Cascade Reactions

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Ruthenium-Catalyzed Synthesis of 2,3-Cyclo[3]dendralenes and Complex Polycycles from Propargyl Alcohols**

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Dedicated to Professor Henning Hopf

Abstract: *Ruthenium-catalyzed cascade transformations for the synthesis of 2,3-cyclo[3]dendralenes and multicomponent processes based thereon to generate complex polycycles are presented. The combination of allylation–cyclization sequences with diene-transmissive Diels–Alder reactions allows the rapid and selective construction of natural-product-like motifs from easily accessible starting materials in a one-pot process and provides a new method to access potential drug candidates.*

The atom-economic construction of complex structures from simple and readily available starting materials is an important goal in the context of sustainable organic synthesis. Multicomponent reaction cascades are of particular value.[1] Because of their cross-conjugated polyene structure, dendralenes are suitable starting materials for the rapid construction of complex products.[2–4] In this context, diene-transmissive Diels–Alder reactions (DTDA) have been studied in particular.[4] Aside from the classical synthesis of different dendralenes,[2,3f,j,4a,e,f,h] various metal-catalyzed processes for dendralene synthesis have been published.[2,3a,g,4c,d,g,5]

Ruthenium-catalyzed transformations of propargyl alcohols provide atom-economic access to many important classes of compounds.[6,7] Recently, we were able to report that cyclopentadienone ruthenium complexes of type **1** (Figure 1) catalyze the allylation and subsequent cyclization or cycloisomerization of heteroarenes, amines, or 1,3-dicarbonyl compounds with 1-ene-4-yn-3-ols (**2**), which are easily accessible from α,β-unsaturated ketones.[7a–c] Our previous studies have shown that the metal–ligand bifunctionality of the catalysts is of crucial importance for the course of the cascade reaction (Scheme 1).[7a–f] Cyclo[3]dendralenes with no structural flexibility are obtained from doubly allylic propargyl alcohol **2a** and cyclic dicarbonyl compounds **3** in very good yields (Scheme 2).[7b] Herein, we report the transfer of the allylation–cyclization sequence to acyclic doubly allylic propargyl alcohols and subsequent diene-transmissive Diels–Alder processes.

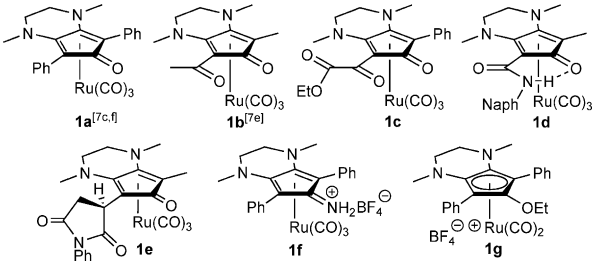
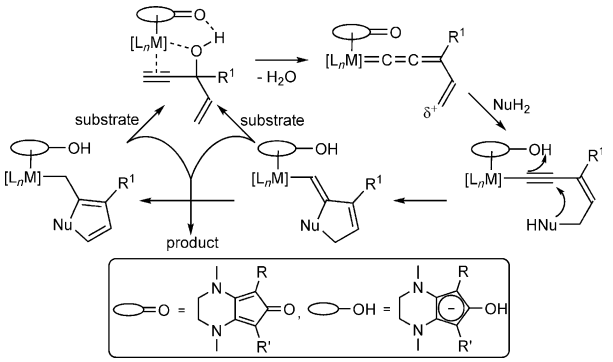
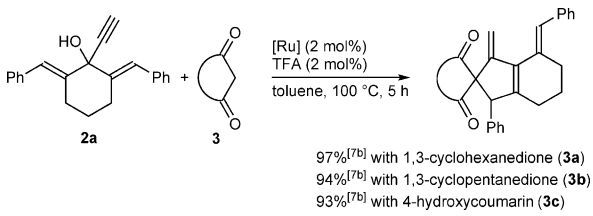


Figure 1. Employed cyclopentadienone ruthenium complexes.



Scheme 1. Possible reaction mechanism of the allylation–cyclization sequence.



Scheme 2. Synthesis of cyclo[3]dendralenes with no structural flexibility.[7b] TFA = trifluoroacetic acid.

Alcohol **2b** reacts with 1,3-cyclohexanedione (**3a**) to yield 2,3-cyclo[3]dendralene **4a** (Scheme 3). A screen of complexes **1a**–**1g** reveals that **1e** in combination with an acidic additive (TFA, 5 mol%) is the most selective and reactive catalyst. Both diastereomers of **1e** give similar results (Table 1, entries 9–11). With catalyst **1a** and TFA, the Diels–Alder adduct **5a** was also formed as a single diastereomer (Table 1, entry 2). After prolonged reaction times, **5a** becomes the main product, whereas increasing the reaction temperature

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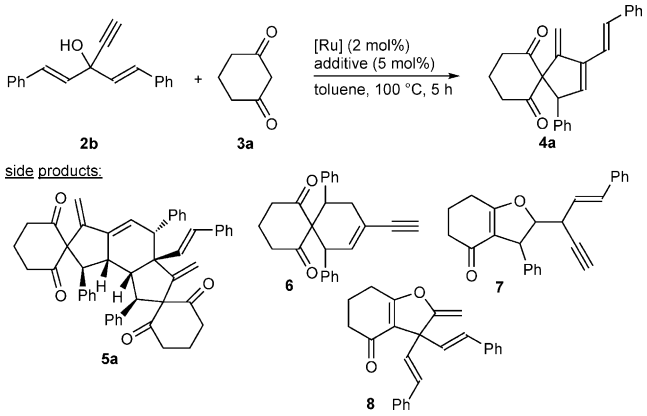


Scheme 3. Ruthenium-catalyzed transformations with 1,3-cyclohexanedione.

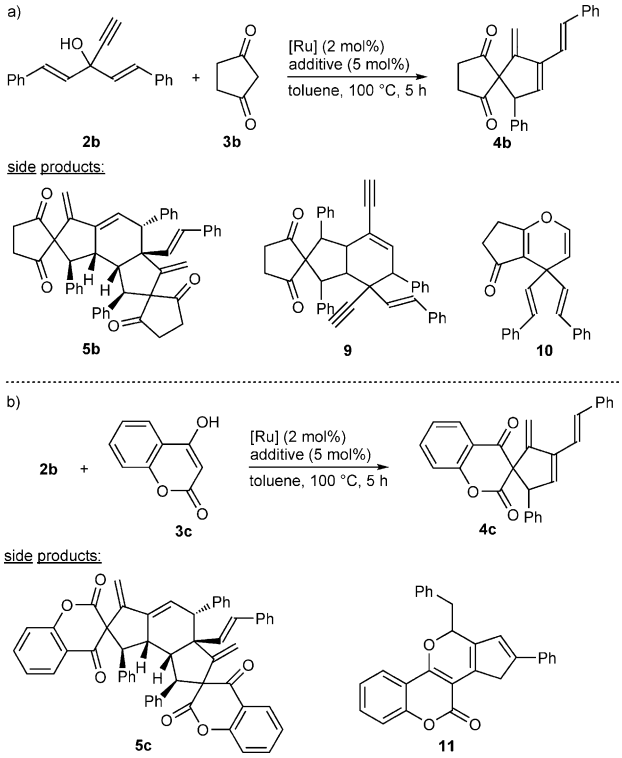
Table 1: Reactions with 1,3-cyclohexanedione.

Entry	Cat.	Additive	**4a** [%]	**5a** [%][a] (d.r.)	**6** [%] (d.r.)	**7** [%] (d.r.)	**8** [%]
1	**1a**	–	17	3 (>20:1)	–	15 (3:2)	40
2	**1a**	TFA	40	39 (>20:1)	<3	–	6
3[b]	**1a**	TFA	89	–	–	–	–
4[c]	**1a**	TFA	15	61 (>20:1)	<3	–	10
5	**1b**	TFA	55	–	22 (4:1)	17 (3:2)	–
6	**1c**	TFA	65	19 (>20:1)	–	–	5
7	**1d**	TFA	21	–	–	67 (3:2)	–
8	**1e**[d]	–	50	5 (>20:1)	–	–	35
9	**1e**[d]	TFA	90	–	–	7 (3:2)	–
10	**1e**[e]	TFA	91	–	–	5 (3:2)	–
11	**1e**[f]	TFA	88	–	–	8 (3:2)	–
12	**1f**	–	20	29 (>20:1)	15 (4:1)	–	18
13	**1f**	TFA	27	–	28 (4:1)	31 (1:1)	–
14	**1f**	DBU	44	25 (>20:1)	–	–	11
15	**1g**	–	12	–	53 (3:1)	–	26
16[g]	–	TFA	–	–	–	–	7

[a] Yield based on **2b**. [b] With microwave irradiation (200 °C, 5 min). [c] Reaction time: 10 h. [d] As a mixture of both diastereomers (1.3:1). [e] Major diastereomer. [f] Minor diastereomer. [g] Formation of the monoallylation product. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

suppresses the formation of the cycloadduct (Table 1, entries 3 and 4). In the absence of an acidic additive, catalyst **1e** still exhibits moderate activity in contrast to **1a**, whereas catalyst **1f** can be used under basic conditions, in particular (Table 1, entries 1, 8, and 14). The more electron-rich complexes **1b** and **1d** lead to an increased formation of side products (Table 1, entries 5 and 7). Finally, the ethylated complex **1g** hardly catalyzes the formation of **4** (Table 1, entry 16). Cycloadduct **5a** is observed when the catalysts **1a** or **1c** are employed under acidic conditions as well as in the reactions catalyzed by complexes **1e** or **1f** under neutral or basic conditions (Table 1, entries 2, 4, 6, 8, 12, and 14). Monoallylation of the nucleophile occurs in the absence of the ruthenium catalyst under acidic conditions. As a side product, compound **8** is formed in low yield (Table 1, entry 16).

Complex **1e** also proves to be the most reactive catalyst with other cyclic β-dicarbonyl compounds (Scheme 4;



Scheme 4. Ruthenium-catalyzed transformations with 1,3-cyclopentanedione or 4-hydroxycoumarin.

Table 2, entries 2, 3, 10, and 11). With nucleophile **3c**, catalyst **1a** leads to a slightly higher stereoselectivity (Table 2, entries 7 and 8). The cycloadducts (**5**) are formed as single diastereomers under neutral and basic conditions (Table 2, entries 2, 4, 5, 10, and 14). With 4-hydroxycoumarin (**3c**), the interesting rearrangement product **11** is observed as a minor product (Table 2, entries 7–14). More acidic conditions (20 mol% TFA) promote the formation of **11** (Table 2, entry 9), whereas it is largely suppressed under basic con-

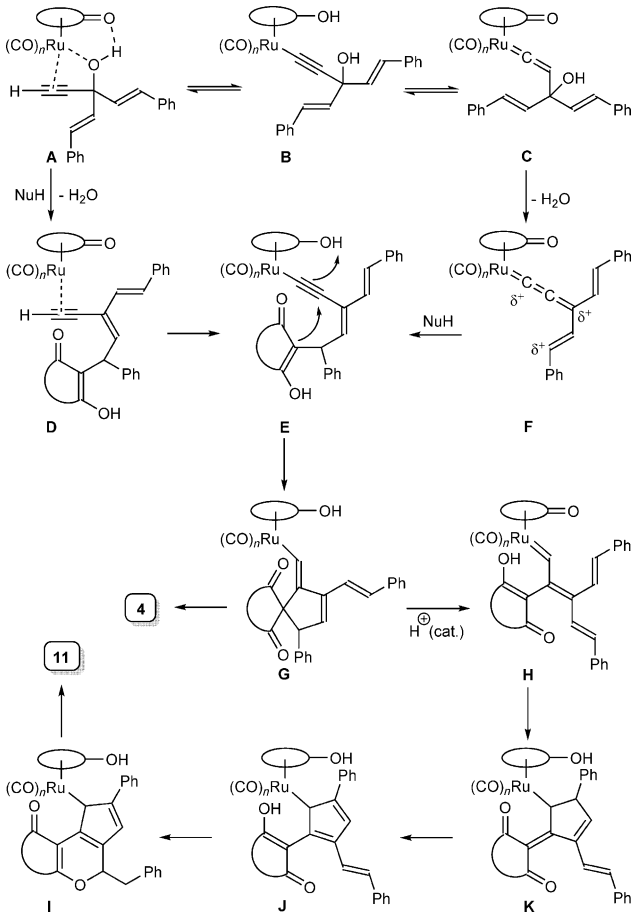
Table 2: Reactions with 1,3-cyclopentanedione or 4-hydroxycoumarin.

Entyr	**3**	Cat.	Additive	**4** [%] (d.r.)	**5** [%][a] (d.r.)	**9** [%][a] (d.r.)	**11** [%]
1	**3b**	**1a**	TFA	54	<3	36 (4:1)	–
2[b]	**3b**	**1e**[c]	–	59	28 (>20:1)	–	–
3	**3b**	**1e**[c]	TFA	67	–	30 (5:1)	–
4	**3b**	**1f**	–	56	27 (>20:1)	10 (4:1)	–
5	**3b**	**1f**	DBU	66	19 (>20:1)	9 (4:1)	–
6[d]	**3b**	–	TFA	–	–	39 (4:1)	–
7	**3c**	**1a**	–	54 (5:2)	7 (>20:1)	–	27
8	**3c**	**1a**	TFA	41 (5:2)	<3	–	50
9	**3c**	**1a**	TFA[e]	11	–	–	86
10	**3c**	**1e**[c]	–	54 (2:1)	18 (>20:1)	–	19
11	**3c**	**1e**[c]	TFA	62 (2:1)	–	–	25
12	**3c**	**1f**	–	39 (3:2)	7 (>20:1)	–	43
13	**3c**	**1f**	TFA	46 (1:1)	7 (>20:1)	–	35
14	**3c**	**1f**	DBU	30 (3:2)	29 (>20:1)	–	12
15[d]	**3c**	–	TFA	–	–	–	–

[a] Yield based on **2b**. [b] **10** (8%) additionally isolated. [c] As a mixture of both diastereomers (1.3:1). [d] Formation of the monoallylation product. [e] TFA (20 mol%).

ditions (catalyst **1f**, DBU; Table 2, entry 14). The allylation step also occurs under acidic conditions in the absence of the ruthenium catalyst (Table 2, entries 6 and 15). With 1,3-cyclopentanedione (**3b**), the double allylation is followed by an intramolecular [4+2] addition to form compound **9**.

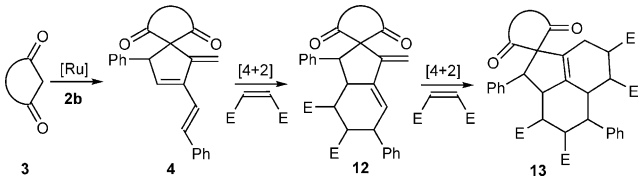
A possible reaction mechanism in accordance with our previous results[7] is shown in Scheme 5. The chelated π-complex **A** is dehydrated via alkynyl derivative **B** and



Scheme 5. Proposed reaction mechanism.

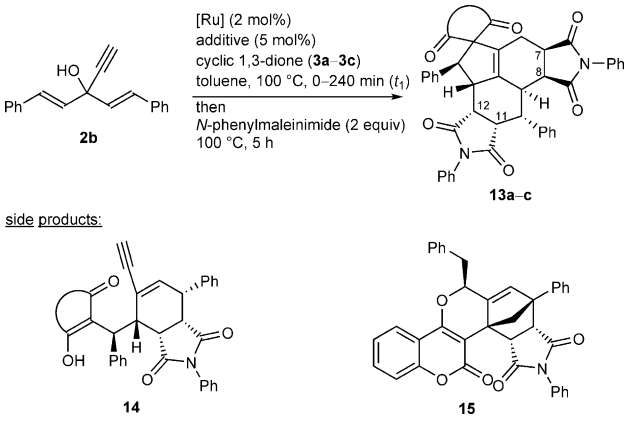
vinylidene complex **C** to form allenylidene species **F**. Nucleophilic attack at the sterically accessible end of the vinyl cumulene results in alkynyl complex **E**. Alternatively, **E** could be formed from **A** via π-complex **D**. Cyclization of **E** promoted by intramolecular protonation leads to spiro compound **G**, which releases product **4** in a reductive elimination process with regeneration of the active catalyst species. For the rearrangement under more acidic conditions, fragmentation of **G** leads to carbene complex **H**, which cyclizes via the doubly vinylogous enol to form **K**. A 1,7-hydrogen shift generates enol **J**, which cyclizes after rotation to form α-pyran **I**. In the following, the cyclodendralene formation was combined with a diene-transmissive Diels–Alder reaction (DTDA) in a one-pot process (Scheme 6).

When *N*-phenylmaleimide is used as the dienophile, product **13** is always isolated as two diastereomers; two



Scheme 6. Cascade process combining allylation, cyclization, and DTDA.

additional diastereomers can be detected in trace amounts (Scheme 7, Table 3). The dienophile always approaches from the less hindered side, *anti* to the corresponding adjacent phenyl group. The formation of several diastereomers is due to the moderate *endo*/*exo* selectivity of the Diels–Alder steps. The double *endo* product is the main component. The configurations were assigned by comparison of the ^3J(H,H) coupling constants with the corresponding dihedral H-C-C-H angles generated from energy-minimized models (MM2 force



Scheme 7. One-pot process combining allylation, cyclization, and DTDA.

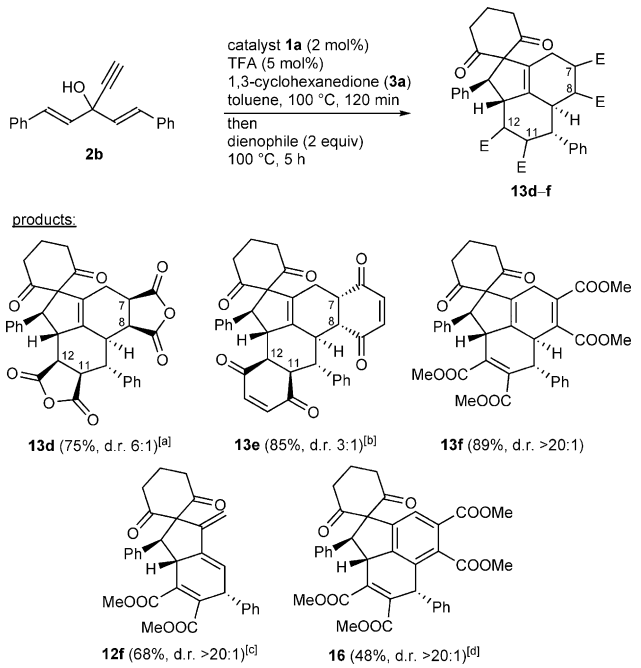
Table 3: Reactions with *N*-phenylmaleimide.

Entry	3	Cat.	Additive	t_1 [min]	13 [%] (d.r.)	14 [%] (d.r.)	15 [%] (d.r.)
1	**3a**	**1a**	TFA	0	39 (5:3)[a]	19 (>20:1)	–
2	**3a**	**1a**	TFA	120	63 (5:2)[a]	–	–
3	**3a**	**1e**[b]	–	120	10 (3:2)[a]	–	–
4	**3a**	**1f**	DBU	120	59 (3:2)[a]	–	–
5	**3b**	**1a**	TFA	0	32 (5:3)[c]	12 (>20:1)	–
6	**3b**	**1a**	TFA	120	53 (5:3)[c]	–	–
7	**3b**	**1e**	–	120	27 (3:2)[c]	–	–
8	**3b**	**1f**	DBU	120	42 (3:2)[c]	–	–
9	**3c**	**1a**	TFA	0	17 (3:2)[a]	12 (>20:1)	6 (>20:1)
10	**3c**	**1a**	TFA	60	26 (3:2)[a]	–	12 (>20:1)
11	**3c**	**1a**	TFA	120	23 (3:2)[a]	–	19 (>20:1)
12	**3c**	**1a**	TFA[d]	240	9 (3:2)[a]	–	41 (>20:1)
13	**3c**	**1e**	–	120	20 (3:2)[a]	–	8 (>20:1)
14	**3c**	**1f**	DBU	120	60 (3:2)[a]	–	–

[a] Major diastereomer: 7,8,11,12-*endo*, minor diastereomer: 7,8-*endo*-11,12-*exo*; trace amounts of two additional diastereomers were detected. [b] As a mixture of both diastereomers (1.3:1). [c] Major diastereomer: 7,8,11,12-*endo*, minor diastereomer: 7,8,11,12-*exo*; trace amounts of two additional diastereomers were detected. [d] TFA (20 mol%).

field) and confirmed by NOESY experiments (see the Supporting Information). When the addition of the dienophile is not delayed, the allylated intermediate can already be intercepted as cycloadduct **14** (Table 3, entries 1, 5, and 9). With nucleophiles **3a** and **3b**, the highest yields of **13** are obtained using the catalyst system **1a**/TFA, followed by the **1f**/DBU system (Table 3, entries 2, 4, 6, and 8). The latter system is superior when using nucleophile **3c**, as cycloadduct **15**, which results from rearrangement product **11**, is not formed under basic conditions (Table 3, entry 14). In contrast, the yield of **15** can be increased to 41% under more acidic conditions (Table 3, entry 12).

Some dienophiles react with higher diastereoselectivity (Scheme 8). Again, both cycloadditions occur strictly *anti*-selective with respect to the corresponding adjacent phenyl group. Using maleic anhydride or *para*-benzoquinone, the first cycloaddition proceeds preferably *exo*. The correspond-



Scheme 8. Reactions with various dienophiles. [a] Major diastereomer: 7,8-*endo*-11,12-*exo*. [b] Major diastereomer: 7,8,11,12-*exo*, minor diastereomer: 7,8,11,12-*endo*. [c] With 1 equiv of the dienophile. [d] From **13f** after three days in air.

ing monoadducts with electron-deficient alkenes (**12a**–**e**) are not formed selectively. The s-*cis*-fixed diene **12** probably reacts faster than the original 2,3-cyclo[3]dendralene **4**. However, with acceptor-substituted alkynes, monoadducts such as **12f** can be selectively synthesized. The corresponding double cycloadduct **13f** is slowly oxidized in air to yield aromatic compound **16**.

In summary, we have presented multicomponent cascade transformations of readily available unsaturated alcohols that are catalyzed by cyclopentadienone ruthenium complexes that yield highly complex polycyclic products with up to nine stereogenic centers in high selectivity. The atom-economic reactions proceed via 2,3-cyclo[3]dendralenes, which can also be generated selectively. The natural-product-like compounds are currently being investigated for potential biological activities. Initial results suggest promising cytotoxic properties of individual derivatives. Asymmetric catalytic variants of the proposed processes using enantiomerically pure axially chiral complexes of type **1** are currently under development.

Keywords: dendralenes · homogeneous catalysis · molecular complexity · multicomponent reactions · ruthenium

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