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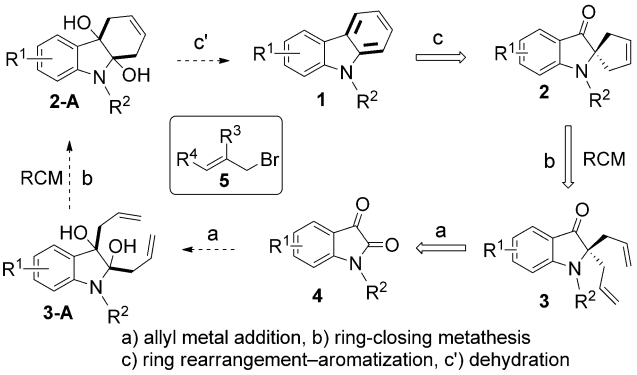
# Synthesis of Carbazole Alkaloids by Ring-Closing Metathesis and Ring Rearrangement–Aromatization

*Kalyan Dhara, Tirtha Mandal, Joydeb Das, and Jyotirmayee Dash**

***Abstract:*** *A process for the assembly of carbazole alkaloids has been developed on the basis of ring-closing metathesis (RCM) and ringrearrangement–aromatization (RRA) as the key steps. This method is based on allyl Grignard addition to isatin derivatives to provide smooth access to 2,2-diallyl 3-oxindole derivatives through a 1,2-allyl shift. The diallyl derivatives were used as RCM precursors to afford a novel class of spirocyclopentene-3-oxindole derivatives, which underwent a novel RRA reaction to afford carbazole derivatives. The synthetic sequence to carbazoles was shortened by combining the RCM and RRA steps in an orthogonal tandem catalytic process. The utility of this methodology was further demonstrated by the straightforward synthesis of carbazole alkaloids, including amukonal derivative, girinimbilol, heptaphylline, and bis(2-hydroxy-3-methylcarbazole).*




***Scheme 1.*** A general approach to carbazoles.

Carbazoles are common motifs in natural products and biologically active molecules.[1] Although diverse synthetic routes to carbazoles have been described, a general and efficient route to carbazole alkaloids is still desirable.[1–4] One of the most commonly used synthetic methods to access carbazole derivatives involves the Buchwald–Hartwig coupling of arylamines with aryl halides, followed by oxidative cyclization.[1,2] A direct catalytic C–H amination process[2g] and iron-mediated process[4f,g] have also been developed for the synthesis of carbazole derivatives. Approaches based on olefin metathesis[5] have also received considerable attention for the construction of aromatic and heteroaromatic compounds.[1a,5e,6] Two methods have been reported for the synthesis of carbazole derivatives from 3-formyl-substituted indoles through RCM–aromatization sequences.[3]

Herein, we disclose a facile synthetic approach to naturally occurring carbazole alkaloids from isatin derivatives by the use of RCM[7] and a novel rearrangement as the key steps. We anticipated that carbazole derivatives **1** could be constructed by the ring rearrangement–aromatization of spirocyclic isatin derivatives **2**, which could be derived from 2,2-diallyl 3-oxindoles **3** by RCM (Scheme 1). The 2,2-diallyl 3-oxindoles **3** could be readily prepared by the addition of allyl metal reagents to the readily available isatin derivatives. Substituted allyl bromides **5** could be used to form the allylic organometallic reagent to enable access to various analogues of carbazole derivatives. Theoretically, carbazoles **1** can be accessed from isatins by a) the addition of an allyl metal reagent to give **3-A**, b) RCM of the diallyl compound **3-A**, and c) aromatization through dehydration of the tetrahydrocarbazole intermediate **2-A** (Scheme 1).

To examine the feasibility of the proposed approach, we prepared a variety of N-substituted isatins **4a–h** (see the Supporting Information) and treated them with an allyl Grignard reagent. We were delighted to observe that when *N*-methylisatin (**4a**) was treated with allylmagnesium bromide in $Et_2O$–THF at 0 °C and the mixture was allowed to warm to room temperature, the 2,2-diallyl-3-oxindole **3a** was formed in 64% yield (Scheme 2). The addition of allylmagnesium chloride to *N*-methylisatin was previously reported to give compound **3a** in low yield (20%).[8] The scope of this Grignard reaction was then explored. Both electron-rich and electron-deficient N-substituted isatins **4** afforded the corresponding 2,2-diallylindolin-3-ones **3** in acceptable yields. The Grignard addition presumably proceeds by the formation of an intermediate **A**, which further reacts with excess allylmagnesium bromide to form the intermediate **B**. The elimination of OMgBr may lead to the indolinium intermediate **C**, which undergoes a 1,2-shift of the allyl group with the elimination of OMgBr to afford the diallyl compound **3** (Scheme 3).

We next prepared unsymmetrical diallyl 3-oxindoles **3i–k** by sequential allyl metal addition to isatins **4** (Scheme 4). Allyl indium addition took place chemoselectively at the C3 position of isatin derivatives. The reaction of isatins **4** with allyl bromides **5a–c** in the presence of indium metal and sodium iodide in DMF at room temperature afforded 3-allyl 3-hydroxy-2-oxindole derivatives **6a–c** in excellent yield (Scheme 4).[9] The subsequent addition of allylmagnesium

[*] K. Dhara,[+] T. Mandal,[+] J. Das, Prof. Dr. J. Dash
Department of Organic Chemistry
Indian Association for the Cultivation of Science
Jadavpur, Kolkata-700032 (India)
E-mail: ocjd@iacs.res.in
[+] These authors contributed equally.

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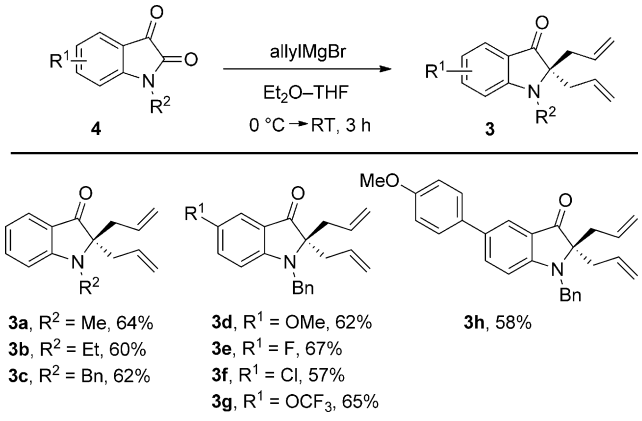
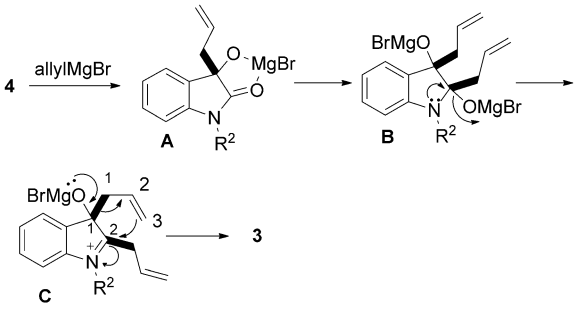



***Scheme 2.*** Exploration of the allyl Grignard addition to isatin derivatives. Reactions conditions: **4** (2.0 mmol, 1.0 equiv), allylmagnesium bromide solution (1 M in $Et_2O$, 5.0 equiv), $Et_2O$–THF (10 mL), room temperature, 3 h. Bn = benzyl.

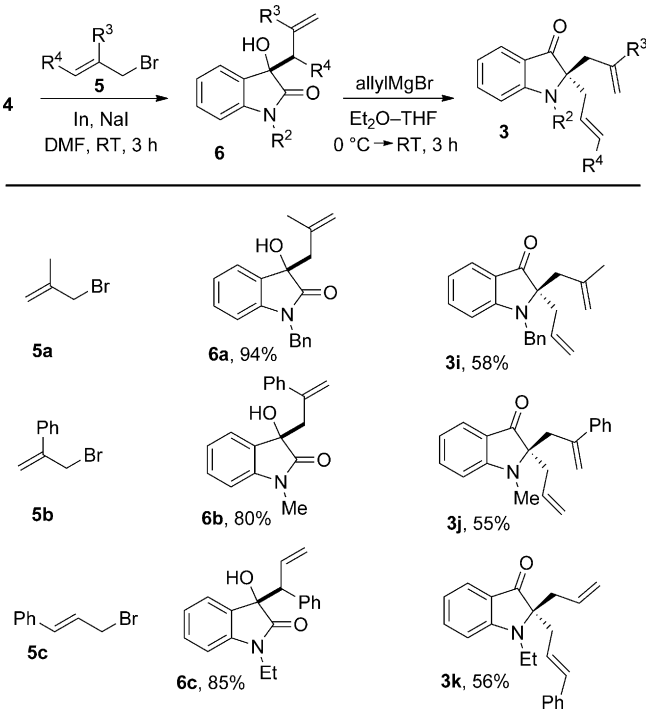



***Scheme 3.*** Proposed rearrangement pathway for the formation of 2,2-diallyl 3-oxindoles **3**.

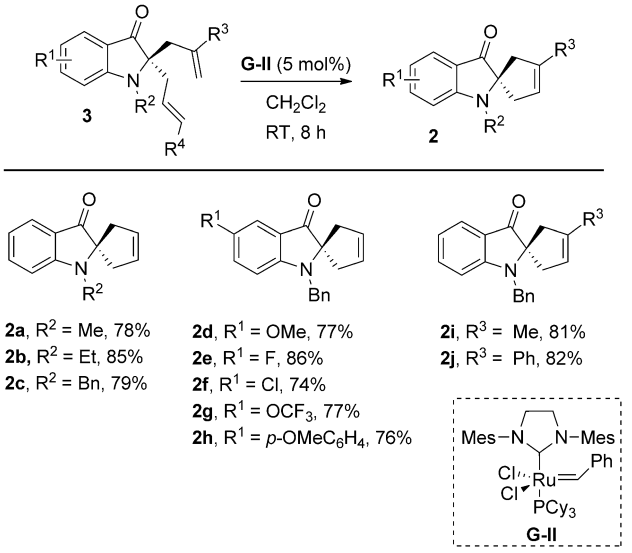
bromide to the monoallyl 2-oxindoles **6a–c** afforded 2,2-diallyl 3-oxindoles **3i–k** in good yield through the 1,2-allyl-shift pathway (Scheme 3).

Ring-closing metathesis (RCM) of the synthesized 2,2-diallyl 3-oxindole precursors **3** was next explored (Scheme 5). RCM of the dialkene **3a** with the Grubbs second-generation catalyst (**G-II**; 5 mol%) in $CH_2Cl_2$ at room temperature provided the desired 2-spirocyclopentene-3-oxindole derivative **2a** in 78% yield. Electron-rich and electron-deficient dialkenyl 3-oxindoles **3** were converted into the corresponding spirocyclic compounds **2** in excellent yield. The structure of the spirocyclic compound **2e** was confirmed by single-crystal X-ray analysis (see Figure S1 in the Supporting Information). RCM of 2-allyl-2-cinnamyl-3-oxindole **3k** afforded the spirocyclic compound **2b** in 85% yield. Several synthetic methods have been reported for the preparation of 3-spirocyclic 2-oxindole derivatives,[10] but few methods are known to give spirocyclic 3-oxindole derivatives.[11] The protocol described herein provides facile access to a novel class of spirocyclic 3-oxindole derivatives. Previously, we reported RCM-based approaches for the synthesis of spirocyclic thiazolidine diones and hydantoins.[12]

To our delight, oxindole **2a** reacted with *p*-toluenesulfonic acid (TsOH; 10 mol%) in toluene at 80°C to afford the carbazole derivative **1a** in 88% yield (Scheme 6; see also



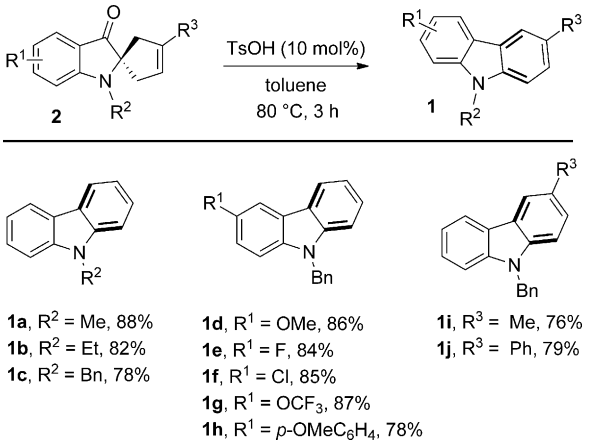

***Scheme 4.*** Sequential addition of allylindium[a] and Grignard reagents[b] to isatin derivatives.[a] Reaction conditions: **4** (2.0 mmol, 1.0 equiv), allyl bromide (1.6 mmol), NaI (1.6 mmol), indium metal (1 mmol), DMF, room temperature. [b] Reaction conditions: **6** (2.0 mmol, 1.0 equiv), allylmagnesium bromide solution (1 M in $Et_2O$, 3.0 equiv), $Et_2O$–THF (10 mL), room temperature, 3 h. DMF = *N*,*N*-dimethylformamide.




***Scheme 5.*** Ring-closing metathesis of diallyl 3-oxindole derivatives. Reaction conditions: **3** (0.3 mmol, 1.0 equiv), **G-II** catalyst (5 mol%), $CH_2Cl_2$ (4 mL), room temperature, 8 h. Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl.

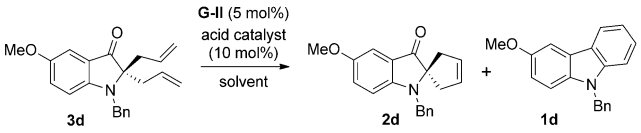
Table S1 in the Supporting Information). The rearrangement also proceeded with Brønsted acids such as triflic acid (TfOH) and trifluoroacetic acid (TFA) in $CH_2Cl_2$ at 45°C. When the Lewis acids $BF_3{\cdot}OEt_2$, $TiCl_4$, and $SnCl_4$ were used as catalysts




***Scheme 6.*** One-pot ring rearrangement–aromatization (RRA) of spirocyclic 3-oxindoles to carbazoles. Reactions conditions: **2** (0.2 mmol, 1.0 equiv), TsOH (10 mol%), toluene (5 mL), 80°C, 3 h.

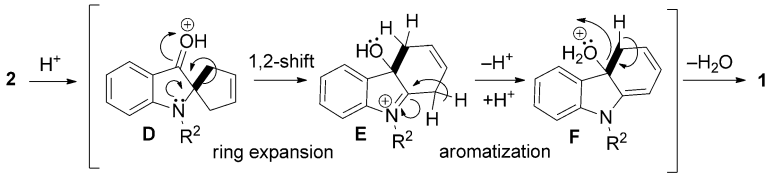
***Table 1:*** Optimization of the one-pot tandem RCM and aromatization reaction.




| Entry | Acid catalyst | Solvent | *T*, *t* | Conv. [%][a] | **2d**/**1d**[a] |
|---|---|---|---|---|---|
| 1 | TsOH | $CH_2Cl_2$ | rt, 12 h | >99 | 80:20 |
| 2 | TsOH | toluene | 80°C, 6 h | >99 (91)[b] | 0:100 |
| 3 | TfOH | $CH_2Cl_2$ | 45°C, 10 h | >99 (88)[b] | 0:100 |
| 4 | TFA | $CH_2Cl_2$ | 45°C, 18 h | >99 (87)[b] | 0:100 |
| 5 | $BF_3$•$Et_2O$ | $CH_2Cl_2$ | 45°C, 12 h | >99 | 70:30 |

[a] The conversion and **2d**/**1d** ratio were determined by $^1$H NMR spectroscopic analysis of the crude product mixture. [b] The yield of **1d** is given in parentheses.

in $CH_2Cl_2$, no reaction occurred at room temperature, and the reaction was sluggish at 45°C (see Table S1). The reaction of spirocyclic 3-oxindoles **2b–j** with TsOH was then investigated in toluene at 80°C. We found that the reaction time and yield were not influenced by the electronic character of the substrate, and the corresponding carbazole derivatives **1b–j** were isolated in excellent yield. In this rearrangement, the carbonyl group is probably protonated, and the nitrogen lone pair facilitates a 1,2-shift leading to the formation of the ring-expanded indolinium-ion intermediate **E**. Loss of water from intermediate **F** then provides the carbazole **1** (Scheme 7).



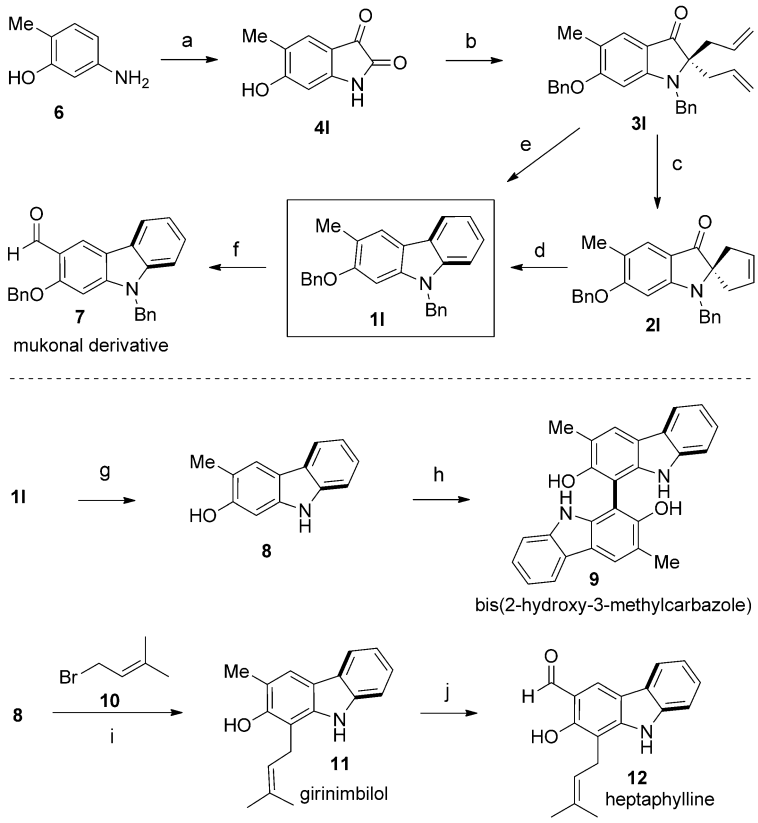

***Scheme 7.*** Proposed mechanism for the aromatization-driven ring rearrangement.

Next, we envisioned the development of a new tandem process in which the RCM and RRA steps would be combined in a single reaction vessel. Tandem processes, which combine multiple steps in a one-pot process, significantly reduce reaction sequences, time, energy, and the usage of solvents and other materials for workup and purification.[13] Owing to the stability of ruthenium-based metathesis catalysts, several examples of tandem reactions involving olefin metathesis have been developed.[14] In a one-pot procedure, the RCM/RRA was performed with 2,2-diallyl-3-oxindole **3d** as the substrate with **G-II** (5 mol%) and acid catalysts (Table 1). Several acid catalysts, including Brønsted acids (TsOH, TfOH,and TFA) and Lewis acids ($BF_3$•$OEt_2$, $TiCl_4$, and $SnCl_4$) were explored for this orthogonal tandem reaction (see Table S2). Although the desired carbazole product **1d** was observed when **3d** was treated with **G-II** (5 mol%) and TsOH (10 mol%) in $CH_2Cl_2$ at room temperature for 12 h, the product mixture consisted mainly of the RCM product **2d** (**2d**/**1d** 80:20; Table 1, entry 1). When the substrate was heated with the same two catalysts in toluene at 80°C for 6 h, the RCM–RRA sequence proceeded efficiently to give **1d** almost exclusively in 91% yield, and when the reaction was carried out with TfOH or TFA as the acid catalyst in $CH_2Cl_2$ at 45°C, the carbazole derivative **1d** was obtained as the sole product in high yield (Table 1, entries 2–4). The reactivity of Lewis acids, such as $BF_3$•$OEt_2$, $TiCl_4$, and $SnCl_4$, was considerably poorer for the rearrangement step, although they did not interfere with the RCM step, as only the RCM product was observed at room temperature (see Table S2).

To further explore the synthetic potential of this protocol in natural product synthesis, we chose substituted isatin derivatives that would provide the requisite functionality for the construction of the carbazole natural products mukonal, girinimbilol, heptaphylline, and 1,1′-bis(2-hydroxy-3-methylcarbazole) (Scheme 8). The carbazole alkaloids-mukonal[15]and bis(2-hydroxy-3-methylcarbazole)[18] are isolated from the stem bark of *Murraya koenigii*. Girinimbilol[16] and heptaphylline[16] are isolated from both the stem bark of *Murraya koenigii* and root bark of *Clausena heptaphylla*.[17] They exhibit broad pharmacological activity, including anti-platelet-aggregation, antimycobacterial, anti-inflamatory, anti-HIV-1, and anti-tumor-promoting activity.[19]

By an optimized Sandmeyer reaction,[20] 6-hydroxy-5-methylisatin (**4l**) was prepared from the aniline derivative **6** in 65% yield. Benzyl protection of **4l**, followed by a Grignard reaction, afforded the desired diallyl-3-oxindole **3l**. RCM of **3l** with **G-II** afforded the spirocyclic 3-oxindole **2l** in 88% yield. The first-generation Grubbs catalyst (**G-I**)[5b] was used forthe large-scale synthesis of **2l** (see the Supporting Information). The spirocyclic compound **2l** underwent one-pot rearrangement–aromatization to afford the carbazole **1l** in 95% yield. When diallyl-3-oxindole **3l** was subjected to the tandem RCM/RRA conditions (5 mol% **G-II**, 10 mol% TsOH in toluene), **1l** was obtained in 86% yield (as compared to 83% in two steps). The oxidation of **1l** with DDQ in




***Scheme 8.*** Synthesis of naturally occurring carbazole alkaloids. a) 1. $CCl_3CH(OH)_2$, $NH_2OH$–HCl, $Na_2SO_4$, 60 °C, 12 h; 2. $H_2SO_4$, 80 °C, 30 min, 65 %; b) 1. BnBr, $K_2CO_3$, DMF, room temperature, 8 h, 95 %; 2. allylMgBr, THF, room temperature, 2 h, 75 %; c) **G-II** (5 mol %), $CH_2Cl_2$, 8 h, room temperature, 88 %, or **G-I** (10 mol %), $CH_2Cl_2$, 18 h, room temperature, 78 %; d) TsOH (10 mol %), toluene, 80 °C, 3 h, 95 %; e) **G-II** (5 mol %), TsOH (10 mol %), 80 °C, 6 h, 86 %; f) DDQ, MeOH, room temperature, 30 min, 91 %; g) 10 % Pd/C, $H_2$, MeOH, 36 h, room temperature, 98 %; h) $CuCl_2$ (10 mol %), DBU, MeCN, 100 °C, 26 h, 51 %; i) **10**, DIPEA, $CH_2Cl_2$, 12 h, room temperature, 67 %; j) DDQ, MeOH, room temperature, 30 min, 85 %. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIPEA = *N*,*N*-diisopropylethylamine.

MeOH provided the *N*- and *O*-benzyl-protected mukonal derivative **7** in 91 % yield.[15b] Hydrogenolysis of the benzyl protecting groups in **1l** provided the 2-hydroxy-3-methylcarbazole (**8**), a common intermediate for the synthesis of a variety of naturally occurring carbazole alkaloids.[21]

Knölker et al. reported the synthesis of the racemic bis(2-hydroxy-3-methylcarbazole) alkaloid **9** from **8** in 38 % yield by the use of chloranil.[22] The biscarbazole alkaloids exhibit potent biological activity and are challenging targets for total synthesis.[18] We employed a novel copper chloride mediated C–C coupling in the presence of DBU to synthesize bis(2-hydroxy-3-methylcarbazole) (**9**) in 51 % yield. Recently, the Knölker group reported the first total synthesis of girinimbilol (mukoenine A, **11**) by opening of the pyran ring of girinimbine.[23] In this study, we attempted a direct *ortho*-prenylation of the phenol group of the carbazole **9** to incorporate the prenyl group. The direct alkylation proceeded smoothly under mild reaction conditions with the Hünig base (DIPEA) at room temperature to afford girinimbilol (**11**) in 67 % yield. Girinimbilol (**11**) was further converted into heptaphylline[23] (**12**) in 85 % yield through oxidation with DDQ.

In summary, the described method makes use of rearranged 2,2-diallyl-3-oxindole products, obtained by allyl Grignard addition to isatin derivatives, as precursors of ring-closing metathesis. The RCM afforded a novel class of spirocyclic 3-oxindoles that undergo a novel aromatization-driven ring rearrangement to provide facile access to carbazole derivatives. Furthermore, we have demonstrated an orthogonal tandem process that combines the RCM and RRA processes in a single reaction vessel. The carbazole derivatives can be synthesized in just two steps from isatin derivatives in improved yield. The method has been used for the synthesis of carbazole natural products in a concise and especially straightforward manner.

## Experimental Section

Typical procedure for one-pot RCM/RRA: **G-II** (8.48 mg, 0.01 mmol, 5 mol %) and TsOH (3.5 mg, 0.02 mmol, 10 mol %) were added to a solution of oxindole **3d** (50 mg, 0.15 mmol) in toluene, and the reaction mixture was heated at 80 °C for 6 h and then concentrated. Purification of the residue by column chromatography (EtOAc–hexane, 10:90–20:80) on silica gel afforded the carbazole **1d** (37 mg, 86 %) as a white solid.

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