J|A|C|S
COMMUNICATIONS

Highly Efficient Ru−Pseudohalide Catalysts for Olefin Metathesis

Jay C. Conrad, Henrietta H. Parnas, Jennifer L. Snelgrove, and Deryn E. Fogg*

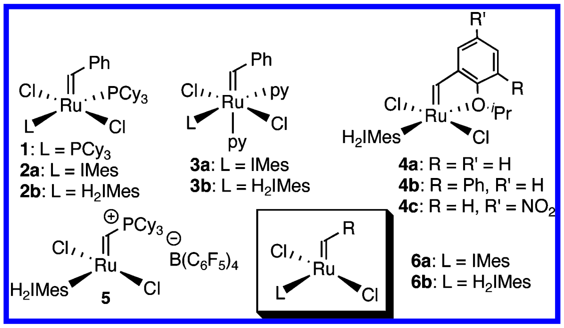
Department of Chemistry, University of Ottawa, Ottawa ON, Canada K1N 6N5

Received December 2, 2004; E-mail: dfogg@science.uottawa.ca

The availability of robust, easily handled ruthenium catalysts for olefin metathesis has had a tremendous impact on organic synthesis.[1] To date, the major goal in Ru catalyst design has focused on increasing the activity of the Grubbs catalyst **1**. Key advances include the development of N-heterocyclic carbene (NHC) complexes **2**,[2] derivatives of **2** containing a labile donor (e.g., PPh_3,[2c] pyridine (**3**),[3] or styrenyl ethers activated by steric[4] or electronic[5] destabilization of the chelate ring (**4**)), and, most recently, phosphonium alkylidene **5**.[6] A limitation, however, lies in the convergence of precatalysts **2**−**5** on **6** as the active species. Because **6** is readily deactivated, advances in activity have not increased catalyst *productivity*; higher activity comes at the price of catalyst lifetime, and turnover numbers remain generally low.[7] The resulting requirement for high catalyst loadings is problematic for reasons of cost (particularly in the industrial setting) and because isolated yields of pure organic products are compromised by difficulties in removing spent **6**. Elimination of heavy metal residues is essential in order to prevent Ru-catalyzed product degradation.[8] We now report new, highly efficient "pseudohalide" catalysts that do not proceed via **6** and which are easily removed following reaction.

Several years ago, we reported that Cl-bridged dimers are implicated in deactivation of Grubbs-class catalysts containing two chloride ligands,[9] and other examples have since emerged.[10,11] This discovery led us to explore routes to catalysts containing alternative anionic ligands, of which bis(perfluorophenoxide) **7** (Scheme 1) emerged as the first example of a high-performing pseudohalide catalyst.[12] Reaction of **3a** with $TlOC_6X_5$ (where X = Cl, Br, instead of F) affords mono(aryloxide) products **8**, owing to the increased ligand bulk. The new complexes were characterized by detailed spectroscopic studies and microanalysis. The geometry shown for **8**, proposed on the basis of DFT calculations, corresponds to that crystallographically established for **7**.[12] The pyridine ligand in **8** is much more labile than that in **7**, resulting in significantly higher metathesis reactivity.

Chart 1. IMes = *N,N′*-Bis(mesityl)imidazol-2-ylidene


1: L = PCy_3
2a: L = IMes
2b: L = H_2IMes
3a: L = IMes
3b: L = H_2IMes
4a: R = R′ = H
4b: R = Ph, R′ = H
4c: R = H, R′ = NO_2
5
6a: L = IMes
6b: L = H_2IMes

We evaluated the efficiency of the new catalysts in RCM of the benchmark substrate **9** and other, more challenging substrates (Table 1). With the exception of the macrocycle syntheses (substrates **17** and **19**), these reactions were carried out in refluxing $CDCl_3$, as probe reactions with **11** and **13** indicated faster RCM in this solvent, versus C_6D_6 or CD_2Cl_2.[13]

Scheme 1

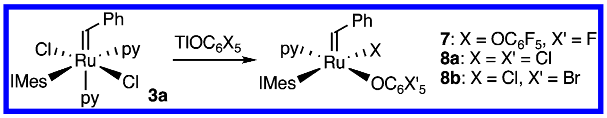
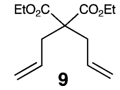
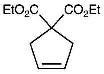
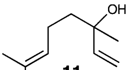
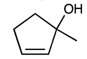
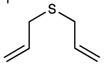
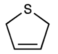
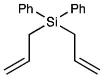
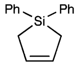
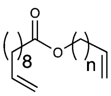
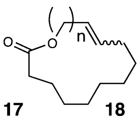
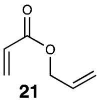
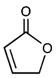
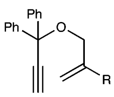
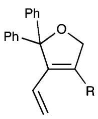

3a
7: X = OC_6F_5, X′ = F
8a: X = X′ = Cl
8b: X = Cl, X′ = Br

Table 1. RCM Efficiency of Pseudohalide versus Chloride Catalysts[a]

Substrate	Product	mol% Ru	Conditions	% Product (*E*:*Z*)
 **9**	 **10**	0.5	$CDCl_3$: Δ, 15 min	**7**, **8a**, **8b**: 100 **2a**, **3a**: 100
 **11**	 **12**	0.5[b]	$CDCl_3$: Δ, 15 min	**7**, **8a**, 8**b:** 100 **2a**, **3a**: 100
 **13**	 **14**	0.5	$CDCl_3$: Δ, 20 min	**7**: 40[c] **8a**: 31[c] **8b**: 100 **3a**: 60[c]
		5	C_7H_8: 80 °C, 1h	**2a**: 100[14]
 **15**	 **16**	5	$CDCl_3$: Δ, 20 min	**7**: 88[d] **8a**: 94[d] **8b**: 100 **2a**: 76[d] **3a**: 100
		5	C_7H_8: 110 °C, 5h	**2b**: 70[15]
 n = 4: **17** n = 2: **19**	 **18** **20**	**n = 4** 5[e]	CH_2Cl_2: Δ, 15 min	**7**: 9 (3:1) **8a**: 72 (4:1) **8b**: 100 (3:1) **3a**: 30 (4:1)
		n = 2 5[e]	C_6H_6: Δ, 15 min	**7**: 29 (4:1) **8a**, **8b:** 100 (9:1) **3a:** 63 (9:1)
 **21**	 **22**	5[f]	$CDCl_3$: Δ, 1 h	**8a**: 73
 R = H: **23** R = Me: **25**	 **24** **26**	**R = H** 0.5	$CDCl_3$: Δ, 15 min	**8b**: 100
		5	C_7H_8: 80 °C, 1h	**2b**: 85[5b]
		1	CH_2Cl_2: 0°C, 1h	**4c**: 98[5b]
		R = Me 5	$CDCl_3$: Δ, 2h	**8b**: 70
			CH_2Cl_2: 40 °C, 20h	**2b**: 20[5b] **4b**: 17[5b] **4c**: 0[5b]

[a] Mol % Ru = minimum required for high conversions in <1 h. [b] At 1 h, 0.05 mol % Ru: **7**, 100; **8a**, 17; **8b**, 34; **2a**, 24; **3a**, 29%. [c] At 3 h, <6% increase; 100% in 15 min at 5 mol % Ru. [d] 100% at 1 h. [e] Ru, diene added dropwise; $[S]_{max}$ = 0.005 M; 100% **18** at 12 h (**7**), 0.5 h (**8a**), 1 h (**3a**). Conversion to **20** plateaus at 87% (**3a**; 1h), 83% (**7**; 3 h); no further change up to 5 h; final *E*:*Z* ratio = 9:1. [f] 1 mol % **8a** added every 10 min.

Catalysts **7**−**8** show high activity at low catalyst loading for ring-closing of substrates **9** and **11**. The high efficiency in RCM of linalool **11** (100% conversion in 15 min at 0.5 mol % Ru) is notable given the presence of a sterically hindered trisubstituted olefin.[16,17] Sulfide **13** presents a different challenge, in the susceptibility of ruthenium to poisoning by soft sulfur donors.[18] Metathesis via **8b**

10.1021/ja042736s CCC: $30.25

Figure 1. Purification of RCM product **10** (5 mol % Ru) by silica gel chromatography. 5% EtOAc:hexanes: **7**, **8**: <100 ppm Ru (**1**: 30 900; **2a**: 57 900 ppm). 15% EtOAc:hexanes: **1**: 2450 ppm Ru (**7**: 600 ppm).

appears unimpeded by coordination of **14**; even at 0.5 mol % Ru, RCM is complete within 20 min. Conversions are lower with the other catalysts (including **3a**), with minimal improvement after 3 h, though **2a** can effect complete RCM[14] at higher loadings and increased temperatures. RCM of diphenyldiallylsilane **15** proves more difficult, and 5 mol % Ru is required for quantitative ring-closing, as previously noted.[15] Catalysts **8b** and **3a** are most effective, though all of the aryloxide catalysts outperform **2a**.

Macrocyclic targets present enthalpic and entropic barriers to ring-closing. The new catalysts show unprecedented efficiency in macrocyclization of substrates **17** and **19**. The products are 14- and 16-membered lactones that constitute the macrocycle cores of gloeosporone and epothilone A.[19−21] RCM of **17** using **1** and related catalysts is reportedly incomplete even after 30 h, while **2b** effects 72−87% ring-closing within 2−4 h.[19] In comparison, **8b** effects quantitative formation of **18** within 15 min. Ring-closing via **7** or **3a** is slower, but proceeds to completion in 12 or 1 h, respectively. RCM of **19** is rapid using either **8a** or **8b**, but plateaus at ca. 85% conversion for both **7** and **3a**.

Acrylate **21** proved unexpectedly[19d] problematic, possibly because chelation of the carbonyl functionality[22] is favorable. RCM proceeds to 73% conversion only on addition of **8b** in five boluses of 1 mol % each, over a period of 1 h. Finally, RCM of ene-yne **23** is facile, even at catalyst loadings an order of magnitude lower than those reported for **2b**. In RCM of sterically encumbered **25**, **8b** significantly outperforms both **2b** and catalysts of type **4**.[5b]

Paquette has pointed out that the efficiency of Ru-catalyzed metathesis in multistep organic syntheses is compromised by difficulties in removing residual Ru.[23a] Ruthenium levels of >2000 ppm remain after chromatography of samples of **10** prepared by RCM with 5 mol % of **1** or **2a** (Figure 1). Use of lead or phosphine (including supported phosphine) additives is reported to reduce the ruthenium content to 200−1200 ppm.[23a−d] Alternatively, two cycles of chromatography, followed by 12 h incubation with activated charcoal, results in <100 ppm Ru.[23e] The aryloxide catalysts, in comparison, have a high affinity for silica, enabling their efficient removal, without incubation, *in a single chromatographic pass*. Thus, RCM of **9** using 5 mol % of **7** or **8**, followed by flash chromatography, affords colorless oils in which the residual Ru content is below the 100 ppm detection limit of ICP-AES (inductively coupled plasma atomic emission spectroscopy). The purity of the organic product obtained by this simple and routine procedure is comparable to the best of the literature methods.

The foregoing demonstrates that the structural diversity of ruthenium metathesis catalysts can be expanded by incorporation of planar pseudohalide ligands, without detriment to catalyst performance. Indeed, the high efficiency and productivity of the aryloxide catalysts, in conjunction with their facile removal from organic products, can be expected to offer new opportunities in organic synthesis, particularly for metathesis of value-added substrates such as natural products.

Acknowledgment. This work was supported by NSERC of Canada, the Canada Foundation for Innovation, and the Ontario Innovation Trust.

Supporting Information Available: Synthetic and catalytic details. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003.
(2) (a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int.* Ed. **1998**, *37*, 2490. (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 262. (c) Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (d) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(3) (a) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *Organometallics* **2001**, *20*, 5314. (b) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035.
(4) (a) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403. (b) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 794.
(5) (a) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038. (b) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318. (c) Zaja, M.; Connon, S. J.; Dunne, A. M.; Rivard, M.; Buschmann, N.; Jiricek, J.; Blechert, S. *Tetrahedron* **2003**, *59*, 6545.
(6) Romero, P. E.; Piers, W. E.; McDonald, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 6161.
(7) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202.
(8) Alcaide, B.; Almendros, P. *Chem.*−*Eur. J.* **2003**, *9*, 1259.
(9) (a) Amoroso, D.; Yap, G. P. A.; Fogg, D. E. *Organometallics* **2002**, *21*, 3335. (b) Amoroso, D.; Snelgrove, J. L.; Conrad, J. C.; Drouin, S. D.; Yap, G. P. A.; Fogg, D. E. *Adv. Synth. Catal.* **2002**, *344*, 757.
(10) Conrad, J. C.; Fogg, D. E. *Curr. Org. Chem.* **2005**, in press.
(11) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414.
(12) Conrad, J. C.; Amoroso, D.; Czechura, P.; Yap, G. P. A.; Fogg, D. E. *Organometallics* **2003**, *22*, 3634.
(13) In preliminary experiments with **19**, RCM rates showed the trend $C_6H_6 > CH_2Cl_2 > CHCl_3$. For RCM of **17**, reaction was faster in CH_2Cl_2.
(14) Spagnol, G.; Heck, M. P.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2002**, *4*, 1767.
(15) Schmidt, B.; Pohler, M.; Costisella, B. *J. Org. Chem.* **2004**, *69*, 1421.
(16) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123.
(17) Braddock, D. C.; Matsuno, A. *Tetrahedron Lett.* **2002**, *43*, 3305.
(18) (a) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592.
(19) (a) Jafarpour, L.; Heck, M.-P.; Baylon, C.; Lee, H. M.; Mioskowski, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 671. (b) Fürstner, A.; Ackermann, L. *Chem. Commun.* **1999**, 95. (c) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942. (d) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. (e) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.
(20) Fürstner, A.; Mathes, C.; Lehmann, C. W. *Chem.*−*Eur. J.* **2001**, *7*, 5299.
(21) Rivkin, A.; Cho, Y. S.; Gabarda, A. E.; Yoshimura, F.; Danishefsky, S. J. *J. Nat. Prod.* **2004**, *67*, 139.
(22) Fürstner, A.; Thiel, O. R.; Lehmann, C. W. *Organometallics* **2002**, *21*, 331.
(23) (a) Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Mendez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259. (b) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411. (c) Maynard, H.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137. (d) Westhus, M.; Gonthier, E.; Brohm, D.; Breinbauer, R. *Tetrahedron Lett.* **2004**, *45*, 3141. (e) Cho, J. H.; Kim, B. M. *Org. Lett.* **2003**, *5*, 531.

JA042736S