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Z-Selective Cross-Metathesis and Homodimerization of 3*E*-1,3-Dienes: Reaction Optimization, Computational Analysis, and Synthetic Applications

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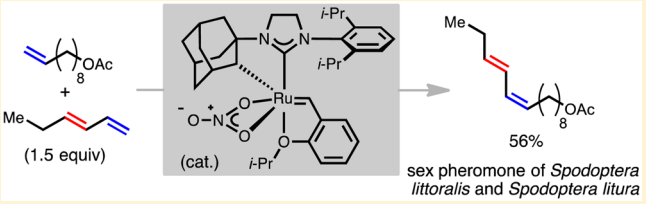
Supporting Information

ABSTRACT: Olefin metathesis reactions with 3*E*-1,3-dienes using *Z*-selective cyclometalated ruthenium benzylidene catalysts are described. In particular, a procedure for employing 3*E*-1,3-dienes in Z-selective homodimerization and cross-metathesis with terminal alkenes is detailed. The reaction takes advantage of the pronounced chemoselectivity of a recently reported ruthenium-based catalyst containing a cyclometalated NHC ligand for terminal alkenes in the presence of internal *E*-alkenes. A wide array of commonly encountered functional groups can be tolerated, and only a small excess (1.5 equiv) of the diene coupling partner is required to achieve high yields of the desired internal *E*,*Z*-diene cross-metathesis product. Computational studies have been performed to elucidate the reaction mechanism. The computations are consistent with a diene-first pathway. The reaction can be used to quickly assemble structurally complex targets. The power of this cross-metathesis reaction is demonstrated by the concise syntheses of two insect pheromones.

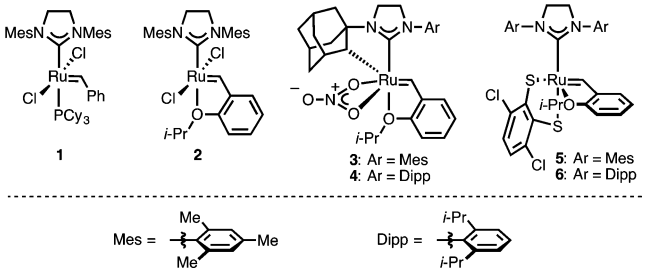


1. INTRODUCTION

Transition-metal-catalyzed olefin metathesis, the redistribution of alkene substituents, is a versatile technique for accessing substituted alkenes.[1] During the past several decades extensive catalyst design and optimization efforts have led to an array of synthetically enabling catalysts, allowing reactivity and selectivity to be controlled through judicious selection of an appropriate catalyst (Chart 1).[1−4]

Despite this impressive progress, certain alkene-containing structural motifs remain challenging to access via olefin metathesis. Internal conjugated dienes are one prominent example. In principle, cross-metathesis would be a powerful strategy for accessing highly substituted conjugated dienes from comparatively simple terminal alkene and 1,3-diene building blocks. However, in practice, cross-metathesis reactions of this type are plagued with complications when standard catalysts, such as ruthenium complexes **1** and **2**, are used. Specifically, in the absence of an electronic or steric bias,[5] the catalyst reacts indiscriminately with both alkenes of the diene to give an intractable mixture of products.

Chart 1. Prominent Ruthenium Olefin Metathesis Catalysts (1−6)



Through a series of recent studies, our lab has developed cyclometalated complexes **3** and **4** as highly *Z*-selective olefin metathesis catalysts that proceed via a side-bound mechanism.[2,3] The fact that these catalysts have high kinetic selectivity for forming *Z*-configured alkene products goes hand-in-hand with another facet of their reactivity: that they react preferentially with terminal and *Z*-configured internal alkenes rather than *E*-configured internal alkenes. Indeed, the pronounced chemoselectivity of these catalysts has been exploited in the development of methods for *Z*-selective ethenolysis reactions of *E*/*Z* internal alkene mixtures to achieve enrichment of the *E*-configured alkene.[6] This principle has been further applied to enable cross-metathesis of nonconjugated dienes containing a terminal alkene and an internal *E*-alkene; catalyst **4** was found to react chemoselectively at the terminal site and subsequently forge the new alkene with >95% *Z*-

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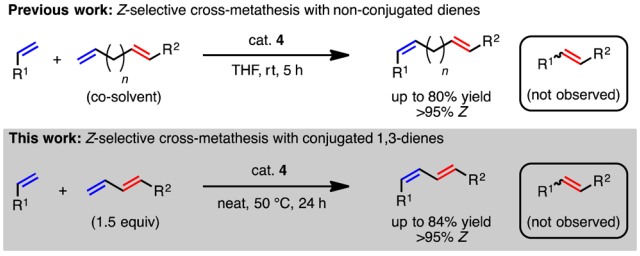
selectivity, leaving any internal *E* alkenes unperturbed (Scheme 1).[7]

Scheme 1. General Depiction of *Z*-Selective Cross-Metathesis with Diene Coupling Partners



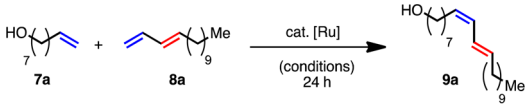
Based on this precedent, we questioned whether catalyst **4** might be similarly effective in promoting *Z*-selective cross-metathesis with terminal 3*E*-1,3-dienes. Such a reaction would be synthetically powerful, since it would allow convenient access to conjugated *E*,*Z*-dienes from readily available starting materials. Several recent literature reports speak to the viability of this idea. In particular, the research groups of Hoveyda and Schrock have used 3*E*-1,3-dienes as reactants with *Z*-selective molybdenum-based monoaryloxide pyrrolide (MAP) catalysts in homodimerization, cross-metathesis with vinyl boronates, and macrocyclization.[8] Moreover, with ruthenium catalyst **5**, Hoveyda recently demonstrated Z-selective ring-opening cross-metathesis between strained cyclic alkenes and 3*E*-1,3-dienes and cross-metathesis between 3*E*-1,3-dienes and allyl alcohol.[4b,c] While these previous reports demonstrate the feasibility of this approach, the existing methods are limited with respect to substrate scope and functional group tolerance. We sought to address these issues by developing a generally applicable procedure for performing Z-selective cross-metathesis with 3*E*-1,3-dienes.

Herein, we describe the results of our investigation. We have developed an operationally convenient method to perform *Z*-selective cross-metathesis and homodimerization with 3*E*-1,3-dienes. Catalyst **4** was found to react exclusively at the terminal alkene without off-target reaction at the internal *E*-alkene. Surprisingly, this cross-metathesis reaction was found to proceed optimally when run neat with only a modest excess of diene (1.5 equiv). Under these conditions, minimal competitive homodimerization of the alkene and diene was observed, which is highly uncommon in cross-metathesis. This finding prompted us to study the reaction via density functional theory to gain deeper insight into the mechanism. Lastly, we show the synthetic utility of the 3*E*-1,3-diene reaction partners in diene homodimerization and ring-opening cross-metathesis, as well as in the synthesis of two insect pheromones.

2. RESULTS AND DISCUSSION

2.1. Optimization of Reaction Conditions. We initiated this study by revisiting the optimal reaction conditions that were previously reported for nonconjugated dienes (1 mol % **4**, rt, 5 h, THF/diene as cosolvents).[7] We first evaluated cross-metathesis between 8-nonene-1-ol (**7a**) and (*E*)-tetradeca-1,3-diene (**8a**). Under reaction conditions that were otherwise identical to our earlier report,[7] we found that replacing the nonconjugated diene with the analogous conjugated 3*E*-1,3-diene **8a** led to <5% product formation. The dramatically lower reactivity in the case of the 3*E*-1,3-diene prompted us to consider the possibility that catalyst **4** reacted with the diene to form a ruthenium vinylcarbene. It has previously been shown that these species are capable of adopting an η^3 coordination mode, which is highly stabilized, requiring a high temperature in order to open a coordination site to enable [2 + 2] cycloaddition with a terminal alkene.[9] With this precedent in mind, we attempted the reaction at higher temperature (70 °C) in DCE and encouragingly found that, under these conditions, the two coupling partners reacted to form the desired product **9a** in 21% yield with >95% *Z*-selectivity (entry 1, Table 1). It is known that efficient ethylene removal is important for achieving high conversion with *Z*-selective catalysts **3** and **4**.[2b,7] Thus, the reaction was optimized with respect to the ethylene removal method, as well as diene equivalents, reaction temperature, and solvent/concentration (entries 1−7). Ultimately, we found that the highest yield (84%) was obtained using the alkene and diene in a 1:1.5 ratio, neat, at 50 °C, with a constant Ar stream over the reaction medium (entry 7). Under

Table 1. Reaction Optimization



entry	Ru catalyst	alkene (**7a**)/diene (**8a**)	solvent (concn)	temp (°C)	ethylene removal method	yield (**9a**)	*Z*-selectivity
1	**4** (2 mol %)	1:~5	DCE (1 M)	70	static vacuum (200 mTorr)	21%[a]	>95%
2	**4** (5 mol %)	1:~5	DCE (1 M)	70	static vacuum (200 mTorr)	53%[a]	>95%
3	**4** (2 mol %)	1:1	neat	70	static vacuum (200 mTorr)	40%[a]	>95%
4	**4** (2 mol %)	1:1.5	neat	70	open vial in glovebox	70%[a]	>95%
5	**4** (2 mol %)	1:1.3	neat	100	open vial in glovebox	–[b]	–
6	**4** (2 mol %)	1:1.5	neat	70	constant Ar flow	68%[a]	>95%
7	**4 (2 mol %)**	**1:1.5**	**neat**	**50**	**constant Ar flow**	**84%[c]**	**>95%**
8	**1** (2 mol %)	1:1.5	neat	50	constant Ar flow	<5%[d]	–
9	**2** (2 mol %)	1:1.5	neat	50	constant Ar flow	<5%[d]	–
10	**5** (2 mol %)	1:1.5	neat	50	constant Ar flow	<5%[d]	–
11	**6** (2 mol %)	1:1.5	neat	50	constant Ar flow	<5%[d]	–

[a]Calculated based on the mass and component ratio (measured by ^{1}H NMR) of a purified mixture of **7a** and **9a**. [b]Alkene chain walking was observed by ^{1}H NMR of the crude reaction mixture, indicating that catalyst **4** decomposed under these reaction conditions. [c]Isolated yield of pure **9a**. [d]Determined by ^{1}H NMR analysis of the crude reaction mixture using nitrobenzene as an internal standard.

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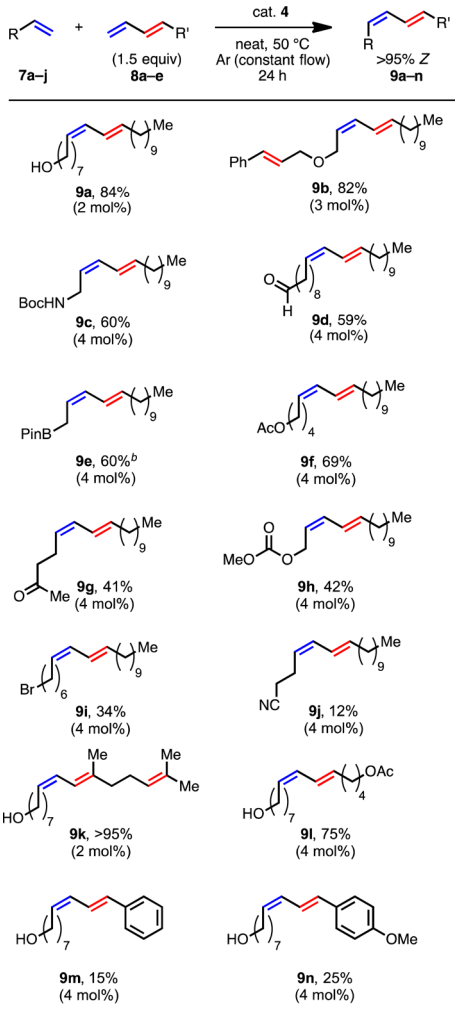
these conditions, alternative commonly used ruthenium-based olefin metathesis catalysts **1** and **2** were ineffective, leading to complex mixtures with <5% desired product **9a** (entries 8 and 9). *Z*-Selective dithiolate catalyst **5**[4c] and its Dipp-substituted congener **6**[4d] also provided <5% yield.

2.2. Evaluation of Substrate Scope. Having optimized the reaction conditions, we next examined the substrate scope. A range of commercially available terminal olefins were tested, along with several readily available 3*E*-1,3-dienes (Table 2).

Table 2. Substrate Scope of Alkene/3*E*-1,3-Diene Cross-Metathesis[a]



[a]Isolated yields. [b]^{1}H NMR yield with nitrobenzene as an internal standard.

Consistent with previous reports using catalyst **4**,[2e,3,6,7] the reaction proved to be compatible with a variety of functional groups. First, **8a** was used as the standard 3*E*-1,3-diene to evaluate different terminal alkene coupling partners. We found that, in addition to an alcohol (**9a**), the reaction tolerated the presence of an ether (**9b**), internal *E*-alkene (**9b**), *N*-Boc amine (**9c**), aldehyde (**9d**), pinacol boronate (**9e**), ester (**9f**), ketone (**9g**), and carbonate (**9h**), providing moderate to high yields of the desired internal *E*,*Z*-diene products with 2–4 mol % of catalyst **4**. Bromo (**9i**) and cyano (**9j**) groups were also somewhat effective, albeit in lower yield.[10] Next, using terminal alkene **7a**, we tested the reaction performance with a few selected 3*E*-1,3-dienes. The diene derived from geranial, containing two internal trisubstituted alkenes, was found to be reactive (**9k**) as was a diene containing a distal acetate group (**9l**). Dienes in conjugation with aromatic rings were also tolerated, though the yields were lower (**9m** and **9n**).[10]

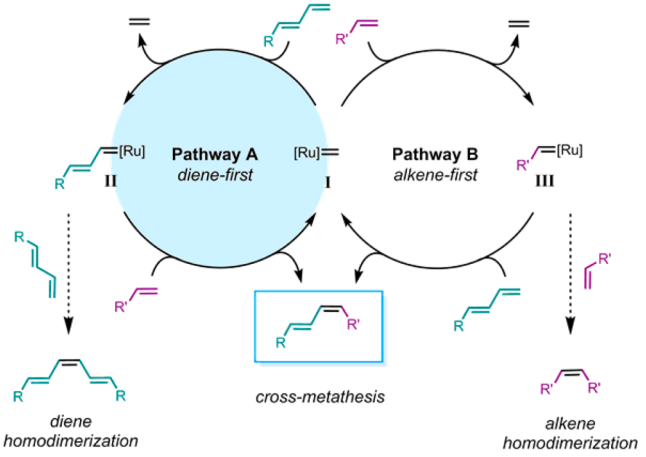
Notably in all cases, the reaction was carried out neat with only a slight excess of the diene coupling partner, speaking to the efficiency, operational simplicity, and green nature of the reaction.

2.3. Computational Studies. Because olefin metathesis reactions are reversible and under thermodynamic control, typically cross-metathesis requires a high molar excess of one of the coupling partners to achieve a high yield of the desired cross-metathesis product. Thus, the fact that this particular reaction is highly selective for cross-metathesis rather than alkene or 3*E*-1,3-diene homodimerization was unexpected and merited further study.

We therefore undertook computational studies using density functional theory (DFT) to understand the mechanism and the origin of the high levels of chemoselectivity in this reaction. Calculations were performed in Gaussian 09,[11] using a theoretical method found to be satisfactory in previous studies of chelated ruthenium catalysts.[2d,6b,12] Geometries were optimized at the B3LYP/6-31G(d)-LANL2DZ (Ru) level. Single-point energy calculations were performed on these geometries using M06/6-311+G(d,p)-SDD (Ru) with the SMD solvation model for *n*-octanol. This solvent was chosen to model reactions run neat with alkenes containing a polar functional group. Propene and *E*-1,3-pentadiene were chosen as model substrates for the calculations.

Productive diene–alkene cross-metathesis can occur via two pathways outlined in Scheme 2. Our studies began with the

Scheme 2. Possible Pathways for Diene–Alkene Cross-Metathesis



methylidene complex derived from **4** (**I** in Scheme 2). In Pathway A, methylidene **I** reacts first with the diene to form a vinylcarbene **II**, which then reacts selectively with the terminal alkene. Alternatively, in Pathway B, methylidene **I** reacts first with the terminal alkene to form alkylidene **III**, which then reacts with the 1,3-diene. We set out to compare these two pathways along with potentially competing homodimerization pathways.

Our calculations show that diene-first Pathway A is favored. The free-energy profile is shown in Scheme 3. The reaction mechanism closely follows previous computational studies of chelated ruthenium catalysts,[2d,6b,12] and olefin π-complexes

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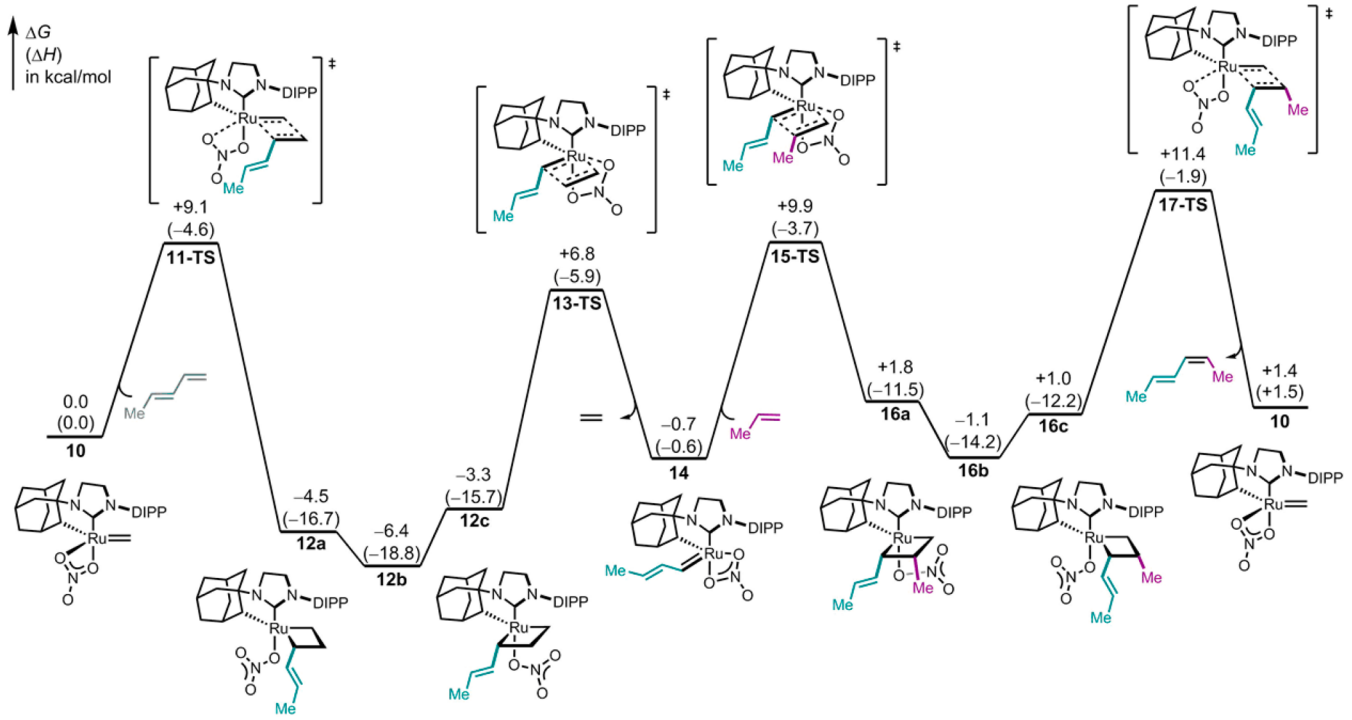
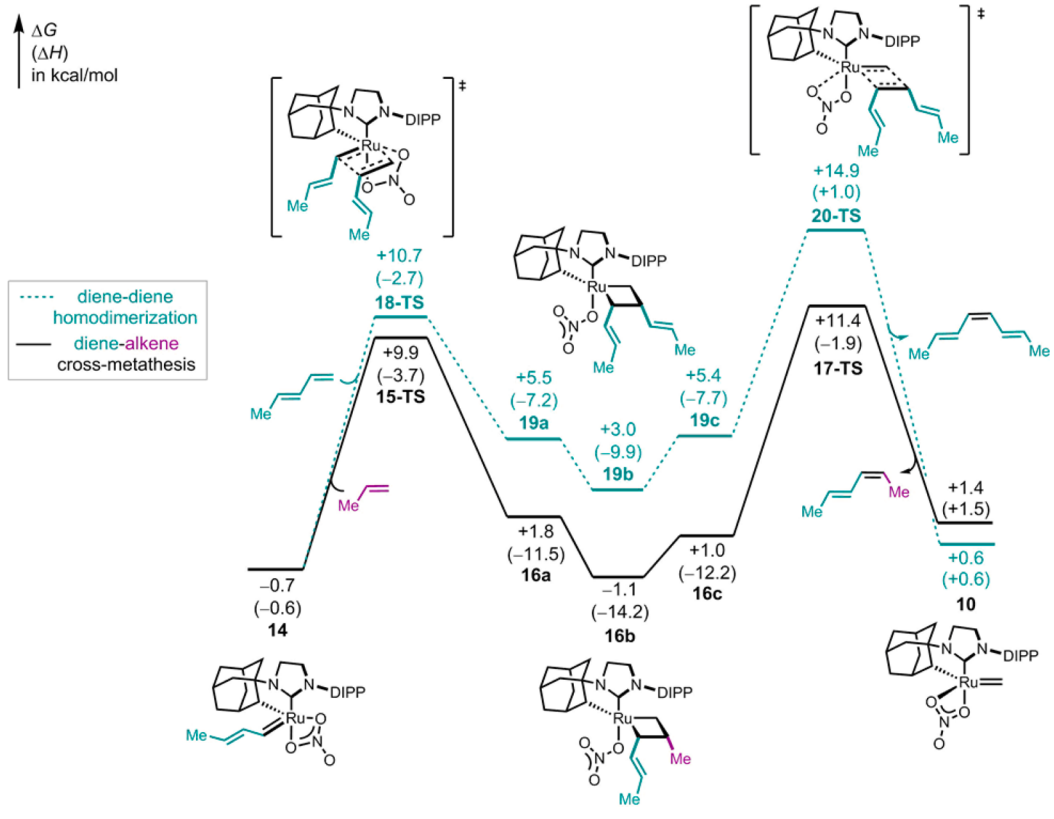
Scheme 3. Most Favorable Pathway A for Diene−Alkene Cross-Metathesis[a]



[a]Gibbs free energies and enthalpies (in parentheses) in kcal/mol. Olefin π-complexes can be located in some cases, but have been omitted. Letters (a, b, c) refer to conformational changes of the nitrate ligand.

Scheme 4. Comparison of Diene−Alkene Cross-Metathesis (Black) and Diene Homodimerization (Green) via Pathway A



have been omitted from Scheme 3 for brevity. Methylidene complex **10** reacts with the 1,3-diene via **11-TS** to form metallacycle **12a**. In line with previous calculations, the nitrate ligand is bidentate in methylidene complex **10**, but shifts to η^1-coordination in metallacyclobutanes such as **12a**.[12b] Rotation of the nitrate and metallacyclobutane with respect to the chelating

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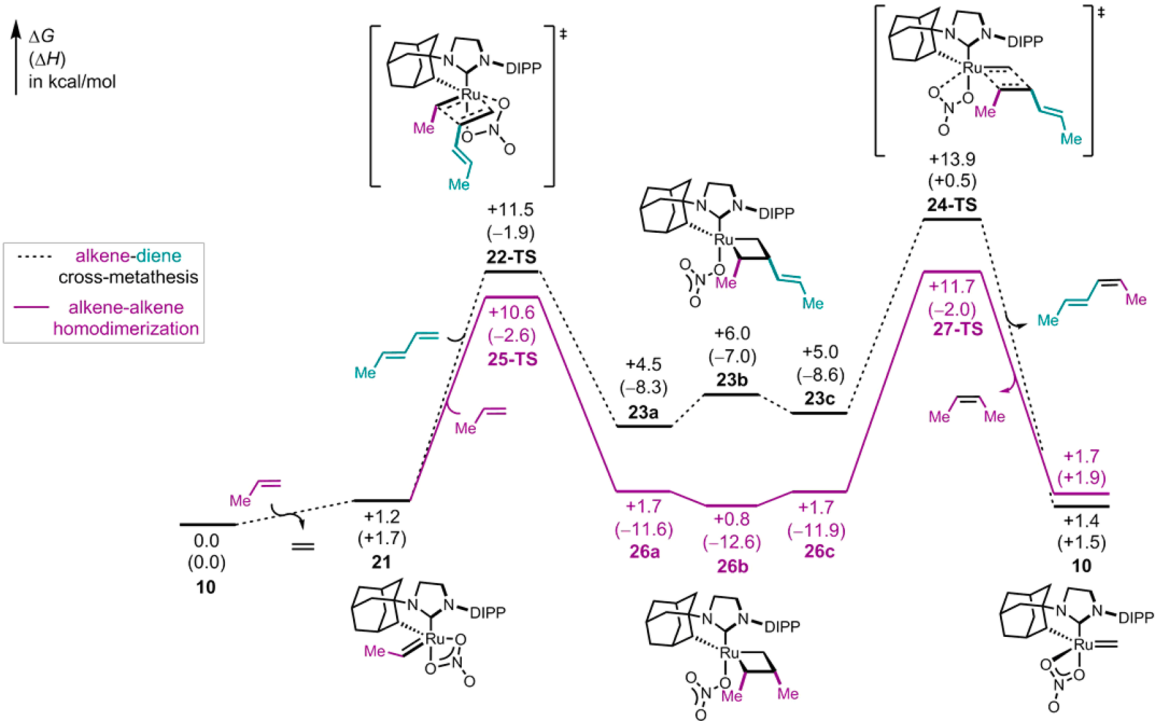
Scheme 5. Comparison of Diene−Alkene Cross-Metathesis (Black) and Alkene Homodimerization (Purple) via Disfavored Pathway B[a]



[a]Initial steps between **10** and **21** have lower barriers and are omitted for brevity (see SI).

NHC (**12b** and **12c**) is necessary prior to ring-opening of the metallacycle via **13-TS** to give vinylcarbene **14**. The terminal alkene then reacts via **15-TS** to form disubstituted metallacycle **16**. The final ring-opening of the disubstituted metallacycle via **17-TS** is rate-limiting, with an overall free energy span of 17.8 kcal/mol (**12b** to **17-TS**).

We have studied the conformations of vinylcarbene **14** in detail, and the most stable (*s*-trans) conformation is depicted in Scheme 3. Although η^3-coordination of vinylcarbenes has been reported (*vide supra*),[9] we were unable to locate such a complex in this system. The energy required to adopt η^3-coordination was estimated to be at least 10 kcal/mol. However, we were able to locate η^3-vinylcarbene complexes derived from non-chelated NHC catalysts such as **1** (see Supporting Information (SI) for details).

We next explored unfavorable homodimerization pathways in comparison to cross-metathesis. In Scheme 4, we compare the favored cross-metathesis Pathway A (black) to diene homodimerization (green), beginning with vinylcarbene **14**. Homodimerization is disfavored by 3.5 kcal/mol in the rate-limiting step (**20-TS**), with an overall free energy span of 21.3 kcal/mol (**12b** to **20-TS**). Thus, diene homodimerization should be accessible, but much slower than the observed cross-metathesis. In addition, the free-energy profile reveals that 2,3-divinylmetallacyclobutane **19** is about 4 kcal/mol less stable than metallacyclobutane **16** in the favored pathway, which parallels the energy difference in the rate-limiting transition states. No significant steric interactions were found in **19** or **20-TS**, suggesting that the destabilization is electronic in origin.

We have also analyzed the alkene-first Pathway B (Scheme 5, black). This pathway is disfavored by 2.5 kcal/mol in the rate-limiting step (**24-TS**). Here also, the primary factor appears to be destabilization of the 3-vinyl metallacyclobutane intermediate: metallacycle **23c** is 4 kcal/mol less stable than isomeric metallacycle **16c** (Scheme 3). We also compared the reactivity of alkylidene **21** with a terminal alkene to give alkene homodimerization (Scheme 5, purple). This pathway is disfavored by only 0.3 kcal/mol compared to cross-metathesis Pathway A, suggesting that the two pathways are competitive. However, the greater stability of vinylcarbene **14** (vs alkylidene **21**) coupled with a small excess of 1,3-diene should favor cross-metathesis through Pathway A.

To ensure that our choice of model substrates was sufficient, we also calculated rate-limiting transition states using larger substrates 1-butene and *E*-1,3-hexadiene. The computed barriers decreased slightly (∼1 kcal/mol), but the relative selectivity was unchanged. Using the larger substrate models, alkene−alkene homodimerization is disfavored by 0.7 kcal/mol, and diene−diene homodimerization is disfavored by 2.5 kcal/mol (see SI for details).

In summary, our calculations revealed that diene-first Pathway A is favored, and diene homodimerization is accessible but much slower than cross-metathesis. Pathways that proceed through 3-vinyl ruthenacyclobutanes are significantly higher in energy, which appears to be an electronic effect, since no significant steric interactions were found. The nature of this destabilization is outside the scope of the present paper, but is the subject of ongoing studies in our laboratories.

2.4. Homodimerization of 3*E*-1,3-Dienes. In light of this computational insight, we next sought to determine whether catalyst **4** was capable of homodimerizing 3*E*-1,3-dienes in the absence of terminal alkenes. To test this, we first subjected diene **8a** to the reaction conditions in the absence of alkene (Table 3) and observed only a 13% yield of *E*,*Z*,*E*-triene **28a** by ^{1}H NMR. We suspected that the low yield could potentially be due to poor solubility of catalyst **4** in neat diene **8a**, as it is a

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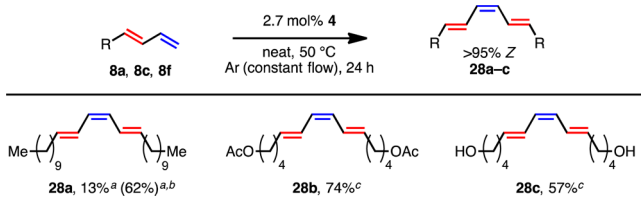
Table 3. Homodimerization of 3*E*-1,3-Dienes

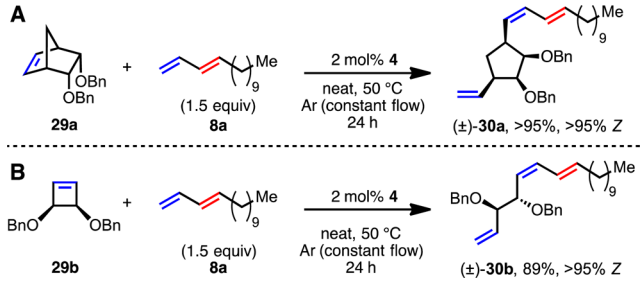


[a]^{1}H NMR yield with nitrobenzene as an internal standard. [b]Reaction in DCE solvent. [c]Isolated yield.

nonpolar hydrocarbon. Indeed, performing the same reaction in DCE yielded 62% of the **28a**. When **8a** was replaced with more polar dienes containing a distal acetate or free alcohol, triene products **28b** and **28c** were obtained in 74% and 57% yield, respectively, under neat conditions.

2.5. Synthetic Applications. Having established 3*E*-1,3-dienes as viable reaction partners in *Z*-selective cross-metathesis and homodimerization, we next sought to demonstrate the utility of this protocol in enabling preparation of more complex molecules. We first tested diene **8a** in ring-opening cross-metathesis with catalyst **4** (Scheme 6).[4b,13] Two strained cyclic

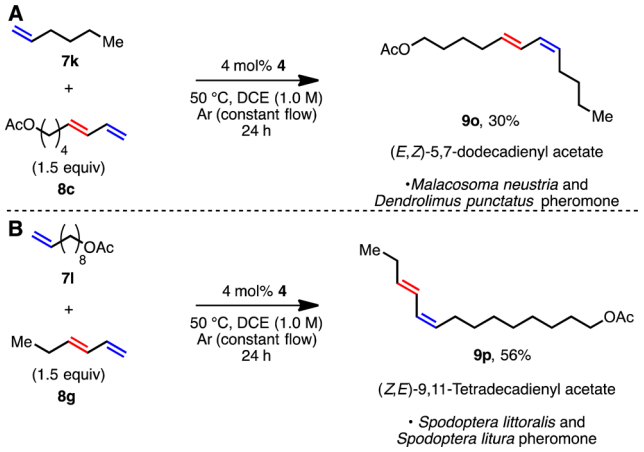
Scheme 6. *Z*-Selective Ring-Opening Cross-Metathesis with 3*E*-1,3-Diene Coupling Partners



alkenes that have previously been used with catalyst **4**, **29a** and **29b**[13,14] were subjected to the standard reaction conditions with diene **8a** as the coupling partner. We were pleased to find that, in both cases, the corresponding highly substituted ring-opened products, (±)-**30a** and (±)-**30b**, were obtained in high yield and with >95% *Z* selectivity.

Insect pheromones have been shown to be effective methods to control pest populations in a safe and environmentally friendly manner.[15] Our research group has previously utilized *Z*-selective cyclometalated catalysts **3** and **4** in concise syntheses of insect pheromones containing internal *Z*-alkenes.[2b,e,16] With this newly optimized protocol for cross-metathesis of 3*E*-1,3-dienes, we thus questioned whether this protocol would allow access to previously inaccessible pheromones containing internal *E*,*Z*,-dienes. We targeted (*E*,*Z*)-5,7-dodecadienyl acetate (**9o**)[17] and (*E*,*Z*)-9,11-dodecadienyl acetate (**9p**)[18] because both would be of potential interest for pest control applications and are accessible from commercially available or readily synthesized starting materials (Scheme 7). Through optimization, we found that the reactions in both cases were higher yielding when run in DCE (1.0 M), rather than neat, possibly due to the volatile nature of one of the reaction components in both cases. The presence of a solvent may help with condensation of the volatile reagent, which is otherwise quickly purged from the reaction vessel under the reaction conditions (constant flow of Ar, 50 °C).

Scheme 7. Synthesis of Insect Pheromones via *Z*-Selective Cross-Metathesis of 3*E*-1,3-Dienes and Terminal Alkenes



Under optimized conditions, pheromones **9o** and **9p** were isolated in 30% and 56% yield, respectively.

3. CONCLUSION

In summary, we have developed a protocol for carrying out *Z*-selective cross-metathesis and homodimerization with 3*E*-1,3-dienes using cyclometalated ruthenium benzylidene catalyst **4**. The optimal reaction conditions for cross-metathesis employ only 1.5 equiv of the diene relative to the terminal alkene. The reaction can be run neat, and a wide variety of synthetically important functional groups are tolerated. Computational evidence is consistent with a diene-first pathway to give a ruthenium vinylcarbene, which reacts preferentially with the terminal olefin. The synthetic utility of the reaction was demonstrated by several examples of Z-selective 3*E*-1,3-diene homodimerization and ring-opening cross-metathesis. Lastly, two insect pheromones containing internal *E*,*Z*-dienes were synthesized in a single convergent step from readily available starting materials using this new protocol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08387.

Experimental details, NMR spectra of new compounds, optimized Cartesian coordinates and energies, details of computational methods (PDF)

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Notes

The authors declare no competing financial interest.

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(10) The composition of the crude reaction mixtures in several of the low-yielding cases (as determined by ^{1}H NMR) merits discussion. With **9i**, the bromide-containing alkene starting material was completely consumed. The alkene homodimerization product was formed in <5% yield. The unreacted 1,3-diene starting material and triene homodimerization byproduct were observed in considerable quantities. Previously, it was found that an alkyl bromide−containing terminal alkene was well tolerated in cross-metathesis with catalyst **4** at 35 °C: (a) Quigley, B. L.; Grubbs, R. H. *Chem. Sci.* **2014**, *5*, 501−506. At an elevated temperature of 50 °C, it is possible that the alkyl bromide and ruthenium catalyst decompose one another, leading to a diminished yield in this case. For a relevant report, see: (b) Lee, J.; Grandner, J. M.; Engle, K. M.; Houk, K. N.; Grubbs, R. H. *J. Am. Chem. Soc.* **2016**, *138*, 7171−7177. In the case of **9j**, the reaction mixture consisted mainly of unreacted starting materials (terminal alkene and terminal 1,3-diene). The triene homodimerization byproduct could not be detected, and it was unclear whether the nitrile-containing alkene homodimerization product was formed. It has previously been observed that use of MeCN as solvent in metathesis reactions with catalyst **4** led to diminished yields compared to other solvents, suggesting the nitriles inhibit metathesis reactivity: (c) Mangold, S. L.; O'Leary, D. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2014**, *136*, 12469−12478. With **9m** and **9n**, the reaction mixture consisted mainly of unreacted starting materials along with 5−10% of homodimerized alkene. The homodimerized triene byproducts were not observed. Our group has found that styrenes are unreactive in *Z*-selective metathesis reactions with catalysts **3** and **4**, possibly due to steric hindrance. Thus, by analogy, the attenuated reactivity with these two 1,3-diene coupling partners could be similarly rooted in steric factors.

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(14) In *Z*-selective ring-opening−cross metathesis reactions between strained cyclic olefins (e.g., **29a** and **29b**) and 1,3-dienes, the mechanism may differ from the diene-first pathway proposed above for cross-metathesis between simple terminal alkenes and 1,3-dienes. Namely, it is possible that the ring-opening step may involve a ruthenium−methylidene rather than a ruthenium vinylcarbene. In a previous report (ref 13c), it was found that the order of metathesis events in *Z*-selective ring-opening-cross-metathesis with cyclometalated ruthenium catalyst **3** is dependent on the nature of the strained cyclic olefin. This point was not explored further in the present study.

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