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Functional group diversity by ruthenium-catalyzed olefin cross-metathesis*

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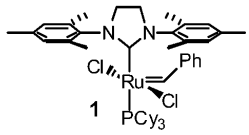
Abstract: Ruthenium-catalyzed olefin cross-metathesis tolerates a wide range of functional groups, including phosphine-boranes, sulfides, amines, phenols, and oxazolines. The high functional group tolerance allows for the use of an olefin as a linchpin for the synthesis of a variety of bi-, tri-, and tetradentate chiral ligands with a high degree of functional group diversity.

The increasing necessity for the synthesis of diverse libraries of compounds demands the development of methods that tolerate a wide range of functional groups. The formation of carbon–carbon bonds by olefin metathesis [1] offers a powerful method for the creation of chemical diversity [2]. In particular, olefin cross-metathesis (CM) can provide access to alkenes bearing a wide range of functional groups [3]. However, the reaction has generally been limited to olefins in which functional groups that may behave as ligands for the catalyst are absent. Herein are detailed our studies on the use of heteroatom containing olefins in the cross-metathesis reaction and applications of this method to the generation of a variety of 2-oxazolylphenol-derived tridentate chiral ligands.

The study was initiated by the observation that ruthenium catalyst **1** readily catalyzed the ring-closing metathesis (RCM) of diallyl disulfide to afford cyclic disulfide **2** in 90% yield. This result is in sharp contrast to the first-generation bis-phosphine catalyst $[(PCy_3)_2Ru(CHPh)Cl_2]$, which was shown to be completely unreactive in this transformation [4]. This observation prompted us to explore the possibility that catalyst **1** may tolerate olefins bearing functional groups that were poor substrates for the first-generation catalyst. To this end, allyl methyl sulfide was reacted with 5 mol% **1** to afford the disubstituted olefin **3** in 69% yield as a 6:1 mixture of *E*:*Z* olefin isomers [5].



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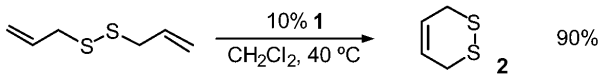

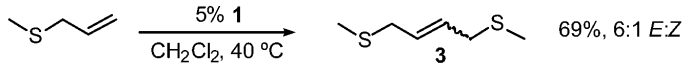

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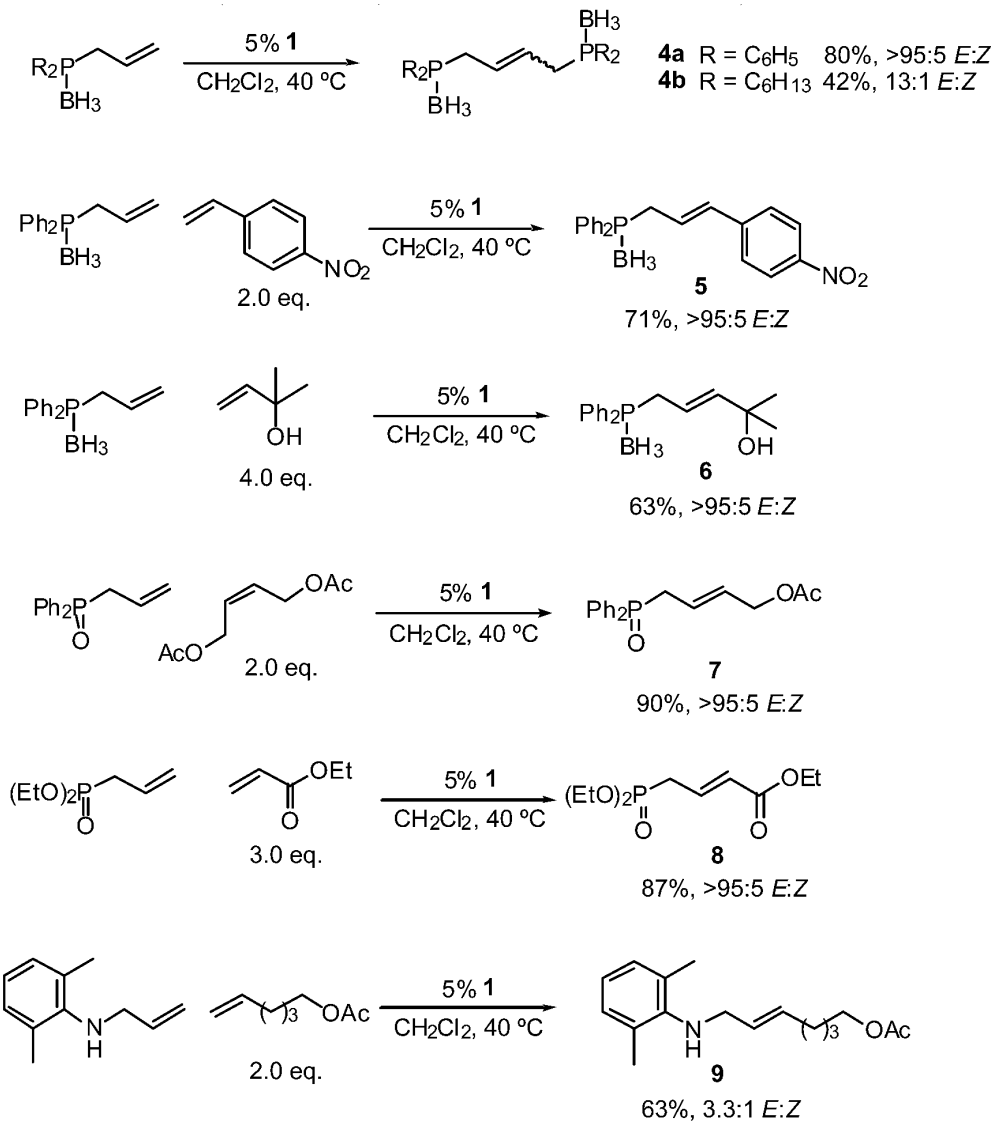
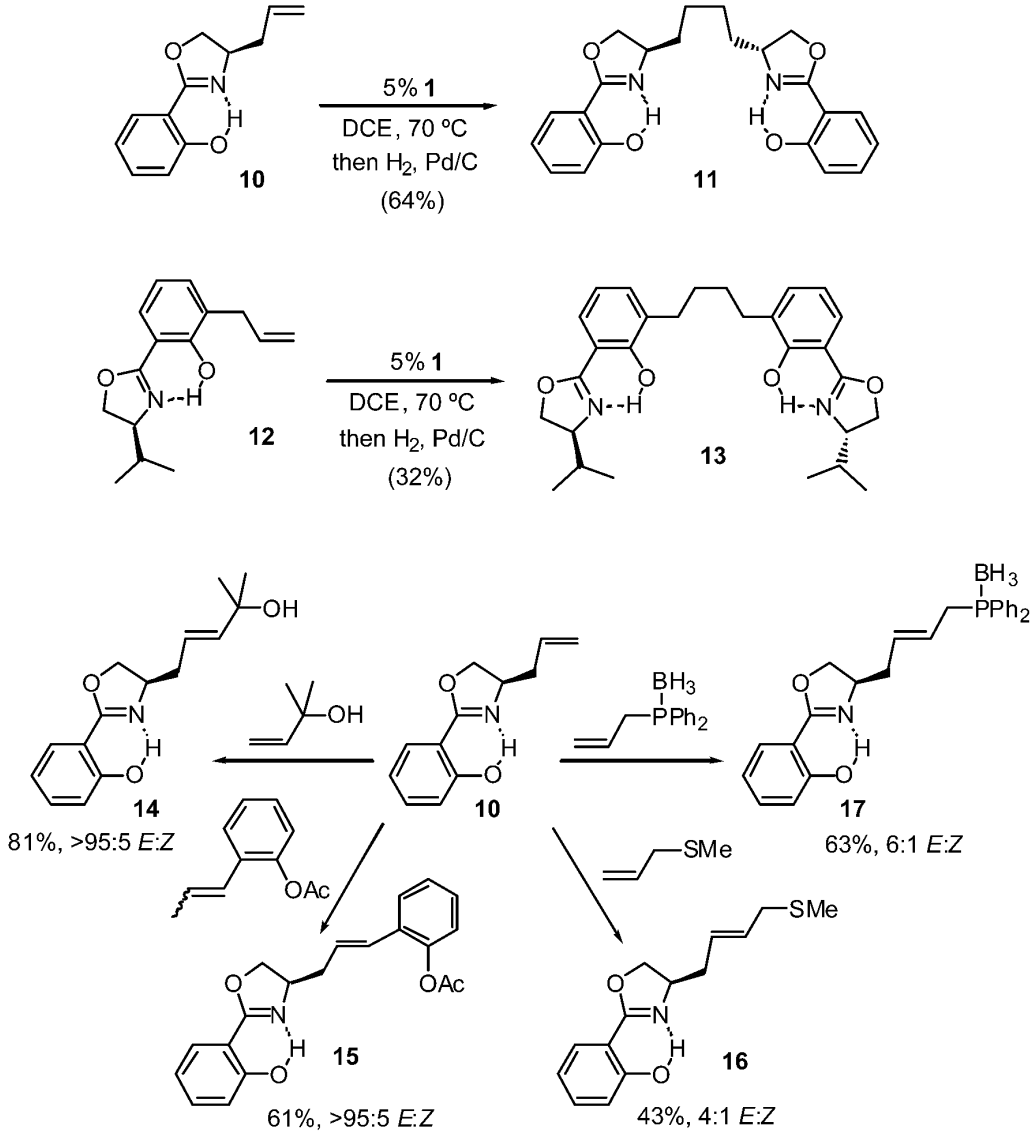
The fact that catalyst **1** tolerates olefins substituted with an allylic sulfide suggested that other functional groups that could behave as ligands for ruthenium might be viable substrates. In an extreme case, the reaction of allyl diphenylphosphine with 5 mol% **1** failed to produce any of the desired cross-metathesis adduct and returned terminal olefin unreacted. This problem was readily remedied by protection of the phosphine as its borane complex [6]. Catalyst **1** catalyzed the dimerization of borane complexes of allyl diphenyl and dicyclohexylphosphine to produce bisphosphines **4a** and **4b** in 80% (>95:5, *E*:*Z*) and 42% (13:1, *E*:*Z*) yield, respectively.



Notably, catalyst **1** failed to dimerize borane-protected vinyl diphenylphosphine. Protected allyl phosphines are not limited to simple dimerization reactions and may be employed as substrates for cross-metathesis. For example, reaction of borane-protected allyl diphenylphosphine with 4-nitrosytrene or 2-methylbutene-2-ol produces phosphines **5** and **6** in 71% and 63% yield, respectively. In the case of **6**, hydrogenation of the olefin and deprotection of the phosphine results in the formation of a P,O-bidentate ligand. Substitution of other oxidation states of phosphorus at the allylic position is also tolerated [7]. For example, 5 mol% of **1** produces phosphine oxide **7** in 90% yield as a sin-

gle olefin isomer from the coupling of allyl diphenylphosphine oxide with 2-butene-1,4-diacetate. Similarly, reaction of diethyl allylphosphonate with ethyl acrylate, catalyzed by 5 mol% **1**, produces **8** in 87% yield with complete control of olefin geometry.



N-Allyl amines were also examined as partners in cross-metathesis reactions. It was found that *N*-aryl-*N*-allyl amine readily participates in the reaction with 5-hexenyl acetate to produce amine **9** in 63% yield as a 3.3:1 mixture of *trans*:*cis* olefin isomers. This reaction stands in sharp contrast to attempted reactions with Fmoc- and Boc-protected allyl amine, which failed to produce any of the desired product and resulted primarily in conversion of the allyl amines into enamines [8].

The successful cross-metathesis of an unprotected *N*-allyl amine prompted us to examine the possibility of applying catalyst **1** for the preparation of a family of 2-oxazolylphenols [9]. Oxazoline **10** was prepared by zinc chloride-catalyzed [10] reaction of 2-cyanophenol with the amino alcohol derived from allylglycine. We were pleased to find that 5 mol% **1** catalyzed the cross-metathesis of **10** to afford a 64% yield of the dimer as a 5:1 mixture of *trans*:*cis* olefin isomers. The control of olefin geometry is

irrelevant as the olefin was hydrogenated to afford **11**, which may serve as salen-like ligand. Similarly, oxazoline **12** (available from the Claisen rearrangement of the corresponding *O*-allyl aryl ether) is readily dimerized with catalyst **1** to produce a 4:1 mixture of *E*:*Z* olefin isomers, which are subsequently hydrogenated. The ability of catalyst **1** to tolerate 2-oxazolylphenol-substituted olefins is noteworthy since it has been shown that Schiff-based ligands (sal) can serve as excellent ligands for related ruthenium complexes [11]. Apparently, the exceptional reactivity of **1** toward olefins [12] exceeds its reactivity towards this bidentate ligand. With these results in hand, we were able to prepare a small family of potentially tridentate 2-oxazolylphenol ligands by the cross-metathesis of **10** with an olefin containing a functional group which could serve as the third coordinating group. For example, 5 mol% **1** catalyzed the reaction of **10** with allyl methyl sulfide to produce **16**, which after hydrogenation of the olefin, may serve as a *O*,*N*,*S*-tridentate chiral ligand. Similarly, deprotection of the phosphine and hydrogenation of the olefin are required to convert **17** into a *O*,*N*,*P*-tridentate chiral ligand.

In conclusion, we have demonstrated that catalyst **1** tolerates functional groups that had been detrimental to the catalytic activity of previous ruthenium metathesis catalysts. This increased scope should further encourage the use of **1** and cross-metathesis as a method for creation of chemical diversity. The ability of **1** to create structures with functional group diversity was demonstrated by the preparation of a small family of 2-oxazoylphenol chiral ligands.

REFERENCES

1. For recent reviews, see: (a) A. Fürstner. *Angew. Chem.* **112**, 3140 (2000); (b) S. Blechert. *Pure Appl. Chem.* **71**, 1393 (1999); (c) R. H. Grubbs and S. Chang. *Tetrahedron* **54**, 4413 (1998).
2. (a) D. Lee, J. K. Sello, S. L. Schreiber. *J. Am. Chem. Soc.* **121**, 10618 (1999); (b) D. L. Boger, W. Chai, R. S. Ozer, C.-M. Andersson. *Bioorg. Med. Chem. Lett.* **7**, 463 (1997).
3. (a) T.-L. Choi, A. K. Chatterjee, R. H. Grubbs. *Angew. Chem. Int. Ed.* **49**, 1277 (2001); (b) A. K. Chatterjee, T.-L. Choi, R. H. Grubbs. *Synlett* 1034 (2001); (c) A. K. Chatterjee, J. P. Morgan, M. Scholl, R. H. Grubbs. *J. Am. Chem. Soc.* **122**, 3783 (2000); (d) H. E. Blackwell, D. J. O'Leary, A. K. Chatterjee, R. A Washenfleder, D. A. Bussman, R. H. Grubbs. *J. Am. Chem. Soc.* **122**, 58 (2000); (e) A. K. Chatterjee and R. H. Grubbs. *Org. Lett.* **1**, 1751 (1999).
4. Y.-S. Shon and T. R. Lee. *Tetrahedron Lett.* **38**, 1283 (1997).
5. For examples of ruthenium-catalyzed RCM of sulfur containing substrates, see: (a) J. D. Moore, K. T. Sprott, P. R. Hanson. *Synlett* 605 (2001); (b) R. M. Garbaccio, S. J. Stachel, D. K. Baeschlin, S. J. Danishefsky. *J. Am. Chem. Soc.* **123**, 10903 (2001).
6. For ruthenium-catalyzed RCM of substrates containing a phosphine-borane group, see: M. Schuman, M. Trevitt, A. Redd, V. Gouverneur. *Angew. Chem. Int. Ed.* **39**, 2491 (2000).
7. For ruthenium-catalyzed RCM of substrates containing a phosphine-oxide group, see: M. Trevitt and V. Gouveneur. *Tetrahedron Lett.* **40**, 7333 (1999).
8. For the use of Ru-carbene catalyst to cleave *N*-allyl amines, see: B. Alcaide, P. Almendros, J. M. Alosnso, M. F. Aly. *Org. Lett.* **3**, 3781 (2001).
9. For a review of oxazoline-based ligands see: (a) P. Braunstein and F. Naud. *Angew. Chem. Int. Ed.* **40**, 680 (2001); (b) A. K. Ghosh, P. Mathivanan, J. Cappiello. *Tetrahedron* **9**, 1 (1998).
10. A. Scheurer, P. Mosset, W. Bauer, R. W. Sallfrank. *Eur. J. Org. Chem.* 3067 (2001).
11. S. Chang, L. Jones II, C. Wang, L. M. Henling, R. H. Grubbs. *Organomet.* **17**, 3460 (1998).
12. M. S. Sanford, J. A. Love, R. H. Grubbs. *J. Am. Chem. Soc.* **123**, 6543 (2001).