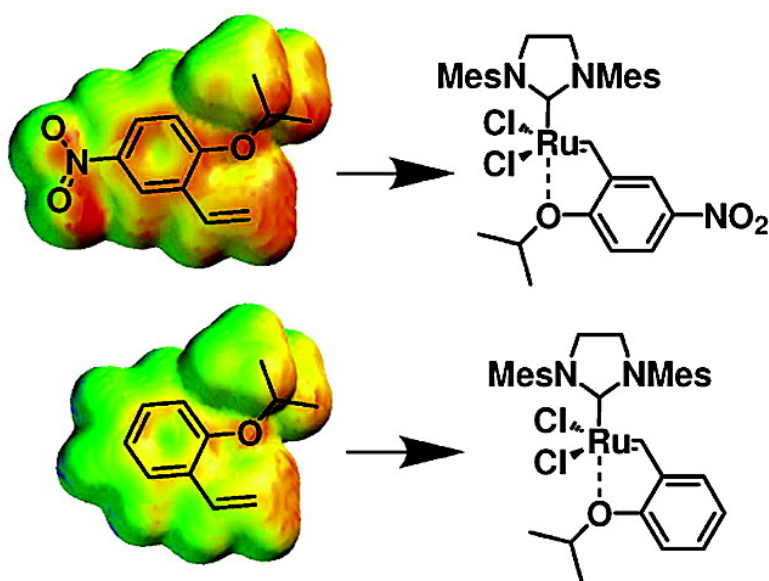


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Nitro-Substituted Hoveyda–Grubbs Ruthenium Carbenes: Enhancement of Catalyst Activity through Electronic Activation

Anna Michrowska,[†] Robert Bujok,[†] Syuzanna Harutyunyan,[†] Volodymyr Sashuk,[†] Grigory Dolgonos,[‡] and Karol Grela^{*†}

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Abstract: The design, synthesis, stability, and catalytic activity of nitro-substituted Hoveyda–Grubbs metathesis catalysts are described. The highly active and stable meta- and para-substituted complexes are attractive from a practical point of view. These catalysts operate in very mild conditions and can be successfully applied in various types of metathesis [ring-closing metathesis, cross-metathesis (CM), and enyne metathesis]. Although the presence of a NO₂ group leads to catalysts that are dramatically more active than both the second-generation Grubbs's catalyst and the phosphine-free Hoveyda's carbene, enhancement of reactivity is somewhat lower than that observed for a sterically activated Hoveyda–Grubbs catalyst. Attempts to combine two modes of activation, steric and electronic, result in severely decreasing a catalyst's stability. The present findings illustrate that different Ru catalysts turned out to be optimal for different applications. Whereas phosphine-free carbenes are catalysts of choice for CM of various electron-deficient substrates, they exhibit lower reactivity in the formation of tetrasubstituted double bonds. This demonstrates that no single catalyst outperforms all others in all possible applications.

Introduction

Recent decades have seen a burgeoning of interest in olefin metathesis, as witnessed by a rapidly growing number of elegant applications.¹ Using this tool, chemists can now efficiently synthesize an impressive range of molecules that only a decade ago required significantly longer and tedious routes. The development of efficient and selective catalysts **1a–c** has been the key to the widespread application of olefin metathesis in organic synthesis.¹

Although the second-generation Grubbs's ruthenium catalyst **1b** possesses in general a very good application profile, combining high activity with an excellent tolerance of a variety of functional groups, the phosphine-free catalyst **2b**, recently introduced by Hoveyda et al.,^{2,3} displays even higher reactivity levels toward electron-deficient substrates, such as acrylonitrile,⁴ fluorinated olefins,⁵ and others.³ Excellent air-stability,

ease of storage, and handling and the possibility of catalyst reuse and immobilization⁶ constitute additional advantages of this system.^{3,7}

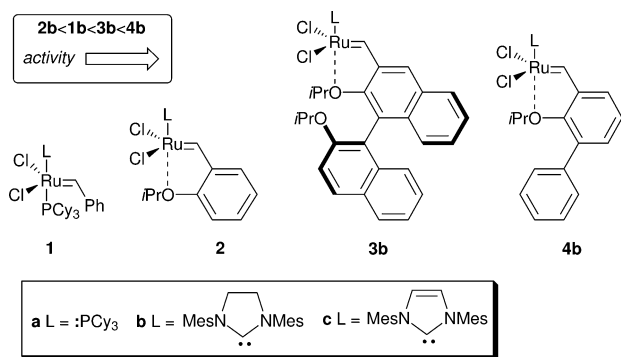
Despite the promising application profile observed in reactions of **2b**, this catalyst proved to initialize slower than **1b**, probably as a result of steric (large isopropoxy group) and electronic factors (*i*PrO → Ru electron donation).⁸ Blechert and Wakamatsu have shown recently that replacement of the isopropoxybenzylidene “ligand” in **2** by BINOL- or biphenyl-based benzylidene results in a large improvement in catalyst activity, as—for example—complex **4b** is drastically more reactive not only than **2b** but also than the “second-generation” Grubbs's catalyst **1b**.^{9,10} Recently, we reported on the preparation of two Hoveyda-type complexes substituted at the benzylidene frag-

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- (1) Pertinent reviews: (a) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592–4633. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (e) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037–2056. (f) Dragutan, V.; Dragutan, I.; Balaban, A. T. *Platinum Metals Rev.* **2001**, *45*, 155–163.
- (2) (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
- (3) For a short review on these catalysts, see: Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 1–16.

- (4) (a) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430–432. For activation of Grubbs's carbene **2b** toward acrylonitrile, via either structural modifications or addition of CuCl, see: (b) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035–4037. (c) Rivard, M.; Blechert, S. *Eur. J. Org. Chem.* **2003**, 2225–2228.
- (5) Imhof, S.; Randl, S.; Blechert, S. *Chem. Commun.* **2001**, 1692–1693.
- (6) For syntheses of supported variants of **2**, see inter alia ref 2b and (a) Kingsbury, J. S.; Garber, S. B.; Giftos, J. M.; Gray, B. L.; Okamoto, M. M.; Farrer, R. A.; Fourkas, J. T.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4251–4255. (b) Grela, K.; Tryznowski, M.; Bieniek, M. *Tetrahedron Lett.* **2002**, *43*, 9055–9059. (c) Connon, S. J.; Dunne, A. M.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3835–3838. (d) Dowden, J.; Savovic, J. *Chem. Commun.* **2001**, 37–38. (e) Yao, Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 3896–3898. (f) Yao, Q.; Zhang, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3395–3398. (g) Connon, S. J.; Blechert, S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1873–1876. (h) Yao, Q.; Zhang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 74–75. (i) Yao, Q.; Motta, A. R. *Tetrahedron Lett.* **2004**, *45*, 2447–2451.
- (7) Catalysts **2** are commercially available from Aldrich Chemical Co.
- (8) For a comparison of relative initiation rates of **1b** and **2b**, see refs 9a,b, 11, and 12.

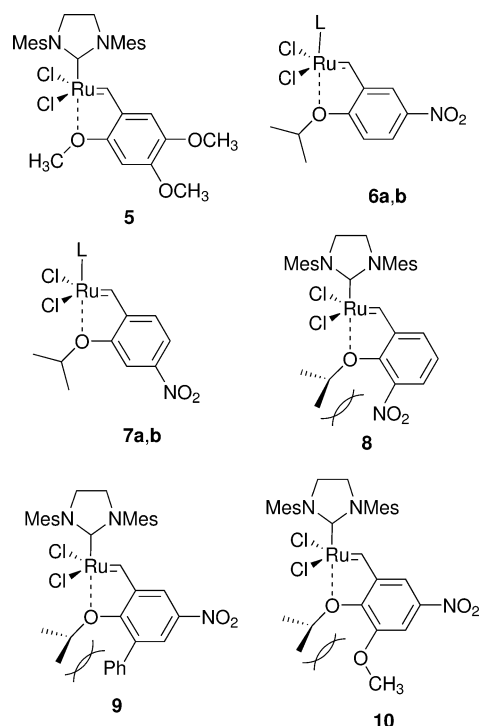
Scheme 1. Family of Ruthenium Catalysts for Alkene Metathesis^a

^a Cy = cyclohexyl; Mes = 2,4,6-trimethylphenyl.

ment. Catalyst **5**, which is very stable and easy to prepare from inexpensive α -asarone, shows activity comparable to that of the parent Hoveyda's carbene **2b**,¹¹ while the nitro-substituted catalyst **6b** possesses a dramatically enhanced reactivity.¹² This observation suggests that decreasing the electron density at the oxygen atom of the ligating *i*PrO fragment of the Hoveyda-type ruthenium carbene results in increasing its catalytic activity. We reckoned that the electron-withdrawing NO₂ group (EWG) in **6b** would weaken *i*PrO → Ru chelation and facilitate initiation of the catalytic cycle.^{12–14} Herein we report a more comprehensive investigation on the synthesis, stability, and application profile of the nitro-substituted complexes **6b** and **7b**, their “first-generation” congeners **6a** and **7a**, and other variations (**8–10**, Scheme 2).

Results and Discussion

Design of Catalysts. The discovery of highly active catalysts **4b** and **6b** prompted us to further investigate the structure–reactivity relationship, in order to fine-tune the catalysts' properties. First, we decided to examine the “pure” electronic effects in the isopropoxybenzylidene sphere of complexes **6** and

Scheme 2

7. The design of catalysts **8–10** was based on the idea that decreasing the electron density in the styrene part of **2** and simultaneously applying a steric bulk^{9b} close to the chelating isopropoxy fragment could result in an even higher increase of catalytic activity (Scheme 2).

Preparation. As illustrated in Scheme 3, we used commercially available nitrosalicylaldehydes **11–13** as starting materials for preparation of the corresponding 2-isopropoxy-5-nitrostyrenes **14–16** via a straightforward alkylation–olefination sequence. Bromination/nitration of phenols **17** and **21**, followed by the alkylation and Stille reactions, gave access to the nitrostyrenes **20** and **23**, respectively.¹⁵ Having in hand 2-isopropoxystyrenes, we attempted to synthesize the catalysts **6–10**. An exchange reaction of the styrene **14** with Grubbs's carbene **1a** in the presence of CuCl, used as a phosphine scavenger, followed by routine flash chromatography leads to the formation of the “first-generation” 5-nitro-substituted carbene **6a** as an air-stable brown microcrystalline solid (83% yield).

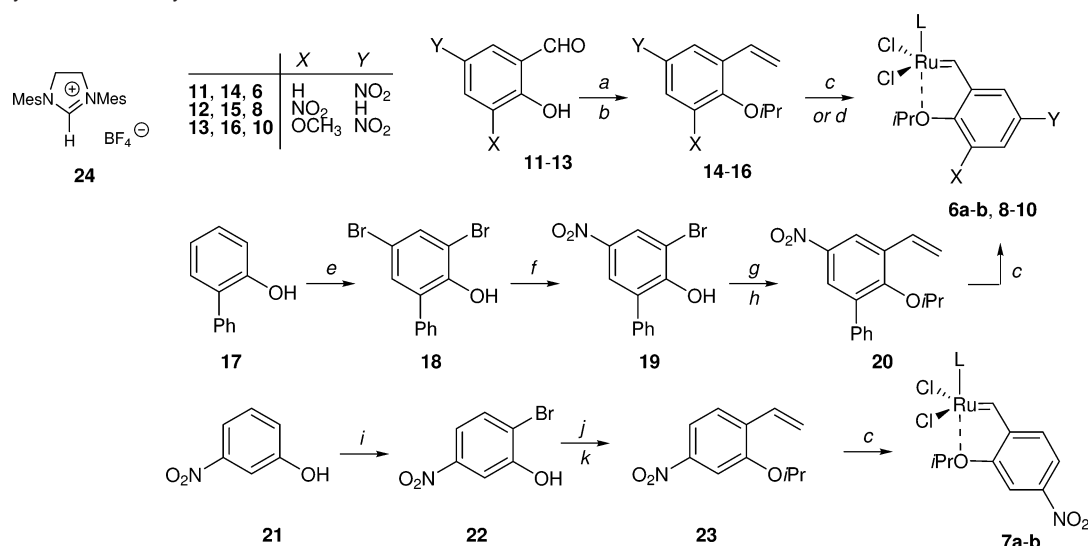
The green microcrystalline complex **6b** can be easily obtained in a similarly good yield (76–83%) by the reaction of **1b** with **14**. In the both cases, the reaction can be conveniently monitored by TLC, using cyclohexane/ethyl acetate (4:1) as the eluent.

As synthesis of **6b** from the relatively expensive **1b** would be somewhat impractical on a larger scale, we adopted a two-step, one-pot process¹¹ using the cheaper “first-generation” carbene **1a** as a Ru source. In this procedure, solid **1a** was stirred with commercial 4,5-dihydroimidazolium salt **24** in the presence of potassium *tert*-pentanolate in *n*-hexane. The in-situ-generated **1b** was then treated in the same flask with a solution of styrene **14** and CuCl, providing, after flash chromatography, complex **6b** in good yield (67–72%).

The reactions of the styrene **23** with Grubbs's carbenes **1a,b** proceeded in a similar manner to give the 4-nitro isomers **7a,b** in good yields (70% and 76%, respectively).

- (9) (a) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 794–796. (b) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403–2405. (c) For an improved synthesis of **4b** and reactivity studies, see: Dunne, A. M.; Mix, S.; Blechert, S. *Tetrahedron Lett.* **2003**, *44*, 2733–2736.
- (10) Extensive studies described in ref 9b,c suggest that a steric bulk adjacent to the chelating isopropoxy moiety of **3b** and **4b** is the crucial factor securing the unusually high activity of these complexes.
- (11) (a) Grela, K.; Kim, M. *Eur. J. Org. Chem.* **2003**, 963–966. (b) For a unique activity of a catalyst derived from **5** in living polymerization of diynes, see: Krause, J. O.; Zarka, M. T.; Anders, U.; Weberskirch, R.; Nuyken, O.; Buchmeiser, M. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 5965–5969.
- (12) (a) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038–4040. For applications of **6b** in target-oriented synthesis, see the following. (b) (–)-Securinine: Honda, T.; Namiki, H.; Kaneda, K.; Mizutani, H. *Org. Lett.* **2004**, *6*, 87–89. (c) An artificial photosynthesis model: Ostrowski, S.; Mikus, A. *Mol. Divers.* **2003**, *6*, 315–321. (d) Harutyunyan, S.; Michrowska, A.; Grela, K. In *Catalysts for Fine Chemical Synthesis*; Roberts, S., Ed; Wiley-Interscience: New York, 2004; Vol. 3, in press.
- (13) (a) After our report on **6b**, another study on the effects of EWG and EDG substituents in the benzylidene part of **2** on the rate of metathesis was published: Zaja, M.; Connon, S. J.; Dunne, A. M.; Rivard, M.; Buschmann, N.; Jiricek, J.; Blechert, S. *Tetrahedron* **2003**, *59*, 6545–6558. (b) For an application of a CN-substituted Hoveyda–Grubbs catalyst, see: Connon, S. J.; Rivard, M.; Zaja, M.; Blechert, S. *Adv. Synth. Catal.* **2003**, *345*, 572–575.
- (14) (a) In the case of Hoveyda–Grubbs complexes, initiation requires dissociation of the aryl ether ligand as well as a metathesis step. The slower rate of initiation of **2a,b** is likely due to the less facile dissociation of the bidentate ligand from the metal center (ref 2). The suppression of oxygen reassociation to the Ru center caused by a para-NO₂ group and the increased electron deficiency at the initiating carbene species should make **6b** more active in olefin metathesis. (b) For other types of Ru metathesis catalysts bearing a NO₂ group, see: De Clercq, B.; Verpoort, F. *Adv. Synth. Catal.* **2002**, *344*, 639–648. (c) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.

(15) See the Supporting Information for experimental details.

Scheme 3. Synthesis of Catalysts 6–10^a

^a Reagents and conditions: (a) K₂CO₃, 20 mol % Cs₂CO₃, *i*PrI, DMF, 40 °C, 1–2 days; **11**, 86%; **12**, 56%; **13**, 71%. (b) (1) Ph₃(Me)P⁺Br⁻, BuLi, THF, –78 °C, 15 min; (2) **11–13**, –78 °C to room temperature, 48 h; **14**, 57%; **15**, 67%; **16**, 63%. (c) **1b**, CuCl, CH₂Cl₂, 30–40 °C, 15–60 min; **6b**, 83%; **7b**, 83%; **10**, 46% or **1a**, CuCl, CH₂Cl₂, 35 °C, 55 min; **6a**, 83%; **7a**, 70%. (d) (1) **24**, *t*C₅H₁₁OK, *n*-hexane, room temperature, 1 h, then **1a**, 80 °C, 30 min; (2) **14**, CuCl, CH₂Cl₂, 40 °C, 1 h, 67–72%. (e) Br₂, AcOH, room temperature, 2 h; 92%. (f) HNO₃, AcOH, 5 °C, 5 min; 39%. (g) K₂CO₃, 20 mol % Cs₂CO₃, *i*PrI, DMF, 40 °C, 1 day; 70%. (h) Bu₃SnCH=CH₂, 5 mol % Pd(Ph₃P)₄, PhMe, reflux, 6 h; 78%. (i) Br₂, AcOH, reflux, 2 h; 55%. (j) K₂CO₃, 20 mol % Cs₂CO₃, *i*PrI, DMF, 35 °C, 2 days; 99%. (k) Bu₃SnCH=CH₂, 3 mol % Pd(Ph₃P)₄, PhMe, reflux, 4 h; 83%.

The preparation of the next member of this family, complex **8**, was more problematic, however. During the reaction between 3-nitro-2-isopropoxystyrene **15** and the Grubbs's complex, we observed by TLC the formation of a new green spot, presumably of the complex **8**, that however disappears completely before all the **1b** was consumed (1 h, 40 °C). All the attempts to capture this unstable product, either by ceasing the reaction at lower conversion or by lowering the temperature, were unsuccessful.¹⁶ A similar behavior was noted in the case of styrene **20**, which formed a green complex, presumably **9**, that decomposed completely during the isolation/purification step.

We surmised that decreasing the steric bulk near the ortho-chelating *i*PrO group would lead to a more stable catalyst. The preparation of **10** following the same straightforward route (Scheme 3) leads to the expected complex as a green solid in 46% yield. In a solid form, this compound can be stored in a refrigerator for several days, but it decomposes quickly in solution (see below).

The observed significant instability of 3-substituted 5-nitro complexes **8–10** indicates that combining two modes of activation, steric and electronic, results in great changes in catalyst properties and involves the risk of “over-bursting”. This rather disappointing result forced us to abandon the preparation of other members of this series, e.g., a 3,5-dinitro Hoveyda analogue.¹⁷

(16) The instability of **8** can be explained in view of the increased steric demand of the nitro group, which tends to be in the same plane as the benzene ring. According to ab initio calculation of the minimum-energy conformation of styrene **15**, the NO₂ group is twisted 22.1° off-plane. See the Supporting Information and ref 33 for computational details.

(17) Recently, the concept of steric and electronic activation has been utilized by Hoveyda et al. in a preparation of chiral ruthenium complexes for asymmetric metathesis. The results show that the steric hindrance exhibits a more pronounced effect on a catalyst's activity. For example, while the introduction of a NO₂ group led to a complex that is 3 times more potent than an unmodified catalyst, a sterically hindered one acts more than 100 times faster in the same model reaction. However, both modes of activation can be successfully combined in this case, as the doubly (sterically and electronically) modified chiral complex possessed the highest level of potency among those studied. Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502–12508.

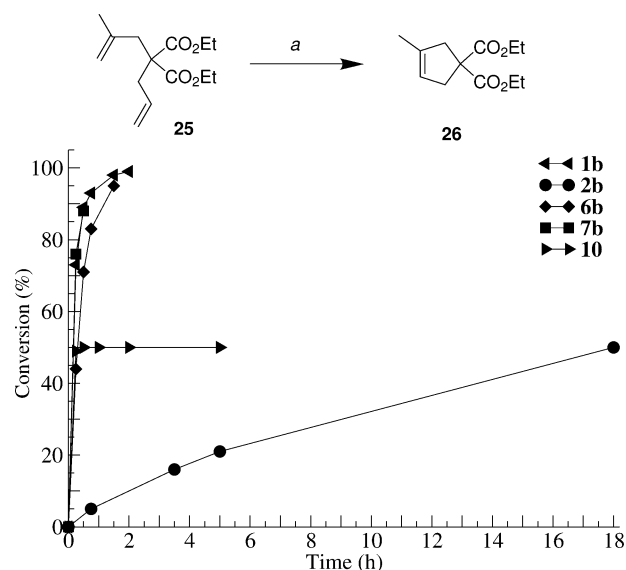


Figure 1. Relative rates of RCM of diene **25** using catalysts **1b**, **2b**, **6b**, **7b**, and **10**. ^a1 mol % catalyst, CH₂Cl₂, room temperature.

Relative Reactivity of Various Ruthenium Catalysts. Having a panel of NHC-containing ruthenium complexes (**1b–7b**, **10**) in hand, we decided to study in detail their catalytic activity. For such comparative investigation of relative activity, we chose a model RCM reaction of diene **25**, leading to the formation of cyclic product **26** bearing a trisubstituted double bond.^{11,12} The results, illustrated in Figure 1, reveal that both catalysts **6b** and **7b** are significantly more reactive than **2b**. The doubly modified complex **10** initializes the reaction; however, it dies after 15 min (Figure 1).

As the above reaction proceeds too fast to allow a more accurate comparison of the activity of such potent catalysts, we focused on the more challenging cyclization of **27** at 0 °C. According to Blechert and Wakamatsu, **1b** gave only ca. 20–30% of cyclized **28** under these conditions.^{9b} Therefore,

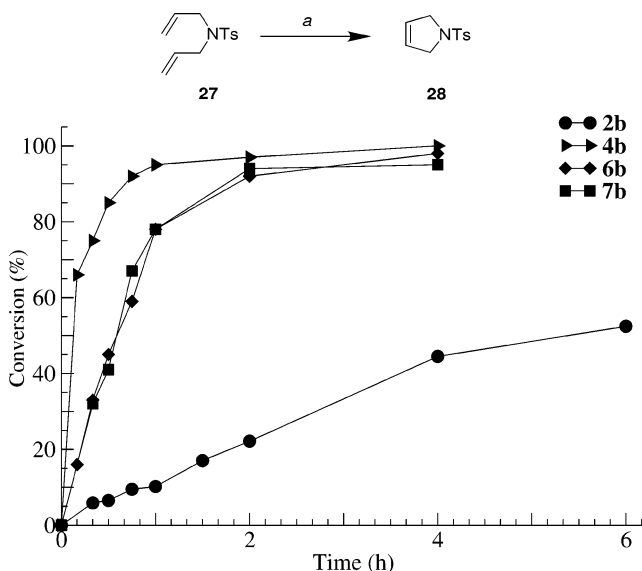


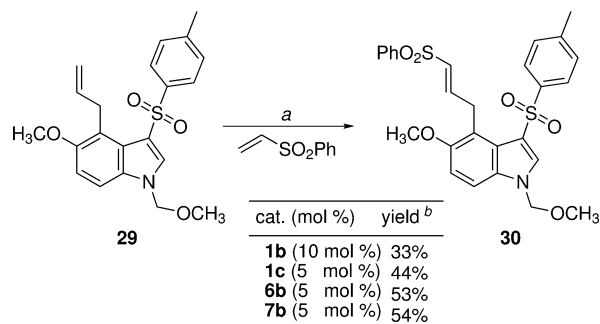
Figure 2. Relative rates of RCM of diene **27** using catalysts **1b**, **2b**, **4b**, **6b**, and **7b**. ^a1 mol % catalyst, CH₂Cl₂, 0 °C.

this transformation could serve as a calibration point for estimating activity of the highly active catalysts. Figure 2 shows the reaction profile at 0 °C for catalysts **2b**, **4b**, **6b**, and **7b**. We have found that although the enhancement of reactivity is somewhat lower than that observed for sterically activated **4b**, the presence of a NO₂ group leads to catalysts that are dramatically more active than **2b**.

Encouraged by these results, we decided to test a broader set of reactions [cross-metathesis (CM), ring-closing metathesis (RCM), and enyne metathesis] in order to obtain a more detailed picture of the application profile of catalysts **6** and **7**.

Utility in Catalytic Cross-Metathesis Reactions.¹⁸ We have recently published a novel CM reaction of α,β -unsaturated sulfones.¹⁹ Scheme 4 shows a comparative study of the performance of catalysts **1b**, **1c**, **6b**, and **7b** in CM of phenyl vinyl sulfone and the highly substituted indole **29**. Although CM of this challenging substrate, a “dead-end intermediate”²⁰ in total synthesis of 1,3,4,5-tetrahydrobenz[*c,d*]indol-4-amine alkaloids,²¹ is possible with Grubbs’s “second-generation” carbene **1b**, the highest conversions and lowest catalyst loadings can be achieved in the case of **6b** and **7b** (Scheme 4). The catalytic CM of selected α,β -unsaturated substrates was then examined. The results compiled in Table 1 illustrate the remarkably wide scope of these catalysts. Thus, (i) the CM reactions of methyl acrylate (entries 1 and 12) and methyl vinyl ketone (entry 7) can be efficiently performed at room temper-

Scheme 4. Comparison of the Activity of Catalysts **1b**, **1c**, **6a**, and **7b** in CM of Phenyl Vinyl Sulfone



^a Conditions: 5–10 mol % catalyst, 2 equiv of phenyl vinyl sulfone, 40 °C, CH₂Cl₂, 16 h. ^b Isolated yields after silica gel chromatography.

ature; (ii) in the case of reactive alkenes, even CM of phenyl vinyl sulfone and acrylonitrile was possible at ambient temperature (entries 2–4, 9) [however, in the case of vinylphosphine oxides²² (entries 5, 11, and 14) and more demanding olefinic partners (e.g., entries 6, 10, and 13), reflux temperature (40 °C) was required to achieve good conversions]; (iii) the indole nitrogen and other functionalities do not require protection. Most remarkably, the new catalyst **6b** can be used for CM of methacrylonitrile, a transformation which is *beyond the scope* of the “second-generation” Grubbs’s carbene **1b** (entry 8).

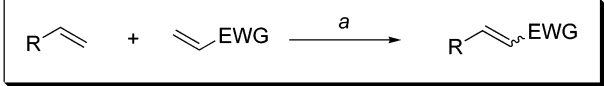
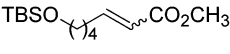
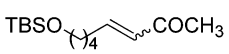
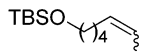
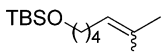
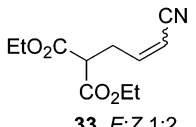
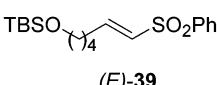
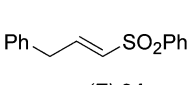
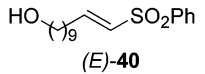
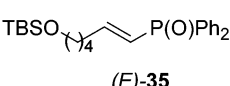
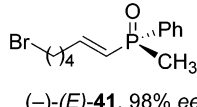
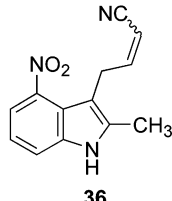

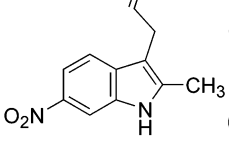
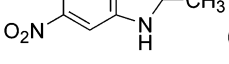
Recently, we described a novel “homo-metathesis”²⁴ reaction of vinyl phosphine oxide **45** catalyzed by **6b**.²² Interestingly, **1b** and **2b** are clearly *less potent* in the formation of **46** (Scheme 5).^{25,26} These examples of demanding CM reactions show that **6b** and **7b** are by all means superior to **1b** and **2b**.

Utility in the Formation of Tri- and Tetrasubstituted C–C Double Bonds. As illustrated in Table 2, the nitro-substituted complexes **6b** and **7b** serve as effective catalysts for formation of di- and trisubstituted double bonds. The RCM and enyne metathesis reactions can be performed efficiently even at 0 °C (Table 2, entries 1–4). Furthermore, the potential of a nitro catalyst for more challenging metathesis reactions has been proved (entries 5–12). Various degrees of substitution of the double bond are tolerated, and even trisubstituted cyclic olefins can be synthesized in usually good yields (entries 5–7). The CM of terminal alkenes with internal olefins (entry 10) and 2-methyl-2-butene²⁷ (entries 8, 9) proceeds very efficiently. In all reported cases, complex **6b** exhibits similar levels of activity as compared with Grubbs’s carbene **1b**. The catalytic *cross-*

- (18) For reviews on catalytic cross-metathesis, see: (a) Vernall, A. J.; Abell, A. D. *Aldrichimica Acta* **2003**, *36*, 93–105. (b) Blechert, S.; Connon, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923. (c) Blackwell, H. E.; O’Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58–71. (d) For a short review on applications to commercial products, see: Pederson, R. L.; Fellows, I. M.; Ung, T. A.; Ishihara, H.; Hajela, S. P. *Adv. Synth. Catal.* **2002**, *344*, 728–735. (e) For a general model for selectivity in olefin CM, see: Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
- (19) (a) Grela, K.; Bieniek, M. *Tetrahedron Lett.* **2001**, *42*, 6425–6428. (b) Grela, K.; Michrowska, A.; Bieniek, M.; Kim, M.; Klajn, R. *Tetrahedron* **2003**, *59*, 4525–4531. (c) For an application of this transformation in the enantioselective synthesis of furanone natural products, see: Evans, P.; Leffray, M. *Tetrahedron* **2003**, *59*, 7973–7981.
- (20) Sierra, M. A.; de la Torre, M. C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1538–1559.
- (21) Mąkosza, M.; Stalewski, J.; Wojciechowski, K.; Danikiewicz, W. *Tetrahedron* **1997**, *53*, 193–214.

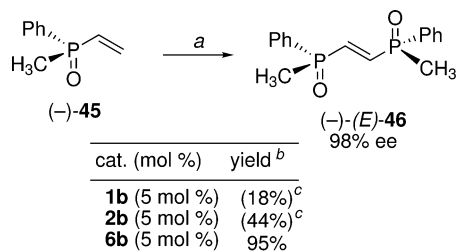
- (22) Demchuk, O. M.; Pietrusiewicz, K. M.; Michrowska, A.; Grela, K. *Org. Lett.* **2003**, *5*, 3217–3220.
- (23) Optical purity was calculated from the ³¹P and ¹H NMR spectra registered in the presence of (*S*)-*N*-[1-(1-naphthyl)ethyl]-3,5-dinitrobenzamide (Kagan shift reagent). Cf. ref. 22 and (a) Pakulski, Z.; Demchuk, O. M.; Kwiatosz, R.; Osiński, P. W.; Wierczyńska, W.; Pietrusiewicz, K. M. *Tetrahedron: Asymmetry* **2003**, *14*, 1459–1462. (b) Deshmukh, M.; Dunach, E.; Juge, S.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 3467–3470.
- (24) The examples of metathesis between two electron-deficient olefins are rare, and good yields have been reported only for homodimerization of acrylates and for cross-metathesis of α,β -unsaturated substrates with styrenes. See: (a) Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417–10418. (b) Chatterjee, A. K.; Toste, F. D.; Choi, T.-L.; Grubbs, R. H. *Adv. Synth. Catal.* **2002**, *344*, 634–637.
- (25) Michrowska, A.; Szmigielska, A.; Demchuk, O. M.; Butenschön, H.; Pietrusiewicz, K. M.; Grela, K. Unpublished.
- (26) The similar lack of activity of **1b** in homocoupling of vinylphosphine oxides has been reported independently: Bisaro, F.; Gouverneur, V. *Tetrahedron Lett.* **2003**, *44*, 7133–7135.
- (27) CM of terminal olefins and 2-methyl-2-butene, reported by Grubbs et al., constitutes a very elegant method of an *allyl-to-prenyl* conversion: Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939–1942.

Table 1. CM of α,β -Substrates Catalyzed by **6b**, **7b**, and Other Ruthenium Carbenes^a

					
entry	product	cat. (mol %) yield (temp, time) ^b	entry	product	cat. (mol %) yield (temp, time)
1 ^c	 31 , <i>E:Z</i> 95:5	6b (1 mol %) 95% (25 °C, 30 min)	7 ⁱ	 37 , <i>E:Z</i> 99:1	6b (2.5 mol %) 82% (25 °C, 30 min) 95% (25 °C, 3 h) ^d
2 ^e	 32 , <i>E:Z</i> 1:2.7	6b (5 mol %) 83% (25 °C, 2 h) ^d 7b (5 mol %) 91% (40 °C, 8 h) 1b (5 mol %) 68% (80 °C, 16 h) ^d	8 ^j	 38 , <i>E:Z</i> 1:2	6b (5 mol %) 58% (40 °C, 16 h) 2b (5 mol %) 40% (40 °C, 16 h) ^d 1b (5 mol %) 0% (80 °C, 24 h)
3 ^e	 33 , <i>E:Z</i> 1:2	6b (5 mol %) 85% (25 °C, 3 h) 87% (25 °C, 30 min) ^d 2b (8 mol %) 79% (40 °C, 6 h) ^f	9 ^g	 (E)-39	6b (2.5 mol %) 90% (25 °C, 16 h) 1b (5 mol %) 85% (40 °C, 16 h)
4 ^g	 (E)-34	6b (5 mol %) 86% (25 °C, 16 h) 1b (5 mol %) 68% (25 °C, 16 h)	10 ^g	 (E)-40	6b (5 mol %) 96% (40 °C, 16 h)
5 ^h	 (E)-35	6b (5 mol %) 82% (40 °C, 16 h) 1b (5 mol %) 82% (40 °C, 16 h)	11	 (-)-(E)-41 , 98% ee ^k	6b (5 mol %) 86% (40 °C, 16 h)
6 ^e	 36	<i>E:Z</i> 1:2.4 9a (5 mol %) 69% (40 °C, 16 h)	12 ^c	 (E)-42 , EWG = CO ₂ CH ₃ 6b (5 mol %) 91% (25 °C, 2 h)	
			13 ^e	 (E)-43 , EWG = CN; <i>E:Z</i> 1:2 6b (5 mol %) 76% (40 °C, 16 h)	
			14 ^h	 (E)-44 , EWG = P(O)Ph ₂ 6b (5 mol %) 76% (40 °C, 16 h)	

^a Conditions: 1–5 mol % catalyst, 25–40 °C, CH₂Cl₂ or 80 °C, toluene. ^b Isolated yields after silica gel chromatography unless stated otherwise. ^c Reaction with 2 equiv of methyl acrylate. ^d Yield determined by GC. ^e Reaction with 2 equiv of acrylonitrile. ^f *(E):(Z)* = 1:3, ref 4. ^g Reaction with 2 equiv of phenyl vinyl sulfone. ^h Reaction with 2 equiv of diphenyl vinyl phosphine oxide. ⁱ Reaction with 2 equiv of methyl vinyl ketone. ^j Reaction with 4 equiv of methacrylonitrile. ^k References 22 and 23.

Scheme 5. Comparison of the Activity of Catalysts **1b** and **6a** in Homocoupling of **(-)-45**²⁵



^a Conditions: 5 mol % catalyst, 40 °C, CH₂Cl₂, 16 h. ^b Isolated yields after silica gel chromatography. ^c Yield determined by ³¹P NMR.

metathesis reactions of 1,1-disubstituted olefins represent, however, a more difficult case for **6b** (entries 11–13).

Having established the application profile of the nitro-substituted Hoveyda-type catalysts in the formation of di- and trisubstituted C–C double bonds, we focused our efforts on the most demanding case—the formation of the tetrasubstituted C–C double bonds.²⁹

As can be seen from Table 3, the NO₂-containing complex **6b** effected the cyclization of substrates **58**, albeit in lower yield (entry 1). The analogous malonate derivative **60** was even more reluctant toward cyclization (Table 3, entry 2).²⁸ Entries 1–3 show that, in general, the Hoveyda-type catalysts are inferior to Grubbs's carbene **1b** in the formation of tetrasubstituted C–C double bonds.²⁹

Stability and Recyclability of Nitro-Substituted Ru Complexes. The ruthenium carbenes **6a,b** and **7a,b** possess very good

(28) Significantly higher yields in the cyclization of dienes shown in Table 3 have been reported in the literature. (a) **61**, 31% (5 mol % of **1b**; 24 h in refluxing DCM; NMR yield); Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (b) **59**, 95% (5 mol % of **1c**; toluene, 80 °C, 24 h; isolated yield); **61**, 47% (5 mol % of **1c**; toluene, 80 °C, 24 h; GC yield); **62**, 75% (5 mol % of **1c**; toluene, 80 °C, 18 h; isolated yield); cf.: Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236–3253.

(29) (a) There are no separate reports devoted to applications of the Hoveyda–Grubbs catalysts for the preparation of tetrasubstituted C–C double bonds. However, Hoveyda et al. have noted that tetrasubstituted olefins were obtained less efficiently through catalytic RCM promoted by **2b** (ref 2). For a possible explanation of the lower level of efficiency observed with **2b**, see ref 3. (b) For some examples of the formation of tetrasubstituted olefins with Hoveyda-type catalysts, see also ref 6b,i.

Table 2. Formation of Di- and Trisubstituted Double Bonds Promoted by **6b**, **7b**, and Other Catalysts^a

entry	substrate	product	cat. (mol %) yield (temp, time) ^b	entry	substrate	product	cat. (mol %) yield (temp, time) ^b
1			6b (1 mol %) 98% (0 °C, 1 h) 1c (5 mol %) 85% (80 °C, 1 h) ^c	7			6b (2.5 mol %) 76% (40 °C, 2 h)
2			6b (1 mol %) 99% (0 °C, 1 h) 4b (1 mol %) 99% (20 °C, 10 min) ^d	8 ^f			6b (1 mol %) 99% (25 °C, 1 h)
3 ^e			6b (1 mol %) 92% (0 °C, 2 h) 7b (1 mol %) 94% (0 °C, 2 h) 4b (1 mol %) 97% (0 °C, 2 h)	9 ^f			6b (1 mol %) 99% (25 °C, 1 h)
4			6b (2.5 mol %) 78% (0 °C, 8 h) 4b (1 mol %) 99% (20 °C, 10 min) ^d	10 ^g			6b (2.5 mol %) 67% (100%) ^e (25 °C, 5 h)
5			6b (1 mol %) 95% (25 °C, 1 h) 4b (1 mol %) 99% (20 °C, 40 min) ^d	11 ^g			6b (5 mol %) 37% (67%) ^h (40 °C, 16 h) 2b (5 mol %) 17% (40 °C, 16 h) ^e
6			6b (2.5 mol %) 82% (40 °C, 1 h) ^e 99% (40 °C, 4 h)	12 ^g			6b (5 mol %) 47% (77%) ^h (40 °C, 16 h) 2b (5 mol %) 54% (40 °C, 16 h) ^e
				13 ⁱ			6b (5 mol %) 5% (40 °C, 16 h) 1b (5 mol %) 0% (40 °C, 24 h)

^a Conditions: 1–5 mol % catalyst, 0–40 °C, CH₂Cl₂ or 80 °C, toluene. ^b Isolated yields after silica gel chromatography unless stated otherwise. ^c Reference 28b. ^d Reference 9b. ^e Yield determined by GC. ^f Reaction with neat 2-methyl-2-butene. Reference 27. ^g Reaction with 2 equiv of (*Z*)-4-(acetoxy)-2-butenyl acetate. ^h Yield based on recovered starting material. ⁱ Reaction with 2 equiv of allyl(trimethyl)silane.

Table 3. Formation of Tetrasubstituted Double Bonds Promoted by **1b**, **2b**, **4b**, **6b**, and **7b**^a

entry	substrate	product	cat. (5 mol %) yield (time) ^a
1			1b : 52% (20 h) 2b : 45% (20 h) 6b : 42% (24 h) 7b : 22% (24 h)
2			1b : 14% (8 h) 2b : 2% (16 h) 4b : 1% (16 h) 6b : 0% (24 h) 7b : 9% (24 h)
3			1b : 20% (20 h) 2b : 7% (20 h) 6b : 0% (20 h) 4b : 17% (20 h)
4			6b (2.5 mol %) 20% (24 h) 6b (5 mol %) 29% (24 h)

^a Conditions: 5 mol % catalyst, 40 °C, CH₂Cl₂. ^b Yields determined by GC.

air, moisture, and thermal stability and can be handled in air and stored for extended periods of time (more than six months

at +4 °C) without decomposition or diminishing of their activity.³⁰ One of the unique properties of the Hoveyda–Grubbs carbene **2b** is that up to 95% of the catalyst can be recovered after the reaction.^{2b} However, no data were provided until now regarding the recyclability of the more active catalysts: **4b** and **6b**.^{9,12} To answer this question, we attempted to isolate the NO₂ catalyst after CM and RCM reactions. It was found that, in many cases, **6b** can be recovered with good to moderate efficiency (70–40%). As an example, in the formation of **47** (99% conversion, Table 2, entry 1), recovered **6b** was obtained in 72% yield. In the preparation of **49** (2.5 mol % of **6b**, 20 °C, 99% conversion, Table 2, entry 4), 40% of the catalyst was isolated after chromatography. However, in the case of CM reaction with acrylate (Table 1, entry 1), no catalyst was recovered. Similarly, prolonged reaction times at higher temperature (Table 3) led to decomposition of the catalyst.³¹

(30) The complex **6b** is stable up to 110 °C and efficiently promotes metathesis at 80 °C in toluene. Grela, K.; Bieniek, M. Unpublished. For the stability of **2b** and **4b**, see refs 2 and 9, respectively.

(31) In general, the recyclability of **6b** is handicapped as compared with that of **2b**, and typically **6b** can be recovered after metathesis reaction only with moderate efficiency. See the Supporting Information for the recovery experiments.

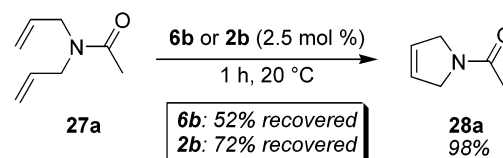


Table 4. Metathesis Reactions Promoted by the First-Generation Catalysts **6a** and **7a**^a

entry	substrate	product	cat. (mol %) yield (temp, time) ^b
1			6a (1 mol%) 90% (25 °C, 1h) ^c
2			6a (1 mol%) 70% (25 °C, 3h) 7a (1 mol%) 68% (25 °C, 8h)
3			6a (2.5 mol%) 99% (25 °C, 24h) 7a (2.5 mol%) 99% (25 °C, 24h)

^a Conditions: 1–2.5 mol % catalyst, 25 °C, CH₂Cl₂. ^b Isolated yields after silica gel chromatography. ^c Determined by GC.

Table 5. Investigation of the First- and Second-Generation Catalysts in Enyne Metathesis of **66**

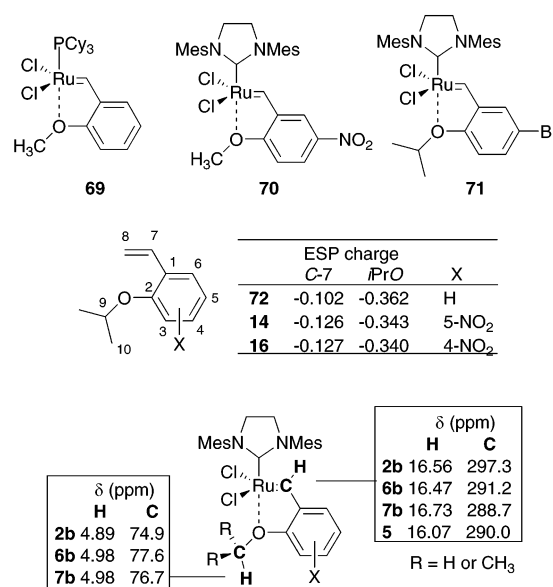
entry	cat. (mol%)	Yield (%) ^b	
		67	68
1	6b	71 (55)	24 (20)
2	5	52 (46)	33 (30)
3	2b	(51)	14 (8)
4	6a	100	0
5	7a	96	0

^a Conditions: 1–2.5 mol % catalyst, CH₂Cl₂, 24 h, 25 °C. ^b Isolated yields after silica gel chromatography. In parentheses are the GC yields.

Synthetic Utility of the First-Generation Complexes **6a and **7a**.** In a second set of experiments, the utility of the first-generation complexes **6a** and **7a** in the formation of various heterocycles via RCM and enyne reactions was revealed (Table 4). Catalyst loadings lower than 5 mol % were sufficient.

In the course of this investigation, we observed that the use of the catalyst **6b** for metathesis of **66** led to the generation of an undesired product **68** (Table 5, entry 1). The same byproduct was formed in reactions promoted by other second-generation Hoveyda-type carbenes (entries 2, 3). A similar lack of selectivity has been reported by Mori for enyne reactions of **1c** with enynes having a 1,1-disubstituted alkene and an internal alkyne motif.³² The byproduct formed in reaction of **66** decomposes easily, leading to undefined material, but could be isolated by a quick flash chromatography on silica gel and characterized by ¹H NMR and HRMS. The proposed structure **68** agrees well with a possible reaction mechanism proposed by Mori.³² Interestingly, both of the first-generation complexes **6a** and **7a** show in this transformation a *high level of selectivity*, leading only to the formation of **67**.

Considerations Regarding the Structure–Activity Relationship of Substituted Hoveyda Catalysts. It has been reported by Hoveyda that the variation from an isopropoxy to a methoxy chelating group has a negative impact on the catalyst performance, since the 2-methoxy analogue **69** (Scheme 5) was

Scheme 6

significantly less stable and less reactive than **2a**.^{2a} In light of this observation, it is worthwhile to note that the electron-donating group (EDG) substituted carbene **5** with a MeO-chelating group shows not only good catalytic activity but also perfect stability.¹¹ An electron-withdrawing group (EWG) analogue, **70** has been therefore prepared from commercially available 2-methoxy-5-nitrobenzaldehyde via olefination and exchange reaction of the resulting styrene with **1b**.¹⁵ However, this complex was difficult to synthesize and purify in good yield (39% of an exchange reaction with **1b**), while the catalyst **5**, bearing electron-donating substituents, was almost quantitatively prepared.¹¹ Moreover, **70** proved to be a less effective catalyst than its *iPr* analogue (only 75% conversion after 2 h in a model reaction shown in Figure 1). The difference in properties of **6b** and **70** indicates that the nature of the ether chelate is more critical to the stability, as well as the activity, of complexes bearing EWGs than of those containing EDG substituents.

In the course of our project aimed at the preparation of the immobilized metathesis catalyst, we prepared the bromo analogue **71** of the Hoveyda catalyst **2b**.^{6b} Although the reactivity patterns of complexes **2b** and **71** were in general similar, the latter system was visibly less reactive in some model reactions.^{19b} These results once again show that even a small variation in the benzylidene sphere can result in a change in the activity of the catalyst.

The effect of substitution of the benzylidene fragment on a catalyst's activity has been studied in detail and interpreted by means of σ^+ values by Blechert et al.¹³ In our current investigation, we decided to perform a preliminary *ab initio* calculation of an electron density distribution, viewed as electrostatic potential (ESP) or Mulliken charges in selected 2-isopropoxystyrenes.³³

This approach should provide more information regarding the relative importance of electron density at either the vinyl

(32) (a) Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678–693. (b) Kitamura, T.; Sato, Y.; Mori, M. *Chem. Commun.* **2001**, 1258–1259.

(33) All the calculations were performed using Gaussian 98 (Gaussian 98, Revision A.11.4; Gaussian, Inc.: Pittsburgh, PA, 2002) on an IRIX64/Linux workstation. The structures of 2-isopropoxystyrenes were optimized using B3LYP with the 6-31G** basis set. Only real values of the analytical harmonic vibrational frequencies confirmed that the geometries under study correspond to the minimum-energy structures.

fragment (precursor of a benzylidene) or the chelating isopropoxy group. The calculated values of ESP charges in 2-isopropoxy-5-nitrostyrene (**14**) and 2-isopropoxy-4-nitrostyrene (**16**) indicate that, in comparison with the unsubstituted 2-isopropoxystyrene **72**, the electron density at the *i*PrO oxygen atom is lowered in both regioisomers, while C-7 carbons show evidently increased ESP charge (Scheme 6).³⁵ The comparison of Mulliken charges³⁴ (ESP not available) in 2-isopropoxy-4-bromostyrene revealed increased electron density at both the *i*PrO oxygen and the C-7 carbon. Although this approach is an oversimplification of a real situation and provides no information regarding the real catalysts, it is in good agreement with activity profiles and NMR spectra of **2b**, **6b**, **7b**, and **71**. Comparison of the 500 MHz ¹H and ¹³C NMR spectra reveals some of the subtle electronic attributes of these systems. As illustrated in Scheme 5, the *i*PrO methine proton and carbon appear more downfield in both **6b** and **7b**. This may be attributed to lower electron density at the *i*PrO center as compared with **2b**. Conversely, Ru=CH carbons in **6b** and **7b** are shifted more upfield.³⁶

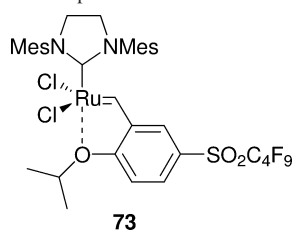
Conclusion

The data reported in this paper witness that the Hoveyda-type catalysts can be significantly improved by changing not only the steric but also the electronic situation in the Ru-chelating isopropoxy fragment. This notion has strong implications for catalyst design and application, which will be studied

(34) Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833.

(35) For a full set of ESP/Mulliken charges, see the Supporting Information.

(36) Similar changes in chemical shifts have been observed for another member of this series, compound **73**: Ru=CH, 16.34 and 289.8; *i*PrO methine proton, 5.01 ppm, and carbon, 78.9 ppm. Arlt, D.; Bieniek, M.; Michrowska, A.; Bujok, R.; Grela K. Unpublished results.



in more detail during our research program. Attempts to combine the two modes of activation of **2**, steric and electronic, resulted in severely decreasing the catalyst's stability. This indicates that the effect of structural modifications of complex **2** does not always correspond to those of the related chiral complexes.¹⁷ Although the presence of a NO₂ group leads to catalysts that are dramatically more active than both **1b** and **2b**, enhancement of reactivity is somewhat lower than that observed for sterically activated **4b**. However, taking in account simple preparation, partial recyclability, excellent stability, and high activity, the nitro-substituted Hoveyda catalysts **6** and **7** are very attractive from a practical point of view,^{12b,c} even if they do not surpass the hindered catalyst **4b** in terms of initiation speed.

Equally noteworthy is the fact that different NHC catalysts turned out to be optimal for different applications. Whereas the phosphine-free carbenes are proven to be catalysts of choice for CM of various electron-deficient alkenes, they exhibit lower reactivity toward tetrasubstituted double bonds. This shows that no single catalyst outperforms all others in all possible applications.³⁷

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Supporting Information Available: Full experimental details, compilation of the instrumentation used, electron density maps and visualizations, and copies of the NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA048794V

(37) For screening of the catalytic performance of catalysts **1b**, **2b**, **4b**, and **6b** in the synthesis of cyclooctenes, see: Sibi, M. P.; Aasmul, M.; Hasegawa, H.; Subramanian, T. *Org. Lett.* **2003**, *5*, 2883–2886.