Efficient synthetic routes to aromatic compounds using ring-closing olefin metathesis followed by dehydration, oxidation, and tautomerization†

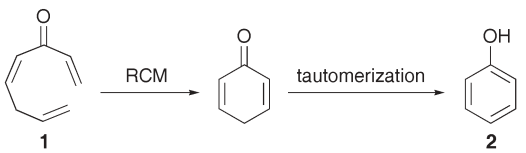
Kazuhiro Yoshida,* Takeharu Toyoshima and Tsuneo Imamoto*

Received (in Cambridge, UK) 12th April 2007, Accepted 20th June 2007
First published as an Advance Article on the web 5th July 2007
DOI: 10.1039/b705581a

A simple synthetic approach to aromatic compounds using combinations of RCM, dehydration, oxidation, and tautomerization is described.

Because of the important roles played by substituted aromatic compounds in organic chemistry, the discovery of new methods for their preparation continues to be an active area of research. From a large number of reactions available, the most commonly used for substituted aromatic compounds is electrophilic aromatic substitution.[1] However, despite advances of the reaction, its potential weak point in terms of difficulty in controlling the regioselectivity of substitution has limited its use with some substitution patterns and substituents. Alternatively, a significant amount of work has been devoted to the stepwise construction of aromatic rings from linear components because it enables perfect regioselective access to the desired aromatic compounds.[2] Most recently, the ring-closing olefin metathesis (RCM), which is one of the most powerful methods to form carbon–carbon double bonds of cyclic compounds,[3] has begun to apply this strategy.[4–6]

Along these lines, we have also reported that phenol derivatives **2**[5m] and benzene derivatives **4**[5h] can be obtained from tandem RCM/tautomerization of 1,4,7-trien-3-ones **1** and RCM/dehydration of 1,4,7-trien-3-ols **3**, respectively (eqn (1) and (2)). However, precursors **1** and **3** could not be readily prepared, especially with regard to the internal *cis* double bond (geometrically). Motivated by this problem, we strived to search for more efficient and general synthetic approaches. Herein we report new efficient and general synthetic methods for phenol, benzene, and resorcinol derivatives, in which the stereoselective construction of the internal double bond of the precursors is no longer a problem.

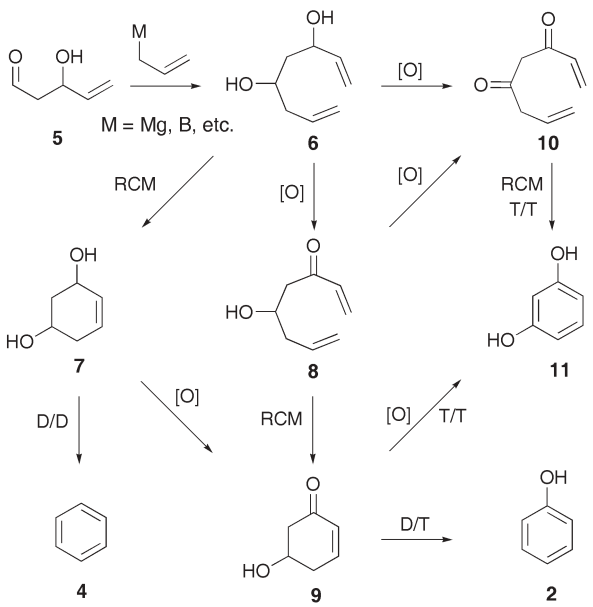


Department of Chemistry, Graduate School of Science, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan. E-mail: kyoshida@faculty.chiba-u.jp; imamoto@faculty.chiba-u.jp; Fax: +81 43 290 2791; Tel: +81 43 290 2790

† Electronic supplementary information (ESI) available: experimental procedures and compound characterization data. See DOI: 10.1039/b705581a

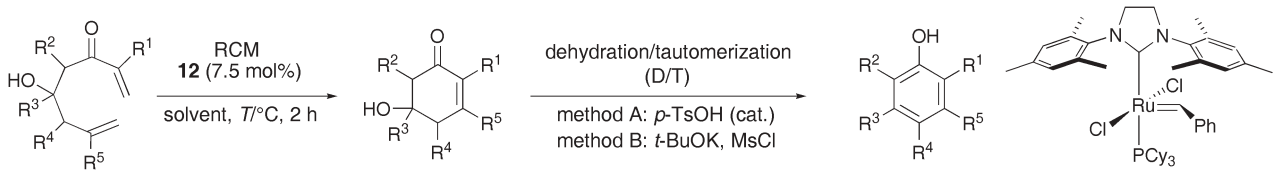
Our strategy is outlined in Scheme 1 and has the following three core objectives: 1) use of highly reliable transformations and easily accessible reagents in all steps; 2) keeping back the problematic formation of the internal *cis* double bond in the last steps (namely, after cyclization); and 3) divergent output (benzene, phenol, and resorcinol) from common precursors. The synthetic route would start from the allylation of readily available aldol product **5** with various allylic metal reagents (M = Mg, B, Sn, *etc.*) to afford 1,7-diene-3,5-diol **6**, which would be the fountainhead for benzene, phenol, and resorcinol derivatives. The formation of benzene derivatives **4** would be achieved by the RCM/dehydration/dehydration of **6** *via* 4-cyclohexene-1,3-diol **7** (route **6–7–4**). After oxidation of **6** at the allylic alcohol position, the RCM/dehydration/tautomerization of 5-hydroxy-1,7-octadien-3-one **8** would produce phenol derivatives **2** *via* 5-hydroxy-2-cyclohexenone **9** (route **6–8–9–2**). The RCM/tautomerization/tautomerization of 1,7-octadiene-3,5-dione **10**, which would be prepared by the oxidation of **6**, would result in the formation of resorcinol derivatives **11** (route **6–10–11**). It should be mentioned that there are other promising routes including **6–7–9–2** and **6–8–9–11**.

Among the above-mentioned routes, we chose to investigate route **6–8–9–2** first, and the results are shown in Table 1.[7,8] In all



Scheme 1

Table 1 Synthesis of phenol derivatives **2** by RCM/dehydration/tautomerization

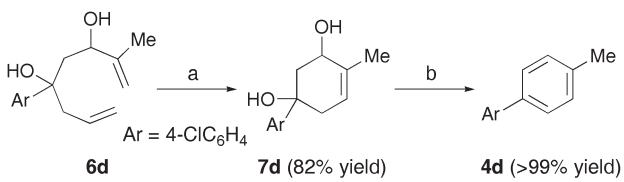


							RCM[a]			D/T[b]	
Entry	Substrate	R^1	R^2	R^3	R^4	R^5	Solvent	T/°C	Yield[c] (%)	Method	Yield[c] (%)
1[d]	**8a**	H	Me	Et	H	H	CH_2Cl_2	rt	84 (**9a**)	A	85 (**2a**)
2	**8b**	Me	H	H	H	H	CH_2Cl_2	40 °C	89 (**9b**)	A	91 (**2b**)
3	**8c**	Me	H	H	Me	H	CH_2Cl_2	40 °C	94 (**9c**)	A	>99 (**2c**)
4	**8d**	Me	H	4-ClC_6H_4	H	H	CH_2Cl_2	40 °C	>99 (**9d**)	A	>99 (**2d**)
5	**8e**	Me	–$(CH_2)_4$–		H	H	CH_2Cl_2	40 °C	>99 (**9e**)	A	>99 (**2e**)
6	**8f**	$CH_2OSiMe_2{}^tBu$	H	Me	H	H	CH_2Cl_2	40 °C	99 (**9f**)	B	88 (**2f**)[e]
7	**8g**	H	H	Ph	H	Me	CH_2Cl_2	40 °C	81(**9g**)[f]	A	>99 (**2g**)
8	**8h**	H	Me	Ph	H	Me	toluene	80 °C	>99 (**9h**)	A	97 (**2h**)
9	**8i**	H	H	H	H	CH_2OBn	toluene	80 °C	84 (**9i**)	A	90 (**2i**)
10	**8j**	H	H	$CH_2C(Me)=CH_2$	H	Me	toluene	100 °C	87 (**9j**)	B	>99 (**2j**)[e]

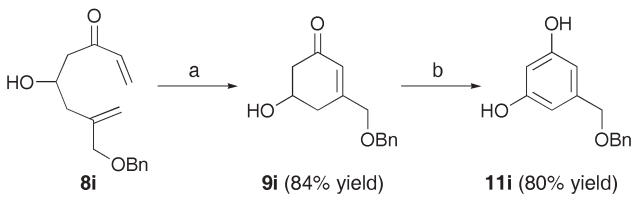
[a] Ring-closing olefin metathesis was carried out with **8** and ruthenium catalyst (**12**, 7.5 mol%) for 2 h. [b] Method A: *p*-toluenesulfonic acid (10 mol%), benzene, 70 °C, overnight. Method B: *t*-BuOK (4.4 eq.), MsCl (3.2 eq.), CH_2Cl_2, rt, 2.5 h. [c] Isolated yield by silica gel chromatography. [d] An one pot procedure using **12** (7.5 mol%) and *p*-toluenesulfonic acid (10 mol%) at the same time in toluene at 70 °C gave a mixture of 83% of **9a** and 17% of **2a**. [e] The corresponding mesylated phenol was obtained. [f] When the amount of catalyst **12** was decreased to 2.5 mol%, the isolated yield of **9g** was decreased to 50%.

cases, as expected, the RCM of **8** with Grubbs' second-generation catalyst **12**[9] proceeded cleanly to afford desired cyclized product **9** as the only identifiable material. Although increasing the steric bulk of the substituents tends to decrease the reaction rates as usual, increasing the temperature led to completion of the reaction in 2 h. For the next dehydration/tautomerization step, we employed two conditions. Most of the isolated **9** (**9a–9e**, **9g–9i**) were converted into the corresponding phenols **2** by treatment of their benzene solution with a catalytic amount of *p*-toluenesulfonic acid. In the case of **9f** that has an acid-sensitive silyl ether, basic conditions (mesylation of the hydroxyl group with *t*-BuOK, followed by elimination) were employed. Similarly, the mesylation/elimination process was also effective for **9j** that was subjected to isomerization of the carbon–carbon double bond from terminal to internal at the R^3 position in the presence of *p*-toluenesulfonic acid.[10]

Our attention was next turned to the formation of benzene derivatives **4** (route **6–7–4**) and resorcinol derivatives **11** (route **6–8–9–11**). Preliminary experiments revealed that both routes show promise. As shown in Scheme 2, the double dehydration of **7d**, which was prepared by RCM of **6d**, with *p*-toluenesulfonic acid gave corresponding benzene derivative **4d** in quantitative yield. Moreover, Swern oxidation of **9i** followed by automatic double tautomerization gave **11i** in good yield (Scheme 3).[11]



Scheme 2 (a) **12** (7.5 mol%), CH_2Cl_2, 40 °C, 2 h; (b) *p*-toluenesulfonic acid (10 mol%), benzene, overnight, 70 °C.



Scheme 3 (a) **12** (7.5 mol%), toluene, 80 °C, 2 h; (b) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1.5 h.

In summary, we have developed new efficient synthetic routes to aromatic compounds, which hold great promise for broad applicability. The advantages are that no inseparable regioisomers are produced, and that all the mild transformations employed, highlighted by RCM, may enable introduction of a wide variety of substituents on aromatic rings. We are currently studying the other routes indicated in Scheme 1 and the routes for the synthesis of catechols and hydroquinones with similar methodology.

We appreciate the financial support from the Sumitomo foundation and from a Grant-in-Aid for Scientific Research, the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references

1 For a comprehensive review, see: *Modern Arene Chemistry*, ed. D. Astruc, Wiley-VCH, Weinheim, 2002.
2 For example, see: (*a*) R. L. Danheiser and S. K. Gee, *J. Org. Chem.*, 1984, **49**, 1672; (*b*) P. Turnbull and H. W. Moore, *J. Org. Chem.*, 1995, **60**, 644; (*c*) K. H. Dötz and P. Tomuschat, *Chem. Soc. Rev.*, 1999, **28**, 187; (*d*) A. R. Katritzky, J. Li and L. Xie, *Tetrahedron*, 1999, **55**, 8263; (*e*) S. Saito and Y. Yamamoto, *Chem. Rev.*, 2000, **100**, 2901; (*f*) S. Serra, C. Fuganti and A. Moro, *J. Org. Chem.*, 2001, **66**, 7883; (*g*) T. Takahashi, M. Ishikawa and S. Huo, *J. Am. Chem. Soc.*, 2002, **124**, 388; (*h*) X. Bi, D. Dong, Q. Liu, W. Pan, L. Zhao and B. Li, *J. Am.*

Chem. Soc., 2005, **127**, 4578; (*i*) Y. Yamamoto, J.-I. Ishii, H. Nishiyama and K. Itoh, *J. Am. Chem. Soc.*, 2005, **127**, 9625.

3 For a comprehensive review, see: (*a*) *Handbook of Metathesis*, ed. R. H. Grubbs, Wiley-VCH, Weinheim, 2003. For reviews, see: (*b*) R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413; (*c*) A. Fürstner, *Angew. Chem.*, 2000, **112**, 3140, (*Angew. Chem., Int. Ed.*, 2000, **39**, 3012); (*d*) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18.

4 For a review, see: T. J. Donohoe, A. J. Orr and M. Bingham, *Angew. Chem.*, 2006, **118**, 2730, (*Angew. Chem., Int. Ed.*, 2006, **45**, 2664).

5 For reports on the direct synthesis of carbocyclic aromatic compounds using RCM, see: (*a*) A. Iuliano, P. Piccioli and D. Fabbri, *Org. Lett.*, 2004, **6**, 3711; (*b*) E. R. Walker, S. Y. Leung and A. G. M. Barrett, *Tetrahedron Lett.*, 2005, **46**, 6537; (*c*) M. C. Bonifacio, C. R. Robertson, J.-Y. Jung and B. T. King, *J. Org. Chem.*, 2005, **70**, 8522; (*d*) S. C. Pelly, C. J. Parkinson, W. A. L. Van Otterlo and C. B. De Koning, *J. Org. Chem.*, 2005, **70**, 10474. For reports using RCM/elimination protocol, see: (*e*) P. Evans, R. Grigg, M. I. Ramzan, V. Sridharan and M. York, *Tetrahedron Lett.*, 1999, **40**, 3021; (*f*) K. S. Huang and E. C. Wang, *Tetrahedron Lett.*, 2001, **42**, 6155; (*g*) Y. Chen, H. V. R. Dias and C. J. Lovely, *Tetrahedron Lett.*, 2003, **44**, 1379; (*h*) K. Yoshida, F. Kawagoe, N. Iwadate, H. Takahashi and T. Imamoto, *Chem.–Asian J.*, 2006, **1**, 611; (*i*) P.-Y. Chen, H.-M. Chen, L.-Y. Chen, J.-Y. Tzeng, J.-C. Tsai, P.-C. Chi, S.-R. Li and E.-C. Wang, *Tetrahedron*, 2007, **63**, 2824. For a report using RCM/oxidation protocol, see: (*j*) S. Kotha and K. Mandal, *Tetrahedron Lett.*, 2004, **45**, 2585; (*k*) S. Ma, F. Yu and J. Zhao, *Synlett*, 2007, 583. For reports using RCM/tautomerization protocol, see :(*l*) W. A. L. van Otterlo, E. L. Ngidi, E. M. Coyanis and C. B. de Koning, *Tetrahedron Lett.*, 2003, **44**, 311; (*m*) K. Yoshida and T. Imamoto, *J. Am. Chem. Soc.*, 2005, **127**, 10470.

6 For selected recent reports on the synthesis of heterocyclic aromatic compounds using RCM, see: (*a*) M. Arisawa, A. Nishida and M. Nakagawa, *J. Organomet. Chem.*, 2006, **691**, 5109; (*b*) T. J. Donohoe, L. P. Fishlock, A. R. Lacy and P. A. Procopiou, *Org. Lett.*, 2007, **9**, 953.

7 The yield ranges to the starting materials were 92–49% (**5** to **6**) and 86–53% (**6** to **8**). See Electronic Supplementary Information† for experimental details.

8 The compounds appearing in this paper are fundamentally stable and showed no deterioration after storage on a bench or in a refrigerator for several months.

9 (*a*) M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953; (*b*) T. M. Trnka, J. P. Morgan, M. S. Sanford, T. E. Wilhelm, M. Scholl, T.-L. Choi, S. Ding, M. W. Day and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 2546.

10 The mesylated phenols were obtained under the conditions in both cases of **9f** and **9j**.

11 Sulikowski and co-workers reported a hydroquinone formation by oxidation/tautomerization/tautomerization of an RCM product in their cycloenedione synthesis, see: W.-D. L. Kwangho, K. Kim and G. A. Sulikowski, *Org. Lett.*, 2005, **7**, 1687.

