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Cross-metathesis reactions of vinyl-chlorins and -porphyrins catalyzed by a "second generation" Grubbs' catalyst†

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The first application of olefin cross-metathesis with vinylchlorins and vinylporphyrins using a "second generation" Grubbs' catalyst is reported. Cross-metathesis products were obtained in good yields with high *E*-stereoselectivity.

Olefin metathesis has recently gained prominence in synthetic organic chemistry.[1] The commercial availability of well-defined transition metal catalysts (Fig. 1), such as the molybdenum alkoxyimido alkylidene **1** developed by Schrock *et al.*[2] and the ruthenium benzylidene catalyst **2** developed by Grubbs' group,[3] has made olefin metathesis practical for application to small molecule synthesis. However, cross-metathesis (CM), a method for the intermolecular formation of carbon–carbon double bonds, has been underutilized when compared to other metathesis reactions. This is due primarily to the lack of reaction selectivity and olefin stereoselectivity.[4] The discovery of the highly active and stable ruthenium-based "second generation" Grubbs' catalyst **3**, which contains a 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ligand,[5] has dramatically advanced the utility of CM. This catalyst was found to catalyze efficiently reactions of previously metathesis-inactive substrates.[6]

Nevertheless, olefin metathesis and CM have seldom been applied to chlorin and porphyrin substrates. One of the few applications of the metathesis reaction in porphyrin-related fields was the ring-opening metathesis polymerization of a porphyrazine benzonorbornadiene derivative catalyzed by ruthenium catalyst **2** reported by Hoffmann's group.[7] In our studies, we were interested in the chemistry and modification of the vinyl groups[8] at the 3-position of vinylchlorins and vinylporphyrins in order to improve their properties as candidates for photodynamic therapy.[9] This is of interest since the nature of the hydrophobic groups and their relative dispositions around tetrapyrrolic macrocycles affect their biodistribution.[10] We anticipate that these reactions will provide new approaches to the direct synthesis of a variety of olefin-containing chlorins and porphyrins.

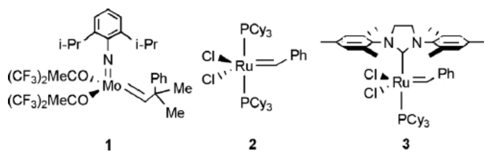
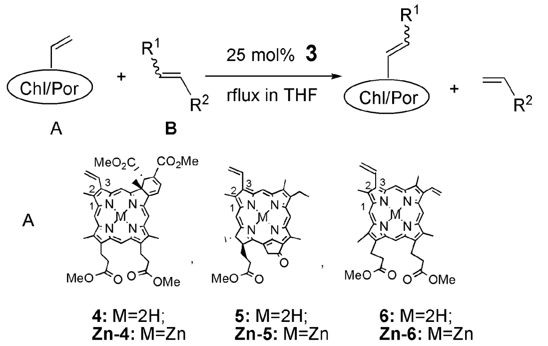


Fig. 1 Commercially available catalysts for olefin metathesis.

Here we report the first CM reaction of vinyl groups on vinylclorins and vinylporphyrins catalyzed by ruthenium catalyst **3**. We chose the ring B-Benzoporphyrin Derivative (BPD)-1,3-diene dimethyl ester **4**, methyl pyropheophorbide **5** (which are chlorins) and protoporphyrin IX dimethyl ester **6** (which is a porphyrin) as substrates for our studies because of their ready availability (Scheme 1). The results are summarized in Table 1.

We expected that, as a terminal aromatic olefin, the vinyl group might undergo CM as do other terminal aromatic olefins.[11] However, the large size of the chlorin or porphyrin rings was anticipated to affect reactivity. Furthermore, resonance effects could also dramatically reduce the reactivity. Initial studies showed that the vinyl group at the 3-position of vinylchlorin was a poor



R^1: alkyl, substituted-alkyl, acetyoxy; R^2: H or same as R^1

Scheme 1 Cross-metathesis between vinylchlorins or vinylporphyrins and olefins.

Table 1 Results of cross-metathesis of vinylchlorins and vinylporphyrins with olefins[a]

Entry	A	B	Yield (%)[b]		*E* : *Z* ratio[c]	Entry	A	B	Yield (%)[b]		*E* : *Z* ratio[c]
1	**Zn-4**	$CH_2{=}CH(CH_2)_3CH_3$	No reaction[d]	—	—	12	**4**	$CH_2{=}CH(CH_2)_3OBn$	10[f]	**4g**	No *Z*
2	**4**	$CH_2{=}CH(CH_2)_3CH_3$	100	**4a**	65:1	13	**Zn-4**	$CH_2{=}CH(CH_2)_3OAc$	50[f]	**4h**	No *Z*
3	**Zn-4**	$CH_2{=}CH(CH_2)_3CH_3$	100	**4a**	No *Z*	14	**4**	$CH_2{=}CHCH_2TMS$	No reaction	—	—
4	**4**	$CH_2{=}CH(CH_2)_5CH_3$	100	**4b**	50:1	15	**Zn-4**	$CH_2{=}CHCH_2TMS$	No reaction	—	—
5	**4**	$CH_2{=}CH(CH_2)_5CH_3$	70[e,f]	**4b**	No *Z*	16	**Zn-4**	$AcOCH_2CH{=}CHCH_2OAc$	54[f]	**4i**	No *Z*
6	**4**	$CH_2{=}CH(CH_2)_5CH_3$	5[g]	**4b**	No *Z*	17	**5**	$CH_2{=}CH(CH_2)_3CH_3$	100	**5a**	No *Z*
7	**4**	$CH_2{=}CH(CH_2)_4Br$	80	**4c**	No *Z*	18	**5**	$CH_2{=}CH(CH_2)_5CH_3$	100	**5b**	14 : 1
8	**Zn-4**	$CH_2{=}CH(CH_2)_4Br$	100	**4c**	No *Z*	19	**Zn-5**	$AcOCH_2CH{=}CHCH_2OAc$	80	**5c**	No *Z*
9	**Zn-4**	$CH_2{=}CH(CH_2)_3Br$	70[h]	**4d**	No *Z*	20	**6**	$CH_2{=}CH(CH_2)_5CH_3$	58[i]	**6a**	40 : 1
10	**Zn-4**	$CH_2{=}CH(CH_2)_2Br$	80[h]	**4e**	No *Z*	21	**Zn-6**	$CH_2{=}CH(CH_2)_5CH_3$	100[i]	**6b**	50 : 1
11	**4**	$CH_2{=}CH(CH_2)_4OH$	5[f]	**4f**	No *Z*						

[a] A : B : catalyst **3** = 1 : 20 : 0.25. [b] Yields were calculated based on ^{1}HNMR spectra of crude products. [c] *E* : *Z* ratio was determined based on ^{1}HNMR spectra. [d] 25 mol% catalyst **2** was applied. [e] 15 mol% catalyst **3** was applied. [f] Isolation yield. [g] 2 equiv. B olefin was utilized. [h] Product was not isolated. [i] The reaction gave a mixture of the three possible products which were not isolated.

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† Electronic supplementary information (ESI) available: comparison of reactivity difference between 3-vinyl and other terminal vinyl; experimental. See http://www.rsc.org/suppdata/cc/b4/b400001c/

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substrate for CM,† which was consistent with our expectations. No detectable products were observed when catalyst **2** was applied to the reaction of **Zn-4** and 1-hexene (entry 1).

On the other hand, the highly active ruthenium N-heterocyclic carbene complex **3** was found to efficiently catalyze the selective CM of the vinylchlorin. Products were obtained in moderate to high yields upon refluxing a vinylchlorin and 20 equiv. of a terminal olefin with 25 mol% of catalyst **3** in dry THF (0.04 M) for 1 h.‡ The relatively high loading of catalyst was required to ensure a high yield. The yield dropped from 100% to 70% when 15 mol% catalyst was used (entries 4 and 5). This is due primarily to the low CM reactivity of the 3-vinyl group. The amount of the partner olefin also needed to be high. When 2 eq. was employed, the yield was only 5% (entry 6). Extending the reaction time did not improve the yield. This observation differs from other reports where cross-metathesis products were still observed after 8 h.[6]

Reactions between ester **4** with simple alkyl-substituted olefins, such as 1-hexene and 1-octene, proceeded very smoothly under the conditions described above with quantitative conversions (entries 2, 3 and 4). Similar results were obtained for methyl pyropheophorbide **5** and simple olefins (entries 17 and 18). Further investigation with functionalized olefins showed that different functional groups affect the reaction. For example, when 6-bromo-1-hexene was utilized, product was obtained in 100% yield (entry 8), which is the same as with simple olefins; however if the bromine was closer to the vinyl group, such as at the 4 or 5 position, yields decreased to around 80% (entries 9 and 10). It was concluded that the inductive effect of an electron withdrawing group slows the reaction. This is consistent with some results that have been reported on CM before.[4] The presence of a hydroxy group resulted in only trace amounts of product (entry 11).

Deactivated olefins, as expected,[4] give decreased yields. This is, to some extent, compensated for by using the Zn complexes which are more active than the free bases (entries 7 and 8).

Highly activated olefins such as allyl trimethysilane undergo self metathesis fast enough to exclude reaction with the tetrapyrrolic substrates. However, other allyl-substituted olefins such as *cis*-1,4-diacetoxy-2-butene reacted to give the allyl-substituted products in moderate (54%) yield for **Zn-4** (entry 16) and in 80% yield with methyl pyropheophorbide **Zn-5** (entry 19). This provides an effective means to introduce substituents at the allylic position.

Most of the reactions reported here proceeded with complete *E*-steroeselectivity. Even in the worst case an *E*/*Z* ratio of 14 : 1 was observed (entry 18). The high stereoselectivity can be rationalized by the steric hinderance provided by the large tetrapyrrolic macrocycles.[12]

In conclusion, we have demonstrated that the imidazolylidene ruthenium benzylidene complex **3** efficiently catalyzed the cross-metathesis of vinyl-chlorins and -porphyrins with a variety of different substituted olefins. While the chlorins were more reactive than the porphyrins, the corresponding zinc complexes all showed similar high activity. As such, the cross-metathesis reaction proved to be an effective way for producing vinyl-substituted chlorins and porphyrins with excellent control of olefin stereoselectivity.

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Notes and references

‡ **General experimental procedure**: An oven-dried flask with condenser was charged with 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 temp. Olefin (0.8 mmol) was immediately added by syringe to the stirred mixture which was then gently refluxed under Ar for 1 h. The mixture was dried by removing the solvent and then purified directly on a silica gel column or preparative TLC. Products were obtained as dark solids.

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