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Tandem Catalysis: Generating Multiple Contiguous Carbon−Carbon Bonds through a Ruthenium-Catalyzed Ring-Closing Metathesis/Kharasch Addition

Benjamin A. Seigal, Cristina Fajardo,[†] and Marc L. Snapper*

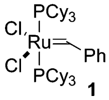
Contribution from the Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

Received August 24, 2005; E-mail: marc.snapper@BC.edu

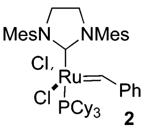
Abstract: Tandem catalysis can offer unique and powerful strategies for converting simple starting materials into more complex products in a single reaction vessel while generating less waste and minimizing handling. In this regard, Grubbs' ruthenium alkylidene $(Cy_3P)_2Cl_2Ru{=}CHPh$ is shown to catalyze two mechanistically distinct transformations to offer a unique protocol that effects multiple bond changes in a single operation. A tandem ruthenium-catalyzed olefin ring-closing metathesis (RCM)/Kharasch addition allows for the facile preparation of bicyclic [3.3.0], [4.3.0], and [5.3.0] ring systems in one step from the appropriately functionalized acyclic precursors. For substrates where the intramolecular Kharasch addition fails, an intermolecular Kharasch addition is possible. By combining the intra- and intermolecular Kharasch additions with RCM, three new contiguous carbon−carbon bonds with multiple stereocenters can be generated by the ruthenium catalyst in a controlled fashion in one operation through two mechanistically distinct pathways.

Introduction

Tandem, domino, and cascade processes[1] can involve multiple chemical transformations in a single reaction vessel, generating less waste and minimizing the excessive handling in multistep processes, while increasing significantly molecular complexity.[2] A particularly valuable tandem or domino process occurs when the different transformations are mediated by the same catalytic precursor.[3] In this regard, Grubbs' ruthenium alkylidenes **1** and **2**, well-known for their olefin metathesis activities,[4] have also been shown to function as procatalysts in olefin isomerizations,[5] olefin hydrogenations,[6] hydrogen atom and radical atom transfer reactions,[7] as well as other transformations.[8]



1



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Examples where these other activities of alkylidenes **1** and **2** are combined with olefin metatheses offer particularly efficient new entries into desired products. For example, as illustrated in Scheme 1, Grubbs' preparation of (−)-muscone through a series of chemoselective ruthenium-catalyzed transformations,

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[†] Current address: Universidad Autónoma de Madrid.

(1) While efforts are being made to define differences between tandem, domino, cascade, concurrent, and sequential catalytic processes, these terms are used interchangeably in this article without bias for the mechanistic implications of their emerging definitions. See ref 2b−d and Tietze, L. F.; Rackelmann, N. *Pure App. Chem.* **2004**, *76*, 1967 for additional discussions.

(2) For reviews on tandem/domino catalysis, see: (a) De Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (c) Ajamian, A.; Gleason, J. L. *Angew, Chem. Int. Ed.* **2004**, *43*, 3754. (d) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365. (e) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (f) Neuschuetz, K.; Velker, J.; Neier, R. *Synthesis* **1998**, *3*, 227−255. (g) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1237−1256. (h) Waldmann, H. *Org. Synth. Highlights II* **1995**, 193−202. (i) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137−165. (j) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167−176. (k) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195−206. (l) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (m) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103−13159. (n) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, 56, 5959. For recent examples of tandem processes, see: (o) Braddock, D. C.; Matsuno, A. *Tetrahedron Lett.* **2002**, *43*, 3305−3308. (p) Molander, G. A.; Brown, G. A.; Storch de Gracia, I. *J Org. Chem.* **2002**, *67*, 3459−3463. (q) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Eur. J.* **2002**, *8*, 1719−1729. (r) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552−4553. (s) Murakami, M.; Ubukata, M.; Ito, Y. *Chem. Lett.* **2002**, 294−295. (t) Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 11152. (u) Breit, B.; Zahn, S. K. *Angew. Chem. Int. Ed.* **2001**, *40*, 1910. (v) Breit, B.; Zahn, S. K. *Angew. Chem. Int. Ed.* **1999**, *38*, 969.

(3) For recent examples, see: (a) Guo, R.; Morris, R. H.; Song, D. *J. Am. Chem. Soc.* **2005**, *127*, 516. (b) Ackermann, L. *Org. Lett.* **2005**, *7*, 439. (c) Ashfeld, B. L.; Miller, K. A.; Smith, A. J.; Tran, K.; Martin, S. F. *Org. Lett.* **2005**, *7*, 1661.

(4) For recent reviews on olefin metatheses, see: (a) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012−3043. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(5) (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390−13391. (b) Schmidt, B. *Eur. J. Org. Chem.* **2003**, 816−819. (c) Schmidt, B. *Chem. Commun.* **2004**, 742−743. (d) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672−7687.

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(7) (a) Tallarico, J. A.; Malnick, L. M.; Snapper, M. L. *J. Org. Chem.* **1999**, *64*, 344−345. (b) Simal, F.; Demonceau, A.; Noels, A. F. *Tetrahedron Lett.* **1999**, *40*, 5689−5693. (c) Bielawski, C. W.; Louie, J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 12872. (d) Quayle, P.; Fengas, D.; Richards, S. *Synlet* **2003**, 1797. (e) Schmidt, B.; Pohler, M.; Costisella, B. *J. Org. Chem.* **2004**, *69*, 1421. (f) Lee, B. T.; Schrader, T. O.; Martín-Matute, B.; Kauffman, C. R.; Zhang, P.; Snapper, M. L. *Tetrahedron* **2004**, *60*, 7391−7396−345.

(8) (a) Maifeld S. V.; Miller R.; Lee D. *Tetrahedron Lett.* **2002**, *36*, 6363−6365. In addition, see: (b) Watson, M. D.; Wagener, K. B. *Macromolecules* **2000**, *33*, 3196−3201. For a recent review of nonmetathetic reactions of Grubbs' catalyst, see: (c) Alcaide, B.; Almendros, P. *Chem. Eur. J.* **2003**, *9*, 1258. For an overview of ruthenium-catalyzed reactions, see: (d) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599−2660. (e) Trost, B. M.; Toste, D. F.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096. (f) De Clercq, B.; Verpoort, F. *Tetrahedron Lett.* **2001**, *42*, 8959.

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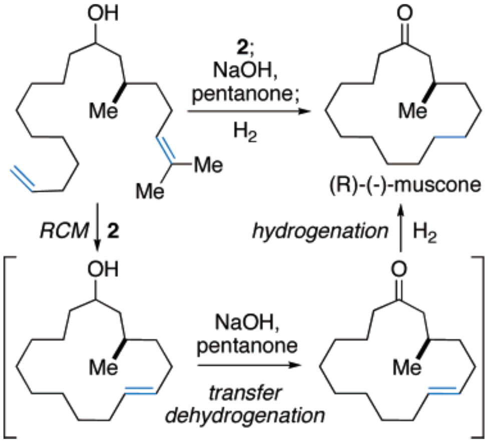
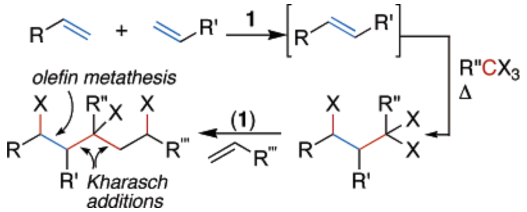
Scheme 1. Preparation of (−)-Muscone



including an olefin metathesis, hydrogen atom transfer, and olefin hydrogenation, illustrates the efficiency that can be achieved in converting an acyclic precursor into the desired natural product in a single reaction vessel.[9] Given the value of the tandem strategies and the range of ruthenium-catalyzed reactions,[10] opportunities for new ruthenium-catalyzed tandem transformations are abundant.

Like olefin metathesis, atom transfer radical additions (e.g. Kharasch additions) have been shown to be powerful methods for forming carbon−carbon bonds.[11] We, and others, have observed that Grubbs' ruthenium alkylidene **1**[12] catalyzes atom transfer radical reactions of haloalkanes across olefins under relatively mild conditions.[7] Given the dual reactivity of this catalyst, it is easy to envision a tandem process involving an olefin metathesis and a radical atom transfer reaction. Indeed, using a specially designed ruthenium alkylidene, Grubbs was able to prepare unique block polymers in a single reaction vessel through a ruthenium-catalyzed ring-opening metathesis polymerization of cyclooctadiene run concurrently with a ruthenium-catalyzed atom transfer radical polymerization methyl methacrylate.[7c] In contrast to this achievement, we demonstrate herein a tandem ruthenium-catalyzed olefin ring-closing metathesis (RCM)/Kharasch addition that allows for the facile preparation of polycyclic compounds in one step from appropriately functionalized acyclic precursors. *In this process, a single metal precursor, **1**, catalyzes the formation of up to three new carbon−carbon and two carbon−halogen bonds in one operation through two mechanistically unique pathways (Scheme 2).*

Scheme 2. Ruthenium-Catalyzed Olefin Metathesis/Double Kharasch Addition; Generation of Five New σ-Bonds in a Single Reaction Flask



Results and Discussion

The trihaloacetimides employed in this study were prepared through either a direct acylation of the amine or through the known a [3,3]-rearrangement of the corresponding allylic imidates;[11g,13] the rearrangement sequence is illustrated in eq 1 (Scheme 3). Since the stereogenic center generated in the rearrangement controls the stereochemistry of the subsequent tandem transformations, an asymmetric introduction of the allylic amidate provides an opportunity to access the bicyclic tandem products prepared in this study in an enantioenriched fashion.[14] Alternatively, the trichloroalkyl substrate **15** was prepared through an alkylation of the corresponding alkyl iodide with trichloromethyllithium as described by Weinreb and coworkers (eq 2).[15]

Scheme 3. Preparation of Starting Dienes

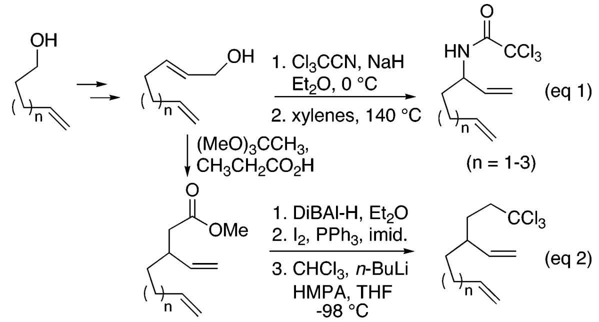


Table 1 illustrates a series of bicyclic ring systems prepared from acyclic dienes through a tandem RCM/intramolecular Kharasch addition reaction sequence. Entries 1−3 indicate that bicyclic [3.3.0], [4.3.0], and [5.3.0] ring systems can be prepared in one step from the corresponding acyclic diene precursors. In these examples, the metathesis reaction forms the 5, 6, or 7-membered rings, at room temperature, followed by a Kharasch addition that generates the 5-membered lactam under more forcing conditions. Interestingly, the tandem protocol employing alkylidene **1** as the catalyst generates compound **6** in higher yields than the known $(Ph_3P)_3RuCl_2$-catalyzed Kharasch addition on the corresponding cyclohexenyl substrate.[16] The stereochemical outcome of the reaction supports an atom transfer radical mechanism compared to a ruthenium-mediated oxidative addition/reductive elimination pathway. The high temperature required for this intramolecular Kharasch addition is attributed to the unfavorable amide bond rotomer required for ring closure

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(9) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312−11313.

(10) For an overview of ruthenium-catalyzed reactions, see: (a) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599−2660. (b) Trost, B. M.; Toste, D. F.; Pinkerton, A. B. *Chem. Rev.*, **2001**, *101*, 2067−2096.

(11) (a) Kharasch, M. S.; Jensen, E. V.; Urry, U. H. *Science* **1945**, *102*, 128. (b) DeMaldè, M.; Minisci, F. Pallini, U.; Volterra, E.; Quilico, A. *Chim. Ind. (Milan)* **1956**, *38*, 371. (c) Asscher, M.; Vofsi, D. *J. Chem. Soc.* **1963**, 1887−1896. (d) De Clercq, B.; Verpoort, F. *Tetrahedron Lett.* **2002**, *43*, 4687−4690 and references therein. (e) Matsumoto, H.; Nakano, T.; Nagai, Y. *Tetrahedron Lett.* **1973**, *14*, 5065−5150. (f) Mori, Y.; Tsuji, J. *Tetrahedron* **1972**, *28*, 29−35. (g) Lee, G. M.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 1281. For recent ruthenium-catalyzed examples, see: (h) Quebatte, L.; Solari, E.; Scopelliti, R.; Severin, K. *Organometallics* **2005**, *24*, 1404. (i) Delaude, L.; Demonceau, A.; Noels, A. F. *Top. Organomet. Chem.* **2004**, *11*, 155. (j) Tutusaus, O.; Delfosse, S.; Demonceau, A.; Noels, A. F.; Vinas, C.; Teixidor, F. *Tetrahedron Lett.* **2003**, *44*, 8421. (k) Tutusaus, O.; Vinas, C.; Nunez, R.; Teixidor, F.; Demonceau, A.; Delfosse, S.; Noels, A. F.; Mata, I.; Molins, E. *J. Am. Chem. Soc.* **2003**, *125*, 11830. (l) De Clercq, B.; Verpoort, F. *J. Organomet. Chem.* **2003**, *672*, 11.

(12) Preliminary screening efforts indicated that Grubbs' alkylidene **1** was more effective in catalyzing the Kharasch addition than the second-generation catalyst **2**.

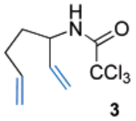
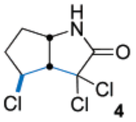
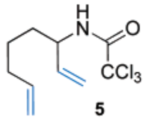
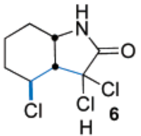
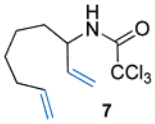
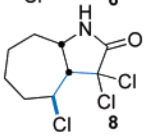
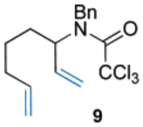
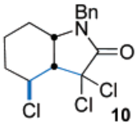
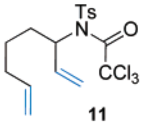
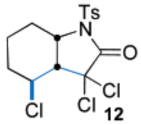
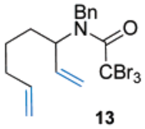
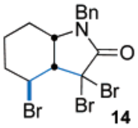
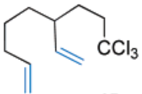
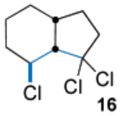
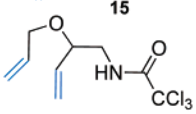
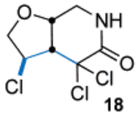
(13) (a) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901 (b) Donohoe, T. J.; Mitchell, L.; Waring, M. J.; Helliwell, M.; Bell, A.; Newcombe, N. J. *Org. Biomol. Chem.* **2003**, *1*, 2173.

(14) For example, see: Anderson, C. E.; Donde, Y.; Douglas, C. J.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 648 and references therein.

(15) Lee, G. M.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 1281.

(16) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682.

Table 1. Tandem RCM/Kharasch Addition

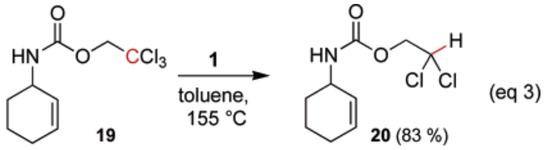
Entry	Diene	Product[a]	Conditions	Yield
(1)	 **3**	 **4**	155 °C 2.25 h	75 %
(2)	 **5**	 **6**	155 °C 1.75 h	85 %
(3)	 **7**	 **8**	155 °C 0.5 h	55 %
(4)	 **9**	 **10**	110 °C 11 h	85 %
(5)	 **11**	 **12**	60 °C 12 h	63 %
(6)	 **13**	 **14**	24 °C[b] 2.5 h	50 %
(7)	 **15**	 **16**	110 °C 7.5 h	89 %
(8)	 **17**	 **18**	155 °C 4.5 h	71 %

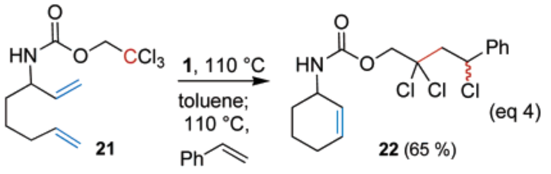
in the radical cyclization. As discussed below, this supposition is supported through studies with the more substituted amides.

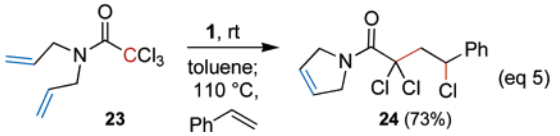
Entries 4 and 5 demonstrate that adding a benzyl or tosyl group to the amide functionality facilitates the Kharasch addition; the reactions proceed at lower temperatures, although requiring longer reaction times. The Kharasch reactivity can be enhanced further by switching the trichloroacetamide to the corresponding tribromoacetamide. As shown in entry 6, the tandem RCM/Kharasch occurs with substrate **13** even at reduced temperatures. It is likely that the higher Kharasch reactivity observed with this substrate contributes to the reduced yield of desired cycloadduct; the radical atom transfer reactivity competes with olefin metathesis, leading not only to the desired adduct **14** but also to a variety of other side products.

Interestingly, the aliphatic substrate **15** provides the highest yield of a tandem cycloadduct **16** (entry 7). Evidently, the conformational freedom offered by removing the amide linkage more than compensates for the reduced Kharasch activity of the trichloroalkyl functionality. An alternative route to the 5,6-ring system is illustrated in entry 8. In this case, a RCM is used to prepare the furanyl ring, followed by a Kharasch addition that installs the 6-membered lactam. Improved yields were observed for the 6-membered ring-forming radical atom transfer ring closure when the tandem process was performed at slightly higher dilutions than the previous examples.

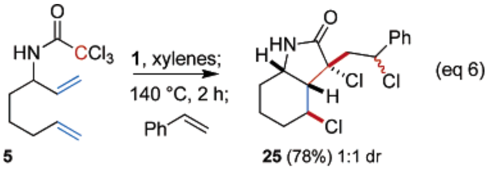
Attempts to generate a 7-membered ring through the radical Kharasch addition of a trichoroethylcarbamate (Troc)-containing substrate were unsuccessful. As illustrated in eq 3, treatment of Troc-protected cyclohexenylamine **19** with Grubbs' ruthenium catalyst **1** led to only reduced product **20**. For substrates where the intramolecular Kharasch addition fails, however, an intermolecular Kharasch addition is possible (eqs 4 and 5). For example, heating diene **21** with alkylidene **1** effects the RCM, followed by addition of styrene, and continued heating allows for an intermolecular Kharasch addition to produce compound **22** as a mixture of diastereomers. In a similar fashion, diene **23**, also participates in a tandem RCM/intermolecular Kharasch addition with styrene to provide compound **24**.

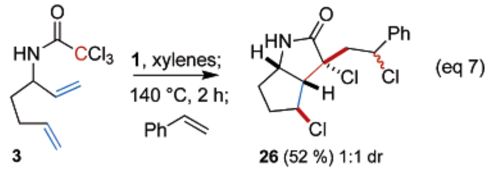






Scheme 4. Tandem RCM/Intramolecular Kharasch/Intermolecular Kharasch





Scheme 4 illustrates two examples of tandem processes extended to include both intra- and intermolecular Kharasch additions. When diene **5** is heated in the presence styrene, compound **25** is generated selectively in 78% yield as a 1:1 mixture of benzyl chlorides (eq 6). In this reaction, Grubbs' catalyst **1** first effects the RCM and then upon heating promotes an intramolecular Kharasch addition, before carrying out an intermolecular Kharasch on **6** with the addition of styrene. The net result is the ruthenium-catalyzed formation of three new contiguous carbon−carbon bonds, two carbon−halogen bonds, and four new stereogenic centers in a single reaction flask. A similar transformation is observed with diene **3** (eq 7). In both cases, these benzyl chloride products (**25** and **26**) are transformed to the corresponding benzyl nitrates upon chromatographic separation with Ag-impregnated silica gel.

Conclusions

In summary, we have shown that Grubbs' ruthenium alkylidene **1** can catalyze two distinct transformations in the same reaction vessel to offer a unique ring-forming protocol, effecting multiple bond changes in a single operation. The outcome is a new tandem RCM/Kharasch addition that converts acyclic halogenated diene precursors into highly functionalized polycyclic systems, versatile intermediates that can be functionalized further through a variety of strategies, including selective reduction of the halogens,[7e] hydrolytic conversion of halogens to α,β-unsaturated carbonyls compounds,[17] generation of olefins through eliminations, or new carbon−carbon bonds through secondary radical atom transfer[16] or alkylation reactions.[18] Indeed, two examples are provided where the tandem RCM/Kharasch addition products are further functionalized in the same reaction flask through a second ruthenium-catalyzed Kharasch addition to provide bicyclic products containing three new adjacent carbon−carbon bonds.

Experimental Section

General Methods. All reactions were carried out under N_2 atmosphere in oven-dried glassware (135 °C, 12 h) using standard air-free manipulation techniques. Starting materials and reagents were purchased from commercial suppliers and used without further purification, except the following: tetrahydrofuran, benzene, diethyl ether, and dichloromethane were dried on alumina columns using a solvent dispensing system;[19] pentane, hexanes, and diethyl ether used in chromatography were distilled prior to use.

RCM/Kharasch Addition. In a glovebox, a solution of the halogenated dienyl substrate (1 equiv) in toluene or xylene (0.2 M) was added to Grubbs' catalyst **1** (5 mol %) in a thick-walled pressure tube and sealed with a Teflon screw cap. The tube was removed from the glovebox and was allowed to stir at ambient temperature. After 2 h the reaction was placed in a heated oil bath and allowed to stir for approximately 2 h. After allowing the tube to cool, the RCM/Kharash product was obtained upon removal of solvent and purification through silica gel chromatography.

RCM/Double Kharasch Addition. In a glovebox, a solution of the halogenated dienyl substrate (1 equiv) in xylenes (0.05 M) was added to Grubbs' catalyst **1** (5 mol %) in a flask and fitted with a reflux condenser. The flask was removed from the glovebox and was allowed to reflux for approximately 2 h, at which time styrene (5 equiv) was added and the reaction was allowed to reflux for an additional 4 h. After allowing the tube to cool, the benzyl chloride products were obtained as an inseparable mixture upon removal of solvent and purification through silica gel chromatography. If the reaction was purified by chromatography on 10% $AgNO_3/SiO_2$ (wt/wt) column (1:4; ethyl acetate:hexane), the nitrated Kharasch diastereomers are isolated individually.

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Supporting Information Available: Experimental procedures and data on new compounds are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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