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Relative Rate Profile for Ring-Closing Metathesis of a Series of 1-Substituted 1,7-Octadienes as Promoted by a 4,5-Dihydroimidazol-2-ylidene-Coordinated Ruthenium Catalyst

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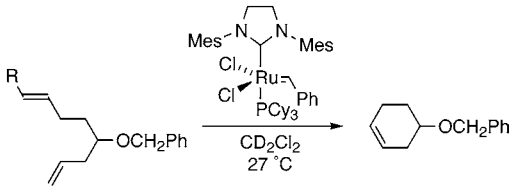
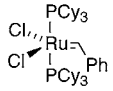
ABSTRACT



This report details the kinetic responses of nine compounds of type 6 to ring-closing metathesis as promoted by 2 to give the identical product 7. The experimental observations have been subjected to Hammett analysis. The ρ value for the composite aromatic derivatives (R = *p*-XC_6H_4–) differs from that of the aliphatic series, although both are negative because electron-donating groups accelerate the reaction.

The adaptability and widespread popularity of ring-closing metathesis (RCM) has been widely attributed to the excellent functional group tolerance of ruthenium-based catalysts such as **1**.[1] Indeed, the striking power of this methodology is extensively reflected in the synthesis of nitrogen heterocycles (including azasugars and alkaloids),[2] structurally modified carbohydrates,[3] lactones and lactams,[4] sulfones,[5] sulfonamides,[6] and the like. While the range of substrates amenable to this chemical transformation is very broad, there has existed a tacit limitation. The heteroatomic functionality has almost invariably been intentionally positioned in a relatively remote relationship to the double bonds taking part in the metathesis process. While this restriction has led to a more advanced definition of RCM reactions such as the large activating effect of an allylic hydroxyl substituent,[7a] substrates carrying an electron-donating or electron-withdrawing group directly attached to a key center of unsaturation have largely been unexplored.[7b]



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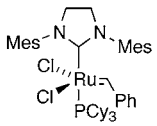

2

The deemphasis surrounding the possible adaptation of functionalized ring-closing metathesis is seemingly rooted

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(3) Reviews: (a) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519. (b) Jorgensen, M.; Hadwiger, P.; Madsen, R.; Stütz, A. E.; Wrodnigg, T. M. *Curr. Org. Chem.* **2000**, *4*, 565.

(4) Some representative examples include: (a) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943. (b) Miller, J. F.; Termin, A.; Koch, K.; Piscopio, A. D. *J. Org. Chem.* **1998**, *63*, 3158. (c) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359. (d) Ripka, A. S.; Bohacek, R. S.; Rich, D. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 357. (e) Sukkari, H. E.; Gesson J. P.; Renoux, B. *Tetrahedron Lett.* **1998**, *39*, 4043.

(5) For illustrative case studies, see: (a) Paquette, L. A.; Fabris, F.; Tae, J.; Gallucci, J.; Hofferberth, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 3391. (b) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361. (c) Grela, K.; Bieniek, M. *Tetrahedron Lett.* **2001**, *42*, 6425.

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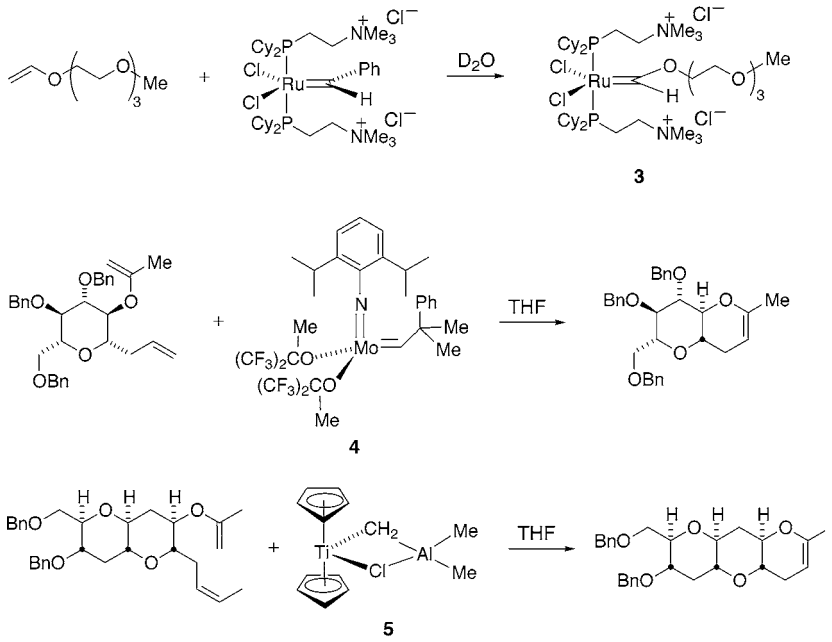

in various observations cited in the prior art. The feasibility of engaging acrylate esters in productive cross metathesis has been recognized for some time.[8] Correspondingly, examples of the involvement of α,β-unsaturated esters in RCM are rather numerous.[9] In contrast, acrylonitrile is a substituted alkene that has eluded virtually all attempts to effect comparable reaction.[10] No examples of the participation of α,β-unsaturated nitriles in RCM have consequently been reported, even when the cyano functionality is situated on the terminus of a 1,3-diene.[11] Conjugated amides appear to enjoy an intermediate position.[12] The ability of α,β-unsaturated ketones to exhibit comparable high performance behavior has surfaced only recently,[13] chiefly as the result of improved catalyst design.

Enol ethers[14a] and enamides[14b] have been reported not to undergo RCM when exposed to **1**. In fact, ethyl vinyl ether has been utilized to terminate living ROMP reactions.[15] These phenomena have been attributed to the ability of ruthenium alkylidenes to generate metathesis-inactive Fischer carbenes such as **3** under these circumstances.[16] This transformation is quantitative and essentially irreversible.[17] For this reason, recourse has been made to other catalysts such as **4** and **5** in order to provide an alternate driving force for RCM in such cases.[18]

In light of these developments, a systematic investigation of the relative rates of RCM of a series of dienes of type **6** has been undertaken to allow for proper comparative analysis. Use has been made of the highly active N-heterocyclic carbene-coordinated metathesis catalyst **2**[19] in order to address steric and electronic effects that might affect this particular promoter.[20] Our guidelines provide not only for attachment of an R− or *p*-XC_6H_4− group directly to a reacting double bond but also for generation of the identical product **7** in every instance.[21]

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(20) Ruthenium catalyst **2** is recognized to alleviate certain limitations brought on by substitution and to promote the metathesis of vinyl siloxanes and fluorinated alkenes.

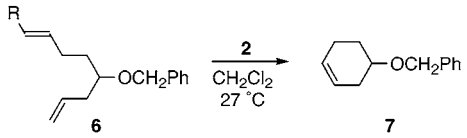
(21) Presence of the remotely positioned benzyloxy substitutent is purposeful. In this way, the volatility of the reactant and particularly the product is reduced sufficiently to facilitate quantitation of the process.

Table 1. Summary of Kinetic Data and Isolated Yield of **7**[a]

substrate **6**, R =	*k*/min [1 mol % run]	*k*/min [5 mol % run]	$t_{1/2}$, min	regression analysis, *r*	k_R/k_H	isolated yield of **7**, %	σ[b]
A. aromatics							
p-$CH_3OC_6H_4-$	0.2647	1.3235	0.5237	0.997	20.9	73	−0.268
C_6H_5-	0.2582	1.2910	0.5369	0.959	20.4	89	−0.010
p-$CF_3C_6H_4-$	0.2335	1.1675	0.5937	0.994	18.5	94	0.540
p-$O_2NC_6H_4-$	0.2069	1.0345	0.6700	0.996	16.4	76	0.778
B. aliphatics							
$-CH_3$	0.0573	0.2865	2.4194	0.967	4.5	90	−0.170
$-COOCH_2CH_3$	0.0175	0.0814	8.5153	0.999	1.3	87	0.450
−H		0.0632	10.9675	0.991	1.0	83	0.000
$-COCH_3$		0.0432	16.0451	0.942	0.68	88	0.502
$-SO_2C_6H_5$		0.0280	24.7553	0.996	0.44	88	0.686

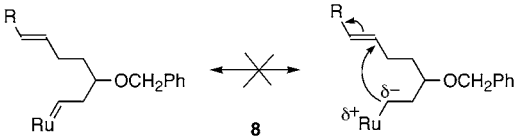
[a] Cyclizations were performed with freshly prepared CD_2Cl_2 solutions of both the substrate and catalyst at 300 K in the probe of a Bruker 400 MHz spectrometer under N_2. Measurement of the rates of the carboethoxy derivative at both catalyst loadings allowed for extrapolation of the 1 mol % rates to the 5 mol % level. [b] Values of σ employed for the aromatic series are those of the *para* substituents (Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley and Sons: New York, 1972; pp 145−147).

The dienes **6** examined in this study exhibit rates that are more than 100-fold faster than rates determined in our earlier investigation[11] (Table 1). Also, $k_{(C6H5)}/k_{(H)} = 20.4$, indicating that the aromatic and aliphatic series differ considerably in their rate profiles. These observations are consistent with the inherently greater proximity of the vinyl substituent R to the reaction center. More significantly, the kinetic data reveal that electron-donating groups enhance the overall reaction rates. This effect is only moderate for the para substituents where faster rates are manifested in the aromatic series. For example, the k_R/k_H ratio for *p*-$CH_3OC_6H_4-$ is 20.9 and changes to 16.4 for *p*-$O_2NC_6H_4-$, a factor of 1.3. The electronic effects are more pronounced for the substituents in the aliphatic series. The k_R/k_H ratio for R = CH_3 is 4.5, while it is 0.68 for the methyl ketone, a factor of 6.7.



A Hammett plot of reaction rates relative to R = H (Figure 1) is seen to be fragmented into two parts, one for aliphatic and one for aromatic substituents. The ρ values in both segments are negative, suggesting that electron-donating substituents accelerate the reaction. This conclusion is consistent, for example, with the faster reaction rates for *p*-$CH_3OC_6H_4-$ and CH_3- in the aromatic and aliphatic series, respectively. A small $\rho = -0.0970$ ($r = 0.924$) for aromatic substituents and a larger $\rho = -0.8801$ ($r = 0.695$) for aliphatic substituents have been found.

The two different ρ values need not indicate that the presence of an aromatic ring effects a change in the reaction sequence. The problem may lie in the unavailability of a consistent set of σ values for all of the compounds in the study. The decreased sensitivity to substitution in the aromatic series may be due to the involvement of a ruthenium benzylidene derivative as the cyclization progresses. Another possible explanation is that the R group in the aliphatic series, being closer to the reacting double bond, hinders generation of the ruthenium alkylidene. Chen has observed that electron-withdrawing substituents on the carbene moiety accelerate ring-opening metathesis.[22] The present results do not conform to this trend, are not compatible with a process involving polarization of the ruthenium species as in **8**, and also do not find rate acceleration by an intramolecular Michael-type cyclization to be kinetically viable.



Bulky R substituents in aliphatics have been shown to severely hinder cyclization with ruthenium alkylidenes.[7b] Presently, the $COOC_2H_5-$, $COCH_3-$, and $SO_2C_6H_5-$ substituted dienes proved to be unreactive to **1**. The ρ value remains constant.

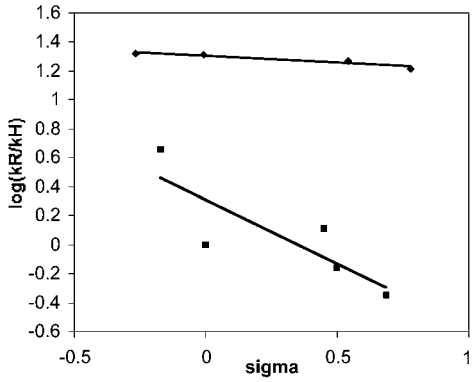


Figure 1. Hammett plot with both series referenced against H. The upper line is defined by the aromatic series and the lower by the aliphatic congeners of **6**.

In summary, the reactivity of a series of structurally related dienes has been studied in detail. However, the multistep nature of the process, the fact that the aromatic and aliphatic series are defined by different ρ values, and the accelerating effect of electron-donor groups make detailed mechanistic analysis a challenging endeavor at this time.

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Acknowledgment. The authors thank Dr. Claudio Sturino (Merck Frosst Canada) for a generous gift of **2**.

Supporting Information Available: Experimental procedures for the preparation of **6**, pertinent spectroscopic data, and a description of the kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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