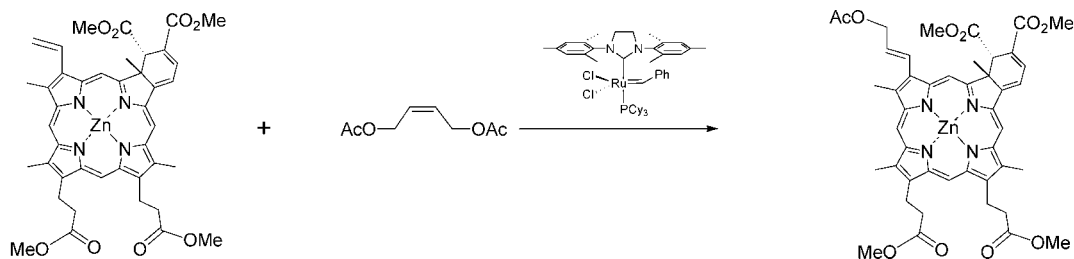# Cross-Metathesis of the Vinyl Group on Tetrapyrrolic Macrocycles: Reactivity, Selectivity, and Mechanism

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To find a general strategy for modifying the peripheral structure of vinylchlorin and porphyrin substrates, cross-metathesis on the vinyl group of these tetrapyrrolic macrocycles was investigated. The *N*-heterocyclic carbene-containing ruthenium complex **3** efficiently catalyzed the cross-metathesis (CM) of vinylchlorins and vinylporphyrins with a variety of olefins in high *E*-stereoselectivity. Different substituents on the olefin dramatically influenced the reaction. While the chlorins were more reactive than the porphyrins (as free bases), the corresponding zinc complexes showed higher activity. The reaction mechanism was investigated, and an empirical model for selective CM was applied to our studies to direct further reactions.

Introduction

Olefin metathesis, the metal-catalyzed redistribution of carbon—carbon double bonds, is now widely considered as one of the most powerful synthetic tools in organic synthesis.[1] A wide range of transformations have become possible for metathesis owing to the advances in commercially available catalysts, e.g., Mo-based Schrock's catalyst **1**[2] and Ru-based Grubbs' catalysts **2**[3] and **3**.[4] These transformations have a variety of applications, including ring-opening metathesis polymerization (ROMP),[5] acyclic diene metathesis polymerization (ADMET),[5] ring-closing metathesis (RCM),[6] ring-opening metathesis (ROM),[7] and cross-metathesis (CM).[7] Through these

reactions, olefin metathesis provides a route to unsaturated molecules that are often challenging or impossible to prepare by other means. Cross metathesis, a method for the intermolecular formation of carbon—carbon double bonds, has been underutilized when compared to the other metathesis reactions. This was due primarily to the lack of reaction selectivity and olefin stereoselectivity.[7] The discovery of the highly active, stable, and easily handled "second generation" Grubbs' catalyst **3**, which contains an N-heterocyclic carbene ligand, 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene, has dramatically improved the chemo- and stereoselectivity of CM and advanced the utility of CM in a variety of situations, such as enantioselective, solid-state, and domino metathesis.[8]
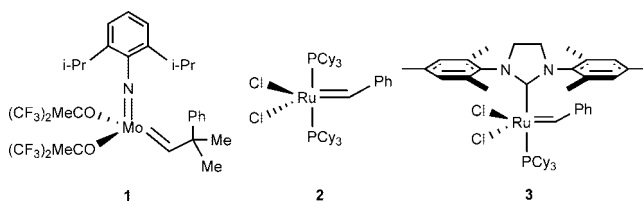
Nevertheless, olefin metathesis and CM have seldom been applied to chlorin and porphyrin substrates. One of the few

(1) (a) Thiel, O. R. *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C. Ed.; Wiley-VCH Berlag GmbH & Co. KGaA: Weinheim, 2004; Vol. 1, p 321. (b) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(2) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; Dimane, M.; O'Regan, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

(3) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.

(4) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.
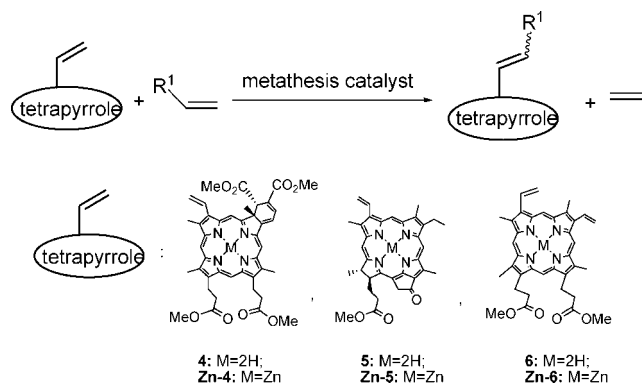
(5) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565.

(6) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.

(7) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(8) Connon, S. J.; Blechert, S. *Top. Organomet. Chem.* **2004**, *11*, 93.

SCHEME 1. CM of the Vinyl Group on Tetrapyrrolic Macrocycles

4: M=2H;
Zn-4: M=Zn

5: M=2H;
Zn-5: M=Zn

6: M=2H;
Zn-6: M=Zn

SCHEME 2. Ring-Closing Metathesis of 7 Catalyzed by Grubbs' Catalyst 2


applications was in an enyne metathesis with purpurinimide for the synthesis of β-galactose-conjugated photosensitizers.[9] In our group's efforts to generate new photosensitizers for photodynamic therapy (PDT),[10] we have extensively studied chlorin substrates such as **4** (ring B-benzoporphyrin derivative (BPD)-1,3-diene dimethyl ester) and **5** (methyl pyropheophorbide *a*) and the porphyrin substrate **6** (protoporphyrin IX dimethyl ester). Previous studies have indicated that the modification of the amphiphilicity of molecules is an important way to modulate the PDT efficacy of photosensitizers.[11] Since one or two vinyl groups are present in our macrocycles, we sought general strategies for modifying the amphiphilicity of these tetrapyrrolic macrocycles by developing the chemistry of the conjugated vinyl group. Cross-metathesis of the vinyl group seemed particularly well suited for this purpose. We anticipated that the successful application of CM reactions in this way would allow the introduction of various functionalities onto the vinyl group, directly modifying the properties, such as amphiphilicity, of the chlorin and porphyrin molecules and thus enhance their utility as PDT agents.

We have previously reported our initial studies in this area,[12] and here we report further studies on the cross-metathesis of tetrapyrrolic macrocycles and the synthesis of a series of vinyl-substituted chlorin and porphyrin derivatives via CM (Scheme 1).

Results and Discussions

Reaction Conditions. To investigate CM reactions with vinylchlorins, we started with the conventional Grubbs' catalyst **2**. Ring B-BPD-1,3-diene dimethyl ester (**4**), a chlorin substrate that is readily available in our hands as a side product during the manufacture of BPDMA (Visudyne), was selected for our initial investigations.[13] A mixture of **4** and 1-hexene was refluxed in dry THF in the presence of 10 mol % of catalyst **2**. No reaction was observed even after refluxing was continued overnight, and the starting material was recovered quantitatively.

Two reasons were possible for this result: the catalyst was not active enough for substrate **4**, or the catalyst was altered as
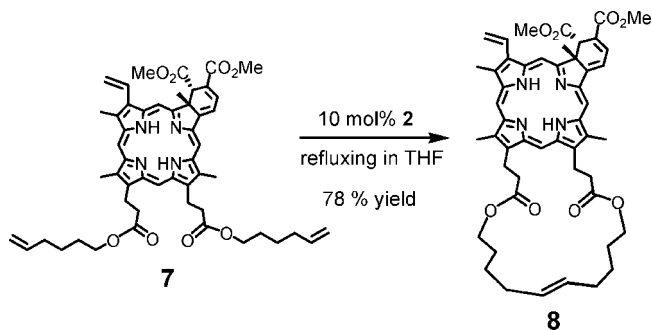
a result of chelation between the ruthenium complex and the chlorin macrocycle. Since the starting material could be quantitatively recovered from the reaction mixture, no other BPD derivatives were observed on analytical TLC, and no change in the UV−vis spectrum was observed, the possibility for chelation is unlikely. Therefore, the most likely reasons are that the vinyl group in this macrocycle is a poor substrate for a CM reaction and/or catalyst **2** is not active enough. This was confirmed by further experiments as shown in Scheme 2.

In the above reaction, a ring-closing metathesis (RCM) occurred smoothly on the terminal vinyl groups, which are distant from the BPD macrocycle, in the presence of catalyst **2** giving a 23-membered ring product. It was surprising that such a large ring was formed via RCM rather than an intermolecular CM product. However, similar results have been noted before, and the trend to form medium to the large sized rings has been recognized as an advantage for RCM in such systems.[6] For this reaction, metathesis occurred readily on the ester-bound vinyl groups with catalyst **2**, while the conjugated vinyl group remained unchanged. These results indicate that the chlorin macrocycle does not apparently deactivate the catalyst **2**; therefore the reason why CM does not occur between **4** and 1-hexene is that the catalyst is not active enough to overcome the low reactivity of the conjugated vinyl group toward metathesis.

On the basis of these results, attention was focused on the use of highly active *N*-heterocyclic carbene catalyst **3**. This second generation Grubbs' catalyst exhibits such high activity that it has been reported to efficiently catalyze reactions of some previously metathesis-inactive substrates.[4]

We were pleased to see that by employing catalyst **3** a CM product **9** was quantitatively obtained from the reaction of **4** and 20 equiv of 1-hexene after refluxing in THF for 1 h under argon (entry 1, Table 1). The product **9** was observed as a slightly less polar spot on analytical TLC as compared to the starting material. ^{1}H NMR spectrum confirmed that CM occurred on the conjugated vinyl group as hoped. Further studies showed that the concentration of vinylchlorin (≥ 0.04 M) and the amount of the simple olefin have to be high enough (20 equiv) to ensure that the reaction proceeds readily. Other simple olefins, such as 1-octene, afforded the same result, and product **10** was obtained quantitatively on the basis of ^{1}H NMR analysis (entry 2).

Despite the relative stability of the catalyst **3** in the presence of moisture and air,[4] in our hands the best results were obtained when the catalyst was transferred and weighed in a glovebox. A relatively high loading of the catalyst was required to ensure a high yield because of the low CM reactivity of the conjugated

(9) Zheng, G.; Graham, A.; Shibata, M.; Missert, J. R.; Oseroff, A., R.; Dougherty, T. J.; Pandey, R. K. *J. Org. Chem.* **2001**, *66*, 8709.

(10) Sternberg, E. D.; Dolphin, D. *Tetrahedron* **1998**, *54*, 4151.

(11) (a) Pandey, R. K.; Sumlin, A. B.; Constantine, S.; Dougherty, T. J. *Photochem. Photobiol.* **1996**, *64*, 194. (b) Pandey, R. K.; Bellnier, D. A.; Smith, K. M.; Dougherty, T. J. *Photochem. Photobiol.* **1992**, *53*, 65. (c) MacDonald, J.; Bellnier, D. A.; Paszkiewicz, G. M.; Whitaker, J. E.; Litchfield, D. J.; Dougherty, T. J. *Photochem. Photobiol.* **1999**, *70*, 789.

(12) Liu, X.; Sternberg, E.; Dolphin, D. *Chem. Commun.* **2004**, 852.

(13) Dolphin, D. *Can. J. Chem.* **1994**, *72*, 1005.

TABLE 1.   CM of Ring B-BPD 4 with Simple Olefins

9, R = n-C$_4$H$_9$; **10**, R = n-C$_6$H$_{13}$
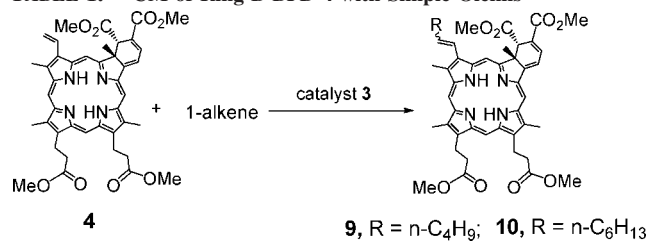
entry	4:1-alkene	catalyst 3 (equiv)	1-alkene	product	yield (%)[a]	E:Z[c]
1	1:20	0.25	1-hexene	**9**	100	65:1
2	1:20	0.25	1-octene	**10**	100	50:1
3	1:20	0.15	1-hexene	**9**	70[b]	no Z

[a] Yields were calculated on the basis of ^{1}H NMR spectra of the crude products. [b] Isolated yield. [c] E:Z ratio was determined by ^{1}H NMR spectroscopy.

TABLE 2.   CM of Methyl Pyropheophorbide *a* 5 with 1-Alkene

11, R = n-C$_4$H$_9$,   **12**, R = n-C$_6$H$_{13}$
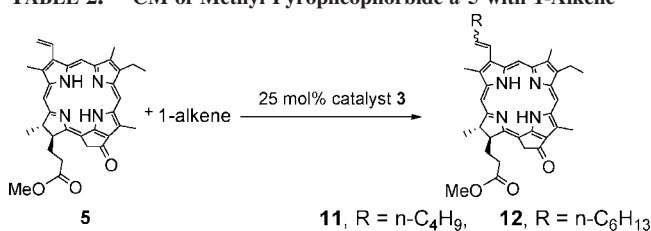
entry	1-alkene	5:1-alkene	yield (%)[a]	product	E:Z[b]
1	1-hexene	1:20	100	**11**	no Z
2	1-octene	1:20	100	**12**	15:1

[a] Yields were calculated on the basis of ^{1}H NMR spectra of the crude products. [b] E:Z ratio was determined by ^{1}H NMR spectroscopy.

TABLE 3.   CM of Protoporphyrin IX Derivatives with 1-Octene

6, M=2H; **Zn-6**, M=Zn   **13**, M=2H; **14**, M=Zn

entry	A	A:B	yield (%)[a]	product	E:Z[b]
1	**6**	1:40	58	**13**	40:1
2	**Zn-6**	1:40	100	**14**	50:1

[a] Yields were calculated based on ^{1}H NMR spectra of the crude products. [b] E:Z ratio was determined by ^{1}H NMR spectroscopy.

Under the general CM conditions in our study, the reaction between protoporphyrin IX dimethyl ester (**6**) and 1-octene afforded the CM product **13** in only 58% yield (entry 1, Table 3). This low yield, however, could be compensated for by using the Zn(II) complex of protoporphyrin IX (**Zn-6**), which give 100% conversion of the CM product under the same conditions (entry 2).

Two initial conclusions can be made from these results. First, Zn-complexes in general are more active toward CM than the corresponding free bases. Second, protoporphyrin IX (**6**) is less active than ring B-BPD (**4**) and methyl pyropheophorbide *a* (**5**), or more generally, the vinylporphyrin is less reactive than vinylchlorin to CM.

The first conclusion can be rationalized by the change of electron density on the tetrapyrrolic macrocycle due to Zn(II) metalation. When Zn(II) is inserted, the macrocycle can be regarded as a dianion ionically bound to the metal ion.[16] Therefore, the ring is more electron-rich than the corresponding free base, and the electron density on the conjugated vinyl group increases as well. Since electron-rich substrates are more favorable toward metathesis,[17] the Zn(II) complexes exhibit higher reactivity.

The reactivity difference between chlorins and porphyrins is also considered to be the result of electronic effects, and related reasoning has been suggested as the main reason for the different reactivity of Fe(III) vinylporphyrins and Fe(III) vinylchlorins in the Vilsmeier formylation reaction (Scheme 3).[18] The formylation of the vinyl group of Fe(III) protoporphyrin IX (**15**) with DMF/POCl$_3$ required 1 h to go to completion, whereas only 90 s was required for the Fe(III) chlorin e_6 (**16**).[18] These results show that the vinyl group in vinylchlorins is more reactive toward electrophiles than that in vinylporphyrins.

Cross-Metathesis with a Variety of Olefin Partners. Besides the simple alkenes aforementioned, olefins with other functional groups were introduced in our later-stage studies. The more reactive Zn-complex, **Zn-4**, was used (Table 4). For most reactions (except entries 6 and 8), the final CM products were obtained as the free bases after treatment with TFA to remove the Zn(II).

For halogenated olefins, such as 6-bromo-1-hexene, product **17** was afforded in 100% conversion via the CM reaction with **Zn-4** (entry 1). With the bromine in closer proximity to the

vinyl group on the vinylchlorin. The yield dropped from 100% to 70% when 0.15 equiv (entry 3) of the catalyst was used instead of 0.25 equiv. It was also found that 1 h was sufficient time to afford these yields and that extending the reaction time did not improve the yields. This observation differs from other reports where cross-metathesis products continued to be produced after 8 h.[14]

Reactivity of Different Tetrapyrrolic Macrocycle Substrates. With these promising results in hand, CM studies of the conjugated vinyl group were extended to other tetrapyrrolic macrocycle systems. It was of interest to determine whether a reactivity difference exists between our different macrocyclic substrates.
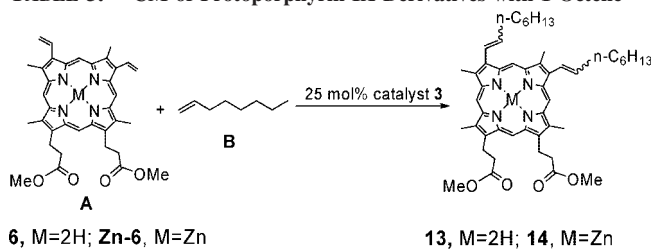
Methyl pyropheophorbide *a* (**5**) is another chlorin macrocycle that has attracted great interest in the studies of photosensitizers in PDT and photosynthetic mechanism.[15] The vinyl group presented in **5** also provides a good substrate for CM. In our studies, the reaction between **5** and 1-hexene or 1-octene afforded CM products **11** and **12** with 100% conversion (Table 2). Thus, **5** exhibits a CM reactivity similar to that of **4**.

Interestingly, further studies suggested that our porphyrin substrate exhibited a different reactivity toward CM than the chlorins. Protoporphyrin IX dimethyl ester (**6**) represents a typical porphyrin macrocycle with two vinyl groups available.

(14) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.

(15) Pandey, R. K. *Biomedical Photonics Handbook*; Vo-Dinh, T., Ed.; CRC Press: Boca Raton, 2003; Vol. 37 (1–2).

(16) Vicente, M. G. H. *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2000; Vol. 4, p 153.

(17) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117.

(18) Nichol, A. W. *J. Chem. Soc. C* **1970**, 9903.

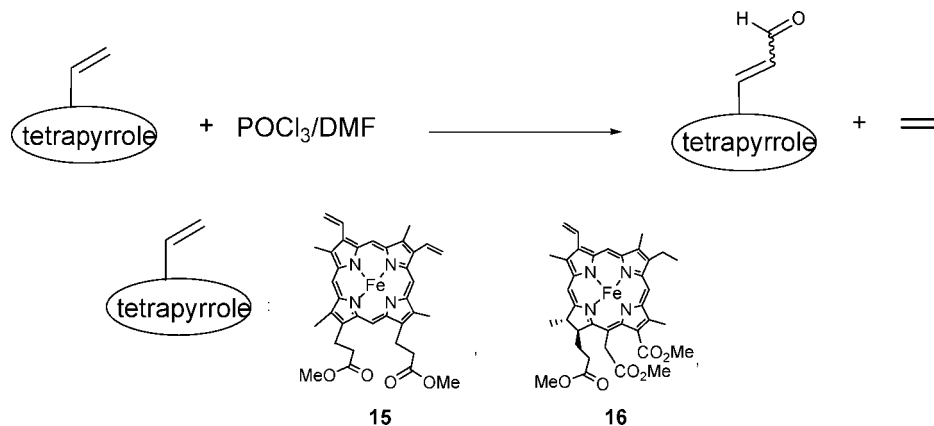**SCHEME 3. Vilsmeier Formylation of Fe(III) Vinylchlorin and Vinylporphyrin Complexes**

TABLE 4. CM of Zn-4 with Terminal Olefin Partners

Entry	R (olefin)	Product	Yield [a]	E:Z [b]
1	⟋⟍⟋⟍Br	**17**	100% [c]	No Z
2	⟋⟍⟍Br	**18** [d]	70% [c]	No Z
3	⟋⟍Br	**19** [d]	80% [c]	No Z
4	⟋⟍⟋⟍OH	**20**	5%	No Z
5	⟋⟍⟋⟍OAc	**21**	50%	No Z
6	⟋⟍⟋⟍O–C(O)–CH(NHBoc)	**22**	55%	No Z
7	⟋⟍⟋⟍⟋CO₂Me	**23**	50%	No Z
8	⟋⟍Si(OMe)₃	**24**	10%	No Z

[a] Isolated yield. [b] E:Z ratio was determined by ^{1}H NMR spectroscopy. [c] Yields were calculated on the basis of ^{1}H NMR spectra of the crude products. [d] Pure product was not successfully isolated because of the close R_f value to the starting material.

double bond, the yield of the CM product decreased; as shown in entries 2 and 3, the conversion yields of the CM reactions with 5-bromo-1-pentene and 4-bromo-1-butene substrate were 68% and 72%, respectively. It is suggested from this result that when this functionality is close to the reactive olefin, it will impact the reaction in an unfavorable way. Crowe and Zhang[19] reported a dramatic difference in yields in the CM between styrene with 4-bromo-1-butene (50%) or 5-bromo-1-pentene (90%) when using Schrock's catalyst **1**. The difference was rationalized as being due to the inductive effect of the bromine. This is not clear in our studies because 5-bromo-1-pentene and 4-bromo-1-butene provided similar results. Instead, our result was considered due to the coordination of the Br atom with the metal center, from which the six- or five-membered ring could form to limit the conversion to the desired CM product.[20]

In addition, a variety of olefin partners with other functional groups were used in our studies. It was observed that when

5-hexen-1-ol was used, the reaction was greatly inhibited and only a 5% yield of the CM product **20** was obtained (entry 4). Protection of the hydroxyl group as the acetate afforded a much better result and **21** was produced in a 50% yield (entry 5). 5-Hexen-1-yl-*N*-Boc-glycinate[21] was found to be a good CM partner and afforded the product **22** in a moderate yield of 55% (entry 6). Thus, CM provides an effective method for introducing an α-amino acid functionality directly onto the vinyl group. Olefins with more than one additional functionality, such as 1-methoxycarbonyl-1,6-heptadiene,[22] also provided good results with CM. Product **23** was obtained in a 50% yield (entry 7), where an α,β-unsaturated ester was introduced directly via CM. For the CM between **Zn-4** and vinyl trimethoxysilane, reaction occurred even though the yield was quite low at 10% for product **24** (entry 8). However, the siloxane product from this reaction is a very useful building block for further transformations, such

(19) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998.
(20) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
(21) Hayashida, O.; Sebo, L.; Rebek, J., Jr *J. Org. Chem.* **2002**, *67*, 8291.
(22) Gastaminza, A. E.; Ferracutti, N. N.; Rodriguez, N. M. *J. Org. Chem.* **1984**, *49*, 3859.

TABLE 5. CM between Vinylchlorin and Allyl-Substituted Olefins

| Entry	A	B	Product	Yield [a]	Z/E [b]
1	**Zn-4**	TMS	No reaction	——	——
2	**Zn-4**	OTMS	No reaction	—	—
3	**Zn-4**	OAc	No reaction	—	—
4	**Zn-4**	TMSO—=—OTMS	**25**[c], R^1=CH_2OH	43%	No Z
5	**Zn-4**	AcO—=—OAc	**26**, R^1=CH_2OAc	54%	No Z
6	**Zn-5**	AcO—=—OAc	**27**, R^1=CH_2OAc	80%	No Z

[a] Isolated yield. [b] E:Z ratio was determined by ^1H NMR spectroscopy. [c] Product **25** was obtained after TBAF deprotection of the TMS groups.

as Suzuki-type aryl halide cross-coupling.[23] The results in Table 4 indicate that different functional groups, such as halides, esters, and α-amino acids, can be readily incorporated onto the vinylchlorin by employing this CM method. The broad reaction scope allows this method to be recognized as a general route for modifying vinylchlorins and vinylporphyrins. When the functionalities are further away from the vinyl group, they have little impact on the reaction; when they are in closer proximity, the yields generally become lower.

In the studies of CM between **Zn-4** and allyl-substituted terminal olefins, such as allyl trimethylsilane, allyloxytrimethylsilane, and allyl acetate, we were surprised to find that no CM products could be obtained (entries 1−3 in Table 5). The starting material **Zn-4** remained unchanged during the reaction. This result was unexpected because allyl-substituted terminal olefins are generally reactive CM partners.[24] Other unexpected but exciting results were that when the symmetric internal allyl-substituted olefins, such as *cis*-1,4-bis((trimethylsilane)oxy)-2-butene and *cis*-1,4-diacetoxy-2-butene, were used, CM products **25** and **26** were readily obtained (entries 4 and 5). Furthermore, CM between Zn(II) methyl pyropheophorbide *a* **Zn-5** and *cis*-1,4-diacetoxy-2-butene afforded an even better result where product **27** was obtained in 80% yield (entry 6). Therefore, CM with symmetric internal allylic olefins provides a valuable method for preparing allylic functionalized chlorins.

Blackwell and co-workers have systematically studied the CM reactivity difference between terminal olefins and symmetric internal olefins in the presence of ruthenium catalyst **2**.[25] Their studies indicated that, in certain cases, higher cross-metathesis yields with better *trans*-selectivity could be achieved by employing symmetric disubstituted internal olefins instead of their monosubstituted terminal counterparts. It was also revealed from their studies that the initiation rate of the terminal allylic olefin with catalyst **2** was much higher than that of the internal disubstituted olefins. These studies provided some very useful hints to rationalize our results. Even though these conclusions

SCHEME 4. Metathesis Pathway for Terminal and Internal Allylic Olefins
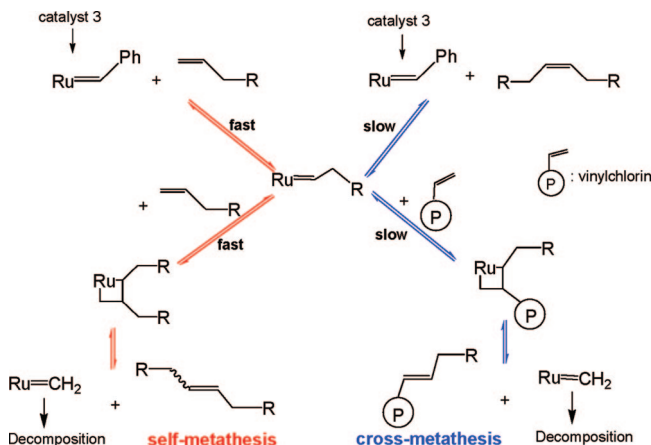
were reached on the basis of reaction with catalyst **2**, the reactivity trend for allylic terminal olefins and internal olefins was believed to be similar to that for catalyst **3**, which was employed in our studies. The observations in our studies are most likely to be the result of the dominant self-metathesis of the terminal olefin with the ruthenium catalyst **3** as illustrated by the red pathway in Scheme 4. This process dominates the catalytic cycle but is unproductive for cross-metathesis. Even though the corresponding product from self-metathesis, i.e. the disubstituted internal olefin, can possibly undergo secondary CM (blue pathway) to give the CM product, the reaction rate for the internal olefin toward catalysis is much slower than the terminal olefin, as aforementioned, and is therefore not competitive enough to take part in the catalytic cycle. Instead, only when disubstituted internal olefins were employed as starting materials were their relatively slow reaction rate toward the catalyst advantageous, as the vinylchlorin can participate in the catalytic cycle and generate the desired cross-metathesis product (blue pathway in Scheme 4).

Preliminary Mechanism Studies for CM of Vinylchlorins. To shed further light on the reactivity of the vinylchlorins toward CM, the reaction of **Zn-4** with only the ruthenium catalyst **3** was carried out. After treatment with TFA,

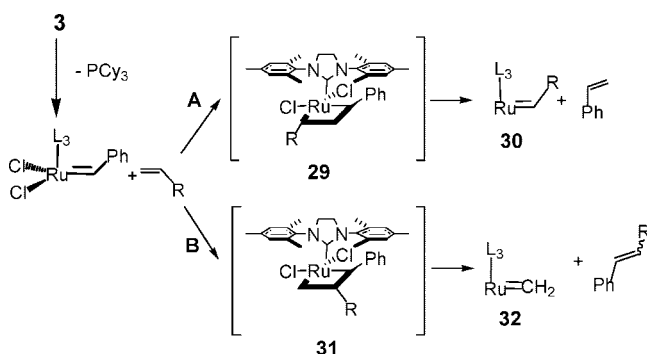(23) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684.
(24) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
(25) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.

SCHEME 5. Reaction between Zn-4 with Ruthenium Catalyst 3
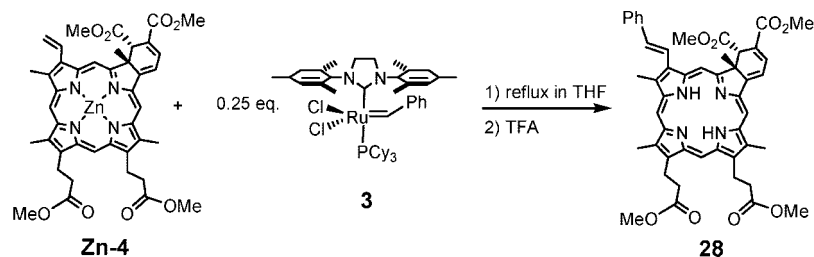
SCHEME 6. Pathways for Reaction between Catalyst 3 and Terminal Olefins

the new material obtained was isolated by silica column chromatography and its structure was shown to be **28** (with only the *E* isomer observed) (Scheme 5). This shows that the vinylchlorin **Zn-4** did not undergo homodimerization in the presence of ruthenium catalyst **3** but instead reacted with **3** to generate the 3-devinyl 3-(2-phenyl-1-ethenyl) derivative **28**.

It has been reported that when the ruthenium benzylidene catalyst reacts with olefins, the reaction may proceed via two different pathways that differ from the orientation of the olefin (Scheme 6).[26] In path A, the olefin binds with the ruthenium benzylidene carbene so that the alkyl substituent is adjacent to the metal. The transition state with structure **29** is formed through this orientation, and the alkylidene complex **30** is then generated. In path B, the transition state **31** has a configuration in which the alkyl group is oriented further away from the metal center, and the methylidene carbene **32** and R=CHPh are then generated from the reaction. It has also been pointed out that when the benzylidene catalyst reacts with sterically unhindered terminal olefins, the alkylidene **29** is the initial carbene product observed. When the steric bulk of the olefin is gradually increased, there is a decrease in the reaction rate. For even bulkier terminal olefins, metathesis lead directly to the formation of the methylidene **32**, i.e., the reaction occurred via pathway B. Therefore, the alkylidene **30** through path A is the kinetically favored product; however, when the steric effect of the bulky substituent becomes predominant, the pathway is shifted to B.

Path B is clearly the route taken by our substrate, in which the transition state **31** was accessed rather than **29** (Scheme 6). This is believed to be primarily due to the steric bulk of the chlorin ring.

On the basis of these results, together with the CM reactivities of simple olefins that have been reported,[27] a reaction pathway for CM between vinylchlorins and olefins in the presence of ruthenium catalyst **3** is proposed in Scheme 7.

According to the literature,[28] catalyst **3** first dissociates the PCy₃ ligand to generate a catalytically active species **I**. This can then react with either simple olefins or vinylchlorins by following route **A** or **B**. Since the CM reactivity of simple olefins is higher than that of the vinylchlorin and an excess of olefin is present under our reaction conditions, the reaction proceeds through pathway **A** (**I** reacts with vinylchlorin through pathway **B** as in Scheme 4 when no simple olefin presented), from which the alkylidene species **II** is formed. Alkylidene species **II** can react either via path **C** to give the self-metathesis product or with vinylchlorin to afford the desired cross-metathesis product through pathway **D**. These two pathways are competitive. If the reaction rates for both pathways are comparable, productive CM products are obtained, which is the result for most of the reactions in our studies. On the other hand, if the reaction rate for path **C** is much higher than that of path **D**, no CM product will be generated. This is exactly the result obtained for reaction between vinylchlorins and terminal allylic-substituted olefins where self-metathesis dominates the catalytic cycle.

CM Studies of Vinylchlorin Based on the Empirical Model. Lack of prediction of product selectivity is the major obstacle that limited the application of CM as a powerful synthetic technique. In order to overcome this limitation, Grubbs and co-workers developed a general empirical model by investigating the selectivity trends for CM reactions with a variety of olefins substrates and catalysts.[24] This model provides useful hints in the prediction of product selectivity in CM reactions. According to the empirical model, olefins can be categorized as one of four types on the basis of their reactivity toward self-metathesis in the presence of a specific catalyst (Scheme 8).[24]

On the basis of our studies and the principles of the model,[24] the conjugated vinyl groups of vinylchlorins can be categorized as type III olefins with the catalyst **3** since they are unable to homodimerize but are able to undergo CM with other olefins. Interestingly, our results also showed a category change of substrate when employing different catalysts, which is another important rule according to the empirical model. As aforementioned, when catalyst **2** is used, no CM occurs on the conjugated vinyl group of the vinylchlorin, but this does not inhibit the catalyst's activity toward other olefins (Scheme 2). Thus the conjugated vinyl group belongs to type IV for catalyst **2** rather than type III by using the highly active catalyst **3**.

All of the olefinic partners employed in our studies, except vinyl siloxane, are type I olefins. To this point, most of the cross-metathesis reactions that we have carried out, according to the empirical model, are reactions between type III (vinylchlorins) and type I olefins (except entry 8, Table 4). For the "isolated" terminal olefins, i.e., olefins that have functionality

(26) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484.
(27) Mol, J. C. *J. Mol. Catal. A: Chem.* **2004**, *213*, 39.
(28) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

SCHEME 7. Cross-Metathesis Mechanism between Vinylchlorin and Olefins
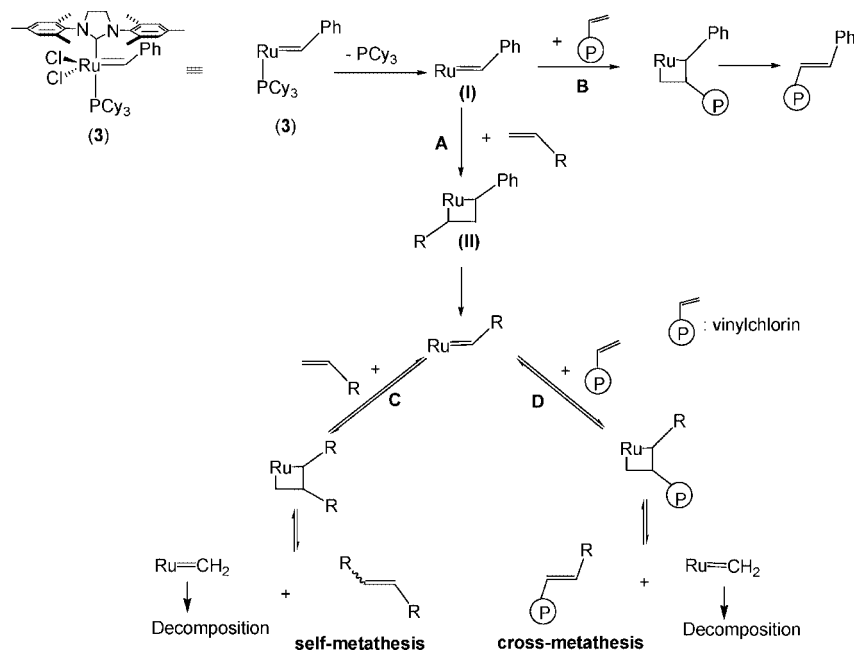
SCHEME 8. Olefin Categorization and Empirical Rules for CM Selectivity

Type I: Rapid homodimerization, homodimers consumable

Type II: Slow homodimerization, homodimers sparingly consumable

Type III: No homodimerization

Type IV: Olefins inert to CM, but do not deactivate catalyst

Olefin Reactivity Increasing ↑

Reaction between two olefins of Type I: Statistical CM

Reaction between two olefins of same type (non-type I): Non-selective CM

Reaction between olefins of two different types: Selective CM

further away from the vinyl group, the selective CM reactions proceed smoothly and can be regarded as good examples for CM between type III and type I olefins. However, the CM reaction with allyl-substituted olefins is an exception to the model. Both allylic monosubstituted terminal olefins and internal disubstituted olefins belong to type I according to the empirical model, but only the internal disubstituted olefins react with our vinylchlorin substrates to give CM products (Table 5) as discussed above.

On the basis of the empirical model, as a type III olefin, the vinylchlorin should be able to undergo selective CM with type II olefins. In the next stage of our studies, it was worthwhile to explore the reactions of **Zn-4** with type II olefins in order to explore the reaction scope and to further examine the applicability of the model to our substrates. According to the model, α,β-unsaturated carbonyl compounds are typical type II substrates with catalyst **3**. Therefore the commercially available acrolein diethyl acetal and methyl acrylate were chosen as type II olefinic partners in our studies (entries 1 and 2 in Table 6).

By following our general procedure, the reaction between **Zn-4** and acrolein diethyl acetal afforded the conjugated aldehyde **34** after treatment with TFA (entry 1). Although the acid-sensitive diethyl acetal CM product **33** could likely be isolated with Et$_3$N-treated silica gel column chromatography, it was more convenient to separate the final aldehyde product **34**. No further attempts were made to isolate compound **33**. The conjugated aldehyde product **34** was found to be quite stable

both in solution and as a solid at room temperature. When methyl acrylate was employed as a substrate in our CM reaction, a positive result was also obtained (entry 2). Product **35**, the vinylchlorin with a conjugated methoxycarbonyl functionality at position 3,[2] was obtained, although yield was not as high as that with the acrolein diethyl acetal, suggesting that the reactivity of methyl acrylate is lower than that of the diethyl acetal.

The success with CM in our studies here provides another direct approach for making chlorins with α,β-unsaturated carbonyl functionalities, which are always of great interest as useful building blocks in organic synthesis.

In addition, CM between **Zn-4** and a type III olefin was studied since CM was expected to occur according to the empirical model. 2-methyl-1-hexene, the 1,1-disubstituted type III olefin was used for this purpose (entry 3, Table 6). Interestingly, none of the expected CM product was generated other than compound **28**, which is formed via the reaction between **Zn-4** and the catalyst **3**. The result suggested that the reactivity of **Zn-4** is so low that it cannot undergo CM with other type III olefins under these conditions. However, as a type III olefin, 2-methyl-1-hexene does not prevent the reaction between vinylchlorin and the catalyst. Compound **28** was thus obtained via route B in Scheme 7.

Grubbs' model for selective CM provides an important reference for prediction of the outcome of CM reaction with vinylchlorin substrates. However, because of the generally poor and unique reactivities of the vinylchlorins, the model does not apply to all situations.

Product Characterizations and Stereoselectivity. One of the critical issues that limit the application of cross-metathesis is the lack of stereoselectivity for CM products. In most of the CM reactions reported in the literature, CM products were obtained as the mixtures of *E* and *Z* isomers with *E* isomers formed in excess because of their thermodynamic stability.

However, it was observed in our investigations that the cross-metathesis reactions with the vinylchlorins and vinylporphyrins all proceeded with excellent *E*-stereoselectivity. As shown in Tables 1–6, most of the reactions in our studies provided

TABLE 6. CM between Zn-4 with Type II and Type III Olefins

Entry	⟋⟍R	Product	Yield [a]	Z/E [b]
1	(OEt, OEt)	**34**	40%	No Z
2	(O, OCH₃)	**35**	20%	No Z
3		**28**	22%	—

a Isolated yield. *b* E:Z ratio was determined by ¹H NMR spectroscopy.

SCHEME 9. Steric Effect in the Formation of CM Intermediate

A
favorable

B
unfavorable
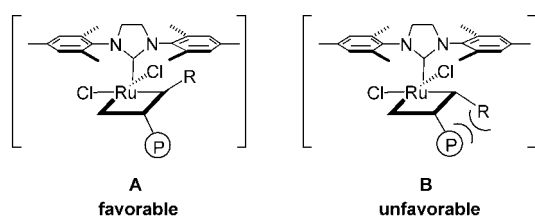
(P) : chlorin or porphyrin

complete *E*-stereoselectivity. For those reactions in which the CM products were obtained as mixtures of *E*- and *Z*-isomers, the *E*:*Z* ratios were in the range of 15:1 (entry 2 in Table 2) to 65:1 (entry 1 in Table 1).

Although a variety of factors control the stereoselectivity of the ultimate CM products, steric effects are believed to account for the remarkable *E*-stereoselectivity for our reactions. In CM, the steric interaction and the close proximity of the bulky substituent to the reacting olefin have been reasonably assumed as the principal reason for the selective formation of the *E*-isomers.[14] In our substrates, the bulky tetrapyrrolic macrocycle is connected directly with the vinyl group. This steric effect can be clearly demonstrated by comparing intermediates **A** and **B** (Scheme 9) that lead to the formation of *E* or *Z* products. Intermediate **A** is more favorable because the bulky tetrapyrrolic macrocycle is in the *trans* position with R group, while the steric repulsion that results from two groups on the same side makes intermediate **B** less favored.

Conclusion

Cross-metathesis has been applied successfully to vinylchlorin and vinylporphyrin substrates by employing the imidazolylidene ruthenium benzylidene complex **3**. Reactions were optimized, and the reactivities of different substrates were studied. The Zn(II) complexes of tetrapyrrolic macrocycles were found to

be more reactive than the corresponding free bases, and the chlorins exhibit reactivity higher than that of the porphyrins. Electronic effects are considered the major reason that leads to these differences. Olefinic partners with a variety of substituents are compatible with the reaction. The internal allylic olefins are more useful than terminal allylic olefins, and this can be explained by the simplified reaction pathway that has been proposed. The empirical model for selective CM was applied successfully in designing and predicting most of the new CM reactions with vinylchlorin substrates. All of the CM products were obtained with high *E*-stereoselectivity due to the steric effects of the bulky tetrapyrrolic macrocycle in the CM intermediate.

The cross-metathesis reaction has proven to be an effective way of producing chlorins and porphyrins with substituted-vinyl groups with excellent *E*-stereoselectivity. This method provides a general strategy for modifying the structure and property of tetrapyrrolic macrocycles.

Experimental Section

Ring B-BPD-1,3-diene Di(5-hexenyl) Ester (7). Ring B-BPD-1,3-diene dimethyl ester (**4**, 1.0 g, 1.37 mmol) was treated with 25% HCl (20 mL) overnight under refrigeration. The dimethyl ester was hydrolyzed to the dicarboxylic acid with some mono acid/mono esters present. The diacid was separated by column chromatography (silica gel, 230−400 mesh, CH_2Cl_2/MeOH, 100:5, v/v) as a black solid (780 mg, 80%). The diacid (100 mg, 0.14 mmol) was refluxed in CH_2Cl_2 for 10 min under nitrogen. Oxalyl chloride (0.5 mL, 5.7 mmol) was then added, and reflux was continued for another 45 min. The reaction mixture was cooled, and the solvent was removed in vacuo. The acid chloride thus obtained was redissolved in dry CH_2Cl_2 (8 mL), and 5-hexene-1-ol (0.17 mL, 1.4 mmol) was added. The mixture was stirred at room temperature under nitrogen overnight. It was then diluted with CH_2Cl_2 (50 mL) and washed with water, 10% $NaHCO_3$, and then water. Solvent and excess 5-hexene-1-ol were removed *in vacuo*. The residue was purified by flash chromatography (silica gel, 230−400 mesh, CH_2Cl_2/MeOH, 100:0.4, v/v) to give ring B-BPD-1,3-diene di(5-

hexenyl) ester **7** as a black solid (85 mg, 70%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.74, 9.68, 9.35, 9.13 (4s, 4H), 8.11 (dd, $J = 18.0$ and 12.0 Hz, 1H), 7.81 (d, $J = 5.7$ Hz, 1H), 7.43 (d, $J = 5.7$ Hz, 1H), 6.35 (d, $J = 18.0$ Hz, 1H), 6.15 (d, $J = 12.0$ Hz, 1H), 5.50−5.46 (m, 2H), 5.04 (s, 1H), 4.79−4.70 (m, 4H), 4.30 (t, $J = 7.8$ Hz, 2H), 4.16 (t, $J = 7.7$ Hz, 2H), 4.05−3.99 (m, 4H), 3.97 (s, 3H), 3.62, 3.47, 3.41 (3s, 3 × 3H), 3.20−3.10 (m, 4H), 2.93 (s, 3H), 1.79 (m, 4H), 1.76 (s, 3H), 1.46−1.16 (m, 8H), −2.31 (br, 2H) ppm. LREIMS (*m/z*): 868 (M$^+$). HRESIMS *m/z*: calcd for C$_{52}$H$_{61}$N$_4$O$_8$ ([M + H]$^+$) 869.4489, found 869.4485.

Ring B-BPD Ring-Closing Metathesis Derivative (8). A mixture of ring B-BPD-1,3-diene di(5-hexenyl) ester **7** (10 mg, 0.011 mmol) and catalyst **2** (1 mg, 0.001 mmol) was placed in 3 mL of freshly distilled dry THF and refluxed for 3 h. The solvent was removed *in vacuo*, and the residue was purified by flash column chromatograph (silica gel, 230−400 mesh, CH$_2$Cl$_2$/MeOH, 100: 0.5, v/v) to give product **8** as a black solid (7 mg, 78%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.74, 9.66, 9.34, 9.13 (4s, 4H), 8.11 (dd, $J = 18.0$ and 12.0 Hz, 1H), 7.81 (d, $J = 5.7$ Hz, 1H), 7.43 (d, $J = 5.7$ Hz, 1H), 6.35 (d, $J = 18.0$ Hz, 1H), 6.15 (d, $J = 12.0$ Hz, 1H), 5.05−5.02 (m, 3H, H-7^1), 4.30−4.28 (m, 2H), 4.16−4.14 (m, 2H), 4.10−3.99 (m, 4H) 3.97 (s, 3H), 3.61, 3.47, 3.41 (3s, 3Me), 3.22−3.10 (m, 4H), 2.92 (s, 3H), 1.76 (t, 4H),1.76 (s, 3H), 1.47−1.11 (m, 8H), −2.31 (s, 2H) ppm. ESIMS (*m/z*): 841.4 ([M + H]$^+$). HREIMS *m/z*: calcd for C$_{50}$H$_{56}$N$_4$O$_8$ (M$^+$) 840.4098, found 840.4100.

General Procedure for Cross-Metathesis Reaction. An oven-dried flask with condenser was charged with Zn-vinylchlorin (0.04 mmol). A solution of catalyst **3** (0.01 mmol), dissolved in freshly distilled dry THF (1 mL), was added via syringe to the flask, and the mixture was stirred at room temperature. Olefin (0.8 mmol) was immediately added by syringe to the stirred mixture, which was then gently refluxed under argon for 1 h. TFA was added to remove the Zn, and the mixture was dried by removing the solvent and then purified on a silica gel column or by preparative TLC. Products were obtained as dark solids.

Representative Cross-Metathesis for Synthesis of 3-Devinyl 3-(1-hexenyl) Ring B-BPD-1,3-diene Dimethyl Ester (9). An oven-dried flask fitted with a condenser was charged with Zn(II) ring B-BPD-1,3-diene dimethyl ester **Zn-4** (32 mg, 0.04 mmol) and 1-hexene (67 mg, 0.1 mL, 0.8 mmol). A solution of catalyst **3** (9 mg, 0.01 mmol) dissolved in freshly distilled dry THF (1 mL) was added via a syringe to the flask. The reaction mixture was gently refluxed under argon for 1 h. Solvent was removed *in vacuo*, and the residue was purified by flash column chromatography (silica gel, 230−400 mesh, CH$_2$Cl$_2$/MeOH, 100:0.5, v/v). The Zn(II) complex thus obtained (32 mg, 95%) was redissolved in CH$_2$Cl$_2$ (10 mL) and treated with trifluoroacetic acid (0.5 mL) for 30 min at room temperature. The mixture was diluted with CH$_2$Cl$_2$ (20 mL) and washed with water, 5% NaHCO$_3$ and water. After drying over sodium sulfate, the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, 230−400 mesh, CH$_2$Cl$_2$/MeOH, 100:0.2, v/v) to give the product 3-devinyl 3-(1-hexenyl) ring B-BPD-1,3-diene dimethyl ester **9** as a black solid (29 mg, 98%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.72, 9.67, 9.36, 9.20 (4s, 4H), 7.81 (d, $J = 5.7$ Hz, 1H), 7.65 (d, $J = 15.9$ Hz, 1H), 7.44 (d, $J = 5.7$ Hz, 1H), 6.64 (td, $J = 15.9$ and 7.0 Hz, 1H), 5.05 (s, 1H), 4.29 (t, $J = 7.7$ Hz, 2H), 4.17 (t, $J = 7.7$ Hz, 2H), 3.97 (s, 3H), 3.65, 3.63, 3.58, 3.46, 3.41, 2.95 (6s, 6Me), 3.20−3.13 (m, 4H), 2.75 (q, $J = 7.0$ Hz, 2H), 1.91−1.68 (m, 4H), 1.78 (s, 3H), 1.15 (t, $J = 7.3$ Hz, 3H), −2.34 (br, 2H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.7, 173.3, 170.6, 167.6, 165.5, 156.6, 152.0 151.0, 140.1, 139.3, 138.2, 137.5, 137.3, 137.2, 136.0, 134.6, 133.8, 132.6, 131.9, 130.9, 122.0, 121.8, 112.4, 99.3, 93.4, 91.9, 52.7, 52.2, 51.7, 51.6, 51.5, 47.9, 37.0, 36.6, 34.3, 32.1, 27.5, 23.1, 22.6, 21.8, 21.5, 14.1, 12.5, 11.6, 11.2 ppm. LREIMS (*m/z*): 788 (M$^+$). Anal. Calcd. for C$_{46}$H$_{52}$N$_4$O$_8$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.75; H, 6.73; N, 7.17. UV−vis (λ_{max}/Abs, CH$_2$Cl$_2$): 355.0 (0.401), 435.1 (0.766), 590.0 (0.138), and 689.9 (0.244)

Supporting Information Available: General methods, experimental procedures and ^{1}H NMR spectra for compounds **7**−**13**, **17**, **20**−**28**, and **34**−**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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