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A New Method for Cross-Metathesis of Terminal Olefins

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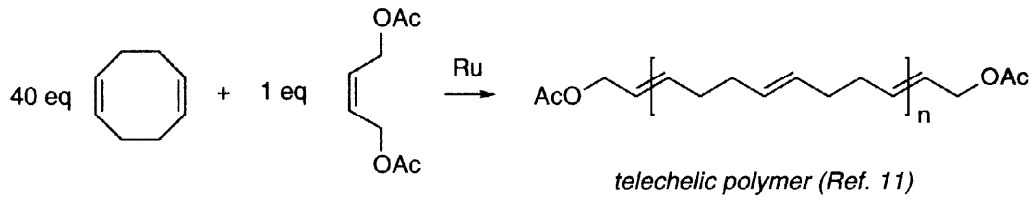
Abstract: A new method for the cross-metathesis of terminal olefins is described. Treatment of terminal olefins with 1-2 equivalents of a symmetric disubstituted *cis* or *trans* olefin and 5 mol% $Cl_2(PCy_3)_2Ru{=}CHPh$ (**1**) in dichloromethane generates the desired cross-metathesis products in good yield.

The recent development of well-defined ruthenium and molybdenum metathesis catalysts has generated renewed interest in methods for the selective cross-metathesis of terminal olefins.[2] Crowe *et al.* have demonstrated that π-substituted terminal olefins such as styrene[3] and acrylonitrile[4] can be used to efficiently functionalize terminal olefins. Crowe has also reported a useful terminal olefin cross-coupling procedure utilizing nucleophilic species such as allyltrimethylsilane.[5] Recently, Blechert *et al.* have shown that certain sterically hindered terminal olefins do not undergo self-metathesis and can be functionalized with a number of commercially available terminal olefins using the Ru and Mo catalysts.[6] The homologation of homoallylglycine derivatives has been reported by Gibson *et al.*[7] Finally, both crossed yne-ene[8] and ring-opening cross-metathesis reactions using Ru and Mo catalysis have been demonstrated.[9,10]

Outlined herein is a new method for the selective cross-metathesis of unhindered alkyl-substituted olefins. This approach was inspired by the synthesis of telechelic polymers[11] *via* ring-opening polymerization/cross metathesis as shown in Scheme 1.



Scheme 1

To probe the viability of this approach for applications in organic synthesis, we have explored the homologation of unhindered terminal alkenes using cross-metathesis with disubstituted internal olefins. Treatment of a terminal olefin such as 9-decen-1-yl benzoate (**2a**) with 1-2 equivalents of a symmetric internal olefin and 5 mol% ruthenium benzylidene **1** in refluxing dichloromethane provides the desired cross-metathesis products in good yields (Table 1). The reactions proceed largely to completion and the starting material homodimer can be easily recovered and recycled in a subsequent cross-metathesis step. In the cases examined thus far, the reaction

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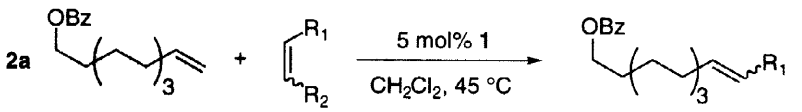
has favored the formation of the *trans* olefin isomer. Higher *trans* selectivity was observed with *cis*-1,4-butenediol derivatives bearing bulky protecting groups.

Our initial efforts focused upon elaborating terminal olefins to the corresponding allylic alcohol derivatives. The commercially available *cis*-2-butene-1,4-diol diacetate[12] (entry 1) provided the homologated allylic acetate in excellent yield (89%, 4.7:1 *E/Z*) using two equivalents of internal olefin in refluxing dichloromethane.[13] When only one equivalent of diacetate was used, the yield decreased (77%) and no significant change in the *trans:cis* ratio was observed (entry 2). The use of two equivalents of diacetate was found to be more efficient than simply using one, two, or four equivalents of allyl acetate (entries 3-5).[14] Employing the diol acetate as solvent (55 equiv., 45 °C, 12 hr) increased the isolated yield to 91%, although with diminished *trans* olefin content (3:1 *E/Z*).[15]

Table 1. Cross Metathesis Reactions

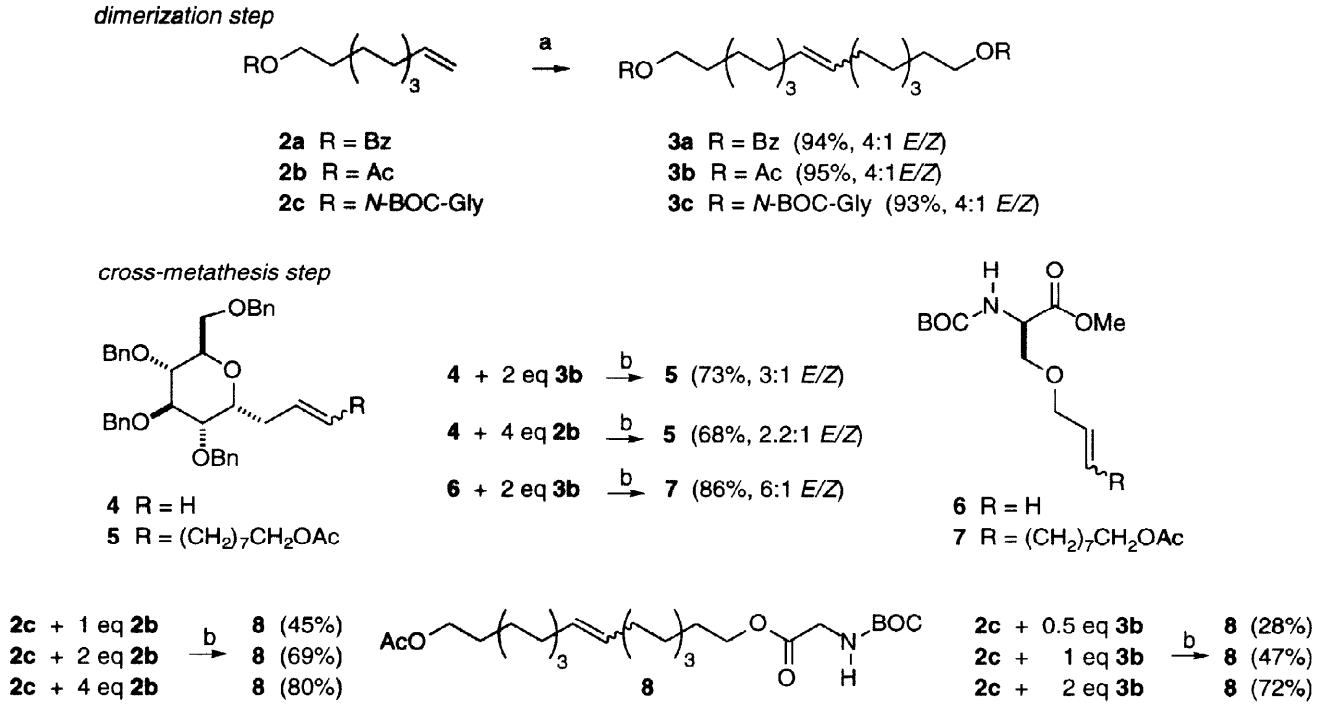


entry	substrate	equiv.	product (%)[a]	*E/Z*[b]
1	$R_1 = R_2 = CH_2OAc$ (*cis*)	2	89	4.7:1
2	$R_1 = R_2 = CH_2OAc$ (*cis*)	1	77	5:1
3	$R_1 = CH_2OAc$, $R_2 = H$	4	81	3:1
4	$R_1 = CH_2OAc$, $R_2 = H$	2	80	4:1
5	$R_1 = CH_2OAc$, $R_2 = H$	1	59	5.7:1
6	$R_1 = R_2 = CH_2OTBS$ (*cis*)	2	77[c]	10:1
7	$R_1 = R_2 = CH_2OtBu$ (*cis*)	2	90	7:1
8	$R_1 = R_2 = CH_2OCH_2Ph$ (*cis*)	2	71[d]	9:1
9	$R_1 = R_2 = CH_2NHBoc$ (*cis*)	4	71	3:1
10	$R_1 = R_2 = CH_2C(O)OMe$ (*trans*)	2	74	3.3:1

[a]Isolated product yields. [b]Determined by ^1H NMR integration. [c]Yield determined after TBAF deprotection of TBS ether. [d]Yield determined after H_2/Pd-C hydrogenation-hydrogenolysis of allyl benzyl ether.

Several ether derivatives of *cis*-1,4-butenediol (entries 6-8) were found to provide good cross-metathesis yields and improved *trans* selectivity. The compatability of nitrogen-containing substrates was probed through the cross-metathesis of BOC-protected *cis*-1,4-diaminobutene (entry 9), which provides a direct route to protected allylic amines. *Trans* disubstituted internal olefins were also found to be reactive. Namely, dimethyl *trans*-3-hexene-1,6-dioate (entry 10) provided the desired homoallylic ester cross product as the major product (74%, 3:1 *E/Z*; recovered homodimer **3a**: 23%).

These initial results demonstrated that *cis* or *trans* disubstituted olefins could be used as efficient coupling partners in cross-metathesis reactions. Accordingly, we have investigated the use of a two-step procedure[16] for terminal olefin cross-metathesis. Several examples are illustrated in Scheme 2.



Scheme 2. Reagents and Conditions: (a) 0.3 mol% **1** / RT / 100 mTorr; (b) Ref. 13.

Dimerization of neat substrates (**2a-c**) with 0.3 mol% **1** *in vacuo* has provided mostly *trans* (4:1) disubstituted olefins in high yield. Homodimer **3b** was subsequently used to functionalize 2,3,4,6-tetra-*O*-benzyl-1-α-*C*-allylglucoside[17] (**4**) in 73% yield (3:1 *E/Z*, recovered homodimer of **4**: 19%). By comparison, the synthesis of **5** using four equivalents of terminal olefin **2b** resulted in a marginally lower yield with slightly lower *trans* selectivity (68%, 2.2:1 *E/Z*). Olefin **3b** was also used to successfully transform *N*-BOC-Serine-(*O*-Allyl)-OMe[18] (**6**) into lipophilic amino acid **7** in excellent yield and improved *trans* selectivity (86%, 6:1 *E/Z*). Cross coupling reactions using 9-decen-1-yl *N*-BOC glycinate (**2c**) and various equivalents of 9-decen-1-yl acetate (**2b**) or the internal olefin homodimer **3b** demonstrate an advantage to adjusting the stoichiometry of a terminal olefin component in cross-metathesis reactions involving two isolated terminal olefins (Scheme 2).

In conclusion, cross-metathesis reactions involving internal disubstituted olefins appear to be a promising method for the homologation of terminal olefins. The method should be of particular use for the functionalization of advanced intermediates in multistep syntheses and for the construction of heterodimeric molecules for research in molecular biology.[19] A full description of this method, including applications to polymer-supported substrates, will be the topic of a forthcoming publication.[20]

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12. Used as delivered from TCI America.
13. **General Procedure for Solution-Phase Cross-Metathesis Reactions.** An oven-dried flask is charged with a magnetic stir bar and ruthenium benzylidene **1** (21 mg, 5 mol%) and capped with a septum under nitrogen atmosphere. CH_2Cl_2 (5 ml) and the disubstituted olefin (1.0 mmol, 2 equiv) are added in succession. The terminal olefin (0.5 mmol, 1 equiv) is added and the septum is quickly replaced with a condenser which is connected to a nitrogen bubbler. The flask is immersed in an oil bath and refluxed (bath temperature: 45 °C) for a period of 12 hr or until the reaction is judged complete by TLC.
14. The use of disubstituted olefins in cross-metathesis reactions minimizes the formation of a methylidene species ($L_4Ru{=}CH_2$) which is a less stable catalyst relative to substituted congeners (i.e. $L_4Ru{=}CHR$). See: Schwab, P. E.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110, and Ullman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484-2489.
15. In contrast, the use of neat allyl acetate provided only marginal amounts of the desired cross-product, presumably due to the statistically favored solvent dimerization which dominates the catalytic cycle.
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