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Ring Opening Cross-Metathesis on Solid Support

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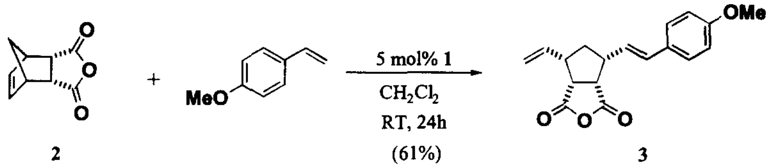
Abstract: Ring opening cross-metathesis (ROM) of bicyclic alkenes with terminal aryl alkenes on solid support was accomplished. A select group of resin-bound bicyclic alkenes underwent highly regioselective ROM with electron rich styrenes. The influence of both electronic and steric factors on regioselectivity was examined. © 1997 Elsevier Science Ltd.

Ring closing-metathesis has been extensively utilized for the synthesis of macrocycles, carbocycles and heterocycles.[1] However, the application of *inter*molecular ring opening cross-metathesis (ROM) for the convergent synthesis of small organic molecules has remained relatively unexplored due in part to a lack of regioselectivity.[2] The influence of steric factors on regioselective ROM of bicyclic and fused alkene systems with aliphatic alkenes has recently been reported.[3] We now wish to report ROM of bicyclic alkenes with terminal *aryl* alkenes on solid support and, most interestingly, the influence of *electronic* and steric factors on regioselectivity.

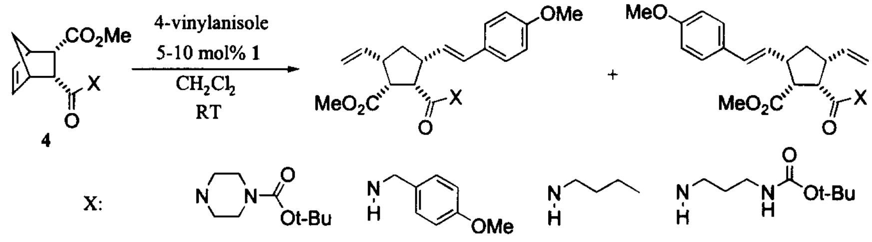
Ring opening metathesis polymerization of bicyclic or fused alkenes often competes with the desired cross-metathesis. Although infinite dilution techniques are widely utilized for solution-phase ROM, application of solid-phase synthesis techniques to ROM is an attractive means of preventing polymerization by isolating the bicyclic or fused alkene on a resin.[4] In addition, a solid-phase methodology can be conveniently incorporated into combinatorial library strategies.[5]

Terminal aryl alkenes have been shown to participate in selective cross-metathesis reactions utilizing a molybdenum alkylidene catalyst.[6] However, an extensive utilization of aryl alkenes in ROM is absent.[7] We chose to evaluate aryl alkene substrates first in solution-phase reactions. For the metathesis reactions described herein the commercially available catalyst $(Cy_3P)_2Cl_2Ru{=}CHPh$, 1, was used.[8] The reaction of bicyclic alkene **2** (0.12 M in dichloromethane) with 4-vinylanisole (5 equiv.) at room temperature in the presence of 1 (5 mol%) produced tetrasubstituted cyclopentane **3** in 61% isolated yield (Scheme 1). Unlike alkyl substituted alkenes, terminal aryl alkenes lead to only the trans-substituted isomers (J_{trans}=16.5 Hz).[2,3] However, non-terminal aryl alkenes (e.g. cis and trans-stilbene, and 1-phenyl-1-propene) were unreactive.



Scheme 1

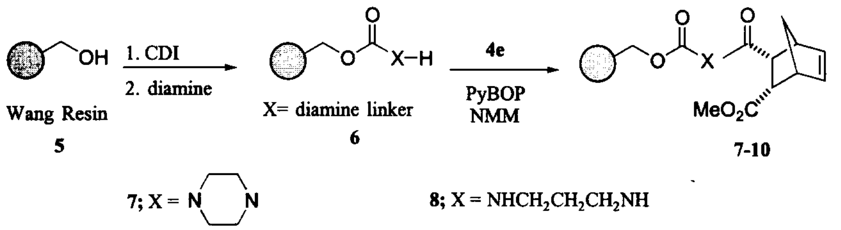
Several unsymmetrically substituted bicyclic alkenes (**4a-d**) were also subjected to ROM with 4-vinylanisole utilizing solution-phase conditions. Syringe pump addition of the bicyclic alkene minimized undesired polymerization.[2] In all cases two isomers were produced (Scheme 2).[9]



	4a	**4b**	**4c**	**4d**
regioisomer ratio (isolated yield)	1.6:1 (61%)	1.5:1 (90%)	1.3:1 (86%)	1.4:1 (62%)

Scheme 2

In order to evaluate solid-phase ROM, a bicyclic alkene substrate was attached to Wang resin, **5** (0.85-1.01 mmol/g). First, **5** was allowed to react with 1,1'-carbonyldiimidizole (CDI) followed by treatment with a primary or secondary diamine to give **6** (Scheme 3).[10] Resin **6** was acylated with *mono*-methyl *cis*-5-norbornene-*endo*-2,3-dicarboxylate, **4** (X = OH), to give resins **7-10**.[11]



8; X = NHCH$_2$CH$_2$CH$_2$NH

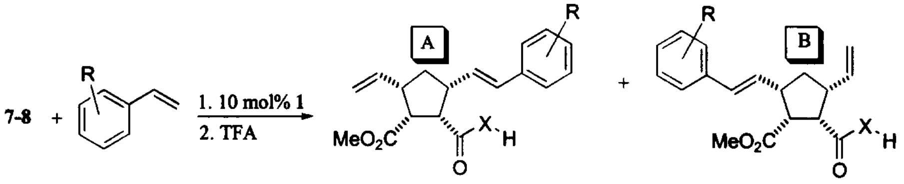
9; X = HNCH$_2$-m-C$_6$H$_4$-CH$_2$NH

10; X = HN(CH$_2$)$_2$O(CH$_2$)$_2$O(CH$_2$)$_2$NH

Scheme 3

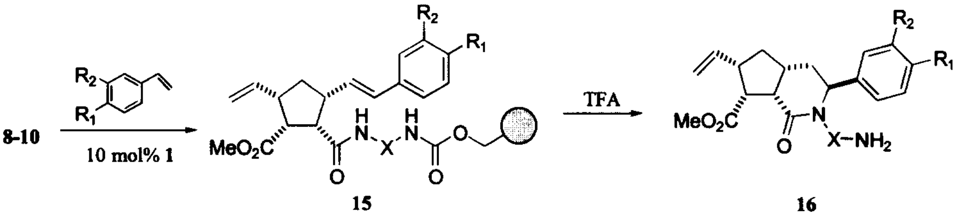
Resin **7** was allowed to react with 4-vinylanisole (10 equiv.) in the presence of **1** (10 mol%) at room temperature for 18h (Scheme 4). Treatment of the resin with 50% trifluoroacetic acid (TFA) in CH_2Cl_2 yielded **11** as a mixture of regioisomers (2.7:1).[9] Likewise, the reaction of resin **8** with 3-chlorostyrene followed by TFA treatment afforded **12** as a mixture of regioisomers (1:1).[9] The overall isolated yields based on resin loading were 60-77%. The solid-phase ROM reaction was compatible with an array of electronically differentiated terminal aryl alkenes including 4-trifluoromethylstyrene and 3-nitrostyrene affording **13** and **14**, respectively. Remarkably, the reaction of 4-vinylanisole with resin **8** in the presence of **1** followed by treatment with 50% TFA produced only *one* ROM product in 77% overall yield (Scheme 5). Structure elucidation of the product revealed the fused bicyclic lactam **16a**.[12] Analysis of the resin-bound ROM product by gel-phase ^{1}H NMR showed the absence of resonances characteristic of **16** and was most consistent with **15**. Cyclization of **15** occurred during the TFA mediated resin cleavage step.[13] Regioselective ROM was only observed in cross-metathesis reactions between terminal styryl ethers and phenols with resin-bound substrates attached through primary diamine linkers.

The relative proximity between the bicyclic alkene substrate and the resin was also investigated. The bicyclic acid **4** (X = OH) was attached to TentaGel S PHB resin, which contained a poly(ethylene glycol) tether, employing a 1,3-propanediamine linker via an analogous protocol to the preparation of resin **8** (*vida supra*). However, ROM with 4-vinylanisole in the presence of **1** gave a mixture of regioisomers (3.3:1) suggesting that close proximity between the bicyclic alkene substrate and the resin was necessary for the enhanced regioselectivity.[14]



Compounds	Resin	X	R	A:B
11	**7**	piperizine	4-OMe	2.7:1
12	**8**	$HNCH_2CH_2CH_2NH$	3-Cl	1:1
13	**8**	$HNCH_2CH_2CH_2NH$	4-CF_3	1.3:1
14	**7**	piperizine	3-NO_2	1.4:1

Scheme 4



Compound	Resin	X	R_1	R_2	% Yield[15]
16a	**8**	$CH_2CH_2CH_2$	OMe	H	77
16b	**8**	$CH_2CH_2CH_2$	OPh	H	53
16c	**9**	CH_2-m-$C_6H_4CH_2$	OMe	H	63
16d	**10**	$(CH_2)_2O(CH_2)_2O(CH_2)_2$	OMe	H	66
16e	**8**	$CH_2CH_2CH_2$	OH	OMe	85

Scheme 5

In summary, we have shown that ring opening cross-metathesis of bicyclic alkenes with terminal aryl alkenes on solid support is an effective means to diastereospecifically synthesize highly functionalized cyclopentane derivatives. In addition, the influence of electronic and steric factors on the enhanced regioselective ROM of resin-bound bicyclic alkenes was demonstrated. Efforts to understand the origin of the regioselective ROM reactions described herein and its extension to solution-phase substrates are currently being pursued.

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