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Synthetic Methods

Mechanistic Insights into the Post-Cyclization Isomerization in Gold-Catalyzed 7-*exo*-*dig*-Hydroarylations

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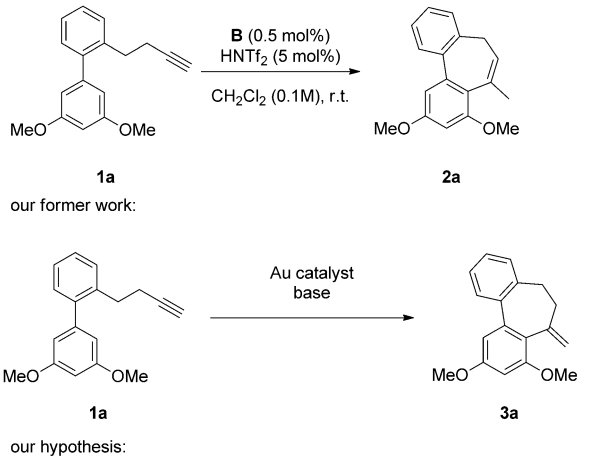
Abstract: The subsequent double-bond isomerization in the synthesis of dibenzocycloheptenes and their heteroaromatic analogues was investigated. In the case of biphenyls, a basic additive completely prevented an isomerization to the thermodynamic product. With electron-rich intramolecular heteroaromatic nucleophiles, the isomerization was still observed, but the kinetic product can be obtained by careful control of the reaction times in most cases. Mechanistic studies demonstrated that a slow isomerization is also possible with the gold catalyst at elevated temperatures, but much faster isomerization rates were observed with acidic additives. An observed initiation period for the gold-catalyzed isomerization indicates that not the homogenous catalyst, but a decomposition product of it may be the catalytically active species.

Introduction

In gold-catalyzed *exo-dig* cyclizations, the primary product often undergoes a subsequent isomerization to the product containing a thermodynamically more stable internal alkene. Although during the construction of methylenecycloheptanes by a gold-catalyzed 7-*exo-dig* cyclization no double-bond isomerization could be observed,[1] in the case of indoles as nucleophiles in gold-catalyzed intramolecular hydroarylations, a double-bond isomerization was observed in some cases.[2] The $AuCl_3$-catalyzed conversion of *N*-propargylindole-2-carboxamides by 6-*exo-dig* hydroarylation selectively led to the isomerized product.[3] Othman and co-workers obtained a mixture of both primary and isomerized product by a 6-*exo-dig* hydroarylation. They could convert the mixture into the internal alkene simply by heating in dichloroethane.[4] An intramolecular 7-*exo-dig* hydroamination reaction reported by Sawamura and co-workers directly delivered the isomerized alkene for most substrates.[5] In this case, the reaction of the isolated *exo*-methylene compound with either a Au^I catalyst or the catalyst in combination with a mild proton source showed mainly decomposition. These results led to the conclusion that the formation of the *exo*-methylene compound followed by a subsequent isomerization cannot play a major role in the isomerization pathway. Instead, pathways starting directly from the vinyl–gold intermediates were favored.[5] δ-Alkynylfuranes are standard substrates for the gold-catalyzed phenol synthesis reported by our group,[6] but a 7-*exo-dig* hydroarylation as side reaction can also be observed under some conditions. Interestingly, the primarily formed *exo*-methylene product isomerized in $CDCl_3$ without addition of any catalyst.[6a] Fitting into the rather intransparent picture, a gold-catalyzed 6-*exo-dig* hydroarylation of *N*-aminophenyl propargyl malonates forming dihydroquinolines delivered, for some substrates, a mixture of the initial and the isomerized product, whereas the addition of 5 mol% of *p*-TsOH led to complete isomerization of the primary product (Scheme 1).[7]



Scheme 1. Accessing two different double-bond isomers from the same substrate.

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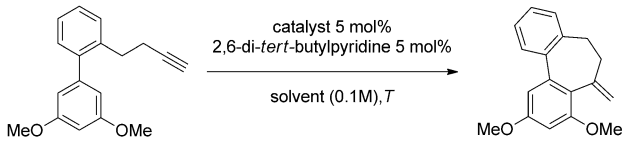
Results and Discussion

In our recent report on the synthesis of dibenzocycloheptatrienes,[8] we found that for many catalyst systems and especially low-catalyst loadings, a mixture of the primary **3a** and the rearranged product **2a** was obtained. Interestingly, **3a** was stable at ambient conditions and the obtained ratio **2a**/**3a** did not change by dissolution in $CDCl_3$ or during performance of column chromatography with silica gel. On the other hand, addition of 5 mol% of $HNTf_2$ as additive successfully gave **2a** in perfect selectivity. This led to the hypothesis that in this case after the initial gold-catalyzed hydroarylation, a subsequent acid-catalyzed isomerization should be the major pathway. Small amounts of strong acid, which are present during the reaction may be, in fact, responsible for the isomerization in the first place. To further investigate this hypothesis and, if possible, to utilize it for a selective synthesis of **3a**, we performed the reaction in the presence of a suitable base to trap traces of acid.

For the optimization of the reaction conditions initially the original conditions for the cyclization were tested in the presence of 5 mol% 2,6-di-*tert*-butylpyridine in dichloromethane (Table 1, entry 1). Unfortunately, no conversion was observed, which can be explained by the coordination of the base to the active site of the catalyst. To circumvent this problem, higher temperatures were applied in benzene as solvent. To our delight, the use of the complexes **B** and **C** (Figure 1) under the elevated temperatures gave a clean conversion to the non-isomerized product in reasonable reaction time and high yield (99% yield after 3 h; Table 1, entries 2 and 3). When $IPrAuNTf_2$ (5 mol%) was used in combination with 5 mol% of base, a slightly lower yield of 88% was obtained after 17 h (Table 1, entry 4). With the related Tedii-Au^INTf_2 (Tedii = (1-cyclopentadecyl-3-(2,6-*dii*sopropyl-phenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene)); **A**) **3a** was obtained in slightly lower yield of 84% after 16 h (Table 1, entry 5). Switching from N-heterocyclic carbene (NHC) to phosphine ligands (PPh_3 and SPhos) gave higher yields again after 16 h of reaction time. Compound PPh_3AuNTf_2 produced **3a** in 94% yield (Table 1, entry 6), $SPhosAuNTf_2$ gave an almost identical yield (95%; Table 1, entry 7).

Table 1. Optimization of the reaction conditions.



1a 3a

Entry[a]	Solvent	Catalyst	T [°C]	t [h]	Yield [%][b]
1	CD_2Cl_2	**B**	RT	48	n.c.[c]
2	C_6D_6	**B**	80	3	99
3	C_6D_6	**C**	80	3	99
4	C_6D_6	$IPrAuNTf_2$	80	17	88
5	C_6D_6	**A**	80	16	84
6	C_6D_6	PPh_3AuNTf_2	80	16	94
7	C_6D_6	$SPhosAuNTf_2$	80	16	95
8	C_6D_6	C	40	72	23
9	C_6D_6	**B**[d]	80	3	95

[a] Reactions were carried out with 0.05 mmol of substrate. [b] Yields were determined by ^1H NMR spectroscopy with tri-*tert*-butylbenzene as internal standard. [c] No conversion. [d] No base was used.

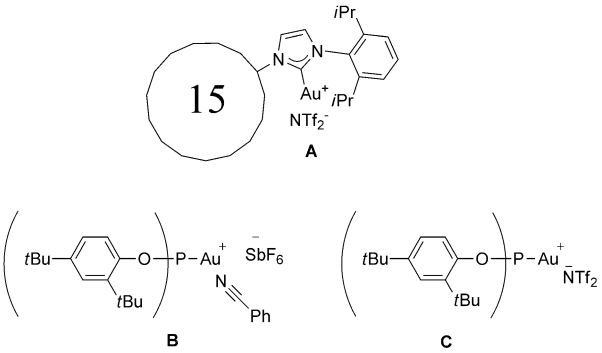
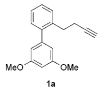
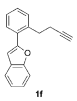
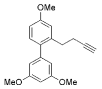
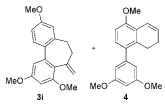
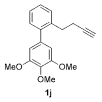
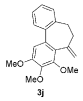
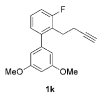
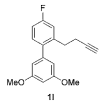
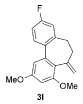
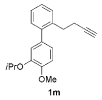
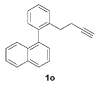
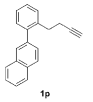


Figure 1. Au^I catalysts used in the optimization.

It is noteworthy that after five days of continued stirring at 80 °C with catalyst **B**, traces of **2a** were observed, whereas in the case of **C**, no isomerization at all was detected. Decreasing the reaction temperature to 40 °C in C_6D_6 was not possible, and only incomplete conversion and 23% yield after 48 hours were obtained (Table 1, entry 8). Finally, we conducted one reaction in the absence of base in benzene as solvent. To our surprise, even in the absence of a base, a high yield of 95% of the desired product could be obtained. This indicates that the polarity of the solvent plays an important role for the post cyclization processes in gold catalysis (entry 9). Attempts to perform the reaction at room temperature without a base failed.

The scope of the transformation was then investigated under the optimized conditions. First, compound **1a** was converted under preparative conditions, which furnished **3a** in an excellent yield of 95% after 3 hours reaction time (Table 2, entry 1). *N*-Heterocycles as nucleophiles were used next. Compound **1b** containing a *tert*-butyloxycarbonyl (Boc)-protected pyrrole showed a complete conversion after only ten minutes, providing the desired product **3b** in 71% yield (Table 2, entry 2). For this type of substrate, a significant drop in yield and selectivity was observed in the absence of base (32% vs 71%), which indicates that for more electron-rich starting materials the use of the base is crucial. Nevertheless, after six hours reaction time, the internal alkene **2b** can be obtained in 65% yield (Table 2, entry 3) even in the presence of the base. When indole **1c** was used, the reaction needed 30 minutes to completion. The tetracyclic compound **3c** was formed in excellent yield of 98% (Table 2, entry 4). In contrast to **1b**, a complete isomerization was not observed under these conditions even after five days. Furan derivatives were investigated as well. 3-Substituted furan derivative **1d** furnished **3d** after only 30 minutes in an excellent yield of 93% (Table 2, entry 5). Similar to the above-described examples, after a prolonged reaction time, an isomerization to thermodynamic product **2d** was observed, although a base was used in the reaction. After 14 hours at 80 °C, **2d** could be isolated in 82% yield (Table 2,

Table 2. Scope of the reaction.

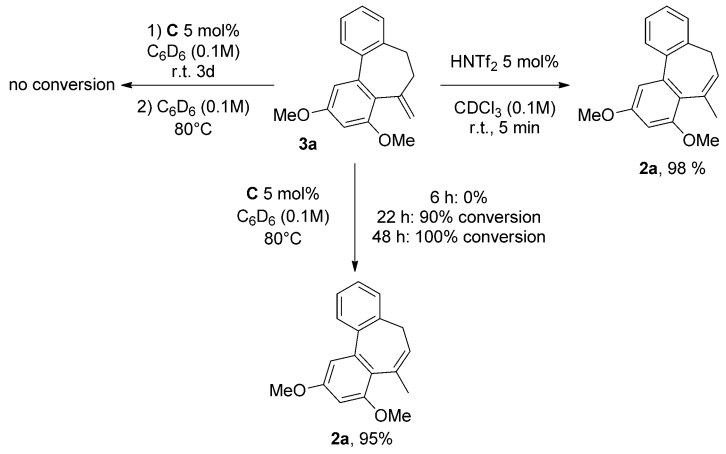
Entry[a]	Substrate	*t*	Product	Yield [%]
1[b]	 1a	3 h	 3a	95
2	 1b	10 min	 3b	71 (32)[c]
3	 1b	6 h	 2b	65
4	 1c	1 h	 3c	98
5	 1d	30 min	 3d	93
6	 1d	14 h	 2d	82
7	 1e	30 min	 3e	53
8	 1f	30 min	 3f	91
9	 1f	72 h	 2f	90
10	 1g	32 h	 2g	84
11	 1h	32 h	 2h	76
12	 1i	3 h	 3i + 4	66 + 33
13	 1j	22 h	 3j	65
14	 1k	3 h	 3k	81
15	 1l	3 h	 3l	77
16	 1m	48 h	 3m	41
17	 1n	72 h	 3n	trace
18	 1o	72 h	n. c.[c]	–
19	 1p	72 h	n. c.[d]	–

[a] Reaction were carried out under the optimized conditions at 0.2 mmol scale in C_6H_6. [b] 0.5 mmol substrate were used. [c] Yield in brackets for the reaction without base. [d] No conversion.

entry 6). The corresponding 2-furan derivative **1e** was also completely converted after 30 minutes, but **3e** was obtained only in moderate yield of 53% (Table 2, entry 7). Interestingly, no product of a gold-catalyzed phenol synthesis was observed.[9] In the case of benzofuran **1f**, the tetracyclic compound **3f** again was obtained in an excellent yield of 91% after 30 minutes (Table 2, entry 8). After a very long reaction time of 72 hours, again, the isomerized product **2f** was obtained in excellent yield of 90% (Table 2, entry 9). Next, we turned our attention to thiophene derivatives. Surprisingly, initial GC-MS analysis after two hours revealed the presence of starting material **1g**, as well as both possible products **2g** and **3g**. This made the selective synthesis of **3g** impossible. After six hours, **1g** was completely converted but still as mixture of **2g** and **3g**. After 32 hours, **3g** was completely transformed to **2g**, which was then isolated in 84% yield (Table 2, entry 10). For compound **1h**, the observed results were similar as for **1h**, finally giving **2h** after 32 hours in 76% yield (Table 2, entry 11). Without the addition of base, decomposition was observed for furane and thiophene derivatives.

As a next step, we tested differently substituted arene nucleophiles. An electron-donating methoxy group at the non-reacting aromatic part of the biaryl substrate **1i** produced **3i** within 3 h, but only in a moderate yield of 66%. This can be explained by the formation of the 6-*endo-dig* hydroarylation product **4** in 33% yield (Table 2, entry 12). Shifting the electron-donating substituent to the other part of the biaryl moiety in **1j** delivered **3j** in 65% yield after 22 hours in a clean reaction (Table 2, entry 13). The longer reaction time and lower yield might be explained by the -I effect of the additional methoxy group that has no positive +M effect onto the reaction center. Both fluorine containing substrates **1k** and **l** delivered the desired products **3k** (Table 2, entry 14) and **3l** (Table 2, entry 15) after three hours in 81% (**3k**) and 77% (**3l**), respectively. The shift of one of the donating groups to a non-conjugated position in respect to the reacting carbon (**1m**) led to an extensively longer reaction time of 48 h and **3m** was obtained in a moderate yield of 41% yield (Table 2, entry 16). Only traces of **3n** could be observed for acetal **1n** even after 72 h reaction time (Table 2, entry 17). Substrates **1o** and **1p**, containing naphthyl groups as possible nucleophiles, did not show any conversion even after extended reaction times of 72 h (Table 2, entries 18 and 19).

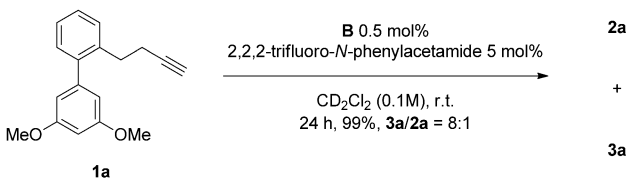
The fact that even in the presence of a base still slow isomerization takes place for some of the substrates led us to the



Scheme 2. Test reactions over the influence of acid during the isomerization step.

conclusion that besides the acid-catalyzed pathway for double-bond isomerization, another pathway might exist. Thus, different test reactions were conducted to shed some light to this issue (Scheme 2). All reactions were carried out at 0.05 mmol scale in deuterated solvents, and the yield was determined by ^{1}H NMR spectroscopy by using tri-*tert*-butylbenzene (TTBB) as internal standard. First, compound **3a** was reacted with 5 mol% $HNTf_2$ in $CDCl_3$ at room temperature. A fast conversion to **2a** was observed after five minutes with 98% NMR yield. The reaction of **3a** with 5 mol% of **C** in C_6D_6 showed no conversion at all even after three days at room temperature. The same result was observed by heating **3a** in C_6D_6 at 80 °C for two days in the absence of any catalyst. But when 5 mol% of **C** was used in C_6D_6 at 80 °C after 48 h, 100% conversion was observed in GC-MS analysis. Interestingly, after six hours, no conversion was detected, whereas already 90% of **3a** was converted into **2a** after 22 hours. The NMR yield after 48 hours was calculated to be 95%. This clearly shows that competing gold-catalyzed pathways for the isomerization step cannot be completely ruled out, although these only seem to operate at elevated temperatures. In this context, it should be noted that whenever isomerized products were obtained, clear signs of catalyst decomposition were visible on the reaction vial. A possible reason for the observed induction period in the isomerization could be the isomerization not being catalyzed by the homogenous catalyst itself but by a decomposition product of the catalyst. Thus, the involvement of heterogeneously catalyzed pathways is also possible.

As a resume, working at lower temperatures seems to be necessary to completely suppress the isomerization. For this purpose, trifluoroacetic acid (TFA)-protected aniline was tested as possible weak base (but still strong enough to capture the proton of the in situ formed $HNTf_2$), which does allow reactions at room temperature.[10] Catalyst **B** (0.5 mol%) and the aniline (5 mol%) were used in CD_2Cl_2 at room temperature. After 24 hours, complete conversion was achieved giving a mixture of **2a** and **3a** in 99% yield, determined by NMR spectroscopy, and a selectivity for **3a** of 8:1. In contrast to this result, the same reaction at room temperature without the additive gave **2a** as major product (Scheme 3).[8]



Scheme 3. Selective reaction providing **3a** at RT.

Conclusion

The isomerization step in the gold-catalyzed synthesis of dibenzocycloheptenes and their analogues with one heteroaromatic ring was investigated. Former experiments in our group led to the conclusion that the isomerization step is not catalyzed by the homogenous gold catalyst but by strong acid, which is formed during the course of the reaction. As a consequence, basic additives could be used to successfully prevent the isomerization of the primary hydroarylation product to the thermodynamic products in the case of biphenyls. In contrast to acidic conditions, electron-rich heteroaromatic systems can also work as nucleophile under these conditions. More electron-rich five-membered heterocycles as nucleophiles led to much higher isomerization rates, and therefore, for some cases even under basic conditions, only the thermodynamic products could be obtained. Mechanistic studies indicate that besides a fast proton-catalyzed pathway, a slower gold-catalyzed isomerization is also conceivable. Most probably, the active species for this isomerization is a degradation product of the catalyst as an induction period was observed for the isomerization. The use of weak nucleophilic bases made it possible to conduct the reaction at room temperature with good selectivity for the kinetic product.

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Keywords: additives · cycloheptenes · gold · hydroarylation · isomerization

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