

Chemoselective Construction of Substituted Conjugated Dienes Using an Olefin Cross-Metathesis Protocol

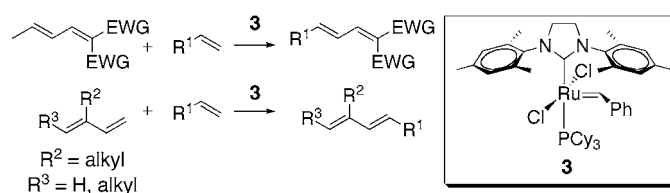
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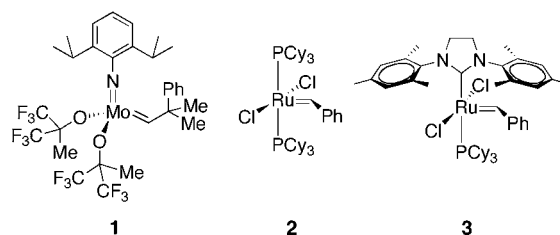
ABSTRACT



Various substituted conjugated dienes have been made by olefin cross-metathesis. Using either electronic or steric “protection,” one of the olefins of the conjugated diene was deactivated relative to the other for cross-metathesis. The reactions proceed with very high chemoselectivity and, when steric deactivation is used, very high diastereoselectivity.

The olefin metathesis reaction has recently gained prominence in synthetic organic chemistry.¹ The commercial availability of well-defined catalysts, such as the molybdenum alkoxyimido alkylidene **1** developed by Schrock et al.² and ruthenium benzylidene catalysts **2**³ and **3**,⁴ have made the olefin metathesis reaction practical for small molecule synthesis. In particular, ring-closing olefin metathesis (RCM) reactions⁵ have been utilized in the construction of a diverse set of organic molecules. There is strong interest in synthesizing conjugated dienes because they appear in a wide array

of naturally occurring molecules and they also function as synthetic building blocks.



A wide variety of methods exist for the construction of conjugated olefins. These include palladium-catalyzed reactions such as the Stille and Suzuki couplings of two olefins as well as the Sonogashira reaction followed by a Lindlar reduction to yield an olefin. The advantages of using olefin

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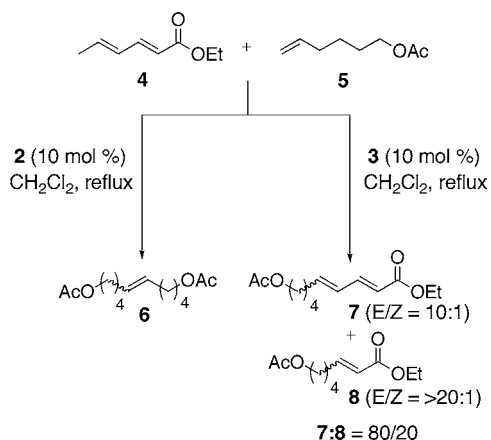
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Scheme 1



metathesis in the construction of conjugated dienes include mild reaction conditions, stability of the reagents, and the wide variety of commercially available olefin partners. 2-Substituted 1,3-butadienes have been synthesized using enyne metathesis,⁶ and there are a few examples of macrocyclic ring-closing metathesis to form conjugated dienes.⁷ However, very little work has been focused on synthesizing conjugated dienes using olefin cross-metathesis due to issues regarding chemo- and diastereoselectivity.

In principle, it should be possible to carry out a cross-metathesis reaction on only one of the olefins in a diene. One way to influence the chemoselectivity would be to sterically or electronically deactivate one of the double bonds in the conjugated diene. Our strategy is based on shielding one of the olefins in the conjugated diene by attaching either electron-withdrawing substituents or steric bulk. Furthermore, by choosing the appropriate electron-withdrawing substituents and olefin cross partners, we will be able to further functionalize the conjugated product. Herein, we report a chemoselective olefin cross-metathesis reaction with conjugated dienes.

Our studies began with the use of ethyl sorbate (**4**) as the protected conjugated diene substrate for the olefin cross-metathesis reaction. When a reaction mixture consisting of **4**, 5-hexenyl acetate (**5**), and catalyst **2** was heated to reflux in CH_2Cl_2 , only homocoupling of **5** occurred (Scheme 1). Both of the olefins in **4** are too deactivated to react with **2**. The more active catalyst **3** reacts with both olefins of the diene to yield **7** and **8** as an 80:20 mixture. The ester functionality is not sufficiently deactivating when catalyst **3** is used, and both olefins of the diene react.

To further reduce the electron density in the α,β -double bond as well as increase the steric bulk, a vinylic bromide was introduced at the α -carbon. Compound **9**, (2*Z*,4*E*)-2-

Table 1. Olefin CM with Electron-Poor Dienes^a

entry	olefin	conjugated diene	product	yield (%) ^b E/Z ratio
1	10	9	16	68 8.5:1
2 ^c	11	9	17	65 10:1
3 ^c	12	9	18	70 7.5:1
4	13	9	19	48 6:1
5	14	15	20	39 >20:1
6	11	15	21	60 >20:1
7	5	15	22	56 5:1

^a Conditions: olefin (1–3 equiv), conjugated diene (1 equiv), and catalyst **3** (5 mol %) for 12 h in refluxing CH_2Cl_2 (0.2 M). ^b Isolated yields. ^c 10 mol % of catalyst **3** was used.

bromoethyl sorbate, was prepared according to a literature procedure by Spitzner et al.⁸ and was used as a 9:1 mixture of 2*Z*/2*E* isomers. This substrate could give synthetically interesting and useful products because both the vinyl bromide and the ester group can be further functionalized.

It was not surprising that the cross-metathesis between allylbenzene (**10**) and **9** in refluxing CH_2Cl_2 failed with catalyst **2**. When the more active catalyst **3** was used in the same system, the α,β -double bond was sufficiently deactivated relative to the γ,δ -double bond to form the desired product **16** in 68% isolated yield (Table 1, entry 1). The diastereoselectivity of the reaction was moderately high: a mixture of *E/Z* isomers in an 8.5:1 ratio was observed. Other functionalized olefins also react chemoselectively with **9** (Table 1, entries 1–4). The diastereoselectivity of the reaction remains moderate in most cases, and is highest when diene **9** undergoes a homocoupling reaction to yield a conjugated triene in >20:1 *E/Z* ratio. When the cross-metathesis reactions were carried out at 25 °C, the only product observed was homocoupled olefin and unreacted diene.

To determine if the protecting ester functionality could be replaced with a bromide, 1,1-dibromo-1,3-butadiene was prepared. Unfortunately, it was found to decompose within hours after preparation and was therefore not a good candidate for the cross-metathesis reaction.⁹ 1,1-Dibromo-1,3-pentadiene (**15**), however, is much more stable and

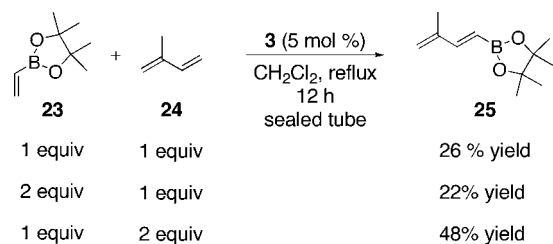
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Scheme 2

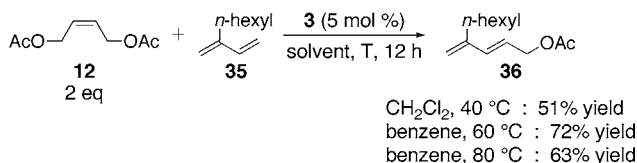


therefore a more viable cross-partner.⁹ The results of the cross-metathesis reactions between 1,1-dibromo-1,3-pentadiene and various olefins are summarized in Table 1, entries 5–7. Entry 5 shows that the yields are modest when methyl acrylate (**14**) is used as the cross-partner, while the use of styrene (**11**) or **5** affords cross-metathesis products in good yields.

The above methodology leads to functionalized butadienes that contain 1,4-disubstitution. To further extend the chemoselective cross-metathesis of conjugated dienes to 2-substituted butadienes, steric shielding of one of the olefins was examined. In the initial test reaction, vinyl boronate **23** reacted with isoprene (**24**) to give the desired diene in 26% yield (Scheme 2). Although the yield was low, only isomer **25** was isolated. Attempts to improve the conversion led to a 48% yield under optimized conditions. One potential reason for the low yield is the low boiling point of isoprene (34 °C) and the higher temperatures needed for the reaction.

Therefore, 3-methyl-1,3-pentadiene (**28**) (bp = 76 °C) was used under the initial reaction conditions, and the desired

Scheme 3



product **30** was isolated in 80% yield (Table 2, entry 1). Table 2 displays the results of cross-metathesis reactions of 1,2-disubstituted 1,3-butadienes with various olefins.¹⁰

Both electron-rich and electron-poor olefins react to give products in good yields with very high chemoselectivity and diastereoselectivity. Since the initial study with isoprene suggested that the substituent in the 2-position caused the high chemoselectivity, further studies were focused on dienes containing only 2-substitution (Scheme 3). A temperature dependence was observed in these reactions; under the conditions used for 1,2-disubstituted 1,3-butadienes, the yields of products were moderate. By changing the solvent from CH₂Cl₂ to benzene and increasing the temperature from 40 °C to 60 °C, the yield increased from 51% to 72%. Raising the temperature to 80 °C resulted in a decreased yield, most likely due to increased catalyst decomposition. This need for higher temperatures may result from the formation of a vinylalkylidene catalyst species, which can be stabilized through vinyl olefin coordination.¹¹

Using the modified conditions, various 2-substituted 1,3-butadienes reacted with functionalized olefins to form the desired dienes in good yields with high chemoselectivity and diastereoselectivity (Table 3). Unreacted diene could be re-isolated in these reactions. When vinyl boronate **23** was the olefin, the reactions were stopped after 2 h and clean product could be isolated. Longer reaction times did not increase the yield and resulted in an unidentified, inseparable impurity. Although 2-substituted 1,3-butadienes do not homocouple and can be considered type III olefins, excess olefin cross partner is needed.¹² The need for excess cross partner may stem from the importance of not allowing the diene to react with the catalyst to form a vinylalkylidene species. The higher concentration of reactive olefin causes less interaction between the catalyst and the diene.

The vinyl bromide-containing dienes as well as the vinyl boronate-containing dienes synthesized above are useful synthetic intermediates and can be further functionalized with ease. The reaction in Scheme 4 illustrates a palladium-catalyzed cross-coupling reaction that results in a highly conjugated system where all of the stereochemistry was set using cross-metathesis. A one-pot cross-metathesis/Suzuki

Table 2. Olefin CM Using 1,2-Disubstituted 1,3-Butadienes^a

entry	olefin	conjugated diene ^b	product ^c	yield (%) ^d
1				80
2	12	28		82
3		28		70
4 ^e	5			77
5 ^{f,g}		29		79

^a Conditions: olefin (1–4 equiv), diene (1 equiv), and catalyst **3** (5 mol %) in refluxing CH₂Cl₂ (0.2 M) for 12 h. ^b 3-Methyl-1,3-pentadiene (**28**) was purchased as a 70:30 mixture of *E/Z* isomers. ^c Only the *E* isomer was observed in all cases; when **28** was the diene, both *E* and *Z* isomers reacted. ^d Isolated yields. ^e Product was not separated from unreacted **5**. ^f Product was not separated from allyl benzoate formed in the reaction. ^g None of the product containing the terminal C=CH₂ group was observed (see ref 10).

(10) The reaction between 1,2-disubstituted 1,3-butadienes and most of the olefins in Table 2 resulted in 7–12% product where the alkyl group in the 1-position was replaced with a terminal olefin (CH₂ group).

(11) This type of vinylalkylidene stabilization has been observed by our group as well as others: (a) Trnka, T. M.; Day, M. W.; Grubbs, R. H. *Organometallics* **2001**, 20, 3845–3847. (b) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, 63, 6082–6083. (c) See ref 3a.

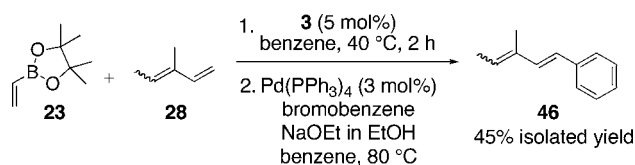
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Table 3. Olefin CM with 2-Substituted 1,3-Butadienes^a

entry	olefin	conjugated diene	product ^b	yield (%) ^c
1 ^d	12	35 (n-hexyl)	36 (n-hexyl)	72 (81)
2 ^e	27	35	39 (n-hexyl)	73
3 ^f	23	35	40 (n-hexyl)	73
4	27	37 (OTBS)	41 (OTBS)	70
5	5	37	42 (OTBS)	75
6 ^f	23	37	43 (OTBS)	69
7 ^{f,g}	23	38 (OTBS)	44 (OTBS)	~40
8 ^e	27	38	45 (OTBS)	63

^a Conditions: olefin (1–4 equiv), diene (1 equiv), and catalyst **3** (5 mol %) in benzene (0.2 M) at 60 °C for 12 h. ^b Only the *E* isomer was observed. ^c Isolated yield. ^d Yield in parentheses refers to reaction using 10 mol % of **3**. ^e Product was not separated from allyl benzoate formed in the reaction. ^f Reaction was stopped after 2 h. ^g Unidentified impurities were present in the isolated product sample.

coupling is shown, which gives a yield comparable to the analogous two-step sequence.¹³

Scheme 4

In conclusion, the electronic or steric deactivation of one olefin in a conjugated diene toward olefin metathesis with catalyst **3** is possible. This “protection” has resulted in highly chemoselective cross-metathesis reactions of 2-bromoethyl sorbate and 1,1-dibromo-1,3-pentadiene with a variety of olefins. It has also led to a highly chemo- and diastereoselective cross-metathesis reaction between 1,2-disubstituted 1,3-butadienes and 2-substituted 1,3-butadienes with a number of olefin partners. The simplicity of use and functional-group tolerance of catalyst **3**, as well as the high chemo- and diastereoselectivity with which these transformations occur, makes this an attractive method for synthesizing functionalized conjugated dienes.

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Supporting Information Available: Experimental procedures and full characterization for dienes **29**, **37**, and **38** and general procedures and full characterization for compounds **16–22**, **30–34**, **36**, and **39–46**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) An overall yield of 51% was achieved when the two steps of the reaction were performed independently.