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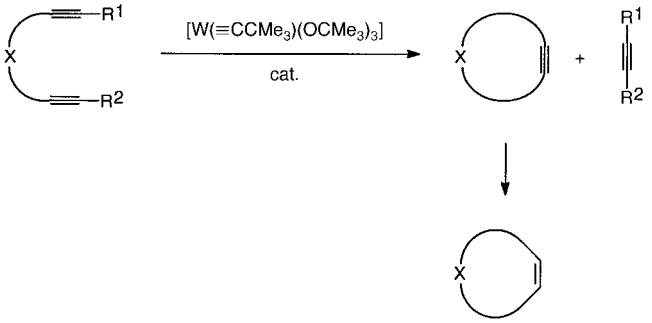
Ring-Closing Metathesis of Functionalized Acetylene Derivatives: A New Entry into Cycloalkynes

Alois Fürstner* and Günter Seidel

Olefin metathesis is rapidly evolving into a prosperous field of research, and as a result of the development of a new generation of performance catalysts with a high tolerance towards functional groups has recently found many applications in organic synthesis.[1, 2] In particular, ring-closing metathesis (RCM) of dienes to cycloalkenes provides good access to carbo- and heterocycles and has been proved to be effective in numerous syntheses of natural products.[2] Medium-sized and macrocyclic rings can also be forged by RCM.[3, 4] The latter, however, are usually obtained as mixtures of *E* and *Z* isomers, the ratio of which can, at present, be neither predicted nor properly controlled. This is a major drawback in target-oriented syntheses as exemplified, for example, by several approaches to epothilone: Although various research teams succeeded in forming the 16-membered ring of this promising chemotherapeutic agent by RCM, separation of the resulting stereoisomeric mixtures were inevitable because only epoxidation of the *Z*-configured cycloalkene leads to the desired target molecule.[5]

In striking contrast to olefin metathesis, the metathesis of alkynes presently plays only a minor role in organic chemistry.[6] Even though the close mechanistic ties between both types of transformations were noticed early on,[7] and various well-defined alkyne metathesis catalysts are available,[8] the applications of alkyne metathesis have until now been confined to the preparation of some special polymers[9] and to the dimerization or cross-metathesis of simple acetylene derivatives.[10]

We now describe the first efficient syntheses of functionalized macrocycles by ring-closing metathesis of diyne substrates (Scheme 1). Partial reduction of the cycloalkyne molecules thus obtained by one of the conventional methods (e.g. Lindlar hydrogenation or hydroboration/protonation) also consitutes a stereoselective route to *Z*-configured cycloalkenes[11] which cannot yet be directly prepared in pure form by RCM.



Scheme 1. Ring-closing metathesis of diynes with **1**.

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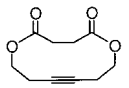
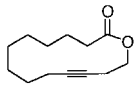
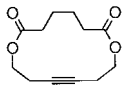
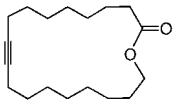
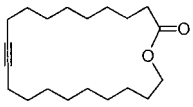
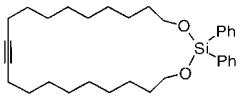
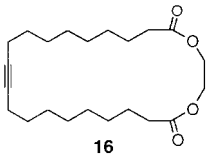
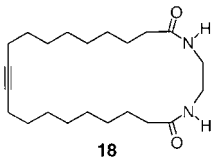
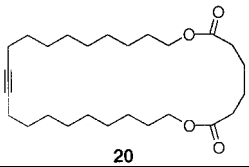
We use the tungsten alkylidyne complex [W(≡CCMe$_3$)-(OCMe$_3$)$_3$] (**1**) developed by Schrock as an alkyne metathesis (pre)catalyst,[12] which is readily obtained from the reaction of [(Me$_3$CO)$_3$W≡W(OCMe$_3$)$_3$] (**2**)[13] with neoheptyne. This complex turned out to be a highly active catalyst for the cyclization of diynes to cycloalkynes (Table 1). Because various functional groups are tolerated in the substrates, it is possible to obtain lactones, lactams, and cyclic silyl ethers of ring sizes 12 or greater in good yields, provided that the reactions are carried out under high dilution conditions ($\leq$0.02 M) in trichlorobenzene (in vacuo, see below), chlorobenzene, toluene, or THF as the solvent, respectively. The formation of minor amounts of cyclodimeric products has been detected in some cases (Table 1, entries 7 and 8).[14] It is necessary to use diyne derivatives with R^1, R^2 ≠ H as the starting materials because of the known incompatibility of catalyst **1** with terminal alkynes.[8] However, we did not notice any significant difference between substrates with R^1, R^2 = Me (entries 1–6, 8–12) and those with R^1, R^2 = Et (entry 7). With 1,2,4-trichlorobenzene as the solvent (b.p. = 214 °C), it is possible to remove the alkyne by-products R^{1}C≡CR^2 (e.g. 2-butyne, 3-hexyne) from the mixture by performing the reactions under reduced pressure (ca. 20 mbar); this seems to have a positive effect on the conversion (entries 4, 7, 10). Whereas the preparation of cycloalkynes by some conventional methods leads to the formation of allenic by-products,[15] this undesirable side reaction does not occur with ring-closing diyne metathesis. The scope of this new method is currently being explored.

Table 1. Synthesis of cycloalkynes by ring-closing metathesis of diynes.[a]

Entry	Substrate	Solvent	Product	Yield [%]
1	[MeC≡C(CH$_2$)$_2$OOC(CH$_2$)]$_2$ **3**	C_6H_5Cl	 **4**	73[c]
2	MeC≡C(CH$_2$)$_8$COO(CH$_2$)$_2$C≡CMe **5**	C_6H_5Cl	 **6**	52
3	[MeC≡C(CH$_2$)$_2$OOC(CH$_2$)$_2$]$_2$ **7**	C_6H_5Cl	 **8**	73[c]
4	**7**	$C_6H_3Cl_3$[b]		79
5	**7**	Toluol		69
6	**7**	THF		64
7	EtC≡C(CH$_2$)$_7$COO(CH$_2$)$_8$C≡CEt **9**	$C_6H_3Cl_3$[b]	 **10**	69[d]
8	MeC≡C(CH$_2$)$_8$COO(CH$_2$)$_9$C≡CMe **11**	C_6H_5Cl	 **12**	52[e]
9	[MeC≡C(CH$_2$)$_9$O]$_2$SiPh$_2$ **13**	C_6H_5Cl	 **14**	55
10	[MeC≡C(CH$_2$)$_8$COOCH$_2$]$_2$ **15**	$C_6H_3Cl_3$[b]	 **16**	97
11	[MeC≡C(CH$_2$)$_8$CONHCH$_2$]$_2$ **17**	C_6H_5Cl	 **18**	90
12	[MeC≡C(CH$_2$)$_9$OOC(CH$_2$)$_2$]$_2$ **19**	C_6H_5Cl	 **20**	52

[a] With [W(≡CCMe$_3$)(OCMe$_3$)$_3$] (**1**, 4–6 mol%) as the catalyst at 80 °C under argon and 1 atm, unless stated otherwise; reaction time 2–19 h. [b] In 1,2,4-trichlorobenzene under reduced pressure (20 mbar). [c] Ca. 10% of the substrate is recovered. [d] 8% of the cyclic dimer is obtained. [e] 6% of the cyclic dimer is obtained.

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Experimental Section

8: A solution of diyne **7** (121 mg, 0.43 mmol) and $[W(\equiv CCMe_3)(OCMe_3)_3]$ (12 mg, 6 mol %) in chlorobenzene (20 mL) was stirred under Ar at 80 °C for 2 h. The solvent was removed in vacuo, and the residue purified by flash chromatography (Merck silica gel, hexane/ethyl acetate 4/1). This led to the recovery of some unchanged starting material **7** (12 mg, 10 %) and afforded the desired cycloalkyne **8** as colorless crystals (70 mg, 73 %). M.p. = 106–107 °C; ^{1}H NMR: $\delta = 4.14$ (t, 4H, $J = 5.5$ Hz), 2.53 (t, 4H, $J = 5.6$ Hz), 2.40 (m, 4H), 1.76 (m, 4H); ^{13}C NMR: $\delta = 173.0$, 77.8, 62.4, 34.8, 24.9, 19.0. MS: *m*/*z* (rel intensity): 224 (< 1, $[M^+]$), 179 (< 1), 166 (1), 152 (1), 137 (1), 129 (3), 111 (7), 101 (4), 78 (100), 66 (21), 55 (10), 41 (8); elemental analysis calcd for $C_{12}H_{16}O_4$ (224.3): C 64.24, H 7.18; found: C 64.14, H 7.15.

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Methoxide Coordination at the Pocket of $[Cu^{II}Tp^{Cum,Me}]$ and a Simple Model for the Cu Center of Galactose Oxidase**

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Functionalized hydrotris(pyrazolyl)borate ligands (Tp^R) have been used to create protected transition metal coordination sites. Pyrazol nitrogen atoms resemble histidine donor groups, and the Tp^R complexes of Fe, Cu, and Zn have

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