A novel ruthenium-catalysed tandem diyne cycloisomerisation—cross metathesis process

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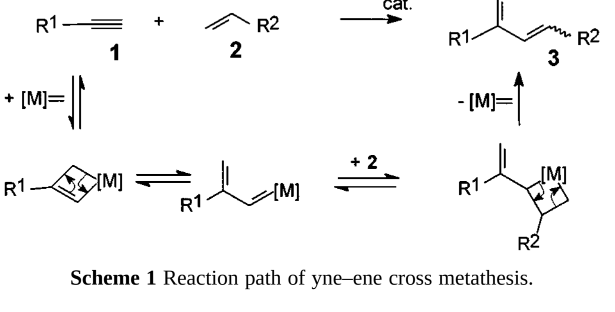
Ruthenium-catalysed cycloisomerisation of hepta-1,6-diynes in the presence of functionalised terminal olefins yields five-membered cyclic products with variable unsaturated side chains and is applicable to the synthesis of highly functionalised hetero- and carbocycles.

The development of well-defined catalysts tolerating a variety of functional groups has significantly widened the scope of olefin metathesis as a synthetic method.[1] Whereas there are numerous examples for the ring closing metathesis (RCM) of dienes and its application in the field of natural product synthesis,[2] little is known about comparable reactions involving alkynes.[3] Only the RCM of enynes has found synthetic application.[4] Very recently, Fürstner and Seidel[5] reported the RCM of diynes to macrocyclic cycloalkynes and acyclic alkynes as stoichiometric by-products. Herein, we describe a tandem process that consists of a diyne cyclisation to a small ring and a cross metathesis with a terminal alkene and its application to the synthesis of functionalised unsaturated carbo- and heterocycles.

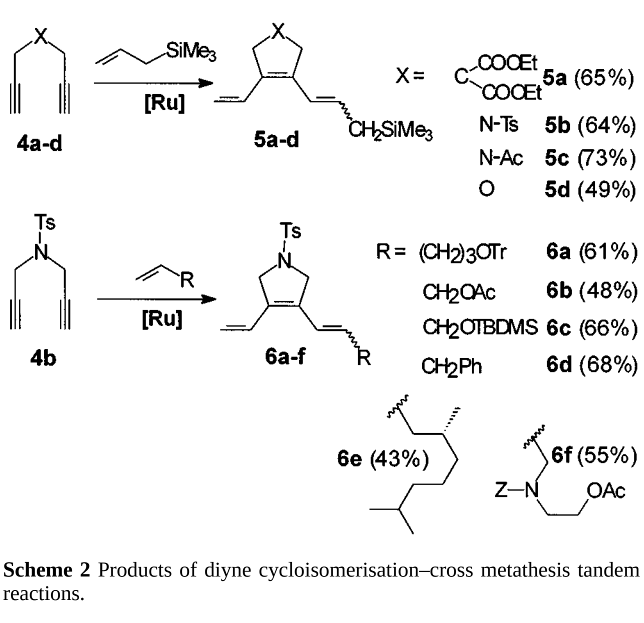
Recently, we presented a selective yne–ene cross metathesis.[6] This reaction was found to be initiated by attack of the catalytic ruthenium–alkylidene complex at the triple bond (Scheme 1), thus, resulting in the formation of a conjugated alkylidene complex. Reaction of this reactive intermediate with the alkene component gives the cross coupling product in a selective manner. In the course of systematic investigations into the metathesis of alkynes[7] it has now been found that the introduction of a second triple bond into the alkyne component at a certain distance leads to an initial diyne cycloisomerisation event without affecting the subsequent cross coupling step.

In the initial experiments hepta-1,6-diyne **4a** was employed. We decided to use allyltrimethylsilane as the alkene component, since it has previously been proven to be a highly efficient cross metathesis coupling agent.[8] When **4a** and 3 equiv. of allyltrimethylsilane were reacted with 10 mol% of the ruthenium catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ (Cy = cyclohexyl) [Ru] introduced by Grubbs and coworkers,[9] a carbocyclic product (**5a**) was isolated in 65% yield (Scheme 2).† In contrast, all attempts to perform the same reaction under catalysis of Schrock's molybdenum catalyst[10] $PhMe_2CCH{=}Mo{=}N[2,6\text{-}({}^{i}Pr_2C_6H_3)][OCMe(CF_3)_2]_2$ ([Mo]) failed. This result is not surprising considering reports describing a [Mo]-catalysed cyclopolymerisation[11] of **4a**.

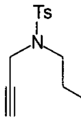


Scheme 1 Reaction path of yne–ene cross metathesis.

Accordingly, all further experiments were conducted under catalysis of [Ru] using the standard conditions mentioned above.‡ Like **4a**, simple N- and O-containing symmetrical diynes are also transformed into heterocyclic products as demonstrated by the synthesis of dihydropyrroles **5b** and **5c** and dihydrofuran **5d**. We also attempted to prepare S-containing heterocycles from diynic sulfides, sulfoxides, and sulfones. Although these heptadiynes have been described as suitable substrates for the [Mo]-catalysed cyclopolymerisation process,[12] rapid isomerisation into the corresponding allenes and no metathesis was observed under our reaction conditions. To further investigate the scope of the reaction we employed various functionalised terminal olefins as alkene components. The use of protected alcohols resulted in formation of the heterocyclic products **6a–c** in acceptable yields. In addition, a terpene derivative and an N- and O-protected amino alcohol were successfully transformed into **6e** and **6f**, respectively. These examples demonstrate that structurally diverse olefins undergo the tandem reaction. With the exception of compounds containing sterically demanding substituents (**6c**, *E/Z* = 5 : 1; **6f**, *E/Z* = 2.5 : 1) all products were isolated as *E/Z* isomer mixtures (1 : 1–1 : 1.5). This lack of selectivity is a common problem of cross metathesis.[1,8] With respect to a second problem often encountered in methathetical cross couplings, the tendency of the coupling partners to self-react, the tandem process proved to be remarkably selective. In all reactions only traces of alkene homodimer were identified. To study the accessibility of six- and seven-membered heterocycles we prepared the appropriate diynic precursors **7** and **8**, respectively. However, no cyclisation took place in the presence of allyltrimethylsilane under standard reaction conditions. Instead, products resulting from yne–ene cross metathesis of the silane with one or both triple bond(s) were identified. This finding indicates the importance of the distance between the two triple



Scheme 2 Products of diyne cycloisomerisation–cross metathesis tandem reactions.



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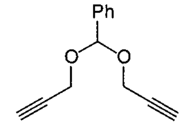

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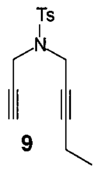

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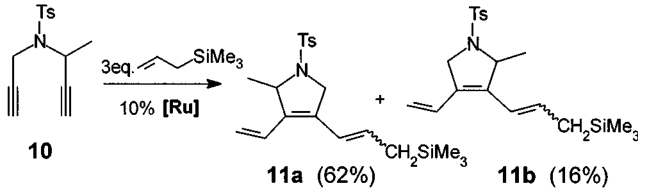
bonds for the cycloisomerisation step. The failure of **9** containing a disubstituted triple bond to undergo the cyclisation might be attributed to a kinetic barrier caused by the additional ethyl substituent.

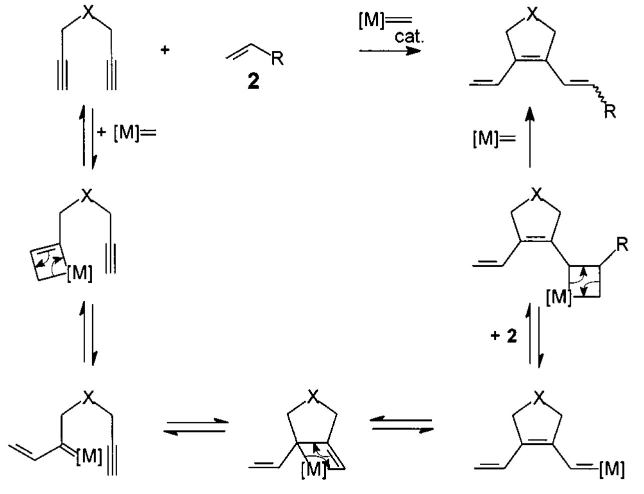
The [Ru]-catalysed reaction of unsymmetrical diyne **10** with allyltrimethylsilane (Scheme 3) demonstrates that the cyclisation–cross metathesis tandem process shows regioselectivity. Considering that **11a** and **11b** were formed in a 4 : 1 ratio under standard conditions, higher selectivities could be observed using different substituents or reaction partners under optimised conditions.



Scheme 3 [Ru]-catalysed reaction of asymmetric diyne **10** with allyltrimethylsilane giving regioisomeric **11a** and **11b**.

For the novel tandem process described above the reaction path depicted in Scheme 4 is proposed. The reaction is assumed to start with the reversible addition of the catalytic carbene complex at one of the triple bonds. Intramolecular addition of the resulting conjugated ruthenium–alkylidene complex to the second triple bond gives rise to a cyclic carbene complex, which directly cross-reacts with the alkene component.

In summary, a new tandem metathesis reaction suitable for the synthesis of functionalised carbo- and heterocycles has been developed. The reaction shows atom economy[13] and combines the cyclisation of a hepta-1,6-diyne with a cross metathesis. A variety of differently substituted five-membered carbo- and heterocycles has been prepared. We are currently exploring the possibility of enhancing the regio- and stereoselectivity of the reaction.



Scheme 4 Proposed pathway of the diyne cycloisomerisation–cross metathesis tandem reaction.

Notes and references

† Synthesis of **5a** employing standard reaction conditions: **4a** (100 mg, 0.424 mmol) and allyltrimethylsilane (140 mg, 1.27 mmol) was dissolved in dry CH_2Cl_2 (3 mL). [Ru] (35 mg, 0.04 mmol) was added and the mixture was stirred for 12 h. The solvent was removed under vacuum and the residue was chromatographed on silica gel using Bu^{t}OMe–hexane (v/v = 1/9) to give **5a** {101 mg, 68%, *E*/*Z*-ratio: 1.1/1}; R_f = 0.6, Bu^{t}OMe–hexane (v/v = 1/4)}; (*E*)-**5a**: δ_H (400 MHz, $CDCl_3$) 6.75 (dd, 1H, *J* 19, 11), 6.29 (d, 1 H, *J* 15), 5.71 (dt, 1H, *J* 15, 8), 5.10 (m, 2H), 4.20 (q, 4H, *J* 7), 3.21 (s, 2H), 3.05 (s, 2H), 1.73 (t, 6H, *J* 7), 1.25 (d, 2H, *J* 8), 0.00 (s, 9H). (*Z*)-**5a**: δ_H (400 MHz, $CDCl_3$) 6.67 (dd, 1H, *J* 19, 11), 6.08 (d, 1H, *J* 12), 5.53 (dt, 1H, *J* 12, 8), 5.10 (m, 2H), 4.20 (q, 4H, *J* 7), 3.37 (s, 2H), 3.21 (s, 2H), 1.73 (t, 6H, *J* 7), 1.61 (d, 2H, *J* 8), 0.02 (s, 9H). δ_C (67.9 MHz, $CDCl_3$) 172.00 (Cq), 171.95 (Cq), 135.06 (Cq), 133.97 (Cq), 130.60 (CH), 130.18 (CH), 129.94 (CH), 129.54 (CH), 121.61 (CH), 119.46 (CH), 114.35 (CH_2), 113.42 (CH_2), 61.52 (CH_2), 57.54 (Cq), 56.78 (Cq), 44.30 (CH_2), 41.41 (CH_2), 40.53 (CH_2), 39.49 (CH_2), 24.42 (CH_2), 21.48 (CH_2), 13.94 (CH_3), −1.89 (CH_3), −1.98 (CH_3). IR (film) 3470(w), 2981(m), 2955(m), 2906(m), 1732(s), 1670(w), 1456(w), 1446(m), 1367(m), 1250(s), 1187(s), 1071(s), 837(s), 760, 695 cm^{-1}. HRMS: Calcd. for [M^+] $C_{19}H_{30}O_4Si$: 350.1913. Found 350.1924.

‡ In all reactions the starting material was completely consumed. In some cases traces of symmetrically disubstituted cyclic products resulting from cycloisomerisation followed by double-cross metathesis were the only identifiable by-products.

1 General reviews on olefin metathesis: R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413; M. Schuster and S. Blechert, *Angew. Chem.*, 1997, **109**, 2124; *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2036; K. J. Ivin and J. C. Mol, *Olefin Metathesis and Metathesis Polymerisation*, Academic Press, New York, 1997.

2 Reviews emphasizing RCM and its application in organic synthesis: R. H. Grubbs, S. J. Miller and G. C. Fu, *Acc. Chem. Res.*, 1995, **28**, 446; S. K. Armstrong, *J. Chem. Soc., Perkin Trans. 1*, 1998, 371.

3 Cross metatheses of alkynes has been reported before ref. 5: D. Villemin and P. Cadiot, *Tetrahedron Lett.*, 1982, **23**, 5139; N. Kaneta, K. Hikichi, S. Asaka, M. Uemura and M. Mori, *Chem. Lett.*, 1995, 1055; J. Sancho and R. R. Schrock, *J. Mol. Catal.*, 1982, **15**, 75; R. R. Schrock, *Polyhedron*, 1995, **22**, 3177.

4 A. Kinoshita and M. Mori, *Synlett*, 1994, 1020; A. Kinoshita and M. Mori, *J. Org. Chem.*, 1996, **61**, 8356; S.-H. Kim, W. J. Zuercher, N. B. Bowden and R. H. Grubbs, *J. Org. Chem.*, 1996, **61**, 1073; W. J. Zuercher, M. Scholl and R. H. Grubbs, *J. Org. Chem.*, 1998, **63**, 4291.

5 A. Fürstner and G. Seidel, *Angew. Chem.*, 1998, **110**, 1758; *Angew. Chem., Int. Ed.*, 1998, **37**, 1734.

6 R. Stragies, M. Schuster and S. Blechert, *Angew. Chem.*, 1997, **109**, 2628; *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2518.

7 For example, see: J.-U. Peters and S. Blechert, *Chem. Commun.*, 1997, 1983.

8 O. Brümmer, A. Rückert and S. Blechert, *Chem. Eur. J.*, 1997, **3**, 441; W. E. Crowe, D. R. Goldberg and Z. J. Zhang, *Tetrahedron Lett.*, 1996, **37**, 2117.

9 P. Schwab, M. B. France, J. W. Ziller and J. W. Grubbs, *Angew. Chem.*, 1995, **107**, 2179; *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2039.

10 R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare and M. O'Regan, *J. Am. Chem. Soc.*, 1990, **112**, 3875.

11 R. R. Schrock, *Acc. Chem. Res.*, 1990, **23**, 158.

12 Y.-S. Gal and S.-K. Choi, *J. Polym. Sci., Sect. A*, 1993, **31**, 345.

13 B. M. Trost, *Angew. Chem.*, 1995, **107**, 285; *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259.

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