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SHORT COMMUNICATION

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# Ruthenium-Catalyzed Cycloisomerization and Its Application to the Synthesis of (±)-Cinchonaminone

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**Keywords:** Heterocycles / Cyclization / Ruthenium / Natural products / Total synthesis

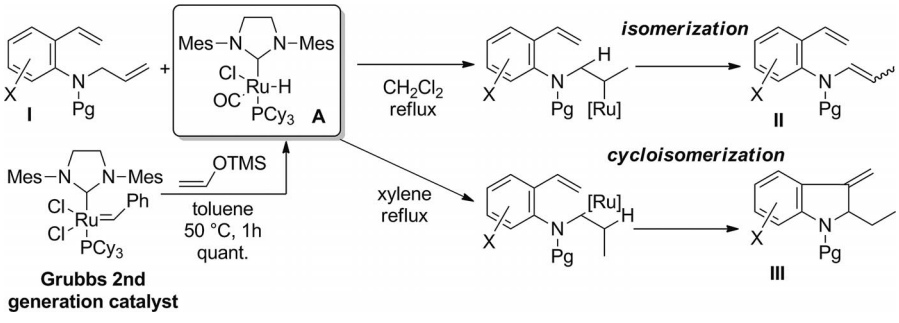
Ru-catalyzed cycloisomerization of a 1,3-diene and the alkene of an *N*-dienyl-2-vinylaniline substrate proceeded smoothly, leading to a 3-exomethylene-2-vinylindole derivative in good yield. This useful synthon was successfully applied to the total synthesis of (±)-cinchonaminone.

## Introduction

Indole derivatives are important cyclic structures in organic synthesis, as they can serve as building blocks for functional materials and as key components in a myriad of bioactive compounds. Consequently, new and more efficient synthetic methods are being actively pursued to prepare this class of nitrogen-containing heterocycles, with selective control of substitution patterns, from readily available and simple substrates.[1]

Previously, we found that ruthenium hydride complex **A** with an N-heterocyclic carbene ligand could be generated in pure form by reaction of the second generation Grubbs catalyst with vinyloxytrimethylsilane (Scheme 1).[2] Complex **A**[2c] showed high catalytic activity in selective terminalolefin isomerization (from **I** to **II**)[2a,3] and/or cycloisomerization of 1,7-dienes (from **I** to **III**)[2b] depending on the reaction temperature.[4] This was most notable in the case of 2,3-disubstituted indole derivatives **III** obtained by cycloisomerization, which are important synthons for biologically active natural products.[5] However, substituents at the 2-position of the indoles obtained by this method are limited to non-functionalized ethyl or longer alkyl groups. Therefore, the synthesis of biologically active 2,3-disubstituted indole derivatives, including cinchonaminone (Figure 1) could be difficult.

In this article, we report the ruthenium-catalyzed cycloisomerization of a 1,3-diene and the alkene of an *N*-dienyl-2-vinylaniline substrate, leading to a substituted, synthetically useful indole derivative with 3-exomethylene and 2-vinyl substituents. The vinyl functionality in the indole would be useful for further transformations, such as hydroboration, ozonolysis, and metathesis. Thus, the synthesis of the naturally occurring 2,3-disubstituted indole compound (±)-cinchonaminone (**1**) was achieved.




Scheme 1. Reported Ru-catalyzed cycloisomerization to yield substituted indole derivatives.

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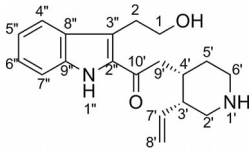
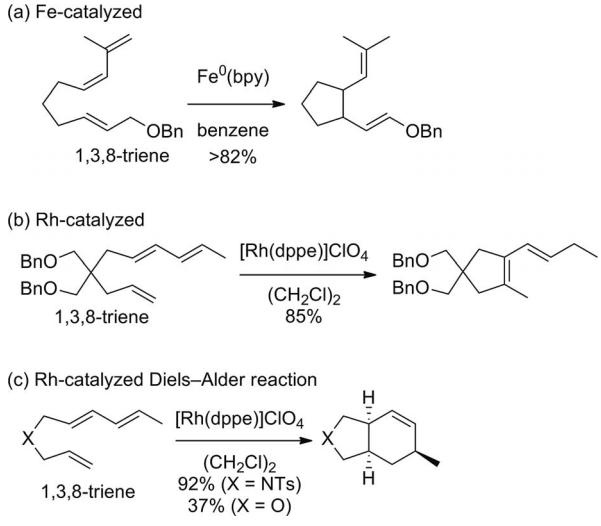



(+)-cinchonaminone [(+)-**1**]

Figure 1. An example of biologically active 2,3-disubstituted indole.

## Results and Discussion

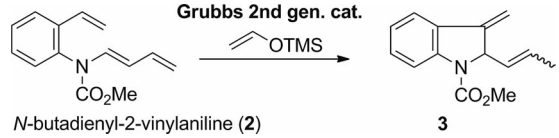
Transition-metal catalyzed carbon–carbon bond-forming reactions have found exceptional utility in organic synthesis. Of particular note are the applications of organotransition metal chemistry in the construction of carbocyclic rings. Although various transition-metal-catalyzed [4+2] cycloadditions (Diels–Alder reaction) of substrates having the 1,3,8- or 1,3,9-triene structure have been reported (Scheme 2a), there are apparently only two examples of the cycloisomerization between a 1,3-diene and the alkene of 1,3,8- or 1,3,9-trienes to form a cyclopentane structure, those catalyzed by Fe or Rh (Scheme 2b and c).[6] In the $Rh^{I}$-catalyzed reaction, the existence of a heteroatom in the tether between the 1,3-diene moiety and the alkene changed the course of the reaction. Namely, although the reaction with the carbon-tethered substrate gave the cycloisomerization product (Scheme 2b), the reaction with the corresponding nitrogen- or oxygen-tethered substrates provided none of the expected cycloisomerization product, but only the Diels–Alder cycloadduct (Scheme 2c).[6b] The synthesis of heterocycles, including that of indoles, by cycloisomerization of a 1,3-diene and the alkene of 1,3,8- or 1,3,9-triene substrates has not been reported until now. As described above, recently we found that the reaction of **I** with **A** gave 2,3-disubstituted indole derivatives **III** by cycloisomerization of the 1,7-diene structure of *N*-allyl-2-vinylanilines (Scheme 1). Thus, we envisioned that **A** might catalyze the reaction of the 1,3,8- or 1,3,9-triene structures of *N*-dienyl-2-vinylaniline, which could undergo intramolecular olefin insertion into the Ru–C bond. On the basis of our previously reported reaction of **A** with *N*-allyl-2-vinylaniline derivatives **I**, *syn* β-H elimination would afford the desired cycloisomerization product, namely, the 3-exomethylene-2-vinylindole derivatives.




Scheme 2. Reported reaction of a 1,3-diene and an alkene.

The reaction catalyzed by **A** was investigated with derivative **2**, which has a 1,3,8-triene structure, and the results are summarized in Table 1. First, a solution of **2**, Grubbs second generation catalyst (10 mol-%), and vinyloxytrimethylsilane (1 equiv.) in xylene was heated at reflux for 1 h. The reaction gave desired cycloisomerized product 3-exomethylene-2-vinylindole derivative **3** in 35% yield (Table 1, Entry 1). When the reaction was carried out at lower temperatures (110–80 °C), the yield of **3** increased (Table 1, Entries 1–4). At 60 °C, the reaction proceeded slowly, and most of the starting material was recovered (Table 1, Entry 5). Consequently, 87% of **3** was isolated when a mixture of **2**, the Grubbs catalyst (5 mol-%), and vinyloxytrimethylsilane (1 equiv.) was heated at reflux in benzene for 1 h (Table 1, Entry 6). In these reactions, none of the Diels–Alder product was obtained.

Table 1. Reaction of the *N*-butadienyl-2-vinylaniline derivative.




*N*-butadienyl-2-vinylaniline (**2**) **3**

| Entry | Grubbs cat. [mol-%] | Solvent | *T* [°C] | *t* [h] | Yield [%] **3** | SM |
|---|---|---|---|---|---|---|
| 1 | 10 | xylene | 140 | 1 | 35[a] | 0 |
| 2 | 10 | toluene | 110 | 1 | 68[a] | 0 |
| 3 | 10 | toluene | 80 | 2 | 62[b] | 25[b] |
| 4 | 10 | benzene | 80 | 1 | 86[a] | 0 |
| 5 | 10 | benzene | 60 | 2 | 12[b] | 62[b] |
| 6 | 5 | benzene | 80 | 1 | 87[a] | 0 |

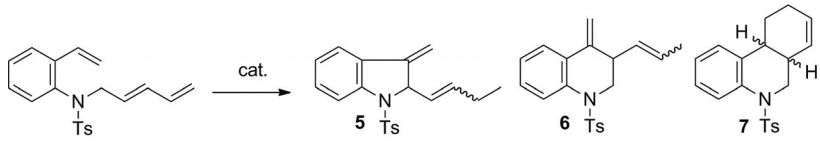
[a] Isolated yield. [b] NMR yield.

The reaction with the corresponding derivative **4** with a 1,3,9-triene structure was next investigated, and the results are summarized in Table 2. A refluxing solution of **4**, the Grubbs catalyst (10 mol-%), and vinyloxytrimethylsilane (1 equiv.) in xylene did not give any of expected cycloisomerized product **5**, but instead, cycloisomerized quinoline derivative **6**[7] and Diels–Alder adduct **7** were obtained in 32 and 31% yield, respectively (Table 2, Entry 1). Although several reaction conditions were examined, that is, changing the solvent, reaction temperature, and catalyst, we could not synthesize **5** (Table 2, Entries 2–4), and we found that at higher reaction temperatures, the Diels–Alder reaction of **4** proceeded smoothly to give **7** in 88% isolated yield (Table 2, Entry 5).

Having expected 3-exomethylene-2-vinylindole derivative **3** in hand, we then applied it to the synthesis of indole alkaloid (±)-cinchonaminone (**1**). This alkaloid was isolated from Cinchonae Cortex (the cortex of *Cinchona succirubra* PAV., Rubiaceae) in 1989 (Figure 1).[8] Although (+)-cin-

Table 2. Reaction of the *N*-pentadienyl-2-vinylaniline derivative.



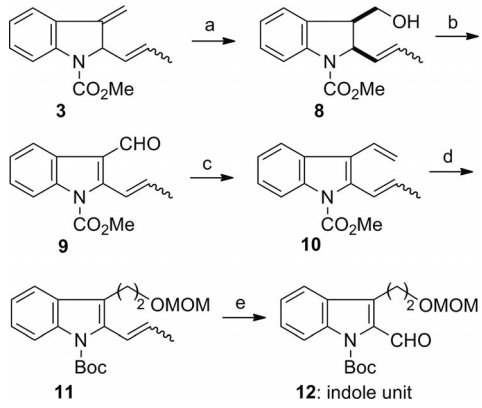

*N*-pentadienyl-2-vinylaniline (**4**)

| Entry | Catalyst [mol-%] | $CH_2$=CHOTMS [equiv.] | Solvent | *T* [°C] | *t* [h] | Yield [%][a] **5** | **6** | **7** | SM **4** |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Grubbs 2nd (10) | 1 | xylene | 140 | 0.5 | 0 | 32 | 31 | 0 |
| 2 | Grubbs 2nd (10) | 1 | toluene | 110 | 2 | 0 | 24 | 17 | 0 |
| 3 | Grubbs 2nd (10) | 1 | benzene | 80 | 2 | 0 | 7 | 26 | 57 |
| 4 | $Ru(CO)HCl(PPh_3)_3$ (5) | – | toluene | 110 | 4 | 0 | 10 | 51 | 0 |
| 5 | – | – | xylene | 140 | 1 | 0 | 0 | 88[b] | 0 |

[a] NMR yield. [b] Isolated yield.

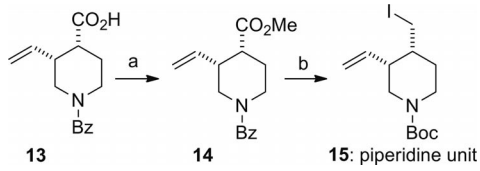
chonaminone is reported to have an inhibitory activity against monoamine oxidase (MAO) from bovine plasma ($IC_{50}$ = 31.7 μM), the total synthesis of **1** has not been reported.

Thus, we decided to synthesize this indole alkaloid and examine its effects on human MAOs. As shown in Scheme 3, regioselective hydroboration of **3** and subsequent TEMPO oxidation led to 3-formyl derivative **9**, which was treated with the Wittig reagent to afford 2,3-divinyl indole **10**. Another regioselective hydroboration of **10** by using $Cy_2BH$ followed by methoxy methyl ether protection of the generated alcohol provided 2-vinylindole derivative **11**. Oxidative cleavage of the olefin moiety of **11** by using a combination of osmium tetroxide and sodium periodate gave 2-formyl indole **12**.



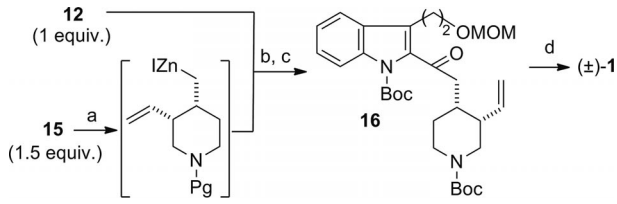

Scheme 3. Synthesis of indole unit. Reagents and conditions: (a) 9-BBN, THF, –20 to 0 °C; then, $H_2O_2$, NaOH, $H_2O$, 86%. (b) TEMPO (10 mol-%), NCS, $Bu_4NCl$ (10 mol-%), $CH_2Cl_2$, $H_2O$ (pH 9), 66% (yield based on recovered starting material: 81%). (c) $Ph_3PMeBr$, $NaN(TMS)_2$, THF, –78 to r.t., 82%. (d) 1. $Cy_2BH$, THF, 0 °C to r.t.; then, $H_2O_2$, NaOH, $H_2O$. 2. MOMCl, *i*$Pr_2NEt$, $CH_2Cl_2$. 3. NaOH, aq. MeOH, reflux. 4. $Boc_2O$, $Et_3N$, DMAP, $CH_2Cl_2$, 62% (4 steps). (e) OsO4 (5 mol-%), $NaIO_4$, aq. dioxane, 45%.

Piperidine **15** was prepared from known **13**[9] in four steps (Scheme 4). The methyl ester and benzoyl groups on **14** were simultaneously reduced with $LiAlH_4$ to give the corresponding amino alcohol, which was treated with $Boc_2O$ and then subjected to iodination to afford **15**.




Scheme 4. Synthesis of the piperidine unit. Reagents and conditions: (a) MeOH, EDC·HCl, DMAP, THF, 91%. (b) 1. $LiAlH_4$, THF, –30 to –5 °C. 2. $Boc_2O$, $Et_3N$, $CH_2Cl_2$. 3. $I_2$, $PPh_3$, imidazole, PhH, reflux, 44% (3 steps).

The coupling of building blocks **12** and **15** leading to the total synthesis of (±)-**1** is shown in Scheme 5. Thus, generation of the corresponding zinc reagent from **15** with Zn followed by reaction with aldehyde **12** resulted in the desired coupling product, which was oxidized with Dess–Martin periodinane to give **16**. Removal of both the methoxymethyl and Boc groups furnished (±)-**1**. The synthesized racemic cinchonaminone [(±)-**1**] exhibited spectroscopic data identical to those reported previously ($^1H$ NMR and $^{13}C$ NMR and HRMS).[8]




Scheme 5. Synthesis of (±)-**1**. Reagents and conditions: (a) Zn, THF, 40 °C. (b) CuCN, LiCl, $BF_3$·$OEt_2$, THF, –78 to –30 °C. (c) Dess–Martin periodinane, $CH_2Cl_2$, 11% (2 steps, yield based on recovered starting material: 30%). (d) 3 M HCl, MeOH, 40 °C, 76%.

## Conclusions

The chemistry described in this communication shows the first example of the Ru-catalyzed cycloisomerization reaction between a 1,3-diene and an alkene leading to a synthetically useful 3-exomethylene-2-vinylindole derivative and its application to the synthesis of racemic cinchonaminone [(±)-**1**]. Synthesis of cinchonaminone analogues by this method and their effects on human MAOs are under investigation to study the structure–activity relationship.

## Experimental Section

**Preparation of *N*-Methoxycarbonyl-3-methylene-2-(1-propenyl)-indoline (3):** Under an Ar atmosphere, to a solution of **2** (591 mg, 2.58 mmol) in benzene (210 mL) was added Grubbs 2nd generation catalyst (109 mg, 0.13 mmol, 5 mol-%) and vinyloxytrimethylsilane (385 μL, 2.58 mmol), and the mixture was heated at reflux for 1 h. Solvents were partially removed under reduced pressure, and the obtained residue was subjected to column chromatography ($SiO_2$, hexane/AcOEt = 20:1) to give **3** (510 mg, 2.23 mmol, 87%, *E*/*Z* = 7:3) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$, 50 °C, *E* isomer): $\delta$ = 7.81 (br., 1 H), 7.41 (d, *J* = 7.7 Hz, 1 H), 7.25 (dd, *J* = 7.7, 7.7 Hz, 1 H), 6.99 (dd, *J* = 7.7, 7.7 Hz, 1 H), 5.74 (dd, *J* = 6.8, 15.0 Hz, 1 H), 5.51 (d, *J* = 2.7 Hz, 1 H), 5.45 (ddq, *J* = 1.8, 7.7, 14.9 Hz, 1 H), 5.18 (d, *J* = 7.2 Hz, 1 H), 4.97 (d, *J* = 2.3 Hz, 1 H), 3.82 (s, 3 H), 1.71 (dd, *J* = 1.8, 6.8 Hz, 3 H) ppm. $^1$H NMR (400 MHz, $CDCl_3$, 50 °C, *Z* isomer): $\delta$ = 7.81 (br., 1 H), 7.41 (d, *J* = 7.7 Hz, 1 H), 7.25 (dd, *J* = 7.7, 7.7 Hz, 1 H), 6.99 (dd, *J* = 7.7, 7.7 Hz, 1 H), 5.70–5.61 (m, 2 H), 5.47 (d, *J* = 2.7 Hz, 1 H), 5.34 (ddq, *J* = 1.8, 9.5, 10.9 Hz, 1 H), 4.93 (d, *J* = 2.3 Hz, 1 H), 3.81 (s, 3 H), 1.71 (dd, *J* = 1.8, 6.8 Hz, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$, *E* isomer): $\delta$ = 153.13, 144.71, 143.70, 129.93, 129.51, 128.10, 127.55, 122.80, 120.57, 115.66, 103.31, 66.03, 52.45, 17.60 ppm. LRMS (EI): *m*/*z* = 229 $[M]^+$. HRMS (EI): calcd. for $C_{14}H_{15}NO_2$ $[M]^+$ 229.1103; found 229.1098. $C_{14}H_{15}NO_2 \cdot 0.25H_2O$ (233.8): calcd. C 71.93, H 6.68, N 5.99; found C 71.99, H 6.48, N 5.90.

**Preparation of (±)-3-(2-Hydroxyethyl)-2-[2-(3-vinylpiperidin-4-yl)-acetyl]indole (1):** A solution of **16** (35 mg, 63 μmol) in 3 M HCl in MeOH (2 mL) was stirred at 40 °C overnight. The solvent was removed under reduced pressured, and the obtained residue was subjected to column chromatography ($SiO_2$, $CHCl_3$/MeOH = 100:0–97:3) to give (±)-**1** (15 mg, 48 μmol, 76%) as a white amorphous solid. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 9.11 (s, 1 H), 7.70 (d, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.35 (dd, *J* = 8.6, 8.6 Hz, 1 H), 7.15 (dd, *J* = 8.0, 8.0 Hz, 1 H), 6.14 (dt, *J* = 9.7, 17.2 Hz, 1 H), 5.13 (dd, *J* = 2.3, 10.3 Hz, 1 H), 5.03 (dd, *J* = 1.7, 17.2 Hz, 1 H), 3.94 (t, *J* = 6.3 Hz, 2 H), 3.37 (t, *J* = 6.3 Hz, 2 H), 3.04 (dt, *J* = 4.0, 12.6 Hz, 1 H), 2.97–2.91 (m, 3 H), 2.80–2.69 (m, 2 H), 2.45 (m, 1 H), 2.38 (m, 1 H), 1.55–1.44 (m, 2 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 192.83, 137.62, 136.01, 132.88, 128.40, 126.45, 121.11, 120.48, 119.51, 116.91, 112.02, 63.19, 51.39, 46.19, 43.90, 43.06, 34.40, 29.06, 28.89 ppm. LRMS (EI): *m*/*z* = 312 $[M]^+$. HRMS (EI): calcd. for $C_{19}H_{25}N_2O_2$ $[M + H]^+$ 313.1911; found 313.1913.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures and full characterization of compounds **2**–**4**, **6**–**12**, **14**–**16**, and (±)-**1**.

## Acknowledgments

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[7] Although it is known that Ru-catalyzed diene cycloisomerization usually leads to five-membered rings, in this case a six-membered ring cyclization is probably the result of 1,3-diene conjugation.

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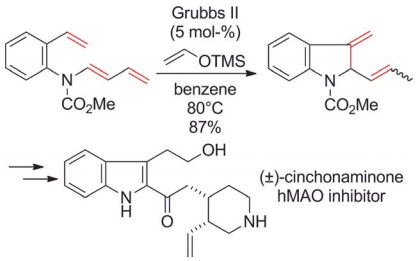




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