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The Role of Gold Acetylides as a Selectivity Trigger and the Importance of *gem*-Diaurated Species in the Gold-Catalyzed Hydroarylating-Aromatization of Arene-Diynes

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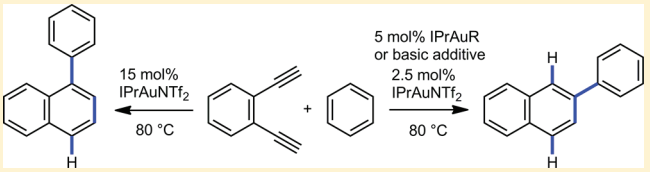
Supporting Information

ABSTRACT: Terminal 1,2-dialkynylarenes undergo an unexpected cyclization hydroarylation reaction toward naphthalene derivatives in benzene as the solvent. The regioselectivity of the reaction can be controlled by careful catalyst tuning. Also, the preparation of a bench-stable cationic amine complex or simple heterogenization of the catalyst on neutral aluminum oxide, which enables efficient catalyst recycling, was possible. Intensive mechanistic investigations were undertaken, giving new insights into the so-far underestimated role of acetylides in gold chemistry. The gold plays a fascinating dual role serving to both catalyze the reaction and activate the substrate by Au−C-σ bond formation. Evidence of *gem*-diaurated compounds playing an important part for gold catalysis is also reported.



1. INTRODUCTION

In the last 11 years, the use of homogeneous gold complexes for a broad array of organic transformations has become an established field in modern organic chemistry.[1] Because of their remarkable ability to activate alkynes, gold complexes are frequently used as catalysts for the nucleophilic addition of heteroatoms to multiple bonds.[2]

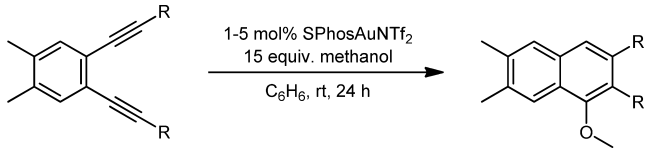
Furthermore, enynes are often applied as substrates that give access to multifaceted reactions with incredible gain of molecular complexity.[3] Recently, diynes have attracted gold chemists as well, opening the field for new domino reactions by initial attack of a nucleophile to the triple bond, followed by subsequent reactions with the so-formed reactive intermediates (for example, an enol ether).[4]

Because of their easy accessibility via 2-fold Sonogashira coupling, we considered 1,2-dialkynyl benzenes as suitable substrates for possible domino reactions with external nucleophiles.[5] In the course of our investigation, we discovered an unexpected cyclization arylation reaction with benzene. The ability to influence the selectivity of this reaction and detailed mechanistic studies are the topics of this contribution.

2. RESULTS

2.1. The Initial Observation: Unexpected Reaction Course and Atypical Regioselectivities. Our initial studies were focused on the intermolecular addition of alcohols to symmetrically substituted 1,2-dialkynyl benzenes. After an intensive catalyst screening for the reaction of *n*-butyl-substituted starting diyne **1a** and methanol,[6] we were able to obtain 65% of the desired α-naphthol derivative **2a** at room temperature (Scheme 1).[7] Besides the SPhos-ligand,[8] other Buchwald-type ligands, NHC ligands,[9] and a MeO-KITPHOS ligand[10] showed comparable results, while simpler phosphanes as well as phosphites and isonitrile ligands were less competent catalysts. A subsequent solvent screening revealed that the best results were obtained with nonpolar solvents, such as benzene or toluene, while an increase in polarity of the solvent, for example, dichloromethane or dioxane, led to a significant decrease in yields.[6] While methyl-substituted diyne **1b** delivered comparable results under the optimized conditions (Scheme 1), no reaction or only slow and unselective conversions were observed with sterically hindered alkynes, such as *tert*-butylacetylene, TMS-protected alkynes, and phenyl-substituted alkynes. Because of their high reactivity, terminal alkynes led to complex mixtures of inseparable products. In addition to the problems resulting from bulky substituents on the alkynes, another drawback of this strategy was the impossibility of controlling the regio- and positional selectivity of the nucleophilic attack in the case of the intermolecular addition of the nucleophile to unsymmetrical substrates.

Scheme 1. Intermolecular Domino Reaction of 1,5-Diynes with Methanol



1a R = *n*Bu
1b R = Me

2a (65%)
2b (50%)

When screening other nucleophiles with terminal diyne **1c** in benzene, instead of the expected products arising from the incorporation of the nucleophile, we observed the incorporation

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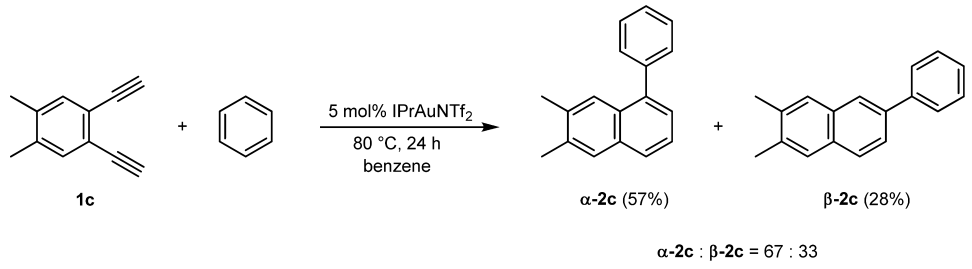
Scheme 2. Intermolecular Addition of Benzene to 1c



of benzene. A mixture of two isomers was isolated; their ratio depended on the nucleophile used in the reaction. Therefore, we performed the reaction in benzene in the absence of other nucleophiles. Two products were gained in an overall yield of 85% and in a 2:1 ratio (Scheme 2). Fortunately, we were able to obtain crystals of both products. The results of the X-ray crystal structure analyses unambiguously proved the formation of α- and β-phenylnaphthalenes ***α*-2c** and ***β*-2c** (Figure 1).

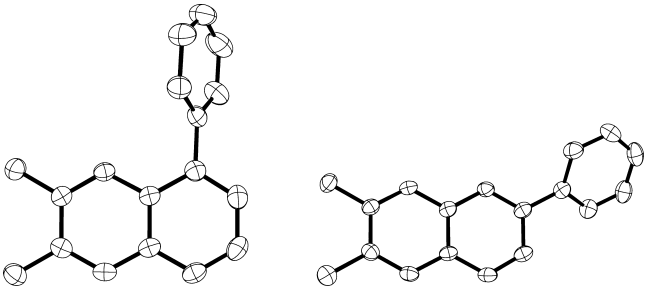
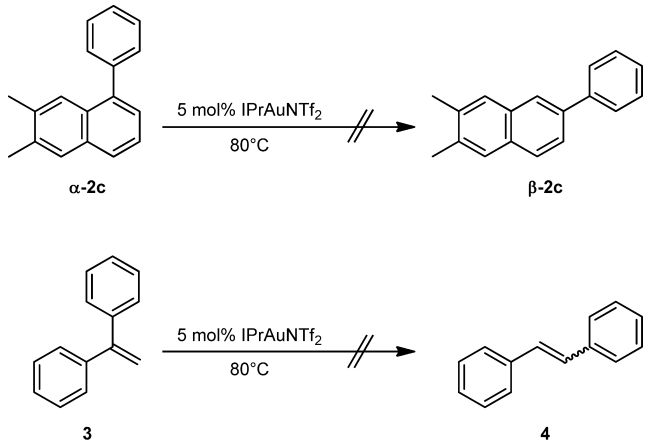


Figure 1. Solid-state molecular structures of ***α*-2c** (left) and ***β*-2c** (right).

2.2. Screenings of Different Parameters and Their Influence on the Selectivity. *2.2.1. Nature of the Catalyst.* Encouraged by these findings, a new catalyst screening was performed for the benzene addition reaction as well (Table 1 and Figure 2). Control experiments without catalyst, with *p*-TsOH, as well as with $AgNTf_2$ did not show promising results. The use of simple complexes, such as AuCl and $AuCl_3$, also led to poor results, even if silver salt[11] was added.[6] In contrast to the addition of methanol, SPhos and KITPHOS complexes only showed moderate performance for the reaction with benzene (entries 12 and 13). Of all the screened gold complexes, only one phosphite complex (entry 15) and the $IPrAuNTf_2$ NHC complex (entry 1) showed good to excellent yields, while structurally related complexes possessed only poor reactivity (entries 7, 8, 9, 14). While most of the complexes led predominantly or exclusively to the formation of the expected α product, significant amounts of the unexpected β-naphthalene were observed with the IPr−NHC complex. Gold-catalyzed intermolecular nucleophilic addition reactions with terminal alkynes usually form the Markovnikov-type products, and only a few examples are reported for the anti-Markovnikov case.[12] A remarkable counterion effect on the selectivity was observed during the screening of different silver salts. While silver hexafluoroantimonate (entry 4) delivered α-naphthalene ***α*-2c** as the main product, silver triflate delivered mainly the β regioisomer (entry 5). Silver triflimide (entry 2) led to an equal mixture of the two isomers. Interestingly, the use of an isolated preactivated gold−triflimide complex instead of the in situ activation led to a slightly different product distribution (α:β = 67:33 vs 51:49; entries 1 and 2). The reason for this difference in ratios might be the incomplete activation process. This was further confirmed through the experiments discussed in section 2.2.5 and indicated by the results of the use of IPrAuCl without any further activation (entry 3). In this case, a high preference for the β-isomer (α:β = 7:93) was found, albeit after prolonged reaction times.

To exclude a formation of the β product by a rearrangement after an initial Markovnikov addition, the α product was subjected to the gold catalyst under the reaction conditions. No conversion to the β product could be observed (Scheme 3, upper part). Furthermore, model substrate **3** was used to verify if a possible alkene formation (from the alkyne and benzene, Markovnikov hydroarylation) in the first reaction step and a subsequent rearrangement to the thermodynamically more stable stilbene derivative **4** are possible (Scheme 3, lower part). Like in the previous case, no isomerization was observed under the reaction conditions. The enyne corresponding to **3** has an entirely different reactivity; see section 2.3.3.

Scheme 3. Control Experiments Excluding a Formation of *β*-2c from *α*-2c



2.2.2. Influence of the Catalyst Loading at Room Temperature. Different sets of experiments were performed to understand the influence of the catalyst on the selectivity. Interestingly, if the reaction was performed not at 80 °C, but at room temperature, a shift in selectivity toward α product ***α*-2c** was detected. However, only low conversions were observed using the identical catalyst loading of 5 mol % (Table 2, entry 1). Therefore, we increased the amount of added catalyst, and complete conversion was possible with 15 mol % catalyst with an excellent α-selectivity (Table 2, entries 2 and 3), albeit after prolonged reaction times.

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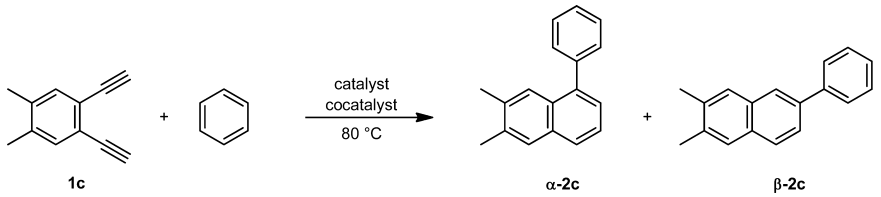
Table 1. Screening of Different Catalysts[a]



entry	catalyst	cocatalyst	time (h)	conv (%)	yield **α**-2c (%)	yield **β**-2c (%)	**α**-2c:**β**-2c	total yield (%)
1	$IPrAuNTf_2$		6	100	60	30	67:33	90
2	IPrAuCl	$AgNTf_2$	24	100	44	42	51:49	86
3	IPrAuCl		10 days	95	5	62	7:93	67
4	IPrAuCl	$AgSbF_6$	24	100	58	20	74:26	78
5	IPrAuCl	AgOTf	24	100	31	48	39:61	79
6	$IPrAu^{III}Cl_3$	$AgNTf_2$	6	100	62	7	90:10	69
7	NACAuCl	$AgNTf_2$	24	44	12	1	92:8	13
8	IBioxAuCl	$AgNTf_2$	24	61	21	2	91:9	23
9	SIPr*i*PrAuCl	$AgNTf_2$	24	88	44	5	90:10	49
10	Ph_3PAuCl	$AgNTf_2$	24	59	18	1	95:5	19
11	$(o\text{-}CF_3\text{-}Ph)_3PAuCl$[b]	$AgNTf_2$	24	83	31	3	91:9	34
12	$SPhosAuNTf_2$		24	95	13	11	54:46	24
13	MeO-KITPHOS-$AuNTf_2$		24	100	13	19	41:59	32
14	$(F_3CCH_2O)_3PAuCl$	$AgNTf_2$	24	66	17	0	100:0	17
15	$(2,4\text{-di-}t\text{BuPhO})_3PAuCl$	$AgNTf_2$	24	100	60	0	100:0	60

[a]Unless stated otherwise, reaction of diyne **1c** (12 mg) was carried out with 5 mol % catalyst and 15 mol % cocatalyst in benzene (0.5 mL) in a small vial at 80 °C. Conversions and yields were determined after 24 h by GC using 1 equiv of hexamethylbenzene as an internal standard. [b]Synthetic procedure and crystallographic data are given in the Supporting Information.

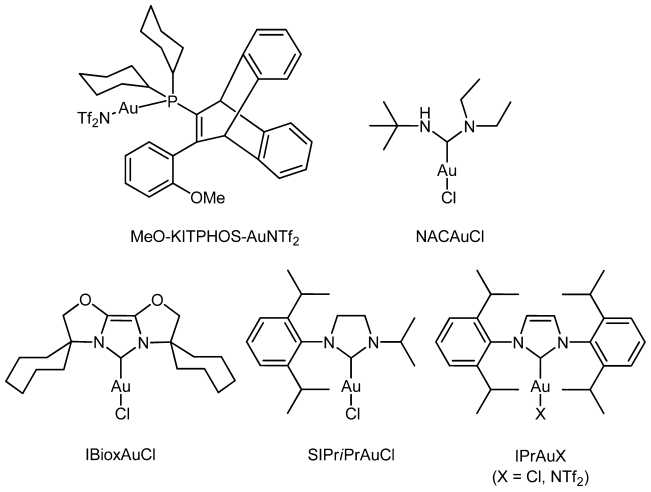


Figure 2. Gold catalysts used for the screening.

2.2.3. Influence of the Temperature on the Selectivity. To investigate the effect of the temperature on the selectivity, reaction temperatures were varied (room temperature; 40, 60, and 80 °C), and the product selectivity was determined via GC techniques after different conversion times.[6] For all the monitored temperatures, a fast conversion to the α product was observed in the beginning of the reaction and almost no β product was formed at this stage. As visible from Figure 3 (reaction at 60 °C) after an initiation phase, a linear formation of the β product was observed and the rate of formation of the α product was slower than before (but also linear). As the rate of the β product formation is higher than that of the α product formation after the initiation phase, the selectivity of the reaction shifts to higher β:α ratios as the reaction progresses (Figure 4). Similar observations could be made from the other experiments at elevated temperatures.

Table 2. Influence of the Catalyst Loading on the Conversion and Yield for $IPrAuNTf_2$ at Room Temperature[a]

entry	catalyst loading (mol %)	temp (°C)	time (h)	conv (%)	yield **α**-2c (%)	yield **β**-2c (%)	**α**-2c:**β**-2c	total yield (%)
1	5	~20 (rt)	48	43	31	1	97:3	32
2	10	~20 (rt)	48	92	70	1	99:1	71
3	15	~20 (rt)	48	100	80	1	99:1	81

[a]Conversions and yields were determined by GC using 1 equiv of hexamethylbenzene as an internal standard.

2.2.4. Catalyst Loading at Elevated Temperature. In addition to the experiments at room temperature from Table 2, we then tested different catalyst loadings, but at elevated temperatures where a competing β pathway should be possible.[6] Figure 5 illustrates the high dependency of the reaction selectivity on the catalyst loading. High catalyst loadings lead to the favored formation of the α isomer, whereas the β product was mainly formed when using low catalyst loadings.

To check if the active catalyst was changed under the reaction conditions at elevated temperatures, the $IPrAuNTf_2$ was heated in benzene for 48 h at 80 °C prior to the addition of the starting material. No effect on the conversion rates or influence on the selectivity was observed.

2.2.5. Additives. Inspired by the finding that the in situ activation led to a different selectivity than the preactivated catalyst (see Table 1), we then focused on the use of different additives (Table 3). An increasing amount of nonactivated IPrAuCl as an additive led to higher amounts of the β product (entries 1−3). Whereas silica gel as an acidic support did not

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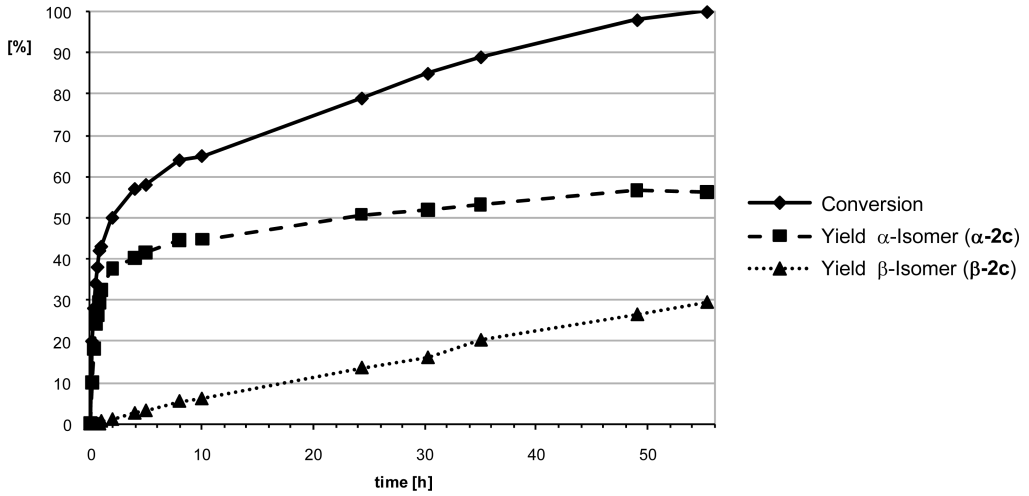

Figure 3. Conversion and yields for different reaction times at 60 °C (5 mol % IPrAuNTf$_2$).

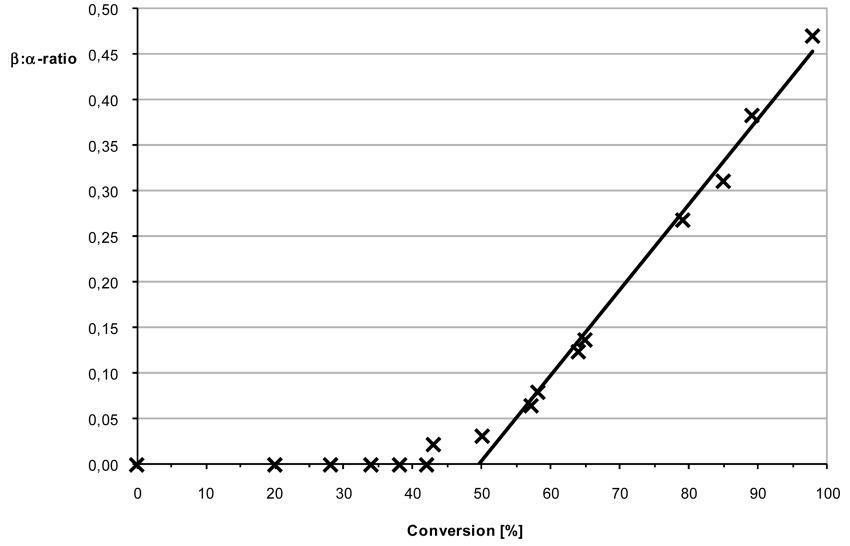

Figure 4. β:α ratios at different conversions (5 mol % IPrAuNTf$_2$, 60 °C).

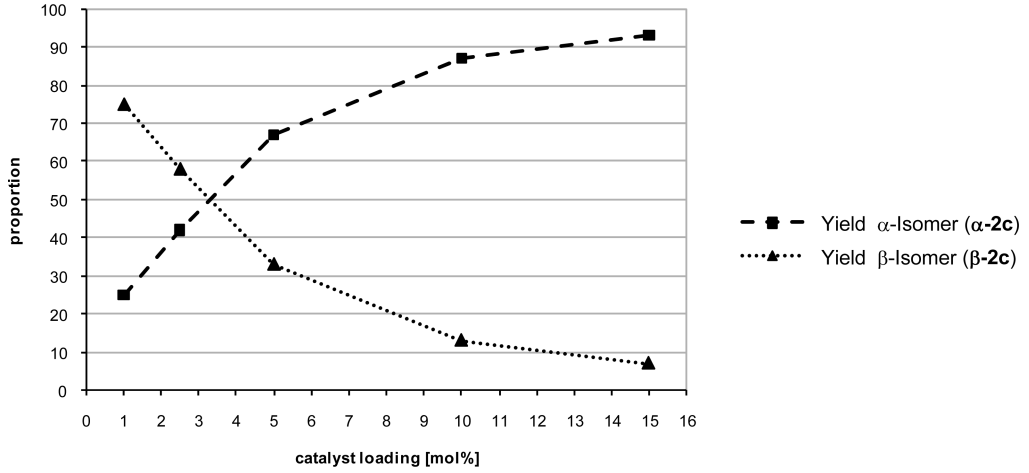

Figure 5. Dependency of the selectivity on the catalyst loading (IPrAuNTf$_2$, 80 °C).

have a great impact on the reaction course (entry 4), the use of both basic and neutral aluminum oxide greatly enhanced the formation of the β isomer (entries 5−8). Even if only 1 equiv of aluminum oxide was used, a significantly higher amount of the β product was formed (entry 5). Furthermore, even at room temperature, a high β-selectivity was possible by the use of additional aluminum oxide, but reaction rates turned out to be low in this case (entry 8). Triethylamine as a basic additive was

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Table 3. Influences of Additives on the Selectivity (5 mol % IPrAuNTf$_2$)[a]

entry	additive	equiv	time (h)	yield *α*-2c (%)	yield *β*-2c (%)	*α*-2c:*β*-2c	total yield (%)
1[b]			6	38	52	42:58	90
2[b]	IPrAuCl	0.1	6	22	67	25:75	89
3[b]	IPrAuCl	0.25	6	18	70	20:80	88
4[c]	SiO_2	1.0	6	52	33	61:39	85
5[c]	Al_2O_3 (neutral)	1.0	24	15	70	18:82	85
6[d]	Al_2O_3 (neutral)		1	3	84	3:97	87
7[d]	Al_2O_3 (basic)		24	3	74	4:96	77
8[d,e]	Al_2O_3 (neutral)		192	9	80	10:90	89
9	NEt_3	1.0	24	2	86	2:98	88
10	NEt_3	0.1	24	2	89	2:98	91

[a]Conversions and yields were determined by GC using 1 equiv of hexamethylbenzene as an internal standard. In all cases, full conversion was observed. [b]2.5 mol % IPrAuNTf$_2$. [c]The additive was heated with the catalyst for 1 h at 80 °C before the standard solution of the substrate and the internal standard were added. [d]The catalyst was loaded on top of a pipet with 500 mg of Al_2O_3. Benzene (2 mL) was flashed through the pipet, and the dried ALOX/catalyst mixture was used in the reaction. [e]Performed at room temperature.

also efficient at 80 °C. With 1 equiv, a nearly perfect *β*-selectivity could be achieved (*α*:*β* = 2:98; entry 9), and even catalytic amounts of triethylamine (10 mol %) delivered an excellent selectivity in comparable reaction times (entry 10).

Different pyridine bases were also tested as additives. Here, only the bulky 2,6-di-*tert*-Bu-pyridine led to complete conversions and the selectivity enhancement was less effective (*α*:*β* = 10:90, 5 mol %, 80 °C) than with triethylamine.[6]

Repeated reaction runs were possible for adsorbed gold catalyst on neutral aluminum oxide (Table 4). Up to five runs

Table 4. Adsorption on Neutral Al_2O_3 (5 mol % IPrAuNTf$_2$, 80 °C)[a]

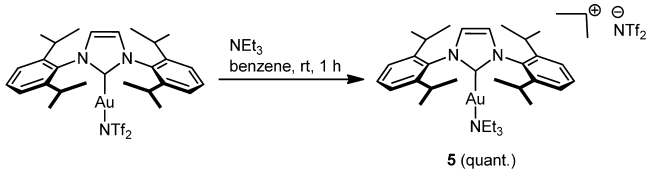
run	conv (%)	time (h)	yield *α*-2c (%)	yield *β*-2c (%)	*α*-2c:*β*-2c	total yield (%)
1	100	1	3	84	3:97	87
2	100	4.5	4	86	4:96	90
3	100	10	4	80	5:95	84
4	100	18	4	82	5:95	86
5	100	26	3	70	4:96	73

[a]The catalyst was loaded on top of a pipet with 500 mg of Al_2O_3. Benzene (2 mL) was flashed through the pipet, and the dried ALOX/catalyst mixture was used in the reaction. Conversions and yields were determined by GC using 1 equiv of hexamethylbenzene as an internal standard. After one run, the ALOX/catalyst system was filtered, washed with benzene, and reused in the next run.

were possible without a significant decrease in the turnover number. After each run, the catalyst could be recovered easily by simple filtration, but the catalytic activity (turnover frequency) decreased; the reaction time increased from 1 to 26 h. Still, overall, a remarkable 100 turnovers were achieved.

Attempts to run the reaction with triethylamine at room temperature failed. Here, a fast formation of a crystalline solid was observed after the addition of the base to the catalyst solution even in the absence of the substrate. Hence, we mixed the gold catalyst with triethylamine in benzene in a larger scale, and we were able to isolate a quantitative amount of the amine complex **5** (Scheme 4). The assignment of the structure could also be confirmed by an X-ray crystal structure analysis (Figure 6).

Scheme 4. Preparation of Amine Complex 5



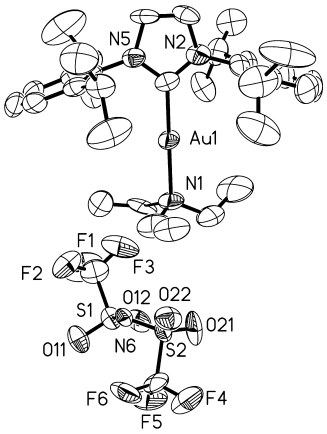
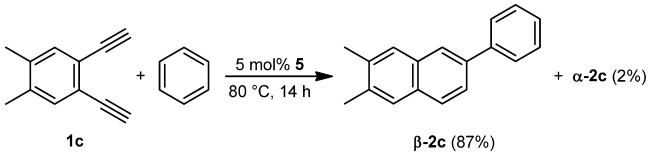


Figure 6. Solid-state molecular structure of **5** (Au–N = 2.092(7) pm; Au–C = 1.949(8) pm; C–Au–N = 179.5(3)°).

To investigate if this new catalyst would be a bench-stable catalyst for the selective formation of the *β*-naphthalene derivative ***β*-2c**, we performed the transformation without any additional additives. To our delight, the desired product was formed in excellent selectivity (*α*:*β* = 2:98, Scheme 5).

Scheme 5. *β*-Selective Reaction with Catalyst 5



2.3. Mechanistic Investigation. *2.3.1. Reactivity of Gold Acetylides Formed under the Reaction Conditions.* On the basis of the high influence of basic additives on the reaction, we concentrated on gaining further insight into the origin of the change in selectivity and the mechanism of this reaction. As the formation of gold acetylides from terminal alkynes is a common reaction under basic conditions,[13] we considered gold acetylides as intermediates in the catalytic cycle.[14]

To verify if a gold acetylide may participate, we synthesized monogold alkynyl complex **6** (Figure 7).[6]

Heating the isolated gold acetylide **6** in benzene and in the absence of additional active catalyst led to no conversion even after 24 h at 80 °C. Additionally, no conversion was observed when a catalytic amount of acetylide **6** (5 mol %) was added to diyne **1c** under the same conditions. Hence, we added additional active catalyst (2.5 mol % IPrAuNTf$_2$) to a mixture

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Scheme 6. Equilibrium between Free Catalyst and Activated Substrate 6

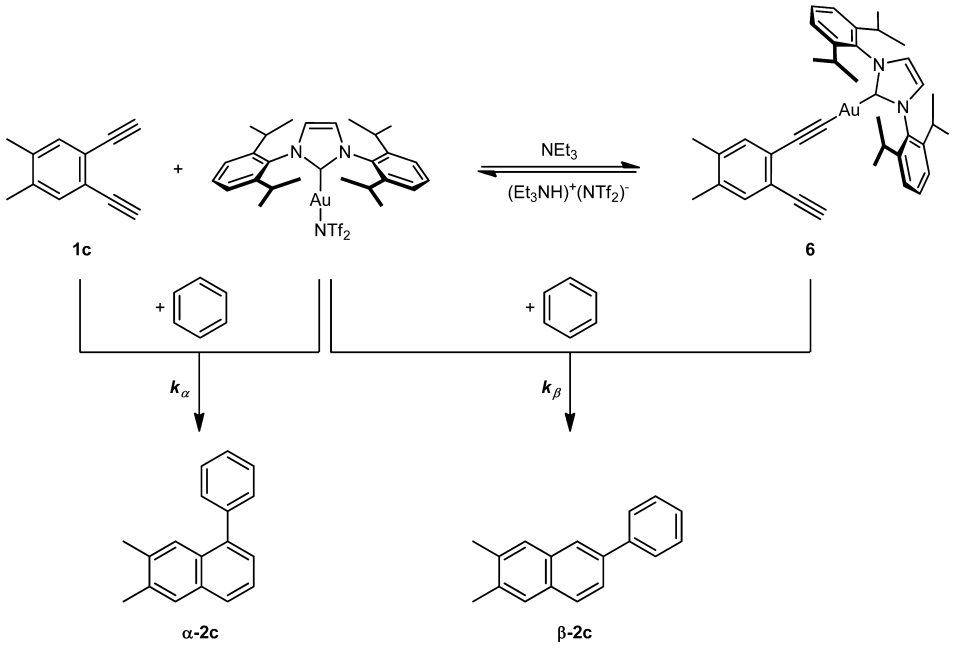

Table 5. Investigation of a Possible Equilibrium between Diyne 1c (5 mol % IPrAuNTf$_2$, 80 °C) and 6 under Different Conditions[a]

entry	catalyst	additive[b]	time (h)	conv (%)	yield α-2c (%)	yield β-2c (%)	α-2c:β-2c	total yield (%)
1	gold acetylide **6**	1 equiv NEt_3	6	9	0	2		2
2	gold acetylide **6**	10 mol % $HNTf_2$	6	100	60	24	72:28	84
3	gold acetylide **6**	1 equiv NEt_3 **and** 10 mol % $HNTf_2$	24	100	2	88	2:98	90
4	$IPrAuNTf_2$		6	100	60	30	67:33	90

[a]Conversions and yields were determined by GC using 1 equiv of hexamethylbenzene as an internal standard. [b]Added after 24 h.

of diyne **1c** and 5 mol % acetylide **6** at 80 °C. In this case, the β product was detected almost exclusively (α:β = 3:97 instead of 42:58 without additive) in 85% yield after 12 h! Thus, the reaction of the active catalyst with acetylide **6** must be considerably faster than that with diyne **1c**, if one considers the 20-fold excess of diyne **1c**. Furthermore, diyne **1c** must be transformed to more reactive acetylide **6** during the catalytic cycle as otherwise an unselective reaction course would be detected after all of the acetylide is consumed. The lack of catalytic activity of the gold acetylide without additional catalyst seems to be paradox; as in the triethylamine case (as described above, the reaction even works with 100 mol % of triethylamine, i.e., 20 equiv of base with respect to the catalyst!), a fast formation of this species should inhibit the further reaction. In this case, a possible equilibrium of free catalyst and acetylide can be considered. This equilibrium should be influenced by the base and the corresponding acid that is formed during acetylide formation (Scheme 6).

To prove this assumption, diyne **1c** was subjected to catalytic amounts of gold acetylide **6** in the presence of different acidic and basic additives (Table 5). As expected, the control experiment with additional triethylamine did not show any catalytic activity (entry 1). Addition of bistrifluoromethanesulfonimide (10 mol %, entry 2) indeed led to catalytic activity; in this case, an even higher α-selectivity was observed than for the reaction without any additive (entry 4). Under the original reaction conditions in the presence of triethylamine, the corresponding triethylammonium triflimide should lead to buffered reaction conditions. Thus, we considered a mixture of

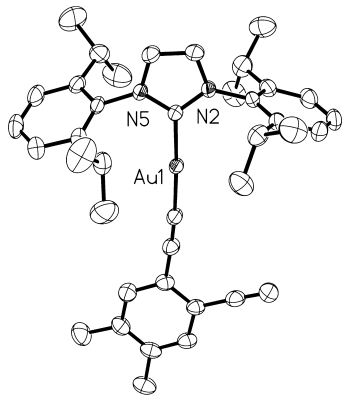

Figure 7. Molecular structure of acetylide **6** in the solid state (Au−C_{alkyne} = 1.984(3) pm; Au−$C_{carbene}$ = 2.010(2) pm; C−Au−C = 177.10(9)°).

these two species to simulate the correct acid-to-base ratio that should exist during the reaction (entry 3). In fact, addition of a premixed solution of triethylamine and bistrifluoromethanesulfonimide to the starting material led to catalytic activity, and excellent β-selectivity was observed (α:β = 2:98). In summary, the selectivity can nicely be explained by the above equilibrium. For an efficient formation of the β product, the acetylide must coexist with active catalyst in solution, which is only possible in a buffered medium. Addition of acid shifts the equilibrium from Scheme 6 to the left side. Therefore, only the diyne **1c** and the

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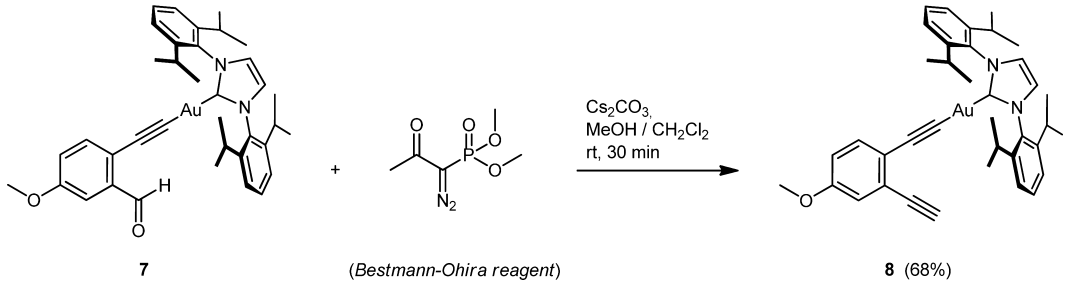
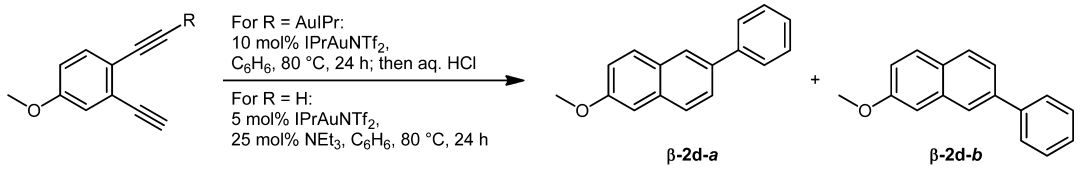
Scheme 7. Bestmann–Ohira Chain Extension of Gold Acetylide 7



7 (*Bestmann-Ohira reagent*) **8** (68%)

Scheme 8. Influence of a Gold Acetylide on the Positional Selectivity



8 R = AuIPr
1d R = H

β-2d-*a* **β-2d-*b***

R = AuIPr (76%) **β-2d-*a*** : **β-2d-*b*** = ~91:9
R = H (81%) **β-2d-*a*** : **β-2d-*b*** = ~37:63

active catalyst coexist, causing the reaction to select for the α product. If no conjugated acid is present, the whole reaction is inhibited as no active catalyst for the β-selective conversion of the acetylide complex **6** is formed. Regarding the frequent use of terminal alkynes as substrates for gold-catalyzed reactions, it seems likely that gold acetylides take part as reactive

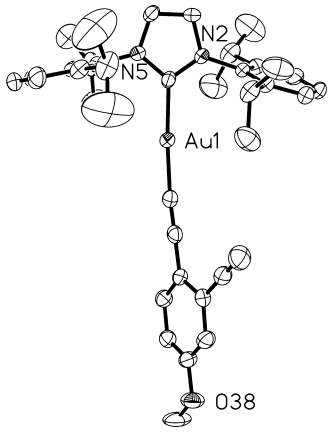


Figure 8. Solid-state molecular structure of **8** ($Au-C_{alkyne}$ = 1.985(5) pm; $Au-C_{carbene}$ = 2.024(5) pm; C–Au–C = 175.50(18)°).

intermediates in many of these reactions. To the best of our knowledge, there are no mechanistic investigations on the effect of these species concerning selectivity as well as reactivity properties. Therefore, we focused our investigations on obtaining more information about the reaction mechanism.

2.3.2. Comparing the Positional Selectivity of Gold Acetylides and Terminal Alkynes. To explore whether the terminal alkyne or the gold acetylide is favored for the benzene addition, we used asymmetrically substituted diyne **1d** as a substrate for the gold catalysis. Furthermore, the corresponding gold acetylide **8** was prepared from aldehyde **7**. A chain extension using an excess of Bestmann–Ohira reagent[15] was possible even in the presence of the gold acetylide moiety (Scheme 7). This strategy was used to avoid problems with the

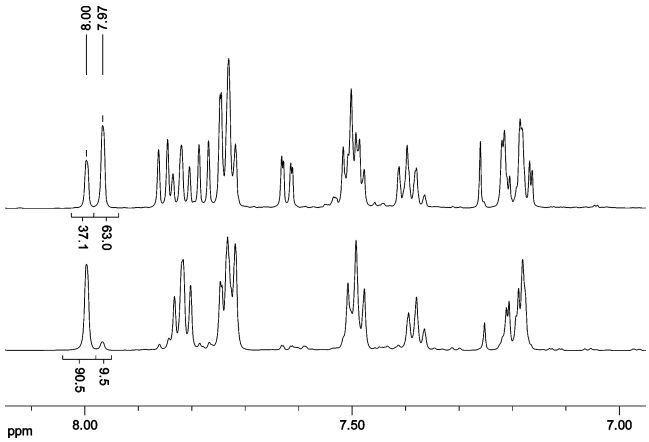


Figure 9. NMR comparison of the reaction of diyne **1d** (top) and the reaction of gold acetylide **8** (bottom).

positional selectivity that should occur by the use of diyne **1d** as the starting material. The assignment of monoacetylide **8** was proven by the results of an X-ray structure analysis (Figure 8).

Both of the substrates were subjected to the gold catalyst, and the selectivity was analyzed by ^{1}H NMR integration (Figure 9, Scheme 8).[6] In the case of gold acetylide **8**, aqueous hydrochloric acid was added after complete conversion to ensure complete protodemetalation. Remarkably, with mono-gold acetylide **8**, a high selectivity was observed. In this case, the benzene was almost exclusively added to the alkyne that had been bearing the NHC–gold unit before! Not surprisingly, the control experiment with substrate **1d**, which contains two terminal alkynes, led to poor selectivity. Furthermore, in this case, a majority of the regioisomer ***β*-2d-*b*** was formed. Here, the selectivity is most probably determined by the difference in pK_a values of the two alkynes based on the mesomeric donor effect of the methoxy group, which only influences the para position. The gold acetylide forms at the more acidic alkyne position meta to the methoxy group, leading to the formation of ***β*-2d-*b*** as the main product.

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Scheme 9. Mechanistic Consideration of a Benzene Addition Prior to the Cycloisomerization

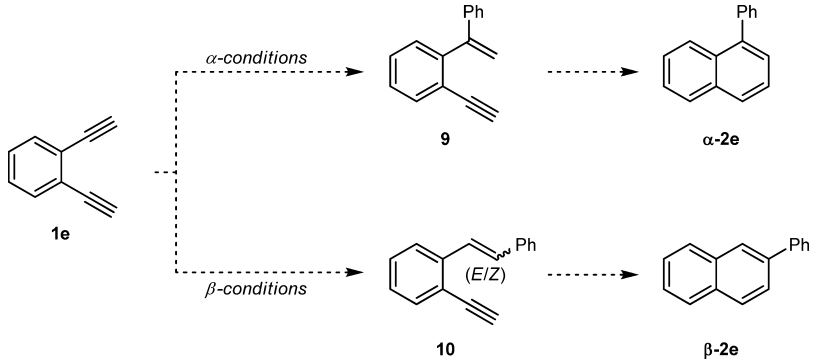
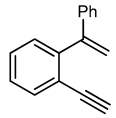
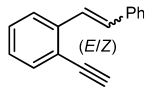
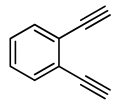


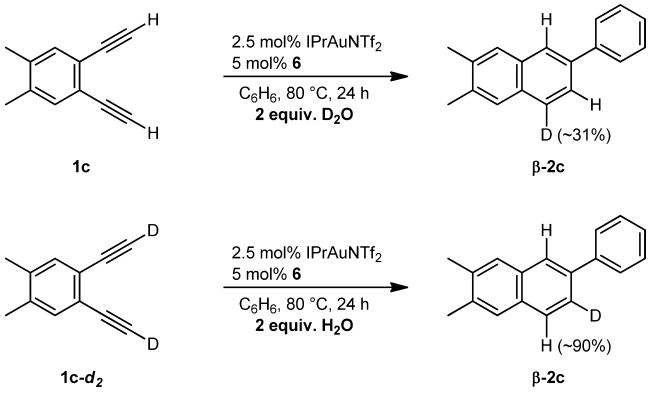
Table 6. Product Distribution for the Conversion of the Possible Intermediates 9 and 10

Entry	Substrate	Conditions	11	α-2e	β-2e
1	 9	1 mol% $IPrAuNTf_2$ C_6D_6 (CD_2Cl_2), rt, 1 h	53 (69)	47 (31)	0 (0)
2	 10	5 mol% $IPrAuNTf_2$ C_6D_6, rt (65 h) → 80 °C (10 h)	slow decomposition		
3	 1e	5 mol% $IPrAuNTf_2$ 10 mol% NEt_3 C_6H_6, 80 °C	0	5	95

2.3.3. Exclusion of the Participation of Enynes Generated by Initial Hydroarylation. One explanation for the difference between terminal alkynes and gold acetylides could be the formation of two regioisomeric enyne systems **9** and **10**, which undergo selective intramolecular cyclization to the naphthalene isomers (Scheme 9). In the case of a terminal alkyne, a Markovnikov-type addition would be expected, which should lead to enyne **9**. This would be consistent with previously reported intermolecular hydroarylations of terminal alkynes.[16] If the gold caused an umpolung of the alkyne in the gold acetylide, the anti-Markovnikov-type addition could lead to the β isomer.

Thus, we synthesized the possible enyne compounds **9** and **10** and subjected them to the catalyst (Table 6). The conversion of enyne **9** in benzene led to an inseparable mixture of products derived from an unselective 5-*exo*-*dig* and 6-*endo*-*dig* cyclization process (entry 1). As there were reports with similar systems using dichloromethane as a solvent,[17] we used these published conditions as well (entry 1; parentheses), but no significant change in selectivity was observed. On the basis of these findings, a mechanism that involves an initial intermolecular formation of an enyne system can be excluded for the formation of the α product. This was also confirmed by the fact that, in all the aforementioned catalyses, we never observed any fulvene derivatives like **11**! The catalysis with regioisomeric stilbene derivative **10** only showed very slow conversion (entry 2). Only a complex mixture of inseparable compounds was observed. To exclude an electronic effect from the methyl groups in **1c**, unsubstituted diyne **1e** was converted under the optimized conditions (entry 3). In contrast to the above-mentioned enyne systems, an exclusive formation of

Scheme 10. Crossover Labeling Experiments with Additional Water



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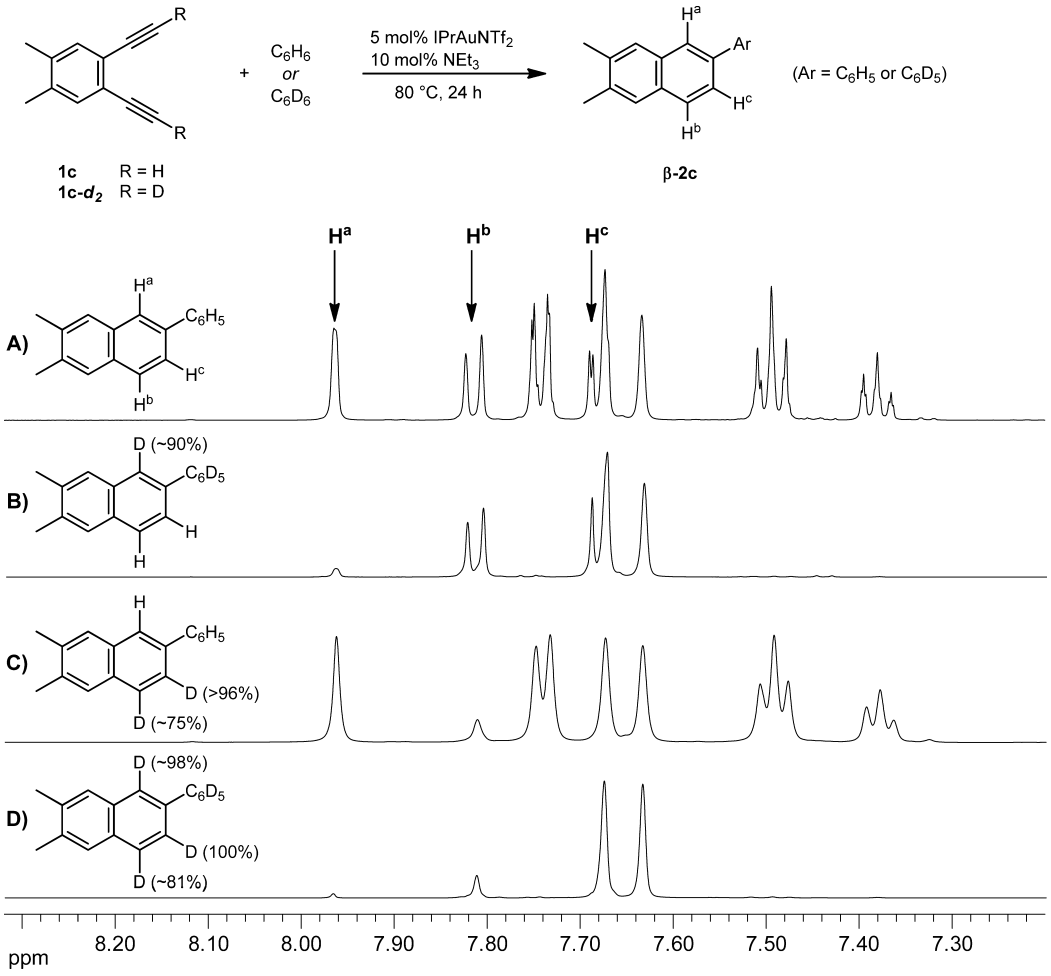

Figure 10. Isotopic labeling studies: (A) **1c** + C_6H_6; (B) **1c** + C_6D_6; (C) **1c**-d_2 + C_6H_6; (D) **1c**-d_2 + C_6D_6.

naphthalene derivates ***α*-2e** and ***β*-2e** could be determined in excellent β-selectivity (entry 3). For this reason, a participation of an enyne of type **10** can also be excluded as intermediates during the formation of the β products.

2.3.4. Isotopic Labeling Experiments. For further mechanistic insights, **1c**-d_2 was prepared. The undeuterated **1c** as well as deuterated **1c**-d_2 were both converted in deuterated and undeuterated solvent with 10 mol % triethylamine as an additive (Scheme 10 and Figure 10).[6] To exclude exchange processes, **1c**-d_2 was heated for 16 h in deuterated benzene. Even when H_2O was added, no H/D exchange was observed. The experiment with undeuterated **1c** in deuterated benzene (under β-promoting conditions) led to a 90% incorporation of the deuterium at the α-position (Figure 10B). The other positions in the product are not affected. The crossover experiment with **1c**-d_2 in undeuterated benzene also showed a nearly quantitative incorporation of a former benzene proton in the α-position. Furthermore, H^c was not affected, and 75% of deuterium was still present in the H^b-position. As there are no other deuterium sources, the high level of deuteration at the H^b-position must originate from a former alkyne (Figure 10C).

Finally, **1c**-d_2 was converted in deuterated benzene. In this case, H^a and H^c were not affected. Interestingly, a moderate H/D exchange was observed for the H^b-position. In this case, traces of water in the solvent are responsible. To prove this assumption, crossover experiments in the presence of an excess of H_2O and D_2O were performed. To avoid a base-catalyzed H/D exchange in the presence of water, gold acetylide **6** was used as an additive. As visible from Scheme 11, only the H^b-position is affected by additional water in the solvent. Here, a remarkable isotopic effect can be monitored, whereas in the case of D_2O, only 31% of D is incorporated in the H^b-position, and in the case of H_2O, 90% of H was embedded (Scheme 11). Furthermore, no water addition was observed even if an excess of water was present.

In combination with the previous experiments, it is obvious that the proton in the H^b-position must originate from the alkyne proton itself and that traces of water in the solvent only play a minor role.

The most plausible explanation is that a gold atom is located at the H^b-position during the last stage of the reaction cascade. As no exchange was visible with benzene at this position and, therefore, also protodemetalation via the benzene is impossible, we elucidated if a possible catalyst transfer from an aryl gold intermediate to diyne **1c** is possible.[18]

2.3.5. Proof of the Catalyst Transfer. Indeed, we could prove a quantitative ligand exchange in a stoichiometric experiment with phenyl gold precursor **12** and starting diyne **1c** (Scheme 12 and Figure 11). As during most of the conversion (with the exception of the final phase), a great excess of diyne **1c** is present under the reaction conditions, it seems very likely that a catalyst transfer of an aryl gold intermediate to starting diyne **1c** occurs during the reaction.

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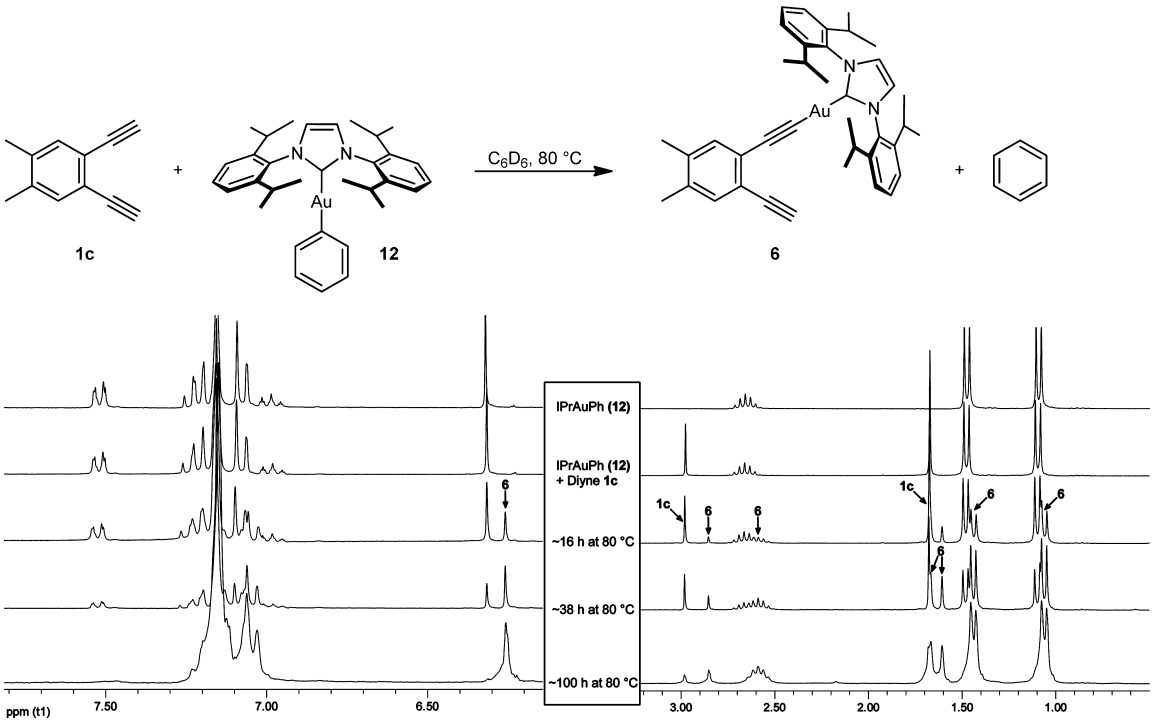


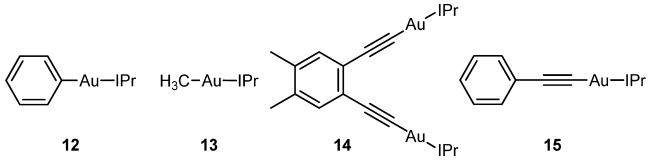
Figure 11. Ligand-exchange experiment.

Catalytic amounts of various organo-gold additives provided further proof for this hypothesis. Even if only 10 mol % of the additive was added at the same time with the catalyst, extremely high β-selectivity was observed for all of the tested species (Table 7). This indicates that a very fast exchange process must take place initiating the β-cycle by formation of the gold acetylide **6**.

Having proven the catalyst transfer mechanism, we wanted to verify the kinetics/product selectivity experiments from Figure 3 under these optimized conditions. The results are shown in Figure 12. We were delighted to see that, indeed, no initiation phase is observed. The β product is formed from the very beginning, and the product formation is almost linear for most of the conversion. Under these optimized conditions, the selectivity for the β product is high throughout the whole conversion; even at the end, a β:α ratio of 98:2 is detected.

2.3.6. Isolation of Stable Organo-Gold Intermediates. As mentioned earlier, our efforts to perform a β-selective reaction at room temperature in the presence of triethylamine failed because of the formation of amine complex **5**. Considering the above-mentioned possibility of adding organo-gold compounds for the initiation of the β-cycle, we were curious if a β-selective reaction was possible at room temperature by the use of gold acetylide **6** as an additive. After the addition of the gold catalyst to the starting diyne and catalytic amounts of acetylide, an immediate precipitation of bronze-colored tiny needles took place and no formation of a naphthalene was monitored. An experiment with stoichiometric amounts of gold acetylide and $IPrAuNTf_2$ gave the same result. By simple filtration of the residue and washings with pentane, we were able to obtain a solid that could be fully characterized (Scheme 11). Fortunately, we were able to obtain crystals suitable for X-ray structure analysis as well. The result of this analysis unambiguously proves the formation of a *gem*-diaurated aryl species **16** (Figure 13). While several reports of related species exist,[14a,19] including an exciting β-naphthyl digold complex of Osawa et al.,[19j] only one other publication reported the isolation of such species from a catalysis reaction. In that

Table 7. Influences of Various Organo-Gold Additives (10 mol %) on the Selectivity (5 mol % $IPrAuNTf_2$, 80 °C)[a]



12 13 14 15

entry	additive	time (h)	yield α-**2c** (%)	yield β-**2c** (%)	α-**2c**:β-**2c**	total yield (%)
1	**12**	6	2	85	2:98	87
2	**13**	6	3	84	3:97	87
3	**14**	13.5	2	93	2:98	95
4	**15**	6	3	88	3:97	91

[a]Conversions and yields were determined by GC using 1 equiv of hexamethylbenzene as an internal standard. Additive and catalyst were added at the same time to a standard solution of substrate and internal standard.

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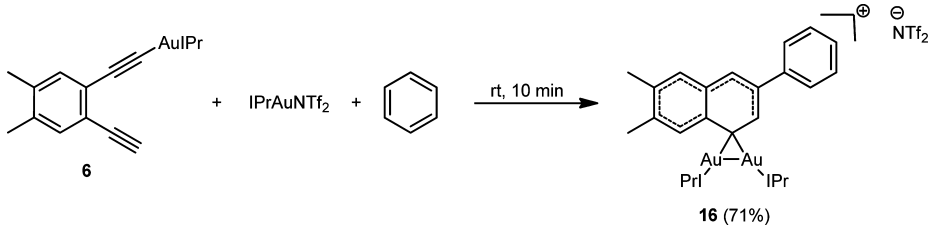
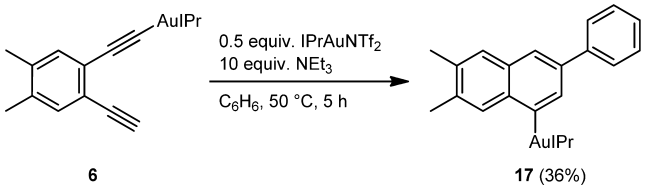
Scheme 11. Stoichiometric Preparation of *gem*-Diaurated Species 16



Scheme 12. Isolation of Monogold Aryl Intermediate 17



case, an allene starting material was applied.[20] Furthermore, no *gem*-diaurated species containing carbene ligands at the metal center can be found in the literature.

Interestingly, no precipitation of complex **16** and no change in color of the reaction media were observed in the presence of triethylamine. However, a complete conversion was visible with thin-layer chromatography, and a new compound could be detected that had a different R_f value than the usual naphthalene products. In a substoichiometric experiment (lower catalyst loadings led to slow conversions in the presence of excess amounts of coordinating triethylamine), we were able to isolate this compound by column chromatography on neutral aluminum oxide (Scheme 12). Again, it was possible to obtain a crystal structure. The results of the analysis are depicted in Figure 14. In this case, a monogold aryl compound **17** was isolated.[2a,b,21] The gold atom is located at the position were the H/D exchange was visible in the deuteration experiments.

A short summary of the relevant data gained from the X-ray crystallographic analyses of the organo-gold intermediates **16** and **17** as well as *β* product ***β*-2c** is depicted in Table 8. The Au—Au bond length of *gem*-diaurated compound **16** of 276.1 pm shows a strong aurophilic interaction,[22] which is consistent with reported data for diaurated compounds.[23] Interestingly, the Au—C1 bond distances (212.5 and 213.8 pm) are also in the range of other known compounds bearing phosphane ligands at the gold atom. This indicates that the influence of the ligand at the metal center plays a minor role. In comparison to the Au—C1 bond length of monogold compound **17** (203.5 pm), a significant elongation in bond length can be observed for the diaurated species. Regarding the naphthalene skeleton, there is an elongation of the C1—C3 bond as well as the C1—C2 bond by the addition of each of the gold atoms. The most

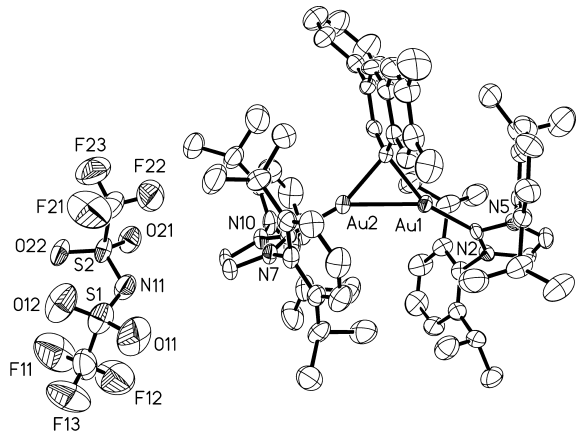


Figure 13. Solid-state molecular structure of **16** (Au—Au = 2.7607(3) pm; Au—$C_{carbene}$ = 2.018(6), 2.008(7) pm; Au—C_{arene} = 2.135(6) pm; Au—Au—$C_{carbene}$ = 152.66(18)°, 149.63(19)°; C_{arene}—Au—Au = 49.54(18)°, 49.74(17)°).

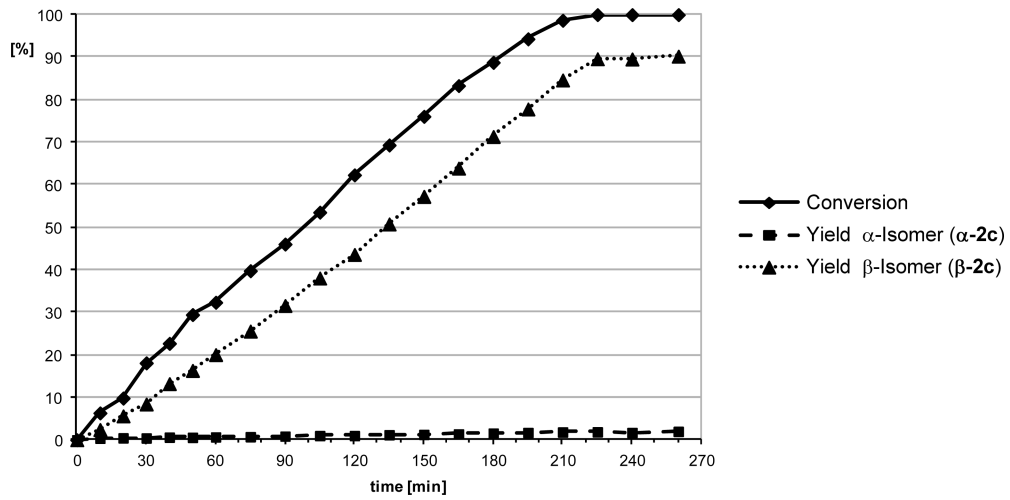


Figure 12. Conversion and yields for different reaction times with the optimized reaction conditions analogue to Table 7, entry 1 (benzene, 80 °C, 5 mol % $IPrAuNTf_2$, 10 mol % IPrAuPh as the additive to induce gold acetylide formation).

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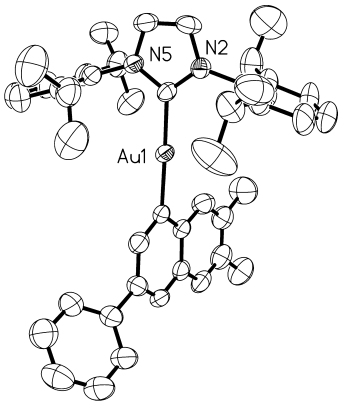


Figure 14. Solid-state molecular structure of **17** ($Au-C_{arene}$ = 2.035(6) pm; $Au-C_{carbene}$ = 2.013(6) pm; C−Au−C = 178.0(2)°).

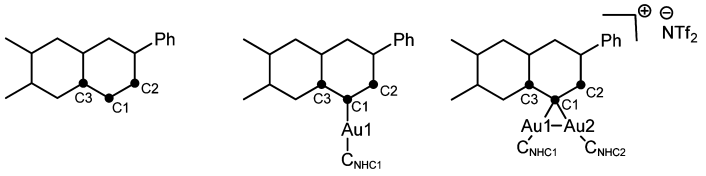
significant change can be monitored for the C1−C3 length, between the naphthalene ***β*-2c** (138.9 pm) and the *gem*-diaurated compound **16** (145.5 pm).

The triangle in the diauryl compound, which is formed by the C1−Au1−Au2 atoms, shows a significant slippage of 10.45° with respect to the naphthalene plane. This might be caused by a steric interaction of the phenyl group and the bulky carbene ligand at the metal center.

2.3.7. Catalytic Activity of the Isolated Intermediates. With the isolated gold intermediates in hand, we tested their catalytic activity for the naphthalene synthesis (Table 9). Not unexpectedly, monogold compound **17** alone did not show any activity. The 5% of product that was obtained most probably stems from protodemetalation via diyne **1c**. As mentioned earlier, the monogold acetylide **6** does not react in the absence of a weak acid as no active cationic catalyst exists (see also Scheme 6). Addition of active catalyst $IPrAuNTf_2$ to this mixture led to a selective conversion to the *β* product (entry 2). This gives further proof that it is the formation of a gold acetylide from organo-gold compound **17** that initiates the *β*-selective cycle. Last, but not least, the *gem*-diaurated species **16** was checked for its catalytic activity (entry 3). In this case, even in the absence of an additional catalyst, a fast conversion to the *β* product was monitored. We assume that, at the elevated temperature, there is an equilibrium between the *gem*-diaurated compound **16**, the monogold aryl **17**, and the active $IPrAuNTf_2$ catalyst.[24]

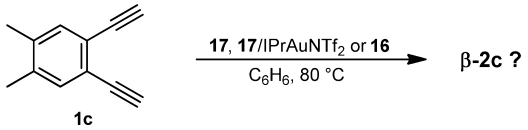
2.4. Discussion of the Possible Reaction Mechanism. Schemes 13 and 14 depict our mechanistic hypothesis of this complex reaction in the presence or in the absence of a base,

Table 8. Comparison of Structural Parameters of *β*-2c, 17, and 16



	β-2c	17	16
Bond distances (pm)			
Au1-Au2	—	—	276.1
Au1-C1	—	203.5	213.8
Au2-C1	—	—	212.5
Au1-C_{NHC1}	—	201.3	201.8
Au2-C_{NHC2}	—	—	201.3
C1-C3	138.9	141.1	145.5
C1-C2	134.2	136.7	138.2
Bond angles (deg)			
C1-Au1-Au2	—	—	49.44
Au1-Au2-C1	—	—	49.85
Au1-C1-Au2	—	—	80.71
Slippage (deg)	—	2.91	10.45
^{13}C NMR shifts (in CD_2Cl_2)			
C1	—	172.58 ppm	not visible
$C_{NHC/Carbene}$	—	197.55 ppm	184.79 ppm

Table 9. Catalytic Activity of Intermediates 16 and 17



entry	catalyst system	time (h)	conv (%)	yield *α*-2c (%)	yield *β*-2c (%)	*α*-2c:*β*-2c	total yield (%)
1	aryl-AuIPr **17** (5 mol %)	24	13	0	5		5
2	aryl-AuIPr **17** (10 mol %) + $IPrAuNTf_2$ (5 mol %)	6	100	2	95	2:98	97
3	$[aryl-(AuIPr)_2][NTf_2]$ **16** (2.5 mol %)	6	100	5	83	6:94	88

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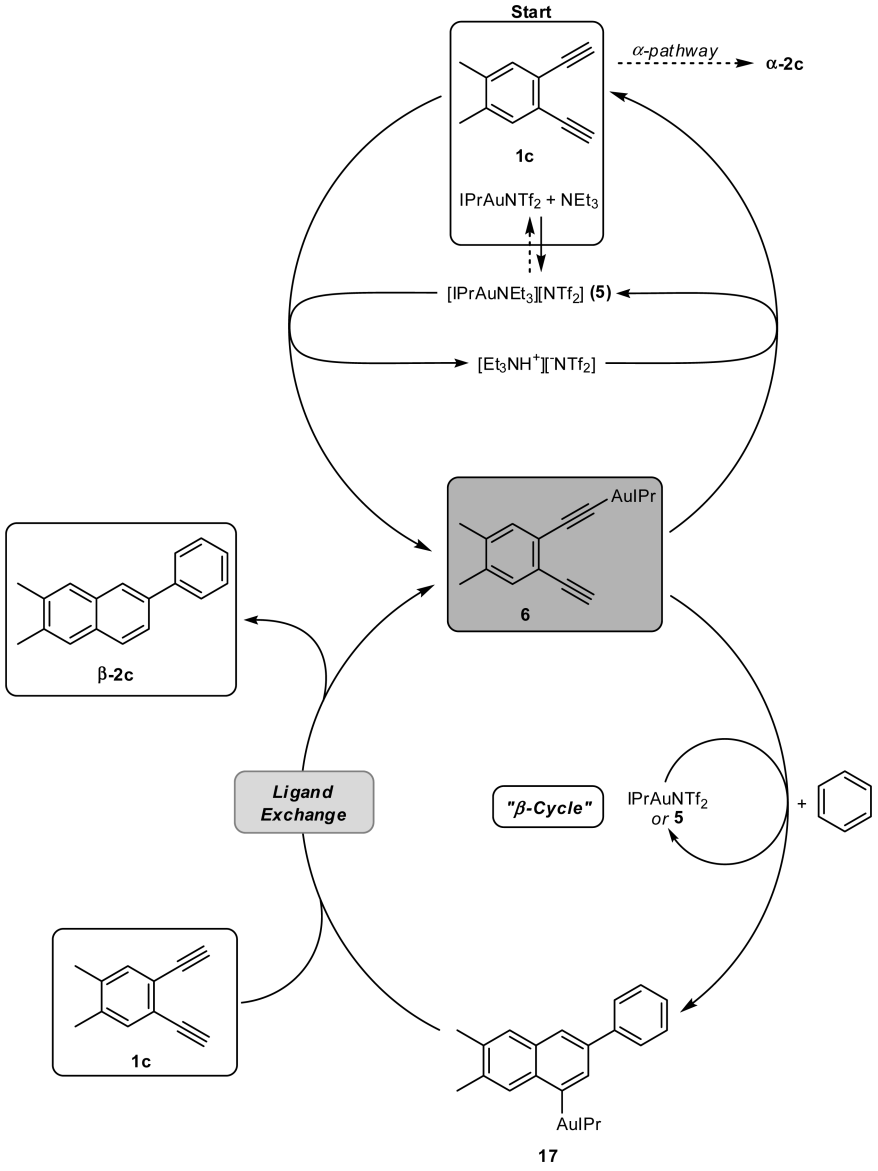
Scheme 13. Mechanistic Consideration for the Catalytic Cycle in the Presence of Triethylamine as Additive



respectively. To avoid a highly complex mechanistic scheme, they are drawn separately.

Scheme 13 is our mechanistic rationale for the reaction involving a base, such as triethylamine, as an initiator of the β-cycle. The upper cycle represents the aforementioned equilibrium between the free catalyst and gold acetylide **6** (from Scheme 6). At room temperature, no product ***β*-2c** is formed. In this case, only gold acetylide **6** can be monitored via thin-layer chromatography, indicating that not enough free catalyst is available at room temperature.

However, at higher temperatures, a balanced equilibrium between the free catalyst and activated substrate **6** exists. Because of the higher reactivity of the gold acetylide **6**, only traces of the α product are now formed. The β-selective catalytic cycle now starts with gold acetylide **6**, which reacts to form the monogold species **17**. A subsequent catalyst transfer from **17** to starting diyne **1c** leads to regeneration of the gold acetylide **6** after release of the β product.

A different mechanism must be considered in the absence of a base (Scheme 14). At the beginning of the reaction, diyne **1c** reacts with free catalyst to produce α-phenyl naphthalene gold intermediate **I**. The proton, which is released during the benzene addition step, then protodemetalates the catalyst, forming the α-product ***α*-2c**. Competing with simple protodemetalation, a catalyst transfer from intermediate **I** to diyne is also possible. This initiates the β-cycle by formation of the key intermediate **6**. A fast cyclization of **6** then takes place, but, at room temperature, all of the free catalyst is trapped via the precipitation of diaurated compound **16**. This also inhibits the α-cycle, which explains the incomplete conversions at room temperature for low catalyst loadings.

At higher temperatures, an equilibrium between diaurated compound **16** and monogold aryl **17** exists, and therefore, free catalyst is available for the reaction. As the amount of free catalyst is reduced, the reaction rate for the α product slows down. The rate-limiting step for the formation of ***β*-2c** is most probably the ligand exchange between monogold compound **17** and diyne **1c**, which regenerates gold acetylide **6**. This assumption is based on the linear reaction course even at the late state of the reaction (otherwise, the formation of ***β*-2c** should accelerate at this stage). The initiation of the β-cycle is also possible by the addition of an external organo-gold

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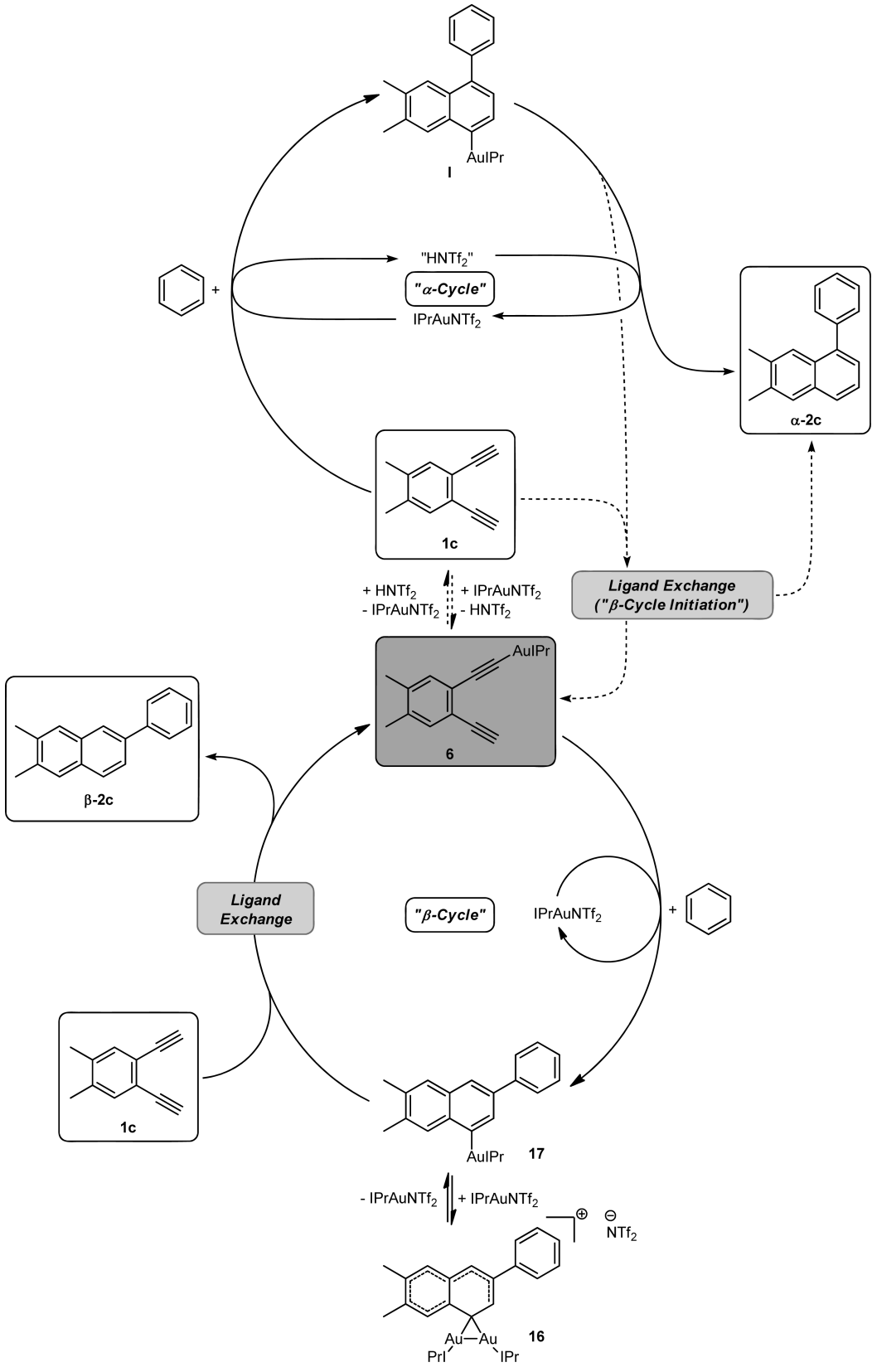
Scheme 14. Mechanistic Consideration without Base



compound. Here, even organo-gold compounds that are not intermediates of the *β*-cycle can be applied as long as they are able to perform a ligand exchange with diyne **1c**. As always, an excess of additive in regard to the activated catalyst was applied, and a constant amount of gold acetylide **6** is available at any time. Thus, the rate-limiting step is no longer the catalyst transfer, and the selectivity is controlled efficiently by the different cyclization rates of free alkyne **1c** and monoacetylide **6**.

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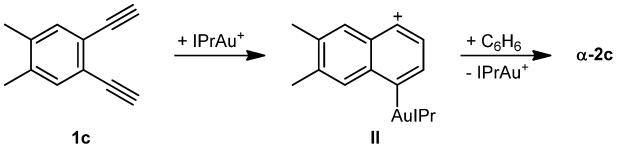
Our mechanistic insight for the selectivity-determining step is still highly speculative. For the α case, we can exclude an initial formation of an enyne via Markovnikov-type addition of benzene onto diyne **1c**. Therefore, an initial cyclization seems likely, which forms a species resembling a naphthyl cation **II** in a benzene solvent cage. Nucleophilic attack of benzene then delivers the final product ***α*-2c** after protodemetalation (Scheme 15).

Scheme 15. Mechanistic Hypothesis for the Formation of *α*-2c



One conceivable mechanistic rationale for the formation of the β product starts with the activation of the terminal alkyne by a second gold atom. A fast cyclization based on the increased nucleophilicity of the gold acetylide then delivers a naphthyl cation **III**. A related yne-yne cyclization where a nucleophilic attack of a gold acetylide onto a gold-activated alkyne takes place has previously been proposed by the Gagosz group during their synthesis of interesting cycloalkynes.[4q]

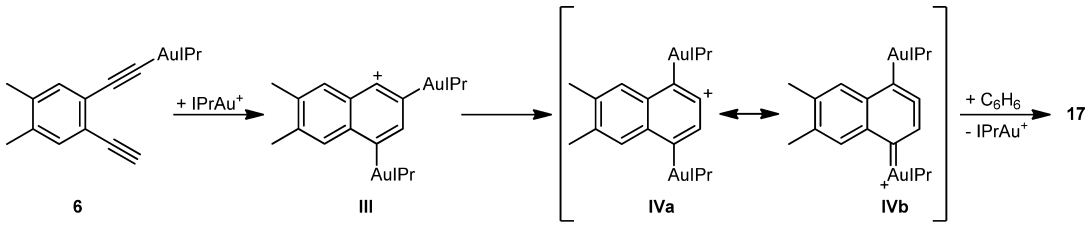
The cationic species **III** then isomerizes in a fast process via a 1,2-shift of the gold atom to β-naphthyl cation **IVa**. The latter might be additionally stabilized by the second gold atom via a mesomeric contribution of a bent allene carbenoid structure **IVb**.[25] Finally, nucleophilic attack by the benzene onto the highly electrophilic β-position delivers monogold organyl **17** after protodemetalation (Scheme 16).

An alternative mechanistic suggestion is shown in Scheme 17. This mechanism also potentially could explain the formation of the β product. An activation at the aurated alkyne **V** activates for the reaction with the benzene to deliver **VI**. A [1,2]-shift of the proton transfer via transition state **VII** would deliver the gold carbenoid **VIII**. Elimination of $[Au]^+$ to intermediate **IX**, which then is activated by the gold catalyst at the other alkyne to deliver **X**, finally provides ***β*-2c** by a [1,2]-shift of a proton.

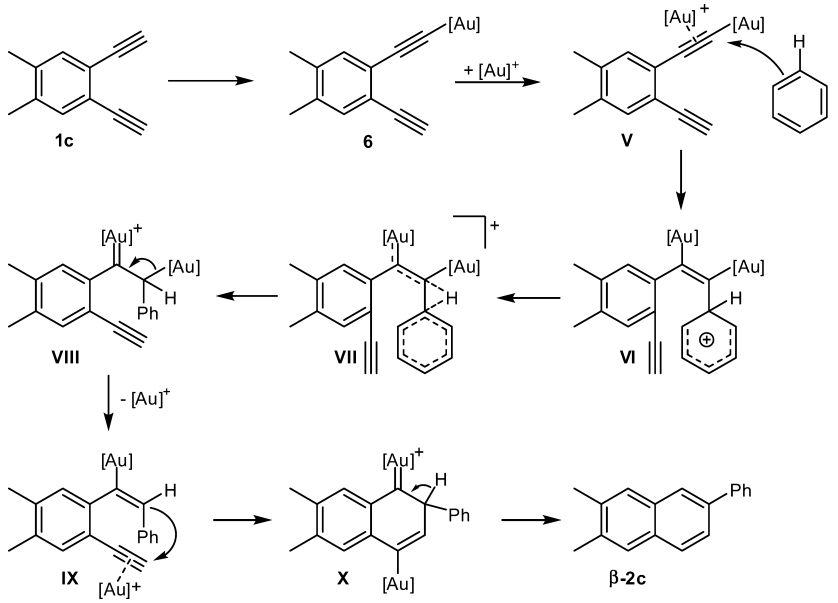
A number of experiments clearly disprove this mechanism. All efforts to add benzene to a preformed gold acetylide failed. Even more important, our labeling studies reported above always show that the proton set free from the benzene always with high selectivity ends up in the α-position of the product (Figure 10B), which cannot be explained by the mechanism from Scheme 17.

The most convincing mechanism that is in accordance with the experiments is depicted in Scheme 18. First, the acetylide **6** is formed by the catalyst transfer or by a basic additive (in the absence of an additive, maybe even directly from the diyne and $IPrAuNTf_2$). The dual activation (intermediate **XI**) then causes a dual role of gold: one gold center activates the triple bond as an electrophile by π-coordination; the gold acetylide reacts as a nucleophile at the β-carbon. Thus, a five-membered ring is closed (**XII**). The latter possesses a fulvene and a gold vinylidene substructure.[26] With benzene **XIII** is formed, a [1,3]-shift of the proton then provides the gold(I) carbenoid **XIV**.

Scheme 16. Mechanistic Hypothesis for the Formation of Monogold Aryl 17



Scheme 17. Mechanistic Model Disproved by the Experimental Results



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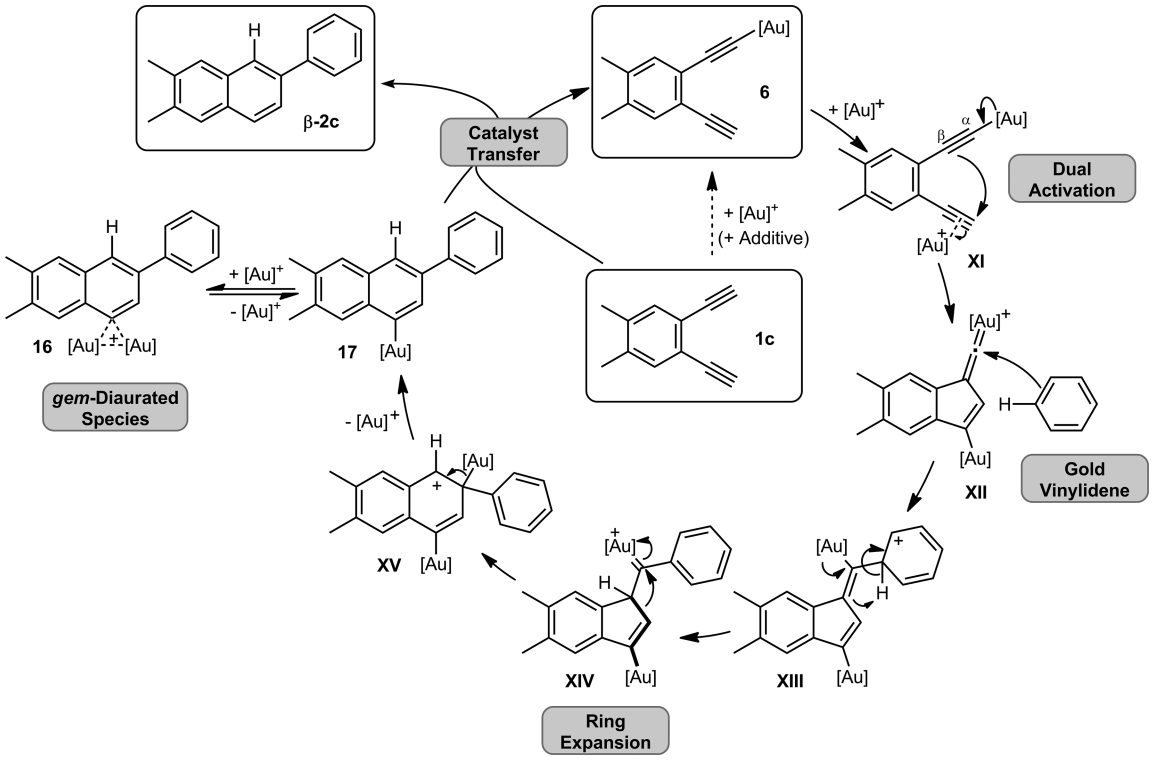
Scheme 18. Best Mechanistic Model to Explain the Observed Experimental Facts



A ring expansion by a [1,2]-shift of the reactive allylic group delivers **XV**.[26f,27] After eliminiation of $[Au]^+$, the observed arylgold(I) complex[28] **17** is formed, the latter in equilibrium with the observed digold species **18**.

3. SUMMARY AND CONCLUSIONS

The results in this paper clearly demonstrate the importance of gold acetylides in reactions bearing terminal alkynes. The results also clearly indicate that these species are highly activated substrates for gold catalysis. To avoid inhibiting the reaction and to ensure efficient conversion, an equilibrium between the activated substrate and the free catalyst is necessary. The generation of gold acetylides can even be achieved without the addition of an external base. In these cases, a catalyst transfer from organo-gold intermediates to the starting alkynes completes the catalytic cycle. Therefore, an induction phase and a shift in the selectivity of the reaction are observed. To circumvent the initiation phase, different additives can be used to preform the acetylides. Even if the acetylide concentrations are low in regard to the free alkynes, their enormous reactivity controls the reaction outcome and perfect selectivitiy can be achieved. For the new cyclization hydroarylation sequence with nonactivated benzene, both α- and β-naphthalene derivatives can be synthesized with high selectivity. Conveniently, both a simple bench-stable cationic amine complex and a recyclable, heterogeneous catalyst can efficiently convert the starting material to the desired β product. Furthermore, the isolation and unambiguous characterization via X-ray crystal structure analysis of the first *gem*-diaurated aryl gold compound stemming from a prior cyclization reaction were possible. This is also the only example for a *gem*-diaurated compound bearing carbene ligands. The high influence of these species on gold catalysis has been demonstrated. Together with other isolated intermediates and labeling experiments, a precise picture of this highly complex reaction was obtained. There is evidence for gold vinylidene complexes being involved. Considering the importance of terminal alkyne substrates in gold catalysis, these results may influence future progress in gold chemistry either by achieving new selectivities for known reactions or by increasing the scope of new reactions based on the high reactivity of gold acetylides.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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