Oxabicyclohexanes

DOI: 10.1002/anie.200701378

# Gold-Catalyzed Intermolecular Addition of Carbonyl Compounds to 1,6-Enynes**

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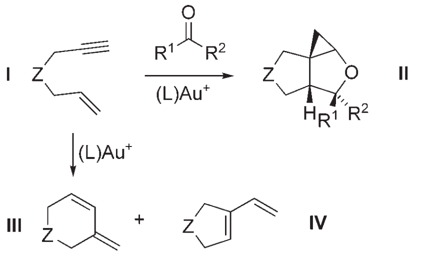
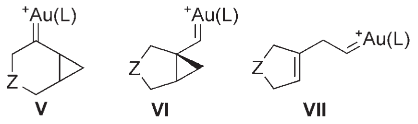
*Dedicated to Professor Lutz F. Tietze on the occasion of his 65th birthday*

Isomerization reactions of 1,6-enynes are catalyzed by complexes of many transition metals and have led to numerous useful and interesting innovations in organic synthesis.[1] Herein we report a novel gold-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes **I** to form 2-oxabicyclo[3.1.0]hexanes of type **II** (Scheme 1). Echavarren et al.[2] have previously described an *intramolecular* gold-catalyzed reaction of enynones, which proceeds through a Prins-type reaction and yields different products.



***Scheme 1.*** Reactions of 1,6-enynes.

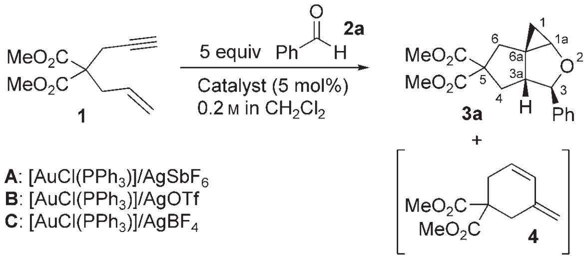
Among the numerous novel reactions using gold complexes as homogeneous catalysts,[3,4] the isomerization of 1,6-enynes shows outstanding versatility. In the absence of an additional reactant, dienes **III** and/or **IV** are formed, which arise from 6-*endo-dig* and 5-*exo-dig* cyclizations to give carbene complexes of type **V** and **VI**, respectively. Preference for **III** or **IV** in a specific case is strongly dependent on the connector Z and on the substituents at the enyne moiety.[5]



The existence of **V** and **VI** was corroborated by DFT calculations, and the existence of **VI** could be proved by cyclopropanation of alkenes.[4d,6] In catalytic processes, **V** and **VI** have been transformed into a variety of interesting products by addition of nucleophiles (arenes[7] and alcohol or water[5]). Furthermore, carbene complexes of type **VII** were postulated as intermediates that are particularly important for the work described herein. The complexes **VII** are rearrangement products of **VI**, and they have been trapped by cyclopropanation of alkenes.[6b]

To optimize the reaction conditions for the conversion **I**→**II**, the influences of the catalyst, the temperature, and the ratio of carbonyl component and enyne were investigated using the reaction of enyne **1** with benzaldehyde (**2a**) as an example (Table 1). As observed with many enyne cyclizations before, in the present case the catalyst [AuCl(PPh$_3$)]/AgSbF$_6$ (**A**) showed particularly high activity (see the Experimental Section). The salts AuCl, AuCl$_3$, CuOTf, PtCl$_2$, and AgSbF$_6$, as well as [AuCl(PPh$_3$)] without the addition of a silver salt

***Table 1:*** Optimization of the reaction conditions for the reaction of **1** with five equivalents of benzaldehyde (**2a**).



**A**: [AuCl(PPh$_3$)]/AgSbF$_6$
**B**: [AuCl(PPh$_3$)]/AgOTf
**C**: [AuCl(PPh$_3$)]/AgBF$_4$

| Entry | Catalyst | Conditions | Yield **3a** [%] |
|---|---|---|---|
| 1 | **A** | 1.5 h −45 °C, no benzaldehyde (**2a**) | –[a] |
| 2 | **A** | 6 h −45 °C, then →RT, 1 equiv benzaldehyde (**2a**) (16 h) | 38 |
| 3 | **A** | 6 h −45 °C, then →RT (16 h) | 68 |
| 4 | **A** | 4 h −20 °C | 66 |
| 5 | **A** | 1.5 h RT | 42 |
| 6 | **B** | 6 h −45 °C, then →RT (12 h) | –[b] |
| 7 | **C** | 6 h −45 °C, then →RT (14 h) | 59 |
| 8 | [AuCl(PPh$_3$)] | 6 h −45 °C, then →RT (13 h) | n. r.[c] |
| 9 | AgSbF$_6$ | 6 h −45 °C, then →RT (15 h) | n. r. |
| 10 | AuCl | 6 h −45 °C, then →RT (12 h) | n. r. |
| 11 | CuOTf | 6 h −45 °C, then →RT (18 h) | n. r. |

[a] Yield of **4**: 49%. [b] Conversion to **3a** <50% after 18 h (GC-MS). [c] n.r. = no reaction.

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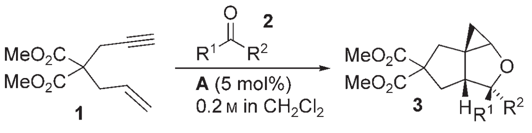
[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 623), the Studienstiftung des deutschen Volkes (scholarship to M.S.) and the Fonds der Chemischen Industrie.

showed no catalytic activity in the addition reaction (Table 1, entries 8–11). Among the weakly coordinating anions that were tested, $SbF_6^-$ proved to be particularly well-suited (Table 1, entries 3, 6, 7). The best yields were obtained when the reaction was carried out at −45 °C with an excess of benzaldehyde (Table 1, entries 1–5).

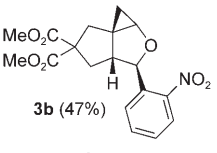
Without addition of an aldehyde, the enyne **1** reacted at low temperature to give the 6-*endo* product **4**, as anticipated[5] (Table 1, entry 1). This product was detected by GC–MS also in the reaction without the excess of benzaldehyde (Table 1, entry 2) and in reactions run at temperatures of −20 °C and above (entries 4, 5). With the exception of a run according to entry 1, the compound was not isolated; at room temperature it was not stable in the presence of the catalyst and gave rise to side products which were not identified. The side product **4** was not formed when the optimal reaction conditions were employed (Table 1, entry 3).

Subsequently, the applicability of the reaction to various carbonyl compounds was investigated (Table 2). The yield was somewhat lower with *ortho*-nitrobenzaldehyde (**2b**); however, with isobutyraldehyde (**2c**) it was approximately the same as with benzaldehyde (**2a**). Acetone (**2d**) and cyclohexanone (**2e**) underwent the addition reaction at temperatures above about 0 °C.

*Table 2:* Products of the intermolecular addition of different aldehydes and ketones to **1**.

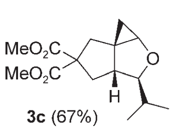


**2, 3 b**, $R^1 = C_6H_4(o\text{-}NO_2)$, $R^2 = H$
**c**, $R^1 = i\text{Pr}$, $R^2 = H$
**d**, $R^1 = R^2 = Me$
**e**, $R^1\text{–}R^2 = (CH_2)_5$



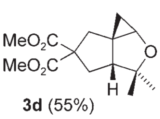
**3b** (47%)

5 equiv **2b**, −50→−25 °C over 5 h



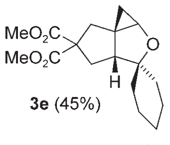
**3c** (67%)

20 equiv **2c**, 6 h −45 °C, then →RT



**3d** (55%)

20 equiv **2d**, 8.5 h −5 °C

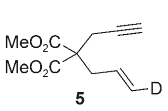
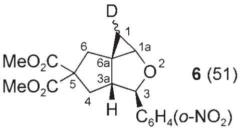
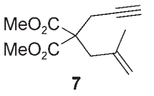
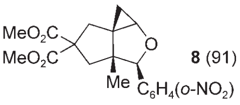
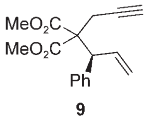
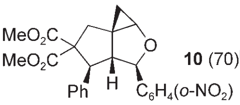
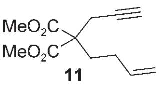
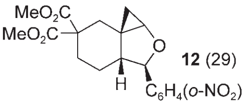
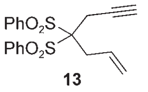
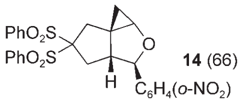
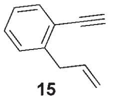
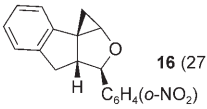


**3e** (45%)

20 equiv **2e**, 16 h 5 °C, then →RT

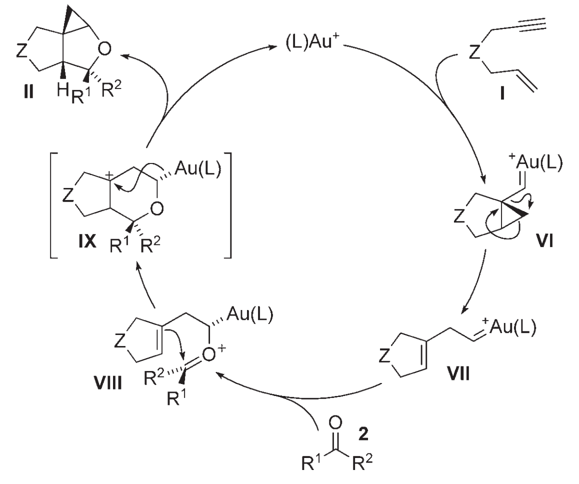
The new reaction was further tested with several 1,6-enynes and the 1,7-enyne **11** (Table 3). The structures of the products **3b**, **8**, **10**, **12**, and **16** were confirmed by X-ray crystal structure analysis.[8] In all cases, the reaction proceeded with complete diastereoselectivity with respect to the stereogenic centers C1a, C3, C3a, and C6a. Solely the diastereomer represented in entry 3 of Table 3 was formed from the chiral substrate **9**.[9] The *trans*-deuterated enyne **5** furnished product **6** as a 1:1 mixture of epimers with respect to C1 (Table 3, entry 1). Substrate **7**, which contains a 1-methylvinyl group, showed a significantly faster reaction than compound **1** (Table 3, entry 2). The formation of two quarternary centers in vicinal positions is remarkable.[10] The bissulfonyl derivative **13** (Table 3, entry 5) gave the product in a yield comparable to that obtained with malonic esters, while substrate **15** with an *ortho*-phenylene moiety as the backbone (Table 3, entry 6) gave a lower yield. Upon application of the stated reaction conditions, 1,6-enynes with terminal substituents at the alkyne or alkene moiety did not yield products of type **3**.

*Table 3:* Addition of *ortho*-nitrobenzaldehyde (**2b**) to various enynes.[a]

| Entry | Enyne | *t* [h] | Product (yield [%]) |
|---|---|---|---|
| 1 |  **5** | 18 |  **6** (51) |
| 2 |  **7** | 4[b] |  **8** (91) |
| 3 |  **9** | 21 |  **10** (70)[c] |
| 4 |  **11** | 43 |  **12** (29) |
| 5 |  **13** | 16 |  **14** (66) |
| 6 |  **15** | 22 |  **16** (27) |

[a] Reaction conditions: 5 equiv aldehyde, 0.2 M enyne in $CH_2Cl_2$, catalyst: 5 mol% **A**, 6 h −45 °C, then →RT. [b] Complete conversion after 4 h at −45 °C. [c] The reaction proceeded without racemization.

A possible reaction mechanism for the formation of the tricyclic products **II** is presented in Scheme 2. Addition of the carbonyl oxygen atom as a primary step is plausible because of the highly electrophilic character of cationic gold carbene complexes. Intermolecular addition reactions of nucleophiles to the isomeric gold carbene intermediates **VI** and **VII** were described by Echavarren and co-workers.[7a] The oxophilic character of the carbene carbon atom is also demonstrated by recent publications: Hashmi et al.[11] proposed an intramolecular addition of a carbonyl oxygen atom to a gold carbene species, and Toste and co-workers[12] described an oxidation of gold carbenes with sulfoxides. The lack of stereoselectivity in the reaction of the deuterated substrate **5** (Table 3, entry 1) suggests an addition to the linear achiral intermediate **VII** leading to **VIII**. The subsequent reaction of **VIII** to **II** could proceed stepwise as the addition of a carbocation to the alkene moiety via the intermediate **IX**. In view of the very high degree of diastereoselectivity for this transformation, a



*Scheme 2.* Mechanistic working hypothesis concerning the formation of the products **II**.

1,3-dipolar cycloaddition to the cyclopentene appears possible; such a reaction is typical for rhodium carbene complexes.[13]

In conclusion, for the first time an intermolecular gold-catalyzed addition of aldehydes and ketones to 1,6-enynes has been observed. This reaction proceeds highly diastereoselectively to yield a novel type of tricyclic compounds as products. Further investigations are required to explore the scope of the reaction and gain deeper insight into the reaction mechanism.

## Experimental Section

Exemplary procedure (see Table 1, entry 3): Under an atmosphere of argon a solution of benzaldehyde (**2a**; 530 mg, 5.0 mmol), enyne **1** (210 mg, 1.0 mmol), and $AgSbF_6$ (17 mg, 50 μmol) in anhydrous $CH_2Cl_2$ (5 mL) was cooled to −45 °C and treated with $[AuCl(PPh_3)]$ (24.7 mg, 50 μmol). The solution turned orange and was kept at −45 °C for 6 h. The cooling device was switched off, which initiated slow warming to room temperature. After an overall reaction time of 22 h, the solution was filtered through celite, which was then washed with $CH_2Cl_2$ (50 mL). Flash column chromatography on silica (25 g, petroleum ether/ethyl acetate 10:1) yielded **3a** (216 mg, 68 %) as a colorless oil. **3a**: $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.22$–7.35 (m, 5 H; Ph-H), 5.09 (dt, $J = 7.5$, 3.7 Hz, 1 H; 3-H), 3.87 (dd, $J = 5.1$, 1.7 Hz, 1 H; 1a-H), 3.84, 3.75 (2 s, 6 H; 2 $OCH_3$), 2.47–2.62 (m, 3 H; 3a-H, 4-H), 2.38 (s, 2 H; 6-H), 1.14 (dd, $J = 6.3$, 1.8 Hz, 1 H; 1-H), 0.98 ppm (dd, $J = 6.2$, 5.1 Hz, 1 H; 1-H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 172.3$, 171.9 (2 s; 2 $CO_2CH_3$), 141.6 (s; Ph), 128.5, 127.7, 125.7 (3 d; Ph), 95.7 (d; C-3), 65.6 (d; C-1a), 61.6 (s; C-5), 55.1 (d; C-3a), 53.0 (q; 2 $OCH_3$), 38.3, 38.0 (2 t; C-4, C-6), 36.5 (s; C-6a), 23.1 ppm (t; C-1); HRMS (EI): $m/z$ calcd for $C_{18}H_{20}O_5$: 316.1311; found: 316.1324 [$M^+$]. Elemental analysis (%) calcd for $C_{18}H_{20}O_5$ (316.35): C 68.34, H 6.37; found: C 68.32, H 6.33.

Received: March 30, 2007

**Keywords:** aldehydes · cyclization · cyclopropane · gold · homogeneous catalysis

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[8] As an example, the crystallographic data of **3b**: colorless crystal (fragment), dimensions $0.47 \times 0.39 \times 0.20$ mm$^3$, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 9.3604(15)$, $b = 9.9285(16)$, $c = 17.935(3)$ Å, $V = 1666.8(5)$ Å$^3$, $\rho = 1.440$ g cm$^{-3}$, $T = 200(2)$ K, $\Theta_{max} = 28.33°$, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, 0.3° $\omega$ scans with CCD area detector, covering a whole sphere in reciprocal space; 16742 reflections measured, 4145 unique ($R_{int} = 0.0320$), 3813 observed ($I > 2\sigma(I)$); intensities were corrected for Lorentz and polarization effects; an empirical absorption correction was applied using SADABS,[14] $\mu = 0.11$ mm$^{-1}$, $T_{min} = 0.95$, $T_{max} = 0.98$, structure solved by direct methods and refined against $F^2$ using the SHELXTL-PLUS (5.10) software package,[15] 273 parameters refined, hydrogen atoms were treated using appropriate riding models, except for those at the central tricycle, which were refined isotropically, Flack absolute structure parameter 0.3(9), goodness of fit 1.09 for observed reflections, final residual values $R1(F) = 0.047$, $wR(F^2) = 0.117$ for observed reflections, residual electron density −0.28 to 0.40 e Å$^{-3}$. CCDC-641967 (**3b**), CCDC-641968 (**8**), CCDC-641969 (**10**), CCDC-

641970 (**12**), and CCDC-641971 (**16**) 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.

[9] Substrate **9** was prepared by enantioselective iridium-catalyzed allylic alkylation in 98% *ee*: G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies, R. Weihofen, *Chem. Commun.* **2007**, 675–691.

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