Pergamon

Tetrahedron Letters 42 (2001) 171–174

TETRAHEDRON LETTERS

Tandem dienyne cross-metathesis/ring-closing metathesis

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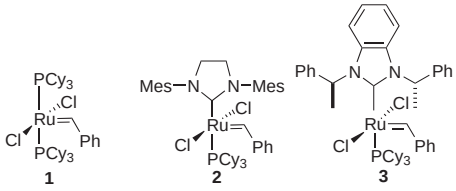
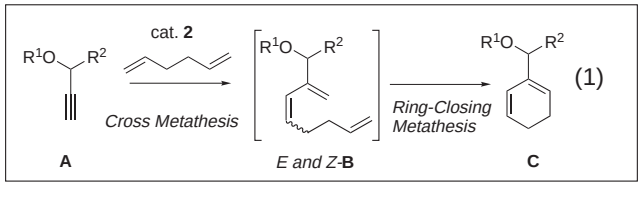
Received 12 October 2000; revised 25 October 2000; accepted 31 October 2000

Abstract—Tandem enyne cross-metathesis/ring-closing metathesis between terminal alkynes and 1,5-hexadiene has been demonstrated using the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene-substituted ruthenium benzylidene complex. Synthesis of 2-substituted 1,3-cyclohexadienes using this one step tandem reaction is reported. In addition, metathesis products were subjected to [4+2] cycloaddition with *N*-methylmaleimide yielding the corresponding cycloadducts in one synthetic step.

The emergence of *N*-heterocyclic carbene-containing ruthenium complexes has increased the scope of alkene metathesis with the Grubbs' ruthenium carbenes (derived from parent catalyst **1**).[1] Complex **2**, which features the electron-rich sigma-donating dihydroimidazolylidene carbene ligand, has been recently employed in a variety of metathesis applications. Ring closing metathesis (RCM) applications have been expanded in part due to the increased activity of complex **2**.[1f] Functional group tolerance using catalyst **2** has been demonstrated both in alkene metathesis[1f] and in intermolecular reactions like enyne cross-metathesis.[2] Here we report a tandem metathesis[3] operation which features cross metathesis of alkynes with 1,5-hexadiene followed in situ by RCM using ruthenium complex **2** (eq. 1). This tandem reaction offers a simple method for the generation of 2-substituted cyclohexadienes in one synthetic step starting from alkynes and 1,5-hexadiene.





Various catalysts and reaction conditions were surveyed to find the optimum conversion to products and to probe the stereoselection in the initial enyne cross metathesis (Table 1). The reaction between propargyl benzoate and 1,5-hexadiene was evaluated using different catalysts and by varying the reaction conditions. In the cross metathesis, a mixture of *Z* and *E* isomers is produced; however, only the *Z* isomer can undergo ring closing metathesis in situ. The parent catalyst **1** gave a 1.1 to 1.0 mixture of cyclohexadiene:triene, reflecting a 1.1 to 1.0 ratio of intermediate *Z* and *E* isomers, in 7% yield. Based on literature precedent, it was surprising that higher conversions were not realized with this catalyst.[4] The highest conversions and shortest reaction times were found instead with catalyst **2** using 9 equiv. of 1,5-hexadiene. Increased temperature resulted in quantitative conversion to products in 1 h (entries 2 versus 3). Elevated temperature (100°C, sealed tube) did not further improve the ratio of 1,3-cyclohexadiene to triene (entry 4) and fewer equivalents of diene resulted in incomplete reaction after 24 h (entry 5). High conversion to products was also realized in benzene and trifluoromethylbenzene,[5] but there was little effect on the product ratio (entries 6, 7).

The chiral benzimidazolylidene catalyst **3**[6] displayed activity comparable to that of the parent Grubbs' catalyst **1** when used in CH_2Cl_2 at reflux. From Table 1 it can be seen that catalysts **1**–**3** have varied activities but exert little influence on product ratios.

The results of tandem enyne cross metathesis/RCM are shown in Table 2. Typical reaction conditions of Table 2 employ 0.06 M alkyne with 9 equiv. 1,5-hexadiene in

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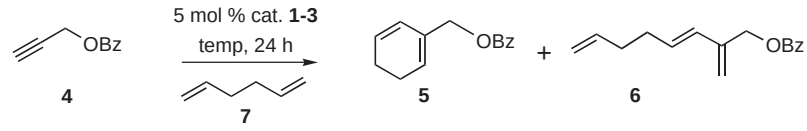
PII: S0040-4039(00)01922-5

Table 1. Effect of catalyst and temperature on tandem metathesis



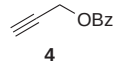
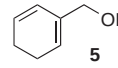
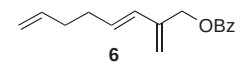
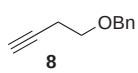
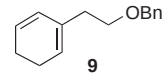
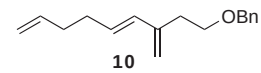
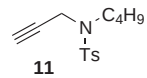
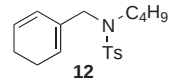
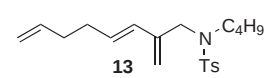
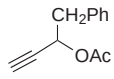
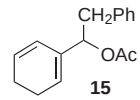
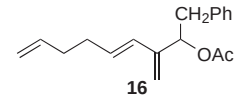
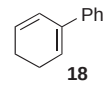
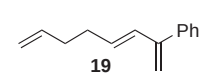
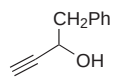
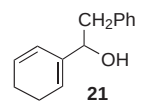
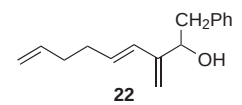
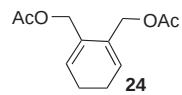
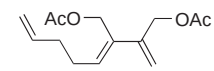
(2)

Entry	Catalyst/solvent	**7** (equiv.)	Temp. (°C)	**5**/**6** (*Z*/*E*)	Conversion (%)[a]
1	**1** (DCM)	9	25	1.1:1.0	7
2	**2** (DCM)	9	25	1.0:1.6	87
3	**2** (DCM)	9	45	1.0:1.2	99[b]
4	**2** (DCM)	9	100	1.0:1.3	99[b]
5	**2** (DCM)	3	25	1.0:1.0	23
6	**2** (PhH)	9	25	1.1:1.0	91
7	**2** ($PhCF_3$)	9	25	1.0:1.5	70
8	**3** (DCM)	9	25	n/d	0
9	**3** (DCM)	9	45	1.3:1.0	15[b]

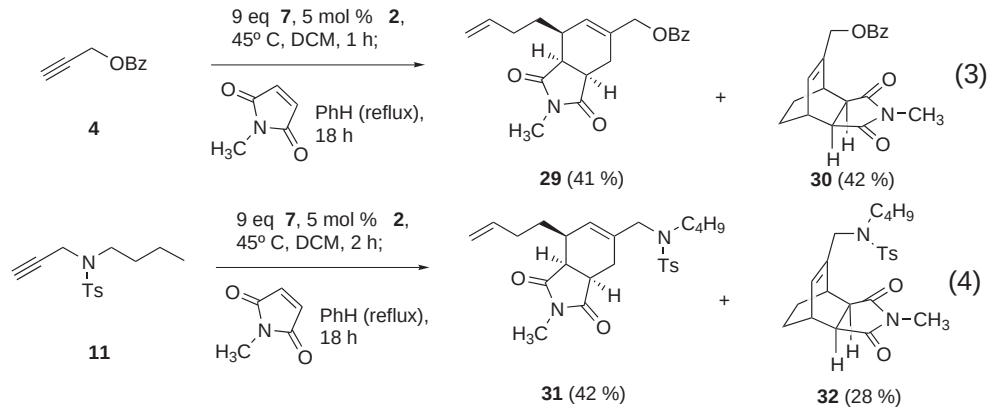
[a] Product conversions and *E*/*Z* ratios were determined by GC.
[b] Reaction time: 1 h.

the presence of 5 mol% **2** in refluxing CH_2Cl_2. Reactions were generally clean, producing the cyclized diene and triene products along with minor but detectable amounts of styrene and 1,5-hexadiene homodimer. Terminal alkynes gave excellent conversions (entries 1–5). Benzyl ether **8** contains a potentially coordinating group and is a difficult substrate in enyne metathesis, but was found to perform well (entry 2). Steric bulk is also well-tolerated (entry 4). Intermolecular metathesis of substituted propargyl alcohol **20** with diene demonstrates that 1-alkenes may be used with free and potentially coordinating[2b] functional groups in demanding alkyne substrates. Selectivity was uniformly low and the data in Table 2 suggest that the alkyne reactant exerts

Table 2. Tandem enyne cross metathesis/ring closing metathesis

Entry	Substrate	Products		Time (h)	Conversion
1	 **4**	 **5**	 **6**	1.0	99 % (1:1.2)
2	 **8**	 **9**	 **10**	2.0	99 % (1:1.5)
3	 **11**	 **12**	 **13**	2.0	99 % (1:1.3)
4	 **14**	 **15**	 **16**	2.0	99 % (1:1.2)
5	 **17**	 **18**	 **19**	0.5	99 % (1:1.4)
6	 **20**	 **21**	 **22**	6.0	48 % (1:1)
7	 **23**	 **24**	 **25**	3.0	68 % (1:1.9)

Conditions: 5 mol % **2**, CH_2Cl_2, 45°C, 9 eq **7**. ( ) = product ratio, determined by GC.



Scheme 1. Tandem metathesis-[4+2] cycloaddition sequence.

little influence on the diastereoselectivity. Internal alkynes produce the desired products albeit with lower conversion; longer reaction time gave additional unidentified products. Reactions conducted using complex **1** failed to give useful conversions in all alkyne substrates explored. For instance, reaction of **4** with 9 equiv. 1,5-hexadiene using 5 mol% **1** at 45°C gave 10% conversion after 1 h along with considerable amounts of homodimer and other unidentified products.

To explore the utility of the diene products obtained from tandem metathesis and to corroborate their structural assignment,[7] the crude mixtures were subjected to Diels–Alder reaction with *N*-methylmaleimide (Scheme 1). The consecutive cycloaddition gives bicyclic products of substantially greater molecular complexity than the alkyne and alkene starting materials.[8]

The effectiveness of this approach is illustrated for two representative terminal alkynes in Scheme 1. The ratios of the intermediate dienes correspond to the isolated yields of cycloadducts. For instance, **4** underwent tandem metathesis (1 h, 45°C) to give a 1:1.2 mixture of **5** and **6** (above, eq. 2), which underwent thermal cycloaddition to yield a 1:1 mixture of cycloadducts, separated by column chromatography in 41 and 42% isolated yield for **29** and **30**, respectively.[9] Similar results were obtained for propargyl amine derivative **11** (eq. 4).

In summary, a novel tandem intermolecular alkyne-diene cross metathesis/in situ ring closing metathesis sequence has been documented. Substrate scope on the alkyne partner suggests that this method will be useful to prepare a variety of 2-substituted-1,3-cyclohexadienes. A consecutive Diels–Alder cycloaddition efficiently provides structurally-complex products. Current investigations are aimed at improving the selectivity in the cross metathesis step and exploring the reaction scope using functionalized dienes.

Acknowledgements

The authors thank the donors of the Petroleum Research Foundation, administered by the American Chemical Society (33298G1) and SUNY Buffalo for financial support of this work. J.A.S. is the recipient of an NIH predoctoral fellowship (GM20439) which is gratefully acknowledged.

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5. For a review of the use of benzotrifluoride solvent, see: Maul, J. J.; Ostrowski, P. J.; Ublacker, G. A.; Linclau, B.; Curran, D. P. In *Modern Solvents in Organic Synthesis*; Knochel, P., Ed.; Springer-Verlag: Berlin, 1999; Vol. 206, p. 79.
6. Rivas, F. M.; Riaz, U.; Smulik, J. A.; Diver, S. T., submitted for publication.
7. Diene **12** and triene **13** were separated by preparative TLC (Table 2, entry 3). Proton NMR of the vinylic region for **12** and **13** is representative: **12** (300 MHz, $CDCl_3$, ppm) δ 5.91 (m, 2H), 5.61 (br s, 1H); **13** (400 MHz, $CDCl_3$, ppm) δ 6.03 (d, $J = 16.0$ Hz, 1H), 5.92 (m, 1H), 5.81 (m, 1H), 5.06 (br s, 2H), 4.99 (br s, 2H).
8. An enyne ring closing metathesis-Diels–Alder reaction has been reported: Heerding, D. A.; Takata, D. T.; Kwon, C.; Huffman, W. F.; Samanen, J. *Tetrahedron Lett*. **1998**, *39*, 6815.
9. *Representative experimental procedure for tandem metathesis/cycloaddition*: To an oven dried 25 mL pressure tube was added 40 mg (0.25 mmol, 1 equiv.) **4**, 0.27 mL (2.25 mmol, 9 equiv.) 1,5-hexadiene, 10.6 mg (12.5 μmol, 5 mol%) 1,3-dimesityl-4,5-dihydroimidazol-2-ylidenetricyclohexylphosphine benzylidene ruthenium dichloride **2** and 4.0 mL CH_2Cl_2. The solution was stirred for 1 h at 45°C. The crude products were filtered through a 3 cm plug of silica to remove spent catalyst using CH_2Cl_2 as eluent and concentrated. The crude product mixture was dissolved in 1.0 mL benzene to which 28 mg (0.25 mmol, 1 equiv.) *N*-methylmaleimide was added. The solution was stirred at reflux for 18 h. The solvent was removed in vacuo (rotary evaporator) to afford a yellow oil that was purified by column chromatography (elution 1:3 ethyl acetate (EA)–hexane) to give **29** as a colorless oil (36.1 mg, 41% yield, analytical TLC: R_f 0.13 (1:3 EA–hexane)) and **30** as a colorless oil (34.3 mg, 42% yield, analytical TLC: R_f 0.08 (1:3 EA–hexane)). Data for **29**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.05 (d, $J = 7.0$ Hz, 2H), 7.57 (t, $J = 7.0$ Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 2H), 5.84 (m, 1H), 5.81 (m, 1H), 5.07 (dd, $J = 17.0$, 1.5 Hz, 1H), 5.00 (dd, $J = 10.5$, 1.5 Hz, 1H), 4.69 (AB q, $J = 7.0$ Hz, 2H), 3.19 (dt, $J = 9.0$, 2.0, 1H), 3.13 (dd, $J = 8.5$, 6.0 Hz, 1H), 2.87 (s, 3H), 2.83 (dd, $J = 15.0$, 1.0 Hz, 1H), 2.34 (m, 2H), 2.25 (m, 2H), 2.04 (m, 1H), 1.88 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 179.3, 177.6, 166.2, 137.9, 134.8, 133.0, 130.9, 129.9, 129.7, 128.3, 115.2, 66.7, 42.7, 40.3, 35.7, 31.9, 30.1, 25.8, 24.7; high-resolution MS (EI^+) molecular ion calcd for $C_{21}H_{23}NO_4$ 353.1627, found 353.1643, error 4.5 ppm. Data for **30**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.05 (d, $J = 7.5$ Hz, 2H), 7.57 (t, $J = 7.5$ Hz, 1H), 7.45 (t, $J = 7.5$ Hz, 2H), 6.14 (d, $J = 5.5$ Hz, 1H), 4.73 (AB q, $J = 8.5$ Hz, 2H), 3.22 (m, 2H), 2.89 (m, 2H), 2.87 (s, 3H), 1.66 (m, 2H), 1.44 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 178.7, 178.3, 166.1, 139.7, 133.0, 129.9, 129.7, 128.3, 127.7, 64.9, 44.6, 43.9, 33.6, 32.0, 24.5, 24.1, 23.8; high-resolution MS (EI^+) molecular ion calcd for $C_{19}H_{19}NO_4$ 325.1314, found 325.1307, error 2.1 ppm.