Advanced Synthesis & Catalysis

Accepted Article

Title: A Silver-Catalyzed Modular Intermolecular Access to 6,6-Spiroketals

Authors: Alexander Ahrens, Niklas F. Heinrich, Simon R, Kohl, Martha Hokamp, Matthias Rudolph, Frank Rominger, and A. Stephen K. Hashmi

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201900988

Link to VoR: http://dx.doi.org/10.1002/adsc.201900988

10.1002/adsc.201900988

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

A Silver-Catalyzed Modular Intermolecular Access to 6,6-Spiroketals

Alexander Ahrens,[a] Niklas F. Heinrich,[a] Simon R. Kohl,[a] Martha Hokamp,[a] Matthias Rudolph,[a] Frank Rominger,[a][+] A. Stephen K. Hashmi[a,b]*

[a] Organisch-Chemisches Institut, Heidelberg University, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany
Fax: (+49)-6221-54-4205; E-mail: hashmi@hashmi.de; Homepage: http://www.hashmi.de
[b] Chemistry Department, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia
[+] Crystallographic investigation

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A modular synthesis of 6,6-spiroketals *via* silver catalysis is reported. By combining an intermolecular Michael addition and a 6-*endo*-*dig* cyclization, this cascade reaction allows the modular preparation of highly substituted 6,6-spiroketals by combining two substrate molecules. Established methods accessing this interesting substructure are complemented by this new transformation. The protocol tolerates diverse substitution patterns and functional groups.

Keywords: Spiroketals; Silver catalysis; Michael addition; Enones; Alkynes

Introduction

The 6,6-spiroketal moiety is a structural motive of high interest, which can be found in a variety of natural products and other biologically active compounds such as Reveromycines,[1] Rubromycines[2] and Griseusines[3] (Figure 1). For example, Griseusin G and especially F have been found to have cytostatic properties with excellent efficiency against human cell lines of melanoma, breast carcinoma, pancreatic cancer, renal carcinoma and colon cancer. Additionally, they possess antibacterial properties.[4]

Recently Brimble *et al.* published insightful reviews on the potential of Griseusin derivates[3] and spiroketals in natural products.[5] Still, predicting structure-activity relation remains a challenge for biological active molecules. This holds true for Griseusin derivates, too.[6] In order to find efficient and selective bioactive compounds which can be utilized as drugs, derivatization of known compounds and novel synthetic strategies enabling new substitution patterns are needed.

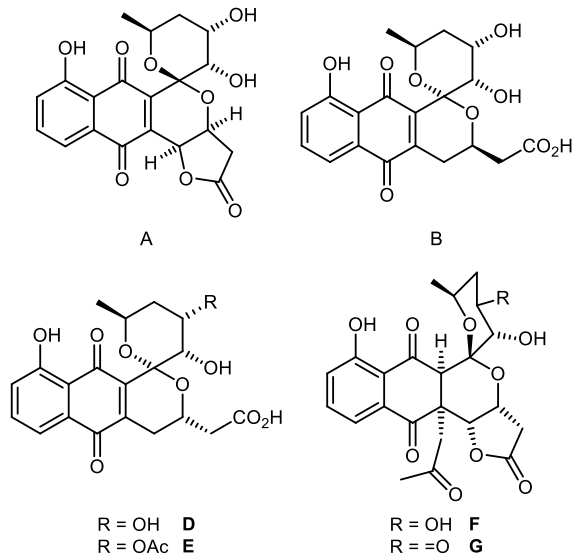


Figure 1. Griseusin derivates found to have interesting biological activity.

The development of synthetic methods towards spiroketals has been an active field in organic synthesis for decades. The most common and widely used path towards spiroketals is based on the intramolecular acid-assisted cyclization of dihydroxy ketones. These intramolecular methods are mild and tolerate a variety of other functional groups, which at the same time limits the modularity of the synthetic approach towards the target molecules; thus often intermolecular convergent synthetic strategies are used.[7] An alternative to this Brønsted acid based approach is the intramolecular cyclization of dihydroxy alkynes *via* π-acid catalysis.[8] This method uses alkynes as less reactive surrogates for a ketone, which enables the use in late stage steps in a complex molecular environment and has been used in several total synthesis, *e.g.* involving gold catalysis.[9] Furthermore, several elegant and enantioselective methods for 6,6-spiroketals have been published

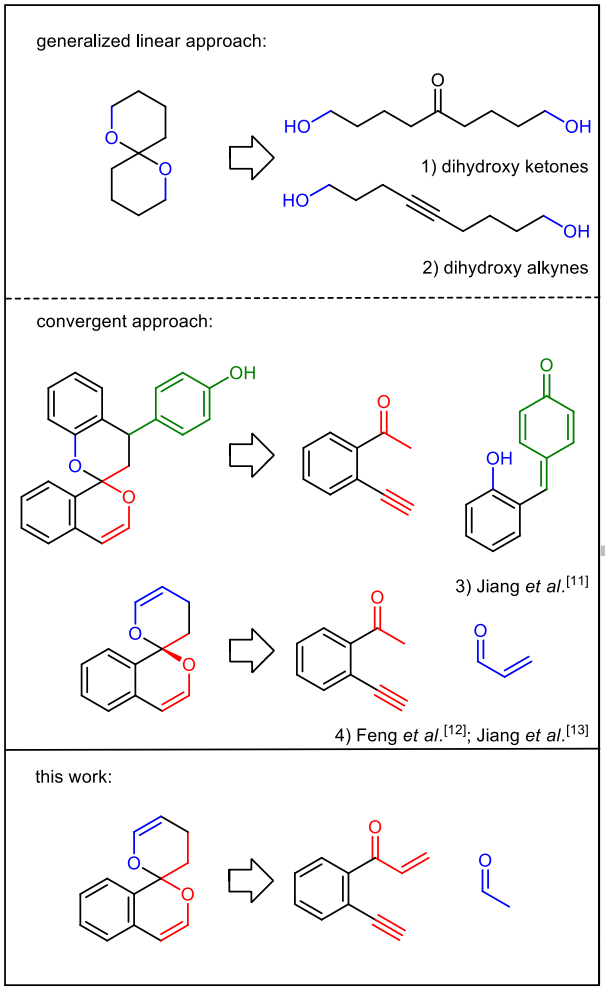
10.1002/adsc.201900988

recently, using different metal salts or organocatalysts.[10] Despite these advances, only a limited number of intramolecular spiroketal formations have been reported, which often require highly reactive compounds such as organolithium compounds or Grignard reagents, accompanied by a low functional group tolerance. Here too, recent works have improved the access to this moiety. Jiang *et al.* introduced a silver salt-mediated transformations using an 1-(2-ethynylphenyl)ethenone and Michael acceptors.[11] The bimetallic and modular approach of Feng *et al.* is also of note, combining a gold-catalyzed cyclization with an enantioselective [4+2] cycloaddition to unsaturated keto esters.[12] Independently, Jiang *et al.* developed an analogous synthetic cut, using silver and scandium synergistic catalysis yielding racemic products.[13]

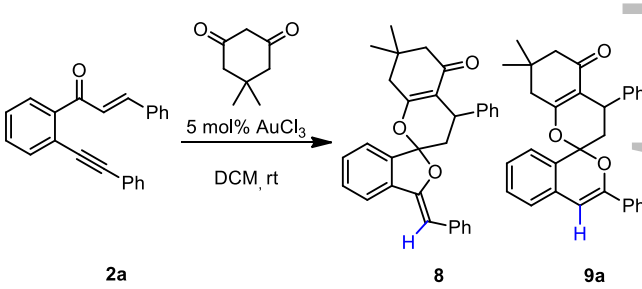
Beyond its appearance in natural products and biologically active compounds of interest, the 6,6-spiroketal motif has been used as skeleton for chiral ligands, enabling various transition-metal-catalyzed asymmetric reactions.[14]
In this light, we set out to develop a mild transition metal-catalyzed synthesis of the spiroketal substructure *via* an intramolecular cyclization and an intermolecular addition to yield the desired scaffold.

Results and Discussion

To access this, we envisioned that a Yamamoto-type[15] π acid catalysis and a Michael addition might deliver a partly unsaturated spiroketal. The cyclization could either proceed as a 5-*exo-dig* or 6-*endo-dig* transformation, with both possible modes contributing a novel and convenient retrosynthetic disconnection (Scheme 1).



Scheme 1. Schematic retrosynthetic disconnections of spiroketals.



Scheme 2. Initial finding of the desired reactivity.

A strong nucleophile would assist the postulated reactivity. Mayr *et al.* investigated the anions of 1,3-diketones in this regard.[16] We deduced that dimedone would be a suitable starting point for our desired transformation. As acceptor a phenyl substituted 1-propenone-5-ethynylbenzene was picked to explore the reactivity.

With 5 mol% $AuCl_3$ in DCM at room temperature a full consumption of the starting material was observed after 16 h. Column chromatography over silica gave both the 5-*exo-dig* and 6-*endo-dig* products as a mixture in an overall yield of 44%. They could be identified by ^{1}H and ^{13}C NMR spectroscopy, as well as HRMS. One of them was very clearly a major product, however, a direct assignment proved difficult at that point (Scheme 2).

Screenings were conducted to identify conditions for a selective and efficient transformation, using 100 mg/ml **2a** in absolute DCM with 1.2 equiv dimedone and 4 Å molecular sieve under air. As keto-enol tautomerism and Michael addition can be influenced by acidic or basic conditions, different additives were tested (Table 1).

10.1002/adsc.201900988

Table 1. Screening of additives with 5 mol% $AuCl_3$ as catalyst.

Entry	Additives	yield **8**[a)]	yield **9a**[a)]
1	none	10%	34%
2	1 equiv Cs_2CO_3	4%	1%
3	10 mol% 2,6-di-*tert*-butylpyridine	3%	33%
4	10 mol% $HNTf_2$	4%	21%
5[b)]	10 equiv H_2O	3%	26%
6	10 mol% Cs_2CO_3	0%	0%

a) Yield and quantity ratio of isomers were determined by ^{1}H NMR spectroscopy with 1,4 dinitrobenzene as internal standard in $CDCl_3$, monitoring the peaks at 6.08 ppm for product **8** and 6.72 ppm for product **9a**. The protons of interest are marked blue in Scheme 2. b) No molecular sieve was added.

Neither the addition of a base nor Brønsted acid additives gave the desired selectivity. Overall, additives diminished the yield, especially with 1 equiv of cesium carbonate as additive. For all reactions (entries 1 to 4) conversions were completed within 16 h. Most likely, the additives induce side reactions or decomposition of the enol ether products, which are known to have a rich chemistry[17] and can easily decompose *via* polymerization or fragmentation reactions. If water was present (entry 5), a slight decrease in yield but a better selectivity was observed. $HNTf_2$ alone decomposed the starting material over the course of 16 h (entry 7), whereas base alone (entry 5) gave no conversion.

Next, different gold(III), gold(I) catalysts as well as other π-acidic transition metal complexes were tested (Table 2).

Notably, gold(III) acetate (entry 2) gave a mixture with poor selectivity, but with inverted major/minor product ratio. None of the other applied gold(III) compounds gave an improvement with respect to gold(III) chloride. The same was true for gold(I) complexes with varying electronic properties. In that series the electron-poor phosphite complex (entry 7) delivered the best yield but only a poor selectivity. Next, different silver(I) salts were tested, which gave good yields at high selectivity. To our delight, the NHC complex IPrAgCl activated by NaBArF gave almost quantitative conversion to a single isomer. Copper(I) catalysts turned out to be less efficient than the silver catalysts. With an optimized yield of 98%, no further optimization was conducted.

Table 2. Screening of catalysts.

Entry	Catalyst (5 mol%)	yield **8**[a)]	yield **9a**[a)]
1	$AuBr_3$	4%	24%
2	$Au(OAc)_3$	35%	23%
3	IPrAu(bph)Cl/NaBArF	0%	0%
4	$IPrAuCl_3$	0%	0%
5	$IPrAu(MeCN)SbF_6$	0%	6%
6	$(Ph)_3PAu(MeCN)SbF_6$	13%	4%
7	$(RO_3P)AuCl$[b)]/NaBArF	18%	30%
8	$AgSbF_6$	1%	77%
9	IPrAgCl	0%	0%
10	IPrAgCl/NaBArF	0%	98%
11	Ag_2CO_3	3%	8%
12	$AgNTf_2$	0%	66%
13	$AgBF_4$	1%	72%
14	AgOTf	0%	76%
15	IPrCuCl/NaBArF	0%	55%

a) Yield and quantity ratio of isomers were determined by ^{1}H NMR with 1,4-dinitrobenzene as internal standard in $CDCl_3$, monitoring the peaks at 6.08 ppm for product **8** and 6.72 ppm for product **9a**. b) R = 2,4-di-tert-butylphenyl

With a selective method in hand, pure product could be obtained by column chromatography and crystals suitable for X-ray single crystal structure analysis were gained by crystallization from DCM and pentane at 4 °C . The analysis enabled the assignment of **9a** being the 6-*exo*-*dig* product (Figure 2).[15]

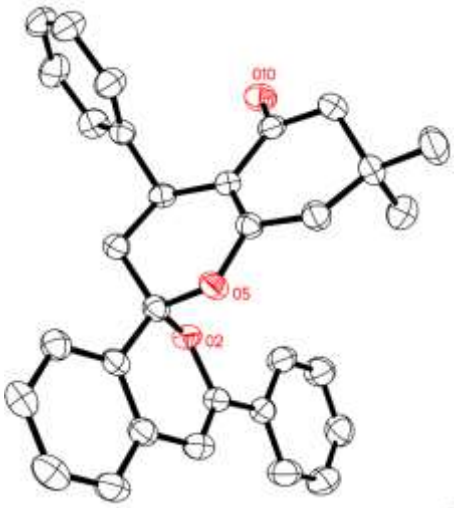


Figure 2. Molecular structure of **9a** in the crystal. Hydrogen atoms were omitted for clarity.[15]

10.1002/adsc.201900988

In addition, the other isomer could be crystallized from a mixture of both products, obtained from a gold(III)-catalyzed reaction, using DCM and pentane at 4 °C. Allowing both compounds to by characterized by X-ray single crystal structure analysis (Figure 3). [18]

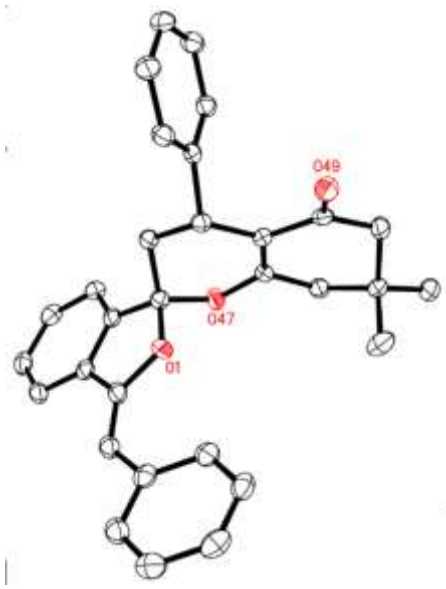
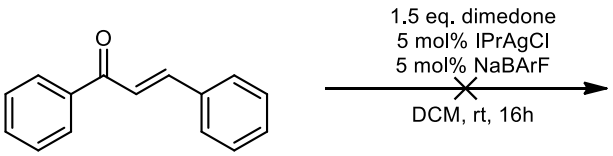


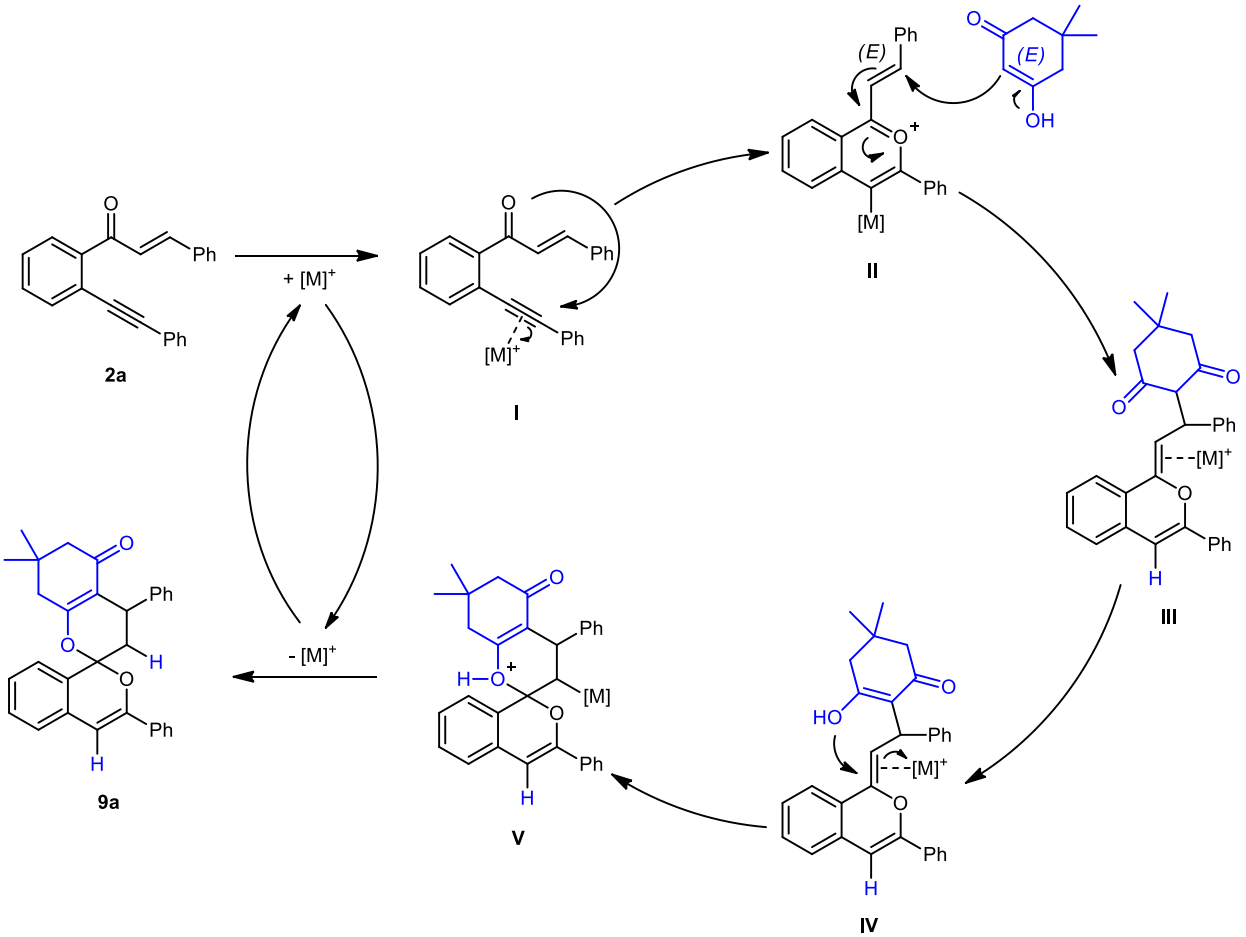
Figure 3. Molecular structure of **8** in the crystal. Hydrogen atoms omitted for clarity.[18]

The intramolecular Yamamoto-type cyclization[15] or the intermolecular Michael addition could be the first step of the transformation. Intramolecular reactions should win over intermolecular ones. To confirm this, (*E*)-chalcone was left to react with dimedone under optimized conditions. (Scheme 3)



Scheme 3. Reaction of (*E*)-chalcone with dimedone under conditions for catalysis.

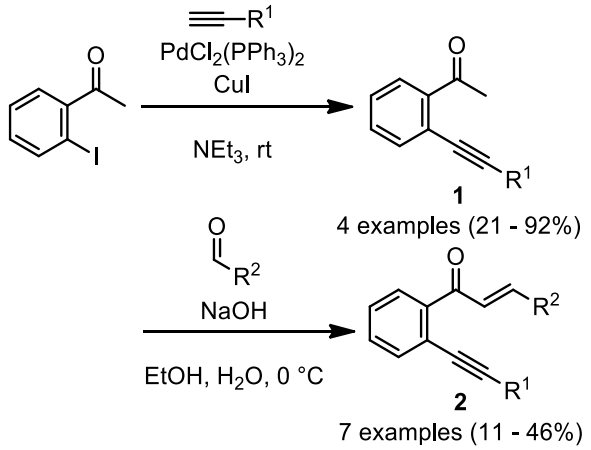
No reaction was observed, as confirmed by TLC and GCMS. On the basis of this experiment and the obtained structures we postulate the following mechanism (Scheme 4). After complexation of the starting material by the carbophilic catalyst $[M]^+$, the carbonyl functionality can attack the activated alkyne, giving intermediate **II**. This intermediate itself is a cationic Michael system and can be attacked by the enol form of dimedone. A proton is released in the process, allowing the protodemetalation of the vinyl metal species. Subsequently, the π-acidic metal cation can now coordinate to and activate the novel enol ether functionality of intermediate **VI**. The 1,3-diketone substructure carries out a nucleophilic attack *via* its oxygen atom on the enol ether, giving intermediate **V.** After protodemetalation, the product is released and the catalyst is regenerated and transferred to the next substrate molecule.



Scheme 4. Postulated mechanism for the spiroketal formation.

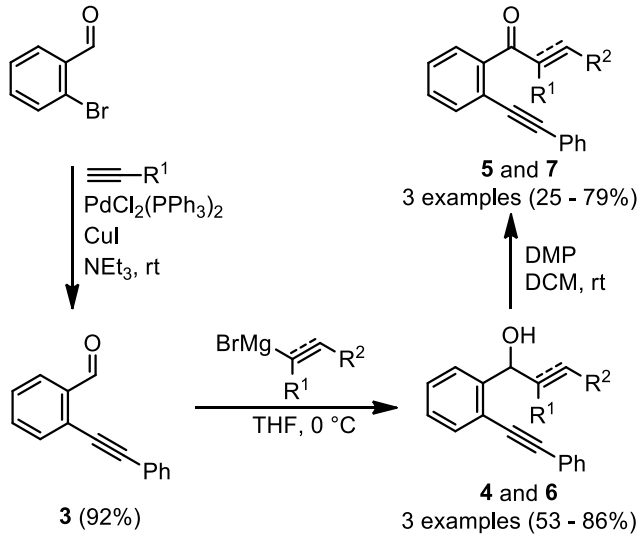
10.1002/adsc.201900988

Next, we set out to determine the synthetic scope of this new transformation. To test the functional group tolerance, as well as the impact of steric and electronic effects, two different strategies towards synthesizing test substrates were applied. The variations of the substitution of the alkyne R^1 and alkene R^2 start from 2-iodoacetophenone (Scheme 5). The alkyne is introduced *via* a Sonogashira coupling. The cheaper alternative 2-bromoacetophenone gave inferior yields under the same conditions (less than 30%). Finally, a cross aldol condensation forms the enone moiety.



Scheme 5. Synthesis of test substrates *via* aldol condensation.

An alternative synthetic approach (Scheme 6) gave access to a wider range of substitution patterns of the enone, as some are not that easily accessible by an aldol reaction. After a Sonogashira coupling, the olefin is introduced by a Grignard addition. The resulting alcohols **4** were then oxidized with Dess-Martin periodinane. The slightly unstable ynone substrate **7** was synthesized in a similar fashion.



Scheme 6. Substrate synthesis via Grignard reaction/oxidation.

Overall, eleven test substrates were obtained (Figure 4) in acceptable to good overall yields.

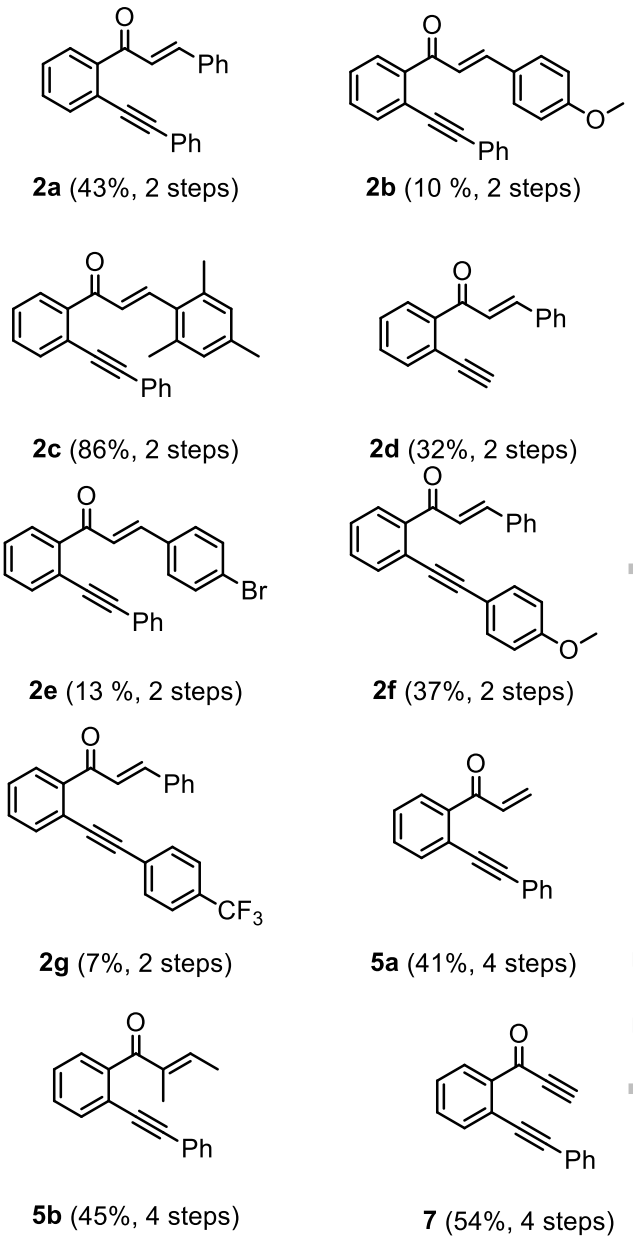
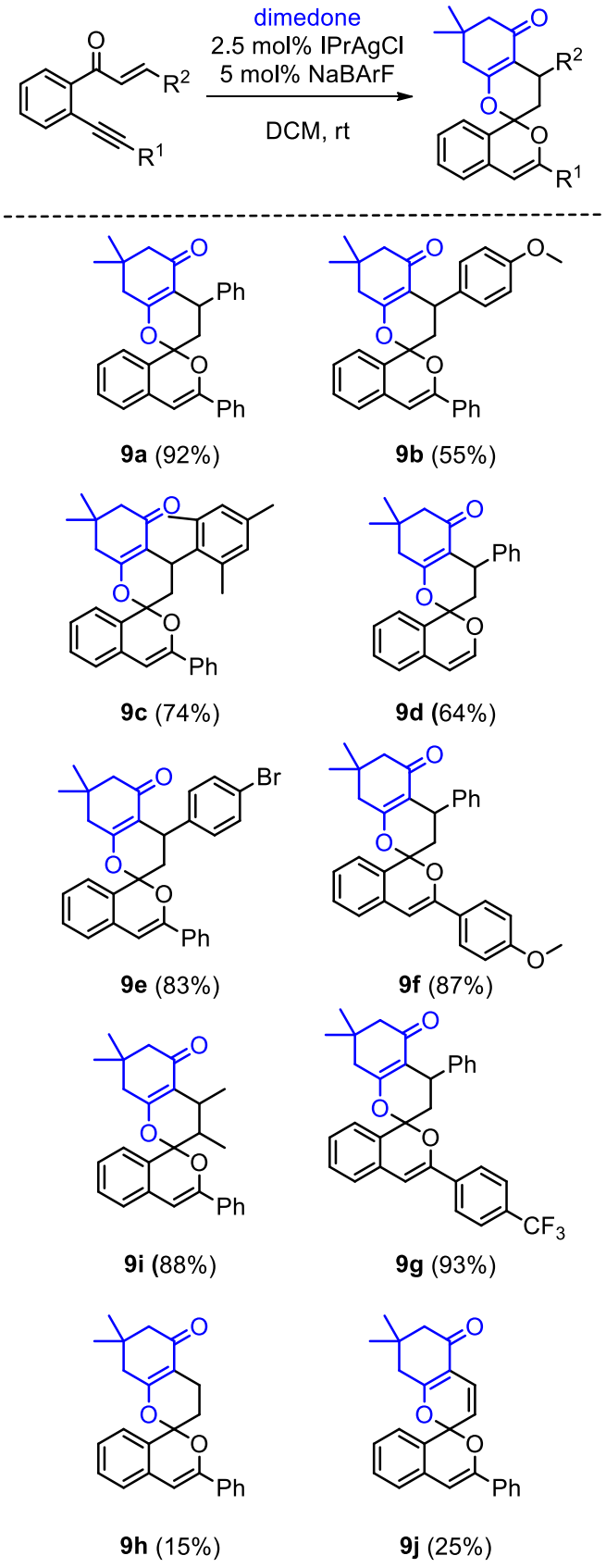


Figure 4. Synthesized test substrates and overall yields.

These test substrates were converted under the optimized conditions in dry DCM with molecular sieve (4 Å), 1.2 equiv of dimedone, but half of the catalyst loading (Scheme 7). The reactions usually took 16-20 h and the products could be purified by column chromatography on silica gel.

10.1002/adsc.201900988



Scheme 7. Catalysis and scope of products.

For all substrates the catalytic transformation was successful and selective. The yields are mostly good, with the exceptions of **8k** and **8i** with yields of 25% and 15%, respectively. This can be explained by the sensitivity of the substrates and products which easily decompose. The other examples demonstrate that the transformation is highly tolerant towards steric and electronic variations of the scaffold. Electron-donating (**9b** and **9f**), electron-withdrawing (**9e** and **9g**) and sterically demanding (**9c**) groups have little influence on the yield. Alkyl-substituted products **9i** can also be obtained in good yields. Brominated compounds **9e** are also accessible in good yield, allowing further functionalization *e.g.* by cross coupling reactions. Although 5 mol% of NaBArF were used while exploring the reaction scope, a later experiment using substrate **2a** confirmed that using 2.5 mol% IPrAgCl and 2.5 mol% NaBArF affected neither the yield nor the reaction time.

The products can be stored in a freezer for months. However, they all show signs of slow decomposition in solution at room temperature. Some products were isolated as a mixture with a second unknown compound with up to 5% impurity as determined by ^{1}H NMR spectroscopy. This compound could not be separated by column chromatography, recrystallization or preparative TLC and could also not be identified.

Next, we tested the applicability of a simple ketone and a silyl enol ether (Figure 5).

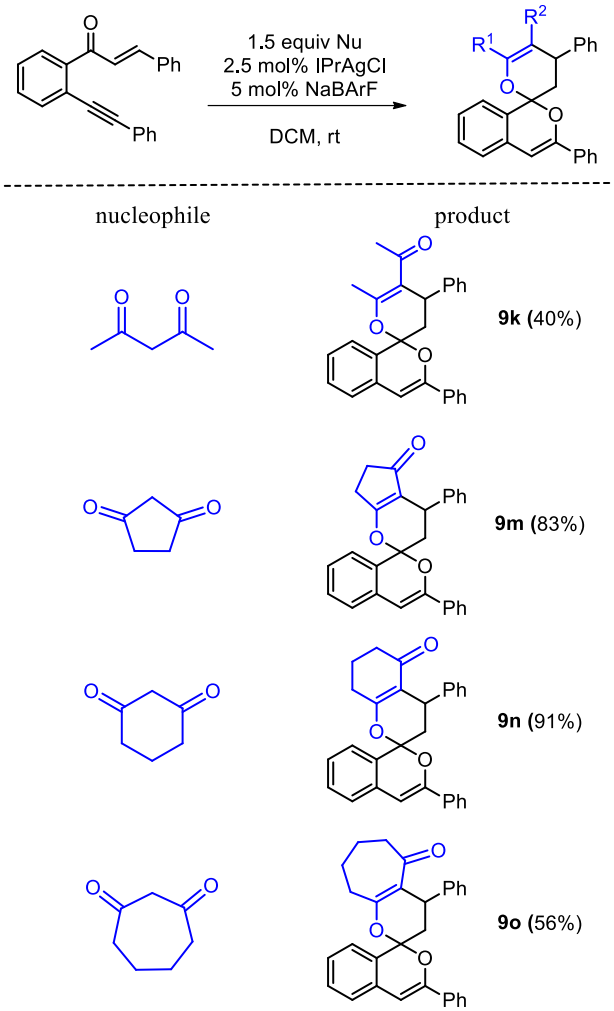
Figure 5. Ketone and silyl enol ether tested as nucleophile.

Again, optimized conditions in dry DCM with molecular sieve (4 Å) and half of the original catalyst loading were used (Scheme 8). As no reaction took place over the course of 16-20 h, additives were tested (Table 3).

Table 3. Reaction conditions for nucleophiles.

Entry	Nucleophile	Additive	Yield
1	acetone	none	0%
2	acetone	3 equiv Cs_2CO_3	0%
3	TMSO-ethene	1.5 equiv CsF	0%
4	TMSO-ethene	1.5 equiv MeOH	0%

However, no improvement could be observed. Other 1,3-diketones were tested as nucleophiles under optimized conditions (Scheme 8).



Scheme 8. Catalysis and scope with 1,3-dicarbonyl compounds as nucleophiles.

The catalysis works well with 1,3-diketones, however, simple acetone – with and without base – showed no conversion, which we attributed to the lower nucleophilicity. The silyl vinyl ether also gave no significant conversion, even in presence of classical activation agents like methanol and fluoride. More flexible 1,3-diketones like acetylacetone and cycloheptane-1,3-dione gave lower yields than their more rigid relatives. Additionally, for cycloheptane-1,3-dione the formation of several unidentified side products was observed.

Conclusion

In conclusion, we have developed a novel highly selective method to prepare diversely substituted 6,6-spiroketals by means of silver catalysis. Due to the high importance as privileged structure in natural products this completely different approach towards this structure nicely complements existing methodologies that are most often based on intramolecular procedures. Our method tolerates a variety of functional groups, allowing easy further manipulation of the products. While some limitations regarding the nucleophile are present, the intermolecular construction of the spirocyclic core should enable modular synthetic approaches which are of high interest for medicinal chemistry. The found reactivity can provide alternative synthetic pathways towards interesting biological active targets such as members of the griseusine family.

Experimental Section

General Procedure for a Silver Catalysis:

In a vial 1 equiv of the substrate, 2.5 mol% of IPrAgCl and1.5 equiv of the nucleophile were dissolved in DCM. Molecular sieve (4 Å) and 2.5 mol% of NaBArF were added at room temperature and the reaction mixture was stirred until the reaction was finished, as confirmed by TLC. The solvent was removed under vacuum and the raw product was purified using column chromatography with silica gel.

(*Z*)-3'-Benzylidene-7,7-dimethyl-4-phenyl-3,4,7,8-tetrahydro-3'H-spiro[chromene-2,1'-isobenzofuran]-5(6H)-one (8)

80 mg (260 µmol) of **2a** was dissolved in 1.5 ml dry DCM. 54.6 mg of dimedone (390 µmol, 1.5 equiv), 84.5 mg of Cs_2CO_3 (260 µmol, 1.0 equiv) and 7.88 mg (26.0 µmol, 10 mol%) $AuCl_3$ were added successively and the reaction mixture was stirred at room temperature for 16 h. After the reaction was finished, as confirmed by TLC, the solvent was removed *in vacuo*. Column chromatography using silica and PE/EA 20/1 as eluent, gave the title compound as a colorless crystalline sold (22 mg, 49.1 µmol, 10/1 **8**/**9a** mixture as determined by ^{1}H NMR spectroscopy, 16%).

R_f (PE/EA 5:1) = 0.44; ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C, TMS): δ = 7.71 – 7.69 (m, 2H), 7.66 – 7.64 (m, 1H), 7.54 – 7.50 (m, 1H), 7.45 – 7.43 (m, 2H), 7.37 – 7.24(m, 6H), 7.22 – 7.18 (m, 1H), 6.12 (s, 1H), 4.19 (ddt, *J* = 11.7, 7.6, 2.1 Hz, 1H), 2.47 – 2.42 (m, 3H), 2.32 (dd, *J* = 17.5, 2.6 Hz, 1H), 2.25 (s, 2H), 1.19 (s, 3H), 1.08 (s, 3H) ppm;^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C): δ = 196.7 (s, 1C), 169.7 (s, 1C), 152.3 (s, 1C), 145.8 (s, 1C), 139.1 (s,1C), 135.9 (s, 2C), 135.5 (s, 1C), 131.2 (d, 1C), 130.0 (d, 1C), 129.2 (d, 2C), 129.1 (d, 2C), 129.1 (d, 2C), 127.6 (d, 1C), 126.9 (d, 1C), 126.5 (d, 1C), 122.8 (s, 1C), 120.6 (s, 1C), 114.8 (s, 1C), 109.3 (s, 1C), 100.13 (d, C), 51.8 (t, 1C), 43.1 (t, 1C), 41.5 (t. 1C), 35.4 (d, 1C), 32.5 (s, 1C), 29.2 (q, 1C), 28.3 (q, 1C) ppm, IR (refl.): $\tilde{\nu}$ = 3058, 3024, 2956, 1661, 1623, 1600, 1493, 1467, 1451, 1426, 1375, 1360, 1286, 1214, 1188, 1159, 1116, 1102, 1076, 1058, 1015, 988, 955, 926, 902, 870, 827, 765, 746, 702, 618 cm^{-1}; HRMS (EI(+), 70 eV): $[C_{31}H_{28}O_3]^+$: calculated 448.2033, found 448.2038; mp = 139 °C.

7,7-Dimethyl-3',4-diphenyl-4,6,7,8-tetrahydrospiro[chromene-2,1'-isochromen]-5(3H)-one (9a)

60.0 mg (195 µmol) of **2a**, 40.9 mg (292 µmol, 1.5 equiv) of dimedone, 5.18 mg (9.80 µmol, 2.5 mol%) of IPrAgCl, 8.44 mg of (9.80 µmol, 2.5 mol%) of NaBArF and 500 µl of DCM were used. After recrystallization from DCM/PE the product was obtained as a yellow crystalline solid (80.2 mg, 179 µmol, 92%).

R_f (PE/EA 5:1) = 0.44; ^{1}H NMR (300 MHz, CD_2Cl_2, 25 °C): δ = 7.70 – 7.67, 7.47 – 7.27, 7.25 – 7.22, 6.72 (s, 1H), 4.36 – 4.29 (s, 1H), 2.82 – 2.64 (m, 2H), 2.32 – 2.06 (m, 4H), 1.11 (s, 3H); 0.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C) δ 196.6 (s, 1C), 167.4 (s, 1C), 149.6 (s, 1C), 146.1 (s, 1C), 134.4 (s, 1C), 131.4 (s,1C), 130.5 (d, 1C), 129.8 (d, 1C), 129.3 (d, 2C), 129.0 (d, 2C), 127.8 (d, 2C), 127.8 (d, 2C), 126.6 (d, 1C), 125.8 (d, 1C), 125.4 (d, 2C), 124.3 (d, 1C), 114.9 (s, 1C), 101.7 (d, 1C), 99.6 (s, 1C), 51.7 (t, 1C), 42.9 (t, 1C), 40.8 (t, 1C), 35.6 (d, 1C), 32.1 (s, 1C), 29.3 (q, 1C), 28.0 (q, 1C) ppm; IR (refl.): $\tilde{\nu}$ = 3027, 2951, 2929, 2857, 1655, 1641, 1620, 1514, 1491, 1465, 1454, 1376, 1358, 1341, 1287, 1257, 1222, 1207, 1159, 1103, 1067, 1042, 1024, 990, 957, 940, 912, 902, 894, 851, 837, 810, 778, 756, 742, 698, 684, 664, 644, 628 cm^{-1}; HRMS (DART(+)): $[C_{31}H_{28}O_3]+H^+$: calculated 449.2111, found 449.2117; mp = 165 °C.

4-(4-Methoxyphenyl)-7,7-dimethyl-3'-phenyl-4,6,7,8-tetrahydrospiro[chromene-2,1'-isochromen]-5(3H)-one (9b)

59.8 mg (176 µmol, 1.0 eq) of **2b,** 29.7 mg (212 µmol, 1.2 eq) of dimedone and 2.40 mg (4.40 µmol, 2.5 mol%) of IPrAgCl were dissolved in 0.5 mL of DCM. Then 3.80 mg (4.40 µmol, 2.5 mol%) of NaBArF were added and the mixture was stirred for 18 h. Purification by preparative TLC (PE:EA = 5:1, R_f = 0.50) gave the title product as orange solid (46.3 mg, 96.8 µmol, 55%).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.70 – 7.65 (m, 2H), 7.44 – 7.40 (m, 3H), 7.38 – 7.35 (m, 2H), 7.33 – 7.29 (m, 2H), 7.26 – 7.22 (m, 2H), 6.92 – 6.87 (m, 2H), 6.69 (s, 1H), 4.38 – 4.31 (m, 1H), 3.82 (s, 1H), 2.83 – 2.77 (m, 1H), 2.74 – 2.66 (m, 1H), 2.31 – 2.26 (m, 1H), 2.26 – 2.21 (m, 1H), 2.20 – 2.15 (m, 1H), 2.14 – 2.08 (m, 1H), 1.12 (s, 3H), 0.94 (s, 3H, *H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ = 196.9 (s, 1C), 167.1 (s, 1C), 158.3 (s, 1C), 149.2 (s, 1C), 137.3 (s, 1C), 134.1 (s, 1C), 131.0 (s, 1C), 130.2 (d, 1C), 129.4 (d, 1C), 129.0 (d, 2C), 128.3 (d, 2C), 128.2 (s, 1C), 127.5 (d, 1C), 125.5 (d, 1C), 125.1 (d, 2C), 123.9 (d, 1C), 115.0 (s, 1C), 114.4 (d, 2C), 101.5 (d, 1C), 99.4 (s, 1C), 55.5 (d, 1C), 51.5 (t, 1C), 42.7 (t, 1C), 40.6 (t, 1C), 34.4 (d, 1C), 31.9 (s, 1C), 29.3 (q, 1C), 27.9 (q, 1C) ppm; IR (refl.): $\tilde{\nu}$ = 2956, 2834, 2248, 1733, 1659, 1625, 1510, 1495, 1456, 1372, 1300, 1287, 1246, 1215, 1176, 1161, 1103, 1069, 1042, 1026, 1042, 1026, 991, 958, 940, 909, 841, 761, 729, 691, 647 cm^{-1}; HRMS (DART(+)): $[C_{32}H_{30}O_4]+H^+$: calculated 479.2217, found 479.2215; mp = 180 °C.

4-Mesityl-7,7-dimethyl-3'-phenyl-4,6,7,8-tetrahydrospiro[chromene-2,1'-isochromen]-5(3H)-one (9c)

50.0 mg (143 µmol, 1.0 eq) of **2c**, 24.0 mg (171 µmol, 1.2 equiv) of dimedone and 1.90 mg (3.60 µmol, 2.5 mol%) of IPrAgCl were dissolved in 0.5 mL of DCM. Then NaBArF (3.10 mg, 3.60 µmol, 2.5 mol%) were added and the mixture was stirred for 18 h. Purification by preparative TLC (PE:EA = 5:1, R_f = 0.43) gave the title product as orange solid (50.2 mg, 106 µmol, 74 %).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ =7.72 – 7.67 (m, 2H), 7.45 – 7.41 (m, 2H), 7.40 – 7.34 (m, 3H), 7.34 – 7.29 (m, 2H), 6.91 (bs, 1H), 6.81 (bs, 1H) 6.71 (s, 1H), 4.85 – 4.78 (m, 1H), 2.97 – 2.89 (m, 1H), 2.65 – 2.57 (m, 1H), 2.50 (s, 3H), 2.36 – 2.27 (m, 1H), 2.34 – 2.26 (m, 1H), 2.33 (s, 3H), 2.27 (s, 3H), 2.18 – 2.13 (m, 1H), 2.05 – 1.99 (m, 1H), 1.05 (s, 3H), 0.88 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ = 197.0 (s, 1C), 165.6 (s, 1C), 149.1 (s, 1C), 137.2 (s, 1C), 136.6 (s, 1C), 135.5 (s, 1C), 134.6 (s, 1C), 134.1 (s, 1C), 131.1 (d, 1C), 131.0 (s, 1C), 130.2 (d, 1C), 129.7 (d, 1C), 129.4 (d, 1C), 128.9 (d, 2C), 128.4 (s, 1C), 127.6 (d, 1C), 125.6 (d, 1C), 124.9 (d, 2C), 123.8 (d, 1C), 116.1 (s, 1C), 101.5 (d, 1C), 99.6 (s, 1C), 51.3 (t, 1C), 42.7 (t, 1C), 34.6 (t, 1C), 32.4 (s, 1C), 29.5 (d, 1C), 29.4 (q, 1C), 28.3 (q, 1C), 21.4 (q, 1C), 21.1 (q, 1C), 20.5 (q, 1C) ppm; IR (relf.): $\tilde{\nu}$ = 2955, 2926, 2869, 1793, 1732, 1661, 1633, 1491, 1456, 1370, 1288, 1213, 1151, 1102, 1068, 1044, 1026, 990, 957, 932, 905. 852, 811, 762, 691, 615 cm^{-1}; HRMS (DART(+)): $[C_{34}H_{34}O_3]+H^+$: calculated 491.2581, found 491.2582; mp = 140 °C.

7,7-Dimethyl-4-phenyl-4,6,7,8-tetrahydrospiro[chromene-2,1'-isochromen]-5(3H)-one (9d)

50.5 mg (217 µmol, 1.0 eq) of **2d,** 36.6 mg (261 µmol, 1.2 equiv) of dimedone and 2.9 mg (5.4 µmol, 2.5 mol%) of IPrAgCl were dissolved in 0.5 mL of DCM. Then 4.6 mg (5.4 µmol, 2.5 mol%) of NaBArF were added and the mixture was stirred for 18 h. Purification by preparative TLC (PE:EA = 2:1, R_f = 0.27) gave the title product as orange solid (51.7 mg, 139 µmol, 64 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.40 – 7.33 (m, 2H), 7.32 – 7.28 (m, 2H), 7.28 – 7.24 (m, 3H), 7.20 – 7.15 (m, 2H), 6.61 (d, ^3J = 6.0 Hz, 1H), 6.06 (d, ^3J = 6.0 Hz, 1H), 4.14 – 4.07 (m, 1H), 2.70 – 2.63 (m, 1H), 2.58 – 2.50 (m, 1H), 2.31 – 2.28 (m, 2H), 2.22 (s, 2H), 1.16 (s, 3H), 1.07 (s, 3H) ppm;^{13}C-NMR (100 MHz, $CDCl_3$,

25°C) δ = 196.7 (s, 1C), 167.2 (s, 1C), 145.3 (s, 1C), 141.6 (d, 1C), 130.1 (d, 1C), 129.6 (s, 1C), 128.8 (d, 2C), 128.3 (s, 1C), 127.7 (d, 1C), 127.3 (d, 2C), 126.4 (d, 1C), 124.8 (d, 1C), 124.2 (d, 1C), 114.8 (s, 1C), 105.8 (d, 1C), 98.9 (s, 1C), 51.3 (t, 1C), 42.7 (t, 1C), 40.8 (t, 1C), 35.1 (d, 1C), 31.9 (s, 1C), 29.7 (q, 1C), 27.9 (q, 1C) ppm; IR (refl.): $\tilde{\nu}$ = 3062, 3027, 2958, 2890, 2870, 2247, 1732, 1712, 1659, 1629, 1492, 1468, 1454, 1374, 1215, 1162, 1102, 1068, 1041, 990, 960, 941, 911, 881, 844, 772, 757, 732, 699, 659, 646, 612 cm^{-1}; HRMS (DART(+)): $[C_{25}H_{24}O_3]+H^+$: calculated 373.1798, found 373.1796; mp = 107 °C.

4-(4-Bromophenyl)-7,7-dimethyl-3'-phenyl-4,6,7,8-tetrahydrospiro[chromene-2,1'-isochromen]-5(3H)-one (9e)

20.7 mg (53.5 µmol, 1.0 equiv) of **2e**, 8.99 mg (64.1 µmol, 1.2 eq) of dimedone and 0.7 0mg (1.40 µmol, 2.5 mol%) of IPrAgCl were dissolved in 0.1 mL of DCM. Then 1.20 mg (1.40 µmol, 2.5 mol) of NaBArF were added and the mixture was stirred for 20 h. Purification by column chromatography (PE:EA = 20:1, R_f = 0.41) gave the title product as orange solid (23.3 mg, 44.4 µmol, 83%).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.66 – 7.63 (m, 2H), 7.47 – 7.43 (m, 3H), 7.40 – 7.35 (m, 4H), 7.34 – 7.30 (m, 2H), 7.20 – 7.18 (m, 2H), 6.69 (s, 1H), 4.35 – 4.31 (m, 1H), 2.81 – 2.76 (m, 1H), 2.66 – 2.61 (m, 1H), 2.30 – 2.26 (m, 1H), 2.26 – 2.20 (m, 1H), 2.20 – 2.16 (m, 1H), 2.16 – 2.10 (m, 1H), 1.10 (s, 3H), 0.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ = 196.9 (s, 1C), 167.7 (s, 1C), 149.1 (s, 1C), 144.1 (s, 1C), 133.9 (s, C), 132.0 (d, 2C), 131.0 (s, 1C), 130.4 (d, 1C), 129.5 (d, 1C), 129.1 (d, 2C), 129.0 (d, 2C), 127.8 (s, 1C), 127.6 (d, 1C), 125.6 (d, 1C), 125.0 (d, 2C), 123.9 (d, 1C), 120.1 (s, 1C) 114.2 (s, 1C), 101.5 (d, 1C), 99.2 (s, 1C), 51.3 (t, 1C), 42.6 (t, 1C), 40.2 (t, 1C), 34.8 (d, 1C), 32.0 (s, 1C), 29.3 (q, 1C), 27.9 (q, 1C) ppm; IR (refl.): $\tilde{\nu}$ = 2962, 2926, 2846, 1640, 1615, 1510, 1480, 1464, 1373, 1358, 1338, 1292, 1265, 1222, 1205, 1113, 1076, 1053, 1021, 990, 958, 945, 916, 900, 850, 843, 812, 778, 758, 740, 700, 684, 662, 644 $cm^{-1;}$ HRMS (EI(+)): $[C_{31}H_{27}O_3Br]$: calculated 526.1144, 528.1123; found 526.1107; 528.1130; mp = 195 °C.

3'-(4-Methoxyphenyl)-7,7-dimethyl-4-phenyl-4,6,7,8-tetrahydrospiro[chromene-2,1'-isochromen]-5(3H)-one (9f)

50.0 mg (148 µmol, 1.0 equiv) of **2f**, 31.1 mg (222 µmol, 1.5 equiv) of dimedone, 1.90 mg (3.70 µmol, 2.5 mol %) of IPrAgCl, 3.20 mg (3.70 µmol, 2.5 mol%) of NaBArF and 500 µl of DCM were used. After column chromatography using PE/EA 10:1 and recrystallization from DCM/PE the product was obtained as a white solid (61.5 mg, 128 µmol, 87%).

R_f (PE/EA 5:1) = 0.18; ^{1}H NMR (300 MHz, C_6D_6, 25 °C, TMS): δ = 7.72 – 7.66 (m, 2H), 7.41 – 7.35 (m, 2H), 7.32 – 7.25 (m, 2H), 7.22 – 7.18 (m, 1H), 7.14 – 6.91 (m, 4H), 6.80 – 6.74 (m, 2H), 6.49 (s, 1H, H7), 4.70 – 4.59 (m, 1H), 3.24 (s, 3H), 2.64 – 2.58 (m, 2H), 2.10 (s, 2H), 2.05 – 1.92 (m, 2H), 0.80 (s, 3H), 0.58 (s, 3H) ppm; ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 194.9 (s, 1C), 166.0 (s, 1C), 161.2 (s, 1C), 149.5 (s, 1C), 145.9 (s, 1C), 131.8 (s, 1C), 129.9 (d, 1C), 128.8 (d, 1C), 128.3 (d, 1C), 128.2 (s, 1C), 127.8 (d, 2C), 126.9 (s 1C), 126.7 (d, 2C), 126.4 (d, 2C), 125.1 (d, 1C), 124.2 (d, 1C), 115.1 (s, 1C, C18), 114.5 (d, 2C), 100.0 (d, 1C), 99.4 (s, 1C), 54.9 (q, 1C), 51.3 (t, 1C), 42.4 (t, 1C), 40.8 (t, 1C), 35.8 (d, 1C), 31.4 (s, 1C), 28.7 (t, 1C), 27.6 (t, 1C) ppm; IR (refl.): $\tilde{\nu}$ = 2952, 1738, 1657, 1630, 1601, 1511, 1490, 1464, 1452, 1421, 1375, 1291, 1247, 1216, 1177, 1161, 1114, 1104, 1065, 1044, 1031, 989, 960, 937, 913, 841, 811, 799, 776, 754, 742, 703, 675, 643, 628 cm^{-1}; HRMS (EI(+)): calcd. for $[C_{32}H_{30}O_4]^+$: calculated 478.21386, found 478.21263; mp = 183 °C.

7,7-Dimethyl-4-phenyl-3'-(4-(trifluoromethyl)phenyl)-4,6,7,8-tetrahydrospiro[chro- mene-2,1'-isochromen]-5(3H)-one (9g)

48.7 mg (129 µmol, 1.0 equiv) of **2g**, 27.2 mg (194 µmol, 1.5 equiv) of dimedone, 1.71 mg (3.33 µmol, 2.5 mol %) of IPrAgCl, 2.88 mg (3.44 µmol, 2.5 mol %) of NaBArF and 500 µl of DCM were used. After recrystallization from DCM/PE the product was obtained as a yellow crystalline solid (55.5 mg, 120 µmol, 93%).

R_f (PE/EA 5:1) = 0.48; ^{1}H- NMR (300 MHz, C_6D_6, 25 °C, TMS): δ = 7.56 – 7.52 (m, 2H), 7.40 – 7.36 (m, 2H), 7.35 – 7.26 (m, 4H), 7.22 – 7.17 (m, 1H), 7.15 – 6.92 (m, 4H), 6.46 (s, 1H), 4.58 – 4.50 (m, 1H), 2.57 (d, *J*=9.4 Hz, 2H), 2.10 – 1.78 (m, 4H), 0.77 (s, 3H), 0.51 (s, 3H) ppm, ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 194.8 (s, 1C), 165.6 (s, 1C), 147.8 (s, 1C), 145.6 (s, 1C), 137.6 (s, 1C), 130.7 (s, 1C), 130.0 (d, 2C), 128.9 (d, 2C), 128.3 (d, 1C), 128.2 (s, 1C), 128.1 (d, 1C), 127.9 (s, 1C), 127.7 (d, 2C), 126.5 (d, 1C), 126.0 (s, 1C), 125.6 (d, 1C), 125.2 (d, 2C), 124.3 (d, 1C), 115.0 (s, 1C), 103.6 (d, 1C), 99.2 (s,1C), 51.3 (t, 1C), 42.3 (t, 1C), 40.7 (t, 1C), 35.7 (d, 1C), 31.5 (s, 1C), 28.4 (t, 1C), 27.7 (t, 1C) ppm; ^{19}F NMR (283 MHz, C_6D_6, 25 °C): δ = -62.29 (s) ppm; IR (refl.): $\tilde{\nu}$ = 3052, 2980, 2876, 2860, 1732, 1725, 1660, 1625, 1495, 1470, 1458, 1370, 1220, 1174, 1100, 1065, 1040, 990, 958, 942, 912, 881, 845, 757, 730, 699, 658 cm^{-1}; HRMS (EI(+)): $[C_{32}H_{27}O_3F_3]$+: calculated 516.19068, found 516.19027; mp = 95 °C.

7,7-Dimethyl-3'-phenyl-4,6,7,8-tetrahydrospiro[chromene-2,1'-isochromen]-5(3H)-one (9h)

40.0 mg (172 µmol, 1.0 eq) of **5a**, 29.0 mg (207 µmol, 1.2 equiv) of dimedone and 2.30 mg (4.30 µmol, 2.5 mol%) of IPrAgCl were dissolved in 0.1 mL of DCM. Then 3.70 mg (4.30 µmol, 2.5 mol%) of NaBArF was added and the mixture was stirred for 20 h. Purification by column chromatography (PE:EA = 5:1, R_f = 0.29) gave the title product as lightly orange oil (9.80 mg, 26.3 µmol, 15%).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.65 – 7.61 (m, 2H), 7.44 – 7.40 (m, 2H), 7.37 – 7.35 (m, 1H), 7.35 – 7.33 (m, 2H), 7.33 – 7.28 (m, 2H), 6.64 (s, 1H), 2.80 – 2.72 (m, 2H), 2.61 – 2.50 (m, 2H), 2.29 (d, ^3J = 1.9 Hz, 2H), 2.21 – 2.05 (m, 2H), 1.02 (s, 3H), 0.95 (s, 3H) ppm;^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ = 198.5 (s, 1C), 166.9 (s, 1C), 149.3 (s, 1C), 134.3 (s, 1C) 131.1 (s, 1C), 130.1 (d, 1C), 129.4 (d, 1C), 128.9 (d, 2C), 128.7 (s, 1C), 127.5 (d, 1C), 125.5 (d, 1C), 125.1 (d, 2C), 123.9 (d, 1C), 111.1 (s, 1C), 101.3 (d, 1C), 99.3 (s, 1C), 51.1 (t, 1C), 42.4 (t, 1C), 32.5 (s, 1C), 28.7 (q, 1C), 28.6 (t, 1C), 28.4 (q, 1C), 14.9 (t, 1C) ppm, IR (refl.): $\tilde{\nu}$ = 3050, 3022, 2980, 1660, 1618, 1597, 1492, 1465, 1450, 1363, 1355, 1280, 1216, 1190, 1149, 1123, 1102, 1066, 1015, 986, 953, 902, 865, 820, 763, 742, 700, 625 cm^{-1}; HRMS (DART(+)): $[C_{25}H_{24}O_3]+H^+$: calculated 373.1798, found 373.1798.

3,4,7,7-Tetramethyl-3'-phenyl-4,6,7,8-tetrahydrospiro [chromene-2,1'-isochromen]-5(3H)-one (9i)

50.0 mg (192 µmol, 1.0 eq) of **5b**, 32.3 mg (230 µmol, 1.2 equiv) of dimedone and 2.60 mg (5.00 µmol, 2.5 mol%) of IPrAgCl were dissolved in 0.5 mL of DCM. Then 4.33 mg (5.00 µmol, 2.5 mol%) of NaBArF were added and the mixture was stirred for 18 h. Purification by preparative TLC (PE:EA = 4:1, R_f = 0.41) gave the title product as colorless solid (67.6 mg, 168 µmol, 89%).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.61 – 7.57 (m, 2H), 7.44 – 7.39 (m, 2H), 7.35 – 7.31 (m, 3H), 7.31 – 7.287 (m, 2H), 6.59 (s, 1H), 2.83 – 2.74 (m, 1H), 2.53 – 2.44 (m, 1H), 2.31 – 2.24 (m, 1H), 2.21 – 2.15 (m, 1H), 2.15 – 2.10 (m, 1H), .02 – 1.95 (m, 1H), 1.44 (d, ^3J = 6.5 Hz, 1H^5), 1.14 (d, ^3J = 6.5 Hz, 1H), 1.03 (s, 3H), 0.89 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ = 198.1 (s, 1C), 165.1 (s, 1C), 149.3 (s, 1C), 134.2 (s, 1C), 131.6 (s, 1C), 129.9 (d, 1C), 129.3 (d, 1C), 128.9 (d, 2C), 127.5 (s, 1C), 127.4 (d, 1C), 125.7 (d, 1C), 124.9 (d, 2C), 124.7 (d, 1C), 117.6 (s, 1C), 102.0 (s, 1C), 100.5 (d, 1C), 51.8 (t, 1C), 42.5 (t, 1C), 41.7 (d, 1C), 31.7 (s, 1C), 30.2 (d, 1C), 29.4 (q, 1C), 27.4 (q, 1C), 18.7 (q, 1C), 15.9 (q, 1C) ppm; IR (refl.): $\tilde{\nu}$ = 3025, 1690, 1653, 1634, 1558, 1492, 1450, 1353, 1260, 1177, 1150, 1120, 1067, 1023, 868, 811, 754, 730, 682 cm^{-1}; HRMS (DART(+)): $[C_{27}H_{29}O_3]+H^+$: calculated 401.2111, found 401.2108; mp = 78 °C.

7,7-Dimethyl-3'-phenyl-7,8-dihydrospiro[chromene-2,1'-isochromen]-5(6*H*)-one (9j)

101 mg (440 µmol, 1.0 equiv) of **7**, 74.1 mg (528 µmol, 1.2 equiv) of dimedone and 5.8 mg (11 µmol, 2.5 mol%) of IPrAgCl were dissolved in 0.1 mL of DCM. Then 10.0 mg (11.0 µmol, 2.5 mol%) of NaBArF was added and the mixture was stirred for 20 h. Purification by column chromatography (PE:EA = 10:1, R_f = 0.33) gave the title product as orange solid (40.7 mg, 110 µmol, 25%).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ =7.65 – 7.6 (m, 2H), 7.36 – 7.29 (m, 3H, *H*), 7.24 (dt, ^3J = 7.4 Hz, ^4J = 1.2 Hz, 1H), 7.17 – 7.14 (m, 1H), 7.14 – 7.09 (m, 1H), 6.84 – 6.80 (m, 1H), 6.39 (s, 1H), 4.97 (d, ^3J = 3.4 Hz 1H), 4.81 (d, ^3J = 3.4 Hz 1H), 2.67 – 2.55 (m, 2H), 2.40 – 2.30 (m, 2H), 1.24 (s, 3H), 1.23 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ = 191.8 (s, 1C), 176.1 (s, 1C), 164.8 (s, 1C), 150.3 (s, 1C), 135.4 (s, 1C), 130.8 (s, 1C), 129.8 (s, 1C), 128.9 (d, 1C), 128.9 (d, 1C), 128.5 (d, 2C), 127.4 (d, 1C), 125.6 (d, 2C), 125.2 (d, 1C), 125.1 (d, 1C), 116.1 (s, 1C), 100.9 (d, 1C), 94.6 (t, 1C), 84.1 (s, 1C), 52.2 (t, 1C), 37.9 (t, 1C), 34.4 (s, 1C), 29.0 (q, 1C), 28.9 (q, 1C) ppm; IR (refl.): $\tilde{\nu}$ = 3065, 3030, 2956, 2892, 2871, 2245, 1730, 1715, 1662, 1625, 1482, 1464, 1450, 1380, 1214, 1160, 1103, 1067, 1040, 990, 960, 942, 911, 880, 843, 771, 760, 732, 701, 65**7**, 646, 610 cm^{-1}; HRMS (DART(+)): $[C_{22}H_{23}O_3]+H^+$: calculated 371.1642, found 371.1641; mp = 117 °C.

1-(6'-Methyl-3,4'-diphenyl-3',4'-dihydrospiro[isochromene-1,2'-pyran]-5'-yl)ethan-1-one (9l)

50.0 mg (162 µmol. 1.0 equiv) of **2a**, 24.4 mg (243 µmol, 25.0 µl) of pentane-2,4-dione, 2.15 mg (4.05 µmol, 2.5 mol %) of IPrAgCl, 3.50 mg (4.05 µmol, 2.5 mol%) of NaBArF and 500 µl of DCM were used. After column chromatography using PE/EA 5:1 and recrystallization from DCM/PE the product was isolated as a yellow crystalline solid (26.4 mg, 64.8 µmol, 40%).

R_f (PE/EA 5:1) = 0.28; ^{1}H NMR (300 MHz, C_6D_6, 25 °C, TMS): δ = 7.82 – 7.76 (m, 2H), 7.38 –7.33 (m, 2H), 7.23 – 7.18 (m, 2H), 7.13 – 6.91 (m, 6H), 6.86 – 6.79 (m, 1H), 6.75 – 6.70 (m, 1H), 5.98 (s, 1H), 5.37 – 5.26 (m, 2H), 4.25 – 4.19 (m, 1H), 2.04 (s, 3H), 1.67 (s, 3H) ppm; ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 202.4 (s, 1C), 202.3 (s, 1C), 151.9 (s, 1C), 149.1 (s, 1C), 142.6 (s, 1C), 133.8 (s, 1C), 130.8 (s, 1C), 129.4 (d, 1C), 129.1 (d, 2C), 128.9 (d, 2C), 128.3 (s, 1C), 128.2 (d, 2C), 127.9 (s, 1C), 127.8 (d, 1C), 127.1 (d, 1C), 125.7 (d, 1C), 125.1 (d, 2C), 123.0 (d, 1C), 102.0 (d, 1C), 100.5 (d, 1C), 75.8 (d, 1C), 41.9 (t, 1C), 30.4 (q, 1C), 27.8 (q, 1C) ppm; IR (refl.): $\tilde{\nu}$ = 3028, 1689, 1655, 1629, 1559, 1490, 1453, 1353, 1258, 1178, 1149, 1121, 1077, 1025, 866, 811, 754, 731, 684 cm^{-1}; HRMS (EI(+), 70 eV): $[C_{28}H_{24}O_3]^+$: calculated 408.17200, found 408.17082; mp = 86 °C.

3',4-Diphenyl-6,7-dihydro-3*H*-spiro[cyclopenta[b]pyran-2,1'-isochromen]-5(4*H*)-one (9m)

50.0 mg (162 µmol. 1.0 equiv) of **2a**, 23.8 mg (243 µmol) of cyclopentane-1,3-dione, 2.15 mg (4.05 µmol, 2.5 mol %) of IPrAgCl, 3.50 mg (4.05 µmol, 2.5 mol%) of NaBArF and 500 µl of DCM were used. After column chromatography using PE/EA 7:1 and recrystallization from DCM/PE the

product was isolated as a colorless crystalline solid (55.2 mg, 136 µmol, 83%).

R_f (PE/EA 2:1) = 0.42; ^{1}H NMR (400 MHz, C_6D_6, 25 °C, TMS): δ = 7.70 – 7.64 (m, 2H), 7.28 – 7.17 (m, 5H), 7.15 – 7.10 (m, 3H), 7.08 – 7.02 (m, 2H), 6.99 (td, *J* = 7.4, 1.3 Hz, 1H), 6.93 (dd, J = 7.7, 1.4 Hz, 1H), 6.50 (s, 1H), 4.44 (ddt, *J* = 10.6, 6.4, 2.1 Hz, 1H), 2.54 – 2.34 (m, 2H), 2.04 – 1.84 (m, 4H) ppm; ^{13}C NMR (100 MHz, C_6D_6, 25 °C): δ = 199.8 (s, 1C), 181.0 (s, 1C), 149.5 (s, 1C), 142.1 (s, 1C), 134.4 (s, 1C), 131.2 (s, 1C), 130.1 (d, 1C), 129.5 (d, 1C), 129.1 (d, 2C), 128.4 (d, 1C), 128.8 (d, 2C), 128.2 (d, 2C), 127.4 (d, 1C), 127.0 (d, 1C), 125.5 (d, 1C), 125.2 (d, 2C), 124.2 (d, 1C), 117.5 (s, 1C), 101.8 (s, 1C), 101.8 (d, 1C), 40.2 (t, 1C), 34.6 (s, 1C), 33.8 (t, 1C), 26.2 (t, 1C) ppm; IR (refl.): $\tilde{\nu}$ = 3052, 3032, 2969, 2937, 2898, 1692, 1631, 1603, 1566, 1493, 1455, 1438, 1455, 1438, 1375, 1360, 1291, 1258, 1207, 1155, 1099, 1078, 1062, 1041, 1024, 962, 950, 906, 877, 849, 810, 763, 735, 718, 701, 690, 639 cm^{-1}; HRMS (EI(+), 70 eV): $[C_{28}H_{22}O_3]^+$: calculated 406.15635, found 406.15474; mp = 156 °C.

3',4-Diphenyl-3,4,7,8-tetrahydrospiro[chromene-2,1'-isochromen]-5(6*H*)-one (9n)

50.0 mg (162 µmol. 1.0 equiv) of **2a**, 27.2 mg (243 µmol) of cyclohexane-1,3-dione, 2.15 mg (4.05 µmol, 2.5 mol %) of IPrAgCl, 3.50 mg (4.05 µmol, 2.5 mol%) of NaBArF and 500 µl of DCM were used. After column chromatography using PE/EA 7:1 and recrystallization from DCM/PE the product was isolated as a colorless crystalline solid (61.9 mg, 147 µmol, 91%).

R_f (PE/EA 2:1) = 0.51; ^{1}H NMR (400 MHz, C_6D_6, 25 °C, TMS): δ = 7.73 – 7.67 (m, 2H), 7.33 – 7.23 (m, 4H), 7.15 – 7.10 (m, 3H), 7.09 – 6.90 (m, 4H), 6.52 (s, 1H), 4.59 (ddd, *J* = 10.6, 8.1, 2.3 Hz, 1H), 2.60 – 2.50 (m, 2H), 2.15 (dtd, *J* = 17.0, 4.4, 1.2 Hz, 1H), 2.00 – 1.88 (m, 2H), 1.79 (dddd, *J* = 18.0, 10.9, 4.9, 2.8 Hz, 1H), 1.52 – 1.36 (m, 1H), 1.23 (dt, *J* = 13.2, 4.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, C_6D_6, 25 °C): δ = 194.7 (s, 1C), 167.7 (s, 1C), 149.5 (s, 1C), 145.8 (s, 1C), 134.5 (s, 1C), 131.4 (s, 1C), 129.9 (d, 1C), 129.4 (d, 1C), 129.0 (d, 2C), 128.8 (d, 2C), 128.7 (s, 1C), 128.4 (d, 1C), 127.9 (s, 1C), 127.6 (d, 1C), 127.3 (d, 1C), 126.4 (d, 1C), 125.4 (d, 1C), 125.2 (d, 2C), 124.2 (d, 1C), 116.7 (s, 1C), 101.8 (d, 1C), 99.2 (d, 1C), 40.7 (t, 1C), 37.2 (t, 1C), 35.6 (d, 1C), 28.8 (t, 1C), 20.2 (t, 1C) ppm; IR (refl.): $\tilde{\nu}$ = 3057, 3031, 2939, 2896, 1750, 1654, 1618, 1491, 1454, 1427, 1373, 1336, 1294, 1262, 1234, 1216, 1192, 1160, 1126, 1104, 1077, 1041, 1026, 1017, 984, 947, 922, 905, 881, 819, 767, 699, 660, 624 cm^{-1}; HRMS (EI(+), 70 eV): $[C_{29}H_{24}O_3]^+$: calculated 420.17200, found 420.17231; mp = 143 °C.

3',4-diphenyl-6,7,8,9-tetrahydro-3*H*-spiro[cyclohepta[*b*]pyran-2,1'-isochromen]-5(4*H*)-one (9o)

50.0 mg (162 µmol. 1.0 equiv) of **2a**, 20.6 mg (243 µmol) of cycloheptane-1,3-dione, 2.15 mg (4.05 µmol, 2.5 mol %) of IPrAgCl, 3.50 mg (4.05 µmol, 2.5 mol%) of NaBArF and 500 µl of DCM were used. After column chromatography using PE/EA 7:1 and recrystallization from DCM/PE the product was isolated as a yellow solid (39.4 mg, 90.7 µmol, 56%), containing an unknown contamination that could not be separated.

R_f (PE/EA 2:1) = 0.48; ^{1}H NMR (400 MHz, C_6D_6, 25 °C, TMS): δ = 7.77 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.37 – 7.32 (m, 2H), 7.24 (dd, *J* = 8.5, 6.8 Hz, 3H), 7.12 – 6.99 (m, 5H), 6.55 (s, 1H), 4.79 (dd, *J* = 10.2, 8.9 Hz, 1H), 2.58 – 2.49 (m, 2H), 2.32 – 2.19 (m, 2H), 2.15 – 2.06 (m, 2H), 1.38 (dt, *J* = 7.4, 4.5 Hz, 2H), 1.31 – 1.25 (m, 2H) ppm; ^{13}C NMR (100 MHz, C_6D_6, 25 °C): δ = 200.0 (s, 1C), 163.5 (s, 1C), 149.5 (s, 1C), 146.1 (s, 1C), 134.6 (s, 1C), 131.5 (s, 1C), 129.8 (d, 1C), 129.4 (d, 1C), 129.0 (d, 2C), 128.8 (d, 2C), 128.4 (d, 2C), 128.0 (s, 1C), 127.9 (d, 1C), 127.2 (d, 1C), 126.4 (d, 1C), 125.3 (d, 2C), 124.2 (d, 1C), 119.4 (s, 1C), 101.6 (d, 1C), 98.7 (s, 1C), 42.3 (t, 1C), 40.2 (t, 1C), 38.1 (d, 1C), 32.0 (t, 1C), 23.6 (t, 1C), 21.2 (t, 1C) ppm; IR (refl.): $\tilde{\nu}$ = 3060, 3027, 2935, 2866, 1953, 1723, 1697, 1633, 1602, 1493, 1454, 1343, 1289, 1216, 1172, 1124, 1099, 1074, 1043, 1027, 99, 972, 946, 910, 865, 814, 754, 699, 640 cm^{-1}; HRMS (EI(+), 70 eV): $[C_{29}H_{24}O_3]^+$: calculated 434.18765, found 434.18905; mp = 78 °C.

References

[1] a) H. Takahashi, H. Osada, H. Koshino, M. Sasaki, R. Onose, M. Nakakoshi, M. Yoshihama, K. Isono, *J. Antibiot.* **1992**, *45*, 1414-1419; b) T. Shimizu, T. Usui, M. Fujikura, M. Kawatani, T. Satoh, K. Machida, N. Kanoh, J.-T. Woo, H. Osada, M. Sodeoka, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3756-3760.

[2] M. Brasholz, S. Sörgel, C. Azap, H.-U. Reißig, *Eur. J. Org. Chem.* **2007**, *34*, 3801-3814.

[3] B. J. Naysmith, P. A. Hume, J. Sperry, M. A. Brimble, *Nat. Prod. Rep.* **2017**, *34*, 25-61.

[4] Z.-G. Ding, J.-Y. Zhao, M.-G. Li, R. Huang, Q.-M. Li, X.-L. Cui, H.-J. Zhu, M.-L. Wen, *J. Nat. Prod.* **2012**, *75*, 1994-1998.

[5] R. M. Gillarda, M. A. Brimble, *Org. Biomol. Chem.* **2019**, *17*, 8272-8307.

[6] A. M. Heapy, A. V. Patterson, J. B. Smaill, S. M. F. Jamieson, C. P. Guise, J. Sperry, P. A. Hume, K. Rathwell, M. A. Brimble, *Bioorg. Med. Chem.* **2013**, *21*, 7971-7980.

[7] F. Perron, K. F. Albizati, *Chem. Rev*. **1989**, *89*, 1617-1661.

[8] B. Liu, J. K. De Brabander, *Org. Lett*. **2006**, *8*, 4907-4910.

[9] a) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev*. **2008**, *37*, 1766-1775; b) M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev*. **2012**, *41*, 2448-2463; c) R. Quach, D. P. Furkert, M. A. Brimble, *Org. Biomol. Chem*. **2017**, *15*, 3098-3104.

[10] a) X. Wang, Z. Han, Z. Wang, K. Ding, *Angew. Chem. Int. Ed*. **2012**, *51*, 936-940; b) I. Čorić, B. List, *Nature* **2012**, *483*, 315-319; c) Z. Sun, G. A. Winschel, A. Borovika, P. Nagorny, *J. Am. Chem. Soc*. **2012**, *134*, 8074-8077; d) J. Y. Hamilton, S. L. Rössler, E. M. Carreira, *J. Am. Chem. Soc*. **2017**, *139*, 8082-8085.

[11] a) S. Liu, X--C. Lan, K. Chen, W.-J. Hao, G. Li, S.-J. Tu, B. Jiang, *Org. Lett*. **2017**, *19*, 3831-3834; b) S. Liu, K. Chen, X.-C. Lan, W.-J. Hao, G. Li, S.-H. Tu, B. Jiang, *Chem. Comm*. **2017**, *53*, 10692-10695; c) J.-K. Qiu, W.-J. Hao, G. Li, B. Jiang, *Adv. Synth. Catal*. **2018**, *360*, 1182-1192.

[12] a) J. Li, L. Lin, B. Hu, X. Lian, G. Wang, X. Liu, X. Feng, *Angew. Chem. Int. Ed*. **2016**, *55*, 6075-6078; *Angew. Chem*. **2016**, *128*, 6179–6182; b) S. Ge, W. Cao, T. Kang, B. Hu, H. Zhang, Z. Su, X. Liu, X. Feng, *Angew. Chem. Int. Ed*. **2019**, *58*, 4017-4021; *Angew. Chem*. **2019**, *131*, 4057-4061.

[13] C.-L. Ji, Y. Pan, F.-Z. Geng, W.-J. Hao, S.-J. Tu, B. Jiang, *Org. Chem. Front*. **2019**, *6*, 474-479.

[14] a) C. Jiménez-Rodríguez, F. X. Roca, Carles Bo, J Benet-Buchholz, E. C. Escudero-Adán, Z. Freixa, P. W. N. M. van Leeuwen, *Dalton Trans*. **2006**, 268-278; b) X. Sala, E. J. García Suárez, Z. Freixa, J. Benet- Buchholz, P. W. N. M. van Leeuwen, *Eur. J. Org. Chem*. **2008**, 6197-6205; c) X. Wang, F. Meng, Y. Wang, Z. Han, Y.- J. Chen, L. Liu, Z. Wang, K. Ding, *Angew. Chem. Int. Ed*. **2012**, *51*, 9276-9282; d) J. Li, L. Lin, B. Hu, X. Lian, G. Wang, X, Liu, X. Feng, *Angew. Chem. Int. Ed*. **2016**, *55*, 6075-6079.

[15] N. Asao, C. S. Chan, K. Takahashi, Y. Yamamoto, *Tetrahedron* **2005**, *61*, 11322-11326.

[16] R. Lucius, R. Loos, H. Mayr, *Angew. Chem. Int. Ed*. **2002**, *41*, 91-95; *Angew. Chem*. **2002**, *114*, 97-102.

[17] F. Effenberger, *Angew. Chem. Int. Ed*. **1969**, *8*, 295-312.

[18] CCDC 1922831 (**8**) and 1922832 (**9a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

10.1002/adsc.201900988

FULL PAPER

A Silver-Catalyzed Modular Intermolecular Access to 6,6-Spiroketals

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Alexander Ahrens, Niklas F. Heinrich, Simon R. Kohl, Martha Hokamp, Matthias Rudolph, Frank Rominger, A. Stephen K. Hashmi*