Pure Appl. Chem., Vol. 78, No. 2, pp. 469–476, 2006.
doi:10.1351/pac200678020469
© 2006 IUPAC

Connecting catalytic cycles by organometallic transformations in situ: Novel perspectives in the olefin metathesis field*

Bernd Schmidt

Department of Chemistry, Organic Chemistry, University of Dortmund, Otto-Hahn-Strasse 6, D-44227 Dortmund, Germany

Abstract: Tandem sequences consisting of an olefin metathesis step and a subsequent non-metathesis reaction become accessible by organometallic transformations of the Ru-carbene species in situ. This contribution highlights some tandem sequences that rely on the conversion of the metathesis catalyst to Ru-hydrides, with special emphasis on the tandem ring-closing metathesis (RCM)–double-bond isomerization sequence.

Keywords: catalysis; ruthenium; metathesis; tandem sequence; isomerization.

INTRODUCTION

Sequential catalytic transformations conducted in one reaction vessel [1–3] are becoming increasingly important, because such methods have a significant impact on the development of environmentally benign production processes. Furthermore, they are increasingly used as tools for the rapid and efficient generation of molecular complexity, which is relevant for target-molecule [4] and diversity-oriented synthesis [5]. The potential of olefin metathesis [6–11] for the development of "one-pot" reaction sequences has rapidly been recognized after the discovery of stable and defined precatalysts based on molybdenum [12] and ruthenium [13]. These "early" metathesis sequences [14–17] rely on the combination of the different modes of olefin metathesis, as outlined for an illustrative example in Fig. 1 [18].

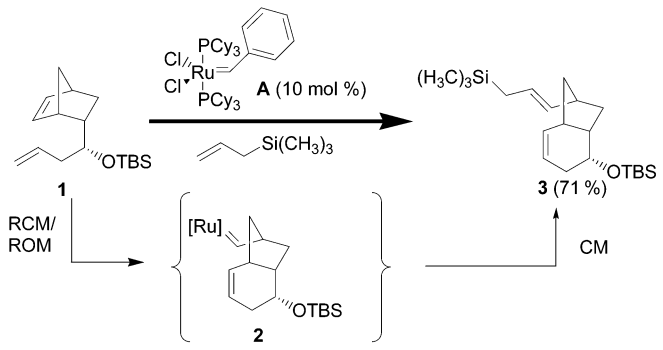

Fig. 1 RCM–ROM–CM sequence for the construction of bicyclic ring systems [18].

Pure Appl. Chem.* **78, 197–523. An issue of reviews and research papers based on lectures presented at the 13th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-13), Geneva, Switzerland, 17–21 July 2005.

In this particular case, norbornene **1** first undergoes a ring-closing/ring-opening metathesis (RCM/ROM) sequence in the presence of first-generation catalyst **A**, giving the new carbene complex **2**, which reacts with allyl trimethyl silane in a cross-metathesis (CM) reaction to the bicyclic product **3**. The value of such RCM–ROM–CM sequences (and related combinations of the individual metathesis steps) has been demonstrated over the past few years by a number of elegant applications to target-molecule synthesis [19–26], such as Blechert's synthesis of the piperidine alkaloid halosaline [27]. The key step of this synthesis is the application of an RCM–ROM–RCM sequence to cyclopentene **4**, resulting in the bicyclic system **5**, which is a precursor for the actual target molecule (Fig. 2). The concept is well described by the term ring rearrangement metathesis (RRM), which is often used for such sequences.

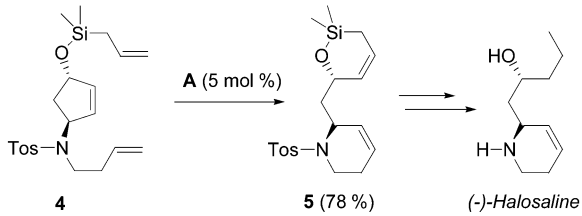

Fig. 2 Application of an RCM–ROM–RCM sequence to the synthesis of (–)-halosaline [27].

Characteristic features of the sequences discussed so far are that no additional reagents or catalysts are required in the course of the sequence, that no change in the nature of the reacting functional group occurs (i.e., an alkene is converted to another alkene) and that all C–C bond-forming steps are catalyzed by the same catalytically active species (i.e., a methylidene complex) via just one catalytic mechanism (i.e., the generally accepted olefin metathesis mechanism). Referring to Tietze's original definition [28] and a taxonomy recently proposed by Fogg and dos Santos for catalytic sequences [2], these processes may be classified as domino or cascade reactions.

By far less thoroughly investigated are reaction sequences that combine an olefin metathesis step (e.g., **6** → **7** in Fig. 3) with a *subsequent non-metathesis–functionalization* of the C–C double bond or the allylic position (e.g., **7** → **8** in Fig. 3). Thus, apart from the metathesis mechanism, at least one additional catalytic mechanism is operating in such sequences, and at least one additional catalytically active species is required.

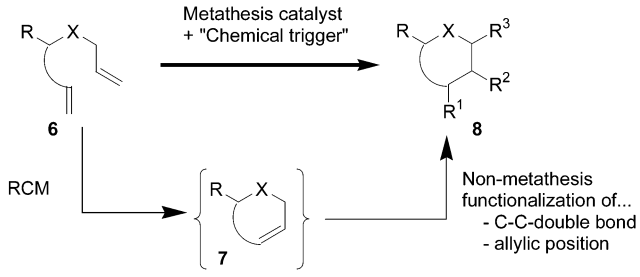

Fig. 3 General concept of metathesis–non-metathesis reaction sequences.

Fogg and dos Santos describe such sequences as "tandem catalysis" and define three different cases. "Orthogonal tandem catalysis" requires two or more precatalysts that have to be compatible under the reaction conditions. For instance, in the olefin metathesis field Ru–Pd-catalyzed metathesis–hydrogenation [29] and metathesis-Heck reaction sequences [30] have been described in the lit-

erature. Particularly attractive from the economical and practical point of view are sequences that require only one precatalyst, which is first transformed into the actual metathesis catalyst and, after completion of the metathesis step, into the catalyst of the non-metathesis reaction. This organometallic transformation may occur with ("assisted tandem catalysis") or without ("auto-tandem-catalysis") additional reagents (described as "chemical triggers" by Fogg and dos Santos) [2]. In other words: Organometallic transformations in situ can be used to connect two originally independent catalytic cycles. In this contribution, we will focus on transformations that are located at the interface of Ru-carbene and Ru-hydride catalyzed reactions [31].

TANDEM METATHESIS–HYDROGENATION

Fogg et al. investigated the reaction of Ru-carbene complex $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (**A**) [32] with molecular hydrogen in the presence of a base [33]. Under these conditions, the benzylidene ligand is cleaved and Ru-hydride complexes are formed, which serve as efficient catalysts for the hydrogenation of polymers resulting from metathesis polymerization [2]. Examples for the application of this tandem sequence to low-molecular-weight products have subsequently been published [34–38]. For instance, Børsting and Nielsen used a tandem RCM–hydrogenation approach for the synthesis of a cyclic dinucleotide such as **9** [39], and Glorius, Fürstner et al. applied this tandem sequence to the synthesis of the macrocyclic alkaloid isooncinotine (Fig. 4) [38]. In both cases, the RCM reaction is conducted under standard conditions, and the reaction vessel is subsequently pressurized to 50 bars of hydrogen at elevated temperatures.

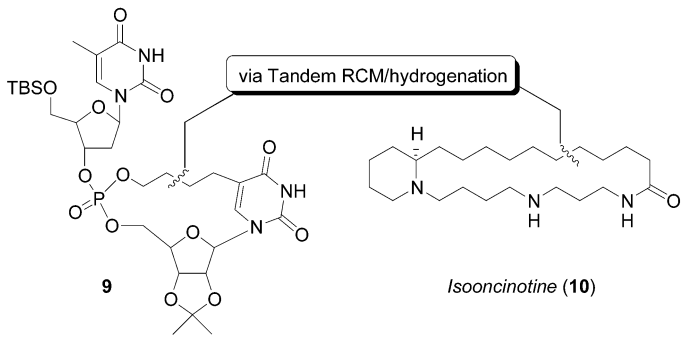

Fig. 4 Examples for the application of tandem RCM–hydrogenation in target-molecule synthesis.

In these cases, molecular hydrogen serves as a chemical trigger and as a reagent. A tandem RCM–hydrogenation sequence where molecular hydrogen is the reagent, but most likely not the chemical trigger was published by us: If NaH is added to a completed metathesis reaction, followed by hydrogen, hydrogenation occurs at much lower temperatures. This observation suggests that the metathesis catalyst is transformed to a hydrogenation catalyst by reaction with the inorganic hydride, rather than molecular hydrogen [36]. The use of silanes as chemical triggers and reagents for a tandem metathesis–hydrogenation process has very recently been described by Dalko et al. [40].

TANDEM METATHESIS–DEHYDROGENATIVE OXIDATION

Ru-catalyzed transfer hydrogenation–dehydrogenation reactions of ketones or secondary alcohols, respectively, have already been described in the 1970s [41]. More recently, it was discovered that the typical Ru-based metathesis precatalysts can also be used to mediate such transformations [42]. Incorporation of transfer hydrogenation steps in metathesis tandem sequences has been realized by

Grubbs et al. [34]. For instance, CM of allylic alcohol **11** and acetate **12** yields alcohol **13**, which is oxidized to enone **14** if diethyl ketone is added as a hydrogen acceptor. Extension of the sequence by an additional step has been used in a synthesis of the fragrant (–)-muscone (**16**). Here, the metathesis precursor **15** is first cyclized to the primary metathesis product, followed by transfer dehydrogenation of the secondary alcohol and final hydrogenation of the C–C double bond (established in the metathesis step) with molecular hydrogen (Fig. 5).

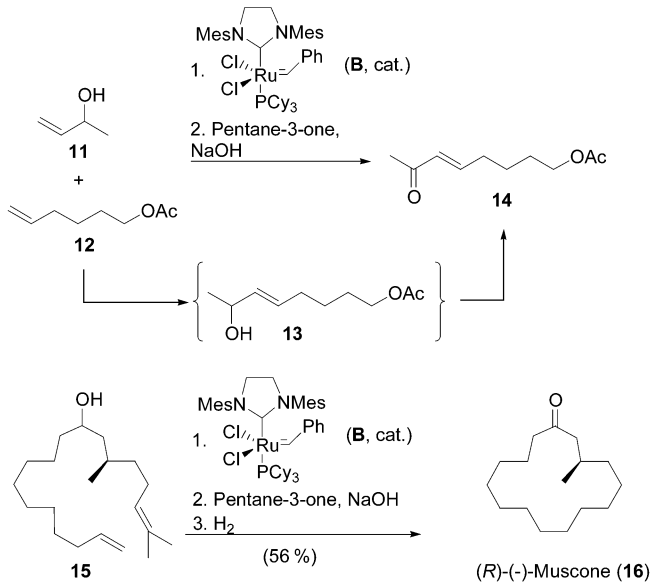

Fig. 5 Incorporation of transfer dehydrogenation steps in metathesis tandem sequences.

Van Otterlo and coworkers recently described a tandem RCM–dehydrogenative oxidation process that proceeds without adding hydrogen scavengers [43]. These authors were able to demonstrate that dienes such as **17** undergo the expected RCM to indenols such as **18** at ambient temperature, while oxidation products **19** were obtained if the reaction was conducted at elevated temperatures (Fig. 6).

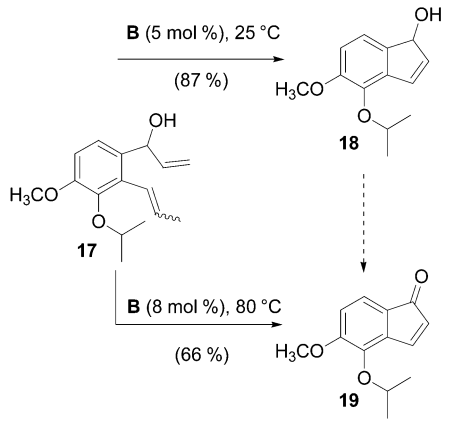

Fig. 6 Tandem RCM-dehydrogenative oxidation without additional hydrogen scavenger.

It is not yet clear what the actual catalyst of the oxidation step is. However, given the mechanism generally accepted for Ru-catalyzed transfer hydrogenation–dehydrogenation reactions [31], it appears to be likely that Ru-hydride species may be involved in one way or the other. Formation of a Ru-hydride by bimolecular decomposition of the second-generation catalyst **B** without addition of further reagents has recently been reported by Grubbs et al. [44].

TANDEM METATHESIS–ISOMERIZATION

Apart from olefin hydrogenation, Ru-hydrides also catalyze olefin isomerization via a hydroruthenation/β-hydride elimination mechanism [45]. In the olefin metathesis field, double-bond isomerization was originally an undesired non-metathesis side reaction [31,46] that might even become the preferred or exclusive pathway [47]. More recently, however, synthetically useful tandem RCM–isomerization reactions have been developed independently by Snapper et al. [48] and by us [49–51]. We thought such a sequence might be extraordinarily valuable for the synthesis of six-membered cyclic enol ethers **20** (Fig. 7). In this particular case, allyl ethers **21** are required for a tandem approach, while the straightforward approach uses enol ethers **22** as starting compounds. The tandem approach offers the following advantages: (a) precursors **21** are more conveniently accessible than **22** in enantiomerically pure form, because numerous well-established enantioselective allylation reactions are available; (b) RCM of **21** is a smooth reaction that is normally achieved with comparatively low amounts of first-generation catalyst **A**, whereas RCM of enol ethers **22** often requires high dilution and the more reactive (but less conveniently available) second-generation ruthenium catalyst **B** or Schrock's molybdenum catalyst [12].

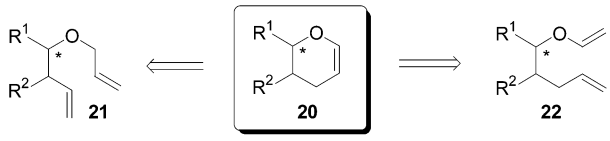

Fig. 7 Tandem approach (**21** → **20**) and enol ether metathesis approach (**22** → **20**) for cyclic enol ethers.

An obvious difficulty in the development of this tandem sequence following the concept outlined in the introduction is that conditions are required to convert the metathesis catalyst to a Ru-hydride without simultaneously promoting an undesired hydrogenation reaction. Snapper et al. [48] solved this problem in their tandem sequence by replacing the inert gas atmosphere by a 95:5 mixture of nitrogen and hydrogen. Under these conditions, isomerization of the primary metathesis products occurs "while keeping the competing olefin hydrogenation to ≤10 %" (Fig. 8) [48].

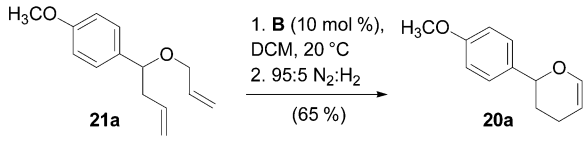

Fig. 8 Snapper's protocol for a tandem RCM–isomerization sequence.

Our approach to overcome this difficulty was to avoid the addition of molecular hydrogen and use other "chemical triggers" to promote the conversion of Ru-carbenes to Ru-hydrides in situ. Four different additives or additive combinations (protocols A–D) have been identified by our group, and representative examples are outlined in the following. Protocol A [51] exploits an observation recently made by Louie and Grubbs [52]: Ethyl vinyl ether was found to react with precatalyst **A** at elevated tem-

peratures to the complex [RuHCl(CO)(PCy_3)$_2$]. We found that addition of ethyl vinyl ether to a completed metathesis reaction in toluene with subsequent heating to reflux indeed induces isomerization of the primary metathesis products to cyclic enol ethers. However, this protocol is limited to five-membered ring systems as exemplified in Fig. 9 for the formation of **20b**.

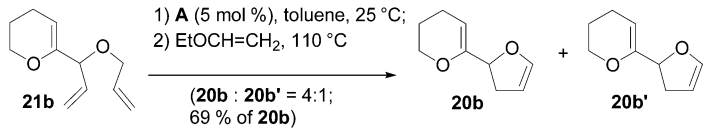

Fig. 9 Schmidt's protocol A for a tandem RCM–isomerization sequence.

Protocol B [49,51] uses sub-stoichiometric amounts of inorganic hydrides, such as $NaBH_4$ or NaH as additives. Under these conditions, five-, six-, and seven-membered cyclic enol ethers can be obtained in preparatively useful yields and selectivities. Only for five-membered ring systems, the undesired higher substituted isomerization products (e.g., **20b'**) were observed, whereas the selectivity for six- and seven-membered oxacycles is normally better than 19:1 in favor of the less-substituted derivatives. Protocol C [50,51] uses 2-propanol as a cosolvent in combination with NaOH in sub-stoichiometric amounts. Compared to protocol B, reaction times are significantly reduced and broader tolerance to functional groups is observed. This protocol is also highly regioselective for the less-substituted isomer. The conversion of **21c** to **20c** (Fig. 10) illustrates both methods.

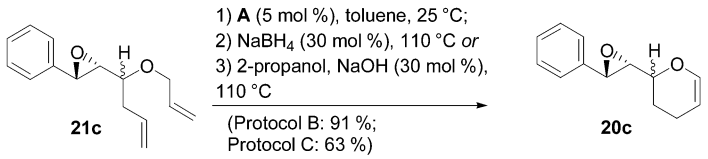

Fig. 10 Schmidt's protocols B and C for a tandem RCM–isomerization sequence.

Protocol D [51] relies on the addition of triethylsilane to the reaction mixture after completion of the metathesis step. This leads not only to an isomerization catalyst, but allows the extension of the sequence by an additional Ru-catalyzed step, which is outlined in Fig. 11 for the conversion of **21d** to **20d**: At ambient temperature, RCM of **21d** occurs, which is followed by a dehydrogenative silylation of the primary alcohol [53] and final double-bond isomerization to yield the silylated cyclic enol ether **20d**.

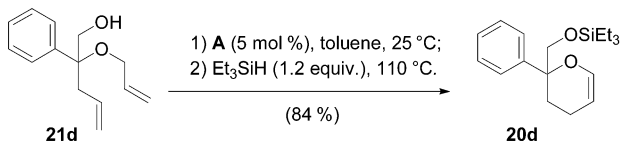

Fig. 11 Schmidt's protocol D for a tandem RCM–isomerization sequence.

Although the actual catalytically active species have not yet been identified, NMR-spectroscopic investigations suggest that all protocols developed in our group rely on the formation of Ru-hydride species in situ. We are currently working toward the application of this method in the synthesis of target molecules.

CONCLUSIONS

Conversion of Ru metathesis catalysts to Ru-hydrides in situ can bridge the gap between originally independent catalytic cycles. As exemplified in this contribution for three tandem sequences, novel valuable synthetic methods may result that will most likely broaden the scope of olefin metathesis beyond the high level that has already been reached today. If other Ru-catalyzed or initiated reactions that do not proceed via Ru-hydrides (e.g., oxidative double-bond functionalization [54] or radical reactions [55–58]) can be combined with olefin metathesis to tandem sequences, even more exciting perspectives evolve from the concept outlined in this contribution.

ACKNOWLEDGMENTS

Generous financial support by the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, and the Department of Chemistry of the University of Dortmund is gratefully acknowledged.

REFERENCES

1. J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan. *Chem. Rev.* **105**, 1001 (2005).
2. D. E. Fogg and E. N. dos Santos. *Coord. Chem. Rev.* **248**, 2365 (2004).
3. A. Ajamian and J. L. Gleason. *Angew. Chem., Int. Ed.* **43**, 3754 (2004).
4. K. C. Nicolaou, P. G. Bulger, D. Sarlah. *Angew. Chem., Int. Ed.* **44**, 4442 (2005).
5. M. D. Burke and S. L. Schreiber. *Angew. Chem., Int. Ed.* **43**, 46 (2004).
6. B. Schmidt and J. Hermanns. *Top. Organomet. Chem.* **13**, 223 (2004).
7. S. J. Connon and S. Blechert. *Top. Organomet. Chem.* **11**, 93 (2004).
8. S. J. Connon and S. Blechert. *Angew. Chem., Int. Ed.* **42**, 1900 (2003).
9. A. Fürstner. *Angew. Chem.* **112**, 3140 (2000).
10. R. R. Schrock. *Top. Organomet. Chem.* **1**, 1 (1998).
11. S. K. Armstrong. *J. Chem. Soc., Perkin Trans. 1* 371 (1998).
12. R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan. *J. Am. Chem. Soc.* **112**, 3875 (1990).
13. G. C. Fu, S. T. Nguyen, R. H. Grubbs, J. W. Ziller. *J. Am. Chem. Soc.* **115**, 9856 (1993).
14. W. J. Zuercher, M. Hashimoto, R. H. Grubbs. *J. Am. Chem. Soc.* **118**, 6634 (1996).
15. J.-A. Funel and J. Prunet. *Synlett* 235 (2005).
16. O. Arjona, A. G. Csaky, J. Plumet. *Eur. J. Org. Chem.* 611 (2003).
17. R. Stragies and S. Blechert. *J. Am. Chem. Soc.* **122**, 9584 (2000).
18. R. Stragies and S. Blechert. *Synlett* 169 (1998).
19. Z. Zhao, L. Song, P. S. Mariano. *Tetrahedron* **61**, 8888 (2005).
20. N. Holub and J. Neidhöfer, S. Blechert. *Org. Lett.* **7**, 1227 (2005).
21. M. Zaja and S. Blechert. *Tetrahedron* **60**, 9629 (2004).
22. J. D. Winkler, S. M. Asselin, S. Shepard, J. Yuan. *Org. Lett.* **6**, 3821 (2004).
23. L. Song, E. N. Duesler, P. S. Mariano. *J. Org. Chem.* **69**, 7284 (2004).
24. J. Neidhöfer and S. Blechert. *Synthesis* 3047 (2004).
25. G. Lesma, S. Crippa, B. Danieli, D. Passarella, A. Sacchetti, A. Silvani, A. Virdis. *Tetrahedron* **60**, 6437 (2004).
26. J. Holtsclaw and M. Koreeda. *Org. Lett.* **6**, 3719 (2004).
27. R. Stragies and S. Blechert. *Tetrahedron* **55**, 8179 (1999).
28. L. F. Tietze. *Chem. Rev.* **96**, 115 (1996).
29. J. Cossy, F. C. Bargiggia, S. BouzBouz. *Org. Lett.* **5**, 459 (2003).
30. R. Grigg and M. York. *Tetrahedron Lett.* **41**, 7255 (2000).

31. B. Schmidt. *Eur. J. Org. Chem.* 1865 (2004).
32. P. Schwab, R. H. Grubbs, J. W. Ziller. *J. Am. Chem. Soc.* **118**, 100 (1996).
33. S. D. Drouin, G. P. A. Yap, D. E. Fogg. *Inorg. Chem.* **39**, 5412 (2000).
34. J. Louie, C. W. Bielawski, R. H. Grubbs. *J. Am. Chem. Soc.* **123**, 11312 (2001).
35. P. Børsting, K. E. Nielsen, P. Nielsen. *Org. Biomol. Chem.* **3**, 2183 (2005).
36. B. Schmidt and M. Pohler. *Org. Biomol. Chem.* **1**, 2512 (2003).
37. A. Fürstner and A. Leitner. *Angew. Chem., Int. Ed.* **42**, 308 (2003).
38. B. Scheiper, F. Glorius, A. Leitner, A. Fürstner. *Proc. Natl. Acad. Sci. USA* **101**, 11960 (2004).
39. P. Børsting and P. Nielsen. *Chem. Commun.* 2140 (2002).
40. C. Menozzi, P. I. Dalko, J. Cossy. *Synlett* 2449 (2005).
41. Y. Sasson and J. Blum. *J. Org. Chem.* **40**, 1887 (1975).
42. C. S. Cho, B. T. Kim, T.-J. Kim, S. C. Shim. *J. Org. Chem.* **66**, 9020 (2001).
43. W. A. L. van Otterlo, E. M. Coyanis, J.-L. Panayides, C. B. de Koning, M. A. Fernandes. *Synlett* 501 (2005).
44. S. H. Hong, M. W. Day, R. H. Grubbs. *J. Am. Chem. Soc.* **126**, 7414 (2004).
45. H. Suzuki and T. Takao. In *Ruthenium in Organic Synthesis*, S.-I. Murahashi (Ed.), Wiley-VCH, Weinheim (2004).
46. B. Alcaide and P. Almendros. *Chem. Eur. J.* **9**, 1259 (2003).
47. C. Cadot, P. I. Dalko, J. Cossy. *Tetrahedron Lett.* **43**, 1839 (2002).
48. A. E. Sutton, B. A. Seigal, D. F. Finnegan, M. L. Snapper. *J. Am. Chem. Soc.* **124**, 13390 (2002).
49. B. Schmidt. *Eur. J. Org. Chem.* 816 (2003).
50. B. Schmidt. *Chem. Commun.* 742 (2004).
51. B. Schmidt. *J. Org. Chem.* **69**, 7672 (2004).
52. J. Louie and R. H. Grubbs. *Organometallics* **21**, 2153 (2002).
53. S. V. Maifeld, R. L. Miller, D. Lee. *Tetrahedron Lett.* **43**, 6363 (2002).
54. B. Plietker and M. Niggemann. *Org. Biomol. Chem.* **2**, 2403 (2004).
55. B. Schmidt, M. Pohler, B. Costisella. *J. Org. Chem.* **69**, 1421 (2004).
56. B. Schmidt and M. Pohler. *J. Organomet. Chem.* **690**, 5552 (2005).
57. B. A. Seigal, C. Fajardo, M. L. Snapper. *J. Am. Chem. Soc.* **127**, 16329 (2005).
58. C. D. Edlin, J. D. Faulkner, P. Quayle. *Tetrahedron Lett.* **47**, 1145 (2006).