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# Synthesis of Symmetrical Trisubstituted Olefins by Cross Metathesis

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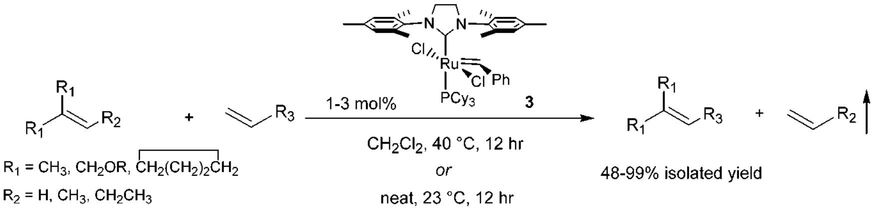
## ABSTRACT



**Trisubstituted alkenes have been prepared via intermolecular olefin cross-metathesis (CM) between α-olefins and symmetrically 1,1-disubstituted olefins using an imidazolylidene ruthenium benzylidene complex. Of particular interest is the synthesis of isoprenoid/prenyl groups by a simple solvent-free CM reaction with isobutylene. In addition, prenyl groups can also be installed by a cross-metathesis of 2-methyl-2-butene with a variety of α-olefins at room temperature with low catalyst loadings.**

Trisubstituted carbon−carbon double bonds are present in a diverse set of organic molecules and the development of new methods for their synthesis remains an ongoing challenge in synthetic organic chemistry. A wide variety of methods have been investigated to date, with Wittig olefinations being the most common.[1] However, the exclusive use of olefin starting materials to generate trisubstituted olefins, instead of using more reactive aldehyde functionalities, would provide a method that is orthogonal to Wittig chemistry.

The olefin metathesis reaction has gained prominence in synthetic organic chemistry as a reliable method for olefin formation.[2] The commercial availability of well-defined single-component homogeneous catalysts, such as $Mo(CHCMe_2Ph)(NAr)[OCMe(CF_3)_2]_2$ **1** developed by Schrock et al.[3] and ruthenium benzylidene catalyst $(PCy_3)_2Cl_2RuCHPh$ **2**,[4] has made the olefin metathesis reaction practical for small molecule synthesis. In particular, ring-closing metathesis (RCM) reactions have been widely utilized in the construction of a variety of organic molecules.

The intermolecular variant of olefin metathesis, olefin cross-metathesis (CM), has received less attention in the literature due to a perceived lack of selectivity and olefin stereoselectivity.[5] However, renewed interest in this area has led to the recent development of new methods in selective CM. Most of this work has been made possible by a new family of ruthenium metathesis catalysts similar to **2**, where a phosphine ligand has been replaced by a 1,3-dimesityl-4,5-dihydroimidazolylidene ligand.[6]

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(1) (a) Burke, S. D.; Hong, J.; Lennox, J. R.; Mongin, A. P. *J. Org. Chem.* **1998**, *63*, 6952. (b) Breit, B.; Zahn, S. K. *Angew. Chem., Int. Ed.* **1999**, *38*, 969. (c) Wang, Q.; Wei, H.; Schlosser, M. *Eur. J. Org. Chem.* **1999**, 3263.

(2) (a) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (c) Kotha, S.; Sreenivasachary, N. *Ind. J. Chem. B* **2001**, *40*, 763.

(3) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; Dimare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (b) Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378. (c) Bazan, G. C.; Oskam, J. H.; Cho, H. N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899.

(4) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (c) Belderrain, T. R.; Grubbs, R. H. *Organometallics* **1997**, *16*, 4001.

(5) Leading references using **1** and **2** in CM: (a) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162. (b) Brummer, O.; Ruckert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441. (c) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.

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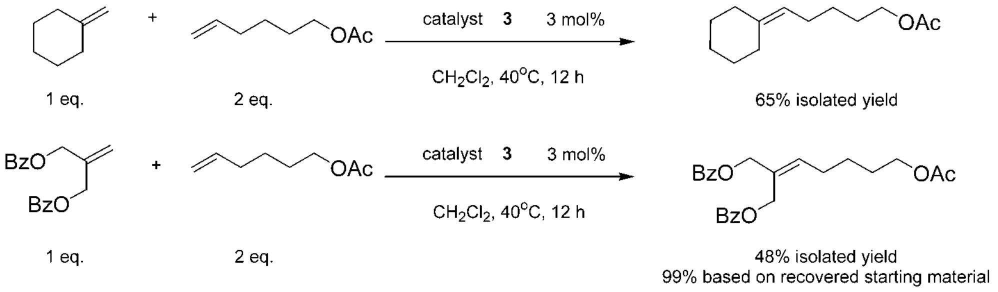
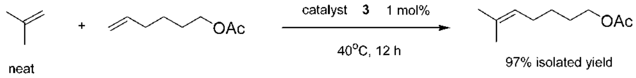
**Scheme 1.** CM of Symmetrical Disubstituted Olefins

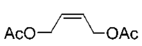
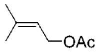
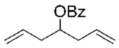
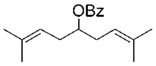
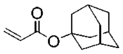
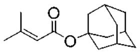
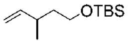
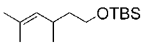
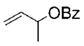
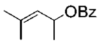


The high activity of these catalyst systems now allows for CM of $\alpha,\beta$-unsaturated carbonyl olefins,[7] vinylphosphonates,[8] and vinylsulfones.[9] In addition, we also reported the cross-metathesis of terminal olefin with 1,1-disubstiuted olefins.[10] Unfortunately, these reactions exhibited low olefin stereoselectivity and required moderately high catalyst loadings and reaction temperatures. In addition, only methyl groups as the second geminal substituent were reported in our initial work. We anticipated that the use of identical substituents on the geminal carbon would expand the substrate scope, without being complicated by the issue of poor stereoselectivity. In this Letter, we report the convenient CM of symmetrical 1,1-disubstituted olefins with a variety of CM partners, including an isoprenoid synthetic route by the homologation of α-olefins with isobutylene or 2-methyl-2-butene.[11]

Our initial work began with the cross-metathesis of isobutylene with terminal olefins (Table 1).[12] These reactions offer a convenient alternative to the use of $Ph_3P{=}C(CH_3)_2$ and the corresponding aldehyde to form prenyl functionality. Prenyl groups are a ubiquitous structural element in many natural products[13] and are also frequently employed in ene chemistry. For example, the reaction works well with simple α-olefins as well as 1,2-disubstiuted olefin starting materials (entry 1). Also, the reactions tolerate substrates that could ring close as demonstrated in the homoallylic hepatadiene case (entry 2). Senecioic acid derivations are also readily available from the CM reaction with the corresponding acrylate ester (entry 3). In addition, a protected secondary allylic alcohol is well tolerated and provides the CM product in quantitative yield (entry 5). With these results in hand, we investigated other symmetrically substituted olefins and found that both methylenecyclohexane and 2-methylene-1,3-dibenzoate work well as CM partners with 5-hexenyl acetate (Scheme 1). Since the 1,1-disubstituted olefin does not dimerize, it can be fully recovered and used in subsequent CM reactions.

**Table 1.** Cross-Metathesis with Isobutylene Using **3**



| entry | metathesis partner | product | isolated yield |
|---|---|---|---|
| 1 |  |  | 88 |
| 2 |  |  | 96 |
| 3 |  |  | 83 |
| 4 |  |  | 72 |
| 5 |  |  | 99 |

Interestingly, we did observe a background dimerization of a small amount of isobutylene to tetramethylethylene, but this did not affect the CM efficiency. The CM efficiency is surprising since the catalyst loadings are very low relative to the amount of bulk olefin in the reaction, with an effective catalyst loading of 0.0001 mol %. The inability of the 1,1-disubstituted olefin to readily homodimerize allows it to serve

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(6) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

(7) (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (b) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1277. (c) Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417.

(8) Chatterjee, A. K.; Choi, T.-L.; Grubbs, R. H. *Synlett* **2001**, 1034.

(9) Grela, K.; Bieniek, M. *Tetrahedron Lett.* **2001**, *42*, 6425.

(10) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751.

(11) Some of these olefins have been demonstrated in other CM systems from this group, see: ref 7c and Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 807.

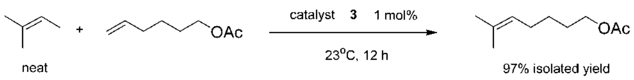
(12) **Typical isobutylene CM procedure:** To an oven dried, 100 mL Fischer−Porter bottle with Teflon stir bar, ruthenium metathesis catalyst (15.0 mg, 0.018 mmol, 1.0 mol %) was added. The bottle was capped with a rubber septum and flushed with dry nitrogen and cooled to −78 °C (or temperature sufficient to freeze substrate). Substrate (1.0 mmol) was injected into the bottle. Once the substrate was frozen, a pressure regulator was attached to the bottle. The bottle was evacuated and backfilled with dry nitrogen 3 times. Subsequently, isobutylene (5−10 mL, 50−100 equiv) was condensed into the bottle. The bottle was backfilled to ~2 psi with nitrogen, sealed, and allowed to slowly warm to room temperature, at which time it was transferred to an oil bath at 40 °C. After stirring for 12−18 h, the bottle was removed from the oil bath and allowed to cool to room temperature. The isobutylene was slowly vented off at room temperature until the pressure apparatus could be safely disassembled. The remaining mixture was taken up in organic solvent for subsequent silica gel chromatography and/or spectrographic characterization.

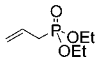
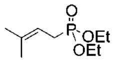
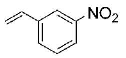
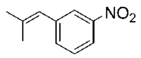
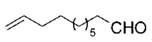
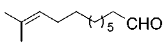
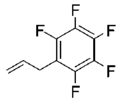
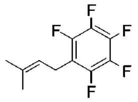
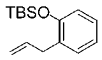
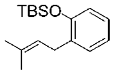
(13) The following paper provides an excellent application of the methods described in this Letter in an allyl to prenyl conversion, see: Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943.

as both a reaction solvent and as an effective cross partner. These factors allow for selective CM to the trisubstituted olefinic product.

However, the background dimerization of isobutylene to tetramethylethylene prompted us to investigate the use of 2,3-dimethyl-2-butene as a more convenient CM partner, since it is a liquid at room temperature (bp 73 °C). Unfortunately, this did not provide a synthetically useful amount of CM product, but we were able to use 2-methyl-2-butene (bp 35−38 °C) as a useful CM partner. In fact, we were surprised to see very efficient CM with this substrate at room temperature (Table 2).[14] This reaction represents the first CM reaction that involves the productive CM of trisubstituted olefins at room temperature.[15−17] Our previous results required higher catalyst loadings (5 mol %) and refluxing $CH_2Cl_2$ to obtain productive CM yields. The substrate scope in these CM is quite general, including allylphosphonates (entry 1) which allow for an efficient synthesis of prenyl diene reagents. In addition to amenability of an electron-deficient styrene (entry 2), unprotected aldehydes work well, allowing direct orthogonality to Wittig methods (entry 3). Substituted allylbenzenes (entries 4 and 5) are also well tolerated in the reaction. Particularly interesting is the CM of phenolic allylbenzene (entry 5), where CM is a convenient alternative to aromatic Claisen chemistry that would initially require the synthesis of tertiary phenoxy ether. One general note is the ease of performing these reactions: no solvent is required, all reagents are handled on the bench, and only ambient temperatures are needed to afford CM products in excellent yield.

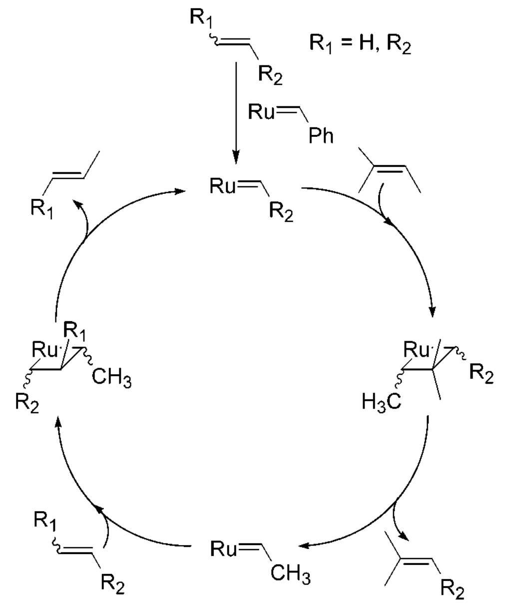
**Table 2.** Cross Metathesis with 2-Methyl-2-butene Using **3**



| entry | metathesis partner | product | isolated yield |
|---|---|---|---|
| 1 |  |  | 97 |
| 2 |  |  | 96 |
| 3 |  |  | 91 |
| 4 |  |  | 91 |
| 5 |  |  | 99 |

At this point, we were interested in understanding the excellent CM observed with 2-methyl-2-butene and decided to investigate the likely propagating species in these reactions. While the reaction of **3** with isobutylene produces the ruthenium isopropylidene and styrene as the kinetic products,[18] reaction with 2-methyl-2-butene results in the exclusive formation of the ruthenium ethylidene complex and *β*,*β*-dimethyl styrene as the kinetic products.[19] These results indicate that the general reaction pathway for 2-methyl-2-butene cross-metathesis is that shown in Scheme 2.

**Scheme 2.** Proposed 2-Methyl-2-butene CM Reaction Pathway



Due to the higher reactivity of terminal olefins toward CM, a significant portion of the terminal olefin may homodimerize before the CM reaction with 2-methyl-2-butene can compete (represented by $R_1 = R_2$). Cross-metathesis with 2-methyl-

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[14] **Typical 2-methyl-2-butene procedure (Table 2, entry 4):** Pentafluoroallylbenzene (225 $\mu$L, 1.468 mmol) from Aldrich Chem. Co. and 2-methyl-2-butene (3.2 mL) from Aldrich Chem. Co. were added simultaneously via syringe to a stirring solution of catalyst **3** (1.25 mg, 0.015 mmol, 1.0 mol %) under a nitrogen atmosphere. The flask was allowed to stir at room temperature for 12 h. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with 20:1 hexane:ethyl acetate to provide the cross-metathesis product (316 mg, 1.337 mmol, 91% yield) as a viscous oil.

[15] Thermodynamically controlled disproportionation of 2-methyl-2-butene and the step-growth ADMET polymerization of 2-methyl-1,5-hexadiene have been reported with **1**: Konzelman, J.; Wagener, K. B. *Macromolecules* **1995**, *28*, 4686.

[16] While the ruthenium benzylidene **2** does not react with trisubstituted olefins, the more reactive ruthenium enoic carbene ($Cl_2(PCy_3)_2Ru{=}CHCO_2$-Cy) undergoes one turnover with 2-methyl-2-pentene to generate the ruthenium propylidene and dimethyl-substituted cyclohexyl acrylate. Ulman, M.; Belderrain, T. R.; Grubbs, R. H. *Tetrahedron Lett.* **2000**, *41*, 4689.

[17] Metathesis depolymerization of polyisoprene has been previously reported with **3**: Craig, S. W.; Manzer, J. A.; Coughlin, E. B. *Macromolecules* **2001**, *34*, 7929.

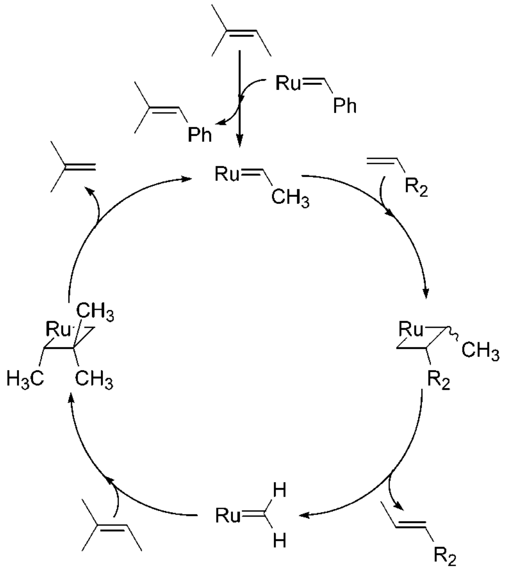
[18] The ruthenium isopropylidene was eventually consumed and finally only ruthenium methylidene was observed. Ruthenium isopropylidene: $^{31}P$ NMR ($C_6D_6$): $\delta = 19.94$ (s). $^1H$ NMR ($C_6D_6$): $\delta = 2.85$ (s, 6H, ortho C*H*$_3$), 2.57 (s, 6H, ortho C*H*$_3$), 2.26 (s, 6H, Ru=C(C*H*$_3$)$_2$), 2.21 (s, 3H, para C*H*$_3$), 2.14 (s, 3H, para C*H*$_3$). For complete spectroscopic characterization of the ruthenium methylidene, see ref 6b.

[19] The ruthenium ethylidene was confirmed by independent generation of the complex by reaction of **3** with *cis*-2-butene or propene. $^{31}P$ NMR ($C_6D_6$): $\delta = 29.05$ (s). $^1H$ NMR ($C_6D_6$): $\delta = 19.03$ (q, $J = 5.7$ Hz, 1H, Ru=C*H*CH$_3$), 2.81 (s, 6H, ortho C*H*$_3$), 2.57 (s, 6H, ortho C*H*$_3$), 2.18 (s, 3H, para C*H*$_3$), 2.10 (s, 3H, para C*H*$_3$), 1.91 (d, $J = 5.7$ Hz, 3H, Ru=CHC*H*$_3$). This is consistent with the results shown with 2-methyl-2-pentene and $Cl_2(PCy_3)_2Ru{=}CHCO_2Cy$. See ref 16.

2-butene produces the ruthenium ethylidene and the geminally dimethyl-substituted product. Depending upon the nature of $R_2$, this trisubstituted olefin may be kinetically resistant to further metathesis. The ruthenium ethylidene reacts with another equivalent of olefin to regenerate the appropriate ruthenium alkylidene and release a methyl-substituted olefin. In the case where $R_1 = H$ or $CH_3$, this volatile propene or 2-butene boils off to effectively remove the methyl groups from the reaction and drives the reaction toward the desired product.[20] If significant amounts of the terminal olefin have homodimerized, methyl-substituted olefins ($R_1 = R_2$) may be produced in this step which are gradually converted to the thermodynamically favored and desired geminally dimethyl-substituted olefin in subsequent cycles. Higher molecular weight homologues of 2-methyl-2-butene such as 2-methyl-2-pentene and 2-methyl-2-hexene may be used as well; however, the heavier fragments are more difficult to drive out of the system at room temperature, resulting in a larger fraction of ethyl- and propyl-substituted products. For certain olefins, such as the allylic benzoate (entry 5, Table 1), CM with 2-methyl-2-butene results in a 6:1 mixture of dimethyl- and methyl-substituted products which cannot be driven to produce the desired cross-product in high conversion.[21] For these olefins, CM with isobutylene is the better route to the desired cross-product.

Unlike the examples shown in Table 1, when it is unfavorable for the olefin (such as acrylates) to cross onto the ruthenium, a second reaction pathway, illustrated in Scheme 3, is primarily responsible for the observed product distribution. In this system, the 2-methyl-2-butene is the more reactive olefin and crosses onto the catalyst to produce the ruthenium ethylidene complex. This can react with the terminal olefin to produce a methyl-substituted olefin and ruthenium methylidene. The methylidene can react with the large excess of 2-methyl-2-butene to produce isobutylene and regenerate the ethylidene. In this pathway, the isobutylene boils off and effectively removes the geminal methyl groups from the reaction, resulting in the preferential generation of methyl-substituted olefin. With these olefins, the 2-methyl-2-butene may serve as practical substitute for propene or 2-butene in CM. This pathway is exemplified by the CM of *n*-butyl acrylate with 2-methyl-2-butene in which *trans*-*n*-butyl crotonate is produced in 83% conversion by $^1$H NMR.

**Scheme 3.** Proposed CM Reaction Pathway with Poor Olefins



In conclusion, the cross-metathesis reactions between symmetrical disubstituted olefins and terminal olefins employing ruthenium alkylidene **3** have been presented. Of particular interest is the convenient conversion of terminal olefins to prenyl groups. This method allows for an efficient one-step formation of trisubstituted olefins under mild reaction conditions and low catalyst loadings and further demonstrates the utility of olefin metathesis in organic synthesis.

**Acknowledgment.** The authors would like to thank Dr. Eric F. Connor, Dr. F. Dean Toste, Dr. Jennifer A. Love, John P. Morgan, and Tina M. Trnka for useful discussions and encouragement. Support has been generously provided by the National Institutes of Health.

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[20] In fact, trace amounts of the 1,2-disubstiuted olefin (<5%) are detectable by $^1$H NMR in the reactions with 2-methyl-2-butene.

[21] Column chromatography yielded a 6:1 ratio of dimethyl-substituted to methyl-substituted cross-products. Resubjection of the product mixture to CM conditions with 2-methyl-2-butene failed to improve the conversion of the dimethyl-substituted product.