Asymmetric Catalysis

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Catalytic, Enantioselective Synthesis of 1,2-*anti*-Diols by Asymmetric Ring-Opening/Cross-Metathesis**

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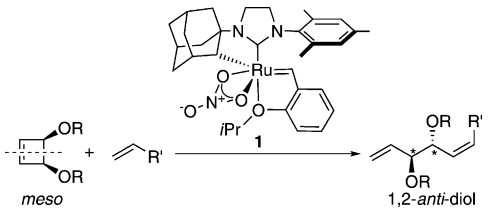
Abstract: *An enantioselective method for the synthesis of 1,2-anti-diols has been developed. A cyclometalated chiral-at-ruthenium complex catalyzes the asymmetric ring-opening/cross-metathesis of dioxygenated cyclobutenes, thus resulting in functionally rich synthetic building blocks. Syntheses of the insect pheromone (+)-endo-brevicomin and monosaccharide ribose demonstrate the synthetic utility of the 1,2-anti-diol fragments generated in the title reaction.*

The formation of multiple stereocenters in a single catalytic transformation is a powerful approach to the synthesis of stereochemically complex targets. While the development of such a transformation must overcome the challenge of simultaneously controlling diastereo- and enantioselectivity, the end result can reduce the step count of a synthesis and improve its atom economy. One commonly encountered motif is the vicinal diol, which is found in natural products and ligands for asymmetric transformations. While the problem of introducing vicinal diols in high enantiopurity has largely been solved by the Sharpless asymmetric dihydroxylation (AD), the formation of 1,2-*anti*-diols remains challenging because of the low enantioselectivity observed in the AD of *cis*-1,2-disubstituted alkenes.[1] Accordingly, a number of methods have been developed for the enantioselective formation of 1,2-*anti* diols, including asymmetric epoxidation/hydrolysis,[2] glycolate aldol,[3] iterative cross-metathesis/allylic substitution,[4] nucleophilic addition to aldehydes,[5] desymmetrizing monofunctionalization,[6] and allene hydroboration/aldehyde allylation.[7] In contrast to many of these methods, an asymmetric ring-opening/cross-metathesis (AROCM) approach (Scheme 1) would consolidate the transformation into a single step and generate a differentiated 1,5-diene fragment in a convergent manner.

Asymmetric olefin metathesis is a powerful C–C bond-forming reaction and has enabled the synthesis of stereochemically complex bioactive compounds.[8] Advances in stereoselective olefin metathesis have resulted in the development of catalysts capable of forming products with high



Scheme 1. AROCM reaction to afford highly enantioenriched 1,2-*anti*-diols.

diastereo-[9] and enantioselectivity.[10] Although the ROCM of cyclobutenes to form racemic products has been demonstrated,[9f,11] previous studies of their AROCM reactions have afforded products with low enantioenrichment.[10i]

It was envisioned that the desymmetrization of suitably substituted *meso*-cyclobutenes by AROCM would afford the 1,2-*anti*-diol motif in perfect *anti* diastereoselectivity and potentially high enantioselectivity upon application of a newly developed cyclometalated metathesis catalyst (**1**, Scheme 1).[12] The resultant 1,5-diene would be a versatile synthetic intermediate because of the differential reactivity of the two alkenes, thus paving the way for further chemoselective transformations. Herein, we report the successful application of **1** to afford highly enantioenriched 1,2-*anti*-diols and demonstrate the versatility of these products in the synthesis of the insect pheromone (+)-*endo*-brevicomin and a derivative of the monosaccharide L-ribose. Pest control strategies utilizing insect pheromones have become a promising alternative to the application of broad-spectrum insecticides, thus underscoring the importance of rapid synthetic routes to (+)-*endo*-brevicomin and related bioactive compounds.[13,14]

Initial attempts to form 1,2-*anti*-diols were carried out with **1**, allyl acetate (**3**), and *cis*-3,4-dibenzyloxycyclobutene (**2**; Table 1), which was synthesized by substitution of commercially available *cis*-3,4-dichlorocyclobutene with sodium phenylmethanolate.[15] The solvent had no effect on the selectivity of the AROCM reaction except for slightly diminished enantioselectivity in CH_2Cl_2 (entry 1). The yield was highest in THF (entry 4). The effect of stoichiometry in AROCM has been explored for a number of catalysts.[10b,i,16] In the current study, an excess of the terminal olefin was optimal (7 equiv, entry 4). As the number of equivalents of terminal olefin were reduced, the yield of the reaction fell, yet a modest yield of 29% could be obtained with 1.2 equivalents of **3**. No bis(cross-product) was observed. Reducing the concentration also resulted in lower yield, thus leading to the optimal reaction conditions, which involve 7 equivalents of **3**

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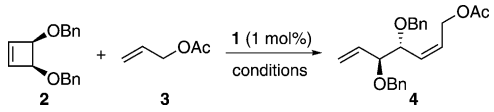
Table 1: Optimization of the AROCM of cyclobutene **2** with **3**.



Entry	Equiv **3**	Conc [M]	Solvent	Yield[a]	*Z* [%][a]	*Z* *ee* [%][b]
1	7	0.5	CH_2Cl_2	35	83	93
2	7	0.5	benzene	49	84	95
3	7	0.5	toluene	52	84	95
4	7	0.5	THF	79	85	95
5	5	0.5	THF	71	84	96
6	3	0.5	THF	63	85	96
7	1.2	0.5	THF	29	87	97
8	7	0.3	THF	72	85	95
9	7	0.1	THF	43	85	95

[a] Determined by GC. [b] Determined by chiral SFC.

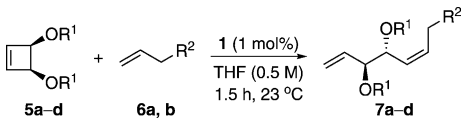
in THF at a concentration of 0.5 M, with respect to **2**, with 1 mol% **1** for a reaction time of 1.5 hours. Notably, although alternative solvents or stoichiometry negatively impacted reaction efficiency, the diastereo- and enantioselectivity remained consistently high, thus demonstrating the robustness of the reaction.

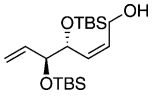
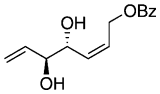
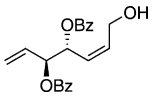
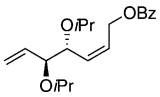
While the synthesis of a 1,2-*anti*-alkoxy motif had been demonstrated, inclusion of alternative protecting groups on the diol motif strengthens the synthetic protocol. These modifications allow a synthetic sequence to be designed such that the feasibility of removing the protecting groups in the presence of other functionality can be taken into account. Moreover, modulation of the size and electronics of the groups on the cyclobutene and terminal olefin reactants would provide a better understanding of the factors contributing to selectivity.

A complement of commonly used hydroxy protecting groups were tolerated on the cyclobutene and terminal olefin reactants,[17] but enantio- and diastereoselectivity were affected by the choice of substituents (Tables 2 and 3). The increased bulkiness of the *tert*-butyldimethylsilyl ether resulted in improved *Z* selectivity and remarkable enantioselectivity (**7a**, Table 2), while hydroxy and benzoate groups on the cyclobutene reactant led to *Z* products with 91% and 96% *ee*, respectively. The same enantioinduction was observed in the products **7a** and **7b**. Isopropoxy substituents on the cyclobutene resulted in abrogation of the catalyst activity, presumably because of the formation of a stable chelating complex.[18]

High enantioselectivities were obtained with a wide range of terminal olefins. Among the O-protecting groups surveyed (**7e**–**h**; Table 3), the *tert*-butyldimethylsilyl group resulted in high enantioselectivity (**7g**), but the more electron-withdrawing benzoate ester was optimal, thus resulting in the highest enantioselectivity (**7f**). Terminal olefins bearing alkyl substituents resulted in higher diastereoselectivity and yield with similar levels of enantioselectivity (**7i**, **j**). The chiral allylation reagent **7k** was synthesized in 91% *ee*, thus affording a functionally useful building block. *Z* and *E* isomers were isolable

Table 2: Scope of the AROCM reaction with respect to cyclobutene substitution.[a]

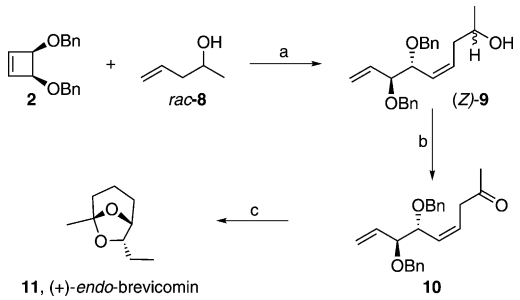


R^1	R^2	Product		Yield [%][b]	*Z* [%][c]	*ee* [%][d] *Z*	*ee* [%][d] *E*
TBS	OH		**7a**	66	88	99	n.d.
H	OBz		**7b**	67	75	91	67
Bz	OH		**7c**	69	75	96	82
*i*Pr	OBz		**7d**	< 5	n.d.	n.d.	n.d.

[a] Used 0.1 mmol cyclobutene and 0.7 mmol terminal olefin. [b] Combined yield for the isolated *E* and *Z* products. [c] Determined by 500 MHz ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral SFC. Bz = benzoyl, TBS = *tert*-butyldimethylsilyl.

from each other by flash or thin-layer chromatography in all cases except for that of **7i**.

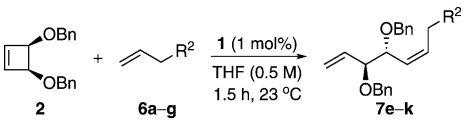
We next explored the synthetic utility of the 1,2-*anti*-diol fragments produced in the AROCM reaction. Cyclic ketals, derived from the 1,2-*anti*-diol motif, feature prominently in the structures of several natural products.[19] Accordingly, we targeted this structure in the context of a synthesis of the insect pheromone (+)-*endo*-brevicomin (**11**, Scheme 2).[20]

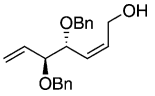
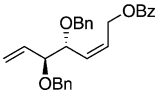
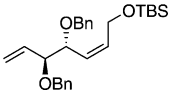
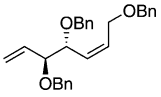
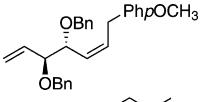
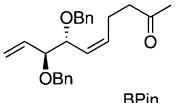
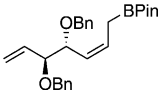


Scheme 2. Enantioselective synthesis of (+)-*endo*-brevicomin. a) **1** (1 mol%), *rac*-**8** (7 equiv), THF, 23 °C, 85% yield, 91% *Z*, 1:1 d.r., 95% *ee*. b) Dess–Martin periodinane (2 equiv), 0-23 °C, 88% yield. c) H_2 (1 atm), Pd/C (10%), MeOH/aq. 1 N HCl, 67% yield.

(+)-*endo*-Brevicomin is a male produced component of the attractive pheromone system of *Dendroctonus frontalis* (southern pine beetle),[19a] a tree-killing insect found in southern North and Central America. It was envisioned that AROCM of **2** with 4-penten-2-ol would set the relative and absolute stereochemistry in the synthesis of (+)-*endo*-brevicomin.

Table 3: Scope of the AROCM reaction with respect to the terminal olefin.[a]



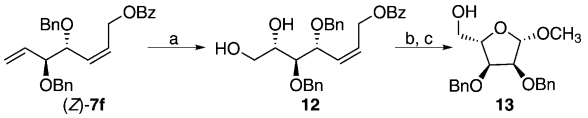
R^2	Product		Yield [%][b]	*Z* [%][c]	*ee* [%][d] *Z*	*E*
OH		**7e**	62	89	93	86
OBz		**7f**	61	88	97	88
OTBS		**7g**	68[e]	87	89	77
OBn		**7h**	64	86	91	n.d.
4-MeOPh		**7i**	76	90	93	79
$CH_2C(O)CH_3$		**7j**	65	90	92	84
BPin		**7k**	50	n.d.[f]	91	n.d.

[a] Used 0.1 mmol cyclobutene and 0.7 mmol terminal olefin. [b] Combined yield of the isolated *E* and *Z* products. [c] Determined by 500 MHz ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral SFC. [e] Yield determined after derivatization to **7e**. [f] Not determined because of instability of the *E* product. Pin = pinacol.

An expedient three-step synthesis of (+)-*endo*-brevicomin was accomplished by the AROCM of **2** with *rac*-**8** to afford **9** (91% *Z*) in 85% yield as an inconsequential mixture of diastereomers (Scheme 2).[21] The mixture of epimeric alcohols was cleanly oxidized to the desired ketone by Dess–Martin periodinane in 88% yield. (*Z*)-**10** was obtained in 95% *ee*, thus indicating high enantioselectivity in the AROCM reaction. Hydrogenation of (*Z*)-**10** in acidic methanol resulted in concomitant reduction of the alkenes, hydrogenolysis of the benzyl groups, and cyclization to form (+)-*endo*-brevicomin in 67% yield in a one-pot transformation.[22]

It was envisioned that the synthetic utility of the 1,5-dienes produced in the AROCM of cyclobutenes could be further underscored by chemoselective functionalization of the two alkenes. For example, the introduction of additional hydroxy groups would enable the rapid synthesis of monosaccharides. In this fashion, a succinct and highly enantioselective synthesis of monosaccharides could function as a robust route to starting materials for complex polysaccharides.

The synthesis of the ribose derivative **13** was carried out to demonstrate the conversion of AROCM products such as **7**



Scheme 3. Enantioselective synthesis of an L-ribose derivative. a) OsO_4 (5 mol%), $K_3Fe(CN)_6$, K_2CO_3, *t*BuOH/water (1:1) , 66% yield, 9:1 d.r. b) O_3 then Me_2S. c) HCl in MeOH (anh.), 47% yield (over two steps).

into useful monosaccharides (Scheme 3). Dihydroxylation of (*Z*)-**7f** catalyzed by OsO_4 afforded a 66% yield of the differentially protected pentanol **12** in 9:1 d.r.[23] Ozonolysis of the remaining double bond afforded the differentially protected L-ribose lactol, which was isolated as the methyl glycoside **13** in 47% yield over two steps.[24] It is hypothesized that a broader collection of monosaccharides will be accessible from the AROCM products by the modification of this synthetic sequence.

In conclusion, the highly enantioselective synthesis of 1,2-*anti*-diols was accomplished by the application of catalyst **1** to the AROCM of *cis*-dioxygenated cyclobutenes. The reaction is robust, tolerating modifications in reaction conditions and substitution on the reactants. Enantioenrichment of the major *Z* isomers was exceptionally high, ranging from 89–99% *ee*. The rapid synthesis of insect pheromone (+)-*endo*-brevicomin afforded the natural product in 95% *ee*. A 1,5-diene generated by the AROCM reaction was chemoselectively functionalized to afford the ribose derivative **13**, thus demonstrating the utility of the building blocks afforded by the title reaction.

Experimental Section

In a glovebox, the cyclobutene **2** (26.6 mg, 0.1 mmol) and allyl benzoate (113 mg, 0.7 mmol, 7 equiv) were dissolved in 0.15 mL THF. A stock solution (50 μL; 0.02 M in THF) of the catalyst **1** was added to this solution. The reaction vial was capped, the reaction mixture stirred for 1.5 h, and then quenched with an excess of ethyl vinyl ether outside of the glove box. The reaction mixture was concentrated and subjected to flash chromatography to afford the desired AROCM product [**7f**, 25.9 mg, 61% yield, 88:12 *Z*/*E*, 97% *ee* (*Z* product), 88% *ee* (*E* product)].

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