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Ru-catalyzed insertion of adjacent diol carbon atoms into C-C bonds: Entry to type II polyketides

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Abstract

Current catalytic processes involving C-C bond activation rely on π -unsaturated coupling partners. Exploiting the concept of transfer hydrogenative coupling, we report here a ruthenium(0)-catalyzed cycloaddition of benzocyclobutenones that functionalizes two adjacent saturated diol C-H bonds. These regio- and diastereoselective processes enable convergent construction of type II polyketide substructures.

Metal-catalyzed C-C bond activation emerged as a discrete field of chemical research (1–4) with reports on the oxidative addition of low valent metal complexes to strained carbocycles to form isolable metallacycles. For example, Halpern described the reaction of cubane and quadricyclane, respectively, with $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ to form rhodacycles (5, 6). The oxidative additions of a platinum(0) complex to diphenylcyclopropenone and benzocyclobutene dione, respectively, to form 4- and 5-membered platinacycles were documented soon thereafter (7, 8). The utility of metallacycles obtained through C-C bond oxidative addition *vis-à-vis* π -bond insertion was demonstrated in stoichiometric alkyne-cyclobutene cycloadditions by Liebeskind (9, 10), who later showed such reactions can be catalyzed by nickel(0) (11). Access to related rhodium-catalyzed cycloadditions was accelerated by Murakami's 1994 report on the hydrogenolysis of acyl C-C bonds (12, 13), along with inter- and intramolecular rhodium-catalyzed ketone-mediated olefin carboacylations reported by Jun (14, 15) and Murakami (16, 17), respectively.

Metal-catalyzed cycloadditions based on the insertion of π -unsaturated reactants into activated C-C bonds now represent a broad area of research (1–4). Intermolecular cycloadditions of cyclobutanone derivatives, which are catalyzed by nickel (11, 18–23) rhodium (24, 25) and ruthenium (24, 26) complexes, comprise a growing subset of these transformations. To our knowledge, the formal insertion of saturated C-H bonds into C-C σ -bonds has not been documented. Here, using the concept of C-C bond forming transfer

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NMR Spectra

hydrogenation (27–29) we now report reactions of this type. Specifically, under the conditions of ruthenium(0) catalysis, benzocyclobutenones react with 1,2-diols to form cycloadducts wherein each vicinal carbinol C-H bond of the 1,2-diol is functionalized to become a C-C bond. The present method provides a convergent means of assembling type II polyketides bearing bridgehead diol motifs (Fig 1).

We have found that ruthenacycles arising via diene-carbonyl oxidative coupling promote dehydrogenation of α -hydroxy esters and 1,2-diols to form vicinal dicarbonyl species, enabling a wide range of formal alcohol C-H functionalizations (28–34). We posited that ruthenacycles obtained upon C-C bond oxidative addition would display similar reactivity. To explore this possibility, benzocyclobutenone **1a** was exposed to racemic *trans*-cyclohexane 1,2-diol **2b** in the presence of the catalyst generated *in situ* from $\text{Ru}_3(\text{CO})_{12}$ and various phosphine ligands (1 M in toluene) at 110 °C for 24 h. This initial screen revealed that the ruthenium(0) catalyst modified by bis(diphenylphosphino)propane (dppp), which is anticipated to be a discrete, mono-nuclear complex (35), provides the product of cycloaddition **3a** in 22% isolated yield with complete *syn*-diastereoselectivity as determined by ^1H NMR analysis (>20:1 dr). The structure of **3a** was corroborated by single crystal x-ray diffraction analysis. Upon increasing reaction temperature (150 °C, xylene solvent), cycloadduct **3a** was obtained in 88% yield.

These conditions were applied to the reaction of benzocyclobutenones **1a–1j** with racemic *trans*-cyclohexane 1,2-diol **2b** (Table 1). The cycloadducts **3a–3j** were isolated in excellent yields. As demonstrated by the formation of **3d**, benzocyclobutenones bearing benzylic substitution delivered products in which three contiguous stereocenters formed in selective fashion. Dione **1e** was converted to cycloadduct **3e**, which embodies the dihydroxy-quinone motif found in numerous type II polyketides (Fig 1). The formation of **3g** and **3h** establish tolerance of halide functional groups, which is important *vis-à-vis* subsequent elaboration. For example, *ortho*-chloro-cycloadduct **3g** was converted to the corresponding dimethylamino-containing product **4** through nucleophilic aromatic substitution (Fig 2, eq. 1). Alternatively, Suzuki coupling of **3g** delivered the pyrimidine-modified compound **5** (Fig 2, eq. 2).

Diverse diols **2a–2i** engaged in the cycloaddition initiated by C-C bond activation (Table 2). Beyond the reaction of symmetric saturated cyclic diols **2a–2c**, we found that non-symmetric diols reacted with high regioselectivity. For example, the cycloadducts **3m–3s** were formed as single regioisomers as determined by ^1H NMR analysis (>20:1 rr). The congested “bay-region” *ortho*-methoxy-substituent found in cycloadduct **3o** and **3p** is a pervasive structural feature among angucycline natural products (36), such as arenimycin and collinone (Fig 1). Fusion to an aromatic ring is not required to induce regiocontrol. As illustrated by the formation of **3q–3s**, alkyl substituents adjacent to the diol enforced complete regioselectivity. Notably, the latter cycloadducts **3r** and **3s**, which were derived from enantiomerically pure starting materials, did not suffer erosion of enantiomeric enrichment in the course of cycloaddition.

The present diol cycloadditions appear to be oxidative processes wherein benzocyclobutenone (50 mol%) accepts two equivalents of hydrogen (Tables 1 and 2). This

assertion was corroborated by the isolation of the ring-opened hydrogenolysis product (2-methoxy-6-methylphenyl)methanol in cycloadditions of cyclobutanone **1a** (Fig 2, eq. 3). As illustrated by the reaction of cyclobutanone **1a** with diol **2b** (Fig 2, eq. 3), α -ketol *dehydro-2b* (Fig 2, eq. 4) and dione *didehydro-2b* (Fig 2, eq. 5) to form **3a**, cycloaddition is possible in oxidative, redox-neutral and reductive modes, respectively. In the latter case, 2-propanol (300 mol%) served as terminal reductant. The use of equimolar quantities of reactant in the redox-neutral reaction (Fig 2, eq. 4) establishes the practicality of applying this methodology to the union of complex fragments.

We posit a general mechanism for the ruthenium-catalyzed cycloaddition (Fig 3). Oxidative addition of a discrete, mono-metallic ruthenium catalyst (**35**) to benzocyclobutenone **1a** provides the ruthena-indanone **I** (**37**), which upon successive addition of the C-Ru bonds to 1,2-dione, *didehydro-2b*, provides the ruthenium(II) diolate complex **III** by way of the benzyruthenium alkoxide **II**. Related additions of ruthenacyclopentadienes to vicinal dicarbonyl compounds have been documented (34). Transfer hydrogenolysis of the ruthenium(II) diolate is accomplished through protonolysis by diol **2b** or ketol *dehydro-2b* to deliver the ruthenium(II) alkoxide **IV**, which suffers β -hydride elimination to furnish the ruthenium hydride **V**. Finally, O-H reductive elimination releases the cycloadduct **3a**. The latter steps of this catalytic mechanism find precedent in $\text{Ru}_3(\text{CO})_{12}$ -catalyzed ketone transfer hydrogenations mediated by 2-propanol (38).

Using the ruthenium precatalyst $(\text{CF}_3\text{CO}_2)\text{Ru}(\text{CO})(\text{PPh}_3)_2 \cdot \text{MeOH}$ in combination with the chiral chelating phosphine ligand (*R*)-SEGPPOS under otherwise standard conditions provided cycloadduct **3a** with promising levels of enantiomeric enrichment (51% ee). We anticipate that, together with recent insights into the structural and physical features of small-molecule antibiotics *vis-à-vis* gram-negative activity (39), this convergent cycloaddition methodology should accelerate progress toward synthetic type II polyketide drugs.

Supplementary Material

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Fig 1. Ruthenium-catalyzed cyclobutenone-diol [4+2]cycloaddition via C-C bond activation – a gateway to type II polyketide natural products.

Fig 2.

Elaboration of cycloadduct **3g** (eq. 1,2) and redox independent cycloaddition from the diol, ketol or dione oxidation levels (eq. 3–5).

Fig 3.
Proposed catalytic mechanism for ruthenium catalyzed benzocyclobutenone-diol cycloaddition.

Table 2

Ruthenium(0)-catalyzed cycloaddition of benzocyclobutenone **1a** or **1d** with diols **2a–2i**. Reported yields refer to material isolated by silica gel chromatography. Products **3a**, **3k–3q** are racemic. Products **3r** and **3s** are enantiomerically enriched. See Supporting Information for further experimental details.

1a or 1d (200 mol%)	rac-2a-i (100 mol%)	3a, 3k-3s

3k , 64% Yield, >20:1 dr	3a , 88% Yield, >20:1 dr <i>x-ray crystal structure</i>	3l , 82% Yield, >20:1 dr

3m , 60% Yield, >20:1 dr Single Regioisomer	3n , 86% Yield, >20:1 dr Single Regioisomer <i>x-ray crystal structure</i>	3o , 81% Yield, R = H [†] 3p , 53% Yield, R = OMe ^{*,†} >20:1 dr, Single Regioisomer

3q , 61% Yield, >20:1 dr [*] Single Regioisomer <i>x-ray crystal structure</i>	3r , 69% Yield, >20:1 dr 95 ee% Single Regioisomer	3s , 61% Yield, >20:1 dr ≥95 ee% Single Regioisomer

* Reaction conducted from ketol oxidation level.

[†] 130 °C.