JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Article

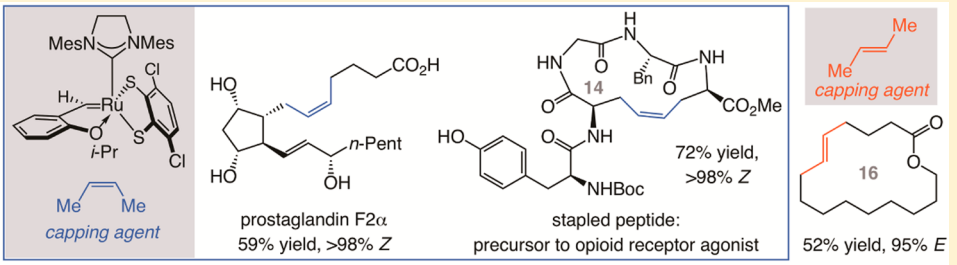
pubs.acs.org/JACS

In Situ Methylene Capping: A General Strategy for Efficient Stereoretentive Catalytic Olefin Metathesis. The Concept, Methodological Implications, and Applications to Synthesis of Biologically Active Compounds

Chaofan Xu,[†] Xiao Shen,[†] and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

Supporting Information



<2% conv without capping agent. Not feasible with other catalyst families (Ru-, Mo- or W-based).

ABSTRACT: In situ methylene capping is introduced as a practical and broadly applicable strategy that can expand the scope of catalyst-controlled stereoselective olefin metathesis considerably. By incorporation of commercially available *Z*-butene together with robust and readily accessible Ru-based dithiolate catalysts developed in these laboratories, a large variety of transformations can be made to proceed with terminal alkenes, without the need for a priori synthesis of a stereochemically defined disubstituted olefin. Reactions thus proceed with significantly higher efficiency and *Z* selectivity as compared to when other Ru-, Mo-, or W-based complexes are utilized. Cross-metathesis with olefins that contain a carboxylic acid, an aldehyde, an allylic alcohol, an aryl olefin, an α substituent, or amino acid residues was carried out to generate the desired products in 47−88% yield and 90:10 to >98:2 *Z*:*E* selectivity. Transformations were equally efficient and stereoselective with a ∼70:30 *Z*-:*E*-butene mixture, which is a byproduct of crude oil cracking. The in situ methylene capping strategy was used with the same Ru catechothiolate complex (no catalyst modification necessary) to perform ring-closing metathesis reactions, generating 14- to 21-membered ring macrocyclic alkenes in 40−70% yield and 96:4−98:2 *Z*:*E* selectivity; here too, reactions were more efficient and *Z*-selective than when the other catalyst classes are employed. The utility of the approach is highlighted by applications to efficient and stereoselective syntheses of several biologically active molecules. This includes a platelet aggregate inhibitor and two members of the prostaglandin family of compounds by catalytic cross-metathesis reactions, and a strained 14-membered ring stapled peptide by means of macrocyclic ring-closing metathesis. The approach presented herein is likely to have a notable effect on broadening the scope of olefin metathesis, as the stability of methylidene complexes is a generally debilitating issue with all types of catalyst systems. Illustrative examples of kinetically controlled *E*-selective cross-metathesis and macrocyclic ring-closing reactions, where *E*-butene serves as the methylene capping agent, are provided.

INTRODUCTION

A hallmark of Ru-dichloro catalysts, which have been pivotal to the emergence of olefin metathesis as a central transformation in chemistry,[1] is their ability to promote reactions of hindered alkenes and in the presence of commonly occurring polar functional units such as a neighboring alcohol, an aldehyde, or a carboxylic acid. Grubbs and co-workers reported in 2011 that kinetic control of *Z*-selectivity[2] can be achieved by substituting anionic chlorides with an alkyl and an oxo ligand.[3] In 2013, we disclosed the design of a sterically and electronically distinct set of Ru-based complexes, containing a monodentate *N*-heterocyclic carbene and, more importantly, a bidentate disulfide[4] ligand, which may be used for efficient catalytic *Z*-selective olefin metathesis.[5] Alkyl/oxo catalysts[3] have proven to be severely inefficient in promoting transformations with aryl-substituted or hindered terminal olefins and/or when an aldehyde is present, and their activity is entirely inhibited by a carboxylic acid.[6] Ru-based catechothiolate catalysts tolerate such functional groups,[6a] but the derived methylidene species decompose too rapidly and reactions involving terminal alkenes,[6a] the most accessible substrate class, are low yielding.

Here, we demonstrate that by adding *Z*-butene to a reaction mixture that contains an appropriate Ru dithiolate catalyst,

Received: June 23, 2017

© XXXX American Chemical Society

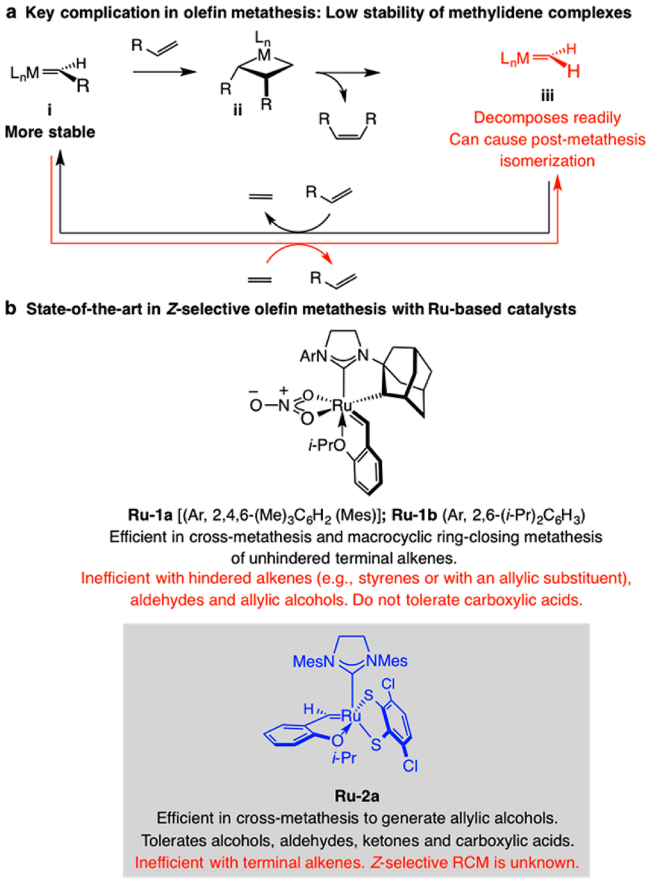
DOI: 10.1021/jacs.7b06552
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

methylidene complex formation can be avoided, and, as a result, an unprecedented range of terminal alkenes may be converted to the desired products by efficient and exceptionally *Z*-selective cross-metathesis (CM) and macrocyclic ring-closing metathesis (MRCM) processes. Equally notable is that stereoselectivity is generally higher when the methylene capping strategy is adopted. The broad applicability and general utility of the approach are highlighted by concise (i.e., little or no protection/deprotection sequences) and stereoselective syntheses of a platelet aggregate inhibitor,[7] prostaglandins E2 and F2α,[8] as well as a 14-membered ring stapled peptide that is a precursor to a potent opioid receptor agonist.[9]

RESULTS AND DISCUSSION

1. General Problem of Methylidene Complex Intermediacy. Monosubstituted alkenes are inexpensive and widely accessible compounds that can be converted to valuable derivatives by olefin metathesis.[1] A general and key problem is that reaction of a carbene or alkylidene (**i**, M = Ru, Mo or W, respectively; Scheme 1a) with a terminal olefin releases the homocoupling product via metallacyclobutane **ii** (one stereoisomer shown) and then methylidene species **iii**, which can decompose at a rate[10] that is fast enough to bring a transformation to a halt. Further complicating matters, the ethylene byproduct can convert the relatively stable **i** to methylidene **iii**. Ethylene removal under vacuum can improve matters to some extent, but methylidene formation is unavoidable as long as a monosubstituted alkene is present.

Scheme 1. Methylidene Problem and the State-of-the-Art in *Z*-Selective Olefin Metathesis with Ru-Based Complexes



The importance of these difficulties is manifested in the context of *Z*-selective olefin metathesis reactions catalyzed by Ru-based carbenes[2] (Scheme 1b). Complexes **Ru-1a,b** may be used for homocoupling,[3a] CM,[3b] or MRCM[11] with monosubstituted olefins; the derived methylidene complexes are sufficiently stable for transformations to proceed with reasonable efficiency. Nonetheless, a small number of instances notwithstanding,[12] reactions are inefficient with olefins containing an allylic or homoallylic substituent or when an aldehyde and/or an allylic alcohol is present, and generally no product is generated when a substrate contains a carboxylic acid.[6a] Moreover, there are no reported examples of reactions with aryl olefins. These are major shortcomings especially because the principal advantage of Ru (vs Mo or W[13]) complexes is that an electrophilic or a Brønsted acid moiety typically does not inhibit catalyst activity.

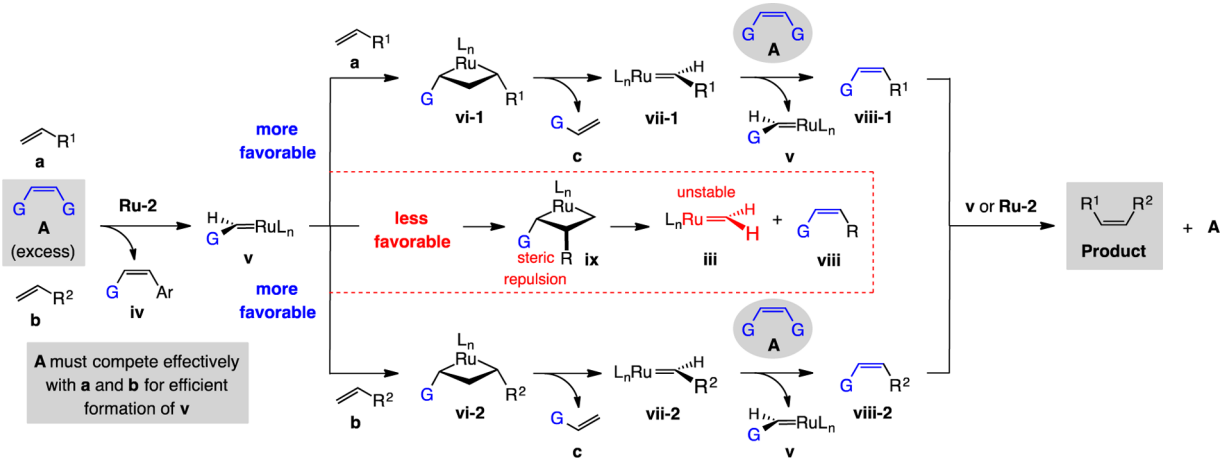
Catechothiolate Ru species (e.g., **Ru-2a**, Scheme 1b) offer functional group compatibility that is similar to that of the original dichloride derivatives[6] and have been used for *Z*-selective ring-opening/cross-metathesis,[14] ring-opening metathesis polymerization,[15] and CM.[6] However, we have shown that the corresponding methylidene complexes (cf., **iii**) are too unstable (partly due to 1,2-shift of the sulfide trans to the NHC to the carbene carbon),[6] and thus reactions with terminal olefins are typically inefficient (i.e., $\leq$10% conversion). There are only a few high yielding examples where one of the substrates is a terminal alkene; in these cases, either the olefin partner is much more reactive[14] (strained bicyclic alkene) so that homocoupling of the former can be largely avoided, and/or H-bonding (between *Z*-2-butene-1,4-diol and sulfide ligands) allows for methylidene formation to be minimized.[6a] There are therefore no available *Z*-selective cross-metathesis protocols that can be used efficiently with a wide range of monosubstituted olefins that might contain an allylic, aryl, alkyl, or a hydroxy substituent and/or an aldehyde or a carboxylic acid moiety.

2. Concept of in Situ Methylene Capping. In search of a solution, we envisaged a strategy that may be referred to as in situ methylene capping. This would entail incorporating a third alkene component (**A**, Scheme 2), the CM of which with monosubstituted olefins (i.e., formation of **v**) would be faster than homocoupling or CM of terminal olefins **a** or **b**, which would instead generate an unstable methylidene complex (**iii**). Ideally, compound **A** would be efficiently converted to Ru-carbene **v**, which might then react with a terminal alkene to afford *Z*-1,2-disubstituted olefin intermediates **viii-1** and **viii-2** via carbene **vii**. Removal of excess **A** (to minimize nonproductive metathesis) and terminal alkene byproduct **c** (to avoid methylidene formation) in vacuo would allow for efficient CM between **viii-1** and **viii-2**, affording the final product and regenerating the capping agent (vs ethylene). We could contemplate the above sequence because, unlike alkyl-oxo species **Ru-1a,b**, catechothiolate complexes are able to promote reactions between disubstituted olefins.[6]

The ideal capping agent must possess several key attributes. Its substituents (G in **A**, Scheme 2) are to be sufficiently large to ensure minimal methylidene formation (i.e., high **vi**/**ix** ratio), and yet it needs to be small enough for **A** to compete effectively with a terminal alkene for reaction with **Ru-2a** so that complex **v** can be generated efficiently (vs methylidene **iii** from homocoupling and/or cross-metathesis of **a** and/or **b**). The capping agent should allow the transformation to be exceptionally stereoretentive; its high stereoisomeric purity

DOI: 10.1021/jacs.7b06552
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

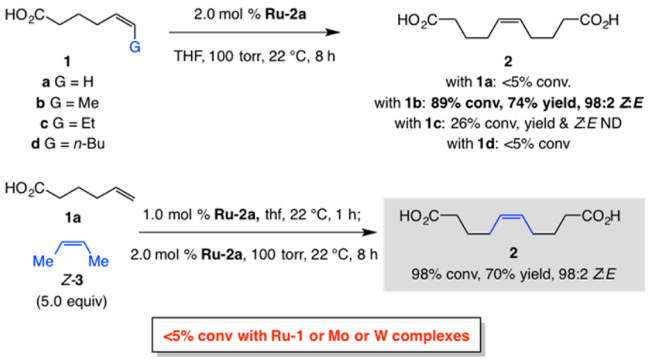
Scheme 2. Concept of in Situ Methylene Capping in Olefin Metathesis



must be directly reflected in the final product. Because excess **A** would have to be removed later, it is imperative that it is readily accessible, inexpensive, and appropriately volatile.

3. Identifying an Effective Methylene Capping Agent. We began by investigating the homocoupling reactions of **1a** and *Z*-1,2-disubstituted alkenes **1b–d** (Scheme 3). There was minimal conversion to **2** when **1a** was subjected to 2.0 mol % **Ru-2a** (<5% conversion (conv), 100 Torr, 22 °C, 8 h). In contrast, with methyl-substituted **1b** (G = Me), the desired product (**2**) was obtained in 74% yield and >98:2 *Z*:*E* ratio.

Scheme 3. Preliminary Studies: Identifying an Effective Capping Agent[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* ratios determined by analysis of ^1H or ^{13}C NMR spectra of unpurified product mixtures (±2%). Yields for purified products (±5%). Experiments were run in duplicate or more. See the Supporting Information for details.

There appears to be a strict requirement on the size of G: reactions with a slightly larger ethyl- and *n*-butyl-substituted **1c** and **1d** were far less efficient (26% and <5% conv, respectively). These findings indicated that *Z*-butene (*Z*-**3**) would be a suitable capping agent. Indeed, treatment of a 1:5 mixture of **1a** with a THF solution of commercially available *Z*-**3** (unpurified) to 3.0 mol % **Ru-2a** afforded **2** in 70% yield and 98:2 *Z*:*E* selectivity. Although when a single batch of 5.0 mol % **Ru-2a** was used, the efficiency and stereoselectivity were similar, the sequential addition procedure allowed for lower total catalyst loading, and we therefore adopted it from here on.

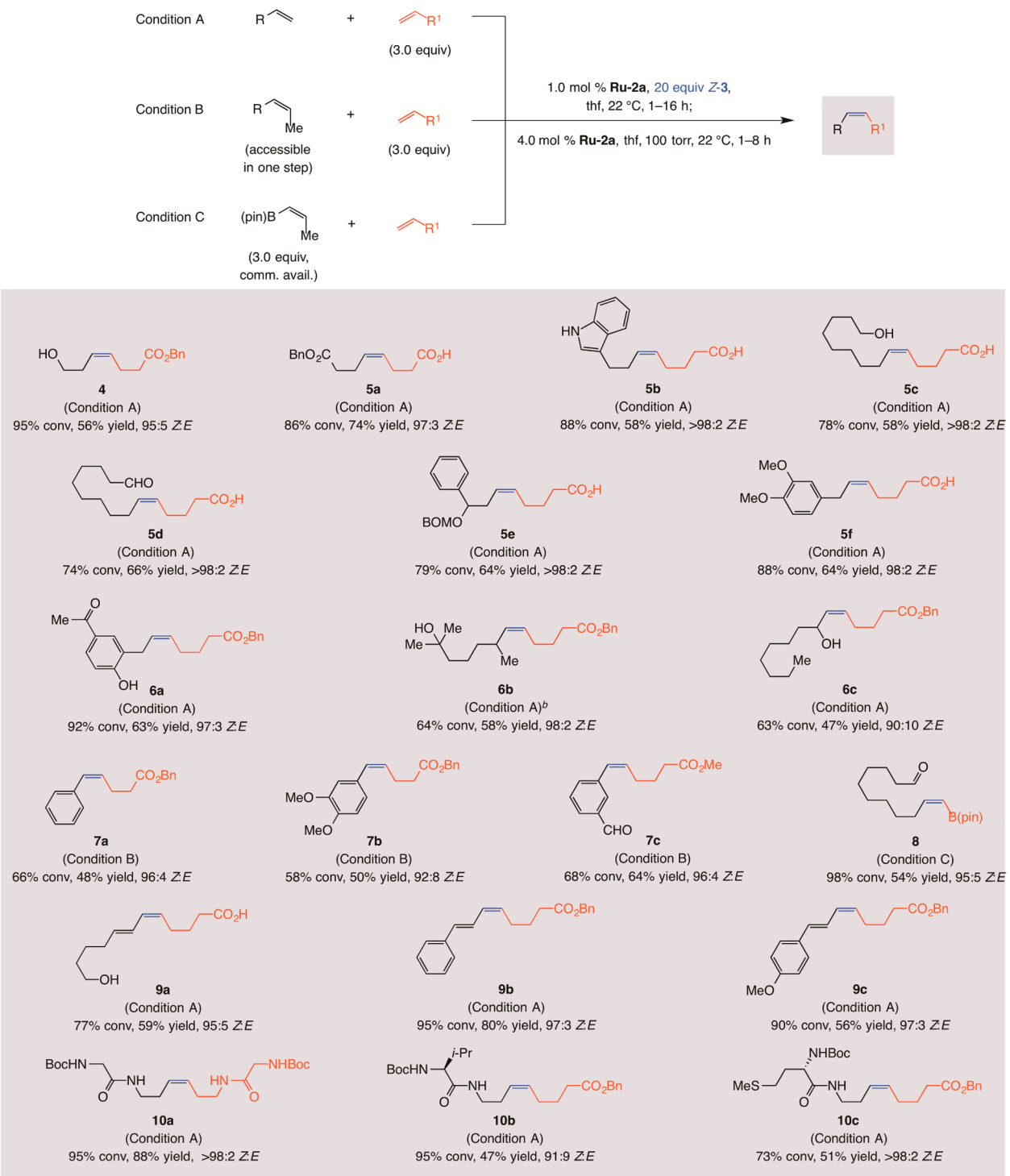
4. *Z*-Selective Cross-Metathesis with a Methylene Capping Agent. We then investigated *Z*-selective CM with focus on cases where high efficiency and/or stereoselectivity are possible only with the combination of **Ru-2a** and *Z*-**3** (Scheme 4). With 5.0 mol % **Ru-2a**, homoallylic alcohol **4** was isolated in 56% yield and 95:5 *Z*:*E* selectivity; there was <20% conversion without *Z*-**3**. With **Ru-1a** there was <5% conversion when the derived *Z*-methyl-substituted alkenes were used as substrates, and with the corresponding terminal alkenes under the previously disclosed conditions[11b,12] [5.0 mol %, THF (0.5 M), 35 °C, 8 h], **4** was isolated in 49% yield and 68:32 *Z*:*E* selectivity. Unlike other instances to be discussed below (Scheme 4), where 1.0 mol % **Ru-2a** and 1 h is sufficient at the first stage, longer reaction times were needed for the homoallylic alcohol, perhaps because internal chelation of the hydroxyl group with the metal center can lower catalyst activity.

Despite the presence of excess carboxylic acid (3.0 equiv), products that also contain an unprotected indole (**5b**), a hydroxy unit (**5c**), an aldehyde group (**5d**), or a *β*-branched substituent (**5e,f**) were isolated in 58–74% yield and 97:3 to >98:2 *Z*:*E* selectivity; in all cases, there was <5% conversion without the capping agent. When 2.0 mmol of the unsaturated ester substrate was used, ~0.3 g of **5a** could be isolated (87% conv, 56% yield) in 98:2 *Z*:*E* selectivity. *para*-Ketone-substituted phenol **6a** was prepared efficiently and with high *Z*-selectivity; this alkene was isolated in 28% yield and 88:12 *Z*:*E* selectivity with **Ru-1a** (under formerly reported conditions[11b,12]). Compounds **6b** and **6c** were secured in 58% and 47% yield and 98:2 and 90:10 *Z*:*E* selectivity, respectively; in the case of **6b**, the terminal alkene bearing an allylic methyl group does not readily undergo homocoupling and was therefore used directly (without methylene capping). Moreover, when 6.5 mol % **Ru-2a** was used in the second stage of the process, **6b** was isolated in 82% yield (89% conv vs 58% yield with 4.0 mol %) and 98:2 *Z*:*E* selectivity. Again, with **Ru-1a**, reactions between the corresponding terminal alkenes were much less efficient and stereoselective (**6b** and **6c** in 76:24 and 55:45 *Z*:*E* selectivity and 14% and 29% yield, respectively). The lower efficiency in the formation of allylic alcohol **6c** is not due to adventitious alkene isomerization because none of the ketone byproduct could be detected. Chelation of the hydroxy group with the Ru center might reduce catalytic activity, an effect that is likely less critical with reactions of less substituted, and thus more reactive, primary allylic alcohols.[6]

With monosubstituted aryl olefins, yields were low due to swift stilbene/methylidene complex formation. Accordingly, *Z*-

DOI: 10.1021/jacs.7b06552
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

Scheme 4. Catalytic *Z*-Selective Cross-Metathesis with *Z*-Butene as the Methyelene Capping Agent[a]



[a](a) Reactions were carried out under N_2 atm. Conversion and *Z*:*E* ratios determined by analysis of ^1H or ^{13}C NMR spectra of unpurified product mixtures (±2%). Yields for purified products (±5%). For **7a–c**, *Z*-*β*-methylstyrene was used (condition B); *Z*-1-propenylboronic acid pinacol ester used to prepare **8** (condition C). (b) *α*-Branched terminal alkene was used directly (without treatment with *Z*-**3**). Experiments were run in duplicate or more. See the Supporting Information for details.

β-methylstyrenes, accessed in one step by catalytic cross-coupling between a commercially available arylboronic acid pinacol ester and *Z*-1-bromopropene, were used to access **7a–c** in 48–64% yield and 92:8–96:4 *Z*:*E* selectivity. The present approach is considerably more efficient and/or stereoselective than what is feasible with alternative catalysts. For example, **7c** was obtained in 65:35 *Z*:*E* selectivity with **Ru-1a** (5.0 mol %, THF, 35 °C, 4 h), and CM with aryl olefins and a tungsten monoaryloxide pyrrolide (MAP) complex[2a] (more *Z*-selective than Mo alkylidenes) afforded the thermodynamically favored isomer predominantly (up to >98% *E*; fast postmetathesis isomerization).

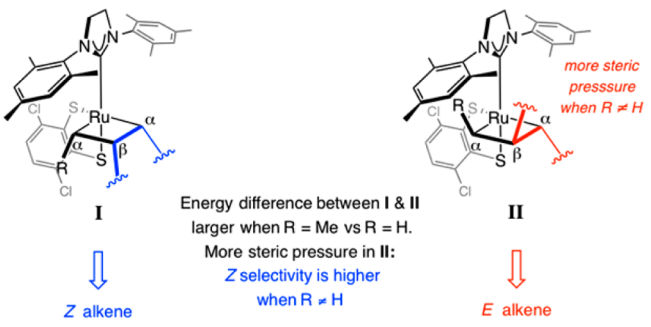
DOI: 10.1021/jacs.7b06552
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

Aldehyde-containing alkenyl-B(pin) **8** (54% yield, 95:5 *Z*:*E*) was synthesized from commercially available *Z*-1-propenylboronic acid pinacol ester. *Z*,*E*-Dienes **9a**–**c** were accessed easily (Scheme 4). The carboxylic acid in **9a** is incompatible with **Ru-1a**,**b** or various Mo-based catalysts. Synthesis of aryl-substituted **9b** and **9c** is inefficient with **Ru-1a**,**b** (≤25% yield),[16] and less stereoselective with a Mo complex due to postmetathesis *Z*-to-*E* interconversion; for example, with a MAP catalyst containing a pentafluorophenylimido ligand[17] (5.0 mol %, 100 Torr, 22 °C, 15 min), **9b** was obtained in 72% yield and 83:17 *Z*:*E* ratio (vs 80% yield, 97:3 *Z*:*E* with **Ru-2a**).

Amino acid-derived alkenes **10a**–**c** were obtained in 47–88% yield and 91:9 to >98:2 *Z*:*E* selectivity (Scheme 4). In sharp contrast, with **Ru-1a** and monosubstituted olefins derived from amino acids glycine (see **10a**) or methionine (see **10c**), there was complete catalyst inhibition (<10% yield),[18] and with a Mo catalyst,[17] *Z* selectivity was entirely eradicated (e.g., **10b** in 32% yield and 50:50 *Z*:*E* with the aforementioned MAP complex vs 47% yield, 91:9 *Z*:*E* with **Ru-2a**).

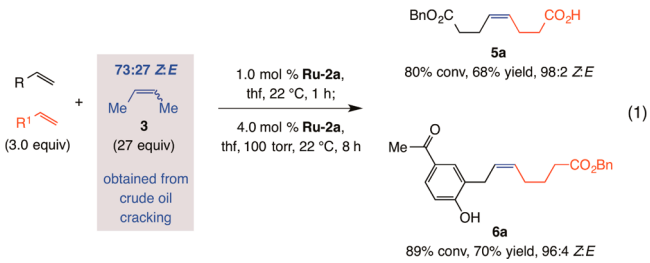
An additional advantage of the strategy described here is that by avoiding the highly reactive methylidene complexes, there is less erosion of kinetic *Z*-selectivity by postmetathesis isomerization; this is partly why reactions with **Ru-1a** and terminal alkenes, regardless of the type of functional group present, are often less *Z*-selective. Furthermore, the combination of **Ru-2a** and the intermediacy of *Z*-methyl-substituted alkene intermediates causes *Z* selectivities to be higher than when terminal alkenes are directly involved (without the capping agent). As an example, with **Ru-2a**, homocoupling of the ester-substituted terminal alkene used to prepare **6c** (Scheme 4) and its *Z*-methyl-substituted alkene derivative proceeded with 78:22 *Z*:*E* and 93:7 *Z*:*E* selectivity (14% and 79% yield), respectively. Control experiments[19] indicate that lower *Z*:*E* ratios in these latter instances in all likelihood originate from a larger energy gap between transition states leading to trisubstituted as compared to disubstituted metallacyclobutanes **I** and **II** (R = Me vs R = H; Scheme 5); greater steric pressure is exerted by

Scheme 5. Origin of Higher *Z*-Selectivity with 1,2-Disubstituted Alkenes



the monodentate *N*-heterocyclic carbene (NHC) on the two substituents in **II** when R is a methyl group (vs one Cα group in a disubstituted metallacyclobutane when R is an H atom).

An important attribute of the approach is that with a stereoisomeric mixture of *E*- and *Z*-butene (*E*- and *Z*-**3**), obtained directly from cracking of crude oil and less expensive than the corresponding pure forms of either isomer, can be used to synthesize the desired products with similar efficiency and stereoselectivity. The examples in eq 1 are representative.



Reaction with *E*-**3** is probably slower because of steric pressure caused by the metallocyclobutane substituent oriented toward the sizable NHC ligand.

5. Application of in Situ Methylene Capping to Preparation of *Z*-Macrocyclic Alkenes. To probe applicability of the capping strategy to MRCM, we first confirmed that monosubstituted olefins in a diene substrate can be capped efficiently and stereoselectively (Scheme 6a). Treatment of a 0.1 molar solution containing diene **11a** and 20 equiv of *Z*-**3** with 1.0 mol % **Ru-2a** delivered **11b** in 89% yield and >98:2 *Z*,*Z*:*Z*,*E* selectivity (22 °C, 1 h); removal of excess *Z*-**3** in vacuo and addition of 4.0 mol % **Ru-2a** afforded macrocyclic alkene **12a** in 56% yield and 96:4 *Z*:*E* selectivity (5.0 mM, 400 Torr, 12 h, 35 °C).

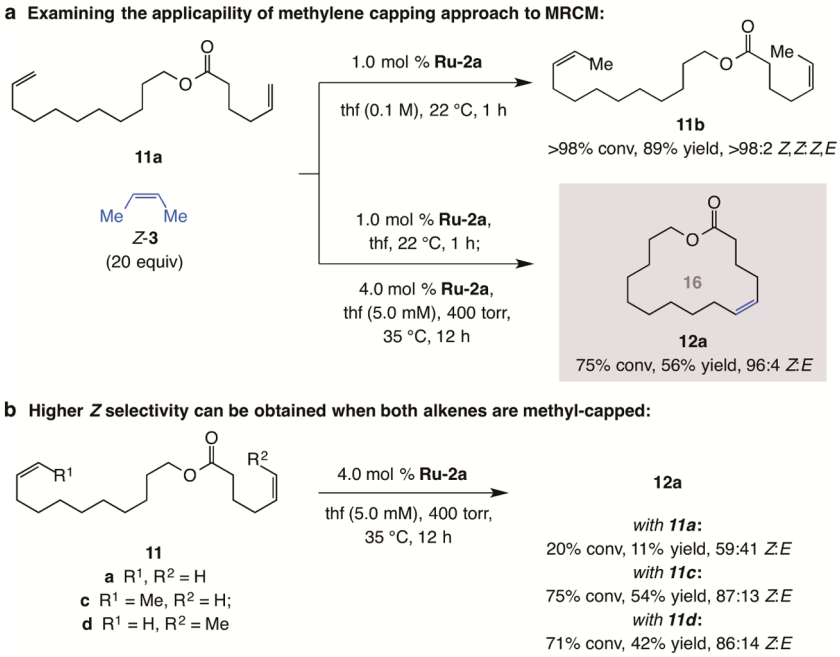
The same conditions with **Ru-2a** but without the capping agent afforded **12a** in only 11% yield and 59:41 *Z*:*E* selectivity (Scheme 6b). There was <10% conversion with 10 mol % **Ru-1a** and **11b**. Cyclization of dienes **11c** and **11d**, with only one *Z*-disubstituted olefin, was less stereoselective (87:13 and 86:14, respectively vs 96:4 *Z*:*E* for **11b**). Moreover, *Z*:*E* ratios for **12a** are not time-dependent, which further underscores the larger energy gap between transition states leading to trisubstituted as compared to disubstituted metallacyclobutanes (see Scheme 5).

The lower *Z* selectivity for **11c**,**d** (Scheme 6b) might be due to competitive homocoupling by the monosubstituted olefin moieties. This generates internal alkene stereoisomeric mixtures that can be directly converted to **12a** with lower *Z* selectivity via a Ru carbene derived from the *Z*-methyl-substituted alkene[20] ("backbiting"). Thus, because of the capping strategy, which diminishes the possibility of homocoupling side reactions and methylidene formation, together with the ability of **Ru-2a** to promote RCM of 1,2-disubstituted olefins efficiently, the scope of *Z*-selective olefin metathesis can be expanded.

6. *Z*-Selective Macrocyclic Ring-Closing Metathesis with a Methylene Capping Agent. We synthesized 14- to 21-membered ring structures in 53–70% yield and in 96:4–98:2 *Z*:*E* selectivity (Scheme 7a); acyclic dienes bearing two terminal alkenes were used as starting materials. These results compare favorably to reactions with **Ru-1a**,**b**, where higher catalyst loadings (7.5 vs 5.0 mol %) and reaction temperatures (60 vs 35 °C) as well as longer reaction times (24 vs 13 h) are required[11] and *Z* selectivity is generally lower.[11a] For example, secondary alcohol **12f** was generated in 56% yield and 65:35 *Z*:*E* ratio with **Ru-1a** as compared to 53% yield and 96:4 *Z*:*E* selectivity with **Ru-2a**. These distinctions may be due to postmetathesis isomerization caused by generation of methylidene complexes in reactions of terminal alkenes with **Ru-1a**,**b** as well as a smaller energy difference between transition states for stereoisomeric disubstituted metallacyclobutanes (see Scheme 5 and related discussion). As was noted, there is minimal reaction between 1,2-disubstituted olefins when **Ru-1a** was used, and, as a result, fully substituted metallacycle intermediates cannot be accessed through this catalyst system.

DOI: 10.1021/jacs.7b06552
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

Scheme 6. Preliminary Studies for Macrocyclic Ring-Closing Metathesis[a]



[a]Reactions were carried out under N_2 atm. Conversion (disappearance of the disubstituted alkene intermediate) and *Z*:*E* ratios determined by analysis of ^{1}H or ^{13}C NMR spectra of unpurified product mixtures (±2%). Yields for purified products (±5%). Experiments were run in duplicate or more. See the Supporting Information for details.

In a limited number of examples, **Ru-1b**,[11b] which contains a larger NHC ligand, stereoselectivity was improved but at the cost of diminished efficiency (e.g., **12f** in 95:5 *Z*:*E*, 45% yield; same conditions as **Ru-1a**).

The case of carboxylic acid **12j** (Scheme 7b) is notable because Mo or W complexes are inapplicable,[21] and there was <5% conversion when **Ru-1a** was used [reported conditions, 1,2-dichloroethane (5.0 mM), 60 °C, 400 Torr, 12 h]. When MRCM of **11a** was performed in the presence of an equivalent of **13**, a highly electrophilic keto-aldehyde **12a** was obtained without significant change in yield or stereoselectivity.

7. Applications to Synthesis of Biologically Active Compounds. The approach outlined above facilitates the synthesis of a variety of biologically active molecules. As highlighted by the examples discussed and illustrated below, the robustness of dithiolate Ru catalysts and their tolerance of key polar functional units, along with the various advantages inherent in adopting the methylene capping strategy, combine to make concise and highly stereoselective multistep sequences possible.

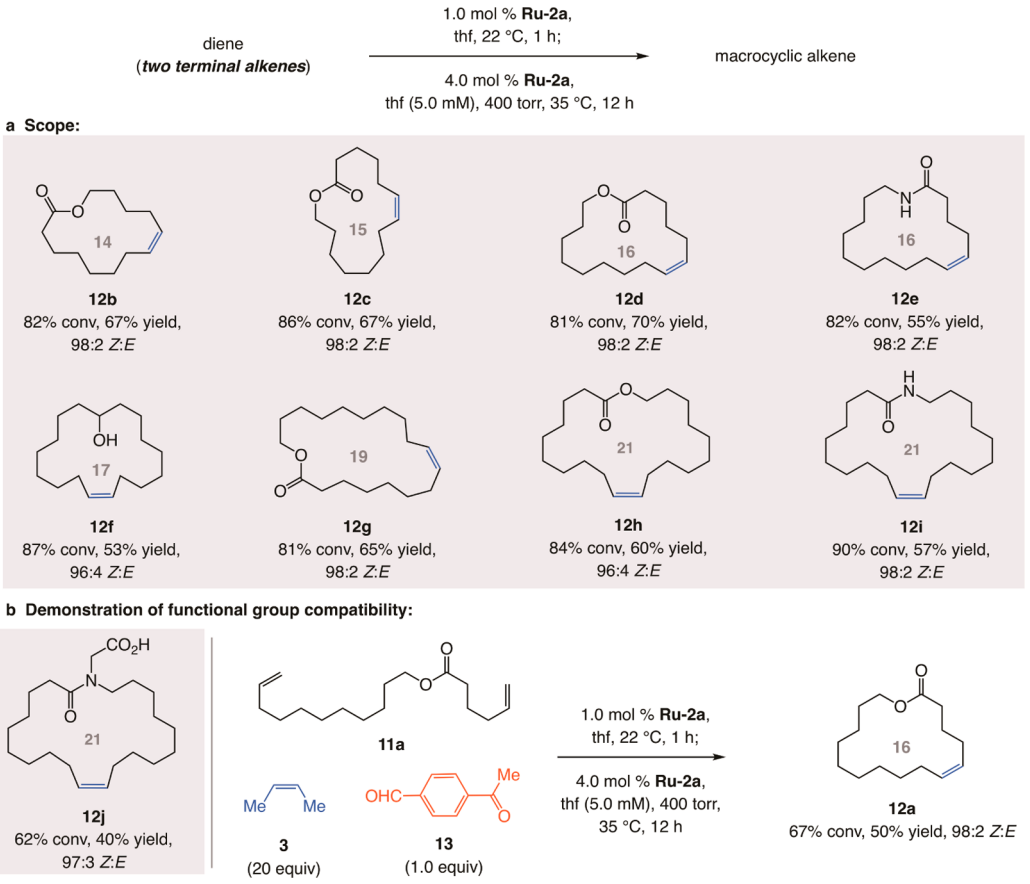
a. Stereoselective Synthesis of a Platelet Aggregate Inhibitor. Preparation of **17** (Scheme 8) demonstrates utility and allows for exploration of the limits of the approach. With **Ru-1a**, CM between **14** and methyl ester **15** afforded **16** in 35% yield and 71:29 *Z*:*E* selectivity, and with **Ru-2a**, reaction between **20** and carboxylic acid **1a** was inefficient (e.g., 25% conv at 20 mol % loading at 22 °C, 32 h; >98:2 *Z*:*E*). This is probably because loss of catechothiolate ligand through reaction with Brønsted acid,[4b] although sufficiently slow for relatively efficient transformations with more reactive olefin substrates, becomes too competitive when aryl olefins are involved. With methyl ester **15**, product **16** was isolated in 58% yield and 96:4 *Z*:*E* ratio. The methylene-capping approach thus furnished access to **16** with better efficiency and considerably higher stereochemical purity as compared to the formerly reported route (42% overall yield, 96:4 *Z*:*E* selectivity in three steps vs 30% overall yield, 80:20 *Z*:*E* in seven steps[7]). Treatment of **16** with lithium hydroxide has been shown to deliver **17**.[7]

b. Stereoselective Synthesis of Prostaglandins without Resorting to Protecting Groups. Prostaglandins E2 and F2α (Scheme 9) belong to a family of potent eicosanoid lipid mediators[8] that play key roles in a range of physiological disorders; several members are "block-buster" drugs.[22] The corresponding CM processes further challenge the limits of the state-of-the-art due to the presence of two alcohol units and a carboxylic acid moiety as well as the possibility of internal chelation between the Ru-carbene with the nearby carbonyl oxygen. Still, treatment of **21a** and unsaturated carboxylic acid **1a** with *Z*-**3** and 2.0 and 1.0 mol % **Ru-2a**, respectively, followed by mixing of the resulting mixtures (no isolation/purification) and addition of **Ru-2a** (15 mol %) under reduced pressure afforded prostaglandin E2 in 51% yield and >98:2 *Z*:*E* selectivity (40% yield and >98:2 *Z*:*E* at 10 mol % loading).

Prostoglandin F2α was synthesized in 59% yield and >98:2 *Z*:*E* selectivity (Scheme 9). Separate treatment of **21a** and **21b** (without **1a**) with the capping agent was necessary so that low catalyst loading would suffice (2.0 mol %). The solutions were then mixed and treated with additional amounts of **Ru-2a** for CM. The amount of Ru dithiolate complex needed to access these multifunctional products is higher than before. Nevertheless, the present approach is still efficient overall as stereoselectivity is exceptionally high, there is no need for protection, and subsequent deprotection/hydrolysis to unmask the hydroxy or the carboxylic acid moieties, which are functional groups, was demonstrated to be central to the exhibited agonist activity.[23] By varying the identity of the reaction partner (e.g., **1a**), desirable analogues can be

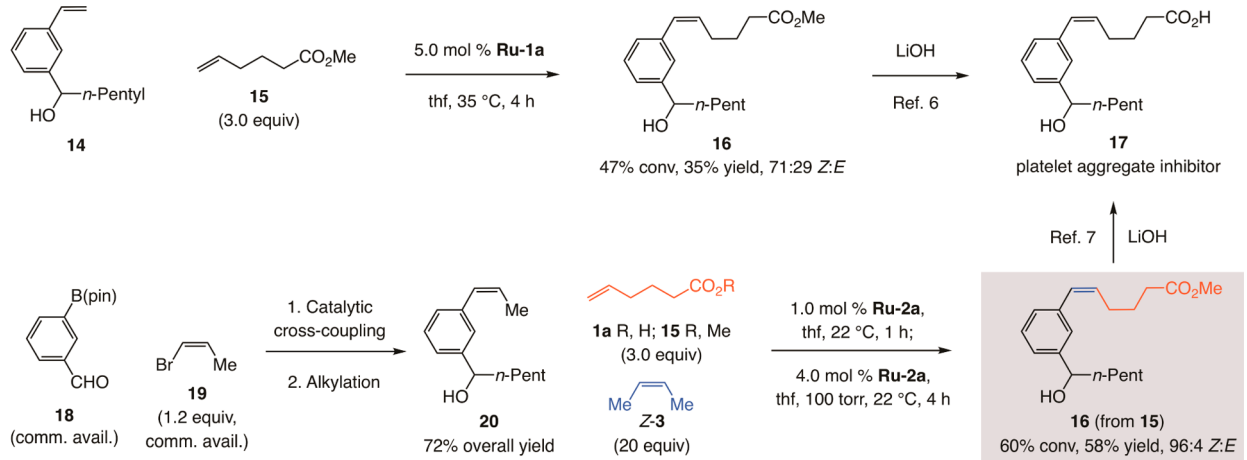
DOI: 10.1021/jacs.7b06552
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 7. *Z*-Selective Macrocyclic Ring-Closing Metathesis with *Z*-Butene as the Methylene Capping Agent[a]



[a]Reactions were carried out under N_2 atm. Conversion (disappearance of the disubstituted alkene intermediate) and *Z*:*E* ratios determined by analysis of ^1H or ^{13}C NMR spectra of unpurified product mixtures (±2%). Yields for purified products (±5%). Experiments were run in duplicate or more. See the Supporting Information for details.

Scheme 8. Application to Stereoselective Synthesis of a Platelet Aggregate Inhibitor[a]



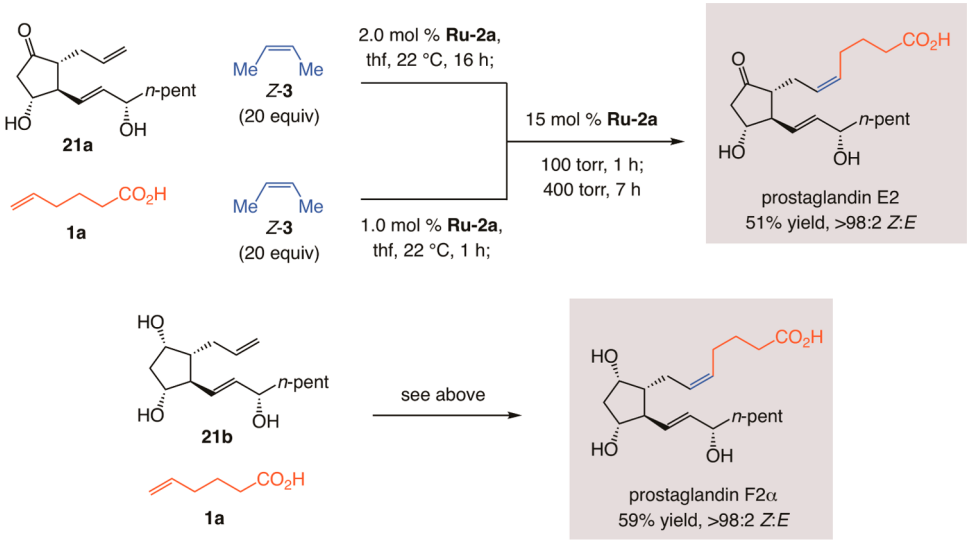
[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* ratios determined by analysis of ^1H NMR spectra of unpurified product mixtures (±2%). Yields for purified products (±5%). Experiments were run in duplicate or more. See the Supporting Information for details.

synthesized directly from the same core molecule (e.g., **21**), accessible in high diastereo- and enantiomeric purity by reported procedures.[24]

c. Stereoselective Synthesis of a Relatively Strained Stapled Peptide. Hydrocarbon-stapled peptides[9,26] are α-helical ligands that have been used for gaining a greater understanding of protein−protein associations and are leading candidates for therapeutic regulation of intercellular interactions.[25] Reliable access to stapled peptides with stereochemically defined olefin linkages makes possible the examination of conformational preferences on biological activity. *Z*-Selective MRCM of peptidic dienes is feasible with **Ru-1a**,**b**[18] but only

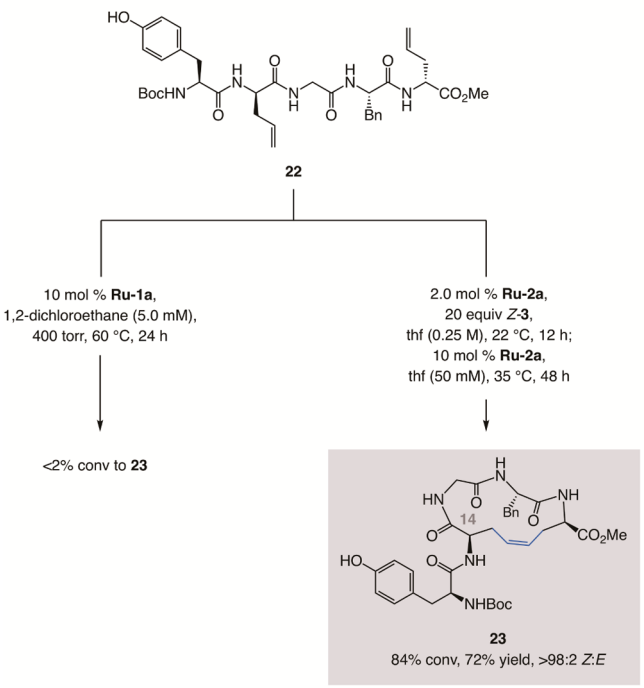
DOI: 10.1021/jacs.7b06552
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 9. *Z*-Selective Cross-Metathesis with a Capping Agent: Application to Stereoselective Synthesis of Prostaglandins[a]



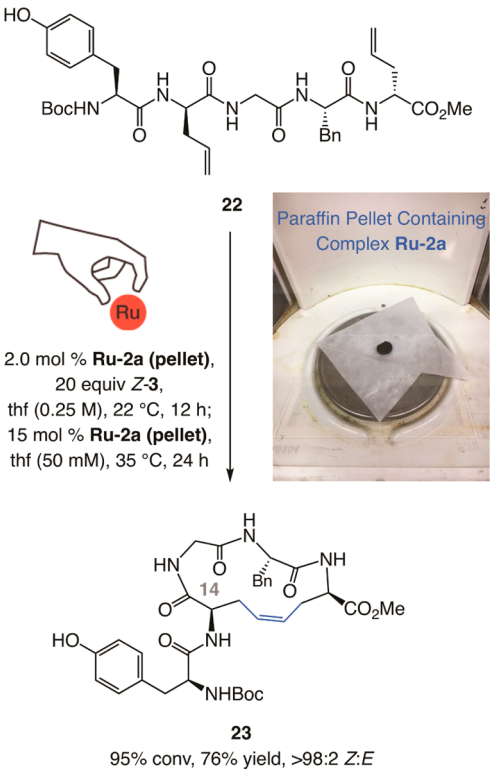
[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* ratios determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields for purified products (±5%). Experiments were run in duplicate or more. See the Supporting Information for details.

Scheme 10. *Z*-Selective Macrocyclic RCM with a Capping Agent: Stereoselective Synthesis of a Stapled Peptide[a]



[a]Reactions were carried out under N_2 atm. Conversion (disappearance of the disubstituted alkene intermediate) and *Z*:*E* ratios determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yield for purified **23** (±5%). Experiments were run in duplicate or more. See the Supporting Information for details.

Scheme 11. Ru Catechothiolate in Paraffin Pellet: Stereoselective Synthesis of a Stapled Peptide



after incorporation of extended hydrocarbon chains. This measure is presumably to ensure placement of Ru carbenes at an appropriately safe distance from a polar functionality, which could lead to reaction inhibition (cf., CM reactions leading to **10a** and **10c**, Scheme 4).

Attempts to carry out MRCM of diene **22** (Scheme 10) with **Ru-1a** did not yield any of the 14-membered ring macrocyclic peptide **23**. In contrast, subjection of **22** to 2.0 mol % **Ru-2a** and **3** (20 equiv; 22 °C, 12 h), followed by removal of the capping agent in vacuo and addition of 10 mol % **Ru-2a**, led to the formation of **23** in 72% yield and >98:2 *Z*:*E* selectivity. Macrocyclic peptide **23** has been converted to a potent δ and μ opioid receptor agonist after a pair of routine transformations.[26]

As noted previously, Ru catechothiolate complexes are robust, as manifested by the fact that they retain their activity in the presence of various polar functional units. Still, what makes their use even more convenient is that the derived

DOI: 10.1021/jacs.7b06552
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

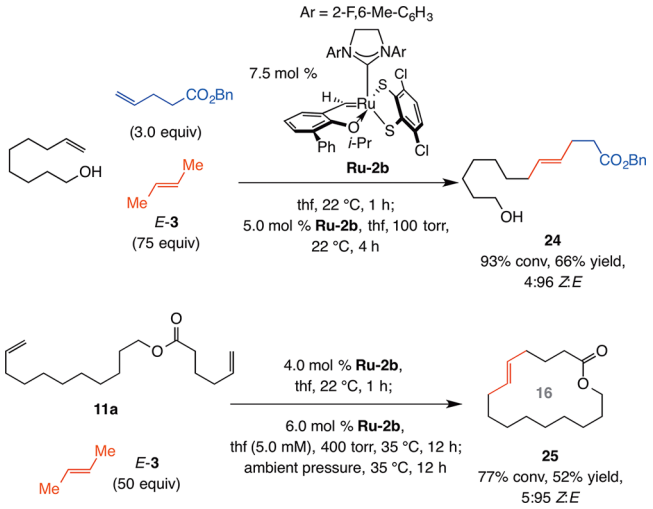
paraffin pellets,[28] which may be sliced with a knife into smaller fragments for multiple applications, may be utilized for further ease of operation. The transformation illustrated in Scheme 11 is a case in point.

CONCLUSIONS

The in situ methylene capping approach offers the possibility of carrying out exceptionally *Z*-selective cross-metathesis and MRCM with substrates that contain naturally ubiquitous functional groups. This advance was made possible because methylidene complex intermediacy can be bypassed by the methylene capping strategy and also as a result of several key attributes of ruthenium catechothiolate catalysts, the ability to promote efficient and highly *Z*-selective reactions with 1,2-disubstituted olefins, and broad functional unit compatibility.[6] Although the strategy of a "sacrificial alkyne" has been applied to a rather limited extent in catalytic nitrile-alkyne cross-metathesis,[27] olefin metathesis has not been the beneficiary of this operationally simple and promising approach.

The strategies outlined here are likely to resolve other key and long-standing problems in olefin metathesis. One relates to the design of kinetically *E*-selective olefin metathesis processes,[29,30] for which the utility of the same class of ruthenium complexes has been noted by others, albeit within a rather confined substrate range.[31] The transformations illustrated in Scheme 12, involving the use of a closely related

Scheme 12. Application to Kinetically Controlled *E*-Selective Cross-Metathesis and Macrocyclic Ring-Closing Metathesis[a]



[a]Reactions were carried out under N_2 atm. Conversion and *Z*:*E* ratios determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields for purified products (±5%). Experiments were run in duplicate or more. See the Supporting Information for details.

derivative of **Ru-2a**, dithiolate complex **Ru-2b**, are representative. The smaller size of the *N*-aryl units in the *N*-heterocyclic carbene ligand of **Ru-2b** can accommodate the increased steric hindrance in the corresponding metallacyclobutane (see **II**, Scheme 5).[29−31] The reason for larger amounts of readily removable *E*-butene is probably its lower reactivity as compared to the aforementioned *Z* isomer, as noted previously vis-à-vis the transformations in eq 1. These findings, which, to the best of our knowledge, represent the first example of kinetically *E*-selective MRCM reaction with a Ru complex, demonstrate that, similar to *Z*-alkene products, a wide range of desirable linear and macrocyclic *E*-olefins, many of which cannot be accessed by the available protocols,[29,30] can now be easily accessed.

There are reactions that can be promoted only by high-oxidation-state Mo-based catalysts but require 1,2-disubstituted olefin substrates.[17] The in situ capping strategy should allow these important catalytic processes to be performed with more easily accessible terminal alkenes as well as deliver products with higher efficiency and stereoisomeric purity.

Applications of the strategies outlined above to other unresolved problems in stereoselective catalytic olefin metathesis are in progress in these laboratories and will be disclosed in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b06552.

Experimental details for all reactions and analytic details for all products (PDF)

AUTHOR INFORMATION

Corresponding Author

*amir.hoveyda@bc.edu

ORCID

Amir H. Hoveyda: 0000-0002-1470-6456

Author Contributions

†C.X. and X.S. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by a grant from the National Science Foundation (CHE-1362763). We are grateful to Dongmin Xu for experimental assistance and to Thach T. Nguyen and Elsie C. Yu for experimental data regarding reactions with Mo MAP complexes and to Ming Joo Koh, Dr. Sebastian Torker, and Malte S. Mikus for valuable discussions. We thank Dr. Levente Ondi, Dr. Janos Balazs Czirok, and Dr. Hasan Mehdi for their support and helpful advice and are grateful to XiMo, AG for gifts of paraffin tablets that contain **Ru-2a**.

REFERENCES

(1) Grubbs, R. H., Wenzel, A. G., O'Leary, D. J., Khosravi, E., Eds. *Handbook of Metathesis*; Wiley−VCH: Weinheim, 2014.

(2) For reviews on catalyst-controlled *Z*-selective olefin metathesis, see: (a) Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 34−44. (b) Hoveyda, A. H. *J. Org. Chem.* **2014**, *79*, 4763−4792. (c) Hoveyda, A. H.; Torker, S.; Khan, R. M. K.; Malcolmson, S. J. In *Handbook of Metathesis*; Grubbs, R. H., O'Leary, D. J., Wentzel, A. G., Khosravi, E., Eds.; Wiley−VCH: Weinheim, Germany, 2015; Vol. 2, pp 508−562.

(3) For selected *Z*-selective homocoupling and cross-metathesis reactions promoted by complexes **Ru-1a**,**b**, see: (a) Keitz, B. K.; Endo, K.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 9686−9688. (b) Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 693−699. (c) Herbert, M. B.; Marx, V. M.; Pederson, R. L.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 310−314. (d) Quigley, B. L.; Grubbs, R. H. *Chem. Sci.* **2014**, *5*, 501−506.

(4) For the original report regarding the design and discovery of Ru-based dithiolate catalysts for *Z*-selective olefin metathesis, see:

DOI: 10.1021/jacs.7b06552
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(a) Khan, R. K. M.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 10258−10261. For a mechanistic investigation that elucidated why unlike catecholate Ru complexes the derived catechothiolates species promote highly *Z*-selective olefin metathesis reactions, see: (b) Khan, R. K. M.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 14337−14340. For a comprehensive study regarding the influence of bidentate anionic and chelating ligands on reactivity on stereoselectivity of olefin metathesis reactions promoted by this class of catalysts, see: (c) Mikus, M. S.; Torker, S.; Xu, C.; Li, B.; Hoveyda, A. H. *Organometallics* **2016**, *35*, 3878−3892.

(5) For Ru-based monochloride/sulfide complexes that have been used to promote *Z*-selective homocoupling and cross-metathesis reactions, see: (a) Occhipinti, G.; Hansen, F. R.; Törnroos, K. W.; Jensen, V. R. *J. Am. Chem. Soc.* **2013**, *135*, 3331−3334. (b) Occhipinti, G.; Koudriavtsev, V.; Törnroos, K. W.; Jensen, V. R. *Dalton Trans.* **2014**, *43*, 11106−11117.

(6) For the design of complex **Ru-2a** and its use in *Z*-selective cross-metathesis reactions that afford a variety of allylic alcohols, see: (a) Koh, M. J.; Khan, R. K. M.; Torker, S.; Yu, M.; Mikus, M.; Hoveyda, A. H. *Nature* **2015**, *517*, 181−186. For an application in complex molecule total synthesis, see: (b) Yu, M.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2015**, *54*, 215−220.

(7) Hachem, A.; Roussel, P.; Ménager, E.; Grée, D.; Le Floc'h, Y.; Grée, R.; Cerletti, C.; Rolland, Y.; Simonet, S.; Verbeuren, T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2511−2514.

(8) Funk, C. D. *Science* **2001**, *294*, 1871−1875.

(9) Chu, Q.; Moellering, R. E.; Hilinski, G. J.; Kim, Y.-W.; Grossmann, T. N.; Yeh, J. T.-H.; Verdine, G. L. *MedChemComm* **2015**, *6*, 111−119.

(10) Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904−9909.

(11) (a) Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 94−97. (b) Rosebrugh, L. E.; Herbert, M. B.; Marx, V. M.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 1276−1279.

(12) Quigley, B. L.; Grubbs, R. H. *Chem. Sci.* **2014**, *5*, 501−506.

(13) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633.

(14) Koh, M. J.; Khan, R. K. M.; Torker, S.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 1968−1972.

(15) Mikus, M. S.; Torker, S.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 4997−5002.

(16) Luo, S.-X.; Cannon, J. S.; Taylor, B. L. H.; Engle, K. M.; Houk, K. N.; Grubbs, R. H. *J. Am. Chem. Soc.* **2016**, *138*, 14039−14046.

(17) Koh, M. J.; Nguyen, T. T.; Lam, J. K.; Torker, S.; Hyvl, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *542*, 80−85.

(18) Mangold, S. L.; O'Leary, D. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2014**, *136*, 12469−12478.

(19) See the Supporting Information for details.

(20) Conrad, J. C.; Eelman, M. D.; Duarte Silva, J. A.; Monfette, S.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2007**, *129*, 1024−1025.

(21) For first examples of catalytic *Z*-selective macrocyclic ring-closing metathesis reactions and applications to complex molecule total synthesis, see: (a) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88−93. (b) Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Chem. - Eur. J.* **2013**, *19*, 2726−2740.

(22) Nair, S. K.; Henegar, K. E. In *Modern Drug Synthesis*; Li, J. J., Johnson, D. S., Eds.; Wiley: New York, 2010; pp 329−338.

(23) Ungrin, M. D.; Carrière, M.-C.; Denis, D.; Lamontagne, S.; Sawyer, N.; Stocco, R.; Tremblay, N.; Metters, K. M.; Abramovitz, M. *Mol. Pharmacol.* **2001**, *59*, 1446−1456.

(24) Coulthard, G.; Erb, W.; Aggarwal, V. K. *Nature* **2012**, *489*, 278−281.

(25) Bird, G. H.; Mazzola, E.; Opoku-Nsiah, K.; Lammert, M. A.; Godes, M.; Neuberg, D. S.; Walensky, L. D. *Nat. Chem. Biol.* **2016**, *12*, 845−852.

(26) Mollica, A.; Guardiani, G.; Davis, P.; Ma, S.-W.; Porreca, F.; Lai, J.; Mannina, L.; Sobolev, A. P.; Hruby, V. J. *J. Med. Chem.* **2007**, *50*, 3138−3142.

(27) Geyer, A. M.; Gdula, R. L.; Wiedner, E. S.; Johnson, M. J. A. *J. Am. Chem. Soc.* **2007**, *129*, 3800−3801.

(28) Ondi, L.; Nagy, G. M.; Czirok, J. B.; Bucsai, A.; Frater, G. E. *Org. Process Res. Dev.* **2016**, *20*, 1709−1716.

(29) For first examples of efficient kinetically controlled *E*-selective cross-metathesis reactions, see: Nguyen, T. T.; Koh, M. J.; Shen, X.; Romiti, F.; Schrock, R. R.; Hoveyda, A. H. *Science* **2016**, *352*, 569−575.

(30) For first examples of kinetically controlled *E*-selective macrocyclic ring-closing metathesis reactions, see: Shen, X.; Nguyen, T. T.; Koh, M. J.; Xu, D.; Speed, A. W. H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *541*, 380−386.

(31) Ahmed, T. S.; Grubbs, R. H. *J. Am. Chem. Soc.* **2017**, *139*, 1532−1537.

DOI: 10.1021/jacs.7b06552
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX