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Copper-Catalyzed Cyclization–Fragmentations of Enynols

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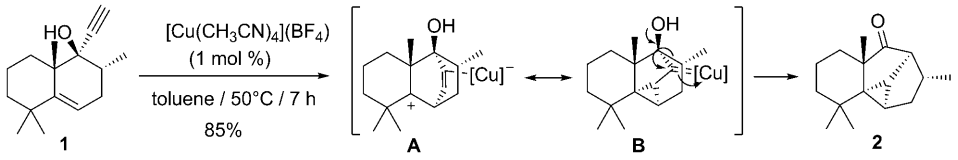
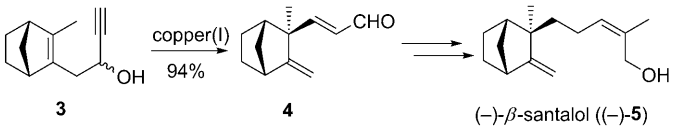
In 2006, our research group has reported the cost-effective cycloisomerization of 5-en-1-yn-3-ols catalyzed by copper (cyclopropanation/1,2-alkyl shift; Scheme 1)[1] and related enynol esters.[2] These cyclopropanation reactions,[3] which lead selectively to complex polycyclic compounds, are generally catalyzed by platinum[4] or gold.[5] During further studies on enynols of type **C**, we discovered that a cyclization–fragmentation pathway (Scheme 2, **C** to **F**) could compete with the cyclopropanation, and that $[Cu(CH_3CN)_4](BF_4)$ was the reagent of choice for promoting this rearrangement, when compared to silver-,[6] gold-,[5b] or platinum-catalysis.



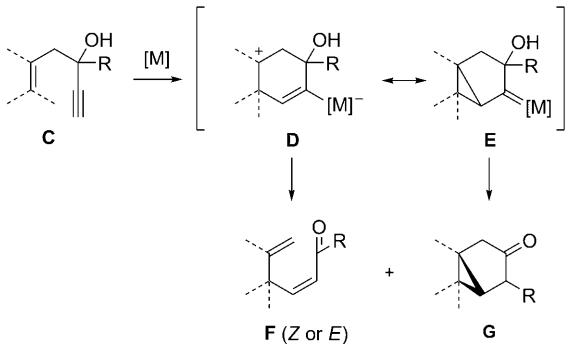
Scheme 1. Cycloisomerization with concomitant 1,2-alkyl shift [Cu] = $CuBF_4$+ligands.[1]

Prior to our work, the silver-promoted cyclization–fragmentation reaction of 5-en-1-yn-3-ols had been reported and correctly interpreted.[6] More recently, an example of a gold/silver-catalyzed cyclization–fragmentation was fortuitously observed and rationalized as a stepwise enyne-Cope rearrangement proceeding via a putative allenol intermediate.[5b]

Recently, we reported a new enantioselective, direct synthesis of the highly prized natural sandalwood odorant (−)-β-santalol (−)-**5**, which is based on a copper-catalyzed cyclization–fragmentation reaction (Scheme 3).[7]



Scheme 3. Synthesis of (−)-β-santalol ((−)-**5**) by cyclization–fragmentation of **3**.[7]



Scheme 2. Enynol cycloisomerization pathways. [M] = MX_n+ligands (M = Au, Pt, Cu).

Herein, we describe the copper(I)-catalyzed cycloisomerization of several 5-en-1-yn-3-ols and an exploratory extension to 6-en-1-yn-4-ols, which has led to the discovery of an unprecedented metathesis fragmentation pathway and has highlighted the complementary reactivity of the copper and gold catalysts.

In a first attempt to generalize the $[Cu(CH_3CN)_4]BF_4$-catalyzed cyclopropanation with concomitant 1,2-H (or 1,2-alkyl) shift (see **1** in Scheme 1),[1] we submitted the seco-analogs **6** and **7**[8] to the same reaction conditions. To our surprise, both diastereomers **6** and **7** overwhelmingly led to the rearranged dienones **8** and **9** (>94%), whereas the expected cyclopropanation/1,2-H shift reaction, which leads to **10**, represented only a very minor pathway (0 to 6%; Table 1). Evidently, the intermediate **H** (or its diastereomer) can also undergo a Grob-type fragmentation, followed by protodemetalation and C−C-double bond isomerization (see also Scheme 2). The cyclopropanation route was however favored to some extent by the use of $PtCl_2$. Moreover, it re-

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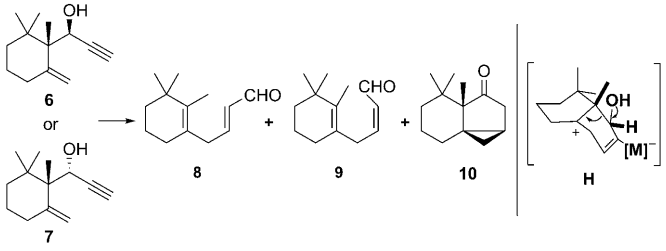
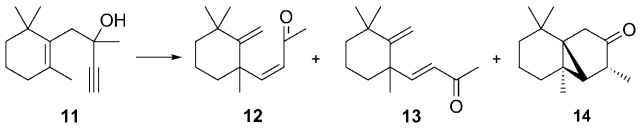
Table 1. Cycloisomerization of **6** and **7**.



Entry	Conditions[a]	GC yield [%]			Combined yield [%][b]
		8	**9**	**10**	
1	**6**, $[Cu(CH_3CN)_4]BF_4$	71	23	6	67
	$Cl(CH_2)_2Cl$, 50 °C, 3 h	76[c]	19	5	62
2	**6**, $PtCl_2$, $Cl(CH_2)_2Cl$, 50 °C, 1 h	30	17	53	78
3	**7**, $[Cu(CH_3CN)_4]BF_4$ toluene, 50 °C, 24 h	>99	0	<1	61
4	**7**, $PtCl_2$, $Cl(CH_2)_2Cl$, 50 °C, 24 h	76	15	9	49

[a] $[Cu(CH_3CN)_4]BF_4$ (5 mol%); $PtCl_2$ (5 mol%). [b] Combined yield of **8**, **9**, and **10**. [c] Yields obtained in toluene, 50 °C, 5 h. [M] = MX*n*+ligands (M = Pt or Cu).

Table 2. Cycloisomerization of **11**.



Entry	Conditions[a]	GC yield [%]		
		12	**13**	**14**
1	$[Cu(CH_3CN)_4]BF_4$ $Cl(CH_2)_2Cl$, 50 °C, 140 min	1	92	7[b]
2	$PtCl_2$ $Cl(CH_2)_2Cl$, 50 °C, 3 h	33	5	62[c]

[a] $[Cu(CH_3CN)_4]BF_4$ (5 mol%); $PtCl_2$ (5 mol%). [b] The epimer of **14** was formed (yield of **13**: 60%). [c] Combined yield of **12**, **13**, and **14**.

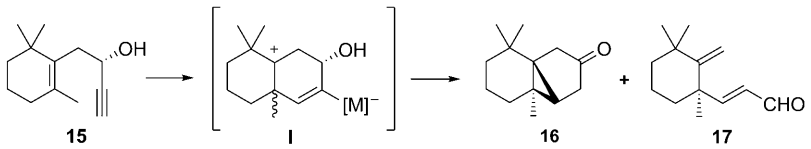
sulted that diastereomers **6** and **7** exhibit different selectivities and reactivities (Table 1, entries 1 and 2 vs. entries 3 and 4).

The ease of fragmentation depends on the ability of the C–C bond to break and to adopt a perpendicular arrangement with respect to the plane defined by the tertiary carbenium-ion system (i.e., parallel to the empty *p* orbital; see intermediate **H** in Table 1; not possible in the example of Scheme 1) and the amount of accompanying strain release.

The same trends were observed with enynol **11**[9] (Table 2). Whereas the copper(I)-catalyzed reaction mostly afforded the cyclization–fragmentation product **13** (Table 2, entry 1), $PtCl_2$ favored the cyclopropanation route (62% of **14**) and dienones **12** and **13** only represented 33 and 5%, respectively, of the product mixture (Table 2, entry 2).

Compared with the tertiary alcohol **11**, the secondary alcohol **15**[2] showed a much higher propensity for the cyclopropanation pathway, but once again, copper catalysis proved to be the most selective (25% of cyclization–fragmentation in toluene; Scheme 4). $[Cu(CH_3CN)_4]BF_4$ in 1,2-dichloroethane gave mainly **16** in excellent yield and $PtCl_2$ led exclusively to **16.** $AgNO_3$ exhibited surprisingly good reactivity for the cyclopropanation reaction (**16**/**17** = 89:11).

Apparently in this case the fragmentation pathway is disfavored as a result of the diminished strain in intermediate **I** (Scheme 4). The ease of fragmentation could also be related to the likelihood or not of **E** (Scheme 2) to undergo a 1,2-R-shift (electrophilicity of the carbenoid and migration aptitude (H > CH_3)). In addition, the use of the copper reagent is supposed to favor the fragmentation pathway because it leads to an intermediate of type **D** (Scheme 2), which has more localized charges. The smaller size and marginal relativistic effects in copper as compared to gold (or platinum)



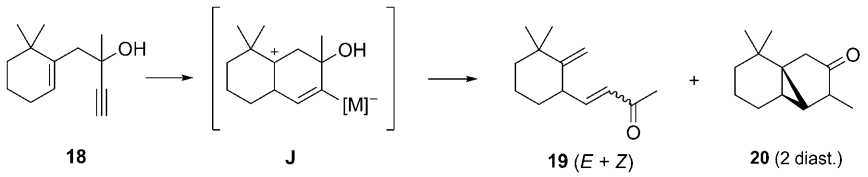
(S)-**15** (70% *ee*)	$[Cu(CH_3CN)_4]BF_4$ (5 mol %)			
	toluene / 70 °C / 1 h	75 (65% *ee*)	25 (63% *ee*)	(67%) [a]
	or $Cl(CH_2)_2Cl$ / 50 °C / 1 h	94 (59% *ee*)	6	(96%) [a]
(S)-**15** (70% *ee*)	$PtCl_2$ (2 mol %)			
	$Cl(CH_2)_2Cl$ / 50 °C / 1 h	100 (37% *ee*)	0	(89%)
(±)-**15**	$AgNO_3$ (10 mol %), KNO_3 (1 equiv)			
	THF / H_2O = 2:1 / 70 °C / 8 h	89	11	(74%) [a]

Scheme 4. Cycloisomerization of **15** with chirality transfer. [a] Combined yield of **16** and **17**. [M] = MX*n*+ligands (M = Cu, Pt, Ag).

might explain why cationic copper complexes are less efficient in stabilizing an adjacent carbocation by backdonation and likewise disfavor the formation of cyclopropylcarbenes (Scheme 2).[10]

The copper-catalyzed reactions exhibit a remarkably high degree of chirality transfer for both the cyclization–fragmentation and the cyclopropanation reactions. The fact that **16** and **17** belong to the same enantiomeric series[11] and show practically the same *ee* value is only possible if the two diastereomeric intermediates **I** (**I**^{1} and **I**^{2} of unknown proportion) evolve both to give **16** and **17** with a 3:1 selectivity.[2b]

The reactivity of **18**[12] (Scheme 5), which contains a trisubstituted C–C double bond, is particularly interesting, as intermediate **J** could in principle also undergo dehydration



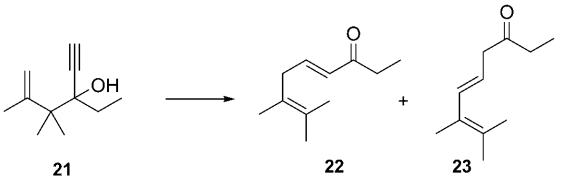
$[Cu(CH_3CN)_4]BF_4$ (5 mol %)	72 : 23	:	2 : 3	73% [a] yield **19** (*E*): 53%
$PtCl_2$ (5 mol %)	20 : 38	:	4 : 38	55% [a]

Scheme 5. Cycloisomerization of **18**. [a] $ClCH_2CH_2Cl$, 50 °C, 30 min.; combined yield of **19** and **20**. [M] = MX*n*+ligands (M = Cu and Pt).

and aromatization, in close analogy to the findings of Barriault and co-workers.[5c]

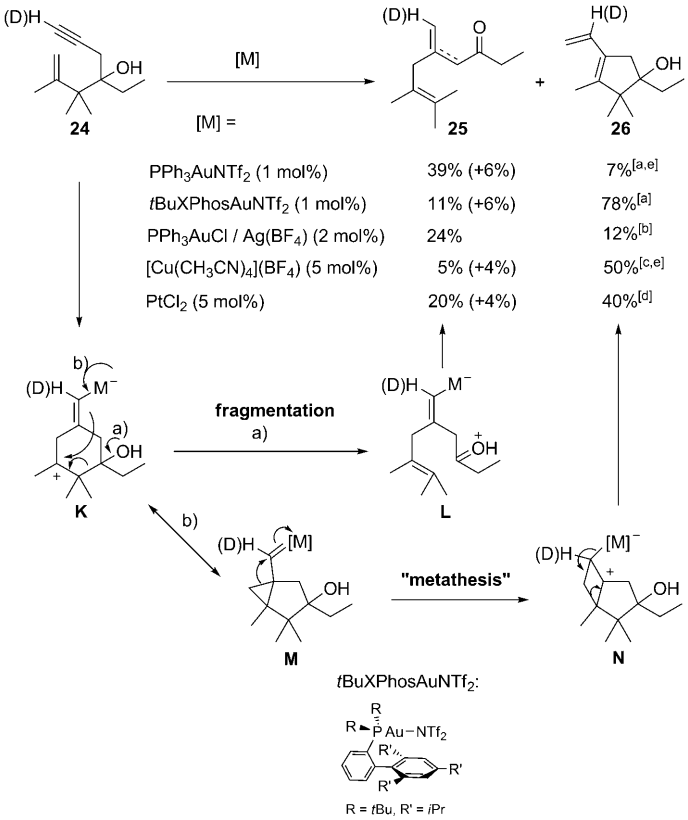
In the event, no dehydration product was detected and the expected products **19** and **20** were formed exclusively. Whereas Cu^I again greatly favored the cyclization–fragmentation reaction, $PtCl_2$ also afforded substantial amounts of cyclopropanation product **20** (Scheme 5).

Finally, the sterically encumbered acyclic propargylic alcohol **21** gave rise exclusively to the cyclization–fragmentation reaction, independent of the nature of the metal (Au, Pt, or Cu; Scheme 6).[13]



$PPh_3AuCl / Ag(BF_4)$ (2 mol %)	100	:	0	56%[a]
$PtCl_2$ (5 mol %)	83	:	17	72%[b,d]
$[Cu(CH_3CN)_4]BF_4$ (5 mol %)	74	:	26	80%[c,d]

Scheme 6. [a] CH_2Cl_2, 0 °C, 24 h. [b] Toluene, 70 °C, 4 h. [c] $ClCH_2CH_2Cl$, 70 °C, 210 min. [d] Combined yield of **22** and **23**.

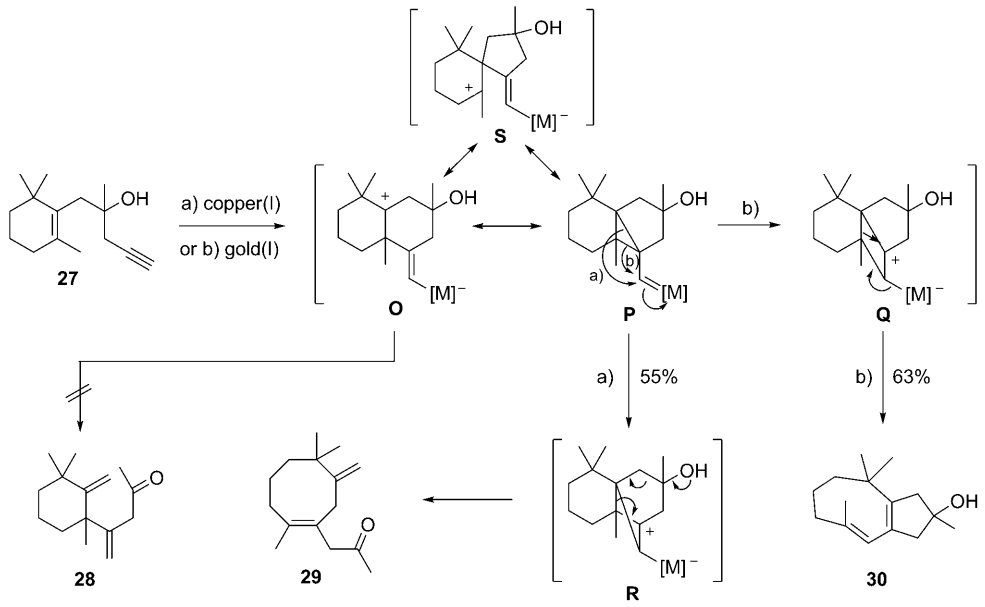


Scheme 7. [a] CH_2Cl_2, 0 °C, 1 h. [b] CH_2Cl_2, 20 °C, 150 min. [c] $ClCH_2CH_2Cl$, 50 °C, 75 min; + formation of 20% of an isomer of **26** (1,5-[H]-rearrangement product according to NMR). [d] $ClCH_2CH_2Cl$, 70 °C, 45 min. [e] Reaction performed on [H]**24** and [D]**24**.

As one of the prerequisites for successful fragmentation is the formation of a carbenium ion in γ-position towards the OH group (regardless of the position of the acetylene), we next explored the reactivity of 6-en-1-yn-4-ols such as enynol **24**[14] in the presence of Au, Pt, or Cu catalysts. Interestingly, the fragmentation pathway was observed with each catalyst used: after the initial 6-*exo*-*dig* cyclization, **K** undergoes fragmentation to afford, after protodemetalation of **L**, ketone **25** (Scheme 7, path a). In competition with the fragmentation pathway, **K** also evolved through the metathesis pathway b; through **M** and **N**)[15] to give variable amounts of the diene alcohol **26**. The shown reaction pathways were further corroborated by performing the reactions with the deuterated compound [D]**24**. This led to the expected products [D]**25** and [D]**26**.

Subtle changes in the nature of the catalyst dramatically change the outcome of the reaction. $[(PPh_3)AuNTf_2]$[5d] and $[PPh_3AuCl]/Ag(BF_4)$ favored the fragmentation with formation of **25**, $[Cu(CH_3CN)_4]BF_4$ and the less electrophilic $[(t\text{BuXPhos})AuNTf_2]$[5d] largely favored the metathesis leading to **26**, and $PtCl_2$ showed intermediate selectivity. This example demonstrates that the aforementioned reactions of 5-en-1-yn-4-ols only in a formal sense represent enyne-Cope rearrangements.[5b]

We next explored the reactivity of enynol **27**[14] in the presence of catalytic amounts of copper(I) or gold(I) catalysts. As compared to **24**, the olefin is part of a ring, and therefore the metathesis reaction would give rise to a synthetically very useful ring enlargement with concomitant



Scheme 8. a) $[Cu(CH_3CN)_4]BF_4$ (5 mol%), $ClCH_2CH_2Cl$, 70°C, 3 h. b) $[(PPh_3)AuNTf_2]$ (1 mol%), CH_2Cl_2, 0°C, 1 h. [M] = $CuBF_4$ or $[AuNTf_2]$ (+ligands).

pentannulation.[16] This reaction mode was indeed followed using $[(PPh_3)AuNTf_2]$ (1 mol%), thus selectively affording (through **P** and **Q**)[15] bicyclic alcohol **30** in 63% yield. On the other hand, $[Cu(CH_3CN)_4]BF_4$ (5 mol%) induced an unprecedented metathesis fragmentation (probably through **P** and **R**) that gave rise to the formation of **29**. The absence of the cyclization–fragmentation product **28** (through fragmentation of **O**) may be due to the fact that intermediate **O** is less strained than **K** (no *gem*-dimethyl group between C^+ and C–OH) (see Scheme 7). Likewise, formal 5-*exo*-*dig* cyclization of **27** would generate a spiro compound **S** which cannot undergo fragmentation (Scheme 8). Based on B3LYP/Lan12*dz*-calculations[17] only species **P**, formed in a concerted manner, could be identified.

In conclusion, we have demonstrated that $[Cu(CH_3CN)_4](BF_4)$ effectively catalyzes the cyclization–fragmentation of 5-en-1-yn-3-ols and have unveiled new fragmentation and metathesis reactions of 6-en-1-yn-4-ols. Further applications of these new reactions are currently under active investigation.

Experimental Section

Synthesis of (±)-13: $[Cu(CH_3CN)_4]BF_4$ (18.2 mg, 0.058 mmol) was added to a solution of **11** (220 mg, 1.07 mmol) in 1,2-dichloroethane (5 mL) at RT under and atmosphere of nitrogen. The mixture was stirred at 50°C for 140 min. The dark-gray mixture was cooled at RT, filtered through a short pad of silica gel and concentrated under reduced pressure. The orange-colored oil (201 mg; **12**/**13**/**14** = 1:92:7)) was purified by chromatography (silica gel; cyclohexane/AcOEt 95:5) to afford **13** (133.0 mg; 60%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (s, 3H), 1.14 (s, 3H), 1.21 (s, 3H), 1.32–1.75 (m, 5H), 1.83–1.92 (m, 1H), 2.26 (s, 3H), 4.93 (s, 1H), 5.06 (s, 1H), 6.07 (d, J = 16.5 Hz, 1H), 6.82 ppm (d, J = 16.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8 (t), 26.9 (q), 29.4 (q), 29.8 (q), 31.5 (q), 36.8 (s), 38.1 (t), 41.0 (t), 42.8 (s), 108.8 (t), 127.6 (d), 158.1 (d), 160.0 (s), 199.2 ppm (s). MS: *m*/*z* (%): 206 $[M]^+$ (21), 191 (58), 173 (18), 163 (42), 149 (27), 147 (36), 135 (65), 133 (47), 123 (81), 107 (78), 91 (54), 81 (44), 43 (100).

Synthesis of 29: $[Cu(CH_3CN)_4]BF_4$ (13.0 mg, 0.042 mmol) was added to a solution of **27** (200 mg, 92% pure; 0.836 mmol) in 1,2-dichloroethane (5 mL) at RT under an atmosphere of nitrogen. The mixture was stirred at 70°C for 3 h. Standard work-up and chromatographic purification (silica gel; cyclohexane/AcOEt 98:2) gave **29** (101.0 mg; 55%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 3H), 1.52–1.56 (m, 4H), 1.64 (t, J = 1.8 Hz, 3H), 2.17 (s, 3H), 2.30–2.39 (broad, 2H), 2.87–2.91 (broad, 2H), 3.13 (s, 2H), 4.72 (broad s,1H), 4.82 ppm (d, J = 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7 (q), 23.7 (t), 29.2 (2q), 29.3 (q), 29.6 (t), 36.7 (t), 38.9 (s), 43.4 (t), 50.0 (t), 110.1 (t), 126.0 (s), 131.1 (s), 158.2 (s), 207.6 ppm (s). MS: *m*/*z* (%): 220 $[M]^+$ (24), 205 (10), 187 (10), 177 (53), 162 (100), 147 (48), 121 (94), 107 (77), 93 (61), 91 (63), 43 (89).

Synthesis of (±)-30: A cooled (0°C) solution of $[(PPh_3)AuNTf_2]$ (13.0 mg, 8.28 μmol) in CH_2Cl_2 (3 mL) was treated with **27** (200 mg, 92% pure; 0.836 mmol) and stirred for 1 h. Standard work-up and chromatographic purification (silica gel; cyclohexane/AcOEt 98:2) gave **30** (116.0 mg; 63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 3H), 1.01 (s, 3H), 1.41 (s, 3H), 1.46–1.54 (m, 1H), 1.65 (split s, 3H), 1.69–1.78 (m, 1H), 1.78–1.86 (m, 2H), 1.93–2.02 (m, 1H), 2.14 (dt, J = 10.7, 2.8 Hz, 1H), 2.35–2.46 (m, 2H), 2.45 (split d, J = 16.4 Hz, 1H), 2.61 (split d, J = 16.4 Hz, 1H), 5.77 ppm (broad s, 1H; NOE with 1.98, but not with 1.65). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5 (q), 23.0 (q), 27.5 (t), 28.6 (q), 34.4 (q), 37.7 (s), 39.7 (t), 42.8 (t), 49.8 (t), 51.4 (t), 77.8 (s), 121.5 (d), 133.1 (s), 145.3 (s), 147.1 ppm (s). MS: *m*/*z* (%): 220 $[M]^+$ (14), 205 (25), 202 (13), 187 (40), 177 (18), 159 (100), 147 (73), 119 (73), 105 (43), 91 (47), 43 (58).

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Keywords: copper · cycloisomerization · fragmentation · gold · rearrangement

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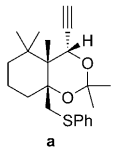

a

[9] Compund **11** was obtained from the corresponding ketone (HCCMgBr (2.2 equiv), $CeCl_3$ (1.2 equiv), LiCl (1.2 equiv), THF, RT (89%).
[10] N. D. Shapiro, F. D. Toste, *Synlett* **2010**, 675.
[11] For the absolute configuration of **16**, see Ref. [2b]. The absolute configuration of **17** was determined by correlation: **17** was oxidized, the resulting acid esterified and the ester side chain hydrogenated: a) $NaClO_2$ (1.15 equiv), isoamylene (4.25 equiv), AcOH (2.3 equiv), H_2O, 45°C, 2 h; b) $Me_2NCH(OMe)_2$ (1.2 equiv), toluene, 110°C, 30 min, separation on chiral capillary column (CP-Chirasil-DEX CB (25 m × 0.25 mm) (Chrompack)): second peak major; c) Raney-Ni-(H_2O) (20%), MeOH, 15 min) to afford an ester $[\alpha]_D^{20}$ +23.6 (c = 1.32, $CHCl_3$) (global yield: 75%) which was identical with compound **6** ($[\alpha]_D^{20}$ +32.7 (c = 1.65, $CHCl_3$)) in: A. Srikrishna, K. Anebouselvy, *J. Org. Chem.* **2001**, *66*, 7102.
[12] Compound **18** was obtained from (6,6-dimethyl-1-cyclohexen-1-yl)-acetaldehyde[2] in three steps: 1) MeLi (1.5 equiv), $CeCl_3$ (1.5 equiv), THF, −78°C, 15 h, 68%; 2) Dess–Martin periodinane (1.3 equiv), CH_2Cl_2, RT, 97%; 3) HCCMgBr (1.2 equiv), THF, RT (53%+starting ketone (25%)).
[13] 4-Ethyl-2,3,3-trimethyl-hept-1-en-5-yn-4-ol possessing a non-terminal acetylene showed lower reactivity: $PtCl_2$ (5 mol%), $ClCH_2CH_2Cl$, 70°C, 5 h gave 5,7,8-trimethyl,4,7-nonadien-3-one (E/Z = 4:1) in 43% yield and the use of $[Cu(CH_3CN)_4]BF_4$ under otherwise identical conditions gave only 14% of rearranged product and 64% of starting material.
[14] Compounds **24** and **27** were prepared by addition of the corresponding methyl ketones to propargylmagnesium bromide (1.5 equiv) in THF in 91 and 47% yield, respectively.
[15] Migration of the cyclopropane C−C bond opposite to the C−C=M bond in **M** (Scheme 7) and P (Scheme 8) leads to the same metathesis product. These reactions proceed via non-classical cations, but for clarity we prefer not to draw partial bonds.
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