Cycloaddition

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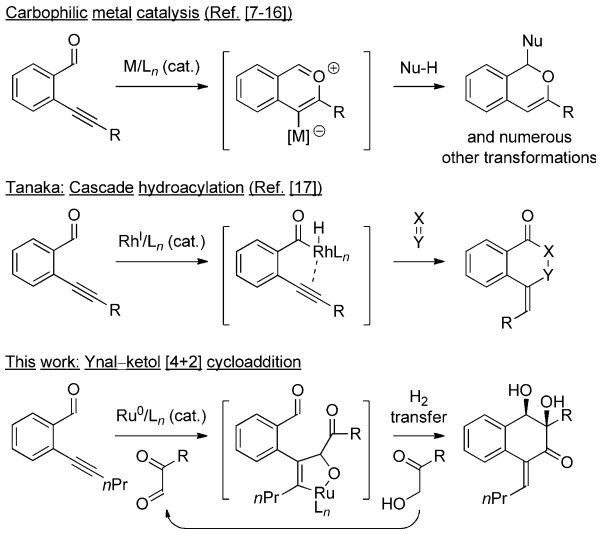
Abstract: *Ruthenium(0) complexes modified by CyJohnPhos or RuPhos catalyze the successive C–C coupling of acetylenic aldehydes with α-ketols to form [4+2] cycloadducts as single diastereomers. This method enables convergent construction of type II polyketide ring systems of the angucycline class.*

In the course of developing C–C bond-forming hydrogenations and transfer hydrogenations,[1] we recently found that zero-valent ruthenium complexes derived from $[Ru_3(CO)_{12}]$ 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 and co-workers,[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 reduction 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-diynes.[5b] Herein, we report that zero-valent ruthenium catalysts promote the [4+2] 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 polyketide 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 based on redox-triggered cycloaddition. The studies presented here are aimed at the rapid formation of angucycline ring systems (Figure 1).[6]



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

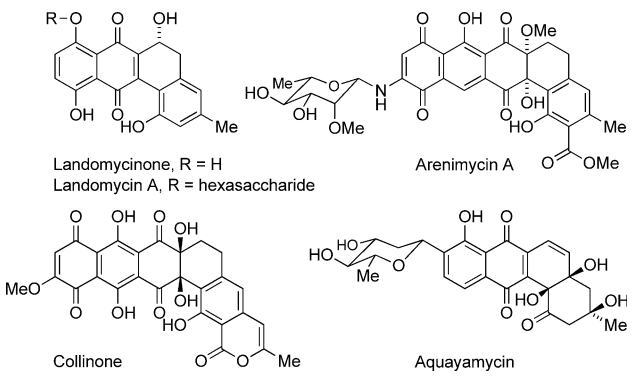


Figure 1. Selected type II polyketides of the angucycline class.

Our initial experiments were guided by our earlier studies on the ruthenium(0)-catalyzed [4+2] cycloadditions of α-hydroxyketones with 3,4-benzannulated 1,5-diynes,[5b] which involved exposure of the reactants to the ruthenium(0) catalyst generated in situ from $[Ru_3(CO)_{12}]$ (2 mol%) and

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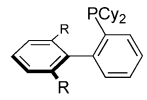
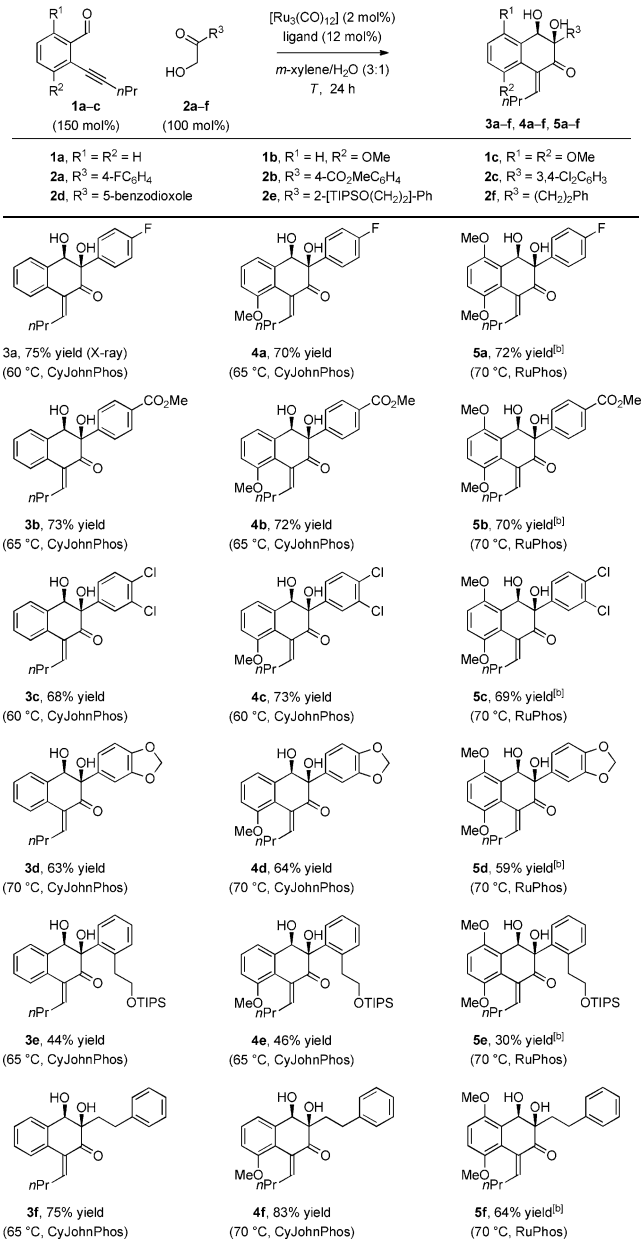


RuPhos, R = O*i*Pr
CyJohnPhos, R = H

Figure 2. Ligands used in this study.

CyJohnPhos (12 mol%; Figure 2), in *m*-xylene/H_2O at 60–85 °C. Gratifyingly, upon application of these reaction conditions to the cycloaddition of the *ortho*-acetylenic arylaldehyde **1a** with the *para*-fluorophenyl α-ketol **2a**, the targeted cycloadduct **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 (see the Supporting Information). Analysis of the crude reaction mixture by ^{19}F NMR spectroscopy revealed the presence of one major byproduct, which was identified as the *anti*-diol (10:1 d.r.), as well as trace quantities of the five-membered ring ketol.[24] Use of an aqueous organic reaction solvent (*m*-xylene/H_2O) 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]

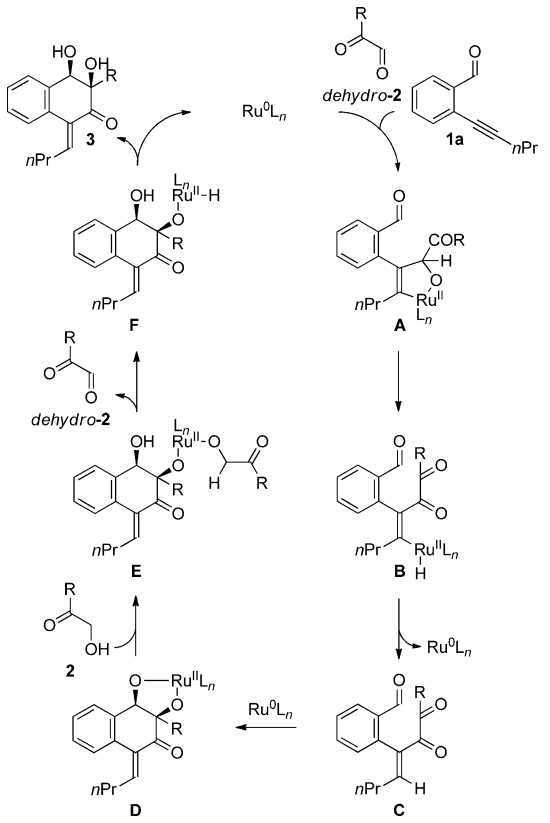
Table 1: Ruthenium(0)-catalyzed [4+2] cycloaddition of *ortho*-acetylenic benzaldehydes (**1a–c**) with α-ketols (**2a–f**).[a]



[a] Yields are of material isolated by silica gel chromatography. See the Supporting Information for further experimental details. [b] [$Ru_3(CO)_{12}$] (3 mol%), RuPhos (18 mol%). TIPS = triisopropylsilyl.

To establish the scope and limitation of this method, acetylenic benzaldehydes (**1a–c**) were reacted with a diverse set of α-ketols (**2a–f**), which incorporate both aryl (**2a–e**) and alkyl (**2f**) substituents (Table 1). In each case, slight variation of reaction temperature was required to suppress formation of undesired isomers. For **1a** and **1b**, the cycloadducts **3a–f** and **4a–f** 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 [$Ru_3(CO)_{12}$] (3 mol%) and use of RuPhos (18 mol%) as ligand (Figure 2). Under these reaction conditions, the cycloadducts **5a–f** were isolated as single diastereomers in moderate to good yields. Among the α-ketols **2a–f**, the *ortho*-substituted aryl ketol **2e** provided the lowest isolated yields of cycloadduct (**3e**, **4e**, **5e**). Analysis of the crude reaction mixtures by ^1H NMR spectroscopy indicated complete consumption of **2e** in reactions with acetylenic benzaldehydes **1a–c**, however, significant quantites of the undesired five-membered cycloadduct were formed. Re-exposure of the six-membered cycloadducts **3e**, **4e**, and **5e** to the reaction conditions resulted in conversion into the same distribution of five- and six-membered ring products obtained from the initial cycloaddition reactions, suggesting **3e**, **4e**, and **5e** have a lower barrier to 1,2-ketol rearrangement.[24]

A plausible catalytic mechanism, illustrated for the coupling of **1a** with **2**, is as follows (Scheme 2): A mononuclear ruthenium(0) complex[25] promotes alkyne–carbonyl oxidative coupling of **1a** with the α-ketoaldehyde *dehydro*-**2** to form the oxaruthenacycle **A**.[2f] For the first turnover of the catalytic cycle, the dicarbonyl partner required for oxidative coupling (*dehydro*-**2**) may be formed through [$Ru_3(CO)_{12}$]-catalyzed dehydrogenation of **2** with hydrogen transfer to **1a**.[4] β-Hydride elimination converts **A** into the vinylruthenium hydride **B**, which upon C–H reductive elimination delivers the tricarbonyl intermediate **C**, regenerating ruthenium(0). The second C–C bond formation may occur by pinacol-type carbonyl–carbonyl oxidative coupling[3] to deliver the dioxaruthenacycle **D**. Protonolytic cleavage of the **D**, mediated by **2**, forms the ruthenium alkoxide **E**. β-Hydride elimination from **V** forms the alkoxyruthenium hydride **F** with concomittant release of *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 **C** to form **D**. Remarkably, the secondary

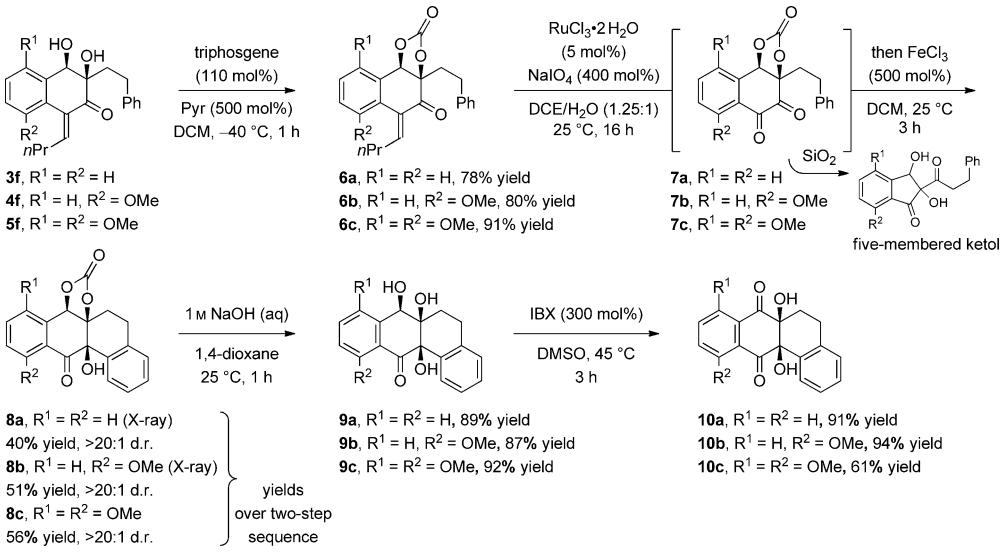


Scheme 2. General catalytic mechanism for ruthenium(0)-catalyzed [4+2] cycloaddition of *ortho*-acetylenic benzaldehydes (**1a–c**) with α-ketols (**2a–f**).

benzylic alcohol of the cycloadduct is not oxidized under these reaction conditions, suggesting ketol dehydrogenation is more rapid. Once the acetylenic aldehyde, which serves as hydrogen acceptor, is consumed no further oxidation occurs.

To illustrate how this new [4+2] cycloaddition methodology broadens access to type II polyketides, the cycloadducts **3f**, **4f**, and **5f** were converted into the respective tetracyclic naphthoquinones **10a**, **10b**, and **10c** bearing the bridgehead diol motif found in many angucycline natural products (Scheme 3).[6] The 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 the diones **7a**, **7b**, and **7c**. Although **7a**, **7b**, and **7c** could be observed by ^{1}H NMR analysis of crude reaction mixtures, attempted isolation by silica-gel chromatography triggered generation of the indicated five-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 **7a**, **7b** and **7c** to $FeCl_3$[27] led to the formation of the desired cyclization products **8a**, **8b**, and **8c**, respectively, as single diastereomers. The structural assignment of **8a** and **8b** was confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information). 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–c**) with α-ketols (**2a–f**) by ruthenium(0)-catalyzed C–C bond-forming transfer hydrogenation. The dense functional group arrays embodied by cycloadducts **3a–f**, **4a–f**, and **5a–f** offer new possibilities for the synthesis of type II polyketides, as demonstrated through the conversion of **3f**, **4f**, and **5f** into 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]



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

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