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Rational Design and Evaluation of Upgraded Grubbs/Hoveyda Olefin Metathesis Catalysts: Polyfunctional Benzylidene Ethers on the Test Bench†

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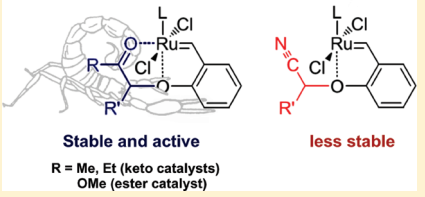
Supporting Information

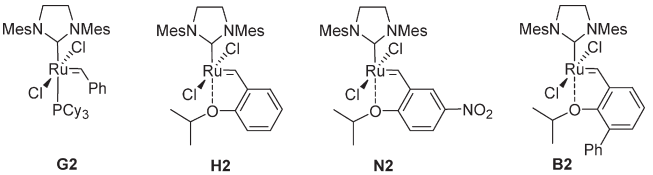
ABSTRACT: The series of upgraded Grubbs/Hoveyda second-generation catalysts $(H_2IMes)(Cl)_2Ru{=}C(H)(C_6H_4OR)$ (**E2** (71% yield), R = CH(Me)(C(O)OMe); **M2** (58% yield), R = $CH(C(O)OMe)_2$; **Kme2** (88% yield), R = $CH_2C(O)Me$; **Ket2** (63% yield), R = $CH_2C(O)Et$); **C2** (58% yield), R = C(Me)CN) were prepared by the reaction of the Grubbs second-generation catalyst $(H_2IMes)(Cl)_2Ru(CHPh)(PCy_3)$ (**G2**) with the appropriate ortho-substituted ether $H(Me)C{=}CHC_6H_4OR$ in the presence of CuCl as a phosphine scavenger. The X-ray structures of these complexes reveal that the terminal oxygen of the ester, ketone, or malonate group installed as the terminal substituent of the benzylidene ether is coordinated to the metal, giving an octahedral structure. In contrast, the nitrile group of the complex **C2** remains uncoordinated. Even more sophisticated complexes, incorporating both a coordinating group R (ester or ketone) as a terminal substituent of the ether and an electron-withdrawing group X (NO_2 or C(O)Me) on the aromatic ring, were synthesized: $(H_2IMes)(Cl)_2Ru{=}C(H)[(C_6H_3X)OR]$ (**NE2** (69% yield), R = CH(Me)(C(O)OMe), X = NO_2; **KE2** (57% yield), R = CH(Me)(C(O)OMe), X = C(O)Me; **KK2** (56% yield), R = $CH_2C(O)Me$, X = C(O)Me). All these complexes were used as catalyst precursors in standard metathesis reactions and compared with commercial catalysts such as Grubbs II (**G2**), Grubbs/Hoveyda II (**H2**), and Nitro catalyst (**N2**). The catalysts **NE2**, **KE2**, **N2**, and **M2** exhibit excellent performances in the RCM of diallyl malonate or the RCM of diallyltosylamide at 0 °C. The catalysts **M2**, **N2**, and **Kme2** are also very efficient for the RCM of allyl methallyl malonate to yield a trisubstituted olefin. The same complexes are also active for cross-metathesis, and several low-loading tests are also presented. Finally, a very challenging example of the synthesis of BILN 2061 (hepatitis C virus HCV NS3 protease inhibitor having antiviral effect in infected humans) is presented, where the best performances are recorded with **E2** (95% conversion) and **N2** (93% conversion). The enhanced activity of the reported complexes is understood in terms of their enhanced stability and their ability to liberate progressively and continuously the active species in solution.



INTRODUCTION

A major outcome of modern discoveries in the field of olefin metathesis[1] is certainly elevation of the art and science of chemical synthesis and a significant enlargement of chemists' view of their own synthetic possibilities.[2] Indeed, with Grubbs catalysts offering a proper solution to most current olefinic C=C bond activation problems, investigators can now envision more innovative and environmentally compatible synthetic procedures at lower time, energy, and money costs.[3,4] For current applications, commercially available first- and second-generation catalysts **G1** ($(PCy_3)_2(Cl)_2Ru{=}C(H)(C_6H_5)$) and **G2** are already remarkably efficient in terms of activity, selectivity, and functional group tolerance (Chart 1).[5] As underscored by several authors,[6,7] the user's choice may need to be guided when more challenging transformations are to be achieved, due to the very large "galaxy"[7] of contemporary *enhanced* catalysts[8] which are now available from the literature.

Chart 1



Within the latter category, Hoveyda catalysts **H1** ((PCy_3)-$(Cl)_2Ru{=}C(H)(C_6H_4$-2-$OPr^i)$, not shown in Chart 1) and their

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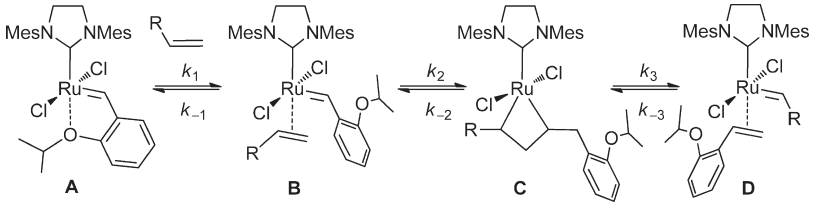
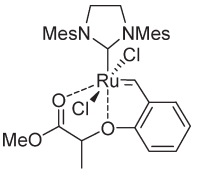
Scheme 1. Basic Working Principle of Hoveyda Catalysts



relevant second-generation Grubbs/Hoveyda congeners **H2**[9] (now existing in upgraded chiral versions)[10] also including Blechert catalysts **B2**[11] continue to attract considerable attention from both academic and applied viewpoints, because, at least on their basic working principle, they are intrinsically offering *a conceptually original solution to the problem of catalyst recovery*. Hoveyda type precatalysts (drawing **A** in Scheme 1) incorporate a chelating *o*-isopropoxybenzylidene moiety, in which the lightly coordinating ether function serves as a lock for the active site. Though the enhanced activity of such catalysts was originally ascribed to a dissociative mechanistic pathway,[9,12] some intriguing observations[13] and recent kinetic studies by Plenio[14] have led to the proposal that the olefinic substrate participates in the rate-limiting step of the initiation reaction. According to such studies (Scheme 1), decoordination of the ether in the presence of an incoming olefin gives the adduct **B** and triggers the initiation step by allowing formation of the key metallacyclobutane **C** via [2 + 2] cycloaddition.[15] Subsequent cycloreversion leads to **D**, from which the styrenyl ether can be released in solution, thereby generating the key 14e complex[16] arising as the active *propagating* species. After total consumption and transformation of the olefinic substrate, the styrenyl ether may be recaptured by the active species in the *termination step*, thus regenerating the precatalyst in its resting state **A**. However, at least for the unmodified Hoveyda catalysts **H2**, the practical effectiveness of the "return" process has been recently questioned, on the basis of simple and reliable experimental observations.[17]

Therefore, a fast *release* of the styrenyl ether corresponds to a high initiation rate, whereas its ability to catch back the propagating species in the *return* process (reverse sequence from **D** to **A**) is crucial for catalyst recovery. In the footprints of Hoveyda and Blechert, we have attempted to enhance the leaving-group properties of the ether through various approaches. The original modifications made in Warsaw consisted of the introduction of certain electron-withdrawing substituents, such as NO_2, on the aromatic ring in a para position relative to the isopropoxy unit, with the aim of labilizing the bonding interaction between the oxygen of the ether function and the metal. Such a strategy proved to be valuable, giving in particular our very efficient "nitro-Hoveyda" catalyst **N2** shown in Chart 1,[18] exhibiting a high initiation rate and a broad application scope.[19] In this context, recent DFT calculations have led to the proposal that both the enhanced activity of this catalyst and its recovery are dependent on the π delocalization between the phenyl and the carbene.[20]

Encouraged by the success of catalyst **N2**, we were prompted to replace the terminal isopropyl substituent of the hemilabile ether functionality by an ester group, originally selected also on account of its electron-withdrawing properties. These initial experiments[21,22] led to the isolation of the new complex **E2**, representing an unprecedented structural type of modified Hoveyda catalyst, where the added ester group coordinates to the metal, thereby contributing to the overall stability of the complex.



E2

The very positive catalytic tests carried out from such a prototype led us to realize that, as also noted by other authors,[23] the global efficiency of an olefin metathesis catalyst is not only due to its ability to generate rapidly the active 14e species, but is in fact the result of *a subtle balance between antinomic properties*, where the stability of the precatalyst plays an important role.[22] In line with these observations, we see in the very recent literature *a renewed interest in precatalysts exhibiting enhanced stability* (in which, for example, the leaving group is an N-heterocyclic carbene,[24] reminiscent of the pioneering work of Herrmann),[25] also including latent photo- or thermoswitchable catalysts.[26]

In a logical continuation of our preliminary investigation,[22] other functional groups were installed as terminal substituents of the benzylidene ether ligand and their respective benefits were evaluated in a series of test reactions presented here. As shown below, we also explored the possibility of obtaining upgraded versions of our various catalysts combining their respective characteristics: namely, the presence of an electron-withdrawing group as a terminal substituent of the ether and of a second group on the aromatic ring of the benzylidene group. The full results of this collaborative investigation[22] are disclosed in the present paper, where the performances of the new catalysts, some of which are now at the point of being commercialized, are also compared with those of the known benchmark prototypes **G2**, **H2**, **N2**, and **B2**.

RESULTS AND DISCUSSION

According to a general procedure originally disclosed by Hoveyda,[9] second-generation Grubbs/Hoveyda type catalysts are directly accessible from a Grubbs second-generation catalyst through a straightforward stoichiometric ligand exchange based on a metathesis cycle where an incoming styrenyl ether serves as the source of the benzylidene ether ligand.

A. Original Design of a New Grubbs/Hoveyda Catalyst by Reaction of G2 with an Ester-Substituted Styrenyl Ether. In the present approach, the appropriate carbene ligand precursor, an ester-substituted styrenyl ether, was prepared by reaction of the commercially available 2-(1-propenyl)phenol with methyl bromopropionate in the presence of a base (Scheme 2, eq 1). It was then reacted with Grubbs II catalyst in the presence of copper(I) chloride, commonly used as a phosphine scavenger,[9]

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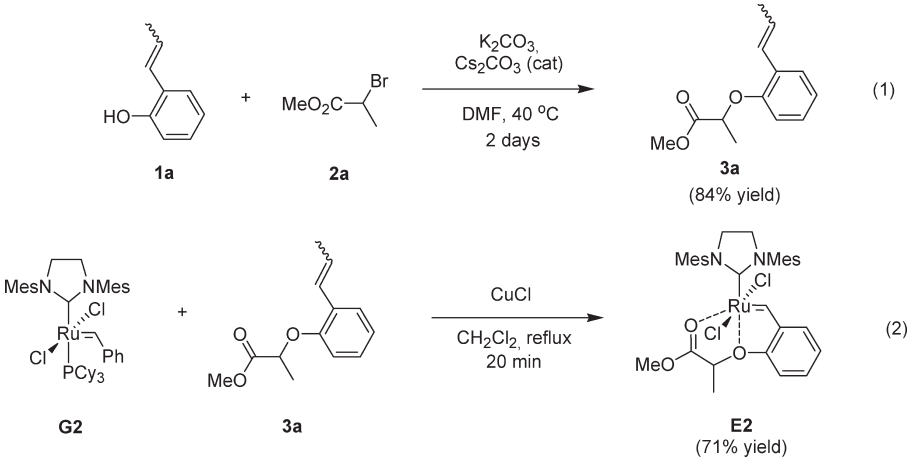
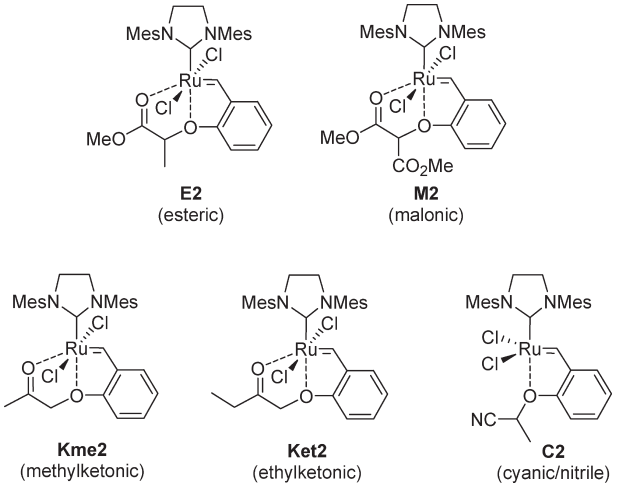
Scheme 2. Stepwise Preparative Procedure of the Catalyst E2



Scheme 3. New Precatalysts Generated from Monofunctionalized Styrenyl Ethers



to afford the desired precatalyst **E2** (Scheme 2, eq 2), recovered in 71% yield in the form of a green crystalline compound.

An X-ray structure analysis of complex **E2**[22] revealed that the global arrangement of ligands around the metal center has characteristics in common with those found in a classical Grubbs/Hoveyda II-type complex, similarly showing the NHC in an apical position, the two mutually trans halides and the carbenic carbon of the chelating carbene ligand occupying the equatorial plane, and the ether group of the chelating carbene occupying the trans position relative to the NHC, with a Ru(1)−O(1) distance of 2.207(2) Å, which is significantly shorter than the corresponding distance of 2.256(1) Å found in the parent **H2** complex. An additional characteristic geometrical feature, however, was found to be the occurrence of a weak bonding interaction, Ru(1)−O(2) = 2.535(1) Å, between the terminal oxygen of the ester functionality and the ruthenium center, thus completing an octahedral basis set.[27] Intuitively, these geometrical parameters might be indicative of a better stabilization of the metal center, and further manipulation of the complex effectively revealed its enhanced stability in air, particularly in the solid state, as well as in solution, allowing its easy purification through a chromatographic column, with both of these properties representing a beneficial practical advantage.

B. Extended Design of Malonic-, Ketyl-, and Nitrile-Functionalized Grubbs/Hoveyda Catalysts. In a logical extension of the above synthetic route, we were prompted to devise a full palette of new catalysts differing in the nature of the potential donor group installed as a terminal substituent of the benzylidene ether (Scheme 3).

The procedure used for their individual preparation was directly inspired from that shown in Scheme 2 for catalyst **E2**, using the specific experimental conditions given in Table 1 for the organic ligand precursors and in Table 3 for the complexes. Thus, in a series of parallel typical experiments, commercially available 2-(1-propenyl)phenol was coupled with the appropriate substrate R−X, in the presence of a base. In most cases, using carbonate as a base produced the coupled product in satisfactory yields, except when dimethyl 2-chloromalonate was used as a coupling partner (entry 2, 37% yield). Even in that case, however, a major improvement was possible by using NaH as a stronger base and a slightly higher temperature, affording the malonate product in 81% yield. The syntheses of the corresponding precatalysts from these ligands proceeded cleanly in dichloromethane, on the model of eq 2 in Scheme 2. The progress of these reactions was monitored by thin-layer chromatography in order to optimize the reaction time. A comparative analysis of the optimized yields and experimental conditions necessary for the generation of these precatalysts is provided in Table 3. It is noteworthy that the ketonic catalysts can be generated under milder conditions and within a shorter time than the others. In contrast, and very strangely, the presence of a phenyl ring as a substituent of the ketonic fragment (Table 3, entry 7) led to a very unstable catalyst which could not be isolated, possibly due to its steric hindrance, an observation revealing the importance of subtle ligand modifications on the reactivity of Hoveyda catalysts. As mentioned in the Introduction, an additional series of "upgraded" precatalysts incorporating two electron-withdrawing groups, namely, X (esteric or ketonic) on the ether and Y (nitro or acyl) on the para position of the aromatic ring relative to the ether, were also synthesized (Scheme 4).

The bifunctionalized styrenyl ethers required for their preparation were obtained according to the experimental procedures shown in Table 2. It is noteworthy that the preparation of

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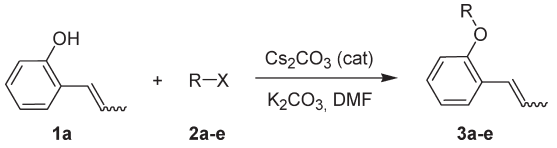
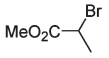
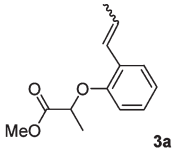
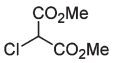
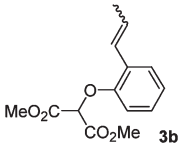
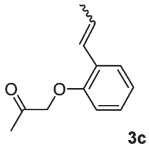
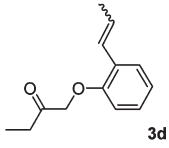
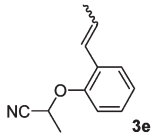
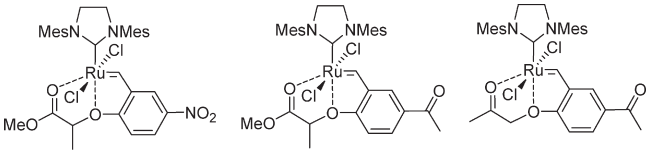
Table 1. Syntheses of Monofunctionalized Styrenyl Ethers



Entry	RX	Conditions	Product	Yield, [%]
1	 **2a**	40 °C, 2 days	 **3a**	84
2	 **2b**	45 °C, 4 days	 **3b**	37
3	 **2c**	50 °C, 20h	 **3c**	73
4	 **2d**	25 °C, 1h	 **3d**	90
5	 **2e**	60 °C, 24h	 **3e**	90

Scheme 4. New Catalysts Generated from Bifunctionalized Styrenyl Ethers



NE2 (nitroesteric) **KE2** (ketoesteric) **KK2** (ketoketonic)

the ligands for keto esteric and keto ketonic catalysts required an additional step consisting of a well established Ru-catalyzed isomerization of the double bond. From these ligands, the preparation of the complexes proceeded straightforwardly under the experimental conditions depicted in Table 3.

C. Structural Analyses of the New Complexes. Some of the precatalysts reported here, namely, **E2**, **M2**, **Ket2**, **Kme2**, and **C2**, gave suitable crystals, which were subjected to X-ray structure analyses. The structure of the prototype **E2** has been briefly described above and in a preliminary account of this work.[22] Crystals of the new ketonic complexes **Ket2** and **Kme2** were grown by slow evaporation of CH_2Cl_2/MeOH solvent mixtures. The respective molecular structures of the two complexes are shown in Figure 1, along with a selection of interatomic distances and bond angles.

Both of these complexes are isostructural with the ester derivative **E2**, with the metal being in the same distorted-octahedral environment. Here, the interatomic distance Ru(1)—O(1) between the ether oxygen and the metal is only 2.1991(19) Å for **Ket2** and 2.2232(18) Å for **Kme2**, which to our knowledge[28] represents the shortest Ru—O distances reported so far for a chelating Hoveyda-type carbene. In addition, the interatomic distance (Ru(1)—O(2) = 2.551 Å for **Ket2** and Ru(1)—O(2) = 2.529 Å for **Kme2**) between the carbonyl group and the metal center are similar to that for **E2** (Ru(1)—O(2) = 2.536 Å), though the difference between the two is probably not chemically significant. The structure of the malonate derivative **M2** is shown in Figure 2.

Since we have here a more electron-withdrawing group as a terminal substituent of the ether, one would intuitively expect the Ru—O(ether) distance to be longer, and this is effectively the case, since the actual value, Ru(1)—O(1) = 2.2780(9) Å, is about 0.1 Å longer than those for the keto complexes (vide supra). Nevertheless, the malonate group adopts a geometry where one of its carbonyl groups lies in the plane of the chelating carbene and is pointing toward the Ru center, even if, in that case, the corresponding interatomic distance Ru(1)—O(2) = 2.775 Å, geometrically correlated with the magnitude of Ru(1)—O(1), is necessarily longer than in the previous case.

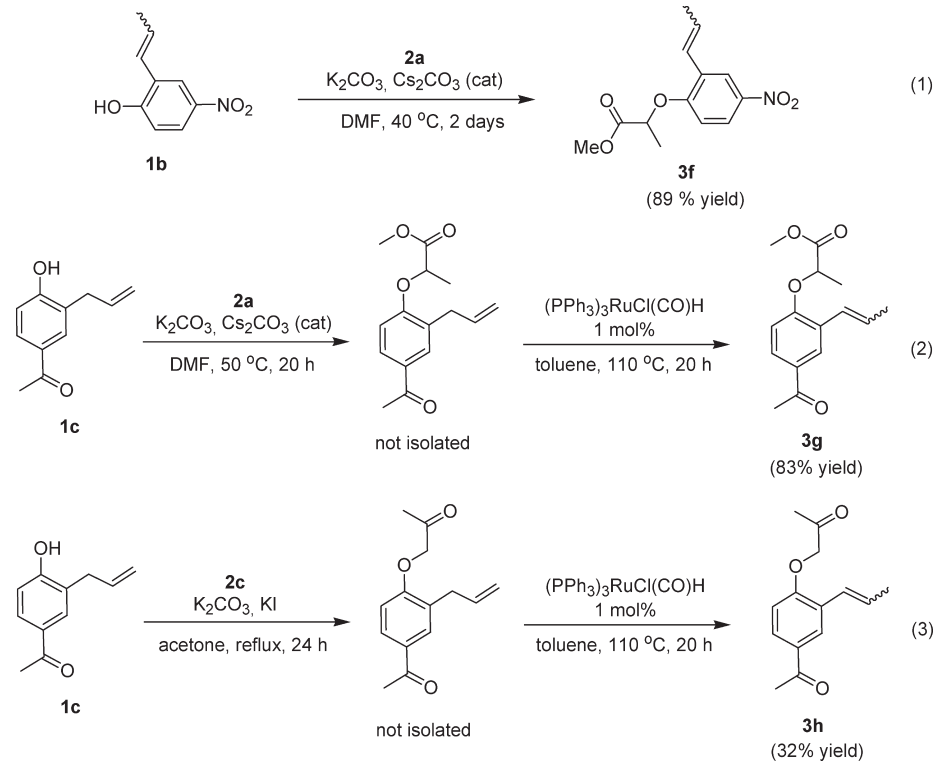
The structure of the nitrile-substituted derivative **C2**, shown in Figure 3, is peculiar, since it does not show any "side-on" bonding interation between the nitrile group and the metal center, the nitrile group being oriented away from the main plane of the chelating carbene ligand. Here, the Ru(1)—O(1) distance is 2.2753(11) Å, the longest of the whole series of complexes reported here and also slightly longer than that in the Hoveyda prototype, but shorter than that in many of its congeners.[26]

D. Catalytic Activity of the New Complexes in RCM. Having in hand a palette of benzylidene-modified ruthenium complexes (Schemes 3 and 4), we first attempted to evaluate their respective catalytic activities in RCM. The overall results are reported in Table 4, whereas the kinetic plot of some specific entries are also shown in Figures 4—6.

a. RCM at 0 °C. In order to compare the respective efficiencies of the above complexes, we first used them in two parallel standard RCM reactions, carried out in identical Schlenk tubes, using diallyl malonate (Figure 4) and diallyltosylamide (Figure 5) as substrates. Since the RCM in the presence of our catalysts appeared to be too fast at room temperature to allow accurate kinetic measurements, we were led to work at 0 °C in such a way to maximize possible differences between the respective efficiencies of the precatalysts. The course of the reactions was monitored by GC, and ethyl vinyl ether was employed to quench the reactions at given time intervals.

The results shown in Figure 4 indicate first that all the ligand modifications introduced in the present work result in an enhancement of activity relative to that of the unmodified Hoveyda catalyst, which appears as the least efficient of the whole series. Though slightly better, Grubbs catalyst **G2** is only moderately efficient under such low-temperature conditions, since its activity reaches a plateau after about 1 h (Figure 4), giving a maximum conversion of 30%. Such a limitation, observable at low temperature, has already been noted by Grubbs himself in a previous comparative analysis of a series of olefin

Table 2. Syntheses of Bifunctionalized Styrenyl Ethers



metathesis catalysts, where the same plateau was observed;[6] it may be due to catalyst decomposition via further attack of the liberated phosphine onto the carbene center, with formation of a phosphorus ylide,[29] an observation which has been made in several instances and highlights the advantage of working with phosphine-free olefin metathesis catalysts.[30] It is also noteworthy that Blechert's catalyst systematically exhibits excellent performance and is (only slightly) surpassed by the polyfunctional "nitro-ester" (**NE2**) and "keto-ester" (**KE2**) catalysts. The monofunctionalized nitro catalyst **N2** initiates slightly less rapidly than Blechert's but leads to a final conversion of 85%, which is 10% superior to the latter. In addition, the ester catalyst **E2** exhibits very good performance, remaining the most efficient of the series of monofunctionalized catalysts having a coordinating group as the terminal substituent of the ether. Very characteristically, it initiates more slowly than Blechert's catalyst **B2** but reaches almost the same conversion after 6 h. Also interesting is the observation that a catalyst such as the nitrile derivative **C2**, whose terminal CN ligand has no interaction with the metal (side-on coordination is inoperative for nitriles), initiates more rapidly than **E2** but is surpassed by the latter after 4 h. For the present series of catalysts, a glance at the shape of kinetic plots indicates that the catalysts having a coordinating group as terminal substituent of the ether are initiating *at slightly lower rate* than the others but are reaching a comparable efficiency in the long run, which seems to indicate that they have a longer lifetime. This may reflect the fact that the active species is *more progressively generated* from such stable precursors or may be also indicative of a better ability of the pendant terminal donor group of the styrenyl ether to catch back the metal center, resulting in a more efficient precatalyst regeneration. About the same order of activities is observed for the closely related RCM reaction shown in Figure 4, which includes the case of the malonic derivative: **H2** < **Kme2** < **M2** < **E2** < **N2** < **B2** < **NE2**. Also characteristically, the malonic derivative, for which the interaction between the malonic group and the metal center was noted to be very weak, initiates very rapidly but is surpassed by the ester derivative **E2** after less than 2 h.

b. RCM at Room Temperature (25 or 30 °C). Under such conditions, which are those of normal utilization, the differences noted above between the performances of the new catalysts examined here are reduced, whereas very good to excellent activities are recorded. Of particular interest is the specific example of the RCM of 2-allyl-2-methallylmalonate (entry 3 of Table 4 and Figure 6), a more challenging case, since it involves the difficult formation of a relatively sterically crowded trisubstituted double bond. Whereas the conversion reached by the Hoveyda catalyst **H2** after 30 min is still only 7%, the malonic catalyst **M2** reaches 97% conversion within the same time, which represents a spectacular performance. Not surprisingly, and due to their close structural similarities, the catalysts **E2**, **M2**, and **Kme2** often exhibit very comparably high performances, as illustrated in particular by the RCM reactions of the substrates shown in entries 5 and 6.

E. Catalytic Activity in Cross-Metathesis Reactions. At the present stage of our investigation, it was also of interest to test the ability of our complexes to promote the CM reaction of electron-deficient olefins, which are rather challenging substrates for ruthenium catalysts. As shown in Table 5, almost all the reactions were found to work at room temperature, with relatively low catalyst loadings. A general analysis of the results shows that our catalysts regularly match the performances of Blechert's catalyst, a very good reference for CM reactions. Here, the excellent performances of the catalysts **Ket2** and **E2** (entries 2 and 3) and **NE2** (entry 5) are noteworthy. Substrate-dependent differences

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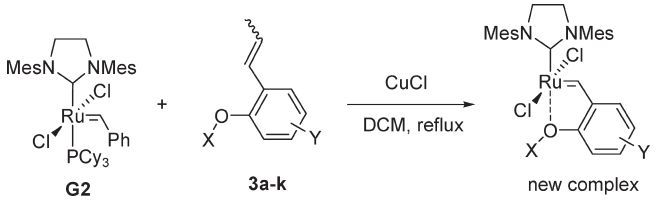
Table 3. Experimental Conditions for the Preparation of the Polyfunctional Precatalysts



Entry	Ligand	Time	Catalyst (yield, %)
1	**3a**	20min.	**E2** (71)
2	**3b**	1h	**M2** (58)
3	**3c**	20min.	**Kme2** (88)
4	**3d**	5min.	**Ket2** (63)
5	**3e**	1h	**C2** (58)
6	**3i**	40min.	-[a]
7	**3j**	20min.	-[a]
8	**3f**	20min.	**NE2** (69)
9	**3g**	20min.	**KE2** (57)
10	**3h**	20min.	**KK2** (56)
11	**3k**	1.5h	-[a]

[a] unstable complex seen to decompose during its attempted isolation.

from one catalyst to the other may be observed but remain difficult to rationalize. In practice, it is noteworthy that the catalysts generated from the monofunctionalized styrenyl esters, exemplified by **E2**, already give very satisfactory results, indicating that there is no real systematic need to invest time in the generation of the polyfunctionalized species. Furthermore, one advantage of **E2** is that it is insensitive to the presence of impurities and can thus even work in an open tube in commercial-grade dichloromethane solvent (Table 5, entry 1).

F. Low-Loading Tests. Attempts to reduce the catalyst loading in metathesis transformations have been an important area of research in recent years; this achievement would lower the process costs, those associated not only with the catalyst but also with the removal of residual ruthenium from products.[3b,15] While several catalysts can efficiently convert di- and trisubstituted dienes into the corresponding RCM product in short reaction times using classical catalyst loadings (1−5 mol %), at very low loadings the catalyst loading limits are 0.0025 and 0.0250 mol %, respectively, for the formation of di- and trisubstituted olefins; however, these limits are under drybox conditions.[31]

Catalysts made by us were able to promote a number of model reactions (Table 6) at loadings from 1.0 to 0.03 mol % *outside of a drybox*. However, a further decrease of the catalyst loading (below 0.03 mol %) showed the limit of these complexes. It seems that, at loadings this low, the careful exclusion of air becomes very important. This is especially visible for reactions done on a relatively small scale (≤1 mmol). We were pleased, however, to observe that the more challenging CM reaction of the sulfone **S16** (Table 6, entry 4) could be achieved in air, using only 0.2 mol % of the ester catalyst. This transformation run on a preparative scale (3 g) produced **P16** in excellent yield.

G. Synthesis of BILN2061 Precursor by RCM. Metathesis has been successfully applied by Boehringer Ingelheim Pharma Inc. in the synthesis of BILN 2061 (Ciluprevir), the first reported

dx.doi.org/10.1021/om200463u |*Organometallics* 2011, 30, 4144–4158

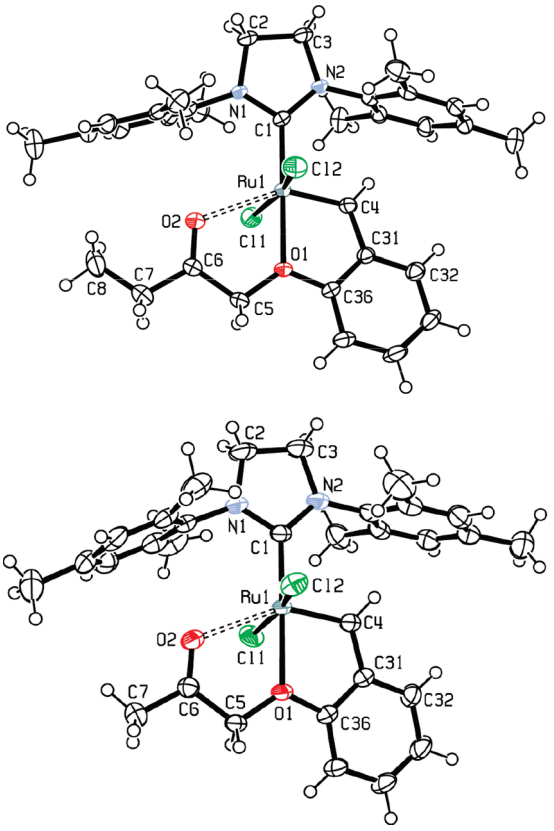


Figure 1. Perspective views of the catalysts **Ket2** (top) and **Kme2** (bottom). Ellipsoids are drawn at the 50% probability level. Selected interatomic distances (Å) and bond angles (deg) are as follows. **Ket2**: Ru(1)−C(1) = 1.980(3), Ru(1)−C(4) = 1.832(3), Ru(1)−O(1) = 2.1991(19), Ru(1)−Cl(1) = 2.3608(9), Ru(1)−Cl(2) = 2.3620(9); Cl(1)−Ru(1)−Cl(2) = 165.17(3), C(1)−Ru(1)−O(1) = 176.05(10), C(4)−Ru(1)−O(1) = 80.58(10), C(1)−Ru(1)−Cl(2) = 90.43(8), O(1)−Ru(1)−Cl(1) = 88.76(7). **Kme2**: Ru(1)−C(1) = 1.985(2), Ru(1)−C(4) = 1.834(3), Ru(1)−O(1) = 2.2232(18), Ru(1)−Cl(1) = 2.3734(14), Ru(1)−Cl(2) = 2.3520(15); Cl(1)−Ru(1)−Cl(2) = 165.79(3), C(1)−Ru(1)−O(1) = 179.06(7), C(4)−Ru(1)−O(1) = 80.56(10), C(1)−Ru(1)−Cl(2) = 95.51(8), O(1)−Ru(1)−Cl(1) = 84.71(7).

hepatitis C virus (HCV) NS3 protease inhibitor to have shown an antiviral effect in infected humans.[32] The HCV infection is a serious cause of chronic liver disease worldwide. The macrocycle peptide BILN 2061 is the first compound of its class to have reached clinical trials and to have shown oral bioavailability and antiviral effects in infected humans. The key step in its preparation is the RCM of the diolefinic compound BILN1 (Table 7), leading to the cyclic 15-membered olefinic compound BILN2. The results show that the ester catalyst **E2** is much more efficient for this reaction than the parent Hoveyda complex **H1** and even outperforms the nitro catalyst **N2** (Figure 7). This figure also reveals that a highly beneficial protocol is to add the catalyst stepwise in two portions, the first one initially (0.4 mol % Ru) and the second one (0.2 mol % Ru) after 1 h.

H. Digression on the Stability of Our Precatalysts in Solution. During the course of the present work, we decided to study the respective stabilities of our complexes in solution, in the absence of olefinic substrate. To do so, three representative complexes were chosen by us: the unmodified Hoveyda catalyst

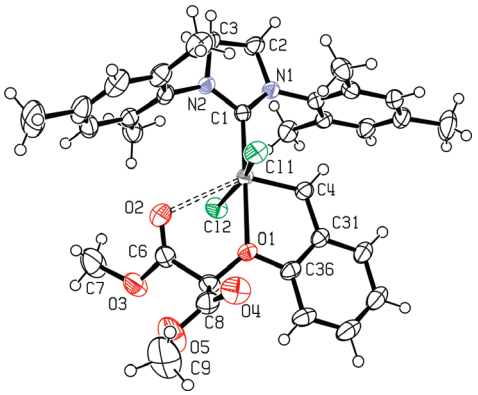


Figure 2. Perspective view of the catalyst **M2**, represented with ellipsoids drawn at the 50% probability level. Selected interatomic distances (Å) and bond angles (deg): Ru(1)−C(1) = 1.9822(11), Ru(1)−C(4) = 1.8285(13), Ru(1)−O(1) = 2.2780(9), Ru(1)−Cl(1) = 2.3603(3), Ru(1)−Cl(2) = 2.3364(3); Cl(1)−Ru(1)−Cl(2) = 163.629(14), C(1)−Ru(1)−O(1) = 179.65(4), C(4)−Ru(1)−O(1) = 80.16(5), C(1)−Ru(1)−Cl(2) = 93.28(3), O(1)−Ru(1)−Cl(1) = 85.29(3).

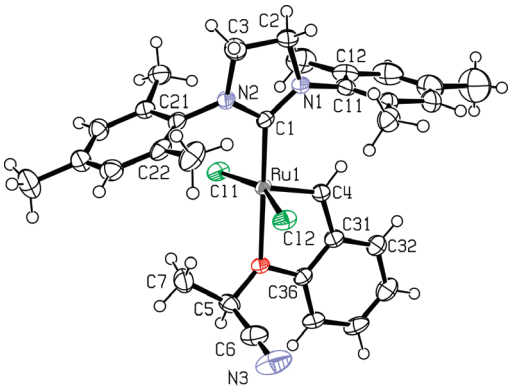
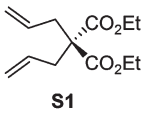
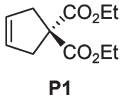
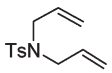
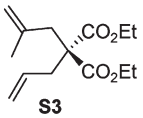
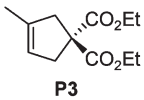
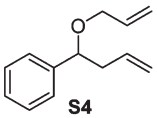
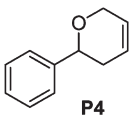
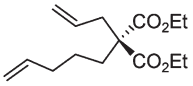
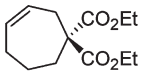
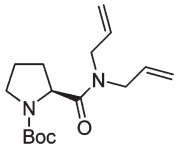
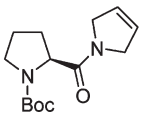


Figure 3. Perspective view of the catalyst **C2**. Ellipsoids are drawn at the 50% probability level. Selected interatomic distances (Å) and bond angles (deg): Ru(1)−C(1) = 1.9677(15), Ru(1)−C(4) = 1.8290(16), Ru(1)−O(1) = 2.2753(11), Ru(1)−Cl(1) = 2.3300(4), Ru(1)−Cl(2) = 2.3264(4); Cl(1)−Ru(1)−Cl(2) = 158.509(18), C(1)−Ru(1)−O(1) = 176.73(5), C(4)−Ru(1)−O(1) = 79.64(6), C(1)−Ru(1)−Cl(2) = 91.84(4), O(1)−Ru(1)−Cl(1) = 86.01(3).

H2, the ester complex **E2** stabilized by the extra Ru···O chelation (representative 18-electron complex), and the cyano-substituted catalyst **C2** as an example of an activated complex, where additional stabilization via chelation is not possible (Figure 8). Dichloromethane, a privileged solvent for olefin metathesis, was logically selected as a solvent for these experimental tests. It is noteworthy that the time over which we followed the decomposition of these precatalysts is much longer than the time required for most catalytic reactions reported here. Thus, at least for the most stable precatalysts tested here, the observed intrinsic decomposition has very little incidence on the course of the catalytic reaction. Importantly, it appears that the ester catalyst **E2** is the most stable of the whole series, immediately followed by the unmodified second-generation Hoveyda catalyst **H2**. As expected, catalyst **C2**, bearing a cyano group with no extra stabilizing interaction with the metal center, undergoes more rapid decomposition.

Table 4. RCM Reactions (0.02 M in CH_2Cl_2)

Entry	Substrate	Catalyst ([mol %])	Conditions Temp [°C], *t* [min]	Product	yield [%][a]
1	 S1	G2 1.0	0 240	 P1	(34)
		H2 1.0	0 240		(14)
		B2 1.0	0 240		(74)
		N2 1.0	0 240		(81)
		E2 1.0	0 240		(60)
		Kme2 1.0	0 240		(58)
		Ket2 1.0	0 240		(49)
		C2 1.0	0 240		(63)
		NE2 1.0	0 240		(87)
		KE2 1.0	0 240		(85)
		KK2 1.0	0 240		(49)
2	 S2	H2 1.0	0 60	 P2	(10)
		B2 1.0	0 60		(95)
		N2 1.0	0 60		(78)
		E2 1.0	0 60		(55)
		M2 1.0	0 60		(78)
		Kme2 1.0	0 60		(54)
		NE2 1.0	0 60		(99)
3	 S3	H2 1.0	30 30	 P3	(7)
		N2 1.0	30 30		(86)
		M2 1.0	30 30		(97)
		Kme2 1.0	30 30		(49)
4	 S4	N2 1.0	25 60	 P4	90 [ref. 18b]
		E2 1.0	25 60		92
		M2 1.0	25 60		89
		Kme2 1.0	25 60		89
5	 S5	E2 1.0	25 60	 P5	75
		M2 1.0	25 60		67
		Kme2 1.0	25 60		71
6	 S6	E2 1.0	25 120	 P6	85
		M2 1.0	25 120		80
		Kme2 1.0	25 120		83

[a] Isolated yields after silica gel chromatography. Yields determined by GC using an internal standard are given in parentheses.

■ CONCLUSION

Whereas the primary objective of the present work was to boost the activity of Hoveyda catalysts by introducing an electron-withdrawing group as a terminal substituent of the "leaving" benzylidene ether group, we have learned that, in cases where such a substituent is an ester group, a ketonic group ,or a malonic group, it functions as an additional coordinating functionality binding the metal center. They constitute a new structural variety of Grubbs/Hoveyda precatalysts having an octahedral geometry and yet exhibiting enhanced catalytic performance. When they are dissolved in dichloromethane in the absence of olefin, the resulting precatalysts differing in the nature of the installed donor group appear to exhibit a stability which, at least for the ester derivative, matches that of the parent Hoveyda complex. A further valuable advantage of these upgraded catalysts is that the presence of an additional coordinating group (ester, ketone, malonate) brings additional protection to the metal center, allowing in particular their manipulation in air and their purification by chromatography. Interestingly, however, their enhanced stability is not detrimental, since these catalysts were found to exhibit systematically higher activity than the unmodified

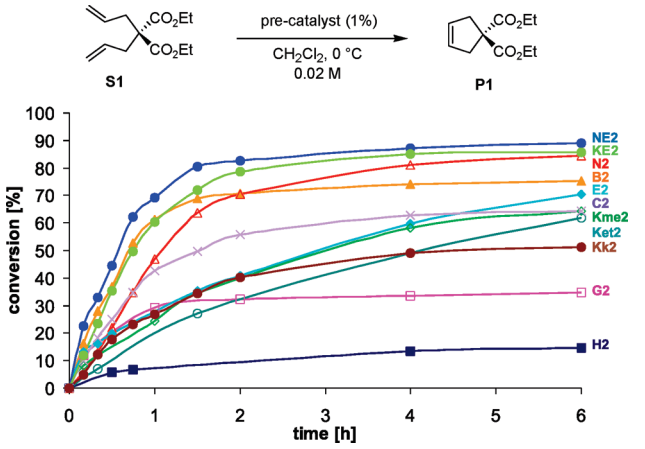


Figure 4. Catalytic activity of **NE2** (●), **KE2** (●), **N2** (△), **B2** (▲), **E2** (◆), **C2** (×), **Kme2** (◇), **Ket2** (○), **KK2** (●), **G2** (□), and **H2** (■) in the RCM of diallyl diethylmalonate (**S1** → **P1**, dichloromethane, 1 mol % of ruthenium precatalyst, 0 °C, 6 h, conversion according to GC using internal standard).

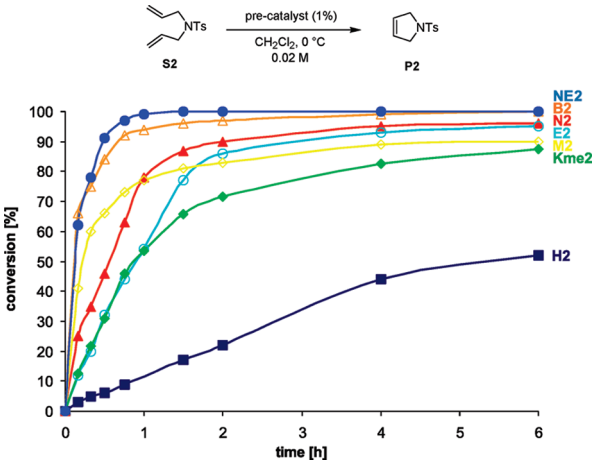


Figure 5. Catalytic activity of **NE2** (●), **B2** (△), **N2** (▲), **E2** (○), **M2** (◇), **Kme2** (◆), and **H2** (■) in RCM involving the formation of a disubstituted double bond (**S2** → **P2**, dichloromethane, 1 mol % of ruthenium precatalyst, 0 °C, 6 h, conversion according to GC using internal standard).

Hoveyda prototype in RCM and CM, for both standard and challenging substrates. The overall excellent performance of these new catalysts may be rationalized in terms of *a more progressive liberation of the active propagating species in the reaction medium* and possibly also (but this remains to be demonstrated) to a better ability of the functionalized styrenyl ether to use its additional pendant coordinating group to recapture the metal center in the "return" process leading to catalyst regeneration. Even more sophisticated upgraded polyfunctional catalysts were accessed by introducing both a coordinating group as a terminal substituent of the ether and an electron-withdrawing group as a substituent of the aromatic ring of the benzylidene moiety.[33] In the latter case, however, we reach a point where the catalyst's efficiency starts to be affected by its lower stability. It also appears that minor differences that are becoming detectable from one precatalyst to the other for a given substrate cannot be fully rationalized and can be only evaluated by experimental catalytic tests, not necessarily transposable from one substrate to the other.

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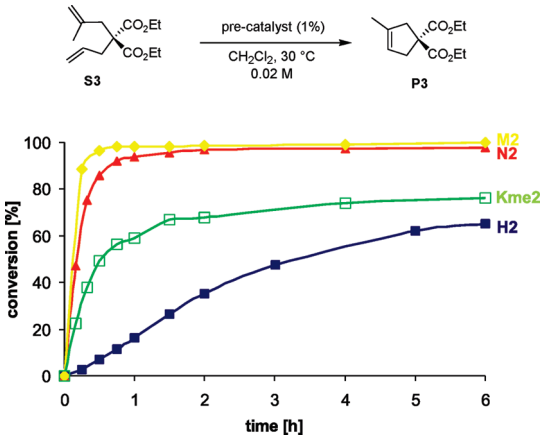


Figure 6. Catalytic activity of **M2** (◆), **N2** (▲), **Kme2** (□), and **H2** (■) in RCM involving the formation of a trisubstituted double bond (**S3** → **P3**, dichloromethane, 1 mol % of ruthenium precatalyst, 30 °C, 6 h, conversion according to GC using internal standard).

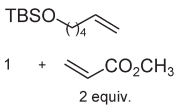
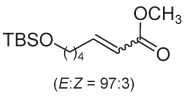
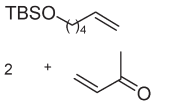
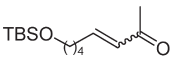
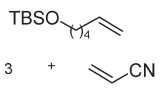
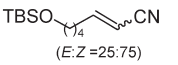
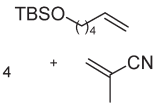
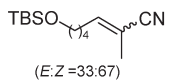
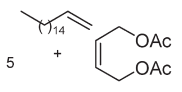
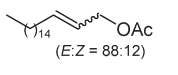
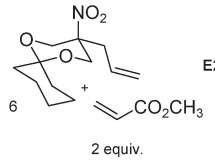
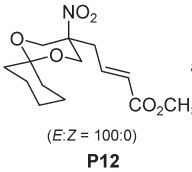
■ EXPERIMENTAL SECTION[34]

General Procedure for Preparation of Ligands. To a suspension of K_2CO_3 (5.64 g, 40.8 mmol) and Cs_2CO_3 (2.65 g, 8.14 mmol) in DMF (100 mL) was added 2-[(1*E*,*Z*)-prop-1-en-1-yl)phenol (2.5 mL, 20.0 mmol). After the mixture was stirred for 30 min at 40 °C, alkylation reagent (24.0 mmol) was added and the reaction mixture was stirred (for 1 h to 4 days) at the same temperature. The reaction mixture was poured into water (40 mL) and extracted with Et_2O (3 × 40 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a crude product. The crude product was purified by column chromatography (using eluents: cyclohexane/ethyl acetate, 10:1 to 5:1 v/v).

*Dimethyl {2-[(1E,Z)-Prop-1-en-1-yl]phenoxy}malonate (**3b**).* Yield: 37%, yellow oil. Isomer mixture *E*/*Z* = 7/3. IR (film): ν 2959, 2852, 1751, 1487, 1437, 1227, 1200, 1161, 1019, 754 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): *E* isomer, δ 1.92 (dd, *J* = 6.6, 1.8 Hz, 3H), 3.85 (s, 6H), 5.20 (s, 1H), 6.30 (dq, *J* = 15.8, 6.6 Hz, 1H), 6.76 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.82 (dd, *J* = 15.8, 1.8 Hz, 1H), 6.98−7.06 (m, 1H), 7.08−7.15 (m, 1H), 7.44 (dd, *J* = 7.7, 1.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): *E* isomer, δ 18.9 (CH_3), 53.2 (CH_3), 77.4 (CH), 113.8 (CH), 123.0 (CH), 125.0 (CH), 126.9 (CH), 127.5 (CH), 127.6 (CH), 128.5 (C), 153.5 (C), 166.1 (C); MS (EI): *m*/*z* (relative intensity) 264 (28, $[M]^{\bullet+}$), 200 (8), 173 (9), 145 (37), 133 (100), 131 (42), 115 (27), 105 (52), 91 (15), 77 (15), 59 (9), 51 (9) 39 (10). HRMS (EI): *m*/*z* calcd for $C_{14}H_{16}O_5$ ($[M]^{\bullet+}$) 264.099 77, found 264.098 89.

*1-{2-[(1E,Z)-Prop-1-en-1-yl]phenoxy}acetone (**3c**).* Yield: 73%, colorless oil. Isomer mixture *E*/*Z* = 7/3. IR (film): ν 3033, 2914, 1722, 1598, 1487, 1452, 1433, 1357, 1229, 1117, 1061, 970, 751, 615, 512 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): *E* isomer, δ 1.92 (dd, *J* = 6.6, 1.7 Hz, 3H), 2.30 (s, 3H), 4.53 (s, 2H), 6.26 (dq, *J* = 15.9, 6.6 Hz, 1H), 6.68 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.78 (dd, *J* = 15.9, 1.7 Hz, 1H), 6.91−7.02 (m, 1H), 7.11−7.17 (m, 1H, *E*), 7.44 (dd, *J* = 7.7, 1.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): *E* isomer, δ 18.9 (CH_3), 26.7 (CH_3), 73.3 (CH_2), 111.7 (CH_2), 121.7 (CH), 125.1 (C), 126.6 (CH), 127.0 (CH), 127.7 (CH), 130.5 (CH), 154.2 (C), 206.1 (C); MS (EI): *m*/*z* (relative intensity) 190 (39, $[M]^{\bullet+}$), 147 (11), 133 (52), 132 (19), 131 (31), 119 (10), 115 (23), 105 (15), 103 (10), 91 (100), 77 (17), 51 (10), 43 (44), 41 (10), 39 (14). HRMS (EI): *m*/*z* calcd for $C_{12}H_{14}O_2$ ($[M]^{\bullet+}$) 190.099 38, found 190.099 01. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.32; H, 7.31.

Table 5. CM Reactions

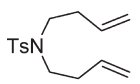
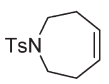
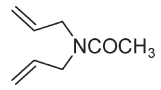
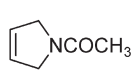
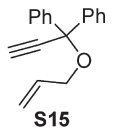
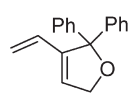
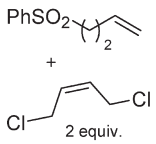
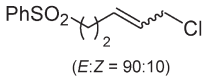
Entry	Substrate	Catalyst ([mol %])	Conditions Temp [°C], *t* [min]	Product	yield [%][a]
1	 2 equiv.	**B2** 2.5	20 20	 (*E*:*Z* = 97:3) **P7**	91 [ref. 11a]
		N2 1.0	25 60		(95)
		Ket2 1.0	25 120		(68)
		E2 1.0	25 20		(59)
		E2 1.0	25 300		(85)
		E2 1.0	25 960		89[b]
		NE2 1.0	25 20		(74)
		NE2 1.0	25 300		(78)
2	 2 equiv.	**B2** 1.0	20 40	 (*E*:*Z* = 100:0) **P8**	(90) [ref. 11a]
		N2 2.5	25 30		82 [ref. 18b]
		Ket2 1.0	25 300		(57)
		E2 1.0	25 30		(50)
		E2 1.0	25 60		82
		NE 1.0	25 40		(65)
3	 2 equiv.	**N2** 5.0	25 120	 (*E*:*Z* =25:75) **P9**	(83) [ref. 18b]
		Ket2 3.0	25 300		(95)
		E2 1.0	25 1440		(59)
		E2 3.0	25 300		(94)70
		C2 3.0	25 1440		(48)
		NE2 1.0	25 300		(45)
		NE2 1.0	25 1440		(51)
4	 4 equiv.	**G2** 5.0	40 1440	 (*E*:*Z* =33:67) **P10**	(30)
		H2 5.0	40 960		(40) [ref. 18b]
		N2 5.0	40 960		58 [ref. 18b]
		E2 5.0	40 960		56
5	 2 equiv.	**N2** 3.0	28 180	 (*E*:*Z* = 88:12) **P11**	85 [ref. 22a]
		N2 1.0	25 120		55
		C2 1.0	25 180		38
		NE2 1.0	25 120		97 [ref. 22a]
		NE2 0.3	25 30		(80)73 [ref. 22a]
		KE2 1.0	25 120		64
6	 2 equiv.	**E2** 2.0	26 300	 (*E*:*Z* = 100:0) **P12**	88 [ref. 22a]

[a] Isolated yields after silica gel chromatography. Yields determined by GC are given in parentheses. [b] Reaction in commercial-grade CH_2Cl_2, on air.

*1-{2-[(1E,Z)-Prop-1-en-1-yl]phenoxy}butan-2-one (**3d**).* Yield: 90%, colorless oil. Isomer mixture *E*/*Z* = 7/3. IR (film): ν 3073, 3033, 2978, 2938, 2912, 2881, 2855, 1722, 1598, 1579, 1487, 1453, 1434, 1406, 1378, 1292, 1245, 1224, 1160, 1114, 1055, 1024, 973, 944, 752 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): *E* isomer, δ 1.11 (t, *J* = 7.3 Hz, 3H), 1.92 (dd, *J* = 6.6, 1.8 Hz, 3H), 2.66 (q, *J* = 7.3 Hz, 2H), 4.55 (s, 2H), 6.26 (dq, *J* = 15.8, 6.6 Hz, 1H), 6.67 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.78 (dq, *J* = 15.8, 1.8 Hz, 1H), 6.91−6.97 (m, 1H), 7.11−7.16 (m, 1H), 7.43 (dd, *J* = 7.7, 1.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): *E* isomer, δ 7.0 (CH_3), 18.9 (CH_3), 32.3 (CH_2), 73.0 (CH_2), 111.6 (CH), 121.6 (CH), 125.1 (C), 126.6 (CH), 127.4 (CH), 127.7 (CH), 130.4 (CH), 154.3 (C), 208.5 (C); MS (EI): *m*/*z* (relative intensity) 204 (72, $[M]^{\bullet+}$), 148 (6), 147 (25), 134 (13), 133 (100), 132 (20), 131 (32), 119 (11), 115 (16), 105 (9), 103 (5), 91 (54), 77 (7), 57 (26), 41 (5). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.45; H, 7.93.

*2-(2-Propenylphenoxy)propionitrile (**3e**).* Yield: 90%, yellow oil. Isomer mixture *E*/*Z* = 5/2. IR (film): ν 3034, 2966, 2916, 2854, 1651, 1600, 1580, 1487, 1447, 1368, 1296, 1264, 1220, 1195, 1165, 1115, 1090, 1057, 1040, 968, 946, 897, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *E* isomer, δ 1.83 (d, *J* = 6.7 Hz, 3H), 1.91 (dd, *J* = 6.6, 1.7 Hz, 3H), 4.84 (q, *J* = 6.7 Hz, 1H), 6.25 (dq, *J* = 15.9, 6.7 Hz, 1H), 6.64 (dd, *J* = 15.9, 1.7 Hz, 1H), 6.98−7.12 (m, 2H), 7.18−7.33 (m, 1H), 7.45 (dd, *J* = 7.7, 1.7 Hz, 1H).

Table 6. "Low Loading" Tests of Metathesis Transformations (0.02 M in CH_2Cl_2)

Entry	Substrate	Catalyst ([mol %])	Conditions[a] Temp [°C], *t* [min]	Product	yield [%][b]
1	 **S13**	**N2** 1.00	0 60	 **P13**	(100)
		C2 1.00	0 60		92
		NE2 0.03	25 30		(41)
		NE2 0.06	25 40		(65)
		KE2 0.06	25 40		(69)
		M2 0.06	25 40		(34)
2	 **S14**	**NE2** 0.03	25 30	 **P14**	(96)
		KE2 0.03	25 30		(90)
		M2 0.03	25 30		(68)
3	 **S15**	**N2** 1.00	0 60	 **P15**	99
		Kme2 1.00	25 15		89
		C2 1.00	0 60		92
		NE2 0.20	25 90		85
		NE2 0.05	25 60		(28)
		KE2 0.20	25 90		93
		M2 0.20	25 90		87
4	 2 equiv.	**H2** 1.0	25 60	 (*E*:*Z* = 90:10) **P16**	(100)
		H2 1.0	25 60		(100)
		H2 0.2	25 180		(67)
		E2 0.2	25 180		(82)
		E2 0.3	25 240		89[c]

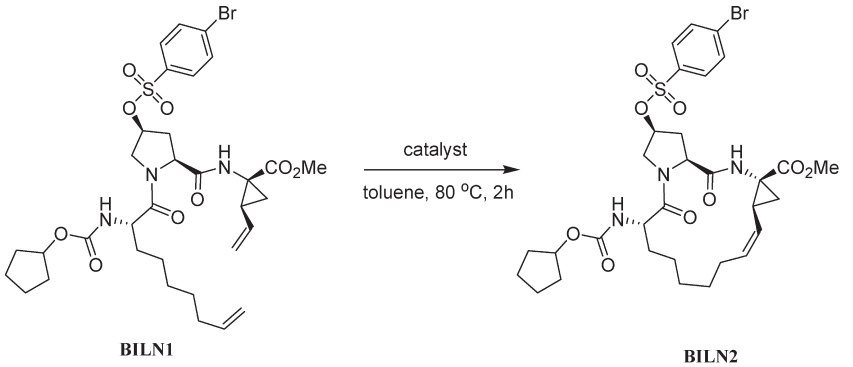
[a] Reactions performed outside of a glovebox. [b] Isolated yields after silica gel chromatography. Yields determined by GC using an internal standard are given in paretheses. [c] Reaction performed on a 15 mmol scale.

^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer, δ 18.8 (CH_3), 19.9 (CH_3), 63.4 (CH), 114.8 (CH), 123.5 (CH), 124.6 (CH), 126.8 (CH), 127.7 (CH), 127.8 (C), 128.1 (C), 130.7 (CH), 153.9 (C). MS (EI): *m*/*z* (relative intensity) 187 (54, $[M]^{\bullet+}$), 158 (7), 133 (23), 105 (100), 77 (18). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.98; H, 7.11; N, 7.53.

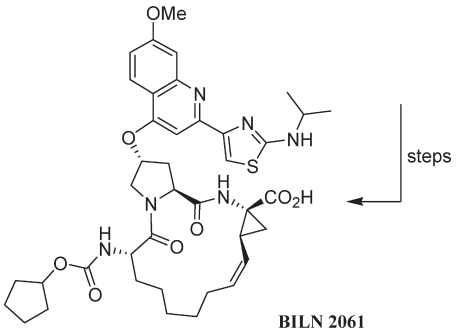
Methyl 2-(4-Acetyl-2-propenylphenoxy)propionate (***3g***). Yield: 96%, yellow oil. Isomer mixture *E*/*Z* = 10/1. IR (film): ν 1732, 1670, 1597, 1573, 1492, 1448, 1436, 1358, 1325, 1302, 1278, 1247, 1133, 1102, 1054, 971, 825, 585 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *E* isomer, δ 1.68 (d, *J* = 7.0 Hz, 3H), 1.92 (dd, *J* = 6.7, 1.7 Hz, 3H), 2.56 (s, 3H), 3.76 (s, 3H), 4,63 (q, *J* = 7.0 Hz, 1H), 6.36 (dq, *J* = 16.0, 6.7 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 6.76 (dd, *J* = 16.0, 1.7 Hz, 1H), 7.75 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.05 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer, δ 18.5 (CH_3), 18.9 (CH_3), 26.3 (CH_3), 52.4 (CH_3), 72.9 (CH), 111.5 (CH), 124.6 (CH), 127.2 (CH_3), 127.6 (C), 128.1 (CH), 128.5 (CH), 130.8 (C), 157.8 (C), 172.0 (C), 196.9 (C). MS (EI): *m*/*z* (relative intensity) 262 (30, $[M]^{\bullet+}$), 247 (11), 203 (12), 161 (38), 43 (100); HRMS (EI): *m*/*z* calcd for $C_{15}H_{18}O_4$ ($[M]^{\bullet+}$) 262.12 051, found 262.119 72.

1-(4-Acetyl-2-propenylphenoxy)propan-2-one (***3h***). Yield: 32%, yellow oil. Isomer mixture *E*/*Z* = 11/1. IR (film): ν 1738, 1669, 1595, 1495, 1426, 1353, 1259, 1180, 1138, 1085, 973, 811, 602 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *E* isomer, δ 1.94 (dd, *J* = 6.6, 1.6 Hz, 3H), 2.32 (s, 3H), 2.57 (s, 3H), 4.63 (s, 2H), 6.39 (dq, *J* = 15.9, 6.6 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 6.75 (dq, *J* = 15.9, 1.6 Hz, 1H), 7.78 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.07 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer, δ 18.9 (CH_3), 26.4 (CH_3), 26.7 (CH_3), 73.1 (CH_2), 110.9 (CH), 124.4 (CH), 127.2 (CH), 127.5 (C), 128.6 (CH), 128.7 (CH), 131.0 (C), 157.7 (C), 196.9 (C), 204.6 (C). MS (EI): *m*/*z* (relative intensity) 232 (36, $[M]^{\bullet+}$), 217 (20), 189 (4), 175 (11), 161 (10), 131 (6), 115 (6), 103 (3), 91 (4), 77 (4), 43 (100). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.13; H, 6.93.

Table 7. Comparative Study of the Activities of Catalysts E2, H1, and N2 in the RCM of BILN1



Entry	Catalyst ([mol%])	Conversion [%][a] BILN1 → BILN2
1	**E2** (0.4)	83[b]
2	**E2** (0.6)	95
3	**H1** (0.4)	60[b]
4	**H1** (0.6)	89
5	**N2** (0.4)	77[b]
6	**N2** (0.6)	93



[a] Conversion is determined by HPLC after 2 h. [b] Conversion is determined by HPLC after 1 h.

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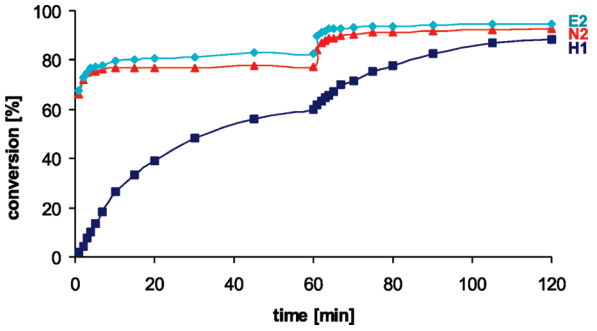

Figure 7. Activity of **E2** (◆), **N2** (▲), and **H1** (■) complexes in the RCM of BILN1 (in toluene, 80 °C, 2 h; catalysts added in two portions (0.4 + 0.2 mol % Ru)). Conversions were determined by HPLC.

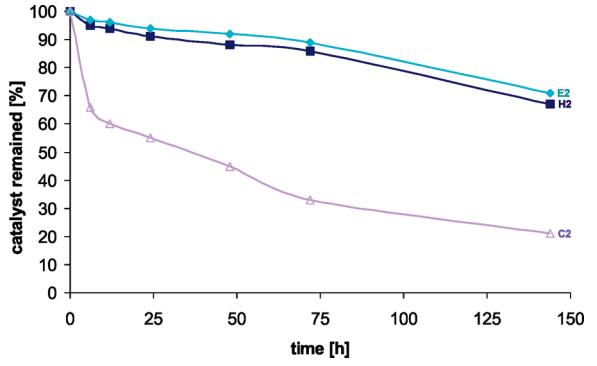

Figure 8. Degradation of representative catalysts in CD_2Cl_2 solution (deoxygenated with argon) at 25 °C using ^{1}H NMR with durene as internal standard. **E2** (◆), **H2** (■), **C2** (△).

*(2-Propenylphenoxy)acetonitrile (**3i**).* Yield: 42%, yellow oil. Isomer mixture *E*/*Z* = 6/3. IR (film): ν 3034, 2966, 2916, 2854, 1651, 1600, 1580, 1487, 1447, 1368, 1296, 1264, 1220, 1195, 1165, 1115, 1090, 1057, 1040, 968, 946, 897, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *E* isomer, δ 1.91 (dd, *J* = 6.7, 1.8 Hz, 3H), 4.76 (s, 2H), 6.24 (dq, *J* = 15.8, 6.7 Hz, 1H), 6.65 (dd, *J* = 15.9, 1.7 Hz, 1H), 6.90−7.12 (m, 2H), 7.18−7.35 (m, 1H), 7.45 (dd, *J* = 7.7, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer, δ 18.8 (CH_3), 54.2 (CH_2), 113.0 (CH), 115.2 (C), 123.4 (CH), 124.5 (CH), 127.0 (CH), 127.8 (CH), 128.2 (C), 130.8 (CH), 153.2 (C); MS (EI): *m*/*z* (relative intensity) 173 (50, $[M]^{\bullet+}$), 144 (20), 105 (100), 77 (21). HRMS (EI): *m*/*z* calcd for $C_{11}H_{11}ON$ ($[M]^{\bullet+}$) 173.0841, found 173.0846. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.50; H, 6.36; N, 7.87.

*1-Phenyl-2-{2-[(1E,Z)-prop-1-en-1-yl]phenoxy}propan-1-one (**3j**).* Yield: 89%, white solid. Mp: 79−81 °C. Isomer mixture *E*/*Z* = 7/3. IR (KBr): ν 3033, 2960, 1690, 1595, 1578, 1486, 1449, 1379, 1301, 1238, 1137, 1090, 1032, 965, 932, 794, 744, 703, 605, 537 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): *E* isomer, δ 1.73 (d, *J* = 6.9 Hz, 3H), 1.89 (dd, *J* = 6.6, 1.7 Hz, 3H), 5.45 (q, *J* = 6.9 Hz, 1H), 6.22 (dq, *J* = 15.9, 6.6 Hz, 1H), 6.69 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.78 (dd, *J* = 15.9, 1.7 Hz, 1H), 6.86−6.94 (m, 1H), 7.02−7.12 (m, 1H), 7.40 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.42−7.48 (m, 2H), 7.53−7.60 (m, 1H), 8.01−8.09 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): *E* isomer, δ 18.7 (CH_3), 18.9 (CH_3), 77.5 (CH), 112.9 (CH), 121.5 (CH), 125.6 (CH), 126.6 (CH), 126.7 (CH), 127.6 (CH), 128.7 (CH_3), 128.9 (CH), 130.5 (CH), 133.5 (CH), 134.3 (C), 154.0 (C), 198.9 (C); MS (EI): *m*/*z* (relative intensity) 266 (32, $[M]^{\bullet+}$), 161 (55), 134 (16), 133 (93), 131 (16), 119 (100), 115 (41), 105 (74), 103 (12), 91 (78), 79 (14), 77 (83), 65 (10), 51 (25), 43 (39), 39 (12); HRMS (EI): *m*/*z* calcd for $C_{18}H_{18}O_2$ ($[M]^{\bullet+}$) 266.130 68, found 266.129 55.

*2-(4-Acetyl-2-propenylphenoxy)propionitrile (**3k**).* Yield: 62%, yellow oil. Isomer mixture *E*/*Z* = 9/1. IR (film): ν 1735, 1651, 1600, 1580, 1487, 1447, 1368, 1296, 1264, 1220, 1195, 1165, 1115, 1090, 1057, 1040, 968, 946, 897, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *E* isomer, δ 1.87 (d, *J* = 6.7 Hz, 3H), 1.94 (dd, *J* = 6.7, 1.8 Hz, 3H), 2.58 (s, 3H), 4,97 (q, *J* = 6.9 Hz, 1H), 6.36 (dq, *J* = 15.9, 6.6 Hz, 1H), 6.65 (dd, *J* = 16.0, 1.7 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 7.83 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.07 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer, δ 18.9 (CH_3), 19.8 (CH_3), 26.4 (CH_3), 62.4 (CH), 112.7 (CH), 117.7 (CH), 123.9 (CH), 127.3 (C), 128.3 (C), 128.5 (CH), 129.1 (CH), 132.1 (C), 156.1 (C), 196.8 (C). MS (EI): *m*/*z* (relative intensity) 229 (36, $[M]^{\bullet+}$), 214 (20), 161 (5), 145 (4), 131 (6), 103 (4), 77 (5), 43 (100). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.08; H, 6.58; N, 5.96.

General Syntheses of Catalysts. A Schlenk tube equipped with a stirring bar was charged with styrene ligand **3a** (0.054 g, 0.24 mmol) and CuCl (0.022 g, 0.22 mmol). The tube was flushed with argon and charged with anhydrous CH_2Cl_2 (10 mL). The ruthenium complex **G2** (0.170 g, 0.20 mmol) was added, and the resulting mixture was stirred at 40 °C for 20 min. After this time, TLC indicated complete conversion of the substrate. The resulting mixture was concentrated in vacuo, the residue was redissolved in AcOEt, and the solution was passed through a Paster pipet containing a small amount of cotton and evaporated to dryness. The crude product was purified by column chromatography (using cyclohexane/ethyl acetate as eluent, 10/1 to 1/1 v/v). After evaporation of the solvents, the resulting solid was collected and washed a few times with AcOEt and with cold *n*-pentane.

*Catalyst **M2**.* Yield: 58%, green microcrystalline solid. IR (KBr): ν 2953, 2919, 2854, 1743, 1597, 1479, 1415, 1264, 1116, 1080, 1034, 852, 748, 580 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (br s, 6H), 2.50 (br s, 12H), 3.67 (s, 6H), 4.12 (s, 4H), 5.28 (s, 1H), 6.58 (d, *J* = 8.3 Hz, 1H), 6.94−7.09 (m, 6H), 7.47 (td, *J* = 9.2, 1.5 Hz, 1H), 16.62 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.1, 51.8, 54.1, 75.6, 112.6, 122.8, 125.0, 128.8, 129.5, 138.1, 145.8, 151.5, 164.9, 209.4, 301.7. MS (ESI$^+$ from $MeOH/CH_2Cl_2$ *m*/*z* 714): the molecular formula was confirmed by comparing the theoretical and experimental isotopic patterns for the $[M]^+$ ion ($C_{33}H_{38}N_2O_5Cl_2Ru$), and these were found to be identical within the experimental error limits.

*Catalyst **Ket2**.* Yield: 63%, green microcrystalline solid. IR (KBr): ν 3425, 3041, 2912, 1714, 1593, 1573, 1478, 1451, 1415, 1262, 1226, 1107, 1034, 1016 849, 753, 729, 579 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.2 Hz, 3H), 2.32 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 6H), 2.50 (s, 12H), 4.12 (s, 4H), 4.71 (s, 2H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.93−7.00 (m, 2H), 7.07 (s, 4H), 7.45−7.50 (m, 1H), 16.63 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 6.8, 19.2, 21.2, 32.5, 51.8, 71.9, 113.0, 122.6, 124.6, 128.7, 129.5, 138.2, 138.6, 146.3, 152.1, 204.6, 210.0, 300.8. MS (EI): *m*/*z* (relative intensity) 654 (2, $[M]^{\bullet+}$), 406 (3), 404 (3), 305 (32), 304 (62), 289 (12), 190 (15), 176 (16), 158 (18), 148 (28), 133 (21), 118 (100), 107 (19), 91 (57), 77 (18), 63 (20), 57 (91), 43 (31), 39 (19). HRMS (EI): *m*/*z* calcd for $C_{32}H_{38}N_2O_2{}^{35}Cl_2{}^{102}Ru$ ($[M]^{\bullet+}$) 654.135 38, found 654.137 90.

*Catalyst **Kme2**.* Yield 88%, green microcrystalline solid. IR (KBr): ν 3448, 2916, 1719, 1594, 1573, 1479, 1415, 1263, 1189, 1110, 1046, 851, 748, 579 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.03 (s, 3H), 2.41 (s, 6H), 2.48 (s, 12H), 4.14 (s, 4H), 4.70 (s, 2H), 6.68 (d, *J* = 8.2 Hz, 1H), 6.94−7.00 (m, 2H), 7.07 (s, 4H), 7.46−7.51 (m, 1H), 16.57 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.2, 21.1, 26.6, 51.7, 73.2, 113.0, 122.7, 124.6, 128.9, 129.4, 138.3, 138.7, 146.1, 152.2, 202.4, 209.8. MS (EI): *m*/*z* (relative intensity) 640 (1, $[M]^{\bullet+}$), 324 (6), 305 (22), 198 (34), 145 (7), 131 (11), 118 (100), 115 (16), 105 (9), 89 (38), 83 (13), 73 (18), 63 (19), 55 (22), 43 (39), 36 (30). HRMS (EI): *m*/*z* calcd for $C_{31}H_{36}N_2O_2{}^{35}Cl_2{}^{102}Ru$ ($[M]^{\bullet+}$) 640.119 73, found 640.118 09.

*Catalyst **C2**.* Yield: 58%,green microcrystalline solid. IR (KBr): ν 3456, 2922, 2851, 1738, 1594, 1572, 1478, 1451, 1424, 1399, 1378, 1295, 1261, 1200, 1158, 1130, 1109, 1034, 941, 853, 797, 750, 579 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.60 (d, *J* = 6.6 Hz, 3H), 2.40 (s, 6H), 2.46

Table 8. Crystal Data and Structure Refinement Details for Complexes Ket2, Kme2, M2, and C2

	Ket2·0.5MeOH	**Kme2**·2CH_2Cl_2	**M2**·1.5CH_2Cl_2·C_6H_{14}	**C2**·2CH_2Cl_2
empirical formula	$C_{32.5}H_{40}Cl_2N_2O_{2.5}Ru$	$C_{33}H_{40}Cl_6N_2O_2Ru$	$C_{40.50}H_{54}Cl_5N_2O_5Ru$	$C_{38}H_{35}Cl_4NP_2Ru$
mol wt (g)	1341.27	1549.45	927.18	810.48
temp (K)	180	180	180	180
λ (Å)		0.71073		
cryst syst	triclinic	triclinic	triclinic	monoclinic
space group	$P\bar{1}$ (No. 2)	$P\bar{1}$ (No. 2)	$C2/c$ (No. 15)	$P2_1/c$ (No. 14)
a (Å)	10.9701(11)	11.913(9)	34.4881(11)	11.9763(4)
b (Å)	11.0589(13)	11.970(7)	15.1596(5)	16.6003(6)
c (Å)	15.1717(15)	15.284(10)	18.2349(6)	18.6197(6)
α (deg)	74.472(9)	106.60(4)		
β (deg)	73.584(9)	93.07(5)	116.1310(10)	102.306(2)
γ (deg)	70.246(10)	117.141(11)		
V (Å^3)	1631.2(3)	1815(2)	8559.2(5)	3616.7(2)
Z	2	2	8	4
D_{calcd} (g cm^{-3})	1.365	1.483	1.439	1.483
μ (mm^{-1})	0.676	0.905	0.723	0.907
F_{000}	694	828	3840	1648
instrument	Oxford Instruments Xcalibur	Oxford Instruments Xcalibur	Bruker D8 Apex II	Bruker D8 Apex II
θ_{max} (deg)	32.06	38.34	37.76	33.05
completeness to θ_{max} (%)	99.0	99.0	92.0	99.0
index ranges	$-13 < h < 13$	$-16 < h < 16$	$-57 < h < 52$	$-15 < h < 18$
	$-12 < k < 13$	$-16 < l < 16$	$-22 < k < 25$	$-25 < k < 25$
	$-18 < l < 18$	$-21 < l < 21$	$-30 < l < 29$	$-28 < l < 25$
no. of rflns collected	70 524	54 028	76 718	75 885
no. of indep rflns	6608	10 379	21 013	13 617
no. of data/restraints/params	6608/0/377	10 379/0/404	21 013/0/423	13 617/0/351
GOF	1.03	1.07	1.116	1.027
R, R_w ($I > 2\sigma(I)$)	R1 = 0.0407	R1 = 0.0363	R1 = 0.0377	R1 = 0.0359
	wR2 = 0.859	wR2 = 0.087	wR2 = 0.1109	wR2 = 0.0893
R, R_w (all data)	R1 = 0.0543	R1 = 0.0408	R1 = 0.0521	R1 = 0.0559
	wR2 = 0.0903	wR2 = 0.092	wR2 = 0.1179	wR2 = 0.0952
resid electr dens (e Å^{-3})	1.18/−0.86	2.05/−1.66	1.212/−0.098	0.756/−0.411

(s, 12H), 4.19 (s, 4H), 5.04−5.08 (m, 1H), 6.95−7.10 (m, 7H), 7.56−7.61 (m, 1H), 16.56 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.1, 18.2, 19.3, 21.0, 21.1, 26.9, 51.5, 60.3, 62.9, 112.4, 123.1, 124.8, 129.3, 129.4, 129.5, 139.0, 144.1, 150.4, 171.1, 209.5, 293.9. MS (TOF FD$^+$ from CH_2Cl_2, m/z 637): the molecular formula was confirmed by comparing the theoretical and experimental isotopic patterns for the $[M]^+$ ion ($C_{31}H_{35}N_3OCl_2Ru$), and these were found to be identical within the experimental error limits.

Catalyst ***KK2***. Yield: 56%, green microcrystalline solid. IR (KBr): ν 2913, 1727, 1681, 1581, 1487, 1415, 1354, 1266, 1203, 1171, 1141, 1074, 1049, 861 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.02 (s, 3H), 2.43 (s, 6H), 2.47 (s, 12H), 2.52 (s, 3H), 4.17 (s, 4H), 4.74 (s, 2H), 6.73 (d, J = 8.6 Hz, 1H), 7.09 (s, 4H), 7.53 (d, J = 2.1 Hz, 1H), 8.13 (dd, J = 2.5, 8.6 Hz, 1H), 16.50 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.2, 21.1, 26.3, 26.5, 51.6, 73.1, 113.0, 122.9, 128.9, 129.5, 133.8, 138.5, 138.7, 145.8, 155.2, 195.8, 201.3, 208.7, 298.5. MS (TOF FD$^+$ from CH_2Cl_2, m/z 682): the molecular formula was confirmed by comparing the theoretical and experimental isotopic patterns for the $[M]^+$ ion ($C_{33}H_{38}N_2O_3Cl_2Ru$), and these were found to be identical within the experimental error limits.

Catalyst ***KE2***. Yield: 57%, green microcrystalline solid. IR (KBr): ν 2914, 1733, 1681, 1605, 1581, 1484, 1415, 1399, 1359,1296, 1264, 1230, 1196, 1177, 1128, 1107, 1088, 1046, 979, 960, 915, 899, 854, 579 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.52 (s, J = 6.7 Hz, 3H), 2.50−2.40 (m, 12H), 3.63 (s, 3H), 4.18 (s, 4H), 4.74 (q, J = 6.7 Hz, 1H), 6.70 (d, J = 8.7 Hz, 1H), 7.09 (bs, 4H), 7.56 (d, J = 2.0 Hz, 1H), 8.14 (dd, J = 2.0, 8.5 Hz, 1H), 16.50 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.0, 17.3, 21.1, 26.2, 51.6, 53.1, 74.2, 112.4, 123.1, 129.1, 129.4, 133.0, 138.6, 139.0, 145.0, 154.6, 170.4, 195.7, 209.1, 296.9. MS (TOF FD$^+$ from CH_2Cl_2, m/z 712): the molecular formula was confirmed by comparing the theoretical and experimental isotopic patterns for the $[M]^+$ ion ($C_{34}H_{40}N_2O_4Cl_2Ru$), and these were found to be identical within the experimental error limits.

General Procedure for Cross-Metathesis Reactions. To a mixture of alkene (0.5 mmol) and cross-metathesis partner (1.0−4.0 mmol) in CH_2Cl_2 (25 mL, c = 0.02 M) was added a Ru catalyst as a solid (0.0015−0.0150 mmol, 0.2−5.0 mol %). The resulting mixture was stirred at 25−40 °C for 0.5−16 h. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/EtOAc).

General Procedure for RCM and Enyne Metathesis Reactions. To a solution of diene (0.5 mmol) in CH_2Cl_2 (25 mL, c = 0.02 M) was added a solution of a Ru catalyst (0.000 15−0.005 00 mmol, 0.03−1.00 mol %). The resulting mixture was stirred at 0−25 °C for 0.5−6 h. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/EtOAc).

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X-ray Diffraction Studies. Crystals of **Ket2** and **Kme2**, **M2**, and **C2** suitable for X-ray diffraction were obtained by recrystallization of the relevant compounds from dichloromethane/methanol, dichloromethane/*n*-hexane, and dichloromethane/*n*-pentane solutions, respectively. Intensity data were collected at low temperature on either an Oxford Diffraction Xcalibur diffractometer (**Ket2** and **Kme2**) or an Bruker D8 Apex II diffractometer (**M2** and **C2**). All calculations were performed on a PC-compatible computer using the WinGX system.[35] Full crystallographic data are given in Table 8. The structures were solved by using the SIR92 program,[36] which revealed in each instance the positions of most non-hydrogen atoms. All remaining non-hydrogen atoms were located by the usual combination of full-matrix least-squares refinement and difference electron density syntheses by using the SHELXL97 program.[36] Atomic scattering factors were taken from the usual tabulations. Anomalous dispersion terms for Ru, P, and Cl atoms were included in F_c. All non-hydrogen atoms were allowed to vibrate anisotropically. All hydrogen atoms were introduced in idealized positions (R_3CH, C−H = 0.96 Å; R_2CH_2, C−H = 0.97 Å; RCH_3, C−H, 0.98 Å; C(sp^2)−H = 0.93 Å; U_{iso} 1.2 or 1.5 times greater than the U_{eq} value of the carbon atom to which the hydrogen atom is attached) and refined as "riding" atoms. For **M2** and **C2**, after the initial structure solution was completed, it was found that 21%, and 23%, respectively, of the total cell volume was filled with disordered solvent molecules, which could not be modeled in terms of atomic sites. From this point on, residual peaks were removed and the solvent region was refined as a diffuse contribution without specific atom positions by using the PLATON[37] module SQUEEZE,[38] which subtracts electron density from the void regions by appropriately modifying the diffraction intensities of the overall structure. An electron count over the solvent region provided an estimate for the number of solvent molecules removed from the cell. The number of electrons thus located was assigned to 1.5 molecule of dichloromethane and 1 molecule of hexane on two different sites per molecule of complex in the case of **M2** and to 2 molecules of dichloromethane on two different sites per molecule of complex in the case of **C2**. The contributions of the solvent molecules were introduced in the formula, formula weight, calculated density, absorption coefficient, and $F(000)$. Applying this procedure led to a dramatic improvement in all refinement parameters and a minimization of residuals.

■ ASSOCIATED CONTENT

Supporting Information. Figures giving NMR characterization data for all new compounds and CIF files giving crystallographic data for **Ket2**, **Kme2**, **M2**, and **C2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

[†]Dedicated to Christian Bruneau on the occasion of his 60th birthday.

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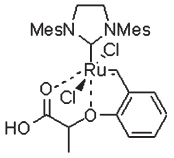
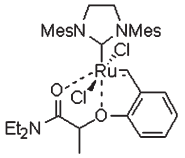


Carb2



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