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Highly *Z*-Selective and Enantioselective Ring-Opening/Cross-Metathesis Catalyzed by a Resolved Stereogenic-at-Ru Complex

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Supporting Information

ABSTRACT: The synthesis of a ruthenium complex that catalyzes *Z*-selective (up to 98% *Z*) asymmetric ring-opening/cross-metathesis with high enantioselectivity (up to 95% ee) is reported. The synthesis of the catalyst features the resolution of a chelating N-heterocyclic carbene complex by ligand substitution with a chiral carboxylate.

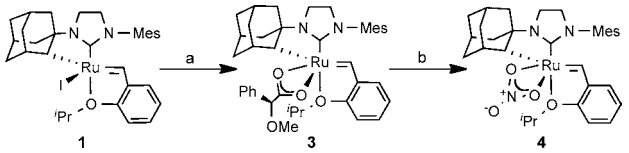
Olefin metathesis is a powerful carbon−carbon bond-forming reaction that is widely used in organic synthesis,[1] polymer chemistry,[2] materials science,[3] and biochemistry.[4] Asymmetric olefin metathesis methodologies have proven useful for the synthesis of enantiopure natural products and other biologically relevant compounds.[5] Consequently, the development of chiral catalysts for methods such as asymmetric ring-opening/cross-metathesis (AROCM) is a field of ongoing interest.[6]

The earliest catalysts, which contained molybdenum, were capable of generating AROCM products in high ee (80−99%) but suffered from limited substrate scope and functional group compatibility.[7] Ruthenium-based catalysts wherein the chirality is built into the N-heterocyclic carbene (NHC) ligand have been developed.[8] Most of these molybdenum and ruthenium catalysts are capable of performing AROCM with high levels of *E* selectivity (up to >98% *E*).[9]

Recently, *Z*-selective AROCM of oxabicycles has been achieved with molybdenum catalysts.[10] While *Z*-selective AROCM has been accomplished with ruthenium catalysts, to date it has been limited to reactions involving heteroatom-substituted terminal olefin cross-partners.[11] Recent advances have produced ruthenium catalysts with chelating NHC ligands possessing exquisite *Z* selectivity in cross-metathesis.[12] We anticipated that enantiopure versions of the newly developed catalysts would exhibit high *Z* selectivity and enantioselectivity in AROCM because of the rigidity imparted by the Ru−C chelate. Herein we report a new homochiral stereogenic-at-ruthenium complex that exhibits high enantioselectivity in the AROCM of norbornene derivatives.

Enantioenriched **4** was synthesized by resolution as shown in Scheme 1. Treatment of racemic iodide **1**[12c] with silver carboxylate **2** cleanly formed a 1:1 mixture of diastereomers in 97% yield. Chromatographic separation of the mixture afforded a 45% yield of **3** (90% of the theoretical maximum) with >95:5 dr. The absolute stereochemistry of complex **3** was confirmed by X-ray crystallography (Figure 1). Sequential treatment of

Scheme 1. Synthesis of Homochiral Complex 4[a]



[a](a) (1) (*S*)-$AgO_2CCH(Ph)(OMe)$ (**2**) (2 equiv), THF, 23 °C, 1.5 h, 97%; (2) chromatographic separation, 45%. (b) (1) *p*TsOH·H_2O, THF, 5 min; (2) $NaNO_3$, THF/MeOH, 15 min, 43%.

carboxylate **3** with *p*-toluenesulfonic acid and sodium nitrate produced the enantioenriched nitrate complex **4** in 43% yield.

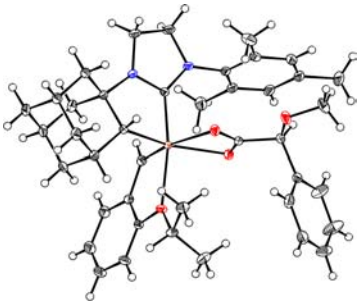
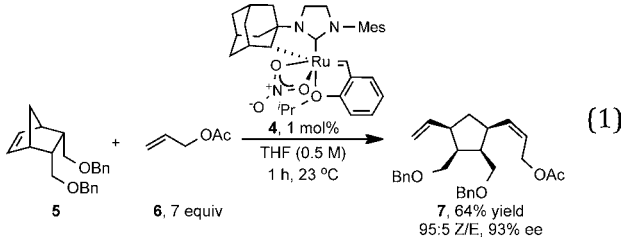


Figure 1. ORTEP drawing of **3**.

While complex **3** exhibited low enantioselectivity in AROCM, a 1 mol % loading of complex **4** catalyzed the reaction of norbornene derivative **5** with excess allyl acetate (**6**) to produce a 64% yield of the diene (1*S*,2*R*,3*S*,4*R*)-**7** with 95% *Z* selectivity and 93% ee (eq 1).[13] The highly selective reaction



(1)

produces four contiguous stereocenters in a tetrasubstituted cyclopentane ring. Optimization of the process revealed that 7

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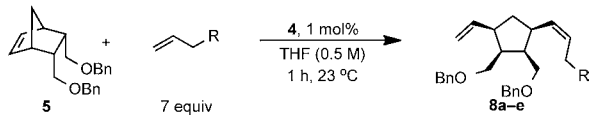
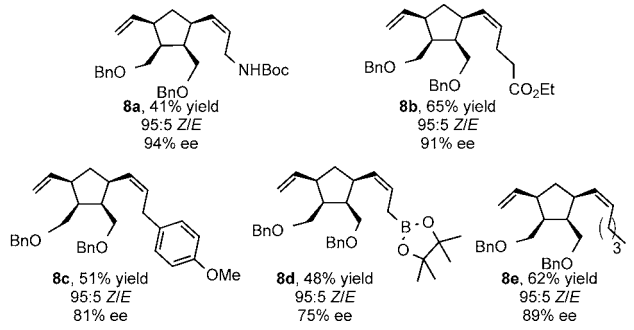
equiv of terminal olefin, a catalyst loading of 1 mol % at 23 °C and a concentration of 0.5 M in tetrahydrofuran (THF) afforded the highest yield and selectivity. Ethereal solvents were optimal, with the catalyst solubility improved in THF over diethyl ether.

To demonstrate the scope of *Z*-selective catalyst **4**, a variety of terminal olefins bearing diverse functionality were employed in order to determine their effect on the efficiency and enantioselectivity of the reaction. As illustrated in Table 1,

Table 1. AROCM with Different Terminal Olefin Partners[a]





[a]Yields correspond to isolated products; *Z*/*E* ratios were determined by 500 MHz ^{1}H NMR analysis of the crude reaction mixtures; the ee's of the pure products were measured with chiral supercritical fluid chromatography (SFC).

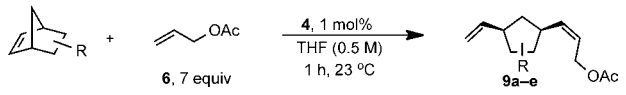
replacing allyl acetate with *N*-Boc-allylamine provided amine-containing product **8a** with equally high enantioselectivity (94% ee). Utilizing an olefin bearing a remote ester did not impact the *Z* selectivity and afforded **8b** with 91% ee.

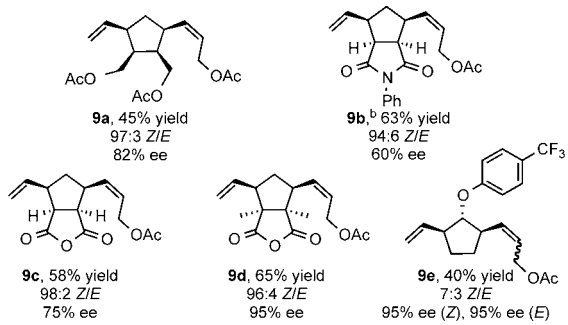
Bulkier allylic substituents such as *p*-methoxyphenyl and pinacol boronic ester gave products **8c** and **8d** with moderate enantioselectivity (81 and 75% ee, respectively). A simple α-olefin such as 1-hexene also gave good yield, *Z* selectivity, and enantioselectivity (**8e**, 89% ee), demonstrating that allylic functionality is not required to confer a selective reaction. The examples in Table 1 suggest that catalyst **4** is capable of producing a range of AROCM products.[14]

The norbornene component was then altered to investigate its impact on the *Z* selectivity and enantioselectivity. As a basis for comparison, the substrates were treated with 7 equiv of allyl acetate under the optimized catalytic conditions. Norbornenes bearing coordinating functionality such as acetate (to form **9a**) and *N*-phenylsuccinimide (to form **9b**) resulted in reduced yield and slower reaction, respectively. The dimethyl-substituted anhydride afforded a 65% yield of **9d**, which contains two vicinal all-carbon quaternary stereocenters, demonstrating the power of AROCM to afford otherwise synthetically challenging products with high ee (95%). Aryl ether **9e** was produced with 95% ee, although interestingly as a 7:3 *Z*/*E* mixture. The results in Table 2 support the observation that substrates bearing 2,3-endo substitution react with high *Z* selectivity, while substrates lacking this substitution pattern show reduced diastereoselectivity.

The fact that (*Z*)-**9e** and (*E*)-**9e** were formed with identical enantioenrichment has important mechanistic implications and

Table 2. Influence of the Norbornene Reactant[a]

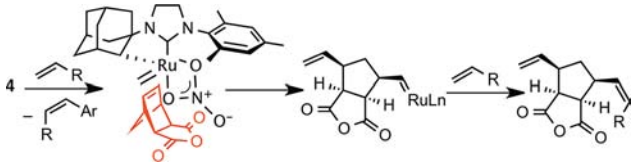




[a]Yields correspond to isolated products; *Z*/*E* ratios were determined by GC; the ee's of the pure products were measured with chiral SFC. [b]Conducted at a catalyst loading of 3 mol % for 5 h.

offers indirect evidence of the active catalytic species. The result suggests that the enantiodetermining step most likely precedes the olefin-geometry-determining step.[15] This conclusion requires the initial enantiodetermining ring-opening event to occur with a ruthenium methylidene (Scheme 2). Subsequent cross-metathesis of the ring-opened product bearing a ruthenium alkylidene with 1 equiv of terminal olefin would then afford the observed product.

Scheme 2. Proposed Model of Enantioselectivity



On the basis of this indirect mechanistic evidence and the absolute configuration of the isolated product, we propose that the methylidene shown in Scheme 2 initially reacts with the norbornene component in an enantioselective ring-opening event. It is hypothesized that the enantioselectivity is governed by the approach of the methylidene to the less-hindered exo face, while the mesityl "cap" forces the bulk of the norbornene component to be oriented away from the NHC ligand.[16] The proposed methylidene is most likely produced by initial cross-metathesis of **4** with a molecule of terminal olefin, resulting in epimerization at the ruthenium center. Studies to provide a better understanding of the mechanism and origin of the enantioselectivity in the AROCM catalyzed by complex **4** are currently underway.

In summary, we have developed an enantioenriched ruthenium metathesis catalyst capable of highly *Z*-selective and enantioselective ROCM. An NHC ligand that chelates through a Ru–C bond is key to the design of the catalyst, which features a stereogenic Ru atom. The reaction is amenable to modification of both the terminal olefin and norbornene components, which significantly broadens the scope of this methodology.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data for the products, and crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) Absolute configurations were assigned by analogy to that of **9c**, which was determined by X-ray crystallography (see the Supporting Information for details).

(14) Attempts to employ a heteroatom-substituted olefin (butyl vinyl ether) resulted in no ROCM product, presumably because of catalyst deactivation.

(15) This assumes that secondary metathesis processes proceed at a negligible rate relative to the productive (ROCM) reaction. Measurements of the formation of **9e** (see the Supporting Information) showed that the *Z*/*E* ratio was constant during the course of the reaction and for several hours after complete conversion.

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