An Efficient Route to Benzene and Phenol Derivatives via Ring-Closing Olefin Metathesis

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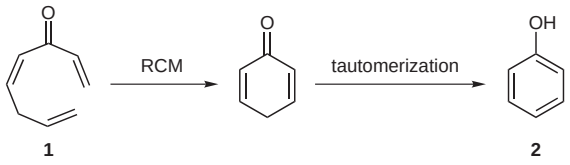
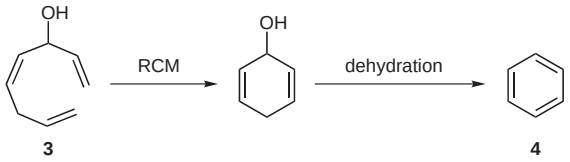
Abstract: Without the formation of inseparable regioisomers, various substituted phenol derivatives **2** and benzene derivatives **4** were prepared through RCM–tautomerization and RCM–dehydration protocols. A new synthetic route to precursors **1** and **3** enabled efficient access to these aromatic compounds.

Key words: annulations, metathesis, ring closure, ruthenium, tautomerism

Ruthenium-catalyzed ring-closing olefin metathesis (RCM) has emerged as a valuable tool for the preparation of substituted aromatic compounds in recent years.[1,2] We have also been interested in the development of synthetic methods for carbocyclic aromatic compounds using RCM.[2g,j] In our first report, we showed that derivatives of phenol (**2**), which are one of the most important classes of aromatic compounds, can be prepared from the corresponding 1,4,7-trien-3-ones **1** using the RCM–tautomerization protocol in which the ketonic tautomers of the phenols are advantageously generated (Equation 1).[2j] In this connection, we recently extended the method to the RCM–dehydration protocol to obtain derivatives of benzene (**4**) by use of the corresponding 1,4,7-trien-3-ols **3** as the starting material (Equation 2).[2g] The most important benefit offered by these methods is that aromatic compounds having various structures can be produced without the formation of inseparable regioisomers.



Equation 1



Equation 2

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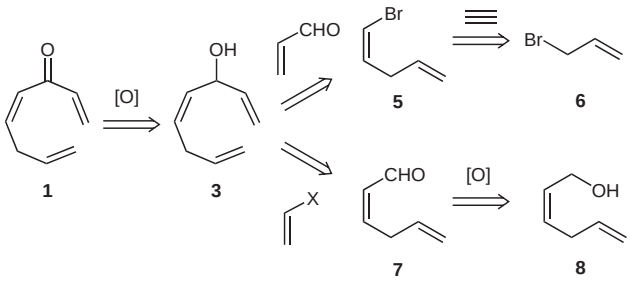
For the synthesis of precursors **1** and **3**, we employed the upper retrosynthetic route in Scheme 1. In this route, 1,4,7-trien-3-ols **3**, which are the precursors not only of benzene derivatives **4** but also of **1**, were constructed by the coupling reaction between α,β-unsaturated aldehydes and **5**. Bromodienes **5** were obtained via the palladium-catalyzed *cis*-selective bromoallylation[3] of alkynes with allyl bromides **6**. Although this route provided a variety of precursors **1** and **3**, there was an important limitation. In the palladium-catalyzed bromoallylation step, available alkynes were limited to terminal or symmetrical internal alkynes. The use of unsymmetrical internal alkynes mostly resulted in a mixture of inseparable regioisomers of **5**.

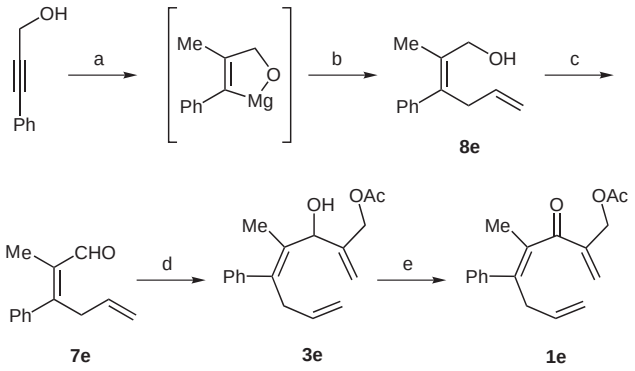


Scheme 1

Herein, we report our continuing study of the synthesis of phenol derivatives **2** and benzene derivatives **4** using RCM, in which precursors **1** and **3** were prepared via the lower retrosynthetic route in Scheme 1. The new route, which extends the scope of resulting aromatic compounds, includes the coupling reaction between 2,5-hexadienals **7** and vinyl halides for the preparation of **3**, and the oxidation of 2,5-hexadienols **8** into **7**.

The route to **1** and **3** performed in this study is exemplified by the synthesis of **1e** and **3e** in Scheme 2. Starting material **8e** was prepared by stereoselective carbometalation of propargyl alcohol followed by allylation[4] developed by Fallis and co-workers. After the oxidation of **8e** with Dess–Martin periodinane, the Nozaki–Hiyama–Kishi reaction[5] of resulting **7e** with 2-iodoallyl acetate gave 1,4,7-trien-3-ol **3e**. Treatment of **3e** with MnO_2 gave corresponding 1,4,7-trien-3-one **1e**. A series of **1** and **3** were likewise prepared in this way[6,7] and were subjected to the RCM reaction.

Table 1 shows the results of the synthesis of benzene derivatives **4**.[8] In all cases, the RCM–dehydration of **3** proceeded well and corresponding benzene derivatives **4**

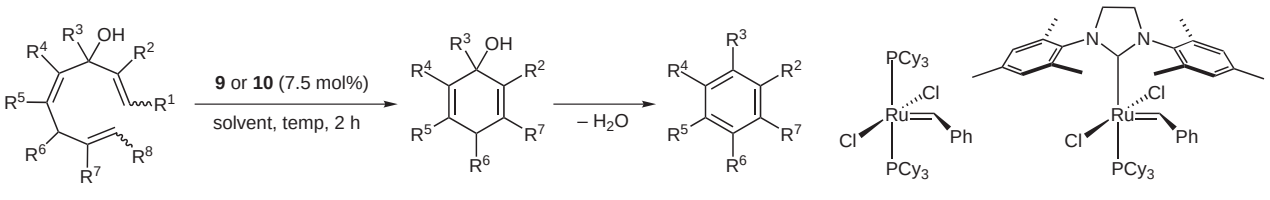


Scheme 2 *Reagents and conditions*: (a) MeMgCl (3.2 equiv), THF–toluene, reflux, 18 h; (b) allyl iodide (3.6 equiv), reflux, 24 h, 79%; (c) Dess–Martin periodinane (2.0 equiv), CH_2Cl_2, r.t., 1 h, 96%; (d) 2-iodoallyl acetate (2.5 equiv), $CrCl_2$ (3.5 equiv), $NiCl_2$ (0.35 mol%), DMF, r.t., overnight, 63%; (e) MnO_2 (30 equiv), CH_2Cl_2, r.t., 24 h, 70%.

were obtained in excellent yields. The rate of the RCM reaction was highly dependent on the number of substituents and their steric hindrance at the reacting double bonds. For the formation of a disubstituted double bond in the RCM reactions that gave benzene derivatives **4a**,**b**, the conditions using Grubbs' first-generation catalyst **9**[9] at room temperature sufficed for the full conversion (entries 1 and 2). In contrast, the reaction of **3c**,**d** that have a methyl group at R^1 or R^8 position required more active Grubbs' second-generation catalyst **10**[10] and higher temperature (40 °C), even though a disubstituted double bond was formed as a result (entries 3 and 4). The formation of a trisubstituted double bond in the RCM also required the latter conditions (entries 5 and 6). A further increase in temperature (80–100 °C) was required for the reactions of **3g**,**h** in which tetrasubstituted double bonds were formed (entries 7 and 8).

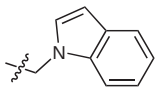
Next, the RCM–tautomerization protocol for the synthesis of phenol derivatives **2** from **1** was examined, and the results are summarized in Table 2.[11] In agreement with the known propensity of the electron-deficient dienic system to be poorly reactive in RCM reactions,[12] the reactivities of 1,4,7-trien-3-ones **1** were lower than those of 1,4,7-trien-3-ols **3**. However, the reactions of **3** proceeded smoothly to give **2** in excellent yields by increasing temperature in the range of 20 °C to 40 °C based on the temperature of the reactions of the corresponding **3** (Table 1 vs. Table 2).

Table 1 Synthesis of Benzene Derivatives **4** by Ruthenium-Catalyzed RCM–Dehydration[a]



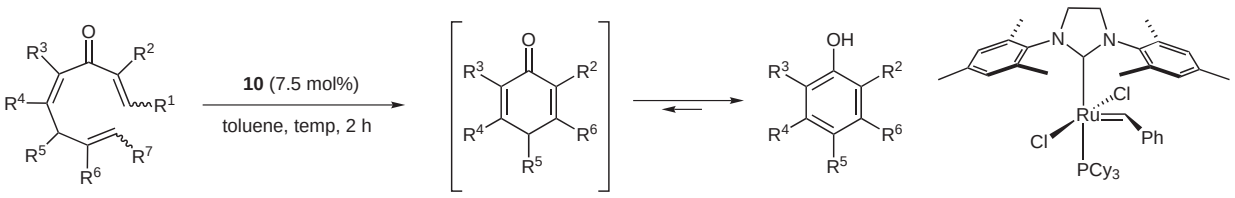
Entry	Substrate	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Product	Cat.	Temp	Yield (%)[b]
1[c]	**3a**	H	H	H	Ph	Me	H	H	H	**4a**	**9**	r.t.	>99
2[d]	**3b**	H	H	Me	H	C_2H_4OTIPS	H	H	H	**4b**	**9**	r.t.	98
3[c]	**3c**	Me	H	H	*i*-Pr	4-FC_6H_4	H	H	H	**4c**	**10**	40 °C	98
4[c,e]	**3d**	H	H	H	Me	Ph	Me	H	Me	**4d**	**10**	40 °C	97
5[d]	**3e**	H	CH_2OAc	H	Me	Ph	H	H	H	**4e**	**10**	40 °C	87
6[d]	**3f**	H	X[f]	H	Me	Ph	H	H	H	**4f**	**10**	40 °C	94
7[d,g]	**3g**	H	Me	H	H	C_2H_4OTIPS	H	Me	H	**4g**	**10**	80 °C	97
8[d,g]	**3h**	H	CH_2OAc	H	Ph	Me	H	Me	H	**4h**	**10**	100 °C	90

[a] RCM was carried out with **3** and ruthenium catalyst (**9** or **10**, 7.5 mol%) in CH_2Cl_2 for 2 h.
[b] Isolated yield.
[c] For the dehydration, the reaction mixture after RCM was treated with PTSA (10 mol%) and stirred for 1 h at r.t.
[d] For the dehydration, the reaction mixture after RCM was treated with silica gel (SiO_2, excess) and stirred for 1 h at r.t.
[e] When the amount of catalyst **10** was decreased to 5.0 mol% or 2.5 mol%, the isolated yield of **4d** was decreased to 94% and 80%, respectively.
[f] X =



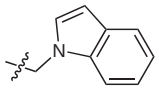
[g] Reaction was carried out in toluene.

Table 2 Synthesis of Phenol Derivatives **2** by Ruthenium-Catalyzed RCM–Tautomerization[a]



Entry	Substrate	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Product	Temp	Yield (%)[b]
1	**1c**	Me	H	*i*-Pr	4-FC_6H_4	H	H	H	**2c**	80 °C	95
2	**1e**	H	CH_2OAc	Me	Ph	H	H	H	**2e**	80 °C	95
3	**1f**	H	X[c]	Me	Ph	H	H	H	**2f**	80 °C	97
4	**1g**	H	Me	H	C_2H_4OTIPS	H	Me	H	**2g**	100 °C	91
5	**1i**	H	Me	Me	Ph	Me	H	Me	**2i**	100 °C	91

[a] Reaction was carried out with **1** and ruthenium catalyst (**10**, 7.5 mol%) in toluene for 2 h.
[b] Isolated yield.
[c] X =



In summary, we have established an efficient synthetic route to carbocyclic aromatic compounds using RCM. Starting with readily available 2,5-hexadienols **8**, a variety of benzene derivatives **4** and phenol derivatives **2** were successfully synthesized. Most of the benzene derivatives and phenol derivatives prepared here cannot be easily obtained by our previous synthetic route. Further developments will be reported in due course.

Acknowledgment

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(6) The yield ranges were >99–62% (**8** to **7**), 76–61% (**7** to **3**), 85–32% (**3** to **1**). For the preparation of **3b**, the reaction of (*E*)-4-[2-(triisopropylsiloxy)ethyl]-3,6-heptadien-2-one which was easily prepared from **7b**, with $C_2H_3MgCl/CeCl_3$ was performed.
(7) The stereoselective hydroalumination of propargyl alcohol followed by allylation developed by Langille and Jamison was employed only for the synthesis of **8b** and **8g**, see: Langille, N. F.; Jamison, T. F. *Org. Lett.* **2006**, *8*, 3761.
(8) **Typical Experimental Procedure for RCM–Dehydration – Synthesis of 4-Acetoxymethyl-2-methylbiphenyl (4e)** To a solution of 1,4,7-trien-3-ol **3e** (43.0 mg, 0.150 mmol) in CH_2Cl_2 (15 mL) was added 7.5 mol% of catalyst **10** (9.3 mg, 0.011 mmol) in one portion under nitrogen. After stirring for 2 h at 40 °C, the reaction mixture was treated with silica gel(excess) and stirred for 1 h at r.t. The mixture was passed through Celite® and the filtrate was concentrated under reduced pressure. Purification by PTLC on silica gel (hexane–EtOAc, 5:1) gave **4e** (31.5 mg, 0.131 mmol, 87%). ^1H NMR ($CDCl_3$): δ = 2.12 (s, 3 H), 2.29 (s, 3 H), 5.12 (s, 2 H), 7.22–7.36 (m, 6 H), 7.41 (t, *J* = 7.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 20.42, 21.06, 66.19, 125.74, 126.91, 128.10, 129.09, 130.05, 130.30, 134.77, 135.72, 141.42, 141.98, 170.95. HRMS–FAB: *m/z* calcd for $C_{16}H_{16}O_2$ [M^+]: 240.1150; found: 240.1152.

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(11) **Typical Experimental Procedure for RCM–Tautomerization – Synthesis of 2-Acetoxymethyl-6-methyl-5-phenylphenol (2e)**
A solution of 1,4,7-trien-3-one **1e** (42.6 mg, 0.150 mmol) in CH_2Cl_2 (15 mL) was treated with 7.5 mol% of catalyst **10** (9.3 mg, 0.011 mmol) in one portion under nitrogen and stirred for 2 h at 80 °C. The mixture was concentrated under reduced pressure and purified by PTLC on silica gel (hexane–EtOAc, 4:1) to give **2e** (36.7 mg, 0.143 mmol, 95%). ^{1}H NMR ($CDCl_3$): δ = 2.13 (s, 3 H), 2.17 (s, 3 H), 5.16 (s, 2 H), 6.82 (d, *J* = 7.9 Hz, 1 H), 7.15 (d, *J* = 7.9 Hz, 1 H), 7.27–7.30 (m, 2 H), 7.33 (tt, *J* = 7.4, 1.2 Hz, 1 H), 7.40 (t, *J* = 7.7 Hz, 2 H), 8.01 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 13.62, 20.95, 63.85, 119.89, 121.78, 124.55, 126.92, 128.03, 128.96, 129.13, 141.53, 144.98, 154.01, 173.97. HRMS–FAB: *m/z* calcd for $C_{16}H_{16}O_3$ [M^+]: 256.1099; found: 256.1095.

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