

Efficient Ruthenium Carbenoid-Catalyzed Cross-Metathesis of Allyl Halides with Olefins

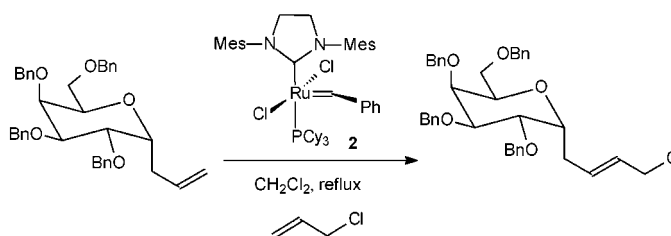
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ABSTRACT



Cross-metatheses of allyl halides and terminal olefins mediated by catalyst **2** are reported and showed good yield and excellent *E/Z* selectivity. The application of these compounds as alkylating reagents is also demonstrated.

Functionalized allyl halides are valuable synthetic synthons. They are widely used as N-, O-, S-, and C-alkylating reagents in organic synthesis and the chemistry industry.¹ However, the synthesis of these simple building blocks is not straightforward and may suffer from harsh conditions, long synthetic sequences, and low overall yields.² Thus, it is necessary to develop more efficient methods for their preparation.

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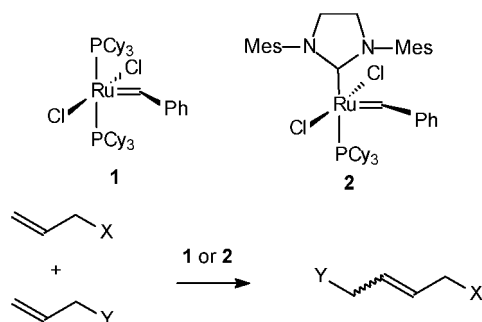
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The past decade has witnessed a great development in olefin metathesis. The discovery of ruthenium-carbene catalysts **1** and **2** has attracted a great deal of attention.³ In particular, catalyst **2**, with its high stability, broad functional group tolerance, and excellent stereoselectivity, has gained widespread application.⁴ Thus, one can readily foresee that cross-metathesis (Scheme 1) of allyl halides with alkenes would provide a promising method for the preparation of substituted allyl halides, which could serve as a handle for further functionalization. So far, only a few examples of cross-metathesis involving allyl halides have

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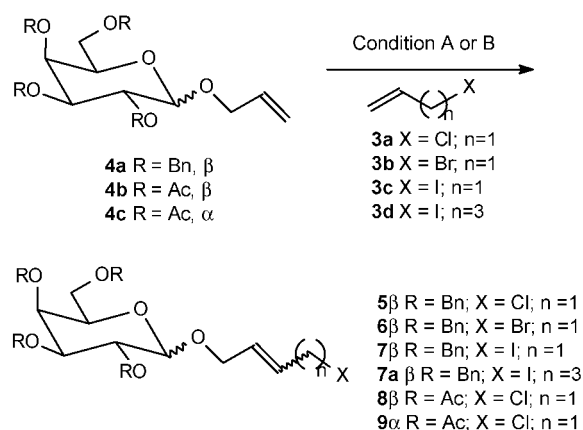
Scheme 1



been reported.^{4d,5} Unfortunately, the reactions using catalyst **1**⁵ could not be reproduced in our hands. Herein we report catalyst **2**-mediated efficient cross-metathesis reactions of olefin-containing sugars, unnatural amino acids, and precursors thereof.

It has been widely reported that catalyst **2** has demonstrated much higher *E/Z* selectivity compared to **1**. To investigate the suitability of catalyst **2** for cross-metathesis of allyl halides, the known perbenzylated *O*-allyl galactopyranoside **4a**^{6,7} was subjected to reaction with different allyl halides under varying conditions (Scheme 2). First, the cross-

Scheme 2



metathesis of **4a** with allyl chloride in CH₂Cl₂ was performed under N₂ at reflux for 6 h to give compound **5** in 75% yield (Table 1) with a greater than 20:1 *E/Z* ratio. Since the NMR signals for the vinyl protons were obscured, the *E/Z* identity was determined on the basis of ¹³C NMR. For the *E* isomer, the allylic chloride-substituted carbon appeared at around δ 44 ppm, while the *Z* isomer appeared upfield by about 5 ppm (δ 38 ppm) due to the γ effect.^{3d,8} From the IR spectrum,

Table 1. Results of Cross-Metathesis of Allyl Halides with Terminal Alkenes

entry	olefin	allyl halide	conditions ^a	product	yield (<i>E/Z</i>)
1	4a	3a	B	5	75% (>20:1)
2	4a	3b	B	6	56% (>20:1)
3	4a	3c	B	7	25% (ND) ^b
4	4a	3a	A	5	51% (4:1)
5	4a	3b	A	6	20% (4:1) ^b
6	4a	3d	A	7a	64% (~5:1) ^{b,c}
7	4b	3a	B	8	65% (17:1)
8	4c	3a	B	9	55% (15:1)
9	4d	3a	B	10	72% (>20:1)

^a Method A: N₂, CH₂Cl₂, 20 mol % **1**, reflux, 6 h. Method B: N₂, CH₂Cl₂, 10 mol % **2**, reflux, 6 h. ^b Yields estimated on the basis of ¹H NMR data of crude reaction mixtures. ^c Prepared from 5-iodo-1-pentene.

the *E* isomer showed a medium to strong absorption band at 968 cm⁻¹ and the *Z* isomer did not show absorption in this range.^{2b} The yields from allyl chloride to allyl iodide decreased dramatically (entries 1–5), presumably due to the increased coordinating ability of iodide toward ruthenium or else by oxidative insertion.

This chelating effect was also hypothesized by Grubbs et al.^{4a} with neighboring carbonyl groups. However, catalyst **2** greatly dampened this chelating effect with improved yield and *E/Z* selectivity compared to catalyst **1**. Interestingly, when the iodide positioning was moved away, such as in entry 6 with 5-iodo-1-pentene, cross-metathesis provided **7a** in 64% yield even when catalyst **1** was used. Attempts to vary the reaction conditions with allyl iodide **3c** provided no improvement in the reaction yields (<10%) when the catalysts were added in portions or the reactions run at room temperature.

Cross-metathesis of galactosides **4b**,⁷ **4c**,⁹ and **4d**¹⁰ (Table 1) gave similar yields and stereoselectivities. These results indicated that the nature of the sugar protecting groups together with the anomeric configurations did not play a significant role in terms of stereo and electronic effects. In all the cases using catalyst **2**, less than 5% of homodimers were observed that could be recycled if desired.

It is worth mentioning that C-linked galactoside **10**, obtained from cross-metathesis of **4d** and allyl chloride, is a very useful alkylating agent that could not be prepared easily through other routes. Presently, C-linked glycosides have gained tremendous attention because of their biological stability. Thus **10** can easily be further functionalized to other C-linked glycomimetics.¹¹

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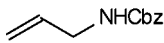
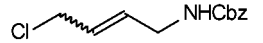
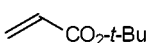
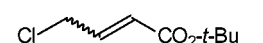
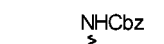

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Table 2. Cross-Metathesis with Allyl Chloride (**3a**)^a

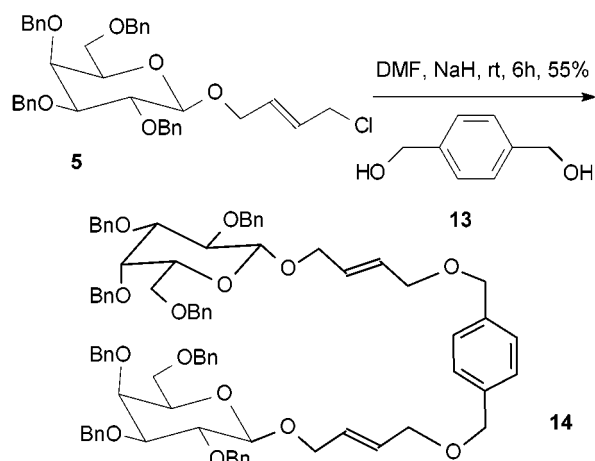
olefin	product	yield (<i>E/Z</i>)
 11a	 12a	65% (>20:1)
 11b	 12b	67% (>20:1)
 11c	 12c	70% (>20:1)

^a Conditions: 10 mol % **2**, CH₂Cl₂, N₂, reflux, 6 h.

To further investigate the scope of this procedure, three noncarbohydrate substrates were chosen for this purpose (Table 2). Under the above conditions with catalyst **2**, compound **11a** reacted with allyl chloride to generate product **12a** in good yield and with excellent stereoselectivity. The second entry is an interesting one, since both the electron-deficient *tert*-butyl acrylate (**11b**) and allyl chloride (**3a**) were poor reacting partners toward catalyst **1**. However, with catalyst **2**, the reaction provided a reasonable yield and remarkable stereoselectivity with the *trans* isomer being the only detectable stereoisomer observed. Compound **12c**, a cross-metathesis product from allyl chloride and allylglycine, is an interesting compound, which can be further functionalized for the synthesis of peptidomimetics.

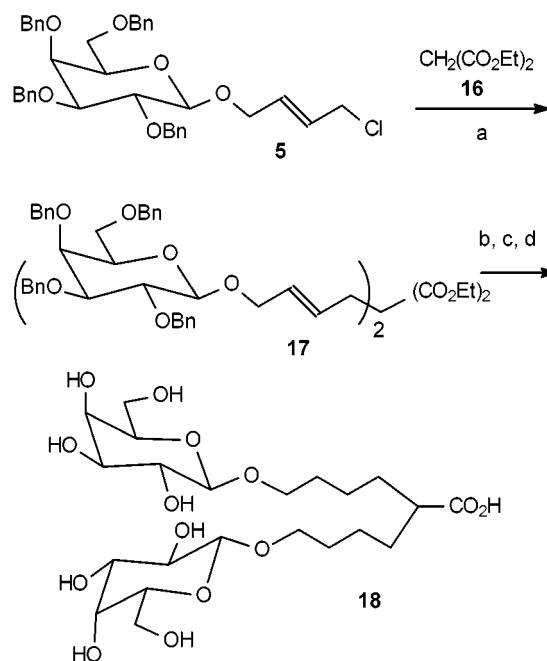
To provide an application of these allyl halides, compound **5** was selected for O-alkylation (Scheme 4). In this case, 1,4-dihydroxymethyl benzene **13** was treated with NaH in DMF and then reacted with **5** to provide **14** in 55% yield at room temperature.

In the second case, the C-alkylating utility of **5** was tested (Scheme 5). After treatment with NaH in dry THF, diethyl malonate **16** reacted smoothly with **5** to provide the double-alkylated malonate ester **17** in an excellent yield at room

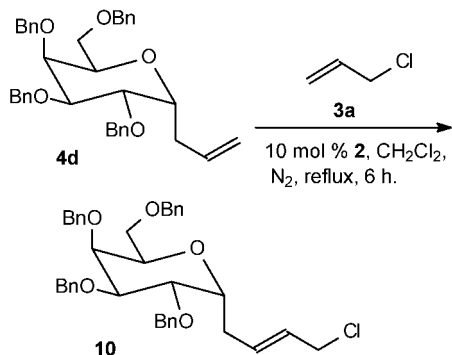
Scheme 4

temperature. The monodecarboxylation of **17** proved to be problematic. Due to the presence of the carbohydrate moiety, common procedures involving DMSO at high temperatures failed.^{12,13} Eventually, ester **17** was hydrolyzed first by refluxing in 2 M KOH/MeOH for 1 day and then decarboxylated in acetonitrile.¹⁴ Interestingly, the acetonitrile had to be degassed and the catalyst CuCl could not be used in more than 25 mol %.¹⁵ Finally, hydrogenolysis provided **18** in a good yield. This fully deprotected **18** can be a useful building block for the synthesis of high-order glycodendrimers.¹⁶

In conclusion, cross-metathesis of allyl halides and mono-substituted olefins mediated by catalyst **2** has been studied

Scheme 5^a

^a Conditions: (a) THF, NaH, rt, 4 h, 90%; (b) 2 M KOH, MeOH, reflux, 1 day, N₂, 85%; (c) 20 mol % CuCl, 24 h, CH₃CN, N₂, 82%; (d) 10% Pd-C, ethanol, 24 h, 95%.

Scheme 3

and was shown to occur in moderate to good yields and with excellent *E/Z* selectivity. The utility of these compounds has also been explored.

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Supporting Information Available: Experimental procedures with spectroscopic data for compounds **5–7a**, **8–10**, **12a–c**, **14**, **17**, and **18**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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