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

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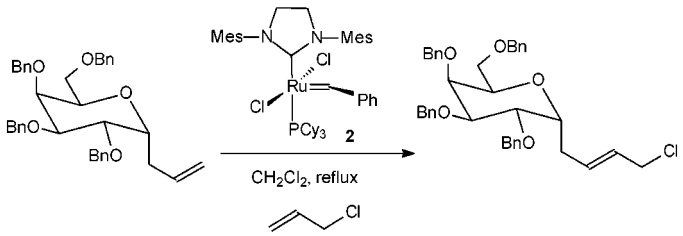
ABSTRACT



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.

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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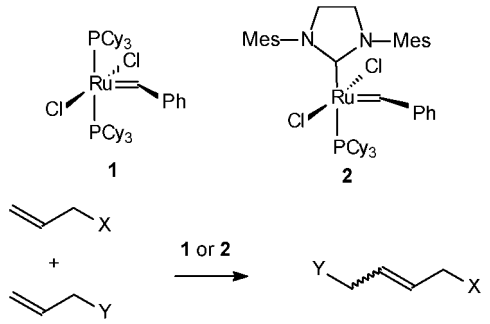
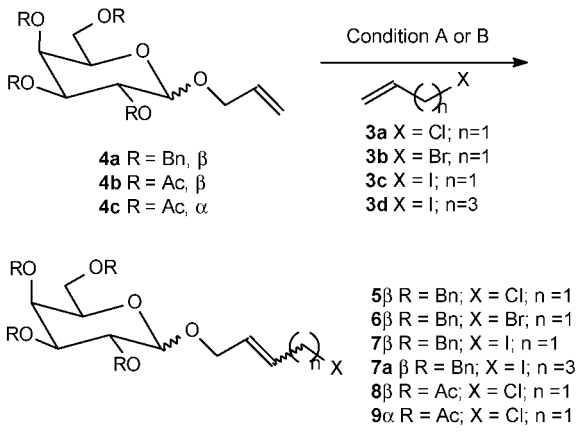
Scheme 1



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 CH_2Cl_2 was performed under N_2 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 ^{13}C 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 (*E/Z*)
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: N_2, CH_2Cl_2, 20 mol % **1**, reflux, 6 h. Method B: N_2, CH_2Cl_2, 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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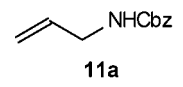
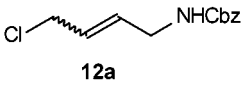
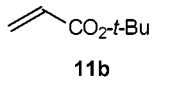
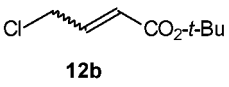
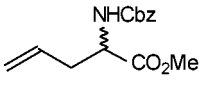
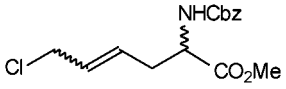
Table 2. Cross-Metathesis with Allyl Chloride (**3a**)[a]

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

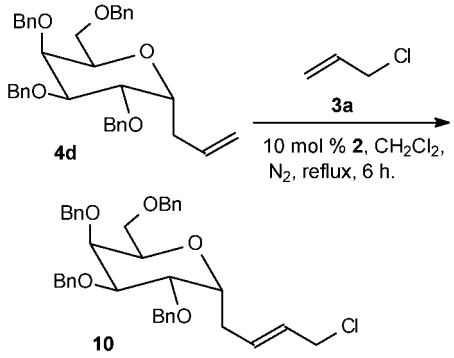
[a] Conditions: 10 mol % **2**, CH_2Cl_2, N_2, reflux, 6 h.

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.

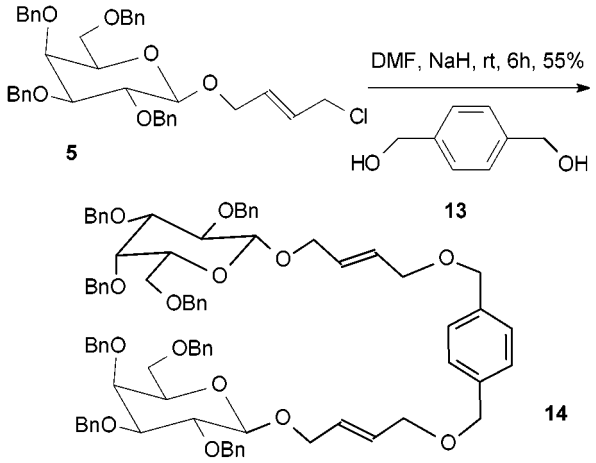
To provide an application of these allyl halides, compound **5** was selected for O-alkylation (Scheme 4). In this case, 1,4-dihydroxymethyl benzene **13** was treated with NaH in DMF and then reacted with **5** to provide **14** in 55% yield at room temperature.

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 3



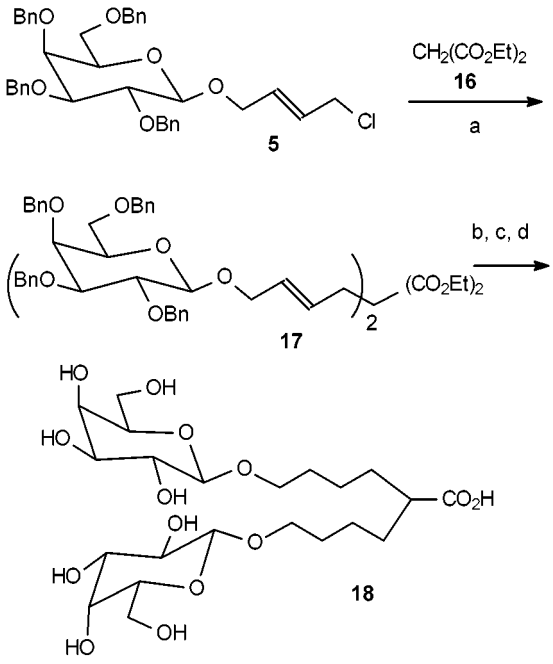
Scheme 4



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 monosubstituted 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, N_2, 85%; (c) 20 mol % CuCl, 24 h, CH_3CN, N_2, 82%; (d) 10% Pd−C, ethanol, 24 h, 95%.

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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