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Cross Metathesis with Strained Exocyclic Enones: Synthesis of 3-Alkylideneoxetan-2-ones from 3-Methyleneoxetan-2-ones

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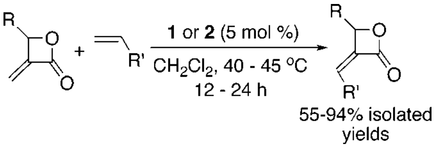
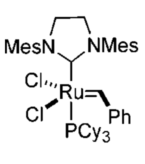
ABSTRACT



3-Alkylideneoxetan-2-ones have been prepared in good to excellent yields with high *Z*-selectivity by olefin cross metathesis with 3-methyleneoxetan-2-ones in the presence of second generation metathesis catalysts 1 or 2.

The emergence of olefin metathesis from industrial application to routine laboratory practice has been nothing short of remarkable. This can be attributed to the development of stable, readily available catalysts that give high yields under mild conditions and are remarkably tolerant of a range of functional groups. Precursor alkenes for olefin metathesis are generally readily available, and the overall process is highly atom-economic. Initial success was most evident with the entropically favored ring-closing metathesis (RCM) reactions, which have been widely exploited for the construction of small, medium, and large ring systems.[1] Cross metathesis (CM), the intermolecular variant, had been, until recently, utilized far less because of problems associated with selectivity (both stereoselectivity and homodimerization vs heterocoupling) and the apparent low and often unpredictable reactivity of many alkene classes. With the emergence of newer metathesis catalysts, CM reactions of even sterically hindered and/or electronically deactivated alkenes have been demonstrated to proceed with high yields and stereoselectivities, greatly enhancing the scope and utility of this metathesis class.[2,3] For example, CM reactions involving deactivated alkenes, such as enones and other conjugated alkenes were, with a few exceptions, unsuccessful until the advent of catalysts such as **1** and **2**, containing ligands with strong σ-donor and poor π-acceptor properties. Although a range of α,β-unsaturated aldehydes, esters, ketones, and nitriles has been cross-coupled in high yields with excellent *E*-diastereoselectivities, to our knowledge, CM reactions with strained exocyclic enones have not yet been examined.



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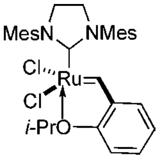

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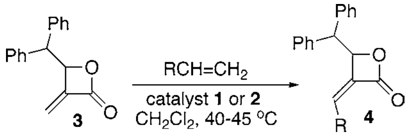
We have been interested in the synthesis and exploitation of oxetanes with exocyclic unsaturation, such as 2-methyleneoxetanes[4] and 3-alkylidene-2-methyleneoxetanes.[5] These novel structures are prepared by treatment of β-lactones or α-alkylidene-β-lactones, respectively, with dimethyltitanocene (the Petasis reagent). Until recently, approaches to α-alkylidene-β-lactones have been limited in scope,[6−13] although a versatile preparation of (*Z*)-α-haloalkylidene-β-lactones via Pd-catalyzed cyclocarbonylations of propargyl alcohols was recently reported.[14] In a prior communication we reported an approach to α-alkylidene-β-lactones via Morita−Baylis−Hillman (MBH)-type adducts.[5] However, the approaches, such as hydroalumination of an alkyne, followed by in situ reaction with an aldehyde,[15] that provided access to methylene-substituted MBH adducts were not consistently high yielding or broadly applicable. Because α-methylene-β-lactones (as opposed to α-alkylidene-β-lactones) were easily prepared from readily accessible Baylis−Hillman adducts, we wondered if CM represented a viable route to functionalized α-alkylidene-β-lactones. There are few examples of either RCM[16] or CM[17−19] involving alkenes exocyclic to a ring. These limited examples involve structurally simple methylenecyclopentanes and cyclohexanes. Herein, we report the first CM reactions between Class I alkenes[2] and strained exocyclic enones.

Table 1. CM Reactions of α-Methylene-β-lactone **3**



entry	R[a]	yield (%)[b]	*Z*:*E*
a	$(CH_2)_2OAc$	84	>20:1
b	$(CH_2)_3OAc$	90	>20:1
c	$(CH_2)_4OAc$	85	14:1
d	$(CH_2)_8OAc$	84	>20:1
e	Ph	55[c]	>20:1
f	$(CH_2)_2CH_3$	94	11:1
g	$(CH_2)_2Br$	93	>20:1
h	CH_2Cl	80	12:1
i	$(CH_2)_2OTBDMS$	88	9:1
j	CH_2OR (see text)	NR	

[a] For experimental conditions see ref 20. Catalyst **1** was used for entries a−g and i; catalyst **2** was used for entry h. [b] All yields are isolated yields for the combined *Z*/*E*-diastereomers. [c] Isolated yield for *Z*-diastereomer only.

CM between α-methylene-β-lactone **3**[5] and simple, yet functionalized, terminal olefins was highly successful as shown in Table 1.[20] Excellent yields of α-alkylidene-β-lactones were obtained with high *Z*-selectivity in the presence of catalyst **1** in CH_2Cl_2 at 40−45 °C. A slight excess of the monosubstituted alkene was employed. Increasing the equivalents of this alkene had no effect on the outcomes of the reactions. Furthermore, allowing the monsubstituted alkene to dimerize first, followed by the addition of lactone **3**, did not alter the results. Increasing the concentration of the reactants (from 0.1 to 0.3−0.4 M) allowed for shorter reaction times (from >48 h to 12−24 h). Catalyst **1** was effective in all cases, except for allyl chloride (entry h); however, lactone **4h** was synthesized using catalyst **2**. Neither **1** nor **2** promoted the coupling of **3** with allyl alcohol or protected allyl alcohols (entry j, R = Bn, Ac, TBDMS, or TBDPS).

The predominant *Z*-stereochemistries of the products **4**, determined by NOESY studies on both major and minor diastereomers, were unexpected, since CM reactions of α,β-unsaturated carbonyl compounds, including 1,1-disubstituted enones, with simple alkenes usually proceed with high *E*-selectivity.[21] The selectivity seen with **1** may be due to steric effects from the $CHPh_2$ group at C4. The group is sufficiently large that it would be anticipated to both direct reaction with the ruthenium alkylidene to the opposite lactone face and to direct the terminal alkenyl substituent toward the carbonyl moiety.

To assess steric effects on stereochemical outcome, α-methylene-β-lactone **5**[5] was reacted with 1-pentene under the standard conditions developed with **3**. α-Alkylidene-β-lactone **6** was isolated in 76% overall yield with a *Z*:*E* ratio of 4.5:1. Although the diastereomeric ratio was lower than that seen with **4f**, the *Z*-selectivity was still substantial. Since

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(20) **General Cross-Metathesis Protocol.** The olefin cross partner (1.5 equiv) was added to a solution of lactone **3** (1 equiv) in CH_2Cl_2 (0.3−0.4 M in lactone). Catalyst **1** or **2** (0.03−0.05 equiv) was added to the solution, which was heated under N_2 at 40−45 °C for 12−24 h. The reaction was monitored by ^1H NMR. Upon consumption of **3** (0.05 equiv catalyst was added after 12 h if the reaction was not progressing), the solution was cooled and concentrated in vacuo, and the brown residue was purified by flash chromatography on silica gel.

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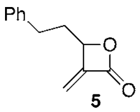
metathesis reactions are known to be reversible, we decided to see if this played a role in the stereochemical outcome of these reactions. The *E*-diastereomer of **4c** and 5-hexenyl acetate (1.5 equiv) in CH_2Cl_2 were heated in the presence of 5 mol % of catalyst **1**. No equilibration to *Z*-**4c** was observed after 24 h. More catalyst (5 mol %) was added, and again no substantial change was seen over the next 24 h. The solution was left heating for another 5 days, and based on ^{1}H NMR, a small amount of the *Z*-diastereomer was observed. Thus, although the reaction was reversible, it appears unlikely that equilibration played a role in the observed stereochemical outcome in the time frame of the reactions shown in the table.



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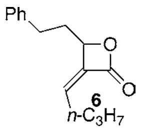

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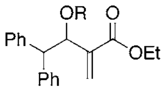
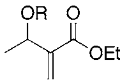
Since the stereochemical outcome of the reaction did not appear to be related to reversibility, we wondered what the diastereoselectivity of CM would be with our precursor MBH adducts, such as **7a**.[5] As mentioned above, previously reported CM reactions with 1,1-disubstituted enones proceeded with high *E*-selectivity. However, to our knowledge, the second substituent employed has been restricted to a methyl group. Thus, we speculated that the more highly substituted **7** might not exhibit the same diastereoselectivity.



7
a = H
b = Ac



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a = H
b = Ac

Unexpectedly, attempted reactions between 1-pentene and either **7a** or the corresponding acetate **7b** in the presence of catalyst **1** under the conditions used with substrate **3** did not give cross product, even with prolonged heating and the addition of more 1-pentene and catalyst. Postulating that steric factors might retard CM reactions of **7**, reactions between 1-pentene and commercially available **8a** or its acetylated analogue **8b** were attempted. The outcomes were the same; no crossed product was observed, even when catalyst loading was increased to 15 mol % with MBH adduct **8b**. Results were the same for the reaction of **8b** and 1-pentene in the presence of catalyst **2**. It is noteworthy that RCM reactions of MBH[22] and related[23] adducts have been reported under similar conditions. At the very least, the results with **7** and **8** suggest that further study on CM reactions of 1,1-disubstituted enones is warranted. The outcomes with **7** and **8** also make the results with **3** and **5** both more interesting and more significant. α-Methylene-*β*-lactones represent masked MBH adducts, since *β*-lactones can be readily hydrolyzed or transesterified. If MBH adducts do prove to be Class IV (non-participatory)[2] with respect to CM, reactions involving α-methylene-*β*-lactones could be used to access intermediates identical or functionally identical to those that would be obtained from CM reactions of MBH adducts.

In conclusion, the first examples of CM reactions of strained exocyclic enones has been described. CM reactions of α-methylene-*β*-lactone **3** proceeded with high efficiency and diastereoselectivity. These results are remarkable because of the strain inherent in the systems, because of the *Z*-selectivity of the reaction and because the ring-opened MBH precursors did not undergo CM under similar conditions. The outcomes further demonstrate the power of olefin CM reactions. Further studies to understand the diastereoselectivity of these reactions, to examine the range of compatible alkene partners, and to convert the CM products to 3-alkylidene-2-methyleneoxetanes are underway.

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Supporting Information Available: Experimental procedures and characterization data, as well as copies of high-resolution ^{1}H and ^{13}C NMR spectra for those new compounds for which elemental analyses are not reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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