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Gold Catalysis

Highly Efficient Gold-Catalyzed Synthesis of Dibenzocycloheptatrienes

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Abstract: Dibenzocycloheptatrienes are obtained by a gold-catalyzed *7-exo-dig* hydroarylation protocol in a highly efficient manner. The gold-catalyzed reaction usually gives the products in high yields and excellent selectivity. This procedure provides an easy and efficient access to dibenzocycloheptanoids, which are an interesting and unique class of natural products. This was underlined by the first total synthesis of reticuol.

Introduction

The gold-catalyzed hydroarylation of alkynes is known as an important and powerful tool for organic synthesis.[1] While for the intramolecular reaction with heteroaromatic systems as nucleophiles,[2] a high flexibility regarding the ring size is reported (even eight-membered rings can be obtained), only one report[3] on the formation of larger ring sizes can be found if nonheterocyclic aromatic rings are applied as nucleophiles.[4]

This topic attracted our attention owing to the importance of the dibenzocycloheptane motif, which could be addressed by a gold-catalyzed cyclization of biaryls bearing a homopropargylic tether. Inspired by former work of Fürstner et al., who applied alkynyl-substituted biaryl systems for the synthesis of phenanthrenes,[5] we assumed that it might be possible to develop conditions to synthesize dibenzocycloheptatrienes by a gold-catalyzed *7-exo-dig* hydroarylation reaction. The addressed structural motif can be found in many pharmacologically active compounds exhibiting interesting biological activities. One example is allocolchicine, which is active against many cancer cell lines.[6] In the last years, several natural products belonging to the class of dibenzocycloheptanoids have been isolated from different sources.[7] Figure 1 depicts, as selected representatives, tenuifolin,[7d,f] which shows antiproliferative activity against tumor cell line DU145, the strongly related reticuol as an inhibitor of cytochrom P450 (CYP3A4),[7b,i] subavenoside E,[7c] showing inhibitory activity against α-glucosidase type IV from *Bacillus stearothermophilus*, dibenzocycloheptadiene sihydroisosubamol,[7c] and subamol.[7a,e]

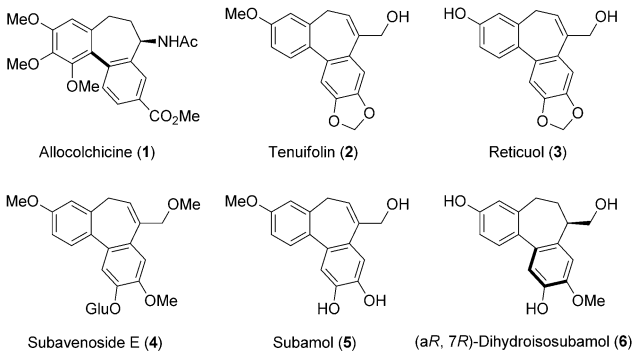

Figure 1. Examples of the dibenzocycloheptane core in natural products.

Besides their biological activity, these compounds are also interesting owing to their dynamic stereochemistry. Compound **4** exists as a mixture of two interconverting diastereomers,[7c] which was shown by in situ NOESY-NMR measurements.[8]

Regarding the dibenzocycloheptanoids, only **2** was already synthesized.[7f] This fact inspired us to develop a methodology for the highly efficient synthesis of dibenzocycloheptatrienes to provide an easy access to this class of natural products.

Results and Discussion

As test substrate homopropargyl-substituted biaryl **7a** was selected (Table 1). To control a selective attack of the lower benzene part, donating methoxy groups were used to prevent a competing *5-exo*/*6-endo* cyclization. We started the optimization of the reaction conditions with [IPrAuNTf$_2$] in CD_2Cl_2 with a catalyst loading of 5 mol%. Complete conversion was observed after 5 h at room temperature, accompanied by an excellent combined yield (entry 1). Unfortunately, besides the original hydroarylation product **9a** (64%), isomerization of the

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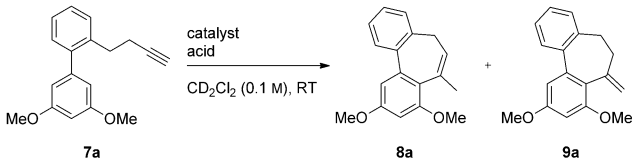
Table 1. Optimization of the reaction conditions.



7a **8a** **9a**

Entry[a]	Catalyst	Acid [5 mol%]	*t* [h]	Yield **9a** (**8a**) [%][b]
1	[IPrAuNTf$_2$] (5 mol%)	–	5.0	98 (34)
2	[XPhosAu(CH$_3$CN)]SbF$_6$ (5 mol%)	–	4.0	84 (40)
3	[(2,4-di-*t*Bu-C$_6$H$_3$O)$_3$PAu(PhCN)]SbF$_6$ (5 mol%)	–	0.1	99 (99)
4	[(2,4-di-*t*Bu-C$_6$H$_3$O)$_3$PAuNTf$_2$] (5 mol%)	–	1.5	99 (57)
5	[(2,4-di-*t*Bu-C$_6$H$_3$O)$_3$PAuCl]/AgSbF$_6$ (5 mol%)	–	0.2	93 (93)
6	[(2,4-di-*t*Bu-C$_6$H$_3$O)$_3$PAu(PhCN)]SbF$_6$ (2 mol%)	–	0.1	99 (99)
7	[(2,4-di-*t*Bu-C$_6$H$_3$O)$_3$PAu(PhCN)]SbF$_6$ (0.5 mol%)	–	5.0	99 (60)
8	[(2,4-di-*t*Bu-C$_6$H$_3$O)$_3$PAu(PhCN)]SbF$_6$ (1 mol%)	HNTf$_2$	0.3	99 (99)
9	[(2,4 di-*t*Bu-C$_6$H$_3$O)$_3$PAu(PhCN)]SbF$_6$ (0.5 mol%)	HNTf$_2$	0.8	98 (98)
10	[(2,4-di-*t*Bu-C$_6$H$_3$O)$_3$PAu(PhCN)]SbF$_6$ (0.1 mol%)	HNTf$_2$	17	87 (87)
11	AgNTf$_2$	–	48	n.c.[c]
12	–	HNTf$_2$	48	n.c.[c]

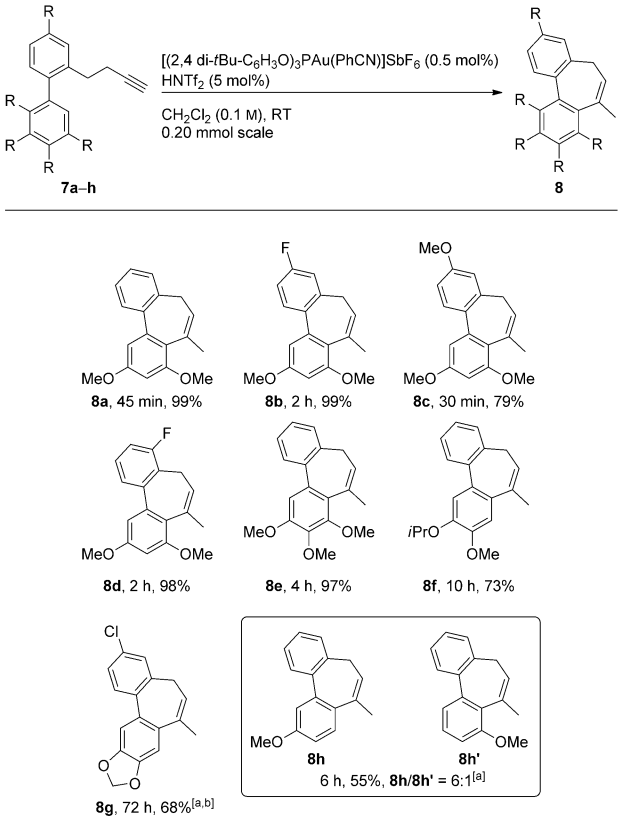
[a] Reactions were carried out with 0.05 mmol of substrate. [b] Yields were determined by ^{1}H NMR spectroscopy with tri-*tert*-butylbenzene as internal standard. The yield in brackets corresponds to the yield of **8a**. [c] n.c. = no conversion.

double bond delivered side product **8a** (34%). This isomerization is a known observation for the products of *7-exo-dig* hydrofunctionalizations.[2h,9] Unfortunately, our attempts to fully isomerize the primer product by shifting the solvent to more acidic $CDCl_3$ did not lead to the selective formation of **8a**. Thus, we considered a further variation of the ligand system to induce further isomerization. We continued the screening of catalysts with [XPhosAu(MeCN)]SbF$_6$ (5 mol%), giving 84% total yield but in low selectivity (40% of **8**) after 4 h (entry 2).

To our delight, 5 mol% of the electron-poor gold catalyst [(2,4-di-*t*Bu-C$_6$H$_3$O)$_3$PAu(PhCN)]SbF$_6$ selectively furnished **8a** in 99% yield after only 5 min (entry 3). The similar gold complex with NTf_2^- instead of SbF_6^- as counter ion was less successful, showing a prolonged reaction time and again a mixture of both products. While the overall yield was excellent (99%), only 57% of **8a** were formed (entry 4). The reaction with 5 mol% [(2,4-di-*t*Bu-C$_6$H$_3$O)$_3$PAuCl], in situ activated by AgSbF$_6$, needed slightly more time until complete conversion was reached and also gave a lower yield of 93% (entry 5). With the optimized catalytic system, we next evaluated the possibility to decrease the catalyst loading. While 2 mol% of catalyst showed no difference (entry 6), with 0.5 mol% of catalyst the reaction time was prolonged to 5 h and the yield of **8a** dropped to 60% (entry 7). To reduce the catalyst loadings further, we considered a non-coordinating acid as additive that could support the isomerization step.

The addition of HNTf$_2$ to a mixture of **8a** and **9a** gave complete conversion to **8a** after only 1 min. With this knowledge in hand, we again tried to decrease the catalyst loading in the presence of additional 5 mol% of HNTf$_2$. By using this combination, the reaction could be conducted with 1 mol% (20 min, 99% **8a**) and even with 0.5 mol (45 min, 98% **8a**) of the gold catalyst (entries 8 and 9). The use of only 0.1 mol% catalyst did not lead to full conversion after 17 h, but still **8a** was formed selectively in a high yield of 87% (entry 10). To demonstrate that the acid itself cannot catalyze the hydroarylation step, the reaction was carried out with 5 mol% of HNTf$_2$, showing not even traces of product after 2 days (entry 12). The control experiment with AgNTf$_2$ as catalyst gave the same result (entry 11).

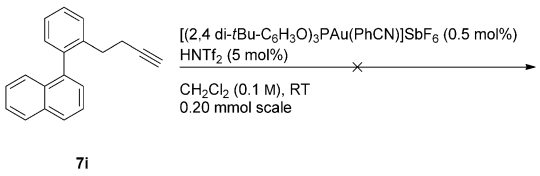
After optimizing the catalyst system, we turned our focus on the evaluation of the scope of the reaction (Scheme 1). The optimized conditions were used on a 0.2 mmol scale. As expected, compound **7a** was nicely converted into the desired product **8a** after 45 min in 99% yield. Next, we investigated the influence of a substituent in 3-position of the arene system bearing the alkynyl tether. **7b** containing a fluoro substituent in this position gave **8b** in 99% yield with a slightly prolonged reaction time, whereas **7c** with a methoxy group was converted completely to **8c** after 30 min, albeit in a slightly reduced yield of 79%. Fortunately, **8c** was the only product observed, which is quite remarkable if one considers the electron-donating properties of the methoxy group that could also induce an attack at the 4-position of the upper arene moiety. The fluoro substituent in the 4-position of **7d** did not lead to any changes compared to **7b**



Scheme 1. Scope of the reaction. [a] The reaction was conducted with 2 mol% of catalyst. [b] The reaction was performed on a 0.5 mmol scale.

in terms of reaction time and yield, and **8d** was formed in 98% yield after 2 h. Interestingly, compound **7e** bearing an additional methoxy group attached to the nucleophilic ring system needed 4 h for completion, but still **8e** was obtained in an excellent yield of 97%. The unsymmetrically substituted substrate **7f** showed an even longer reaction time, yielding **8f** in 73%. **7g** containing the less donating methylenedioxy moiety did not give complete conversion with 0.5 mol% of catalyst; even with 2 mol% the reaction needed 72 h to proceed, furnishing **8g** in 68% yield. For compound **7h,** a mixture of two products corresponding to an attack in *para*- (**8h**) or *ortho*-position (**8h′**) of the methoxy group was obtained after 6 h. This reaction was also conducted with 2 mol% of catalyst, giving the products in 55% overall yield in a ratio of 6:1 (**8h**/**8h′**) from **7h**.

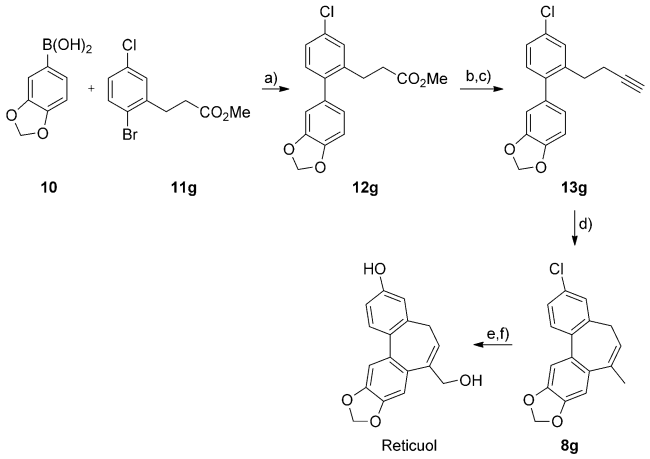
Substrate **7i** was also prepared and tested under the optimized conditions. Similar molecules were successfully cyclized to phenanthrenes with platinum or gold catalysts in earlier[4a,10] and recent work,[3] but unfortunately no conversion was observed (Scheme 2). Next, we tried to accelerate the reaction by



Scheme 2. Nonreacting substrate **7i**.

conducting it at 80 °C in DCE with 5 mol% of [XPhosAu(CH$_3$CN)]SbF$_6$ (because of the superior heat stability of this catalyst)[11] and 5 mol% HNTf$_2$ as additive. Even after several days of heating, only traces of the desired product were observed by GC-MS analysis. The major product showed a molecular ion peak with $m/z = 274$, strongly supporting simple water addition to the alkyne. Under anhydrous conditions, even after several days of heating, GC-MS and NMR analysis showed solely starting material. Unfortunately we do not have an explanation for the failure of this reaction.

To demonstrate the great potential of this transformation, the first total synthesis of reticuol was accomplished. This natural product was isolated from *Cinnamomum Burmani* and showed inhibition of CYP3 A4[7i] and from *Cinnamomum reticulatum*.[7b] Biphenyl **12g** was synthesized from the boronic acid **10** and aryl bromide **11g** in a Pd-catalyzed Suzuki–Miyaura cross coupling reaction in an excellent yield of 97%. **13g** was then smoothly obtained after DIBAHL-H (diisobutylaluminium hydride) reduction and subsequent Seyferth–Gilbert homologation in 91% overall yield. In the key step, the tetracyclic core of **8g** was synthesized by following the gold-catalyzed hydroarylation strategy in 68% yield. The phenolic hydroxyl group was then introduced by a Pd-catalyzed hydroxylation with KOH,[12] furnishing the phenol in an excellent yield of 94%. Reticuol was finally obtained after allylic oxidation of the olefinic methyl group. In total, reticuol was synthesized in six steps



Scheme 3. First total synthesis of reticuol. Conditions: a) **10** (1.5 equiv), Pd(OAc)$_2$ (5.0 mol%), PPh$_3$ (10 mol%), K$_2$CO$_3$ (4.0 equiv), DME/water 3:1, 80 °C, 13 h, 97%; b) DIBAL-H (2.0 equiv), abs. CH$_2$Cl$_2$, −90 °C, 2 h, 99%; c) Bestmann–Ohira reagent (1.5 equiv), Cs$_2$CO$_3$ (3.0 equiv), abs. MeOH, 0 °C–RT, 1 h, 92%; d) [(2,4-di-*t*Bu-C$_6$H$_3$O)$_3$PAu(PhCN)]SbF$_6$ (2.0 mol%), HNTf$_2$ (5.0 mol%), CH$_2$Cl$_2$, RT, 72 h, 68%; e) Pd$_2$dba$_3$ (2.0 mol%; dba = dibenzylideneacetone), *t*BuXPhos (8 mol%), KOH (4.0 equiv), 1,4-dioxane/water 1:1, 100 °C, 24 h, 94%; f) SeO$_2$ (2.0 equiv), 1,4-dioxane/HCOOH 3:1, 2 h, then NaBH$_4$ (4.0 equiv), MeOH, 30 min, 74%.

with an overall yield of 42% (Scheme 3), which corresponds to an average yield of 86% per step.

Conclusion

In conclusion, we have developed a selective *7-exo-dig* hydroarylation with aromatic nucleophiles. This reaction offers a rapid access towards highly interesting dibenzocyclotrienes. These compounds have great potential in the synthesis of several natural products, as it was shown with the first total synthesis of reticuol. In addition, continued studies regarding the atropisomerism of these compounds are ongoing in our laboratories and will be reported in due course.

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Keywords: dibenzocycloheptanoids · gold · hydroarylation · natural products · total synthesis

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