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Kinetic Benchmarking Reveals the Competence of Prenyl Groups in Ring-Closing Metathesis

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Supporting Information Placeholder
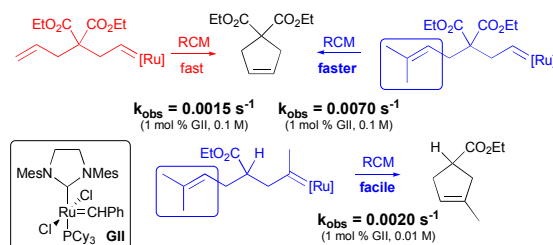
ABSTRACT: A series of prenyl-containing malonates are kinetically benchmarked against the standard allyl-containing congeners using a ruthenium benzylidene pre-catalyst for ring-closing metatheses. The prenyl grouping is found to be a superior acceptor olefin compared to an allyl group in RCM processes with ruthenium alkylidenes derived from terminal alkenes. The prenyl group is also found to be a highly competent acceptor for a ruthenium alkylidene derived from a 1,1-disubstituted olefin in a RCM process.

The advent of well-defined ruthenium benzylidene pre-catalysts for ring-closing metathesis (RCM) has revolutionised organic synthesis, as showcased by countless examples of highly successful acyclic diene RCM reactions.[1] These possibilities are perhaps best illustrated in Grubbs' standard characterization method[2] which utilize diethylmalonate substrates **1-3** respectively as increasingly difficult RCM substrates as testbeds for new catalyst types. These substrates are all characterized by being unsubstituted at the termini of the participating olefins. In contrast, the RCM of terminal olefins with alkenes that are geminally disubstituted at their terminus (*e.g.*, the prenyl group) in ruthenium benzylidene catalysed RCM reactions have limited literature precedent.[3-12] While these examples have shown that such olefin combinations are *possible* in RCM reactions, the prenyl grouping is most often employed as a matter of synthetic expediency to derive the RCM substrate from readily available terpene building blocks,[5,9] or in RCM reactions demonstrated directly on monoterpenes.[4] It has also been employed as a rational design feature to direct initiation to another olefin,[8a,11,12] and it has certainly been noted that the prenyl group functions surprisingly well in selected RCM reactions.[3a,4a,7e] However, to the best of our knowledge, there have been no direct kinetic comparison of RCM reactions using acyclic dienes with terminal alkenes versus an acyclic diene where one of the alkenes is now geminally disubstituted at its terminus. Herein, we report on such activities, and experimentally demonstrate that prenyl groups are excellent acceptor olefins in ring-closing metatheses.
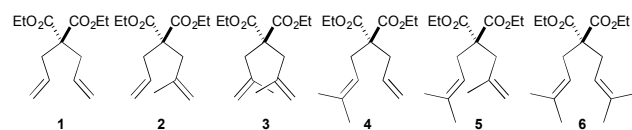

Table 1. Ring-closing metatheses of substrates 1-6 with GII catalyst.[a]

entry	substrate	time (h)	product	yield[b]
1	**1**	1	**7**	99
2	**2**	1	**8**	100
3	**3**	24	**9**	0[c]
4	**4**	1	**7**	99
5	**5**	24	**8**	42
6	**6**	24	**7**	0[c]

[a] RCM were performed with 10 mol % GII catalyst in refluxing CH$_2$Cl$_2$ solution at 0.01 M; [b] isolated % yield after chromatography; [c] RCM runs were quenched with diethylene glycol vinyl ether to avoid false positives on concentration.

Our investigations began by preparation of malonates **4-6** and comparison of their – previously unexplored – RCM reactivity with known malonates **1-3** using Grubbs second generation catalyst (GII)[13] as the ruthenium benzylidene pre-catalyst. As expected, malonates **1-3** behaved as previously described (Ta-

ble 1, entries 1-3).[2] Inspection of the results for malonates **4** and **6** reveals that the although (productive) initiation on a prenyl group (entry 6) is evidently not possible under these conditions (substrate **6** was completely unchanged), the prenyl group is a perfectly competent acceptor olefin in ring-closing metathesis reactions after initiation on an allyl group (entry 4). In the case of methallyl-prenyl malonate **5** (entry 5), assuming that (productive) prenyl group initiation is still prohibited, initiation at the methallyl unit followed by productive RCM onto the prenyl grouping is evidently also possible, albeit the overall process is considerably slower.
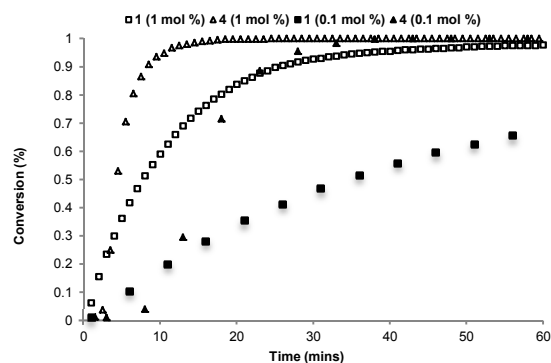
Figure 1. Plot of time vs conversion for malonates **1** vs **4** into disubstituted alkene **7** at 1 and 0.1 mol % GII loading.

^{1}H NMR plots of time vs conversion under Grubbs' standard conditions[2] (1 mol % GII, 0.1 M CD$_2$Cl$_2$, 30 °C) for diallyl **1** versus allylprenyl **4** malonate substrates (Figure 1) showed that although the latter showed a more pronounced induction period, it reached quantitative conversion in less than 20 minutes whereas the former did not quite reach quantitative conversion after 1 h.[14] These differences were even more pronounced at 0.1 mol % GII catalyst loading, with the RCM of **4** being complete in less than 40 minutes, and RCM of **1** reaching 68% conversion in 1 h (Figure 1).[15]
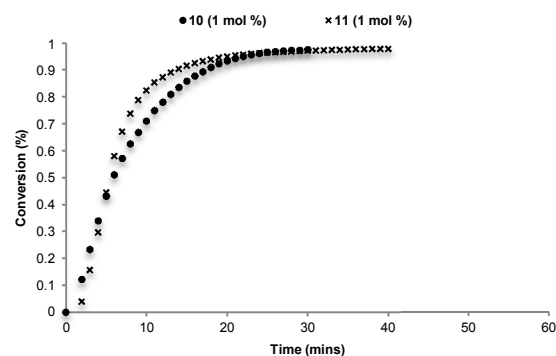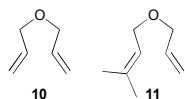
Figure 2. Plot of conversion of diallyl ether **10** vs allylprenyl ether **11** into dihydrofuran at 1 mol % GII loading.

Thus, not only is the prenyl group a competent acceptor in this RCM substrate, it is also beneficially allows reduced catalyst loading and shorter reaction times. To the best of our knowledge, this is a previously unrecognised benefit of using the prenyl group in RCM reactions. However, a parallel study using diallyl ether **10** versus allylprenyl ether **11**[12] (Figure 2),

did not reveal such distinct differences, although a more pronounced induction period was still observed for the prenyl containing substrate, and a marginally faster subsequent rate ensues. We therefore attribute the very fast RCM reaction of allylprenyl malonate **4** to a pre-organisation effect where the prenyl group preferentially adopts a *pseudo*-equatorial position avoiding detrimental interactions with the malonate groupings (Figure 3).[16] From these experiments with the malonate substrates and their ether analogues, the conclusion is that all things being equal, *the prenyl group is at least as competent as an allyl group in accepting a ruthenium alkylidene derived from a terminal alkene.*
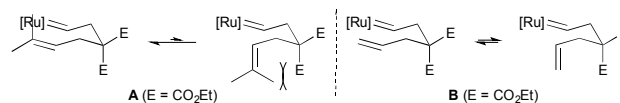
Figure 3. Preorganisation of prenyl group (left) in alkylidene **A** of substrate **4** vs reduced preorganization of allyl group (right) in alkylidene **B** of substrate **1**.

We next questioned whether it was possible for a prenyl grouping to *competently* accept a ruthenium alkylidene derived from a 1,1-disubstituted olefin in a RCM process. Substrate **5** (Table 1, entry 5) partially answered this question (knowing that productive initiation is prohibited at the prenyl group), but it does not allow kinetic separation of the ring-closing event from the expected slow initiation process at the methallyl group. The very limited literature precedents for this ring-closing mode had not previously addressed this issue.[17] Accordingly, we targeted relay ring closing metathesis (RRCM)[10] substrate **16** to uncouple these two factors (Scheme 1).

Scheme 1. Synthesis of RRCM substrate 16.
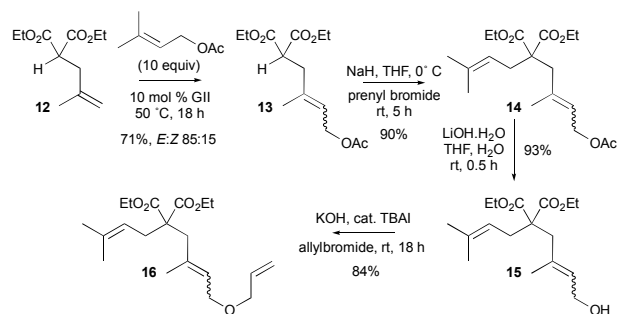
Thus, methallyl malonate **12** was subject to a cross-metathesis with prenyl acetate as inspired by the studies of Robinson (Scheme 1).[18] The resulting trisubstituted olefin **13** was subsequently *C*-allylated, hydrolysed and *O*-allylated to give RRCM substrate **16**.

With RRCM substrate **16** in hand, we were pleased to find that the action of 10 mol % GII catalyst (refluxing CH$_2$Cl$_2$ solution, 0.01 M, 1 h) gave trisubstituted cyclic olefin **8** in 83% isolated yield. This is a significant improvement on the previously obtained 42% yield (in 24 h) obtained for methallyl substrate **5** under the same reaction conditions (Table 1, entry 5), and confirms that the rate determining step in the RCM of malonate **5** is initiation at the methallyl grouping (and where productive initiation at the prenyl grouping is prohibited). To the best of our knowledge, this is the first example of a RRCM utilizing a prenyl group as the final acceptor olefin. Moreover,

2

while it is to be expected that the RRCM approach here facilitates the overall conversion of **16** (compared to **5**) into **8**, by overcoming slow initiation, *this experiment also reveals that the inherent proclivity for RCM of an alkylidene derived from a 1,1-disubstituted olefin onto a prenyl group is surprisingly facile.* However, ^{1}H NMR monitoring, under the standard conditions of Grubbs[2] (1 mol % GII, 0.1 M CD_2Cl_2, 30 ˚C), of methallylprenyl malonate **5** versus RRCM substrate **16** revealed that both reactions were sluggish over the course of 1 h, which could be partially ameliorated by the use of 10 mol % GII catalyst and an increase of temperature to 35 ˚C for RRCM of substrate **16** (Figure 4).
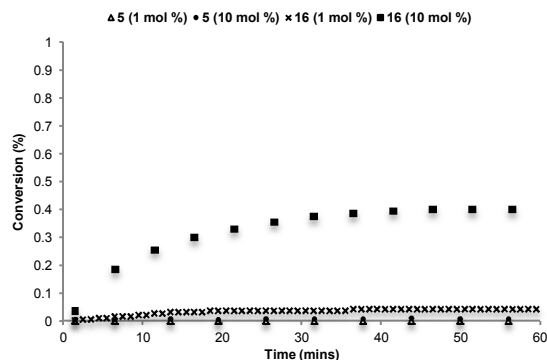

Figure 4. Plot of time vs conversion for malonates **5** vs **16** into trisubstituted alkene **8** at 1 and 10 mol % GII loading.

We suspected that the malonate group was also influencing the ring-closure of RRCM substrate **16**, where intermediate isoalkylidene **C** (post-relay) cannot escape a detrimental interaction with one or other of the ester groups in the presumed envelope-like conformation necessary for RCM (Figure 5). We therefore conjectured that a monoester substrate might alleviate this interaction via one reactive conformation of isoalkylidene **D**.
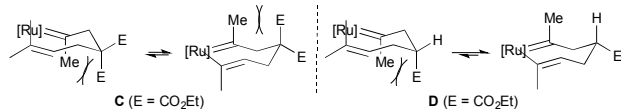

Figure 5. Postulated detrimental interaction of isoalkylidene **C** with malonate ester (left) vs potentially alleviated interaction in monoester isoalkylidene **D** (right).

Scheme 2. Synthesis of monoesters 17 (left) and 19 (right).
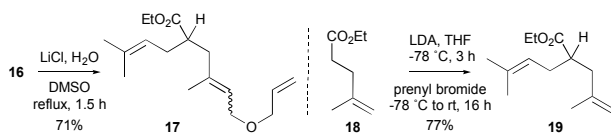
Accordingly, malonate **16** was subjected to Krapcho decarboxylation[19] yielding new monoester RRCM substrate **17**, and non-relay monoester **19** was prepared by alkylation of ester **18** (Scheme 2). ^{1}H NMR monitoring of the metathesis reaction of the former (1 mol % GII, 0.01 M[20] CD_2Cl_2, 35 ˚C) now showed rapid conversion to the ring-closed product **20** (Figure 6). A comparison with the monoester **19** under the same conditions, clearly demonstrates that once slow initiation has been circumvented, and – by comparison with malonate **16** – once any other deleterious factors have been eliminated, the *prenyl group is also a highly competent acceptor for a ruthenium*

alkylidene derived from a 1,1-disubstituted olefin in a RCM process.
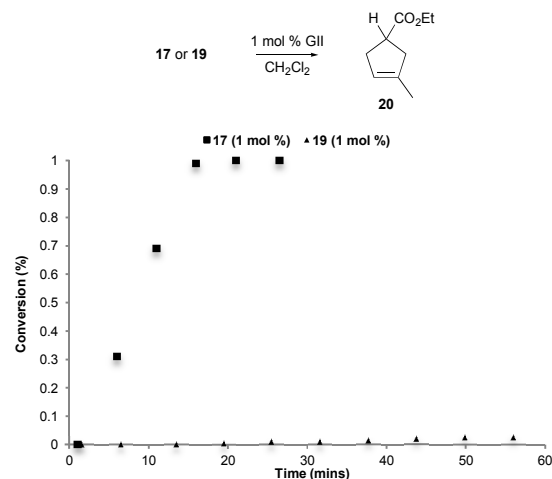
Figure 6. Plot of time vs conversion for malonates **17** vs **19** into trisubstituted alkene **20** at 1 mol % GII loading.

The kinetic data obtained from the NMR monitoring experiments (*c.f.*, Figures 1, 2, 4 and 6) can be manipulated to extract rate constant (k_{obs}) as previously described (Table 2).[2] Thus the diallyl vs allylprenyl substrates can be directly compared, where the RCM of the prenyl containing compounds proceed faster (entries 1-4). For monoester relay substrate **17** (entry 5), it is important to appreciate here that a direct control experiment of a ruthenium alkylidene derived from a 1,1-disubstituted olefin closing onto an allyl group is not possible, since preferential initiation would occur instead at the allyl group thereby compromising the comparison. However, notwithstanding this, it is notable that the overall closure of substrate **17** leading to trisusbstituted olefin **20** (entry 5) is faster than the RCM of the typically employed allylmethallyl malonate **2** to give trisubstituted alkene **8** (entry 6), as well as faster than the RCM of the simplest (and usually considered as the easiest) diallyl malonate substrate **1** to give disubstituted olefin **7** (entry 1).

Table 2. Observed rate constants for RCM substrates.[a,b]

entry	substrate	k_{obs} (s[-1])
1	diallyl malonate **1**	0.0015 (0.0020)[c] [0.0002][d]
2	allylprenyl malonate **4**	0.0070 [0.0031][d]
3	diallyl ether **10**	0.0023 [0.0004][d]
4	allylprenyl ether **11**	0.0033 [0.0004][d]
5	monoester relay **17**	0.0020[e]
6	allylmethallyl malonate **2**	0.0008 (0.0012)[c]

[a] Rate constants were extracted from ln([SM]) vs time plots as previously described (ref 2); [b] data acquired conducted under the standard conditions of Grubbs: 1 mol % GII, 0.1 M CD_2Cl_2, 30 ˚C (ref 2); [c] figure in parentheses is the k_{obs} reported by Grubbs for this substrate (ref 2); [d] figure in square parentheses is the corresponding k_{obs} at 0.1 mol % GII loading; [e] 35 ˚C, 0.01 M.

Thus, the prenyl moiety has been experimentally demonstrated to be a perfectly competent or even superior acceptor olefin compared to an allyl group in RCM processes with ruthenium alkylidenes derived from terminal alkenes. In addition, through the application of Hoye's excellent RRCM methodology,

3

which allows uncoupling of slow initiation from the subsequent RCM event, the prenyl group was also revealed to be a highly competent acceptor for a ruthenium alkylidene derived from a 1,1-disubstituted olefin in a RCM process. These findings should aid in the rational design and incorporation of prenyl groups in other olefin metathesis processes.[21]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterising data and copies of ^{1}H and ^{13}C NMR spectra for compounds **2-8**, **13-17** and **19** (PDF). See also ref 21.

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ACKNOWLEDGMENT

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(21) ^{1}H NMR, ^{13}C NMR and RCM kinetic data is available via a data repository as: Bahou, K. A.; Braddock, D. C. Imperial College

HPC Data Repository, 2017. DOI: 10.14469/hpc/2707 (accessed July 2017).

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