Published in final edited form as:

Angew Chem Int Ed Engl. 2015 June 8; 54(24): 7134–7138. doi:10.1002/anie.201501505.

Tandem Z-selective cross metathesis – dihydroxylation for the synthesis of *anti*-1,2-diols**

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Abstract

A stereoselective synthesis of anti-1,2-diols has been developed using a multitasking Ru-catalyst in an assisted tandem catalysis protocol. A cyclometalated ruthenium complex catalyzes first a Z-selective cross metathesis of two terminal olefins followed by a stereospecific dihydroxylation. Both steps are catalyzed by Ru, as the Ru-complex is converted to a dihydroxylation catalyst upon addition of NaIO₄. A variety of olefins are transformed into valuable highly functionalized and stereodefined molecules. Mechanistic experiments are performed to probe the nature of the oxidation step and catalyst inhibition pathways. These experiments point the way to more broadly applicable tandem catalytic transformations.

Keywords

tandem catalysis; Z-selective; metathesis; dihydroxylation; anti diol

Highly functionalized and stereochemically complex motifs are attractive targets in synthesis due to their diverse molecular interactions in therapeutic and other specialty applications. Efficient synthesis of densely functionalized targets from simple starting materials is thus an important challenge. Assisted tandem catalysis, where coupled catalytic processes are effected by a single catalyst, can significantly increase molecular complexity.^[1] Ruthenium metathesis catalysts have frequently been used in tandem reactions since the C–C bond formation step in olefin metathesis can be coupled to a structural elaboration step which introduces additional functionality.^[2] In 2006, Blechert^{2k} and Snapper^{2l} demonstrated that cross metathesis using second generation catalysts **Ru-1** or **Ru-2** followed by Ru-catalyzed dihydroxylation in the presence of NaIO₄ as an oxidant led to the corresponding diol (Scheme 1). The dihydroxylation step is highly stereospecific, and thus diol diastereoselectivity is determined by olefin geometry. Since the metathesis occurs under thermodynamic (i.e. substrate) control, primarily *E* olefins were produced, leading to

**This work was financially supported by the ONR (N000141410650), the NIH (5R01GM031332-27) and the NSF (CHE-1212767). Mr. L. M. Henling is thanked for X-ray crystallography. NMR spectra were obtained by instruments supported by the NIH (RR027690). We thank Dr. John Hartung for helpful discussion. Materia, Inc. is thanked for donation of metathesis catalysts.

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predominantly *syn*-diol products. Thus *anti*-diols,^[3] which are important motifs in natural products as well as intermediates in synthesis, are inaccessible by these methods. If a *catalyst controlled* cross metathesis could be coupled to a dihydroxylation, then *anti*-diols with predictable and high levels of diastereoselectivity could be accessed. Using this multitasking approach, simple allyl alcohol and allyl amine derivatives could be transformed into valuable densely functionalized products in a catalyst controlled fashion.

Significant progress has been made in the development of Z-selective olefin metathesis catalysts using Ru,^[4–8] Mo^[9–11] and W^[12] alkylidene complexes.^[13] Highly Z-selective cyclometalated Ru complexes (**Ru-3** and **Ru-4**, Figure 1) have been investigated by our group for diverse applications.^[14,15] However, these complexes have not been demonstrated to be viable for tandem catalysis, despite the potential to significantly increase the molecular complexity with high stereocontrol in a single-pot sequence.

It is proposed that cyclometalated complexes would be able to catalyze the dihydroxylation of olefins if conditions could be identified to generate a suitably oxidized ruthenium species.^{2k–2m} We anticipated that under acidic aqueous oxidizing conditions, the adamantyl C–Ru bond would be cleaved, generating a species similar to that generated in dihydroxylation with **Ru-2**.^{2k} Furthermore, we proposed that catalyst controlled Z-selectivity in cross metathesis with **Ru-3** or **Ru-4** would be translated into high *anti*-selectivity via a stereospecific pathway. Herein, the successful development of a tandem Z-selective metathesis – dihydroxylation is reported, as well as preliminary mechanistic studies which shed light on catalyst inhibition pathways.

The homodimerization – dihydroxylation of allyl butyrate was examined in order to determine the effect of catalyst and reaction conditions on selectivity (Table 1). The metathesis step was performed under static vacuum conditions, in order to keep the concentration of ethylene in solution low. Shing's conditions of NaIO₄ in 3:3:1 EtOAc:MeCN:H₂O^[16,17] were used for the dihydroxylation step. Brønsted^[18] and Lewis acids^[19] have been demonstrated to accelerate dihydroxylation.^[20] Second generation complex **Ru-2**, which is expected to operate under thermodynamic control of olefin geometry, generated the *syn* diol product with 8:1 selectivity (entry 1). Use of cyclometalated mesityl substituted **Ru-3** and diisopropylphenyl substituted **Ru-4** generated the desired product **6a** in 56% and 68% yield, respectively, with only trace quantities of the *syn* diol by-product (entries 2 and 3). This *anti*-selectivity can be attributed to the high Z-selectivity of these catalysts in cross metathesis.^[6,21]

Achieving high activity and Z-selectivity has been found to depend on the removal of ethylene from solution. Performing the metathesis under static vacuum was critical, as the yield was diminished to 49% when the metathesis step was performed at 1 atm (entry 4).^[22] The use of additives, such as *n*Bu₄NCl during dihydroxylation, or ethyl vinyl ether after the metathesis reaction, did not improve the yield (entries 5 and 6). Increasing the loading of catalyst **Ru-4** (5 mol%) or CeCl₃ (30 mol%) resulted in a small decrease in efficiency (54% and 60% yield respectively, entries 7 and 8), while performing the dihydroxylation in the absence of a Lewis acid co-catalyst still resulted in productive dihydroxylation, albeit in

only 31% yield (entry 9). Other acids, such as H₂SO₄ and YbCl₃ were also less effective than CeCl₃, producing **6a** in 56% and 61% yield respectively (entries 10 and 11).

With optimized conditions in hand, we next examined the scope of the Z-selective homodimerization – dihydroxylation. A wide variety of densely functionalized, stereodefined *anti*-diols could be prepared from comparatively simple starting materials (Table 2). Esters, carbonates, carbamates and amine derivatives were all well tolerated, generating the resulting *anti*-diol in up to 72% yield. The molecular structure of **6c** was determined by X-ray crystallography, supporting the *anti*-stereochemistry (Figure 2).^[23] In addition to probing the overall tandem process, the independent metathesis step was also monitored in each case to ensure high Z-selectivity,^[24] since only the homodimerization of allyl acetate has been explored previously with these chelated catalysts.^[5]

Achieving unsymmetrical substitution patterns via heterocross metathesis – dihydroxylation is an appealing target, particularly if differentially protected products can be obtained. Z-selective heterocross metathesis can be achieved by using an excess of one of the olefin partners.^[21,25] Tosyl and Cbz protected allyl amine were used as coupling partners with allyl butyrate or allyl benzoate (Table 2), generating the corresponding substituted amino triols in up to 63% yield. Such orthogonally protected products are valuable building blocks for target oriented synthesis.

We next examined the tandem methodology on gram scale in order to probe scalability of the process. Allyl benzoate was subjected to cross metathesis with 0.5 mol% catalyst **Ru-4** in an open vial in an inert atmosphere glove box, followed by dihydroxylation using the standard conditions outside the glove box (Scheme 2). Isolation of the target diol was conveniently achieved without the need for column chromatography: trituration of the crude reaction mixture with ether provided **6c** in 66% yield.

In order to probe the role of Ru in the dihydroxylation step, a series of control experiments were performed. Firstly, Z-2-butenyl 1,4-diacetate **7** was subjected to the standard dihydroxylation conditions in the presence or absence of catalyst **Ru-4** (Scheme 3A). Without **Ru-4**, no conversion was observed, indicating that Ru is a catalyst for *both* the metathesis and dihydroxylation steps. In the presence of **Ru-4** (1 mol%), *anti*-diol **6b** was generated as a single diastereomer, thus confirming the stereospecificity of the dihydroxylation.

Next, the relative reactivity of electron neutral and deficient internal olefins toward dihydroxylation with **Ru-4** was investigated. Z-4-butene **8** was subjected to the standard dihydroxylation conditions with **Ru-4** (1 mol%), and no diol was observed (Scheme 3B). Furthermore, when a 1:1 mixture of **8** and Z-2-butenyl 1,4-diacetate **7** was subjected to the same conditions, no diol from either alkene was observed (Scheme 3C). Since **7** is successfully dihydroxylated when it is the only substrate present, this result indicates that **8** is not only unreactive, but also *inhibits* dihydroxylation of **7**. We propose that formation of a stable ruthenate ester from a [3+2] cycloaddition between **8** and a Ru species with at least two oxo ligands sequesters the ruthenium catalyst, making it unavailable for catalysis of dihydroxylation of **7**. Hydrolysis of osmate esters is known to be a slow step in the osmium

catalyzed dihydroxylation of certain olefins.^[26,27] The allylic functional groups could either be acting as electron withdrawing groups to render the Ru center more electrophilic, or as coordinating groups.^[28]

In order to probe the inherent reactivity of cross metathesis intermediates containing functionality on only one side of the olefin, we performed the tandem sequence using allyl benzoate and 1-pentene. Under standard conditions, no product was obtained (Scheme 4A). However when the volatiles were removed *in vacuo* prior to addition of the reagents for dihydroxylation, diol **10** was produced in 33% yield under unoptimized conditions (Scheme 4B). Therefore removal of the inhibitory olefins 4-octene and residual 1-pentene lead to restoration of the dihydroxylation activity, albeit with slightly lower efficiency.^[29] This result points the way to expansion of the substrate scope for this tandem transformation.

In summary we have disclosed an assisted tandem catalysis procedure for the *Z*-selective cross metathesis – dihydroxylation of terminal olefins to yield *anti*-diols. Ruthenium catalyzes both transformations, and the *Z*-selectivity observed in the cross metathesis is translated to *anti*-selectivity via the stereospecific dihydroxylation. Densely functionalized *anti*-diols with four contiguous heteroatom substituted carbon atoms can be synthesized from simple allyl alcohol and allyl amine derivatives. The behaviour of the *in situ* generated Ru-based oxidation catalyst was probed with unfunctionalized electron rich alkenes, and these were found to inhibit dihydroxylation. Further studies are ongoing to elucidate details of the reaction mechanism. It is envisioned that this methodology will have applications in target oriented synthesis involving *anti*-diols, and the mechanistic insights will help to uncover further applications of cyclometalated ruthenium alkylidene catalysts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Second generation (**Ru-1** and **Ru-2**) and cyclometalated (**Ru-3** and **Ru-4**) ruthenium alkylidene complexes

Figure 2.

POV-ray depiction of the structure of *anti*-diol **6c** determined by X-ray crystallography.

Atoms are represented by ellipsoids at the 50% probability level. The crystal was disordered as it contained two conformers – only one has been shown for clarity.

Blechert (2006) and Snapper (2006):

This work:

Scheme 1.

Tandem metathesis–dihydroxylation. Blechert and Snapper demonstrated that substrate controlled cross metathesis generally leads to *syn*-diols. We demonstrate that Z -selective catalysts lead to *anti*-diols in a catalyst controlled fashion via the Z -olefin.

Scheme 2.

Gram scale tandem Z-selective metathesis – dihydroxylation

Scheme 3.

A) Ruthenium catalyst **Ru-4** is required for dihydroxylation. B) *Z*-4-octene **8** is unreactive in dihydroxylation. C) **8** *inhibits* the dihydroxylation of **7**. *Oxidation conditions*: NaIO₄ (2 eq), CeCl₃ (10 mol%), EtOAc:MeCN:H₂O (3:3:1), 20 min, 0 °C.

A) Standard conditions: 0% yield

B) Removal of volatiles after metathesis step: 33% yield

Scheme 4.

Cross metathesis – dihydroxylation of allyl benzoate and 1-pentene under standard conditions (A) and with removal of volatile intermediates prior to the oxidation step (B).

Table 1

Effect of catalyst, additives and conditions on the tandem Z-selective metathesis – dihydroxylation reaction.

Entry	Ru	Acid	Changes from standard	Yield 6a (<i>anti</i>)[<i>a</i>]	Yield (<i>syn</i>)
1	Ru-2	CeCl ₃	none	5	40
2	Ru-3	CeCl ₃	none	56	12
3	Ru-4	CeCl ₃	none	68	3
4	Ru-4	CeCl ₃	No static vacuum	49	4
5	Ru-4	CeCl ₃	<i>n</i> Bu ₄ NCl (10 mol%) during dihydroxylation	62	5
6	Ru-4	CeCl ₃	Ethyl vinyl ether (1 eq) after metathesis step	47	2
7	Ru-4	CeCl ₃	5 mol% Ru-4	54	7
8	Ru-4	CeCl ₃	30 mol% CeCl ₃	60	4
9	Ru-4	None	none	31	1
10	Ru-4	H ₂ SO ₄	none	56	5
11	Ru-4	YbCl ₃	none	61	3

[*a*] Determined by integration of the crude ¹H NMR spectrum using mesitylene as an internal standard.

Table 2

Tandem Z-selective homodimerization – dihydroxylation of allyl substituted terminal olefins

$\text{5} \xrightarrow[\text{2. NaIO}_4 \text{ (2 eq), CeCl}_3 \text{ (10 mol\%)}]{\text{1. Ru-4 (1.5 mol\%)}} \text{6}$
 THF (1.3M), 40 °C, 4 hr (static vacuum)
 EtOAc:MeCN:H₂O (3:3:1), 20 min, 0 °C

Entry	R (5)	Product	6	Yield (%)
1	OCOnPr (5a)		6a	72
2	OAc (5b)		6b	59
3	OBz (5c)		6c	71
4[a]	OCO ₂ Ph (5d)		6d	61
5	OCONHR (5e)		6e	63
6	OCONHR (5f)		6f	39
7	NHTs (5g)		6g	70
8	NHCbz (5h)		6h	53

[a] Using 1 mol% catalyst in an open vial in the glove box

Table 3

Z-selective heterocross metathesis – dihydroxylation of allyl substituted terminal olefins

Entry	R¹	R²	Product	6	Yield (%)
1	NHTs	OCOnPr		6i	63[a]
2	NHTs	OBz		6j	39
3	NHCbz	OBz		6k	55
4	NHCbz	OCOnPr		6l	47

[a] 1.5 mol% **Ru-4**, 35 °C