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Synthesis of Styrenes Using Ruthenium-Catalyzed Ring-Closing Enyne Metathesis

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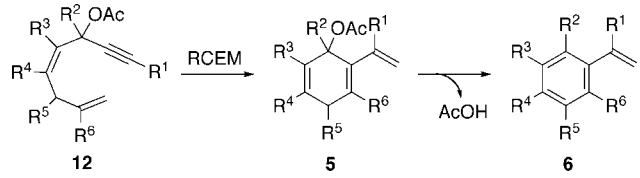
ABSTRACT



The synthesis of substituted styrenes was achieved by ring-closing enyne metathesis (RCEM)/elimination of enyne substrates 12. The synthetic approach was also effective for a different type of enyne substrate 14, yielding corresponding styrene 15.

Substituted styrenes are used extensively as key synthetic intermediates in organic[1] and polymer chemistry.[2] Functional group transformations on existing aromatic rings are generally employed for the synthesis of styrenes. For example, the Wittig olefination of aryl carbonyl compounds,[3] the transition-metal-catalyzed cross-coupling reaction of aryl halides,[4] the Heck reaction of aryl halides,[5] and the elimination of aryl alcohols to generate a double bond[6] have been widely exploited for the synthesis of styrenes. On the other hand, there are few reports[7] of the construction of benzene rings of styrenes from acyclic precursors despite the fact that unique styrenes can be obtained with this entirely different procedure.

Recently, the formation of carbocyclic and heterocyclic aromatic compounds with ruthenium-catalyzed ring-closing olefin metathesis (RCM)[8] has attracted much attention.[9−11] Since RCM is a very powerful reaction to form carbon−carbon double bonds of cyclic compounds with its operational simplicity, high chemoselectivity, and remarkable functional group tolerance, it is valid to apply this reaction to the

(1) For examples, see: (a) Fassina, V.; Ramminger, C.; Seferin, M.; Monteiro, A. L. *Tetrahedron* **2000**, *56*, 7403–7409. (b) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990–7995.

(2) Styrene Polymers. In *Encyclopedia of Polymer Science and Engineering*, 2nd ed.; Moore, E. R., Ed.; Wiley-Interscience: New York, 1989; Vol. 16 and references cited therein.

(3) For recent examples, see: (a) Srikrishna, A.; Babu, R. R.; Ravikumar, P. C. *Synlett* **2007**, 655–657. (b) Tietze, L. F.; Brasche, G.; Grube, A.; Boehnke, N.; Stadler, C. *Chem. Eur. J.* **2007**, *13*, 8543–8563.

(4) For recent examples, see: (a) Zeng, F.; Stehouwer, J. S.; Jarkas, N.; Voll, R. J.; Williams, L.; Camp, V. M.; Votaw, J. R.; Owens, M. J.; Kilts, C. D.; Nemeroff, C. B.; Goodman, M. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3044–3047. (b) Achmatowicz, M.; Chan, J.; Wheeler, P.; Liu, L.; Faul, M. M. *Tetrahedron Lett.* **2007**, *48*, 4825–4829.

(5) For recent examples, see: (a) Kotoku, N.; Kato, T.; Narumi, F.; Ohtani, E.; Kamada, S.; Aoki, S.; Okada, N.; Nakagawa, S.; Kobayashi, M. *Bioorg. Med. Chem.* **2006**, *14*, 7446–7457. (b) Huang, W.-S.; Wang, Y.; Sundaramoorthi, R.; Thomas, R. M.; Wen, D.; Liu, S.; Lentini, S. P.; Das, S.; Banda, G.; Sawyer, T. K.; Shakespeare, W. C. *Tetrahedron Lett.* **2007**, *48*, 7388–7391.

(6) For recent examples, see: (a) Antane, S.; Caufield, C. E.; Hu, W.; Keeney, D.; Labthavikul, P.; Morris, K.; Naughton, S. M.; Petersen, P. J.; Rasmussen, B. A.; Singh, G.; Yang, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 176–180. (b) Nakamura, S.; Sugano, Y.; Kikuchi, F.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6532–6535.

(7) For examples, see: (a) Gevorgyan, V.; Yamamoto, Y. *J. Organomet. Chem.* **1999**, *576*, 232–247. (b) Xi, Z.; Li, Z.; Umeda, C.; Guan, H.; Li, P.; Kotora, M.; Takahashi, T. *Tetrahedron* **2002**, *58*, 1107–1117. (c) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736–3737.

(8) For a comprehensive review, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH; Weinheim, Germany, 2003 For reviews, see: (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (e) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251.

(9) For a review, see: Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2664–2670.

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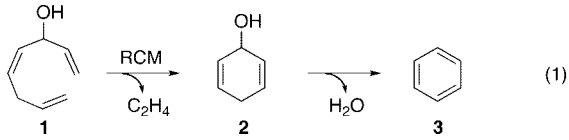
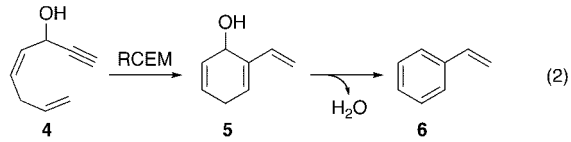
synthesis of various aromatic compounds. In our pursuit of new methods for the synthesis of carbocyclic aromatic compounds using RCM,[12] we found that substituted benzenes **3** can be synthesized in excellent yields by RCM of 1,4,7-trien-3-ols **1**, followed by dehydration of cyclohexa-2,5-dienols **2** (eq 1).[12b] In this study, we examined the extension of acyclic precursors **1** to enyne substrates **4** and the synthesis of styrenes **6** by ring-closing enyne metathesis (RCEM)[13]/elimination of **4** via cyclized product **5** (eq 2).



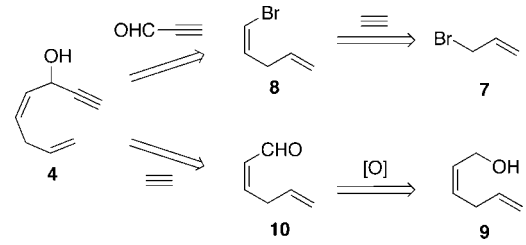
(1)



(2)

Two synthetic strategies for required 4,7-octadien-1-yn-3-ols **4** are outlined in Scheme 1. The upper route involves palladium-catalyzed cis-selective bromoallylation[14] of alkynes with allyl bromides **7** and the coupling of resulting bromodienes **8** with acetylenic aldehydes. The lower route involves the oxidation of 2,5-hexadienols **9**, which can be obtained by stereoselective carbometalation of propargyl alcohol followed by allylation,[15] and the alkynylation of the resulting 2,5-hexadienals **10** with terminal alkynes. In fact, a series

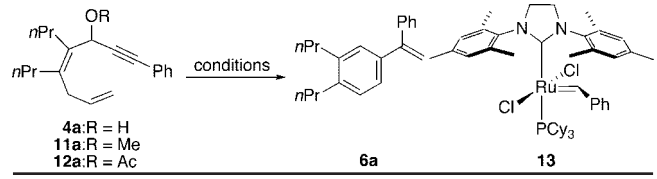
Scheme 1



of **4** with versatile substitution patterns could be prepared with these routes.[16]

We first surveyed the reaction conditions for the synthesis of styrene **6a** from **4a** that was chosen as model substrate (Table 1). When RCEM of **4a** with Grubbs second-

Table 1. Survey of Reaction Conditions for Synthesis of Styrene **6a**[a]



entry	substrate	catalyst	atmosphere	temp (°C)	time (h)	yield (%)[b]
1	**4a**	**13** (7.5 mol %)	N_2	80	2	9[c]
2	**4a**	**13** (7.5 mol %)	C_2H_4	80	2	3[c]
3[d]	**4a**	$PtBr_2$ (2 mol %)	N_2	120	15	4[c]
4	**11a**	**13** (7.5 mol %)	N_2	80	2	9[c]
5	**12a**	**13** (7.5 mol %)	N_2	80	2	92
6	**12a**	**13** (7.5 mol %)	N_2	rt	2	23
7	**12a**	**13** (7.5 mol %)	C_2H_4	80	2	76

[a] The reaction was carried out with **4a**, **11a**, or **12a** and ruthenium catalyst **13** in toluene at 80 °C for 2 h. The reaction mixture was treated with *p*-toluenesulfonic acid (15 mol %) at room temperature for 1 h. [b] Isolated yield by silica gel chromatography. [c] NMR yield by ^{1}H NMR analysis with 1,4-bis(trimethylsilyl)benzene as the internal standard. [d] The reaction was carried out with **4a** and $PtBr_2$ (2 mol %) in 1,4-dioxane at 120 °C for 15 h.

generation catalyst **13**[17] at 80 °C followed by dehydration with a catalytic amount of *p*-toluenesulfonic acid was carried out, **6a** was obtained in a disappointingly low yield of 9% (Table 1, entry 1).[18] Similar reaction conditions under ethylene atmosphere (Mori's conditions)[19] fared much worse, giving **6a** in 3% yield (Table 1, entry 2). Furthermore, $PtBr_2$-catalyzed enyne metathesis conditions[20] reported by Yama-

(10) For reports on the direct synthesis of carbocyclic aromatic compounds with RCM, see: (a) Iuliano, A.; Piccioli, P.; Fabbri, D. *Org. Lett.* **2004**, *6*, 3711–3714. (b) Walker, E. R.; Leung, S. Y.; Barrett, A. G. M. *Tetrahedron Lett.* **2005**, *46*, 6537–6540. (c) Bonifacio, M. C.; Robertson, C. R.; Jung, J.-Y.; King, B. T. *J. Org. Chem.* **2005**, *70*, 8522–8526. (d) Pelly, S. C.; Parkinson, C. J.; Van Otterlo, W. A. L.; De Koning, C. B. *J. Org. Chem.* **2005**, *70*, 10474–10481. (e) Collins, S. K.; Grandbois, A.; Vachon, M. P.; Côté, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2923–2926. For reports with RCM/elimination protocol, see: (f) Evans, P.; Grigg, R.; Ramzan, M. I.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1999**, *40*, 3021–3024. (g) Huang, K. S.; Wang, E. C. *Tetrahedron Lett.* **2001**, *42*, 6155–6157. (h) Chen, Y.; Dias, H. V. R.; Lovely, C. J. *Tetrahedron Lett.* **2003**, *44*, 1379–1382. (i) Chen, P.-Y.; Chen, H.-M.; Chen, L.-Y.; Tzeng, J.-Y.; Tsai, J.-C.; Chi, P.-C.; Li, S.-R.; Wang, E.-C. *Tetrahedron* **2007**, *63*, 2824–2828For reports with RCM/oxidation protocol, see: (j) Kotha, S.; Mandal, K. *Tetrahedron Lett.* **2004**, *45*, 2585–2588. (k) Ma, S.; Yu, F.; Zhao, J. *Synlett* **2007**, 583–586. (l) Kotha, S.; Shah, V. R.; Mandal, K. *Adv. Synth. Catal.* **2007**, *349*, 1159–1172. For a report with RCM/tautomerization protocol, see: (m) van Otterlo, W. A. L.; Ngidi, E. L.; Coyanis, E. M.; de Koning, C. B. *Tetrahedron Lett.* **2003**, *44*, 311–313.

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(12) (a) Yoshida, K.; Imamoto, T. *J. Am. Chem. Soc.* **2005**, *127*, 10470–10471. (b) Yoshida, K.; Kawagoe, F.; Iwadate, N.; Takahashi, H.; Imamoto, T. *Chem. Asian J.* **2006**, *1*, 611–613. (c) Yoshida, K.; Horiuchi, S.; Iwadate, N.; Kawagoe, F.; Imamoto, T. *Synlett* **2007**, 1561–1564. (d) Yoshida, K.; Toyoshima, T.; Imamoto, T. *Chem. Commun.* **2007**, 3774–3776.

(13) (a) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133–154. (b) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1–18. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382. (d) Lippstreu, J. J.; Straub, B. F. *J. Am. Chem. Soc.* **2005**, *127*, 7444–7457.

(14) (a) Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55–63. (b) Llebaria, A.; Camps, F.; Moreto, J. M. *Tetrahedron* **1993**, *49*, 1283–1296. (c) Bäckvall, J.-E.; Nilsson, Y. I. M.; Gatti, R. G. P. *Organometallics* **1995**, *14*, 4242–4246. (d) Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4317–4320.

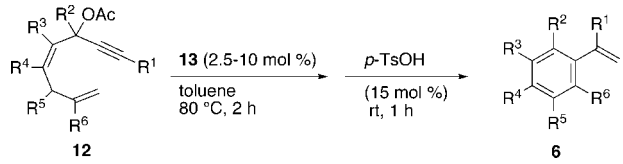
(15) Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989–2992.

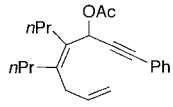
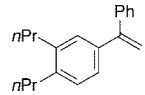
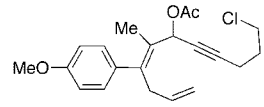
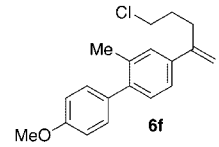
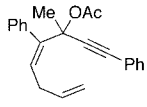
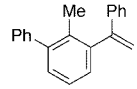
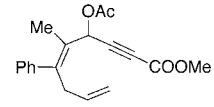
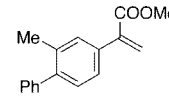
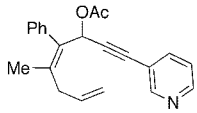
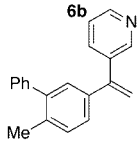
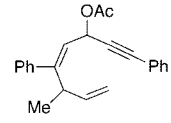
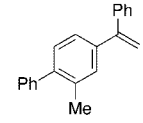
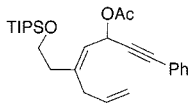
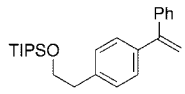
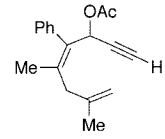
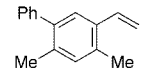
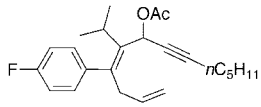
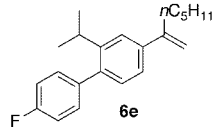
(16) See the Supporting Information for experimental details. The yields of the products reported in this paper were 100−54% (**4** to **12**), 70% (**4a** to **11a**), 39−37% (**8** to **4**), and 92−31% (**10** to **4**).

(17) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (b) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546–2558.

(18) The low yield is due to the RCEM step, not the elimination step. A large amount of decomposed products by reacting **4a** with *p*-toluenesulfonic acid was obtained after the reaction.

Table 2. Synthesis of Styrenes **6** by RCEM/Elimination[a]



entry	substrate	product	yield (%)[b]	entry	substrate	product	yield (%)[b]
1[c]	 **12a**	 **6a**	99[d]	6	 **12f**	 **6f**	86
2	 **12b**	 **6b**	84	7	 **12g**	 **6g**	90
3[c]	 **12c**	 **6c**	81	8	 **12h**	 **6h**	53[f]
4[e]	 **12d**	 **6d**	78	9[g]	 **12i**	 **6i**	34[h]
5	 **12e**	 **6e**	82				

[a] Enyne metathesis was carried out with **12** and ruthenium catalyst (**13**, 7.5 mol %) in toluene at 80 °C for 2 h. The reaction mixture was treated with *p*-toluenesulfonic acid (15 mol %) at room temperature for 1 h. [b] Isolated yield by silica gel chromatography. [c] The reaction was carried out with 2.5 mol % **13**. [d] When the amount of catalyst **13** was decreased to 0.5 mol %, the isolated yield of **6a** was decreased to 15%. [e] 2,6-Di-*tert*-butylpyridine (1.2 equiv) was added as an additive in the RCEM step. [f] Starting material **12h** was recovered in 20% yield. [g] The reaction was carried out with 10 mol % **13**. Stilbene-type dimer was formed as a byproduct in 18% yield. [h] When the amount of catalyst **13** was decreased to 2.5 mol %, the isolated yields of **6i** and the dimer were decreased to 9% and 5%, respectively.

moto and co-workers were also not effective (Table 1, entry 3). Since these results could be attributed to the free hydroxyl group at the propargyl position of **4a**,[21] we next performed the reaction with substrates protected at the hydroxyl group. Although no improvement was observed when methyl-protected substrate **11a** was employed (Table 1, entry 4), a dramatic improvement was observed when acyl-protected substrate **12a** was employed in RCEM/elimination with Grubbs second-generation catalyst **13**, where **6a** was furnished in 92% isolated yield (Table 1, entry 5). Changing the temperature of the RCEM step from 80 °C to room temperature resulted in a decrease in reactivity (Table 1, entry 5 vs entry 6) and performing the reaction at 80 °C under ethylene atmosphere also decreased the yield from 92% to 76% (Table 1, entry 5 vs entry 7).[22]

After acquiring basic data, we examined the generality of the synthesis of styrenes **6** from acyl-protected substrates **12** using RCEM/elimination. The results are summarized in Table 2. All RCEM reactions were conducted with Grubbs second-generation catalyst **13** in toluene at 80 °C for 2 h. The formation of styrenes having aryl substituents (Table 2,

(19) Mori and co-workers reported the beneficial effects of ethylene atmosphere in RCEM of enyne substrates having terminal alkyne, see: Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082–6083.

(20) In 2005, Yamamoto and co-workers reported an efficient synthesis of vinylnaphthalenes by $PtBr_2$-catalyzed enyne metathesis/elimination, see: Bajracharya, G. B.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 892–897.

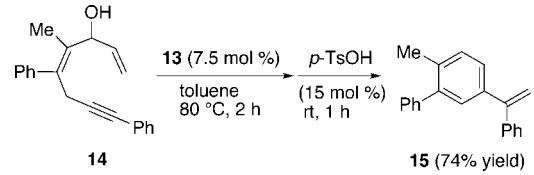
(21) (a) Mori, M.; Tonogaki, K.; Nishiguchi, N. *J. Org. Chem.* **2002**, *67*, 224–226. (b) Funel, J.-A.; Prunet, J. *J. Org. Chem.* **2004**, *69*, 4555–4558.

(22) Although enyne substrate **12a** does not have a terminal alkyne, the deleterious effect of ethylene was out of our assumption. The reason for the effect is not known at this stage.

entries 1−4) as well as alkyl substituents (Table 2, entries 5 and 6) at the R^1 position was accomplished without any problems. Because of the great functional group tolerance of the catalyst, introduction of a pyridyl, a haloalkyl, or an ester group at the R^1 position could be successfully achieved (Table 2, entries 3, 6, and 7). Introduction of substituents at the R^2, R^3, or R^4 position was also accomplished and did not give a significant difference on the reactivity of RCEM (Table 2, entries 1−7). It must be noted that deprotection of silyl ether occurred when the reaction of **12d** was carried out under the above-mentioned conditions. Since it could be assumed that the deprotection was caused by acetic acid that was produced slowly by spontaneous aromatization in the RCEM step at 80 °C, we examined the effect of adding a base to trap the acetic acid in this reaction. As a result, the addition of 2,6-di-*tert*-butylpyridine (1.2 equiv) successfully suppressed the deprotection and desired styrene **6d** was obtained in 78% yield (Table 2, entry 4). It is noteworthy that the addition of pyridine instead of 2,6-di-*tert*-butylpyridine resulted in decreased activity of the catalyst and the recovery of a large amount of **12d**. In contrast to the results obtained by introducing a substituent at the R^1, R^2, R^3, or R^4 position, the introduction of a substituent at the R^5 position retarded the reaction. When the reaction of **12h** having a methyl group at the R^5 position was performed, desired **6h** was obtained in 53% yield (Table 2, entry 8). Introduction of a methyl group at the R^6 position further decreased the reactivity. However, a certain extent of reactivity could be gained by introducing a hydrogen at the R^1 position, although the isolated yield of **6i** was still low at 34% (Table 2, entry 9). In this case, a problematic side reaction that involved dimerization of **6i** to give the stilbene-type dimer occurred even under diluted conditions.

To extend the scope of RCEM/elimination, we examined the synthesis of styrene from a different type of enyne substrate, 1,4-octadien-7-yn-3-ol **14**,[23] which has terminal alkene and alkyne at opposite positions relative to 4,7-octadien-1-yn-3-ol **4**. As a result, the reaction of **14** with Grubbs second-generation catalyst **13** followed by dehydration gave corresponding styrene **15** in 74% yield (Scheme 2). It is interesting that RCEM of **14** having no free propargyl hydroxyl group proceeded well without acyl protection.

Scheme 2



14 **15** (74% yield)

In summary, we have developed an efficient approach for the synthesis of substituted styrenes, which utilizes RCEM/elimination. Because of the high reliability of the employed transformations, this approach can provide a wide variety of styrenes without the formation of undesirable regioisomers.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) **14** was prepared by reacting (*E*)-2-methyl-3,6-diphenyl-2-hexen-5-ynal with vinylmagnesium chloride (81% yield).