

Synthesis of Trisubstituted Alkenes via
Olefin Cross-Metathesis

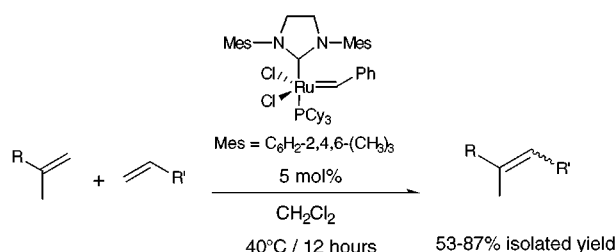
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ABSTRACT



Trisubstituted alkenes have been prepared for the first time via intermolecular olefin cross-metathesis, using 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ruthenium alkylidene complexes 3a,b in good yields with moderate *E* selectivity. In addition, protected alcohols near the geminal disubstituted olefin improve reactivity for cross-metathesis.

Trisubstituted carbon–carbon double bonds are a recurring motif in a diverse array of organic molecules. Therefore, new stereoselective methods for generating trisubstituted olefins remains an ongoing challenge in the area of synthetic organic chemistry. A wide variety of methods have been investigated to date including intramolecular Claisen rearrangements,^{1,2} Wittig olefination,³ Julia couplings,⁴ Peterson olefination,⁵ alkylation of sulfonyl hydrazones,⁶ and direct methods for the preparation of fluorinated trisubstituted alkenes.⁷ Transi-

tion metal mediated routes including hydromagnesization,⁸ hydrozirconation,⁹ and the use of organocuprates¹⁰ have also

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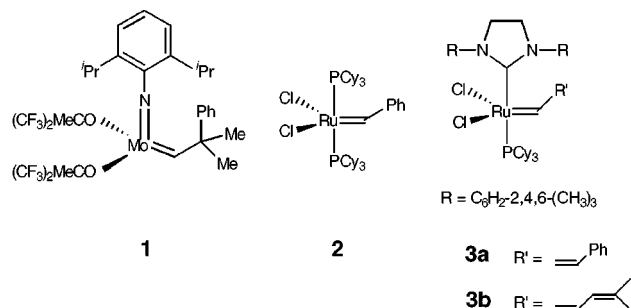
Table 1. Results of Geminal Disubstituted Olefin Cross-Metathesis with Terminal Olefins Using 5 mol % of Catalyst **3a,b**^a

entry	1,1-geminal olefin	terminal α -olefin ^b	product	yield ^c	E/Z ratio ^d
1				67 ^e	3:1
2				87	3.4:1
3				53	2.5:1
4				60	2.3:1
5				80	2.8:1
6				81	4:1

^a Benzylidene carbene **3a** and dimethylvinylidene carbene **3b** gave comparable results. ^b Reactions were performed with 2 equiv of α -olefin, except entry 1 where 3 equiv was used. ^c Isolated yields. ^d Ratios determined by NMR. ^e Please see ref 19.

been reported but often suffer from use of harsh stoichiometric reagents.

The olefin metathesis reaction has recently gained prominence in synthetic organic chemistry.¹¹ The commercial availability of well-defined catalysts, such as the molybdenum alkoxyimido alkylidene **1** developed by Schrock et al.¹² and ruthenium benzylidene catalyst **2** developed by the



Caltech group,¹³ has made the olefin metathesis reaction practical for small molecule synthesis. In particular, ring-closing olefin metathesis (RCM) reactions¹⁴ have been widely utilized in the construction of a diverse variety of organic molecules.

The intermolecular variant of olefin metathesis, terminal olefin cross-metathesis, has received less attention in the literature due to issues of product and olefin stereoisomer selectivity. However, renewed interest in this area has led to the recent development of new methodology for the selective cross-metathesis of terminal olefins using both **1** and **2**.¹⁵ In an attempt to extend cross-metathesis beyond α -olefins, however, Crowe et al. reported that disubstituted olefins were unreactive cross-metathesis partners with styrene using **1**.¹⁶

Recently, an additional member of the family of ruthenium-based catalysts, the highly active ruthenium-based olefin

metathesis catalysts **3a,b** containing 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ligands, have been reported to catalyze the RCM of a wide variety of substituted dienes while exhibiting excellent functional group tolerance.¹⁷ The high activity of these catalysts for RCM prompted us to investigate their potential application in cross-metathesis. We report herein the first example of cross-metathesis between geminal disubstituted olefins and terminal olefins to generate trisubstituted olefinic products.¹⁸ Our studies began with the use of 2-methyl-1-undecene **4** as a unfunctionalized geminal disubstituted olefin for cross-metathesis (Table 1, entries

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1–4). Substrate **4** proved to be a reactive substrate for cross-metathesis, coupling vinylidioxolane^{15c} **5**, allyl sulfone^{15f} **6**, and 1,4-diacetoxy-*cis*-2,3-butene^{15d} **7** in good yields with moderate *trans* stereoselectivity. Particularly notable, allyl sulfone **6** is a very reactive substrate for cross-metathesis (87% isolated yield, Table 1, entry 2) using **3a,b**, but it yields no cross-metathesis product using **2**.

Functionalized disubstituted olefins (Table 1, entries 5 and 6) also proved to be excellent substrates for this reaction and showed improved yields relative to that of **4**. We observe that the benzoate ester functionality may increase reactivity of the geminal olefins with the catalytic ruthenium species. In addition, maintaining a low concentration of terminal olefin

(18) **Representative Experimental Procedure:** 2-methyl-1-undecene (110 μ L, 0.5 mmol) and 5-hexenyl acetate (170 μ L, 1.0 mmol) were simultaneously added via syringe to a stirring solution of **3** (20 mg, 0.024 mmol, 4.8 mol %) in CH₂Cl₂ (2.5 mL). The flask was fitted with a condenser and refluxed under nitrogen for 12 h. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 \times 10 cm), eluting with 9:1 hexane:ethyl acetate. A clear oil was obtained (83 mg, 60% yield, 2.3:1 *trans/cis* as determined by the relative intensity of alkene ¹³C peaks at 125.0 and 124.2 ppm). ¹H NMR (300 MHz, CDCl₃, ppm): 5.08 (1H, t, *J* = 2.0 Hz), 4.04 (2H, t, *J* = 6.0 Hz), 2.03 (3H, obs s), 2.01–1.91 (2H, m), 1.69–1.59 (2H, m), 1.56 (3H, obs s), 1.47–1.05 (16H, broad m), 1.05–0.84 (3H, t, *J* = 6.8 Hz). ¹³C NMR (75 MHz, CDCl₃, ppm): 171.7, 136.7, 136.4, 125.0, 124.2, 123.3, 65.1, 40.3, 32.5, 32.3, 30.2, 29.9, 28.8, 28.6, 28.5, 28.0, 26.7, 23.2, 21.5, 16.4, 14.7. *R*_f = 0.35 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for C₁₈H₃₄O₂ [M]⁺ 282.2559, found 282.2556.

homodimer also increases the cross-metathesis yields.¹⁹ Finally, it should be noted that in all reactions the disubstituted olefin does not undergo self-metathesis, enabling quantitative recovery of unreacted material.

In conclusion, the first examples of cross-metathesis reactions between geminal disubstituted olefins and terminal olefins employing ruthenium alkylidenes **3a,b** have been presented. Protected allylic and homoallylic alcohols are suitable under the reaction conditions. This method allows for a efficient one-step formation of functionalized trisubstituted olefins under mild reaction conditions and further demonstrates the utility of olefin metathesis in organic synthesis.

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(19) In the reaction shown in Table 1, entry 1, the vinylidioxolane component (3 equiv) was added in four equal parts over a 6 h period. This maintained a low concentration of dioxolane homodimer and increased the isolated yield of cross-metathesis product by 10%.