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Ruthenium(0) Catalyzed Endiyne–α-Ketol [4 + 2] Cycloaddition: Convergent Assembly of Type II Polyketide Substructures via C–C Bond Forming Transfer Hydrogenation

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Supporting Information

ABSTRACT: Upon exposure of 3,4-benzannulated 1,5-diynes (benzo-endiynes) to α-ketols (α-hydroxyketones) in the presence of Ru(0) catalysts derived from $Ru_3(CO)_{12}$ and RuPhos or CyJohnPhos, successive redox-triggered C–C coupling occurs to generate products of [4 + 2] cycloaddition. The proposed catalytic mechanism involves consecutive alkyne-carbonyl oxidative couplings to form transient oxaruthanacycles that suffer α-ketol mediated transfer hydrogenolysis. This process provides a new, convergent means of assembling Type II polyketide substructures.

Despite the importance of Type II polyketides to human medicine, there is a paucity of metal catalyzed C–C couplings that specifically target substructures evident in this class of natural product.[1−5] The most commonly utilized methods for the convergent assembly of Type II polyketides are stoichiometric benzannulations,[1] including the Hauser benzannulation,[2] Diels–Alder type benzannulation,[3] the Dötz benzannulation,[4] and aryne-mediated benzannulation.[5] As amply demonstrated,[2−5] these protocols have greatly broadened access to Type II polyketides. Still, to date, all commercial Type II polyketides are prepared through fermentation or semisynthesis, suggesting a further expansion of the lexicon of synthetic methods is required to meet the daunting synthetic challenges posed by this natural product family.

Using a reactivity pattern where alcohol oxidation is balanced by reductive carbonyl addition,[6] we have developed a broad, new family of catalytic C–C couplings for the synthesis of Type I polyketide natural products (allylation,[7] crotylation,[8] propargylation[9]) and terpenoid natural products (*n*-prenylation and *n*-geranylation,[10] *tert*-prenylation,[11] *tert*-(hydroxy)prenylation[12]). These methods have been used to great effect to streamline total synthesis.[6b] In efforts toward a parallel suite of catalytic methods for Type II polyketide construction, we recently developed a Ru(0) catalyzed diene–diol [4 + 2] cycloaddition (Figure 1, eq 1).[13,14] Here, we report a redox-triggered [4 + 2] cycloaddition of 3,4-benzannulated 1,5-diynes (benzo-endiynes)[15−19] with α-ketols (Figure 1, eq 2) and demonstrate how this process may be applied to the convergent assembly of Type II polyketide substructures.

As use of diol reactants requires a sacrificial H-acceptor, our initial studies focused on the [4 + 2] cycloaddition of diyne **1a** with α-ketol **2b**. Using the Ru(0) catalyst generated *in situ* from $Ru_3(CO)_{12}$ (2 mol %) and RuPhos at 130 °C in *m*-xylene solvent,

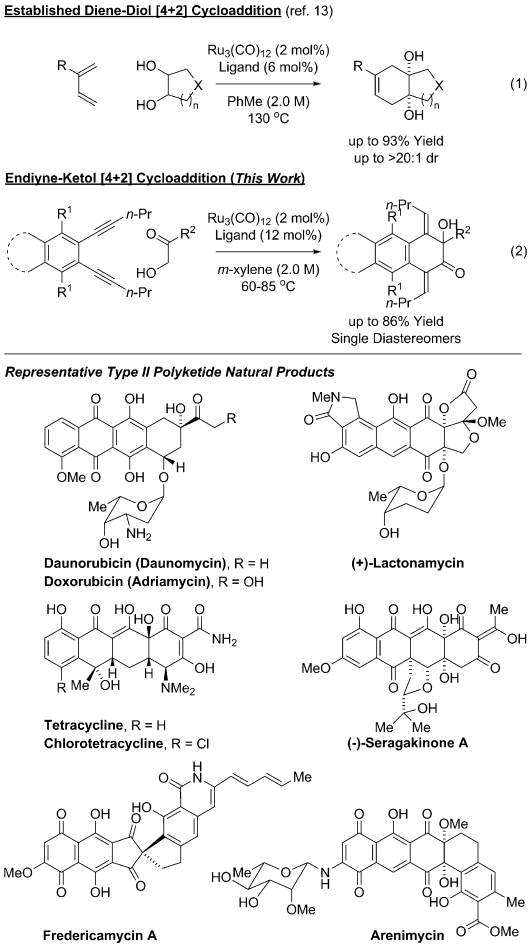

Figure 1. Ru(0) catalyzed transfer hydrogenative [4 + 2] cycloadditions and representative Type II polyketide natural products.

a 17% conversion to the cycloadduct **3b** was observed along with the isomeric compounds *iso*-**3b**, **6b**, and *iso*-**6b** (Table 1, entry 1). Under these reaction conditions at 130 °C, these isomers were found to exist in equilibrium with one another.[20] Specifically, each isomer could be purified and resubjected to the reaction conditions to generate the same distribution of products. Fortunately, unlike other Ru(0) catalyzed C–C couplings we have developed,[13,14] the present reaction could be performed at

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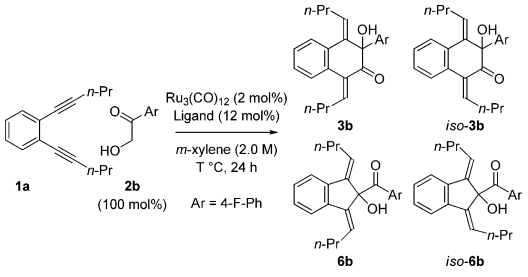
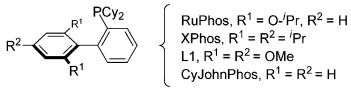
Table 1. Selected Optimization Experiments in the Ru(0) Catalyzed Cycloaddition of Diyne 1a with α-Ketol 2b



entry	1a (mol%)	additive[b]	ligand	T (°C)	2b	3b	*iso*-3b	6b	*iso*-6b[a]
1	300	$AdCO_2H$	RuPhos	130	0	17	17	8	58
2	300	$AdCO_2H$	RuPhos	80	0	41	22	37	0
3	300	$AdCO_2H$	RuPhos	60	0	56	11	33	0
4	300	$AdCO_2H$	RuPhos	40	100	0	0	0	0
5	300	---	RuPhos	60	42	29	5	24	0
6	300	H_2O	RuPhos	60	0	66	6	28	0
7	150	H_2O	RuPhos	60	0	62	11	27	0
8	150	H_2O	PCy_3	60	100	0	0	0	0
9	150	H_2O	XPhos	60	0	64	3	33	0
10	150	H_2O	L1	60	0	58	14	28	0
⇨ **11**	**150**	**H_2O**	**CyJohnPhos**	**60**	**0**	**75 (68)[c]**	2	23	0

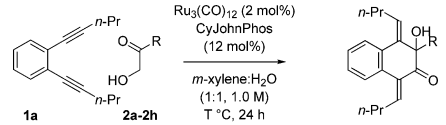


[a]Conversion determined by ^{19}F NMR analysis of crude reaction mixtures. [b]$AdCO_2H$ refers to 1-adamantanecarboxylic acid. H_2O (0.1 mL). [c]Isolated yield of single isomer. See Supporting Information (SI) for further details.

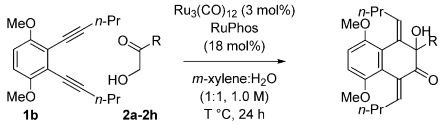
significantly lower temperature, which assisted in preserving kinetic selectivity for the desired cycloadduct **3b** (Table 1, entries 1−3). The prior experiments were conducted in the presence of a carboxylic acid cocatalyst, 1-adamantanecarboxylic acid. A mechanistic rationale for the effect of the carboxylic acid cocatalyst has been described in detail.[14c] In the absence of 1-adamantanecarboxylic acid, conversion is significantly lower (Table 1, entry 5). It was found, however, that water cosolvent promotes higher conversion than the carboxylic acid additive (Table 1, entry 6), although significant quantities of the undesired isomers persisted (Table 1, entry 7). Finally, through further evaluation of ligand (Table 1, entries 8−11), it was found that optimal conversion and kinetic selectivity for cycloadduct **3b** are obtained using CyJohnPhos (Table 1, entry 11).

Under these latter conditions, the cycloadduct **3b** could be obtained in 68% isolated yield as a single isomer. These optimized conditions were applied to the [4 + 2] cycloaddition of diynes **1a**−**1c** with α-ketols **2a**−**2h** (Table 2). Notwithstanding minor variations in temperature, which were made to accommodate the solubility of the α-ketol or to suppress isomer formation, the desired cycloadducts **3a**−**3h**, **4a**−**4h**, and **5a**−**5h** were typically isolated in moderate to good yield and, with the exception of **3e**, in isomerically pure form. Aryl-substituted ketols **2a**−**2f** generally provided higher isolated yields of cycloadducts than the alkyl-substituted ketols **2g** and **2h**, although conversion and selectivity were dependent upon the diyne **1a**−**1c**. The structural assignment of cycloadducts **3a**−**3h**, **4a**−**4h**, and **5a**−**5h** is supported by single crystal X-ray diffraction analysis of **3d** and **5d**. To evaluate the prospect of regioselective cycloaddition, the nonsymmetric diyne **1d**, for which the alkyne termini are substituted by *n*-propyl and *tert*-butyl groups, was reacted with ketol **2d** under standard conditions (Scheme 1). Remarkably, the cycloadduct *t*-Bu-**5d** forms as a single regioisomer. Similarly, the

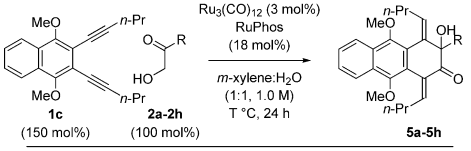
Table 2. Ru(0) Catalyzed Cycloaddition of Diynes 1a−1c with α-Ketols 2a−2h[a]



entry	T °C	α-ketol	R group	product	yield
1	60	**2a**	Ph	**3a**	64%
2	60	**2b**	4-F-Ph	**3b**	68%
3	70	**2c**	4-CN-Ph	**3c**	66%
4	75	**2d**	4-(CO_2Me)Ph	**3d** (X-ray)	75%
5	60	**2e**	3-MeOPh	**3e**	71%[b]
6	65	**2f**	3,4-Cl_2Ph	**3f**	64%
7	60	**2g**	$(CH_2)_2$Ph	**3g**	30%
8	75	**2h**	CH_2OTBDPS	**3h**	45%



entry	T °C	α-ketol	R group	product	yield
1	85	**2a**	Ph	**4a**	65%
2	85	**2b**	4-F-Ph	**4b**	85%
3	75	**2c**	4-CN-Ph	**4c**	62%
4	85	**2d**	4-(CO_2Me)Ph	**4d**	81%
5	85	**2e**	3-MeOPh	**4e**	69%
6	85	**2f**	3,4-Cl_2Ph	**4f**	72%
7	85	**2g**	$(CH_2)_2$Ph	**4g**	60%[c]
8	85	**2h**	CH_2OR (R = TBS, TBDPS)	**4h**	trace



entry	T °C	α-ketol	R group	product	yield
1	70	**2a**	Ph	**5a**	75%
2	70	**2b**	4-F-Ph	**5b**	63%
3	75	**2c**	4-CN-Ph	**5c**	71%
4	75	**2d**	4-(CO_2Me)Ph	**5d** (X-ray)	73%
5	60	**2e**	3-MeOPh	**5e**	77%
6	60	**2f**	3,4-Cl_2Ph	**5f**	86%
7	80	**2g**	$(CH_2)_2$Ph	**5g**	70%
8	85	**2h**	CH_2OTBS	**5h**	40%

[a]Yields are of isomerically pure material isolated by silica gel chromatography. [b]Isolated as a 4:1 ratio of **3e** and **6e**. [c]$Ru_3(CO)_{12}$ (5 mol %), RuPhos (30 mol %), 16 h. See SI for further details.

monomethoxy-substituted diyne **1e** reacts with ketol **2d** to deliver cycloadduct *des*-MeO-**4d** as a single regioisomer.

To further evaluate cycloadducts **3a**−**3h**, **4a**−**4h**, and **5a**−**5h** as potential precursors to Type II polyketides, compound **4g** was subjected to a series of functional group interconversions (Scheme 2). Highly diastereoselective Meerwein−Ponndorf−Verley reduction of cycloadduct **4g** could be achieved in the absence of 1,4-reduction to furnish the *cis*-diol **7** in 84% yield.[21] To our knowledge, hydroxyl-directed 1,2-reductions of this type were hitherto unknown. Conversion of diol **7** to the cyclic carbonate[22] followed by chemoselective oxidative cleavage[23] of the less hindered olefin delivered ketone **8**. The hindered olefin embedded within **8** participates in peracid mediated epoxidation,[24] to provide compound **9** as a single diastereomer. The stereochemical assignment of compound **9** is tentative and

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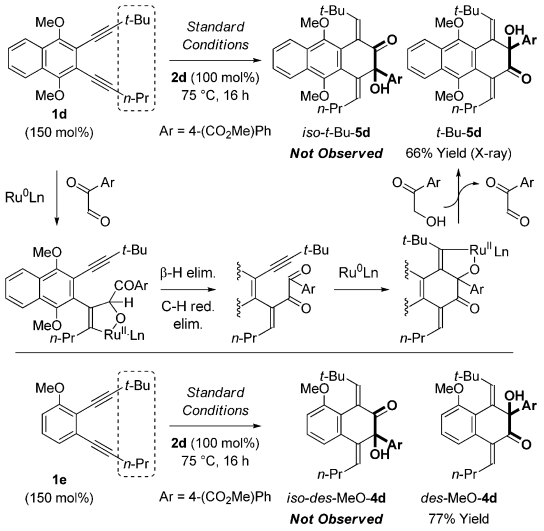
Scheme 1. Regioselective Cycloaddition of Nonsymmetric Diynes 1d and 1e and Catalytic Mechanism



assumes epoxidation from the convex face of the bicycle. The synthesis of compound **9** supports the feasibility of using the present cycloaddition methodology for the synthesis of the ever-growing class of Type II polyketides that incorporate vicinal bridgehead *cis*-diol moieties. In a parallel series of experiments, the *ortho*-substituted ketol **2i** was prepared and exposed to diyne **1b** under standard conditions for redox-triggered cycloaddition to furnish adduct **4i**. Removal of the silyl protecting group delivered compound **10**, which is currently being explored as a model system in a synthetic route to landomycin A.[25]

New reactivity fuels the development of new functional group interconversions and, ultimately, broad, new strategies for chemical synthesis. By exploiting the native reducing ability of alcohols to drive successive oxidative coupling events, we herewith demonstrate that 3,4-benzannulated 1,5-diynes **1a**–**1c** and ketols **2a**–**2h** may be combined to furnish [4 + 2] cycloadducts **3a**–**3h**, **4a**–**4h**, and **5a**–**5h**. This method enables convergent assembly of Type II polyketide substructures and contributes to an emergent family of transfer hydrogenative cycloadditions.[13] Future studies will focus on synthetic applications of the present methodology and the discovery of related cycloadditions based on successive C–C coupling of *bis*(π-unsaturated) reactants with vicinally dioxygenated partners.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. Single crystal X-ray diffraction data for **3d**, **5d**, *t*-Bu-**5d**, and **10**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02755.

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Notes

The authors declare no competing financial interest.

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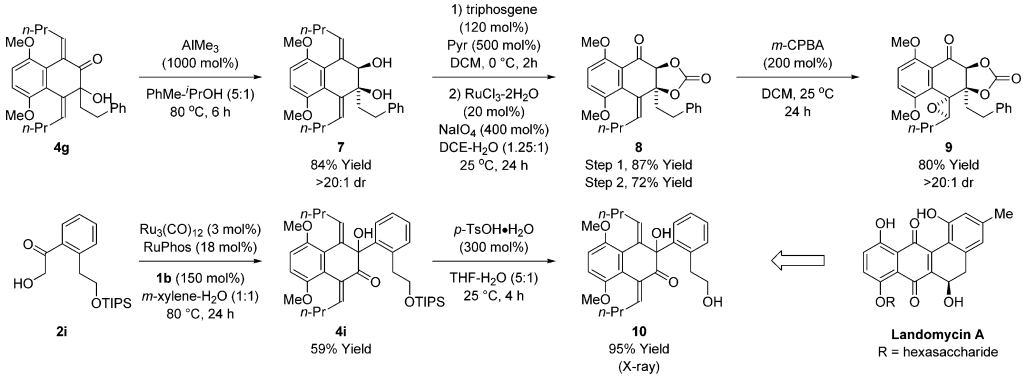
Scheme 2. Preliminary Studies on the Elaboration of Cycloadduct 4g and Synthesis of Landomycin A Model System 10[a]



[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR analysis of crude reaction mixtures.

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