes to spirocyclic systems

In the context of our interest in the reaction of NHC-bound homoenolate equivalents with electrophilic systems,[15] we have recently reported the NHC-homoenolate annulation with 2'-hydroxy chalcones[15b] and 2-enoylpyridines/2-enoyl pyridine

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† Electronic Supplementary Information (ESI) available: Details of the experimental procedure, characterization data of all compounds, and single crystal X-ray data of **3a**. CCDC 1413690. For details, see: DOI: 10.1039/x0xx00000x

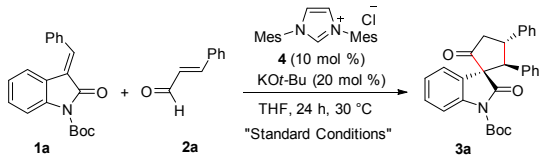
N-oxides[15a] resulting in the diastereoselective synthesis of cyclopentane-fused coumarins and β-lactone-fused cyclopentanes respectively. Inspired by these results, we envisioned that homoenolate annulation with isatilidenes could result in a straightforward synthesis of spirooxindoles. Herein, we report the highly diastereoselective formal [3+2] annulation reaction of enals with isatilidenes resulting in the formation of cyclopentanone-fused spirooxindole derivatives possessing an all-carbon quaternary spiro-stereogenic center (Scheme 1, eq 1).[16,17] It is noteworthy that spirooxindoles are associated with interesting biological properties and this core structure can be found in various natural products and medicinally relevant molecules.[18]

Results and discussion

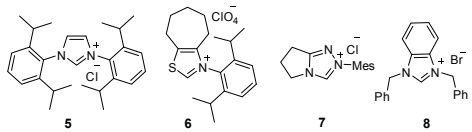
Given the importance of spirooxindole-based heterocycles and in view of our interest in NHC-organocatalysis, the present study was initiated by treating the *N*-Boc isatilidene **1a** with cinnamaldehyde **2a** in the presence of NHC generated from the imidazolium salt **4** using KO-*t*Bu as the base. To our delight, under these conditions, the cyclopentanone-fused spirooxindole **3a** was formed in 51% yield and an excellent diastereoselectivity of >20:1 (Table 1, entry 1). The *N*-protection of isatilidene **1a** was mandatory for the reaction and attempted experiments with *N*-unprotected **1a** was not successful. The reactions performed using sterically demanding NHCs derived from the precursors **5-7** furnished inferior results (entries 2-4). However, reaction attempted using the imidazolium salt **8** afforded **3a** in 59% yield, but with reduced diastereoselectivity of 3:1 (entry 5). Hence, further studies were carried out using NHC generated from **4**. A rapid screening of bases revealed that other organic (including DBU and Et_3N) and inorganic (including K_2CO_3 and Cs_2CO_3) bases are not beneficial for this spiroannulation reaction (entries 7-10). Variation of solvents indicated that except THF, other solvents furnished very low yield of the desired product **3a** (entries 11-14). Interestingly, when the reaction was performed using 15 mol % of **4** and 30 mol % of KO*t*-Bu, the yield of **3a** was improved to 59% maintaining the excellent diastereoselectivity (entry 15). Under this condition, use of 1.5 equiv of enal **2a** afforded **3a** in 71% yield and >20:1 diastereoselectivity (entry 16).[19] Further attempts to improve the yield of **3a** by the use of Lewis acids and Brønsted acids as additives were unsuccessful (not shown in Table 1). It may be mentioned that under the present reaction conditions, the spirocyclopentene[12] as well as the [4+3] annulation products were not observed.[13,14]

The spirooxindole derivative **3a** was characterized using routine spectroscopic techniques. Finally, the structure and the relative stereochemistry of the three chiral centers in **3a** was confirmed by using single-crystal X-ray analysis (Figure 1).[20]

Table 1. Optimization of reaction conditions[a]



entry	variation of the standard conditions[a]	yield of **3a** (%)[b,c]
1	none	51
2	**5** instead of **4**	<5
3	**6** instead of **4**	21
4	**7** instead of **4**	<5
5	**8** instead of **4**	59[d]
6	50 °C instead of 30 °C	41
7	DBU instead of KO*t*-Bu	29
8	Et_3N instead of KO*t*-Bu	<5
9	K_2CO_3 instead of KO*t*-Bu	23
10	Cs_2CO_3 instead of KO*t*-Bu	<5
11	DME instead of THF	<5
12	1,4-dioxane instead of THF	11
13	CH_2Cl_2 instead of THF	<5
14	toluene instead of THF	26
15	15 mol % of **4** and 30 mol % of KO*t*-Bu	59
16	*15 mol % of **4**, 30 mol % of KO*t*-Bu and 1.5 equiv of **2a***	*71*



[a] Standard conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), **4** (10 mol %), KO*t*-Bu (20 mol %), THF (1.0 mL), 30 °C and 40 h. [b] Isolated yield of the product. [c] The diastereoselectivity observed by ^{1}H NMR of crude products was >20:1 unless indicated. [d] The *dr* of 3:1 was observed.

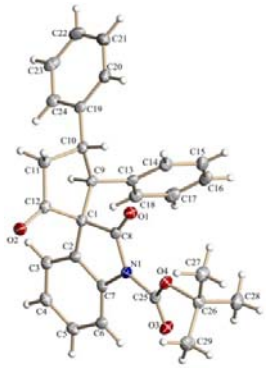
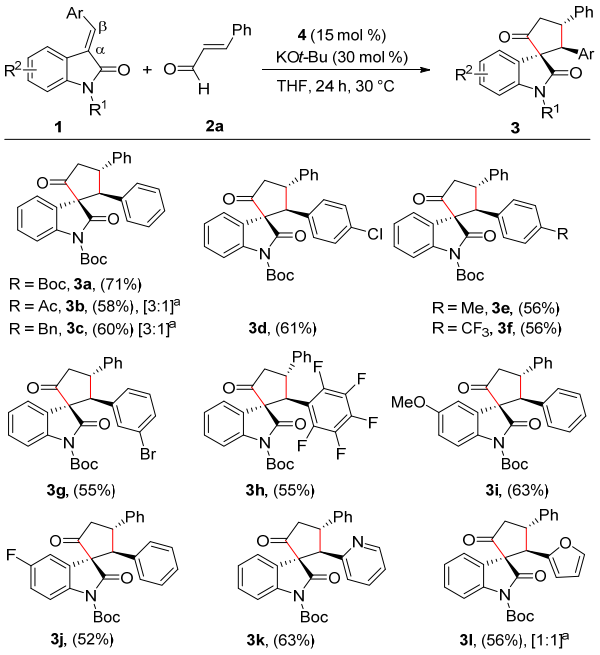


Figure 1. ORTEP diagram of **3a** (50% probability factor for the thermal ellipsoids)

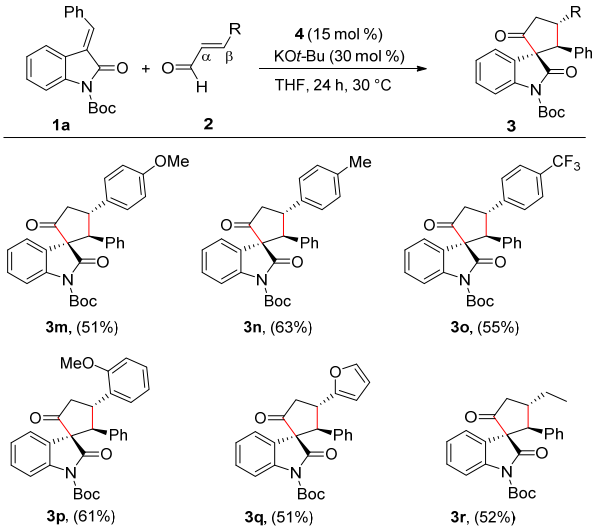
With the reaction conditions for the diastereoselective synthesis of cyclopentanone-fused spirooxindoles, we then examined the scope and limitations of this annulation reaction. First, we studied the variation of the isatilidene moiety (Scheme 2). When acetyl protection on nitrogen was used, the product **3b** was formed in 58% yield, but with reduced diastereoselectivity of 3:1. However, *N*-benzyl protection afforded the desired product **3c** in 60% yield in >20:1 *dr*. A series of isatilidenes with different substitution on the β-aryl ring underwent smooth annulation reaction resulting in the formation of the spirooxindoles in moderate to good yields (**3d-3h**). The substitution at the β-aryl ring of **1** did not affect

the diastereoselectivity of the reaction and in all cases the spirocompound was isolated in >20:1 *dr*. It is noteworthy that the pentafluoroaryl substitution on the β-aryl ring furnished the expected product **3h** in 55% yield. Moreover, electron-releasing and -withdrawing substituents are tolerated at the indolin-2-one moiety, and the desired products are formed in moderate to good yields (**3i, 3j**). In addition, β-heteroaryl substituted isatilidenes also afforded the spiroheterocycles in moderate to good yields (**3k, 3l**). Notably, in the case of β-furyl substrate, the product **3l** was formed in 56% yield and 1:1 *dr*. Disappointingly, β-alkyl substituted isatilidenes did not undergo the present homoenolate annulation reaction under the optimized reaction conditions.



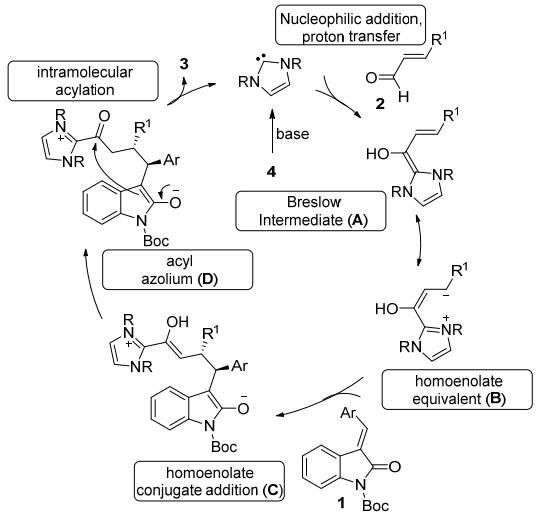
Scheme 2. Substrate scope for the synthesis of cyclopentanone-fused spirooxindoles. Variation of isatilidenes. General reaction conditions: **1** (0.50 mmol), **2a** (0.75 mmol), **4** (15 mol %), KO*t*-Bu (30 mol %), THF (2.0 mL) at 30 °C for 40 h. Isolated yields of products after flash column chromatography are provided and *dr* is >20:1 unless indicated. [a] The diastereomeric ratio determined by ^{1}H NMR of the crude reaction mixture.

Next, we evaluated the scope of the reaction with various α,β-unsaturated aldehyde derivatives. Interestingly, electron-realeasing and -withdrawing groups at the 4-position of β-aryl ring are well- tolerated and the corresponding cyclopentanone-fused spiroheterocycles are formed in moderate yields (**3m-3o**). Moreover, 2-methoxy cinnamaldehyde afforded the desired product **3p** in 61% yield. Additionally, β-furyl enal afforded the desired spiroheterocycle **3q** in 51% yield. Gratifyingly, an alkyl substituent at the β-position of the enal was also tolerated and the target product **3r** was isolated in 52% yield. In all cases, the cyclopentanone-fused spiroheterocycles were formed in high diastereoselectivity of >20:1.



Scheme 3. Variation of enals. General reaction conditions: **1a** (0.50 mmol), **2** (0.75 mmol), **4** (15 mol %), KO*t*-Bu (30 mol %), THF (2.0 mL) at 30 °C for 40 h. Isolated yields of products are provided and *dr* is >20:1 in all cases.

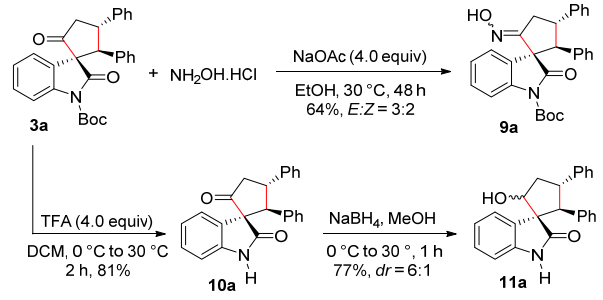
The tentative mechanism of this transformation is shown in Scheme 4. The free carbene generated from the imidazolium salt **4** undergoes nucleophilic addition to the enal followed by a proton transfer allows the formation of the nucleophilic Breslow intermediate (**A**).[21] This is in resonance with the homoenolate equivalent **B**. The selective conjugate addition of homoenolate equivalent to isatilidene **1** generates the enol intermediate **C**, which on tautomerization forms the acyl azolium intermediate **D**. An intramolecular *C*-acylation can result in the formation of the spirocyclic compound **3** regenerating the free carbene.



Scheme 4. Proposed mechanism of the reaction

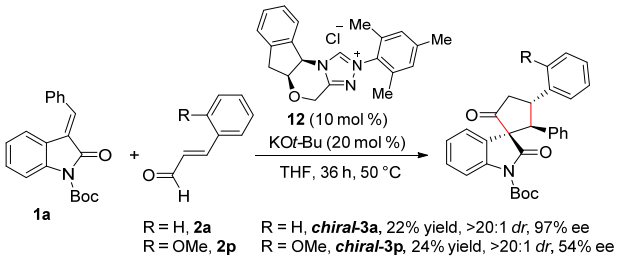
We also carried out functionalization of the cyclopentanone-fused spirooxindole **3a**. Treatment of **3a** with hydroxylamine hydrochloride under basic conditions afforded the corresponding spirooxindole oxime **9a** in 64% yield and in

E:Z ratio of 3:2 (Scheme 5). The product **9a** could be a substrate for the Beckmann rearrangement leading to the spiro δ-lactams. Moreover, *N*-Boc deprotection under trfluoroacetic acid (TFA) conditions furnished *N*-unprotected spirooxindole derivative **10a** in 81% yield. Selective reduction of the keto group in **10a** using $NaBH_4$ resulted in the formation of the cyclopentanol-fused spirooxindole **11a** in 77% yield and a moderate *dr* of 6:1.



Scheme 5. Functionalization of cyclopentanone-fused spirooxindoles

Furthermore, we performed experiments on the enantioselective version of this reaction.[22] Reaction of *N*-Boc isatilidene **1a** with enal **2a** in the presence NHC generated from the chiral amino indanol-derived triazolium salt **8** using KO-*t*Bu as the base resulted in the enantioselective synthesis of the cyclopentanone-fused spirooxindole ***chiral*-3a** in 22% yield, and excellent diastereoselectivity of >20:1 and in 97% ee (Scheme 6). Although the yield of ***chiral*-3a** is less, the high diastereoselectivity and enantioselectivity observed in this reaction is noteworthy. Notably, when the reaction of **1a** was performed with 2-methoxy cinnamaldehyde **2p** under the present reaction conditions, the desired product ***chiral*-3p** was isolated in 24% yield and in high diastereoselectivity of >20:1, but the ee value dropped to 54%.



Scheme 6. Enantioselective synthesis of cyclopentanone-fused spirooxindoles

Conclusion

In conclusion, we have developed the NHC-catalyzed reaction of α,β-unsaturated aldehydes with isatilidene derivatives resulting in the diastereoselective synthesis of cyclopentanone-fused spirooxindoles bearing an all-carbon quaternary spiro-stereogenic center. The reaction proceeds via the generation of homoenolate intermediates, which underwent a formal [3+2] annulation reaction to afford the desired products. In view of the interesting biological properties of spirooxindoles, and their ubiquity in various natural products and medicinally important molecules, it is anticipated that the cyclopentanone-fused spirooxindoles synthesized herein may have potential biological properties.

Experimental section

*Procedure for the synthesis of **3a***. To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the imidazolium salt **4** (0.027 g, 0.075 mmol) and the (*E*)-3-benzylidene-2-oxoindoline-1-carboxylate **1a** (0.160 g, 0.5 mmol). Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added THF (2.0 mL) under argon atmosphere. The resultant reaction mixture was kept stirring at 30 °C. To this mixture was added *trans* cinnamaldehyde **2a** (0.099 g, 94 µL, 0.75 mmol) followed by KO*t*-Bu (0.017 gm, 0.15 mmol). Then the reaction mixture was stirred at 30 °C for 40 h. After 40 h, the solvent was evaporated and the crude residue was purified by flash column chromatography to afford *tert*-butyl -2',5-dioxo-2,3-diphenyl spiro[cyclopentane-1,3'-indoline]-1'-carboxylate **3a** as a white solid (0.161 g, 71% yield).

R_f (Pet. ether /EtOAc = 80/20): 0.61; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.66 (d, *J* = 8.1 Hz, 1H), 7.35-7.25 (m, 7H), 7.20-7.16 (m, 1H), 7.09-7.02 (m, 5H), 4.89-4.81 (m, 1H), 4.01 (d, *J* = 12.3 Hz, 1H), 3.45-3.38 (m, 1H), 2.84-2.77 (m, 1H), 1.52 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 209.27, 170.84, 148.42, 141.00, 140.58, 134.27, 129.42, 128.93, 128.37, 127.81, 127.54, 127.18, 126.76, 125.06, 123.21, 115.30, 84.50, 70.97, 60.67, 47.66, 41.06, 28.09. **HRMS** calculated $[M+Na]^+$ for $C_{29}H_{27}O_4NNa$: 476.1832, found: 476.1833. **FTIR (cm$^-$1)** 3023, 2403, 1742, 1661, 1607, 1482, 1354, 1258, 1216, 1150, 1092, 1026, 928, 842, 767, 670.

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