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Ruthenium(0) Catalyzed [4+2] Cycloaddition of Acetylenic Aldehydes with α -Ketols: Convergent Construction of Angucycline Ring Systems**

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Graphical Abstract

Transfer Hydrogenative Cycloaddition. Ruthenium(0) complexes modified by CyJohnPhos or RuPhos catalyze the successive C-C coupling of acetylenic aldehydes with α -ketols to form [4+2] cycloadducts as single diastereomers. This method enables convergent construction of type II polyketide ring systems of the angucycline class.

Keywords

Cycloaddition; Ruthenium; Transfer Hydrogenation; Angucycline; Polyketide

In the course of developing C-C bond forming hydrogenations and transfer hydrogenations,^[1] we recently found that zero-valent ruthenium complexes derived from $\text{Ru}_3(\text{CO})_{12}$ and phosphine ligands catalyze a diverse array of C-C couplings between vicinally dioxygenated hydrocarbons (e.g. diols, ketols, diones) and π -unsaturated reactants, including dienes,^[2a–c] acrylates,^[2d] α -olefins,^[2e] alkynes^[2f] and vinyl acetates.^[2g] As in related ruthenium(0) catalyzed Pauson-Khand type reactions reported by Chatani,^[3] these transformations proceed through catalytic mechanisms involving C=C/C=O oxidative coupling to form oxaruthenacycles.^[2c] However, rather than carbonylating, as in Pauson-Khand type reactions, the oxaruthenacycles undergo hydrogenolysis by dehydrogenating alcohol reactants,^[4] releasing product and regenerating the carbonyl partner required for oxidative coupling. This pattern of reactivity served as the basis for the design of novel [4+2] cycloadditions of 1,2-diols with dienes^[5a] and α -ketols with 3,4-benzannulated 1,5-diyne.^[5b] Here, we report that zero-valent ruthenium catalysts promote the [4+2]

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cycloaddition of α -ketols with *ortho*-acetylenic benzaldehydes and demonstrate how this transformation enables concise construction of ring systems found in type II polyketides of the angucycline class.^[6] This cycloaddition is unique among metal catalyzed reactions of *ortho*-acetylenic benzaldehydes (Scheme 1).^[7–17]

Type II polyketides natural products such as the tetracyclines, daunorubicin and doxorubicin have found broad use in human medicine.^[18] Although total synthesis potentially offers entry to otherwise inaccessible analogues, current manufacturing routes rely on fermentation or semi-synthesis, suggesting improved methods for *de novo* chemical synthesis are necessary. The most common methods used for the construction of type II polyketides are stoichiometric benzannulations,^[19] such as the Hauser reaction,^[20] Diels-Alder benzannulations,^[21] the Dötz reaction,^[22] and aryne-mediated benzannulation.^[23] To further broaden access to type II polyketides, we have begun to develop convergent methods for their assembly that target ubiquitous substructures *via* redox-triggered cycloaddition. The studies presented here are aimed at the rapid formation of angucycline ring systems (Figure 1).^[6]

Our initial experiments were guided by earlier studies conducted from our laboratory on the ruthenium(0)-catalyzed [4+2] cycloadditions of α -hydroxyketones with 3,4-benzannulated 1,5-dienes,^[5b] which involved exposure of the reactants to the ruthenium(0) catalyst generated *in situ* from Ru₃(CO)₁₂ (2 mol%) and CyJohnPhos (12 mol%) (Figure 2) in *m*-xylene-H₂O at 60–85 °C. Gratifyingly, upon application of these conditions to the cycloaddition of *ortho*-acetylenic arylaldehyde **1a** with the *para*-fluorophenyl α -ketol **2a**, the targeted product of [4+2] cycloaddition **3a** could be isolated as a single stereoisomer in 75% yield (Table 1). The *syn*-diol and (*E*)-olefin stereochemistry were corroborated by single crystal X-ray diffraction analysis. Analysis of the crude reaction mixture by ¹⁹F NMR revealed the presence of one major byproduct, which was identified as the *anti*-diol (10:1 dr), as well as trace quantities of the 5-membered ring ketol.^[24] Use of an aqueous organic reaction solvent (*m*-xylene-H₂O) was crucial in terms of enforcing *syn*-diastereoselectivity and minimizing formation of numerous byproducts. Additionally, precise control of reaction temperature was required to preserve (*E*)-alkene geometry and mitigate 1,2-ketol rearrangement.^[24]

To establish the scope and limitation of this method, acetylenic benzaldehydes **1a–1c** were reacted with a diverse set of α -ketols **2a–2f**, which incorporate both aryl (**2a–2e**) and alkyl (**2f**) substituents (Table 1). In each case, minor variation of temperature was required to suppress formation of undesired isomers. For acetylenic benzaldehydes **1a** and **1b**, the cycloadducts **3a–3f** and **4a–4f** were formed in moderate to good yields and were isolated in diastereomerically pure form. The *ortho,ortho*-dimethoxy substituted acetylenic benzaldehyde **1c** proved to be less reactive, requiring enhanced loadings of Ru₃(CO)₁₂ (3 mol%) and use of RuPhos (18 mol%) as ligand (Figure 2). Under these conditions, cycloadducts **5a–5f** were isolated as single diastereomers in moderate to good yields. Among the α -ketols **2a–2f**, the *ortho*-substituted aryl ketol **2e** provided the lowest isolated yields of cycloadduct (**3e**, **4e**, **5e**). Analysis of crude reaction mixtures by ¹H NMR indicated complete consumption of ketol **2e** in reactions with acetylenic benzaldehydes **1a–1c**, however, significant quantities of the undesired 5-membered cycloadduct were formed.

Reexposure of the 6-membered cycloadducts **3e**, **4e** and **5e** to the reaction conditions resulted in conversion to the same distribution of 5- and 6-membered ring products obtained from initial cycloaddition reactions, suggesting cycloadducts **3e**, **4e** and **5e** have a lower barrier to 1,2-ketol rearrangement.^[24]

A plausible catalytic mechanism, illustrated for the coupling of acetylenic aldehyde **1a** with α -ketol **2**, is as follows (Scheme 2). A mononuclear ruthenium(0) complex^[25] promotes alkyne-carbonyl oxidative coupling of acetylenic aldehyde **1a** with α -ketoaldehyde *dehydro-2* to form oxaruthenacycle **I**.^[2f] For the first turnover of the catalytic cycle, the dicarbonyl partner required for oxidative coupling, *dehydro-2*, may be formed through Ru₃(CO)₁₂ catalyzed dehydrogenation of α -ketol **2** with hydrogen transfer to alkyne **1a**.^[4] β -Hydride elimination converts oxaruthenacycle **I** to the vinylruthenium hydride **II**, which upon C-H reductive elimination delivers the tricarbonyl intermediate **III**, regenerating ruthenium(0). The second C-C bond formation may occur *via* pinacol-type carbonyl-carbonyl oxidative coupling³ to deliver dioxaruthenacycle **IV**. Protonolytic cleavage of the complex **IV** mediated by α -ketol **2** forms the ruthenium alkoxide **V**. β -Hydride elimination from alkoxide **V** forms alkoxyruthenium hydride **VI** with concomitant release of α -ketoaldehyde *dehydro-2*. Finally, O-H reductive elimination delivers the product of cycloaddition, returning ruthenium to its zero-valent form to close the catalytic cycle. An alternate pathway for formation of the second C-C bond involves aldol reaction of a ruthenium enediolate derived from tricarbonyl intermediate **III** to form dioxaruthenacycle **IV**. Remarkably, the secondary benzylic alcohol of the cycloadducts are not oxidized under these conditions, suggesting ketol dehydrogenation is more rapid. Once the acetylenic aldehyde is consumed, which serves as hydrogen acceptor, no further oxidation occurs.

To illustrate how this new [4+2] cycloaddition methodology broadens access to type II polyketides, cycloadducts **3f**, **4f** and **5f** were converted to the respective tetracyclic naphthoquinones **10a**, **10b** and **10c** bearing the bridgehead diol motif found in many angucycline natural products (Scheme 3).^[6] Diols **3f**, **4f** and **5f** were first treated with triphosgene to furnish the respective cyclic carbonates **6a**, **6b** and **6c** which were then subjected to ruthenium-catalyzed oxidative cleavage^[26] to form diones **7a**, **7b** and **7c**. Although diones **7a**, **7b** and **7c** could be observed by ¹H NMR analysis of crude reaction mixtures, attempted isolation by silica-gel chromatography triggered generation of the indicated 5-membered α -ketols.^[24] Therefore, direct Friedel-Crafts-type cyclization of the crude diones **7a**, **7b** and **7c** was attempted. To our delight, exposure of diones **7a**, **7b** and **7c** to FeCl₃^[27] led to the formation of the desired cyclization products **8a**, **8b** and **8c** as single diastereomers. The structural assignment of compounds **8a** and **8b** was confirmed by single crystal X-ray diffraction analysis. Basic hydrolysis of the carbonate provided the *syn*-triols **9a**, **9b** and **9c**, which upon IBX-mediated oxidation^[28] furnished the tetracyclic naphthoquinones **10a**, **10b** and **10c**.

In summary, we report a novel [4+2] cycloaddition of *ortho*-acetylenic benzaldehydes **1a–1c** with α -ketols **2a–2f** *via* ruthenium(0) catalyzed C-C bond forming transfer hydrogenation. The dense functional group arrays embodied by cycloadducts **3a–3f**, **4a–4f** and **5a–5f** offer new possibilities for the synthesis of type II polyketides, as demonstrated through the

conversion of cycloadducts **3f**, **4f** and **5f** to tetracyclic naphthoquinones **10a**, **10b** and **10c**, respectively, bearing the bridgehead diol substructure often found in angucycline natural products.^[6] More broadly, the transformations reported in this account contribute to a growing body of redox-neutral C-C bond formations that emanate from the merger of carbonyl addition and transfer hydrogenation.^[1a]

Supplementary Material

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Landomycinone, R = H**Landomycin A, R = hexasaccharide** **Arenimycin A** **Collinone** **Aquayamycin**

Figure 1.
Selected type II polyketides of the angucycline class.

RuPhos, R = O-*i*Pr

CyJohnPhos, R = H

Figure 2.
Ligands used in this study.

Carbophilic Metal Catalysis (ref. 7-16) **Tanaka: Cascade Hydroacylation (ref. 17)** **This Work: Ynal-Ketol [4+2] Cycloaddition**

Scheme 1.
Metal catalyzed C-C couplings of *ortho*-acetylenic benzaldehydes.

Scheme 2.

General catalytic mechanism for ruthenium(0) catalyzed [4+2] cycloaddition of *ortho*-acetylenic benzaldehydes **1a–1c** with α -ketols **2a–2f**.

Scheme 3.

Conversion of cycloadducts **3f**, **4f** and **5f** to tetracyclic naphthoquinones **10a**, **10b** and **10c**, respectively, bearing the bridgehead diol motif found in many angucycline natural products.

Table 1

Ruthenium(0) catalyzed [4+2] cycloaddition of *ortho*-acetylenic benzaldehydes **1a–1c** with α -ketols **2a–2f**.^a

1a , R ¹ = R ² = H 2a , R ³ = 4-F-Ph 2d , R ³ = 5-benzodioxole	1b , R ¹ = H, R ² = OMe 2b , R ³ = 4-CO ₂ Me-Ph 2e , R ³ = 2-[TIPSO(CH ₂) ₂]-Ph	1c , R ¹ = R ² = OMe 2c , R ³ = 3,4-Cl ₂ -Ph 2f , R ³ = (CH ₂) ₂ Ph
3a , 75% Yield (X-ray) (60 °C, CyJohnPhos)	4a , 70% Yield (65 °C, CyJohnPhos)	5a , 72% Yield ^b (70 °C, RuPhos)
3b , 73% Yield (65 °C, CyJohnPhos)	4b , 72% Yield (65 °C, CyJohnPhos)	5b , 70% Yield ^b (70 °C, RuPhos)
3c , 68% Yield (60 °C, CyJohnPhos)	4c , 73% Yield (60 °C, CyJohnPhos)	5c , 69% Yield ^b (70 °C, RuPhos)
3d , 63% Yield (70 °C, CyJohnPhos)	4d , 64% Yield (70 °C, CyJohnPhos)	5d , 59% Yield ^b (70 °C, RuPhos)
3e , 44% Yield (65 °C, CyJohnPhos)	4e , 46% Yield (65 °C, CyJohnPhos)	5e , 30% Yield ^b (70 °C, RuPhos)
3f , 75% Yield (65 °C, CyJohnPhos)	4f , 83% Yield (70 °C, CyJohnPhos)	5f , 64% Yield ^b (70 °C, RuPhos)

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.^bRu₃(CO)₁₂ (3 mol%), RuPhos (18 mol%).