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Ring Expansion of Cyclic 1,2-Diols to form Medium Sized Rings via Ruthenium Catalyzed Transfer Hydrogenative [4+2] Cycloaddition

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Abstract

A new method for the ring expansion of cyclic diols is described. Using improved conditions for the ruthenium(0) catalyzed cycloaddition of cyclic 1,2-diols with 1,3-dienes, fused [n.4.0] bicycles 3a–3r (n = 3–6) are formed, which upon exposure to iodosobenzene diacetate engage in oxidative cleavage to form the 9–12 membered rings 4a–4r.

Introduction

Our laboratory has developed a suite of catalytic C–C bond formations that enable direct alcohol C–H functionalization.¹ These transformations operate through two principal modes of reactivity. In initial work employing iridium² or ruthenium(II)³ precatalysts, hydrogen exchange between primary alcohols and π -unsaturated reactants serves to generate aldehyde-organometal pairs *en route* to products of carbonyl addition.^{2,3} In more recent work using ruthenium(0) precatalysts derived from $\text{Ru}_3(\text{CO})_{12}$, pathways involving secondary alcohol mediated transfer hydrogenolysis of oxometallacycles derived upon ketone-unsaturate oxidative coupling are operative.⁴ Based on the latter reactivity mode, conjugated dienes were found to engage vicinal diols by way of their corresponding 1,2-diones to form products of formal [4+2] cycloaddition.⁵ In this account, we disclose a concise synthesis of medium sized (9–12 membered) 1,6-diketones *via* ruthenium(0) catalyzed diol-diene [4+2] cycloaddition followed by iodosobenzene diacetate, $\text{PhI}(\text{OAc})_2$, mediated oxidative cleavage of the resulting fused [n.4.0] bicycles (Scheme 1).⁶

Results and Discussion

Medium sized rings play a central role in fragrance chemistry,⁷ and are useful building blocks in asymmetric synthesis.⁸ It was reasoned that medium sized rings could be accessed from abundant and inexpensive reactants, cycloalkane diols **1a–1e** and 1,3-dienes **2a–2c**,

using a [4+2] cycloaddition recently developed in our laboratory,⁵ as the anticipated products of cycloaddition **3a–3o**, fused [n.3.0] bicycles possessing bridgehead hydroxyl moieties, should readily undergo oxidative cleavage to form the corresponding 9–12 membered 1,6-diketones **4a–4o**.^{6,9} Beyond broadening access to medium sized rings, this exercise would provide a valuable opportunity to refine and further explore the capabilities of the key transfer hydrogenative cycloaddition methodology.⁵ For example, as our initially reported conditions for cycloaddition employ BIPHEP (\$475 USD/5g),¹⁰ a rather expensive ligand, an effort was made to identify low-cost ligands that display equal or superior levels of performance.

In the event, it was found that the reaction of cycloalkane diols **1a–1e** with 1,3-dienes **2a–2c** could be performed efficiently using *rac*-BINAP (\$98 USD/5g)¹⁰ or dppp (\$60 USD/10g)¹⁰ as ligand to deliver cycloadducts **3a–3o** (Table 1). Nine of the fifteen cycloadducts were previously unreported, and for the six known cycloadducts use of *rac*-BINAP or dppp provided comparable or, in most cases, better isolated yields than those obtained using BIPHEP. Notably, a relatively short reaction time was observed in the cycloaddition to form **3m** (4 hrs), which may be attributed to acceleration of the oxidative coupling of butadiene **2a** to the transient 1,2-dione due to the LUMO lowering σ -inductive effect of the ether oxygen. Inspired by this finding, the cycloaddition of diols **1f** and **1g**, which are derived from D-glucose, with butadiene **2a** were explored. The cycloaddition of diols **1f** delivered the cycloadduct **3p** in 96% yield as an equimolar mixture of diastereomers (eq. 1). For the more highly oxygenated diol **1g**, the cycloadduct **3q** is obtained in 48% yield as 3:1 mixture of diastereomers (eq. 2).

(1)

(2)

With cycloadducts **3a–3q** in hand, conditions for diol oxidative cleavage were explored. Here, it was important to identify conditions that avoid isomerization of the resulting β,γ -unsaturated ketones to the conjugated enones. Recently reported conditions employing iodosobenzene diacetate, $\text{PhI}(\text{OAc})_2$, proved especially simple, mild and effective.⁶ Upon exposure of cycloadducts **3a–3o** to $\text{PhI}(\text{OAc})_2$ in dichloromethane solvent at room

temperature, the 9–12 membered 1,6-diketones **4a–4o** were generated in good to excellent yield without any isomerization to the conjugated enones (Table 2). As illustrated in the conversion of cycloadducts **3p** and **3q** to the 10-membered 1,6-diketones **4p** and **4q** (eq. 3 and 4), respectively, these conditions also were effective in more complex settings. To further illustrate the unique features of this ring expansion protocol, cyclohexane tetraol **1h** was subjected to double cycloaddition employing butadiene **2a**, which delivers tricycle **3r** in a remarkable 92% yield, followed by iodosobenzene diacetate mediated oxidative cleavage to form **4r** (eq. 5). The structure of **4r** was corroborated by single crystal X-ray diffraction analysis.

(3)

(4)

(5)

Conclusion

In summary, we report a novel method for the ring expansion of cycloalkane diols to form 9–12 membered 1,6-diketones. This ring expansion protocol takes advantage of recently reported ruthenium catalyzed transfer hydrogenative diol-diene [4+2] cycloaddition to form fused [n.4.0] bicycles that are subject to iodosobenzene diacetate mediated oxidative

cleavage. Future studies will focus on the developed of related C-C bond forming transfer hydrogenations including the redox triggered C-C coupling of amines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Synthesis of 9–12 membered macrocyclic 1,6-diketones *via* ruthenium(0) catalyzed diol-diene [4+2] cycloaddition.

Table 1

Ruthenium(0) catalyzed reaction of cycloalkane diols **1a–1e** with dienes **2a–2c** to form products of [4+2] cycloaddition **3a–3o**.^a

^a **1a**, *n* = 1, X = CH₂; **1b**, *n* = 2, X = CH₂; **1c**, *n* = 3, X = CH₂; **1d**, *n* = 4, X = CH₂; **1e**, *n* = 1, X = O; **2a**, R = H; **2b**, R = Me; **2c**, R = (CH₂)₂CH=CHMe. Yields are of material isolated by silica gel chromatography.

^b The *cis*-1,2-diol was employed.

^c 10 mol% 3,5-Me₂BzOH added, 7 hrs.

^d 10 mol% 3,5-Me₂BzOH added, (**2c** 400 mol%).

^e The *trans*-1,2-diol was employed.

^f (**2c**, 300 mol%).

^g 10 mol% 3,5-Me₂BzOH added, 18 hrs, (**2c** 400 mol%).

^h 4 hrs, 5:1 mixture of olefin regioisomers.

ⁱ8 hrs, 14:1 mixture of olefin regioisomers. See Supporting Information for further details.

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Table 2

Oxidative cleavage of cycloadducts **3a–3o** mediated by iodosobenzene diacetate to form the 9–12 membered 1,6-diketones **4a–4o**.^a

4a , 88% Yield	4b , 86% Yield	4c , 91% Yield

4d , 88% Yield	4e , 93% Yield	4f , 92% Yield

4g , 99% Yield	4h , 93% Yield	4i , 79% Yield

4j , 99% Yield	4k , 73% Yield	4l , 81% Yield

4m , 78% Yield	4n , 85% Yield	4o , 75% Yield

^aYields are of material isolated by silica gel chromatography and represent the average of two runs. See Supporting Information for further details.