

Ring-Closing Olefin Metathesis for the Synthesis of Benzene Derivatives

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Abstract: Benzene derivatives were synthesized in excellent yield from 1,4,7-trien-3-ols by tandem ruthenium-catalyzed ring-closing olefin metathesis (RCM)/dehydration. The method was extended to the tandem RCM/oxidation process to obtain phenol and aniline derivatives. This method displays many advantages over aromatic-substitution-based classical routes.

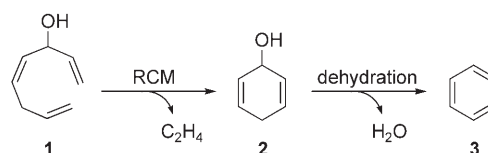
Keywords: aromatic compounds · dehydration · metathesis · oxidation · ring closure

Introduction

The synthesis of benzene derivatives has long been a major subject in organic synthesis owing to their widespread distribution in nature and importance in industrial chemistry. The classic approach based on aromatic substitution, in which a substituent is introduced onto a pre-existing arene, has a potential weak point in terms of difficulty in controlling regioselectivity on the aromatic ring.^[1] In this context, building up the aromatic moiety from acyclic precursors has received growing interest as a promising countermeasure.^[2] Recently, the application of ring-closing olefin metathesis (RCM)^[3] to this strategy has emerged as an interesting variant because of its high reactivity and almost-ideal functional-group tolerance.^[4,5] Herein, we report a simple and efficient synthesis of benzene derivatives, which employs ruthenium-catalyzed tandem RCM/dehydration and RCM/oxidation processes.

Results and Discussion

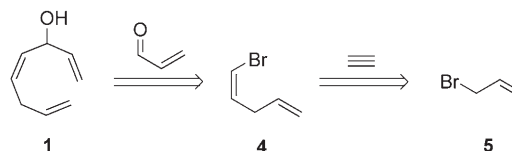
The concept of tandem RCM/dehydration^[6] for the construction of benzene derivatives is shown in Scheme 1. It is anticipated that the RCM of 1,4,7-trien-3-ol (**1**) would give



Scheme 1. Tandem RCM/dehydration procedure.

cyclohexa-2,5-dienol (**2**), from which benzene derivative **3** could be formed after dehydration.

Most of the required 1,4,7-trien-3-ols **1** were easily prepared as reported by us in an earlier study of the synthesis of phenol derivatives.^[5i,7] Thus, the coupling reaction of an α,β -unsaturated aldehyde/ketone with bromodiene **4**, which was synthesized by the palladium-catalyzed bromoallylation^[8] of the appropriate alkyne with allyl bromide **5**, gave the desired **1** with versatile substitution patterns (Scheme 2).

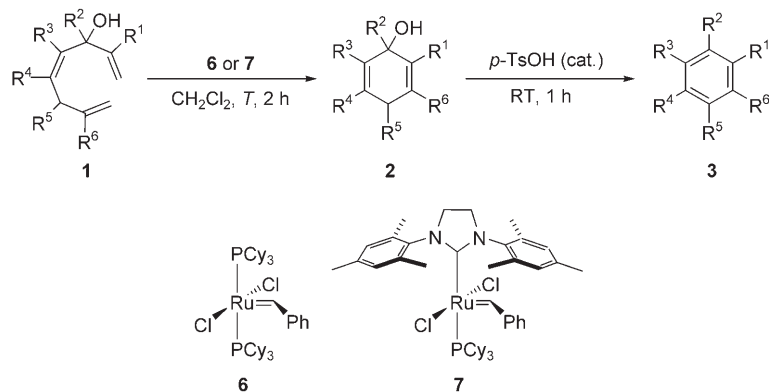


Scheme 2. Retrosynthetic analysis of 1,4,7-trien-3-ol (**1**).

The viability of the RCM/dehydration process was first tested on substrate **1a**, which has a propyl group as both R³ and R⁴ (Table 1). To our delight, when RCM was carried out with Grubbs' first-generation catalyst **6**^[9] at room temperature for 2 h, **2a** was quantitatively obtained, which slowly but spontaneously dehydrated to form 1,2-dipropyl-

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Table 1. Synthesis of benzene derivatives **3** by tandem ruthenium-catalyzed RCM/dehydration.^[a]


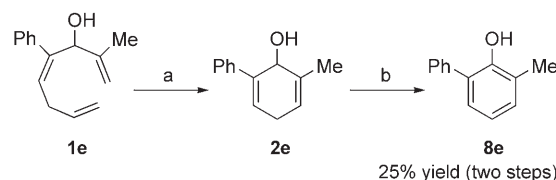
Entry	Substrate	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Product	Catalyst	T	Yield [%] ^[b]
1	1a	H	H	<i>n</i> Pr	<i>n</i> Pr	H	H	3a	6	RT	>99
2	1b	H	H	Ph	H	H	H	3b	6	RT	97
3	1c	H	H	Ph	D	H	H	3c	6	RT	96
4	1d	Me	H	<i>n</i> Pr	<i>n</i> Pr	H	H	3d	6	RT	>99
5	1e	Me	H	Ph	H	H	H	3e	6	RT	>99
6	1f	Et	H	SiMe ₃	H	H	H	3f	6	RT	94
7	1g	Me	H	(CH ₂) ₂ OMe	Ph	H	H	3g	6	RT	99
8	1h	H	Me	Ph	H	H	H	3h	6	RT	80
9	1i	Me	H	Ph	H	Me	H	3i	6	RT	84
10	1j	Ph	H	Ph	H	H	H	3j	7	RT	96
11	1k	(CH ₂) ₂ OH	H	Ph	H	H	H	3k	7	40°C	84
12	1l	(CH ₂) ₂ OAc	H	Ph	H	H	H	3l	7	40°C	>99
13	1m	Me	H	Ph	H	H	Me	3m	7	40°C	91
14 ^[c]	1n	I	H	Ph	H	H	H	3n	7	80°C	0
15 ^[c]	1o	Cl	H	<i>n</i> Pr	<i>n</i> Pr	H	H	3o	7	80°C	86

[a] RCM was carried out with **1** and ruthenium catalyst (**6** or **7**, 7.5 mol%) in CH₂Cl₂ for 2 h. The reaction mixture was treated with *p*-toluenesulfonic acid (*p*-TsOH; 10 mol%) and stirred for 1 h at room temperature. [b] Yield of product isolated by silica-gel chromatography. [c] The reaction was carried out with **7** (15 mol%) in toluene. Cy = cyclohexyl.

benzene **3a**. The dehydration was accelerated by treating the RCM mixture with a catalytic amount of *p*-TsOH. As a result, **3a** was obtained in >99% yield over two steps (Table 1, entry 1). The tandem RCM/dehydration process appears to be general with a number of substrates. As with **1a**, cyclizations with trienols that contain no or only one substituent on the terminal olefins (**1b–i**) were nearly quantitative with catalyst **6** (Table 1, entries 2–9). Increasing the steric bulk on the terminal olefins decreased the reaction rate in the RCM step; therefore, Grubbs' second-generation catalyst **7**^[10] was required to complete these reactions in 2 h (Table 1, entries 10–12). The formation of a tetrasubstituted double bond in the RCM also required second-generation catalyst **7** with an increase in temperature (40°C; Table 1,

Abstract in Japanese:

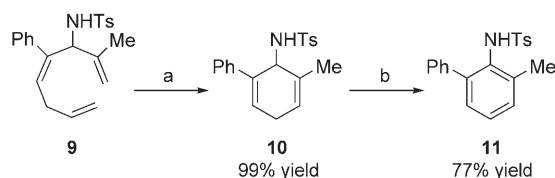
様々な置換基を有する 1,4,7-トリエン-3-オール **1** に対して、連続的閉環オレフィンメタセシス/酸触媒脱水反応を行うことによって、従来の手法では得難い置換ベンゼン誘導体 **3** を単一の生成物として得た。さらに、本手法を応用した連続的閉環オレフィンメタセシス/酸化反応によって、フェノール及びアニリン誘導体を得た。これらのアプローチは、置換芳香族化合物合成法として、従来の芳香族置換反応にはない多くの利点を有している。



Scheme 3. Tandem RCM/oxidation of **1e**. a) **6** (7.5 mol%), CH₂Cl₂, room temperature, 2 h; b) *N*-*tert*-butylbenzenesulfinimidoyl chloride (1.5 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 2.0 equiv), CH₂Cl₂.

corresponding phenol **8e**. However, we were disappointed with the low yield of the product, which resulted from the inevitable competition for formation of benzene **3e** by the dehydration. Unfortunately, our attempts to improve the yield of **8e** by changing the oxidizing agent have so far been unsuccessful.^[13]

On the basis of these experiments, we next applied the RCM/oxidation process to the synthesis of aniline derivatives (Scheme 4). The RCM of 1,4,7-trien-3-amine **9** with Grubbs' second-generation catalyst **7** afforded cyclized product **10** in 99% yield, which suffered less from unfavorable elimination. Subsequent oxidation of **10** with MnO₂ gave the corresponding aniline derivative **11** in 77% yield.



Scheme 4. Tandem RCM/oxidation of **9**. a) **7** (7.5 mol %), CH₂Cl₂, 40 °C, 2 h; b) MnO₂ (excess), room temperature.

Conclusions

We have developed a simple and efficient synthesis of benzene derivatives by employing ruthenium-catalyzed tandem RCM/dehydration and RCM/oxidation processes. The synthetic method explored holds promise for the preparation of benzene derivatives with various structure types. Further studies of the utility of RCM for the synthesis of versatile benzene derivatives are under way.

Experimental Section

General procedure of the tandem RCM/dehydration for the synthesis of **3**: Catalyst **6** or **7** (7.5 mol %, 0.015 mmol) was added in one portion to a solution of **1** (0.200 mmol) in CH₂Cl₂ (20 mL, 0.01 M) under nitrogen at room temperature. After 2 h of stirring, the reaction mixture was treated with *p*-TsOH (0.020 mmol) and stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure and separated by silica-gel column chromatography or preparative TLC on silica gel to give **3**.

Acknowledgement

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