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Cross-metathesis of allyl halides with olefins bearing an α-alkoxy amide group ☆

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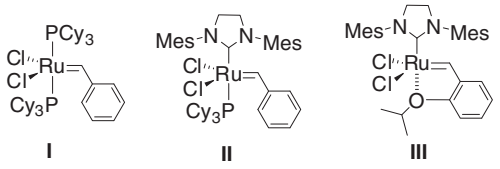
ABSTRACT

We have examined whether the allyl halide cross-metathesis reaction tolerates α-alkoxy amide groups. Ruthenium-based catalysts **I**–**III** did not catalyze the cross-metathesis of allyl halides in the presence of an α-alkoxy *N*,*N*-dimethylamide group to any appreciable extent, but the reaction could tolerate either a bulky *N*,*N*-diisopropylamide or Weinreb amide group. In particular, the Grubbs–Hoveyda–Blechert 2nd generation catalyst (**III**) efficiently catalyzed the cross-metathesis of allyl halides with olefins bearing a Weinreb amide group.

A great deal of progress in olefin cross-metathesis (CM) has been achieved over the last decade. Many organic chemists have utilized CM in their syntheses[1] following the emergence of ruthenium-based catalysts, such as the Grubbs catalyst (**I**),[2] Grubbs 2nd generation catalyst (**II**)[3] and Grubbs–Hoveyda–Blechert 2nd generation catalyst (**III**).[4] These catalysts are highly active, relatively stable, and tolerant of a variety of organic functional groups (Fig. 1).

In natural product syntheses, an allyl halide moiety is frequently incorporated by building onto an existing aldehyde group via an olefination–reduction–halogenation sequence,[5] while the CM of an allyl halide offers a synthetic shortcut that can substitute for several functional group transformations in the sequence. Ruthenium-based catalysts **I**–**III** have been used in a number of cases over the past decade to promote the CM of allyl halides for the synthesis of functionalized allyl halides.[6–14] The reaction tolerates a variety of functional groups including ester, cyanide, benzyl ether, silyl ether, and the hydroxyl group. The CM of allyl halides has also been employed successfully in the syntheses of several natural products. For example, Hong and co-workers developed an elegant tandem allyl halide CM/S_N2' reaction methodology for the construction of *O*-heterocycles, and applied this tandem reaction in the syntheses of subglutinol B[15] and (±)-diospongin A.[16] Ghosh and Xu synthesized a segment of (−)-spongidepsin utilizing the CM of allyl chloride.[17] Frequently, α-alkoxy amide groups are used in natural product synthesis due to their strong chelation of



I II III

Figure 1. Grubbs catalyst (**I**), Grubbs 2nd generation catalyst (**II**) and Grubbs–Hoveyda–Blechert 2nd generation catalyst (**III**).

metal cations, such as Li^+, Na^+, Mg^{2+}, and K^+,[18] but no reports have yet appeared that address whether the CM of allyl halides can tolerate an α-alkoxy amide. We now describe our successful use of allyl halide CM to synthesize functionalized allyl halides that bear an α-alkoxy amide group.

Our initial attempt to determine whether the CM of allyl halides would tolerate such a group involved the preparation of α-alkoxy amide **6b** by the S_N2 reaction of pentenol **3** with chloroacetamide **1** (Scheme 1).[19] The CM of allyl chloride with α-alkoxy *N*,*N*-dimethylamide **6b** was carried out in the presence of ruthenium complexes **I**–**III**. Contrary to our expectation, this reaction with amide **6b** did not afford allyl halides **11a**–**b**, and most of the starting material was recovered (Table 1, entry 1). We considered that the *N*,*N*-dimethylamide group of **6b** could act as a ligand for catalysts **I**–**III**,[20] and reasoned that bulky alkyl substituents or electron-withdrawing groups might hinder any disfavorable interactions with **I**–**III**. Williamson ether synthesis of pentenol **3** with chloroacetamide **7** and the coupling of acid **9b** with *N*-methoxy-*N*-methylamine yielded amides **8** and **10b**, respectively. Although

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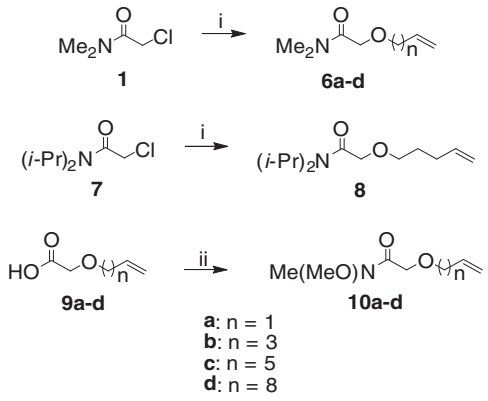


Scheme 1. Reagent and conditions: (i) NaH, THF, prop-2-en-1-ol (**2**)/pent-4-en-1-ol (**3**)/hept-5-en-1-ol (**4**)/dec-9-en-1-ol (**5**), rt, overnight, 63-94%; (ii) Me(MeO)NH, hydroxybenzotriazole (HOBt), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), Et_3N, CH_2Cl_2, rt, overnight, 78–90%.

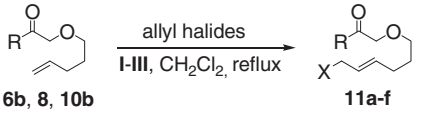
conversion was incomplete, the CM of allyl halides with bulky *N*,*N*-diisopropylamide **8** generated allyl halides **11c–d** in the presence of catalyst **III** in 53% and 44% yields, respectively (50–60% conversion, Table 1, entries 4 and 5).

We then turned our attention to the CM of allyl halides with Weinreb amide **10b**. To our delight, amide **10b** was converted completely to allyl halides **11e–f** by the CM of allyl halides promoted by catalyst **III**, in 69% and 90% yields, respectively (Table 1, entries 11 and 12). These results strongly indicated that the *N*,*N*-dimethylamide group of **6b** is responsible for the putative inactivation of ruthenium complexes **I–III**. In contrast to catalyst **III**, Grubbs catalyst (**I**) or Grubbs 2nd generation catalyst (**II**) did not catalyze the CM of allyl halides with Weinreb amide **10b** to any appreciable extent (Table 1, entry 6).[21]

We next sought to investigate the effect of the distance between the amide group and terminal olefin moiety on the success of CM of allyl halides catalyzed by **III**. Williamson ether synthesis of alcohols **2**, **4,** and **5** with chloroacetamide **1** led to the formation of the corresponding *N*,*N*-dimethylamides **6a**,**c–d**. Readily available carboxylic acids **9a**,**c–d**[22] were transformed into **10a**,**c–d** by coupling with *N*-methoxy-*N*-methylamine (Scheme 1). The CM of allyl halides with *N*,*N*-dimethylamides **6a**,**c–d** furnished no **12a–c**, but the Weinreb amides **10a**,**c–d** underwent smooth CM to produce **12d–i** in good yields, with little effect due to the distance between the amide group and the terminal olefin moiety (Table 2). Interestingly, the *E*/*Z* selectivity of the reactions with α-allyloxyamide **10a** was superior to that obtained in the reactions with **10b–d** (16–20:1 vs 6:1, Table 2, entries 2 and 3). The results further substantiate our hypothesis that an *N*,*N*-dimethylamide group impedes the CM of allyl halides catalyzed by **I–III**.

In summary, we have prepared functionalized allyl halides that possess an α-alkoxy amide group by the CM of allyl halides catalyzed by the Grubbs–Hoveyda–Blechert 2nd generation catalyst (**III**) in good yield with good *E*/*Z* selectivity. The findings from this investigation indicate that ruthenium complexes **I–III** do not tolerate olefins that bear an *N*,*N*-dimethylamide group. This problem

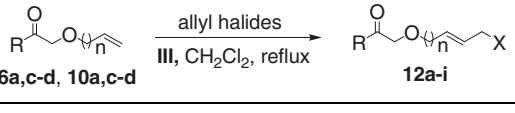
Table 1
Cross-metathesis of allyl halides in the presence of substituted amides



Entry	Compound #	R	X	Conditions	Yield (%)	Ratio *E*:*Z*[a]
1	**6b**	NMe_2	Cl, or Br	**I**, **II** or **III** (10 mol %), 24 h	**11a-b**, N[b]	
2	**8**	N(*i*-Pr)$_2$	Cl	**I** (10 mol %), 24 h	**11c**, 8	3:1
3	**8**	N(*i*-Pr)$_2$	Cl	**II** (10 mol %), 24 h	**11c**, 10	7:1
4	**8**	N(*i*-Pr)$_2$	Cl	**III** (20 mol %),[c] 4 h	**11c**, 53	8:1
5	**8**	N(*i*-Pr)$_2$	Br	**III** (20 mol %),[c] 4 h	**11d**, 44	5:1
6	**10b**	N(OMe)Me	Cl	**I** or **II** (10 mol %), 3 h	**11e**, N[b]	
7	**10b**	N(OMe)Me	Cl	**III** (20 mol %),[c] 5 h	**11e**, 69	9:1
8	**10b**	N(OMe)Me	Br	**III** (10 mol %), 2 h	**11f**, 90	7:1

[a] The ratio was determined by the analysis of ^{1}H 500 MHz NMR spectra.
[b] No product formation was detected and most of the starting material was recovered.
[c] Total 20 mol % (time 0, 10 mol %; time 2 h, 10 mol %) of **III** was used to complete the reaction.

Table 2
Effect of the distance between an amide group and olefin moiety on the cross-metathesis of allyl halides



Entry	Compound #	R	X	Conditions	Yield (%)	Ratio *E*:*Z*[a]
1	**6a**,**c** or **d** (*n* = 1, 5, or 8)	NMe_2	Cl	10 mol %, 24 h	**12a–c**, N[b]	
2	**10a**, *n* = 1	N(OMe)Me	Cl	20 mol %,[c] 3 h	**12d**, 74	20:1
3	**10a**, *n* = 1	N(OMe)Me	Br	10 mol %, 3 h	**12e**, 65	16:1
4	**10c**, *n* = 5	N(OMe)Me	Cl	20 mol %,[c] 3 h	**12f**, 97	6:1
5	**10c**, *n* = 5	N(OMe)Me	Br	10 mol %, 2 h	**12g**, 89	6:1
6	**10d**, *n* = 8	N(OMe)Me	Cl	20 mol %,[c] 2 h	**12h**, 95	6:1
7	**10d**, *n* = 8	N(OMe)Me	Br	10 mol %, 2 h	**12i**, 88	6:1

[a] The ratio was determined by the analysis of ^{1}H 500 MHz NMR spectra.
[b] No product formation was detected and most of the starting material was recovered.
[c] Total 20 mol % (time 0, 10 mol %; time 2 h, 10 mol %) of **III** was used to complete the reaction.

was readily remedied by *N*,*N*-diisopropylamide or a Weinreb amide group. In particular, the Grubbs–Hoveyda–Blechert 2nd generation catalyst (**III**) efficiently catalyzed the CM of allyl halides with olefins bearing a Weinreb amide group, and the results appeared largely independent of the distance between the amide group and the terminal alkene moiety.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.043.

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21. Our preliminary study revealed that ruthenium-based catalysts **I**–**III** likewise did not catalyze the CM of allyl halides with the *N*,*N*-dimethyl 5-heptenamide, but the Grubbs–Hoveyda–Blechert 2nd generation catalyst (**III**) did efficiently catalyze the CM of allyl halides with *N*-methoxy-*N*-methyl 5-heptenamide.
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