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Enantioselective Ruthenium Catalyzed Benzocyclobutenone-Ketol Cycloaddition: Merging C-C Bond Activation and Transfer Hydrogenative Coupling for Type II Polyketide Construction

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Abstract

The first enantioselective intermolecular metal catalyzed cycloadditions of benzocyclobutenones via C-C bond oxidative addition are described. In the presence of a ruthenium(0) complex modified by (*R*)-DM-SEGPHOS, tetralone-derived ketols and benzocyclobutenones combine to form cycloadducts with complete regio- and diastereoselectivity and high enantioselectivity. Using this method, the “bay region” substructure of the angucycline natural products arenimycin was prepared.

Graphical Abstract

Following pioneering work by Liebeskind,^{1,2} Jun³ and Murakami,⁴ the insertion of π -bonds into metallacycles obtained through C-C bond oxidative addition has matured into an active area of research.⁵ Despite substantial progress in this field, several key challenges persist. The use of directing groups is often required to overcome the kinetic and thermodynamic barriers posed by the activation of relatively strong and stable C-C bonds. Many C-C bond activation initiated C-C couplings are restricted to intramolecular processes. Finally, beyond reactions of donor-acceptor cyclopropanes,^{6,7} enantioselective intermolecular metal-catalyzed C-C bond activation initiated C-C couplings are exceptionally uncommon.⁸

In connection with studies of transfer hydrogenative C-C bond formation,⁹ we recently developed a novel class of ruthenium(0)-catalyzed cycloadditions of vicinal diols, ketols or

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Supporting Information Available: Experimental procedures and spectral data. HPLC traces of racemic and enantiomerically enriched products. Crystallographic data for **3h'**. Tins material is available free of charge *via* the internet at <http://pubs.acs.org>.

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diones.^{9d,10} These processes operate through a common mechanistic motif wherein oxidative formation of ruthenium(II) metallacycles, which is accompanied or triggered by dione addition, is followed by diol- or ketol-mediated transfer hydrogenolysis of the ruthenacycle to release product and regenerate the reactive dione (Figure 1).^{9d} Recently, we found that ruthenacycles obtained via C-C bond oxidative addition to benzocyclobutenones are catalytically competent in transformations of this type, providing a kinetic pathway for the insertion of adjacent carbon atoms of vicinal diols, ketols or diones into C-C σ -bonds.¹⁰ⁱ Based on this finding, we now report the first examples of enantioselective intermolecular metal catalyzed cycloadditions of benzocyclobutenones.^{11–14}

In an initial set of experiments (Table 1), a series of benzocyclobutenone derivatives **1a–1d** were exposed to equimolar quantities of the tetralone-derived ketols **2a–2c** (or diols) in the presence of the mononuclear ruthenium(0) catalyst¹⁵ derived from Ru₃(CO)₁₂ and (*R*)-SEGPHOS in *m*-xylene (1 M) at 150 °C. The reaction of the unsubstituted benzocyclobutenone **1a** with the unsubstituted diol **2a** led to the formation of cycloadduct **3a** with complete regio- and diastereoselectivity, but in nearly racemic form (Table 1, entry 1). However, using the corresponding *ortho*-methoxy-substituted benzocyclobutenone **1b**, cycloadduct **3b** was formed with significant levels of enantiomeric enrichment (Table 1, entry 2). Based on this result, an effort was made to define substituents that would both enforce optimal levels of enantiomeric enrichment and facilitate entry to naturally occurring type II polyketides of the angucycline class (*vide infra*). Toward this end, incorporation of a triisopropylsilyl (TIPS) ether at C2 of the benzocyclobutenone, as in **1c**, and, for the ketol partner, a benzyloxy substituent at C8, as in **2c**, conspired to improve the degree of asymmetric induction. Thus, the reaction of benzocyclobutenone **1c** and ketol **2c** delivered cycloadduct **3h** with complete regio- and diastereoselectivity as a 94:6 ratio of enantiomers (Table 1, entry 8). Finally, using (*R*)-DM-SEGPHOS as ligand and a slight excess of benzocyclobutenone **1c**, cycloadduct **3h** was generated in 96% yield as a single regio- and diastereomer as a 97:3 ratio of enantiomers (Table 1, entry 9).

The scope of the enantioselective ruthenium catalyzed benzocyclobutenone-ketol cycloaddition was evaluated (Table 2). Retaining key structural features required to enforce high levels of asymmetric induction, an otherwise diverse set of benzocyclobutenones **1c**, **1e–11**, were reacted with ketol **2c** to furnish cycloadducts **3h–3p**. In each case, complete regio- and diastereoselectivity were accompanied by excellent levels of enantiomeric enrichment. The formation of **3o** and **3p** illustrates tolerance of activated aryl chlorides. Variation of the ketol partner also was explored. As demonstrated by the formation of cycloadducts **3q–3s**, electron releasing substituents that reside in *para*-relationship with respect to the ketone improve enantioselectivity, precluding the need for an *ortho*-benzyloxy-group. For example, in the formation of cycloadduct **3r**, a 99:1 enantiomeric ratio is observed. The formation of **3r** also demonstrates compatibility with amine functional groups.

Underscoring the utility of this method *vis-à-vis* construction of type II polyketides, in particular, the angucycline antibiotics arenimycins A–D, collinone and SF22446A1–A3/SF22446B1–B3,^{16–19} benzocyclobutenone **1c** was exposed to ketol **2g** under standard conditions for ruthenium-catalyzed cycloaddition (Scheme 1). The cycloadduct **3t** was

formed in good yield and incorporates the highly congested “bay region” motif found in arenimycin. To further demonstrate relevance to type II polyketide construction, cycloadduct **3h** was subjected to silyl-deprotection followed by oxidation of the resulting alcohol to form the dione **4h** (eq 1). Additionally, cycloadduct **3o** was subjected to an S_NAr reaction to form compound **4o**, which incorporates a dimethylamino motif. Dimethylamino groups frequently occur in type II polyketide antibiotics (e.g. the tetracyclines) and, as recently demonstrated by Hergenrother, introduction of unhindered amines endows certain rigid “Gram-(+) only” antibacterials with Gram-(−) activity by conferring membrane permeability.²⁰

(eq. 1)

(eq. 2)

Finally, the ability to achieve high levels of enantioselectivity in cycloadditions of chiral racemic benzocyclobutenones **1c**, **1e-11** has implications regarding the nature of the C-C bond oxidative addition event. High levels of enantiomeric enrichment persist at equimolar loadings of benzocyclobutenone and ketol (Table 1, entry 8) and do not depend on stoichiometry, which suggests kinetic resolution of benzocyclobutenones **1c**, **1e-11** is not operative. Rather, these data corroborate a catalytic mechanism wherein stereoablative cycloreversion to form a discrete α -oxo-*ortho*-quinodimethane or “*ortho*-quinoid ketene methide”²¹ is followed by enantiodetermining C-C bond oxidative addition to form a ruthenaindanone complex (Figure 2).²² The indicated stereochemical model for ruthenaindanone formation accounts for structural features of the benzocyclobutenone that are required to enforce high levels of enantioselectivity, specifically, non-bonded interactions between the methoxy and triisopropylsiloxy groups of the α -oxo-*ortho*-quinodimethane with the xylyl moieties of DM-SEGP_{HOS}.

In summary, we report the first enantioselective intermolecular metal catalyzed cycloadditions of benzocyclobutenones via C-C bond oxidative addition. Using a mononuclear¹⁵ ruthenium(0) complex derived from Ru₃(CO)₁₂ and (*R*)-DM-SEGP_{HOS},

tetralone-derived ketols and benzocyclobutenones react to form cycloadducts with complete regio- and diastereoselectivity and high enantioselectivity. Whereas the majority of methods for convergent type II polyketide construction require use of stoichiometric carbanions under cryogenic conditions (e.g. the Hauser-Kraus annulation,^{23,24} aryne-mediated cycloadditions²⁵), the present method assembles type II polyketide motifs in the absence of stoichiometric byproducts under non-cryogenic conditions. In an initial synthetic application, this method was used to prepare the congested “bay region” substructure characteristic of the angucycline antibiotics arenimycin, collinone and SF22446A1-A3/SF22446B1-B3.^{16–19} Future studies are aimed at defining ketol partners for the synthesis of linear tetracycline antibiotics.²⁶

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
General catalytic mechanism for ruthenium(0) catalyzed cycloaddition of diols, ketols or diones.

Figure 2. Stereoablative cycloreversion precedes oxidative addition and stereochemical model for ruthenaindanone formation.

Arenimycin A Active against MRSA, MIC = 0.05 $\mu\text{g/mL}$

Bridgehead stereochemistry unknown

Never prepared *via* total synthesis **Collinone**Active against VRE, MIC = 16 $\mu\text{g/mL}$

Bridgehead stereochemistry unknown

Never prepared *via* total synthesis**Arenimycin A** **Arenimycin B** **Arenimycin C** **Arenimycin D** **Scheme 1.**

Arenimycins A-D and collinone, antibacterial angucyclines that incorporate a bridgehead diol motif, and reaction of benzocyclobutenone **1c** with ketol **2g** to form cycloadduct **3t**^a.

^aFor structurally related angucycline natural products, SF22446A1-A3 and SF22446B1-B3, see Ref. 19. Reaction was performed on 0.20 mmol scale. Yield of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase E1PEC analysis. See Supporting Information for further experimental details.

Table 1.

Selected optimization experiments in the enantioselective intermolecular ruthenium catalyzed cycloaddition of benzocyclobutenones.^a

entry	R ¹	R ²	1a-1d	R ³	2a-2c	3a-3h	yield (%), dr, rr	er
1 ^b	H	H	1a	H	2a	3a	87, >20:1, >20:1	53:47
2 ^b	OMe	H	1b	H	2a	3b	83, >20:1, >20:1	81:19
3	OMe	H	1b	OMe	2b	3c	77, >20:1, >20:1	58:42
4	OMe	H	1b	OBn	2c	3d	79, >20:1, >20:1	76:24
5 ^b	OMe	OTIPS	1c	H	2a	3e	75, >20:1, >20:1	87:13
6	OMe	OTIPS	1c	OMe	2b	3f	78, >20:1, >20:1	89:11
7	OMe	OTBS	1d	OMe	2b	3g	74, >20:1, >20:1	80:20
8	OMe	OTIPS	1c	OBn	2c	3h	79, >20:1, >20:1	94:6
9 ^c	OMe	OTIPS	1c	OBn	2c	3h	96, >20:1, >20:1	97:3

^aYields are of material isolated by silica gel chromatography. Enantioselectivity values were determined by HPLC analysis on a chiral stationary phase. (*R*)-SEGPHOS (Ar = phenyl).

^bReaction was conducted from the diol oxidation level, **1a-1c** (200 mol%).

^c**1c** (130 mol%), (*R*)-DM-SEGPEIOS (Ar = 3,5-xylyl). See the Supporting Information for further experimental details.

Table 2.

Enantioselective intermolecular ruthenium(0) catalyzed cycloaddition of benzocyclobutenones **1c**, **1e-1l** with ketols **2c-2f** to form cycloadducts **3h-3s**.^a

^a All reactions were performed on a 0.20 mmol scale. Yield of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

^bX-ray structure obtained after removal of silyl ether (**3h'**).

^c36 h.

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