Ruthenium-Catalyzed Olefin Cross Metathesis of Styrenes as an Alternative to the Heck and Cross-Coupling Reactions

Arnab K. Chatterjee, F. Dean Toste, Tae-Lim Choi, Robert H. Grubbs*

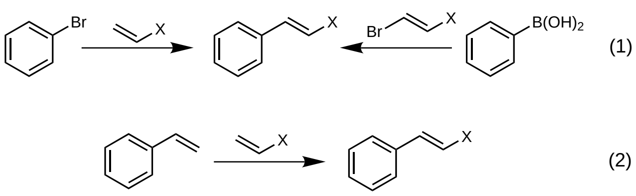
Arnold and Mabel Beckman Laboratories for Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, USA
Fax: (+1)-626-564-9297, e-mail: rhg@caltech.edu

Received: March 26, 2002; Accepted: May 25, 2002

Abstract: The use of olefin cross metathesis as a method for the formation of styrenyl-olefins is described using allylic substituted olefins and electron-deficient olefins. These methods provide an orthogonal method to alternative olefination strategies, such as the Heck reaction. These methods have also been employed in the total synthesis of 3-flavanols.

Keywords: cross metathesis; 3-flavanols, *N*-heterocyclic carbene (NHC) ligands; homogeneous catalysis; ruthenium; styrenes

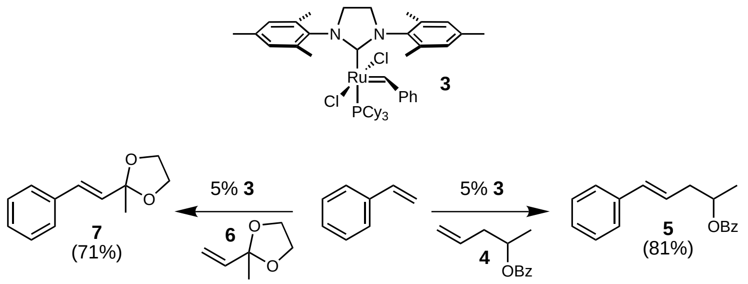
Functionalized styrenes are important building blocks for organic synthesis. Therefore, preparation of these compounds must allow for variation in both the aromatic and olefinic portions of the styrene. Since the olefin often undergoes further manipulation, it is imperative that the alkene geometry is controlled during the coupling reaction. The Heck reaction,[1] and cross-coupling reactions such as the Suzuki reaction,[2] have often been employed because of the availability of aryl halides and boronic acids and because of excellent control of the olefin geometry (Scheme 1, equation 1). However, the latter is often limited by access to the coupling partners (vinyl halides and triflates). On the other hand, the Heck reaction employs simple olefins as coupling partner; however, the reaction operates best with olefins substituted with electron-withdrawing groups. The commercial availability of a large number of styrenes prompted us to examine the possibility of employing olefin cross metathesis as an alternative entry into this class of molecules (Scheme 1, equation 2). Notably, this reaction should be amenable to utilizing simple olefins as coupling partners and as such should circumvent some of the aforementioned limitations.



Scheme 1. Alternative styrene olefination strategies.

Olefin metathesis has developed into a highly useful reaction for the synthesis of complex organic molecules by ring-closing metathesis (RCM) and ring-opening metathesis polymerization (ROMP). Due to the commercial availability of well-defined single component catalysts $Mo(CHCMe_2Ph)(NAr)[OCMe(CF_3)_2]_2$ (**1**)[3] and $(PCy_3)_2Cl_2RuCHPh$ (**2**),[4] organic chemists have subjected highly valuable substrates, in many cases synthesized in multi-step processes, to RCM and ROMP reactions. On the other hand, olefin cross metathesis (CM) has been underutilized when compared to other metathesis processes and this is due primarily to the lack of product selectivity and olefin stereoselectvity.[5] However, styrenes represent one of the classes of olefins used in CM with ill-defined catalyst systems,[6] **1**[7] and **2**,[8] because of high *trans* selectivity in the cross product and the slow dimerization of styrene to stilbene, allowing for selective cross-coupling. In all these cases, an excess of styrene was used in the reaction to consume as much terminal olefin as possible. However, CM products were only obtained in moderate yields and only terminal olefins are employable in CM with **1** and **2**. Therefore, increasing the efficiency and substrate scope of styrene CM reactions would be advantageous in organic synthesis as a viable alternative to Heck and other cross-coupling methods. With the recent advent of imidazolylidene-based catalysts systems, such as **3**, there has been an expanded set of reports of successful CM. In fact, the range of electron-deficient olefins that participate in CM with **3** now include α,β-unsaturated carbonyl-containing olefins,[9] vinylphosphonates,[10] vinylsulfones,[11] and perfluorinated alkane[12] containing olefins. With these successes in hand, we wished to investigate styrene CM with catalyst **3**.

To this end, we examined the cross metathesis reaction of styrene with a variety of cross partners using ruthenium alkylidene **3** (Scheme 2). Reaction of styrene with 2 equivalents of homoallylic benzoate **4**, catalyzed by 5 mol % of **3**, affords the substituted styrene **5** in 81%



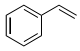
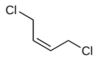
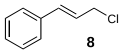
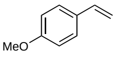
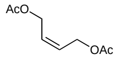
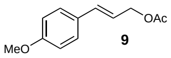
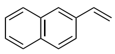
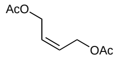
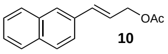
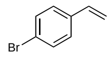
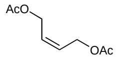
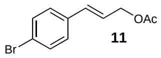
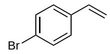
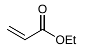
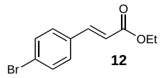
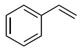
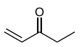
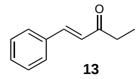
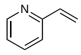
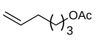
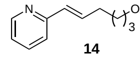
Scheme 2. Initial styrene CM using **3**.

yield as a single olefin isomer. The compatibility of the benzoate functionality that may eliminate using basic Wittig conditions is another advantage of the CM method to these compounds. Similarly, reaction of ketal **6** with styrene produced cinnamyl ketone **7** in 71% also as a single olefin isomer. Notably, this is the first example of styrene CM in the presence of a fully substituted allylic carbon atom, and does not affect the course of the reaction. This prompted us to examine the cross metathesis reaction of olefins bearing allylic substituents which would not be tolerated in the Heck and cross-coupling reactions, providing direct orthogonality to those methods.

Allylic halides are not tolerated in the Heck and cross-coupling reactions because of their propensity to undergo ionization by palladium(0). On the other hand, reaction of styrene with *cis*-butene-1,4-dichloride (2 equiv.), catalyzed by 5 mol % of **3**, produced *trans*-cinnamyl chloride **8** in 93% yield without any ionization of the chloride (Table 1). Notably, the analogous reaction catalyzed by the ruthenium bis-phosphine catalyst **2** produced **8** in only 23% yield, and further demonstrates the enhanced catalytic activity of **3**. The reaction can be extended to the production of cinnamyl acetates. For example, 5 mol % of **3** catalyzes the reaction of *cis*-butene-1,4-diacetate (2 equiv.) with 4-methoxysytrene and 2-vinylnaphthelene to produce cinnamyl acetates **9** and **10** in 83% and 81% yield, respectively. Substitution of a halide on the aromatic ring of the styrene is also incompatible with the palladium(0) methods because of the competing oxidative addition into the aryl-halide bond. In sharp contrast, the reaction of 4-bromosytrene with *cis*-butene-1,4-diacetate, catalyzed by 5 mol % of **3**, afford **11** in 93% yield as a single olefin isomer.

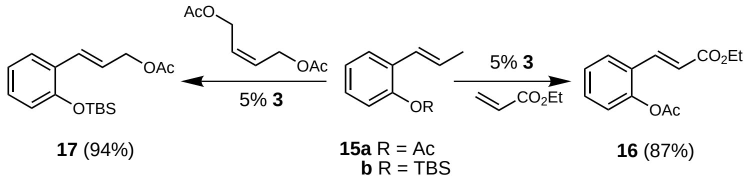
We also examined the cross metathesis of reaction of styrene with electron-poor olefins traditionally employed in the Heck reaction.[13] For example, 5 mol % of **3** catalyzes the reaction of 4-bromostyrene with ethyl acrylate to afford ethyl cinnamate **12** in 98% yield as a single olefin isomer, and demonstrates a direct CM route to this compound. In addition, vinyl ketones are excellent CM partners with styrene as demonstrated in the quantitative CM to enone **13**. Surprisingly, we discovered that heteroaromatic compounds are also compatible for catalytic CM with **3**, in the CM of 2-vinylpyridine with 5-hexenyl acetate to form **14** in moderate yield, despite the ability of pyridine to serve as an excellent ligand for these catalytic complexes.[14]

Table 1. Styrene cross metathesis with catalyst **3** (5 mol%).

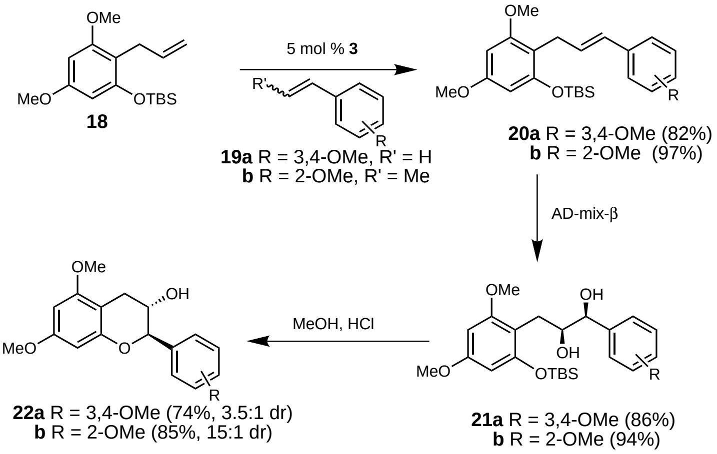
Styrene	Coupling Partner	Product	Isolated Yield (*E*:*Z* ratio)[a]
		 **8**	93% >20:1
		 **9**	83% >20:1
		 **10**	81% >20:1
		 **11**	93% >20:1
		 **12**	98% >20:1
		 **13**	99% >20:1
		 **14**	45% >20:1

[a] Determined by ^{1}H and ^{13}C NMR.

This also prompted us to examine the use of *ortho*-alkoxy substituted styrenes in CM. Similar to the pyridine result described in Table 1, *ortho*-alkoxy groups in the benzylidene have been observed to coordinate to the ruthenium center, and these substrates also have the potential complication of catalyst inhibition.[15] We were pleased to find that the reaction of 2-acetoxy-β-methylstyrene (**15a**) with ethyl acrylate, catalyzed by 5 mol % of **3**, proceeded smoothly to afford cinnamate **16** in 87% yield (Scheme 3). Similarly, reaction of *ortho*-silyloxystyrene **15b** with 1,4-*cis*-butene diacetate produced **17** as a single olefin isomer in 94% isolated yield demonstrating the compatibility of several different phenolic protecting groups to the CM conditions.



Scheme 3. *ortho*-Phenol cross metathesis.



Scheme 4. Cross metathesis route to 3-flavinols.

With these results in hand, we examined application of this method to the synthesis of 3-flavanols (Scheme 4).[16] To this end, reaction of allylbenzene **18** with 3,4-dimethoxystyrene **19a**, catalyzed by 5 mol % of **3** afforded **20a** in 82% yield as a single *trans* olefin isomer. Similarly, the reaction of β-methylstyrene **19b** with **18** produced **20b** in 97% yield. Sharpless asymmetric dihydroxylation of propenes **20a** and **20b**, with AD-mix-β, afforded diols **21a** and **21b** in 86% and 93% yield, respectively. Finally, reaction of the diols with methanolic hydrochloric acid produced the flavanols in good yields.[17] The 3,4-dimethoxyphenyl-substituted flavanol (permethylcatechin) **20a** was produced as a 3.5:1 mixture of *trans:cis* diastereomers. On the other hand, the 2-methoxyphenyl group produced the flavanol with significantly better distereoselectivity (15:1). These reactions provide a method for synthesizing a large set of flavanols by employing other commercially available styrene CM partners.[18]

In conclusion, we have demonstrated that the *N*-heterocyclic carbene-based ruthenium complex **3** efficiently catalyzes the cross-coupling of styrenes with a variety of substituted olefins. As such, the cross-metathesis reaction produces substituted styrenes with excellent control of olefin geometry from readily available starting materials. Furthermore, the cross metathesis reaction is tolerant of aryl and allylic halides which is complimentary to the Heck and cross-coupling reactions.

Experimental Section

General Procedures

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230 – 400 mesh) from EM Science. All other chemicals were purchased from the Aldrich or TCI America and used as delivered unless noted otherwise. CH_2Cl_2 was purified by passage through a solvent column prior to use. Catalyst **3** was stored and manipulated on the bench. NMR spectra were recorded on a Varian Mercury 300 MHz NMR spectrometer.

Representative Cross Metathesis Procedure (for Compound 17)

cis-2-Butene-1,4-diacetate from TCI America (95 μL, 0.51 mmol, 2.0 equiv.) was added *via* syringe to a stirring solution of **3** (15 mg, 0.018 mmol, 5.7 mol %) and 2-*tert*-butyldimethylsilyloxy-β-methylstyrene (76 mg, 0.31 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL, 0.15 M in styrene) under a nitrogen atmosphere. The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with 20:1 hexane:ethyl acetate to provide cross product **17** ($R_f = 0.51$ in 9:1 hexane:ethyl acetate) as a viscous oil; yield: 88 mg (0.29 mmol, 94%).

References and Notes

[1] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009.

[2] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; A. Suzuki, *J. Organmet. Chem.* **1999**, *576*, 147.

[3] G. C. Bazan, J. H. Oskam, H. N. Cho, L. Y. Park, R. R. Schrock, *J. Am. Chem. Soc.* **1991**, *113*, 6899–6907.

[4] P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 2039; P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100.

[5] For a summary on CM using **1** and **2**, see: H. E. Blackwell, D. J. O'Leary, A. K. Chatterjee, R. A. Washenfelder, D. A. Bussmann, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 58.

[6] S. Warwel, W. Winkelmuller, *J. Mol. Cat.* **1985**, *28*, 247.

[7] W. E. Crowe, Z. J. Zhang, *J. Am. Chem. Soc.* **1993**, *115*, 10998; W. E. Crowe, D. R. Goldberg, Z. J. Zhang, *Tetrahedron Lett.* **1996**, *37*, 2117.

[8] F. J. Feher, D. Soulivong, A. G. Eklund, K. D. Wyndham, *Chem. Commun.* **1997**, 1186; S. C. G. Biagini, S. E. Gibson, S. P. Keen, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2485; C. M. Huwe, T. J. Woltering, J. Jiricek, G. Weitz-Schmidt, C.-H. Wong *Bioorg. Med. Chem.* **1999**, 773; U. Eichelberger, M. Mansourova, L. Henning, M. Findeisen, S. Giesa, D. Muller, P. Welzel, *Tetrahedron* **2001**, *57*, 9737; Y. Yammamoto, M. Takahashi, N. Miyaura, *Synlett* **2002**, 128.

[9] A. K. Chatterjee, J. P. Morgan, M. Scholl, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 3783; T.-L. Choi, A. K. Chatterjee, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2000**, *39*, 1277; T.-L. Choi, C. W. Lee, A. K. Chatterjee, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 10417.

[10] A. K. Chatterjee, T.-L. Choi, R. H. Grubbs, *Synlett* **2001**, 1034.

[11] K. Grela, M. Bieniek, *Tetrahedron Lett.* **2001**, *42*, 6425.

[12] S. Imhof, S. Randl, S. Blechert, *Chem. Commun.* **2001**, 1692.

[13] Similar CM partners have been employed in a sequential metathesis and hydrogenation process: J. Louie, C. W. Bielawski, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 11312.

[14] M. S. Sanford, J. A. Love, R. H. Grubbs, *Organometallics* **2001**, *20*, 5314.

[15] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 5977; S. Randl, N. Buschmann, S. J. Connon, S. Blechert, *Synlett* **2001**, 1547.

[16] For a similar approach to flavanols by CM using **2** see: D. Forget-Champagne, M. Mondon, N. Fonteneau, J.-P. Gesson, *Tetrahedron Lett.* **2001**, *42*, 7229.

[17] H. Van Rensburg, P. S. van Heerdeen, D. Ferreira, *J. Chem. Soc. Perkin Trans. 1* **1997**, 3415.

[18] CM has been recently demonstrated in other total synthesis: C. A. Verbicky, C. K. Zercher, *Tetrahedron Lett.* **2000**, *41*, 8723–8727; C. Bohm, O. Reiser *Org. Lett.* **2001**, *3*, 1315; A. B. Smith, C. M. Adams, S. A. Kozmin, D. V. Paone *J. Am. Chem. Soc.* **2001**, *123*, 5925.