

# A New Synthetic Approach to Phenol Derivatives: Use of Ring-Closing Olefin Metathesis

Kazuhiro Yoshida\* and Tsuneo Imamoto\*

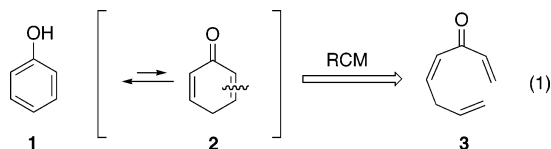
Department of Chemistry, Faculty of Science, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

Received February 9, 2005; E-mail: kyoshida@faculty.chiba-u.jp; imamoto@faculty.chiba-u.jp

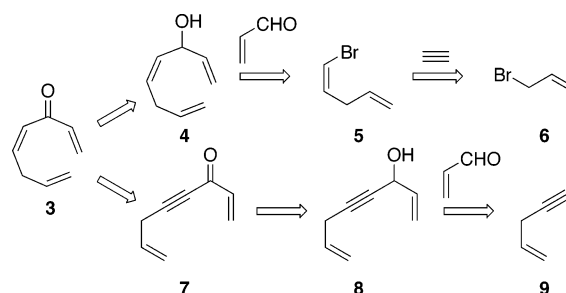
Electrophilic aromatic substitution, which is represented by the Friedel–Crafts reaction, is a very important means for preparing substituted aromatic compounds.<sup>1</sup> However, because of its stringent reaction conditions and the nonselective substitution onto the aromatic rings, it often does not give the product demanded by synthetic chemists. One alternative approach is the direct construction of aromatic rings from linear components. For example, the cyclotrimerization of acetylenes, which was first developed by Reppe, offers a straightforward synthesis of aromatic derivatives.<sup>2</sup> However, in most cases, the unsolved problem of the selective orientation of the substituents on the aromatic rings surfaces again.

Ring-closing olefin metathesis (RCM) has become one of the most important methods for constructing cyclic compounds of various sizes in organic synthesis.<sup>3</sup> The tremendous success of this reaction is largely due to the discovery by Grubbs et al. of active and well-defined ruthenium catalysts,<sup>4,5</sup> which exhibit not only high reactivity but also tolerance to a variety of functional groups. Herein we report a new synthetic approach to phenol derivatives, which are one of the most important classes of aromatic compounds, from linear precursors, utilizing the ruthenium-catalyzed RCM reaction.<sup>6</sup>

As phenol **1** is in equilibrium with ketonic tautomer **2**, we anticipated that 1,4,7-trien-3-one **3** would be a potential precursor of **1** if the RCM reaction were carried out to form **2** (eq 1). Because



Scheme 1



of the functional group tolerance of the Grubbs' catalysts, it seemed promising to adopt these compounds even if they possessed carbonyl and phenol hydroxyl groups on their frameworks.

Two synthetic strategies for the required trienone **3** are outlined in Scheme 1. The upper route involves the oxidation of trienol **4**, the coupling of bromodiene **5** with  $\alpha,\beta$ -unsaturated aldehyde, and the palladium-catalyzed bromoallylation<sup>7</sup> of alkyne with allyl bromide **6**. The formation of **3** can also be achieved through the lower route in Scheme 1. Thus, trienone **3** might be derived from **7** by the cis-addition of an adduct to the triple bond (e.g., hydrogenation with Lindlar catalyst). **7**, in turn, would result from the oxidation of **8**, which could be prepared by the coupling of enyne **9** with  $\alpha,\beta$ -unsaturated aldehyde.

In fact, several trienones **3** with versatile substitution patterns were easily prepared with these synthetic sequences in high yields.<sup>8</sup>

With the desired precursors in hand, the RCM reactions were performed, and the results are summarized in Table 1. When the reaction of **3a** was carried out with 7.5 mol % Grubbs' first-

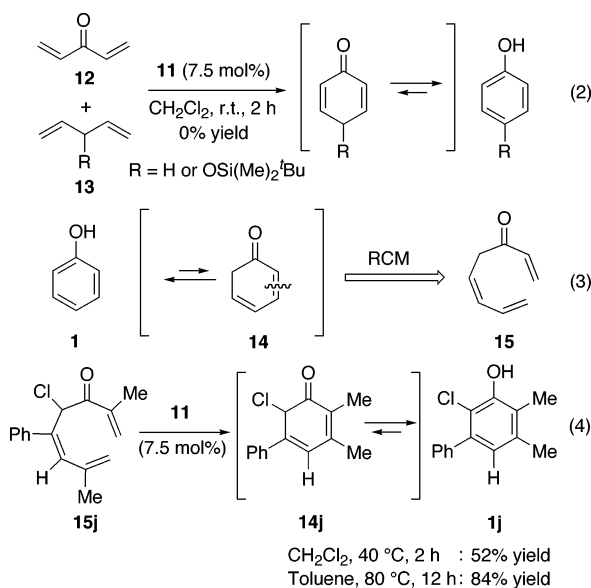
Table 1. Synthesis of Phenol Derivatives **1** by Ruthenium-Catalyzed Ring-Closing Olefin Metathesis<sup>a</sup>

entry	substrate	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	R <sup>7</sup>	product	catalyst (mol %)	temp	yield <sup>b</sup> (%)
1	<b>3a</b>	H	H	<sup>n</sup> Pr	<sup>n</sup> Pr	H	H	H	<b>1a</b>	<b>10</b> (7.5)	r.t.	87
2	<b>3a</b>	H	H	<sup>n</sup> Pr	<sup>n</sup> Pr	H	H	H	<b>1a</b>	<b>11</b> (7.5)	r.t.	93
3	<b>3a</b>	H	H	<sup>n</sup> Pr	<sup>n</sup> Pr	H	H	H	<b>1a</b>	<b>11</b> (5.0)	r.t.	88
4	<b>3a</b>	H	H	<sup>n</sup> Pr	<sup>n</sup> Pr	H	H	H	<b>1a</b>	<b>11</b> (2.5)	r.t.	48
5	<b>3b</b>	H	H	Ph	H	H	H	H	<b>1b</b>	<b>11</b> (7.5)	r.t.	90
6	<b>3c</b>	H	H	Ph	D	H	H	H	<b>1c</b>	<b>11</b> (7.5)	r.t.	92
7	<b>3d</b>	H	Me	<sup>n</sup> Pr	<sup>n</sup> Pr	H	H	H	<b>1d</b>	<b>11</b> (7.5)	r.t.	92
8	<b>3e</b>	H	Et	SiMe <sub>3</sub>	H	H	H	H	<b>1e</b>	<b>11</b> (7.5)	r.t.	97
9	<b>3f</b>	H	C <sub>2</sub> H <sub>4</sub> OH	Ph	H	H	H	H	<b>1f</b>	<b>11</b> (7.5)	r.t.	93
10	<b>3g</b>	H	C <sub>2</sub> H <sub>4</sub> OAc	Ph	H	H	H	H	<b>1g</b>	<b>11</b> (7.5)	r.t.	98
11	<b>3h</b>	H	Me	Ph	H	H	Me	H	<b>1h</b>	<b>11</b> (7.5)	r.t.	40
12	<b>3h</b>	H	Me	Ph	H	H	Me	H	<b>1h</b>	<b>11</b> (7.5)	40 °C	92
13	<b>3i</b>	Me	H	H	H	OSi(Me) <sub>2</sub> Bu	H	Me	<b>1i</b>	<b>11</b> (7.5)	40 °C	0

<sup>a</sup> Reactions were carried out with trienone **3** and ruthenium catalyst (**10** or **11**, 2.5–7.5 mol %) in CH<sub>2</sub>Cl<sub>2</sub> for 2 h. <sup>b</sup> Isolated yield by silica gel chromatography.

generation catalyst **10**<sup>4</sup> at room temperature for 2 h, 2,3-dipropylphenol (**1a**) was formed in 87% yield (entry 1). Switching to Grubbs' second-generation catalyst **11**<sup>5</sup> resulted in a faster reaction in 93% yield (entry 2). When the amount of catalyst **11** was decreased to 5.0 or 2.5 mol %, the chemical yields were decreased to 88% and 48%, respectively (entries 3 and 4).<sup>9</sup> Therefore, we decided that the conditions for entry 2 were the optimum. Under those conditions, precursors **3b** and **3c** were converted in 90% yield into 2-phenylphenol (**1b**) and in 92% yield into 3-deutero-2-phenylphenol (**1c**), respectively (entries 5 and 6). The formation of a trisubstituted double bond in the RCM reactions that gave phenols **1d–g** proceeded without any problems (entries 7–10). Although the RCM reaction of **3h**, where a tetrasubstituted double bond was formed, was slow at room temperature (entry 11), an increase in the temperature led to the full conversion into **1h** in 92% yield (entry 12). One exception was the cyclization of trienone **3i** that bore no terminal olefins, which resulted in recovery of the substrate, even when **11** was used under reflux in CH<sub>2</sub>Cl<sub>2</sub> (entry 13).

We were interested in the tandem cross-metathesis/RCM between dienone **12** and diene **13** to construct phenol derivatives (eq 2), because there would be many difficulties derived from predictability in product selectivity and stereoselectivity. Unfortunately, our preliminary investigations met with failure. None of the desired phenols could be detected by TLC or <sup>1</sup>H NMR measurement of the crude reaction mixtures, probably owing to oligomerization. A detailed design of the substrates with regard to steric and electronic properties will be necessary to achieve this kind of reaction.<sup>10</sup>



Finally, we conducted another experiment as an extension of the RCM reaction. Because phenol **1** is also in equilibrium with ketonic tautomer **14**, we speculated that phenol **1** might be formed from 1,5,7-trien-3-one **15** as well as trienone **3** (eq 3).

As expected, the RCM reaction of **15j**<sup>11</sup> in CH<sub>2</sub>Cl<sub>2</sub> at 40 °C for 2 h gave the corresponding phenol **1j**, although the chemical yield was moderate (eq 4). Further attempts at improving the conversion by changing the solvent to toluene and increasing the temperature to 80 °C as well as the reaction time led to an 84% yield.

In conclusion, we have developed a new synthetic approach to phenol derivatives, utilizing the ruthenium-catalyzed RCM reaction. Most of the phenols prepared here cannot be easily obtained by conventional methods. Ongoing research involves the extension of the RCM reaction to other substrates and the development of tandem cross-metathesis/RCM from two linear components for the synthesis of phenol derivatives.

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**Supporting Information Available:** Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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