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Regioselective Cross-Metathesis Reaction Induced by Steric Hindrance

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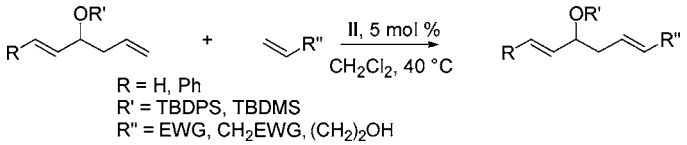
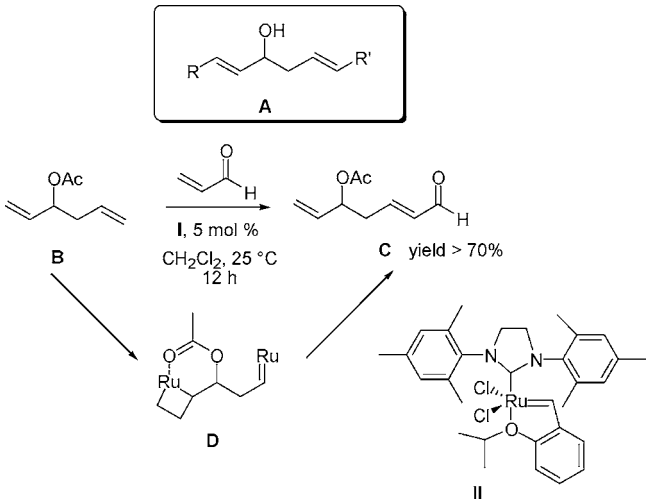
ABSTRACT



When hexa-1,5-dien-3-ol is protected with bulky groups, a regioselective cross-metathesis reaction can take place at the C5–C6 double bond.

In the past decade, olefin cross-metathesis has gained a position of increasing significance.[1] As an acyclic carbon−carbon double-bond-forming tool, cross-metathesis has numerous advantages. It requires in general 1−5 mol % catalyst, and a wide range of functional groups are tolerated.[2] The reaction is efficient in atom economy, as the only byproduct formed is gaseous ethylene. Furthermore, high levels of chemo-, regio-, and stereoselectivity can be attained as well as high yields.[3] As tetrafibricin,[4] lienomycin,[5] and amphidinol 3[6] are constituted by several units of type **A**, we became interested in obtaining these units from hexa-1,5-dien-3-ol by using chemo- and regioselective cross-metathesis reactions. Recently, we reported that a chemoselective cross-metathesis reaction can take place between 3-acetoxy-hexa-1,5-diene **B** and acrolein, to produce a single cross-coupling product **C**[7] when promoted by the commercially available catalyst **II**[8] (Scheme 1).

Scheme 1. Chemoselective Cross-Metathesis Reaction



The selectivity observed might be due to deactivation of the double bond at C1−C2 by the electron-withdrawing

(1) For a recent review on cross-metathesis, see: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. See also: Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury J. S.; Harrity J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8.

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(8) (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

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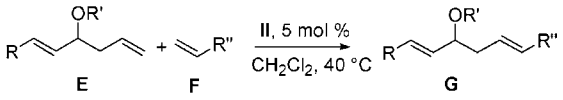
Scheme 2. Regioselective Cross-Metathesis Reaction



R = H, Ph
R' = TBDPS, TBDMS
R'' = EWG, CH_2EWG, $(CH_2)_2OH$

acetoxy group or because an unreactive six-membered chelate **D** is formed that results in a selective cross-metathesis of the homoallylic unit (Scheme 1).[7]

Here, we would like to report that regioselectivity can be induced by steric hindrance and that a regioselective cross-metathesis reaction, promoted by ruthenium catalyst **II**, can take place between protected hexa-1,5-dien-3-ols of type **E** and olefins of type **F** when the hydroxy protecting group in **E** is bulky such as with the *tert*-butyldiphenylsilyl or the *tert*-butyldimethylsilyl (Scheme 2).

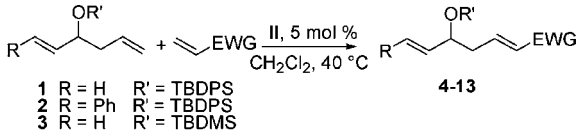
All cross-metathesis reactions were performed under argon in CH_2Cl_2 at reflux in the presence of 5 mol % catalyst **II**, 1 equiv of the protected hexa-1,5-dien- 3-ol of type **E**, and 3 equiv of various olefins of type **F** to produce compounds of type **G**.

Our preliminary studies focused on *tert*-butyl-diphenyl-silyloxy-3-hexa-1,5-diene **1** and various electron-deficient olefins. When **1** was treated with catalyst **II** in the presence of acrolein, the unsaturated aldehyde **4** was isolated in 56% yield and with excellent stereoselectivity (*E*/*Z* ratio of 20/1) as observed by ^{1}H NMR spectroscopy and GC/MS (Table 1, entry 1). This result led us to examine the cross-metathesis reaction of **1** with other various electron-deficient olefins such as ethyl acrylate, acrylic acid, ethyl vinyl ketone, and acrylonitrile. The results are summarized in Table 1.

Excellent yields (>70%) and (*E*)-stereoselectivity were attained (*E*/*Z* = 20/1) except when **1** was treated with acrylonitrile, where a low yield of **8** was obtained (23%). Furthermore, the major stereoisomer was the (*Z*)-isomer and the degree of stereoselectivity was low, as the ratio *Z*/*E* was 3/1 (Table 1, entry 5). As in previous cross-metathesis reactions with acrylonitrile, the (*Z*)-stereoselectivity must be kinetically controlled or related to the presence of the electron-withdrawing properties of the cyano substituent.[9,10] It is worth noting that cross-metathesis products involving the C1−C2 double bond of **1** were not detected in the reaction media. The regioselectivity of the cross-metathesis reaction between **1** and electron-deficient olefins can be attributed to steric effects imposed by the silyl ether group adjacent to the allylic functionality.

The cross-metathesis reaction of 3-silyloxyhexa-1,5-diene **2** with ethyl acrylate and acrylic acid was also examined. As with compound **1**, excellent yields and (*E*)-stereoselectivity were obtained in the preparation of **9** and **10** (Table 1,

Table 1. Cross-Metathesis Reaction between 3-Silyloxyhexa-1,5-dienes and Various Electron-Deficient Olefins



1 R = H R' = TBDPS
2 R = Ph R' = TBDPS
3 R = H R' = TBDMS

Entry				Yield%	*E*/*Z*
1	**1**	H	**4**	56	20/1
2	**1**	OEt	**5**	71	20/1
3	**1**	OH	**6**	81	20/1
4	**1**		**7**	76	20/1
5	**1**	CN	**8**	23	1/3
6	**2**	OEt	**9**	78	20/1
7	**2**	OH	**10**	83	20/1
8	**3**	H	**11**	52	20/1
9	**3**	OEt	**12**	77	20/1
10	**3**		**13**	80	20/1

entries 6, 7). Other bulky silyl protecting groups, such as a *tert*-butyldimethylsilyl ether, can also be used to protect the C1−C2 double bond of hexa-1,5-dien-3-ol. When the *tert*-butyldimethylsilyloxy-3-hexa-1,5-diene **3** was treated with **II** in the presence of acrolein, ethyl acrylate, and ethyl vinyl ketone, the cross-metathesis compounds **11**−**13** were obtained in good yields and with good stereoselectivity (*E*/*Z* = 20/1) (Table 1, entries 8−10).

β,γ-Unsaturated ester, acid, alcohol, and cyano compounds were also examined as cross-metathesis partners to study the influence of the remote position of a polar group on the course of the reaction. The results are reported in Table 2. When compound **1** was treated with **14**−**16** in the presence of catalyst **II**, the corresponding cross-metathesis compounds **18** (80%), **19** (77%) and **20** (48%) were respectively isolated with very good regioselectivity but with moderate stereoselectivity (*E*/*Z* = 3/1) (Table 2, Entries 1−3). The presence of a cyano group decreases the yield of the cross-metathesis product as evidenced by the reaction between **1** and allyl-cyanide **17**, which led to compound **21** in low yield (23%)

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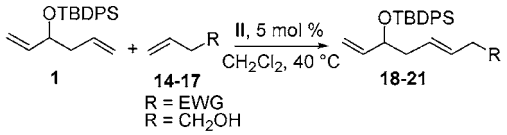
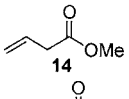
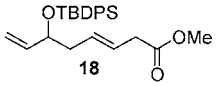
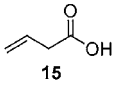
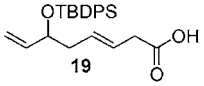
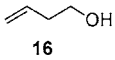
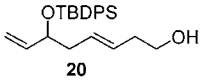
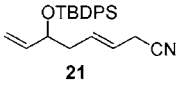
(10) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430.

Table 2. Cross-Metathesis Reaction between 3-Silyloxyhexa-1,5-diene **1** and Olefins **14**−**17**



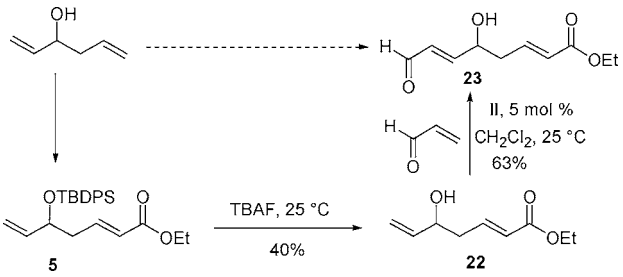
Entry	1	R	OTBDPS EWG	Yield%	*E*/*Z*
1	1	 **14**	 **18**	80	3/1
2	1	 **15**	 **19**	77	3/1
3	1	 **16**	 **20**	48	3/1
4	1	 **17**	 **21**	23	3/1

and with an *E*/*Z* ratio of 3/1 in favor of the (*E*)-isomer (Table 2, entry 4).

Since the enoate double bond is deactivated by the electron-withdrawing carbonyl group, and as cross-metathesis reactions can be performed without the protection of hydroxy groups, it should be possible to transform hexa-1,5-dien-3-ol, via compound **5**, to the functionalized 1,5-diene **23**, which could be an important precursor for the synthesis of many natural products (Scheme 3).

To verify this hypothesis, compound **5** was deprotected with tetra-*n*-butylammonium fluoride (THF at 25 °C) to produce alcohol **22** in 40% yield, and this compound was

Scheme 3. Functionalization of Hexa-1,5-dien-3-ol Using Cross-Metathesis Reactions



then treated with acrolein in the presence of catalyst **II** to produce the expected product **23** in 63% yield.

The cross-metathesis reaction was regioselective, as the dialdehyde was never observed (Scheme 3). This result implies that catalyst **II** does not insert into the double bond that is connected to an electron-withdrawing group but inserts instead into the terminal double bond to form a ruthenium complex that can react with acrolein to produce **23** (Scheme 3).

In conclusion, regioselective cross-metathesis reactions can occur with protected hexa-1,5-dien-3-ols when they are protected by sterically hindered groups such as *tert*-butyldiphenylsilyl or *tert*-butyldimethylsilyl groups. Furthermore, good stereoselectivity is observed with electron-deficient olefins, and poor stereoselectivity is obtained with olefins having polar functionalized groups at the β-position. Regioselective cross-metathesis reactions will be used in the synthesis of natural products, and the results will be reported in due course.

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