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Synthesis of *cis*-Fused Carbo-Bicycles by Domino Enyne Cross-Metathesis/ Intramolecular Diels–Alder Reaction

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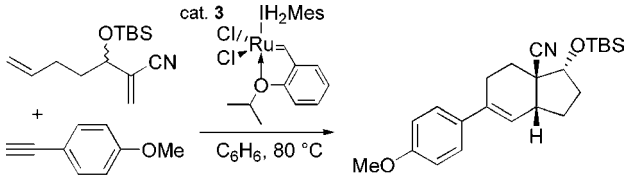
ABSTRACT



IH_2Mes = 1,3-Bis-mesityl-4,5-dihydroimidazol-2-ylidene

A sequential combination of Ru-catalyzed enyne cross-metathesis (EYCM) and intramolecular Diels–Alder reaction (IMDA) is described. Different terminal alkynes and α,ω-dienes obtained by a Baylis–Hillman reaction were transformed into substituted *cis*-hexahydro-1*H*-indenes and *cis*-hexahydro-2*H*-naphthalin-1-ones.

Since the first reports on enyne cross-metathesis,[1] the synthetic potential of this process has caught the attention of many researchers.[2] Useful catalysts for these cross-couplings are the first and second generation Grubbs' catalysts **1**[3] ($(PCy_3)_2Cl_2Ru{=}CHPh$) and **2**[4] ($(IH_2Mes)(PCy_3)Cl_2Ru{=}CHPh$), as well as the phosphine-free complex **3**[5] ($(IH_2Mes)Cl_2Ru{=}CH\text{-}C_6H_4(2\text{-}O\mathit{i}Pr)$). The latter complexes exhibit both increased reactivity and stability.[6]

Dienes obtained from these couplings are useful building blocks for the construction of carbo- and heterocyclic arrays by subsequent cycloaddition reactions. Intermolecular Diels–Alder reactions with 1,3-disubstituted 1,3-dienes obtained by enyne cross-metathesis (CM) gave, for example, tetrahydropyridines,[7] pseudo-oligosaccharides,[8] or cyclic phenylalanine derivatives.[9]

Combinations of enyne CM and subsequent intramolecular Diels–Alder reaction involving olefins other than ethylene[10] have not been reported so far.

There are two options available for synthesizing the key trienes. There could be an enyne CM either between an α,ω-enyne and a terminal olefin or between a terminal alkyne and an α,ω-diene. The subsequent cycloaddition should give either bridged or linear bicycles (Scheme 1).

The synthetic challenge of an enyne CM using α,ω-dienes is the suppression of unwanted intramolecular metathesis in favor of the cross-coupling. We were especially interested in investigating route **b** (Scheme 1), because the resultant carbo-bicycles are important synthetic building blocks.

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(4) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(5) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973.

(6) (a) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2002**, *2*, 2271. (b) Giessert, A. J.; Snyder, L.; Markham, J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 1793. (c) Mori, M.; Tonogaki, K.; Nishiguchi, N. *J. Org. Chem.* **2002**, *67*, 224. (d) Stragies, R.; Voigtmann, U.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 5465.

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(8) Schürer, S. C.; Blechert, S. *Chem. Commun.* **1999**, 1203.

(9) Kotha, S.; Halder, S.; Brahmachari, E. *Tetrahedron* **2002**, *58*, 9203.

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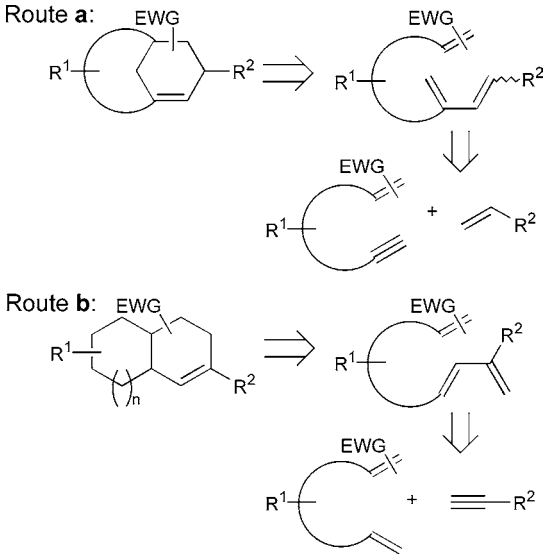
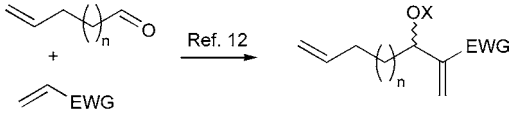
Scheme 1. Available Options for EYCM/IMDA Sequences



Suitable starting α,ω-dienes are Baylis−Hillman[11] reaction products **4**−**8**, which undergo ring-closing metathesis relatively slowly for steric and electronic reasons.[12] We expected enyne cross-metathesis to selectively involve the electronically neutral, monosubstituted double bond (Scheme 2).

Scheme 2. Access to α,ω-Dienes via the Baylis−Hillman Reaction

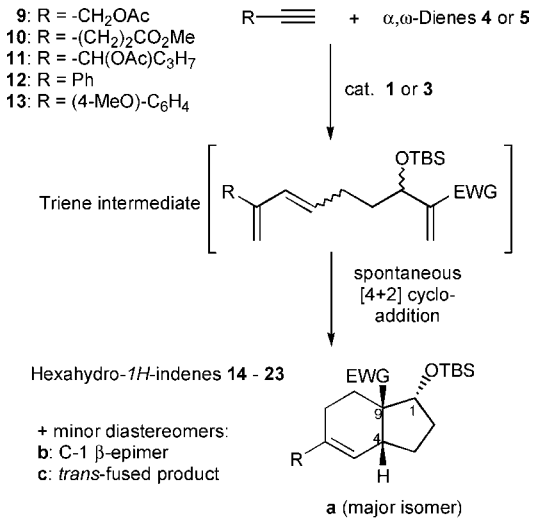


4: n = 1; EWG = CO_2Me; X = TBS
5: n = 1; EWG = CN; X = TBS
6: n = 2; EWG = CO_2Me; X = H
7: n = 2; EWG = CO_2Me; X = TBS
8: n = 2; EWG = CN; X = TBS

The hydroxy function generated during the Baylis−Hillman reaction offers the possibility of oxidation to a ketone to increase electron withdrawal from the dienophile double bond and thus accelerate a potentially sluggish Diels−Alder reaction. However, it was expected that a bulky substituent adjacent to a stereocenter neighboring the dienophile unit would improve the cycloaddition diastereoselectivity.[13] Therefore the hydroxy function was protected as a TBS-ether.

The reactions of the α,ω-dienes **4** and **5** with different terminal alkynes **9**−**13** led to the formation of trienes, which cyclized spontaneously under the reaction conditions to afford the cycloadducts **14**−**23**. In all cases the triene intermediates were formed as an *E*/*Z* mixture.[14] The *Z*-trienes underwent cycloaddition faster than the *E*-isomers. When metathesis was performed at 45 °C or below, the cyclization was not complete. Therefore the resulting mixtures of mostly *E*-trienes and bicycles were brought to full conversion by additional heating in toluene. Preparative reactions were carried out in closed screw-cap glass vials with 0.2 M α,ω-diene solution and 1.25 equiv of alkyne. Their results are given in Table 1.

Table 1. Results of Enyne CM/Cycloaddition Sequence



entry	alkyne	α,ω-diene	catalyst (mol %)	method	yield[a] (**a**:**b**:**c** ratio)
1	**9**	**4**	**1** (7.5)	**A**	59% **14** (5:1:0)
2	**9**	**5**	**1** (7.5)	**A**	20% **15** (14:1:2)
3	**10**	**4**	**1** (7.5)	**A**	64% **16** (5:1:0)
4	**10**	**5**	**1** (7.5)	**A**	34% **17** (10:1:2)
5	**11**	**4**	**3** (5.0)	**B**	69% **18** (14:1:0)
6	**11**	**5**	**3** (5.0)	**B**	64% **19** (10:1:5)
7	**12**	**4**	**3** (5.0)	**C**	34% **20**[b] (5:1:0)
8	**12**	**5**	**3** (5.0)	**C**	90% **21** (5:0:1)
9	**13**	**4**	**3** (7.5)	**C**	64% **22** (9:1:0)
10	**13**	**5**	**3** (7.5)	**C**	62% **23** (20:1:4)

[a] Refers to isolated yields after chromatography. [b] Inseparable mixture of cycloadducts and starting α,ω-diene; yield determined by NMR.

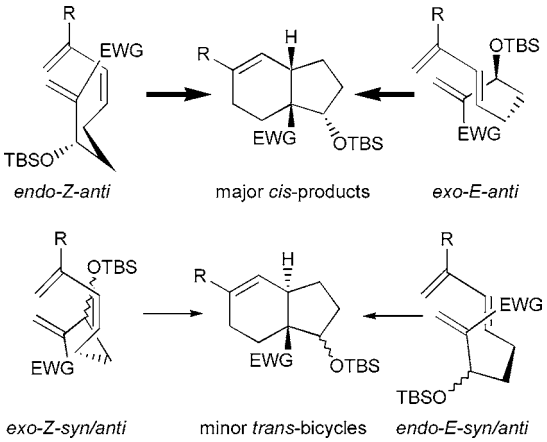
In initial test reactions (monitored by NMR) the catalysts **1**−**3** were compared in each α,ω-diene−alkyne combination. These experiments revealed that the choice of the appropriate catalyst depended on the alkyne's structure. For example, propargyl acetate **9** and methyl pent-4-ynoate **10** were converted only by the first generation catalyst **1**, whereas the α-branched propargyl acetate **11** and the phenyl acetylenes **12** and **13** were converted much better by the chelated second generation complex **3**. Grubbs' catalyst **2** gave similar

(11) Review: Basaviah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.
(12) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430.
(13) This was confirmed by experiments with the OH-precursor of **4**, where the cycloadducts' C-1 α:β ratio was only 2:1 (see Table 1).
(14) *E*/*Z* ratio varied between 2:1 and 1:2, as observed by NMR of crude reaction mixtures.

results to **3** with alkyne **11**, but only poor conversion of phenyl acetylenes. Beside the cross-products, variable amounts of homo-dimers and unconverted α,ω-dienes were found after metathesis. Ring-closed products were not detected in any reaction. The presence of an acrylonitrile moiety in substrate **5** led to a low degree of conversion in reactions catalyzed by **1** and did not cause similar problems in reactions catalyzed by **2** or **3** (Table 1).

The 1,6-disubstituted hexahydro-1*H*-indenes **14**−**23** were formed predominantly as *cis*-fused bicycles with relative *anti*-stereochemistry between C-1 and C-9. Minor amounts of *trans*-fused bicycles were formed only in the nitrile series starting with α,ω-diene **5** (Table 1). This leads to the conclusion that both *E*/*Z*-triene isomers reacted to the same major cycloadduct diastereomer passing transition states with different *endo*/*exo* orientation. As *exo*-*Z* transition states are obviously too strained to be considered likely, this gives further support to the right assignment of the ring fusion of major *cis*-products[15] (Scheme 3).

Scheme 3. Proposed Cycloaddition Transition States



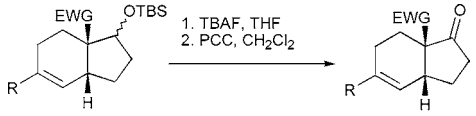
The separation of diastereomers was difficult at this stage but became possible after subsequent reactions. A short reaction sequence of TBS deprotection with tetrabutylammonium fluoride (TBAF) and oxidation of the crude alcohols using pyridinium chlorochromate (PCC) led to the corresponding bicyclic ketones. These were obtained as pure *cis*-isomers in good yields after chromatography (Scheme 4). This methodology has been applied to a rapid and stereoselective access to the steroid analogues **26**−**28**.

Yields (isolated) refer only to *cis*-fused starting TBS-ethers within the eventual *cis*/*trans* mixture (see Table 1).

After achievement of the synthesis of perhydroindene derivatives, we were interested in applying this synthetic concept to the formation of decalines. Starting with the homologous α,ω-dienes **7** and **8**, enyne cross-metathesis with terminal alkynes **9**−**12** led to the formation of trienes **29**−**34** with medium to high yields (Table 2). As before, the use of different catalysts **1**−**3** was necessary for good conversions, depending on the alkyne used.

(15) The stereochemistry of byproducts was assigned on the basis of comparable NMR shifts of the bridgehead H-4 in both *cis*-fused diastereomers and is in agreement with molecular modelling using PC Spartan as well as with the oxidation results (Scheme 4).

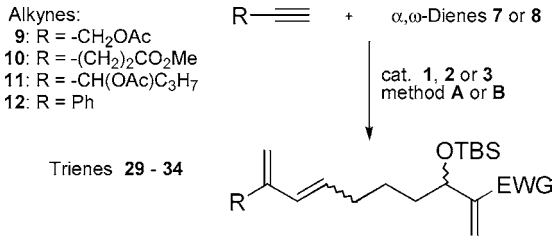
Scheme 4. Synthesis of *cis*-Fused Bicyclic Ketones[a]



18: R = -CH(OAc)C_3H_7, EWG = -CO_2Me — **24** (69 %)
19: R = -CH(OAc)C_3H_7, EWG = -CN — **25** (87 %)
21: R = Ph, EWG = -CN — **26** (65 %)
22: R = (4-MeO)-C_6H_4, EWG = -CO_2Me — **27** (64 %)
23: R = (4-MeO)-C_6H_4, EWG = -CN — **28** (86 %)

[a] Yields (isolated) refer only to *cis*-fused starting TBS-ethers within the eventual *cis*/*trans* mixture (see Table 1).

Table 2. Enyne CM with Homologous α,ω-Dienes



Method **A**: 7.5 mol % **1**; CH_2Cl_2; rt; 24h
Method **B**: 5 mol % **2** or **3**; CH_2Cl_2; 45 °C; 24h

entry	alkyne	α,ω-diene	catalyst	method	yield[a] of trienes	*E*:*Z* ratio
1	**9**	**7**	**1**	**A**	60% **29**	0.8
2	**10**	**7**	**1**	**A**	65% **30**	0.7
3	**11**	**7**	**3**	**B**	83% **31**	1.3
4	**11**	**8**	**2**	**B**	60% **32**	1.1
5	**12**	**7**	**3**	**B**	88% **33**	2.0
6	**12**	**8**	**3**	**B**	90% **34**	0.5

[a] Refers to isolated yields after chromatography.

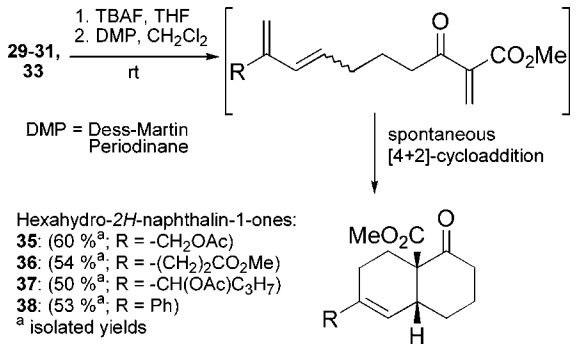
In contrast to the reaction sequences leading to hexahydro-1*H*-indenes, during metathesis reactions starting with **7** or **8** no spontaneous intramolecular cycloaddition of the product trienes (formed as an *E*/*Z* mixture) occurred. Additional heating in toluene or hexane led to slow cyclization of *E*-trienes forming four different octahydronaphthalene diastereomers. At 80 °C the *Z*-trienes underwent a 1,5-H-shift with comparable rate, and above 90 °C unspecific decomposition became predominant.

Because a selective thermal intramolecular cycloaddition of single activated trienes **29**−**34** is not possible, triggering the Diels−Alder reaction by double activation of the dienophile unit after metathesis seemed to be promising. α-Acyl acrylates and α-acyl acrylonitriles are known to be unstable and highly reactive.

The metathesis product trienes **29**−**34** were deprotected using TBAF. The crude product alcohols were then subjected

to Dess−Martin oxidation. During this operation the α-acyl acrylate intermediates spontaneously cyclized to form exclusively *cis*-fused 7-substituted hexahydro-2*H*-naphthalin-1-one-10-carboxylic esters **35**−**38** (Scheme 5).

Scheme 5. Triggered Intramolecular Cycloaddition



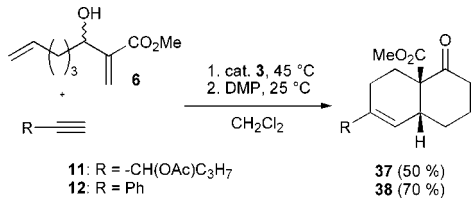
Product yields and *E*/*Z* ratios of starting trienes suggest again that a stereoconvergent transformation of both *E*- and *Z*-trienes into the corresponding *cis*-fused cycloadducts occurred. Stereochemical assignments for the decaline derivatives **35**−**38** were done on the basis of NMR data and molecular modeling using PC Spartan (see Supporting Information for details).

Although the trienes **32** and **34** containing an acrylonitrile moiety could be deprotected to the corresponding allylic alcohols, their subsequent oxidation resulted in the formation of oligo- or polymeric products instead of bicyclic cycloadducts.

Because catalyst **3** gave high conversion of alkynes **11** and **12** (Tables 1 and 2) and is known to tolerate the unprotected hydroxy functionality of Baylis−Hillman alcohol **6**,[12] a much shorter synthetic route to the bicyclic ketones **37** and **38** without TBS protection and deprotection steps was envisaged.

One-pot addition of Dess−Martin periodinane to the reaction mixture after enyne cross-metathesis gave these bicyclic ketones in higher overall yields than the longer reaction sequence via the TBS-ethers (Scheme 6).

Scheme 6 Shorter One-Pot Reaction Route



In conclusion, we have presented a new reaction sequence of enyne cross-metathesis and intramolecular Diels−Alder reaction, which allows for the rapid and stereoselective synthesis of *cis*-fused, functionalized hexahydroindene and decaline derivatives. Several terminal alkynes have been used for coupling but require utilization of different metathesis catalysts for good conversions.

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

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