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CROSS-METATHESIS REACTION OF 1-ALLYLATED ß-CARBOLINE AND ISOQUINOLINE DERIVATIVES

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Abstract - *N*-Protected 1-allyl-1,2,3,4-tetrahydro-ß-carboline and 1-allyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline were subjected to the cross-metathesis reaction with functionalized olefins using second-generation Grubbs catalyst. The products were obtained in moderate to good yield with high (*E*)-selectivity.

Olefin metathesis reaction has become one of the most powerful tools for the synthesis of complex organic molecules.[1] While most widely used reaction is ring closing metathesis, cross-metathesis (CM) has come to attract increasing attention since a more active and stable second-generation catalyst (**1**) was developed.[2] CM reaction has provided new methodology for simple olefins to transform to functionalized olefins. Although CM reaction has been applied to the synthesis of natural products,[2e, 3] its application to the synthesis of alkaloids has not yet been much explored.[4] We have been investigating the method for the synthesis of chiral 1-substituted ß-carboline[5] and isoquinoline[6] derivatives and showed that the compounds are useful precursors for the synthesis of indole[7] and isoquinoline[8] alkaloids. Although we have already applied the functionality of allyl groups of 1-allylated ß-carboline and isoquinoline to synthesize some indole alkaloids[7] and a pyrrolidinoisoquinoline,[8b] more widely applicable transformation of allyl group is required to obtain various kinds of alkaloids. Thus, we have investigated the CM reaction of allylated ß-carboline and isoquinoline to obtain further functionalized olefins which were used for the transformation to indole and isoquinoline alkaloids. In this paper we report these results.

We first attempted the CM reaction of 1-allyltetrahydro-ß-carboline (**2**) which was considered to be a potential precursor to synthesize indole alkaloids and was easily prepared from 3,4-dihydro-ß-carboline[9] by addition reaction of allylmagnesium bromide followed by protection of nitrogen at 2 position.

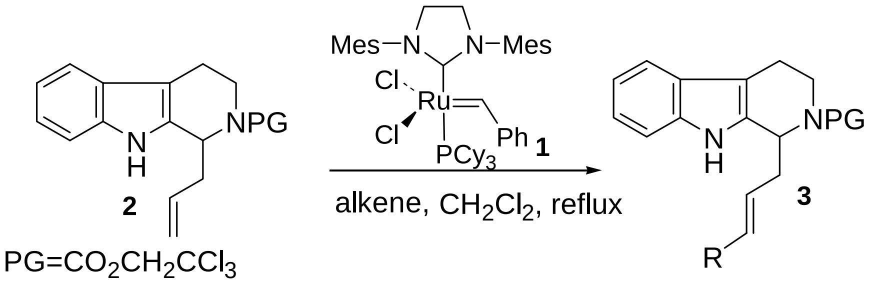
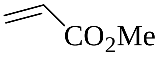
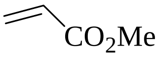
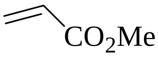
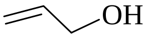
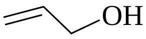
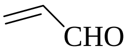
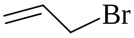
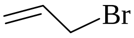
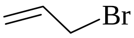


Table 1 Cross-metathesis Reaction of **2** with Functionalized Olefins

entry	alkene	catalyst (mol%)	time (h)	R	yield (%)
1	 (5 equiv.)	5	6	CO_2Me	94
2	 (5 equiv.)	3	6	CO_2Me	91
3	 (1 equiv.)	3	6	CO_2Me	81
4	 (5 equiv.)	10	8	CH_2OH	74
5	 (5 equiv.)	5	9	CH_2OH	41
6	 (5 equiv.)	10	6	CHO	44
7	 (5 equiv.)	5	1	CH_2Br	93
8	 (5 equiv.)	3	1	CH_2Br	75
9	 (1 equiv.)	3	2	CH_2Br	75

The CM reactions of **2** with some functionalized olefins were performed under Ar in CH_2Cl_2 at the reflux temperature (Table 1). Only the (*E*)-stereo isomer was obtained in all reactions and (*Z*)-isomer was not detected by NMR spectrum. The reaction with methyl acrylate proceeded in high yield even when 3 mol% of catalyst was used, but the yield slightly decreased by the use of one equivalent of methyl acrylate. In the reaction of allyl alcohol or acrolein, a moderate yield of the product was obtained accompanied by the recovery of the starting material. When allyl alcohol was employed, 10 mol% of catalyst (**1**) was required to proceed the reaction in good yield. Allyl alcohol was thought to inactivate the catalyst (**1**) by coordination. Allyl bromide was found to react rapidly to give the CM product in high yield. The products *via* the CM reaction with acrylate, acrolein and allyl alcohol would be of use for intermediates toward the synthesis of corynantheoid[10] and heteroyohimboid[11] alkaloids. Next, we investigated the CM reaction of 1-allyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**4**) which was considered to be a useful precursor for the synthesis of isoqunoline alkaloids. The substrate (**4**) was easily prepared from the reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline[12]with allylmagnesium bromide followed by protection of nitrogen. The results of the CM reaction of **4** with some functionalized olefins were shown in Table 2. The reaction with acrylate proceeded in the presence of 3 mol% of the catalyst to give the corresponding product in high yield with high (*E*)-olefin selectivity. Less bulkiness of tetrahydroisoquinoline nucleus than tetrahydro-ß-carboline nucleus was considered to give the result that (*Z*)-isomer was slightly produced. (*E*)-Olefin was obtained more selectively when ethyl acrylate was employed instead of methyl acrylate. Although the yield slightly decreased by the use of one equivalent

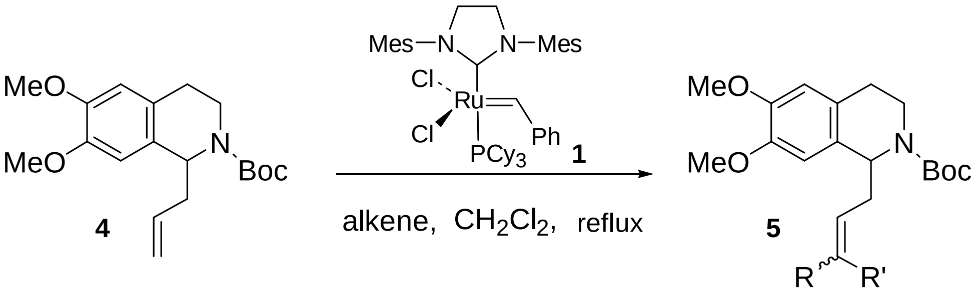
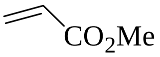
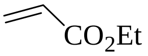
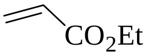
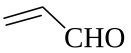
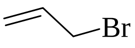
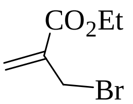


Table 2 Cross-metathesis Reaction of **4** with Functionalized Olefins

entry	alkene	catalyst (mol%)	time (h)	R	R’	yield (%)	*E*:*Z*
1	 CO$_2$Me (5 equiv.)	3	1	CO$_2$Me	H	87	12:1
2	 CO$_2$Et (5 equiv.)	3	4	CO$_2$Et	H	92	20:1
3	 CO$_2$Et (1 equiv.)	3	5	CO$_2$Et	H	82	a)
4	 CHO (5 equiv.)	5	26.5	CHO	H	65	a)
5	 Br (5 equiv.)	5	2	CH$_2$Br	H	80	a)
6	 CO$_2$Et * Br (5 equiv.)	10	4.5	CO$_2$Et	CH$_2$Br	27	b)

*The reaction was run in benzene at the reflux temperature.
a) Only the (*E*)-isomer was obtained.
b) Only one geometrical isomer was obtained. The geometry was not determined.

of ethyl acrylate, a (*E*)-product was exclusively obtained. In the case of the reaction using acrolein, the yield was slightly low with the recovery of the starting material. It was found that cross-metathesis reaction with ethyl 2-bromomethylacrylate proceeded to generate the trisubstituted multifunctional olefin (entry 6). The product obtained from the reaction with acrylate and/or acrolein is considered to be an intermediate for the synthesis of emetine.[13]

In conclusion, allyl groups which were sited at a 1-position of 1,2,3,4-tetrahydro-ß-carboline and 1,2,3,4-tetrahydro-5,6-dimethoxyisoquinoline were found to react with functionalized olefin to give the CM products in moderate to good yield with high (*E*)-olefin selectivity. We are now investigating the synthesis of some alkaloids employing CM products obtained from an optically active **2** or **4**. These results will be reported in due course.

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