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PAPER

Alkene isomerization/enamide-ene and diene metathesis for the construction of indoles, quinolines, benzofurans and chromenes with a chiral cyclopropane substituent†

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A synthetic method for bicyclic heterocycles, such as indole, benzofuran and chromene derivatives bearing a chiral cyclopropane at the 2-position, was established using isomerization of a terminal olefin and enamide-ene or diene metathesis. This route can also be applied to chiral 2-cyclopropylquinoline synthesis (both *cis* and *trans*).

Introduction

An asymmetric center adjacent to heterocyclic structures is a motif shared by various biologically active, natural and unnatural compounds. In many cases, the lack of an appropriate synthetic method renders the construction of such asymmetric centers a challenge.[1]

The chemistry of indole is one of the most active areas of heterocyclic chemistry. Indole research remains at the forefront of biological and medicinal chemistry. The most ubiquitous of the bioactive alkaloids known are based on the indole nucleus.[2] 2-Substituted indoles are also potential intermediates for synthesizing many alkaloids and pharmacologically important substances.[3] While the methods for the preparation of 3-substituted indoles are well established, there is still need for yet easier access to 2-substituted indoles. In this regard, the construction of an asymmetric center adjacent to the 2-position of an indole continues to be a challenging topic.[4]

In our work on medicinal chemistry with cyclopropane as a key conformationally restricted unit,[5] potent H_3 and/or H_4 receptor antagonists **1** with a low nanomolar K_i were successfully identified (Fig. 1).[6] In the course of our studies on H_3/H_4 receptor ligands, we designed the chiral 2-cyclopropylindole derivatives **2a** and **2b**. However, when we started this project, there was no report on the synthesis of indole derivatives bearing a chiral cyclopropane at the 2-position. Therefore, we decided to establish an efficient synthetic method for this kind of chiral indole derivative. We report here one of the first synthetic examples of indoles with a chiral cyclopropane at the 2-position using alkene isomerization and enamide-ene ring-closing metathesis (RCM) as the key strategy. The method was also effectively applied to the preparation of other chiral cyclopropyl heterocycles, such as quinoline, benzofuran and chromene derivatives.

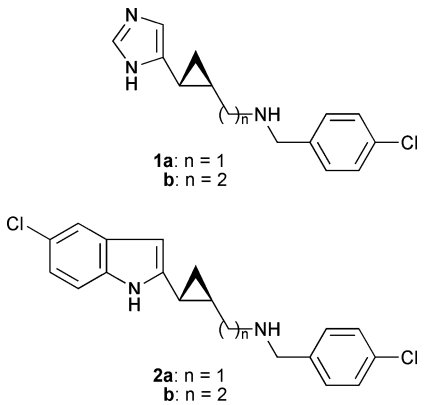

Fig. 1 Our designed compound.

Results and discussion

Synthesis of chiral 2-*trans*-cyclopropylindole derivatives

In 2002, we reported an alkene isomerization/enamide-ene RCM to provide indoles effectively.[7] An allylic amide **3** was isomerized to the corresponding enamide **4**, the RCM of which provided the corresponding indole **5** in excellent overall yield (Scheme 1, for example, from **3Aa** to **5Aa**). This method is applicable to the synthesis of 2-substituted indoles **5Ab** (R = Me), **5Ac** (R = Et) and **5Ad** (R = Ph). However, it was difficult to synthesize those indole derivatives having a bulky substituent, such as *iso*-propyl or *iso*-butyl groups, because the first step, the isomerization of **3Ae** (R = *i*Pr) and **3Af** (R = *i*Bu), did not proceed at all (Scheme 1).[8] We then examined the Ru catalyst-induced isomerization of diene **3Ag**, having a chiral cyclopropane substituent, which was obtained

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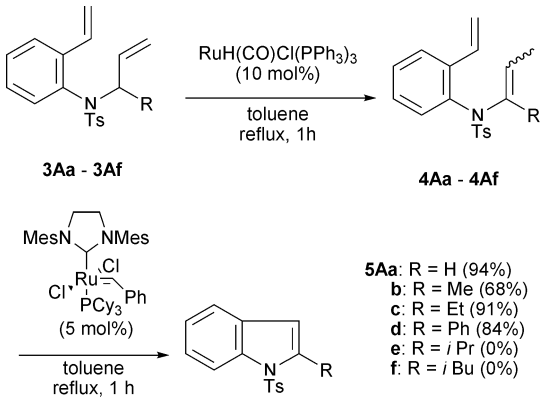
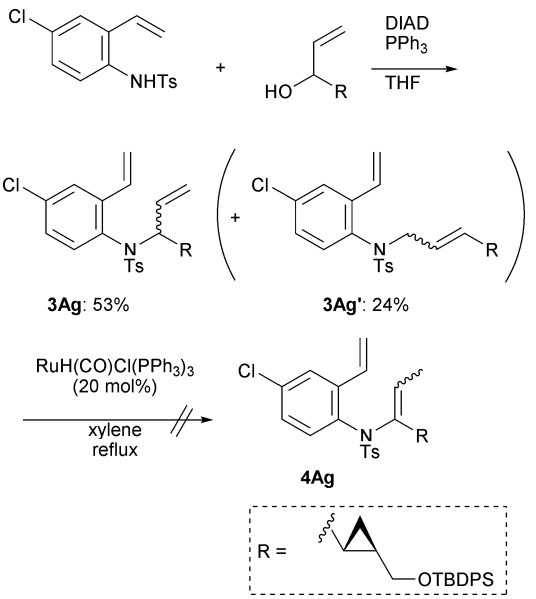
† Electronic supplementary information (ESI) available: Experimental details, and ^{1}H and ^{13}C NMR spectra of compounds **2a**, **2b**, **5Bf**, **5Bg**, **5Bh**, **5De**, **5Df**, **5Dh**, **5Di**, **6e**, **6f**, **6g**, **6h**, **6i**, **6j**, **7**, **8**, **9**, **10**, **11**, **12e**, **12f**, **12h**, **12i**, **12j**, **13a**, **13b**, **13c**, **14a**, **14b**, **14c**, **15a**, **15b** and **15c**. See DOI: 10.1039/c0ob00597e



Scheme 1 Our previous synthesis of 2-alkyl indoles.

as a separable mixture with its regioisomer **3Ag′**. However, the isomerization of **3Ag** likewise did not proceed at all (Scheme 2).



Scheme 2 Synthesis and reaction of **3Ag**.

Based on these results, we considered that the steric demand of the substrates might pose an obstacle to the initial isomerization, namely the terminal olefin reaction site is too sterically crowded to allow the isomerization to occur. Therefore, focusing on the synthesis of **2**, we decided to continue our experiments by changing the nitrogen substituent to a less hindered one and planned to prepare the *N*-acetyl-2-ethynylaniline derivative **3Bg** (Fig. 2), which has an acetyl protecting group that is smaller than the toluenesulfonyl (Ts) group, as a substrate for 2-substituted indole synthesis. Thus, the establishment of a general and alternative synthetic route for the *N*-allyl-2-vinylaniline derivatives **3** (Scheme 3) was needed, since our previous method (route A in Scheme 3) had two problems.

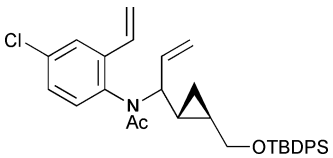
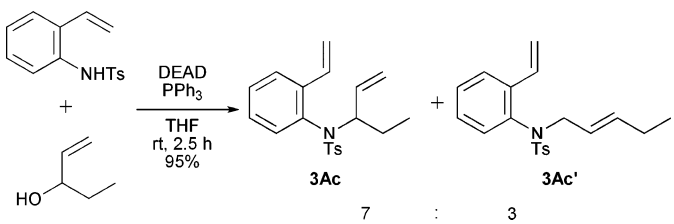


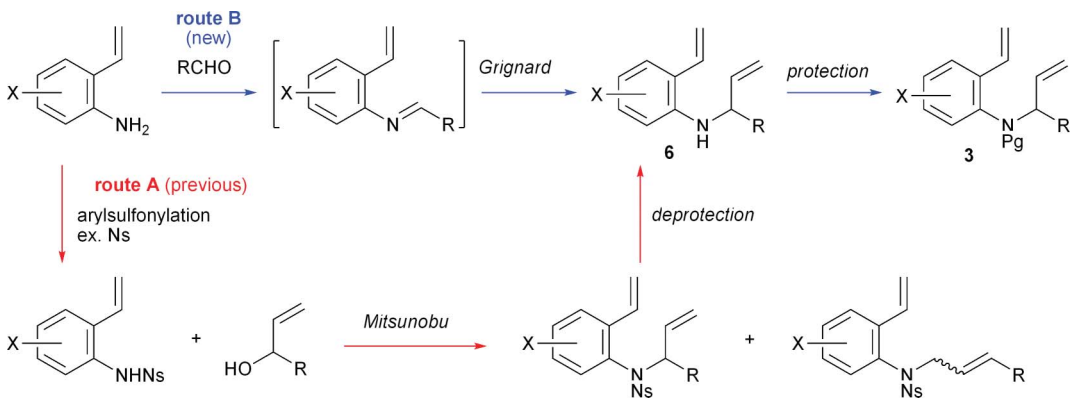
Fig. 2 Structure of **3Bg**.

(1) Substrates **3** were sometimes obtained as a mixture of regioisomers by the Mitsunobu reaction of the corresponding *N*-*p*-toluenesulfonyl-2-ethenylaniline and allyl alcohol. For example, the inseparable **3Ac** and SN2′ product *N*-pent-2-en-1-yl-*N*-*p*-toluenesulfonyl-2-ethenylaniline, **3Ac′**, were isolated in a ratio of 7 : 3 (Scheme 4).

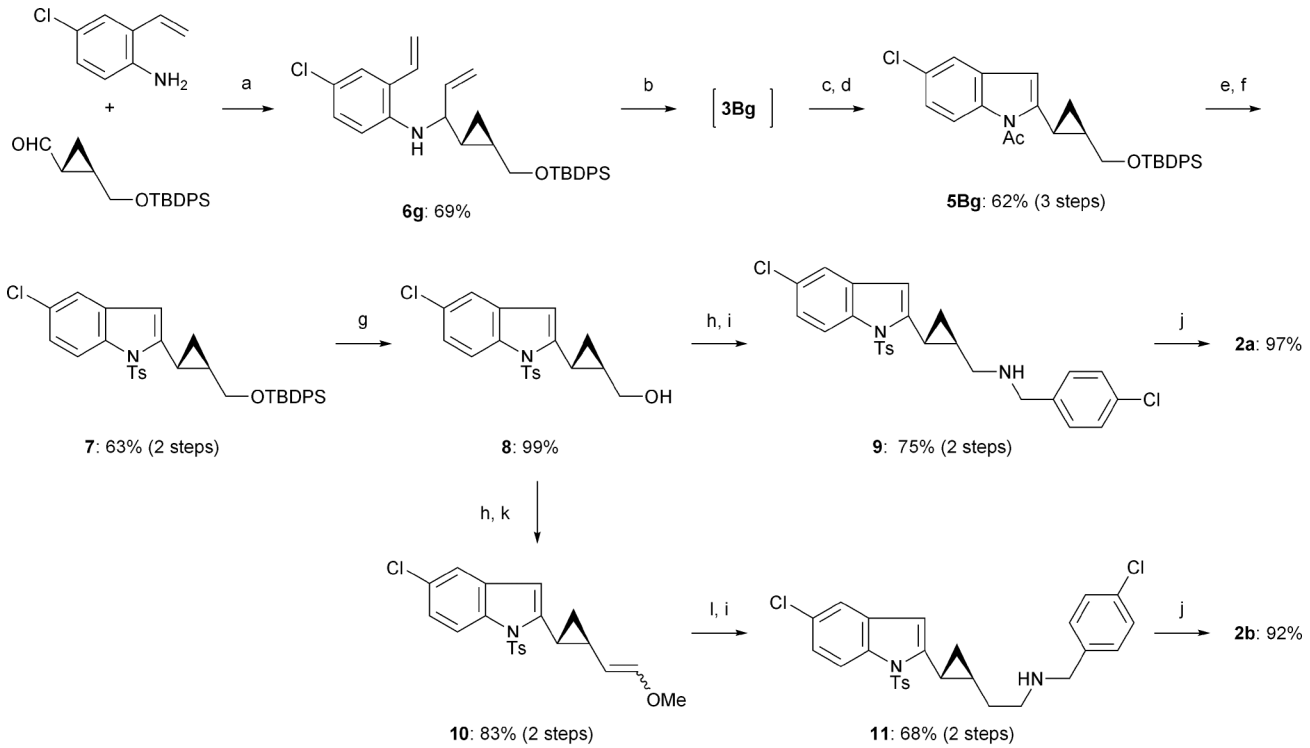


Scheme 4 Our previous preparation method of **3Ac**.

(2) In order for the Mitsunobu reaction to proceed, a dissociative NH on 2-ethenylaniline was required. Thus, while the highly electron-withdrawing sulfonyl groups were suitable nitrogen protecting groups, the acetyl was not. Hence, with our previous method toward **3Bg** (Fig. 2), after the Mitsunobu reaction, removal of the sulfonyl group, such as 4-nitrobenzensulfonyl (Ns), and subsequent reprotection of the amino group by an acetyl



Scheme 3 General and alternative synthesis plan of **3**.



conditions a) ether, MS 4A, then CH_2=CHMgBr, BF_3•Et_2O, ether, -40 - 0 °C; b) Ac_2O, *i* Pr_2NEt, toluene, reflux; c) RuH(CO)Cl(PPh_3)$_3$ (20 mol%), xylene, reflux; d) Grubbs (II) (20 mol%), toluene, reflux; e) K_2CO_3, MeOH, THF; f) NaH, TsCl, THF, 0 °C; g) Bu_4NF, THF; h) Dess-Martin periodinane, CH_2Cl_2; i) 4-chlorobenzylamine, NaBH(OAc)$_3$, CH_2Cl_2, MS4A; j)KOH, EtOH, reflux; k) $MeOCH_2PPh_3Cl$, NaN(TMS)$_2$, THF, 0 °C; l) *c*HCl : THF (1:12)

Scheme 5 Synthesis of **2a** and **2b**.

group was still needed, which resulted in more steps and lower yields (Scheme 3, route A).

Therefore, we planned to establish an alternative preparative method for the diene substrate, including **3Bg**, for the isomerization/enamide-ene metathesis. Thus, as shown in route B in Scheme 3, we expected that the Grignard reaction of an imine, which was made from 2-ethenylaniline and a chiral cyclopropyl aldehyde, with vinylmagnesium bromide would easily lead to the diene **6** without a protecting group on the aromatic amine, where a regioisomer could not be produced. The aromatic nitrogen on **6** could be easily protected by the acetyl or other protecting groups.

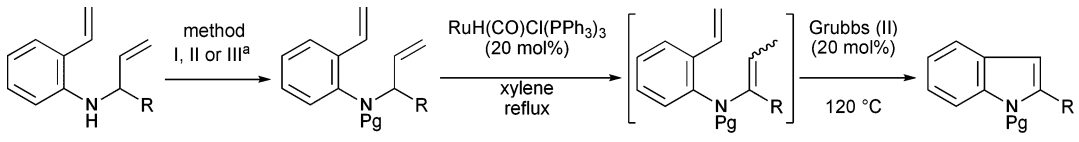
The reaction of 4-chloro-2-vinylaniline and the chiral *trans*-cyclopropyl aldehyde[9] with molecular sieve pore size 4 Å (MS 4A) in Et_2O gave the desired imine, which was subjected to the Grignard reaction without purification. When the reaction was performed with vinylmagnesium bromide in Et_2O in the presence of BF_3·Et_2O, the desired product, **6g**, was produced in 69% yield (2 steps). Upon treatment with acetic anhydride and Hünig's base, **6g** was successfully converted to *N*-acetyl substrate **3Bg** for the indole ring-closure. When subjected to isomerization using RuH(CO)Cl(PPh_3)$_3$ in refluxing xylene and a subsequent enamide-ene RCM with 2nd generation Grubbs catalyst in refluxing toluene, **3Bg** gave the desired indole **5Bg**, bearing a chiral *trans*-cyclopropane at the 2-position, in 62% yield (3 steps). Compound **5Bg** was successfully converted to target molecules **2a** and **2b** in 45% (6 steps) and 32% yield (8 steps), respectively, as shown in Scheme 5.

Scope and limitation of the 2-substituted indole synthesis

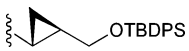
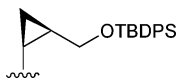
As far as we know, this is a novel example of a chiral 2-cyclopropylindole synthesis.[4d] Hence, we carried out experiments to investigate the scope and limitation of the indole synthesis method. First, in order to examine the effects of the protecting group on the nitrogen and also the substituent on the alpha position of nitrogen, we prepared the substrates **3Be**, **f**, **h** (Pg = Ac), **3Ce** (Pg = Bn), and **3De**, **f**, **h–j** (Pg = CHO) (Table 1) from the corresponding precursors, the *N*-allyl-2-vinylaniline derivatives **6e** (R = *i*Pr), **6f** (R = *i*Bu), **6h** (R = *c*Pr), **6i** (R = chiral *trans*-*c*Pr) and **6j** (R = chiral *cis*-cPr), in good to excellent yields. These substrates were subsequently subjected to our synthetic method for 2-substituted indoles, and the results are summarized in Table 1.

We attempted the isomerization of **3Be** (Pg = Ac, R = *i*Pr) using RuH(CO)Cl(PPh_3)$_3$.[10] However, **3Be** was recovered and none of the desired enamide was obtained (Table 1, entry 1). The substrate **3Ce** (Pg = Bn, R = *i*Pr) was also barely isomerized to the corresponding enamine (entry 2) under conditions using 20 mol% of ruthenium hydride. We found that **3De** (Pg = CHO, R = *i*Pr) was isomerized to the corresponding enamide in 23% yield and, when 1 equivalent of RuH(CO)Cl(PPh_3)$_3$ was used, **3De** was effectively isomerized to **4De**, which was further converted to **5De** in quantitative yield (3 steps, entry 3). In contrast, the isomerization of **3Bf** and **3Df** proceeded (entries 4 and 5) using 20 mol% of RuH(CO)Cl(PPh_3)$_3$, and subsequent enamide-ene RCM of the isobutyl substituted substrates **4Bf** (Pg = Ac, R = *i*Bu) and **4Df** (Pg = CHO, R = *i*Bu) provided the corresponding

Table 1 Synthesis of 2-alkyl indoles



6 3 4 5

Entry	R	6	Method from **6** to **3**	3	Pg	Yield of **5** (%, 3 steps)
1	*i*Pr	**6e**	I	**3Be**	Ac	0[b]
2	*i*Pr		II	**3Ce**	Bn	0[b]
3	*i*Pr		III	**3De**	CHO	23, quant.[c]
4	*i*Bu	**6f**	I	**3Bf**	Ac	26[d]
5	*i*Bu		III	**3Df**	CHO	94
6	*c*Pr	**6h**	I	**3Bh**	Ac	70
7	*c*Pr		III	**3Dh**	CHO	93
8		**6i**	III	**3Di**	CHO	74
9		**6j**	III	**3Dj**	CHO	0[b]

[a] Method I: Ac_2O, iPr_2NEt, toluene, reflux; method II: BnBr, iPr_2NEt·DMF, 100 °C; method III: HCOOH, Ac_2O, THF, 0–60 °C; [b] The transformation of **3** to **4** did not proceed. [c] In the isomerization step from **3** to **4**, 1 equiv. of $RuH(CO)Cl(PPH_3)_3$ was used in refluxing toluene. [d] **4Bd** was isolated and RCM was performed in refluxing toluene.

indoles **5Bf** and **5Df** in 26 and 94% yield, respectively (3 steps). On the other hand, the isomerization of **3Af** (Pg = Ts, R = *i*Bu) did not proceed at all (Scheme 1), even though, like **4Bf** and **4Df**, it has an *i*Bu substituent. These results support our hypothesis that, in sterically hindered substrates, the isomerization appears not to proceed. The isomerization of **3Bh** (Pg = Ac, R = *c*Pr) and **3Dh** (Pg = CHO, R = *c*Pr) also proceeded as expected. The obtained **4Bh** and **4Dh** were successfully converted to indoles **5Bh** and **5Dh** bearing a cyclopropyl substituent at the 2-position by enamide-ene RCM in 70 and 93% yield, respectively (entries 6 and 7).

Thus, we have succeeded in synthesizing 2-cyclopropyl indoles **5Bh** and **5Dh**, and isopropyl indole **5De**, using a combination of isomerization and enamide-ene RCM. This method was next applied to the chiral 2-*trans* and 2-*cis* cyclopropylindole syntheses. As shown in Table 1, a chiral 2-*trans* cyclopropylindole, **5Di**, was prepared in good yield (entry 8), although the corresponding 2-*cis*-cyclopropylindole derivative, **5Dj**, was not obtained (entry 9), probably due to the significant steric hindrance around the allyl moiety bearing the *cis*-cyclopropane structure in the isomerization.

Synthesis of quinoline, benzofuran and chromene derivatives

Next, we applied the above method to construct other chiral cyclopropyl heterocycles, *e.g.*, quinoline, benzofuran and chromene derivatives. The structural diversity and biological importance of these heterocycles, found in various natural products, have made them attractive targets for synthesis.

As shown in Table 2, 2-alkyl quinolines (**12e**, **f**, **h**), and also chiral *cis*-cyclopropyl and *trans*-cyclopropyl quinolines (**12i** and **j**), were obtained by the diene RCM of **3De**, **3Df**, **3Dh**, **3Di** and **3Dj** in good to excellent yields. The chiral 2-*trans*-cyclopropyl quinoline derivatives were previously prepared by a Suzuki–Miyaura coupling of the *trans*-cyclopropylboronic acids and 2-[(trifluoromethylsulfonyl)oxy]quinoline.[11] However, no synthetic examples of chiral 2-*cis*-cyclopropyl quinoline derivatives have been reported so far. Furthermore, these methods are useful for preparing chiral 2-cyclopropyl oxygen-containing heterocycles, namely chromene and benzofuran derivatives (Scheme 6), the syntheses of which have not been reported either.

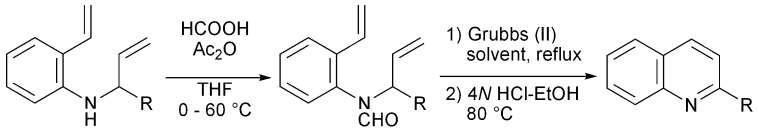
Conclusion

We have developed a new method for the preparation of chiral 2-*trans*-cyclopropyl indoles using alkene isomerization/enamide-ene RCM, which successfully led to our H_4 antagonist candidates. Moreover, this method is applicable to the synthesis of chiral 2-cyclopropyl quinolines, benzofurans, and chromene derivatives (both *cis* and *trans*).

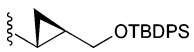
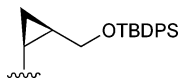
Experimental section

General procedure for α,ω-diene (6) synthesis. A solution of aldehyde, aniline and MS4A in Et_2O (SM 0.2 M) was stirred at rt for 10 h. After the addition of Et_2O (SM 0.1 M), to the resulting solution was added BF_3·Et_2O at –40 °C and the mixture stirred at the same temperature for 30 min. After the addition of vinyl magnesium bromide (1.0 M in THF) or vinyl magnesium chloride (1.46 M in THF) at –40 °C, the mixture was heated gradually to 0 °C and stirred for 15 h. After the addition of sat. aq. NH_4Cl, the mixture was partitioned between AcOEt and sat. aq. NH_4Cl. The organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated at reduced pressure. The residue

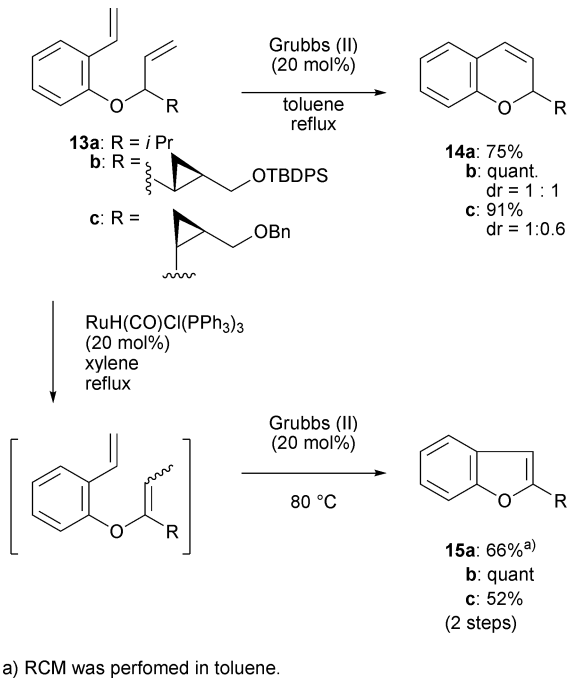
Table 2 Synthesis of 2-alkyl quinolines



6 3D 12

Entry	R	6	Grubbs (II) (mol%)	Solvent	Yield of **12** (%, 3 step)
1	*i*Pr	**6e**	10	CH_2Cl_2	76
2	*i*Bu	**6f**	10	CH_2Cl_2	87
3	*c*Pr	**6h**	10	CH_2Cl_2	77
4		**6i**	20	benzene	67[a]
5		**6j**	20	benzene	67[a]

[a] The corresponding TBDPS was removed and a hydroxy compound obtained.



Scheme 6 Synthesis of 2-alkyl chromene and benzofuran derivatives.

was purified by Flash silica gel column chromatography (hexane) to give the α,ω-diene as a pale yellow oil.

(1*R*,2*R*)-2-*t*-Butyldiphenylsilyloxymethyl-1-[1-(4-chloro-2-vinyl-phenylamino)prop-2-en-1-yl]cyclopropane (6g). 6g (35 mg, 69.3 mmol, 2 steps 69%, dr = 1 : 1) was prepared from (1*R*, 2*R*)-2-(*tert*-butyldiphenylsilyloxy)methyl-1-formyl cyclopropane[5a] (34 mg, 99.8 mmol), 2-vinyl-4-chloroaniline[12] (16 mg, 102 mmol), MS4A (33 mg), $BF_3{\cdot}Et_2O$ (60 mL, 0.486 mmol) and vinyl magnesium bromide (1.00 M in THF, 230 mL, 0.230 mmol). $[\alpha]_D^{21}$ –12.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, diastereomeric mixture): δ 7.68–7.66 (4H, m), 7.44–7.34 (6H, m), 7.22–7.20 (1H, m), 7.04–7.02 (1H, m), 6.73–6.64 (1H, m), 6.48–6.44 (1H, m), 5.81–5.73 (1H, m), 5.63–5.56 (1H, m), 5.31–5.12 (3H, m), 4.00 (1H, brs), 3.80–3.72 (1H, m), 3.41–3.21 (2H, m), 1.11–1.01 (10H, m), 0.98–0.92 (1H, m) and 0.54–0.41 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.09, 138.24, 137.87, 135.57, 135.55, 133.73, 133.69, 133.67, 131.67, 131.53, 129.63, 129.62, 128.19, 128.11, 127.66, 127.62, 126.77, 126.67, 125.56, 125.46, 121.96, 121.90, 117.33, 115.64, 115.43, 113.25, 113.20, 66.75, 66.48, 59.60, 59.00, 26.91, 26.86, 22.54, 22.11, 19.48, 19.22, 19.20, 18.57, 7.86 and 7.67; LR-MS (FAB): *m*/*z* 501 (M^+); anal. calc. for $C_{31}H_{36}ClNOSi$: C, 74.15; H, 7.23; N, 2.79; found: C, 73.86; H, 7.33; N, 2.97%.

General procedure for *N*-acetyl 2-alkyl indole derivative (5B) synthesis.

Acetylation. A solution of α,ω-diene (**6**), *N*,*N*-diisopropylethylamine (10 equiv.) and acetic anhydride (10 equiv.) in toluene (SM 0.1 M) was refluxed for 24 h. After cooling and addition of sat. aq. $NaHCO_3$, the reaction mixture was partitioned between AcOEt and sat. aq. $NaHCO_3$. The organic layers were washed with sat. aq. NH_4Cl and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give *N*-acetyl derivative (**3B**) as a yellow oil.

Isomerization and RCM. The mixture of the corresponding **3B** and $Ru(CO)HCl(PPh_3)_3$ (20 mol%) in xylene (SM 0.1 M) was refluxed for 24 h. After cooling, Grubbs' 2nd generation catalyst (20 mol%) was added and the resulting mixture stirred at 120 °C for 5 h. After cooling, the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the *N*-acetylindole derivative (**5B**) as a colorless oil.

Acknowledgements

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Notes and references

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