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Combining Gold and Palladium Catalysis: One-Pot Access to Pentasubstituted Arenes from Furan–Yne and En–Diyne Substrates

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Abstract: A series of furan–yne systems was transformed into the corresponding tetrasubstituted annelated phenol derivatives that bear one bromo group. The two-step procedure consisted of a phenol synthesis and a subsequent electrophilic bromination with *N*-bromosuccinimide (NBS). The reactions can be performed in a one-pot procedure with the same precatalyst. The halogenation reaction is highly selective only in the presence of the gold catalyst. En–diyne substrates were also suitable starting materials; then the pentasubstituted aromatic core showed a completely different substitution pattern for the phenolic products. Furthermore, a one-pot protocol that consisted of a gold-catalyzed phenol synthesis, a gold-catalyzed halogenation reaction, and a palladium-catalyzed Suzuki coupling was established. The overall efficiency of this procedure was excellent and the substrate scope of the reaction was broad.

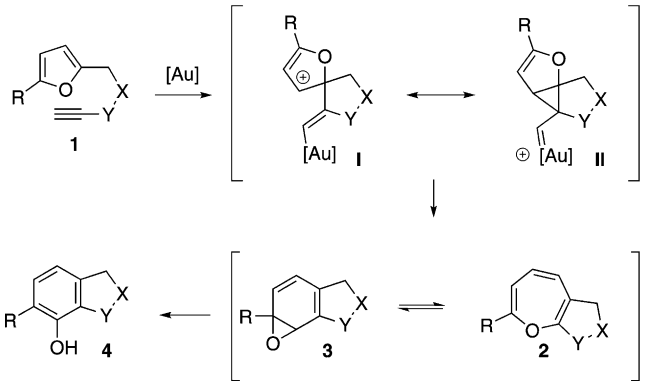
Keywords: arenes · furans · gold · one-pot reaction · palladium

Introduction

The extraordinary ability of gold to activate multiple bonds has led to a large number of new approaches for the construction of diverse carbo- and heterocyclic structures.[1]

The advantages with respect to classical routes are the mild reaction conditions, often combined with high atom economy,[2] and a significant increase in molecular complexity.[3] Furthermore, the functional-group tolerance and the chemoselectivity is often amazing, which is demonstrated by the increasing number of synthetic chemists who are using gold-catalyzed reactions for protecting-group free access to complex targets.[1h,4]

Since 2000, our group[5]—and in the years that have followed, the groups of Echavarren[6] and Shi[7]—have contributed a series of publications on a complex gold-catalyzed (and other transition metals)[5b,6] furan–yne rearrangement that offers a versatile tool for the synthesis of a broad range of different heterocycles such as dihydroisoindoles, tetrahydroisoquinolines, dihydroisobenzofurans, isochromans, dihydrobenzofurans, chromanes, dihydroindoles, and tetrahydroquinolines (Scheme 1).



Scheme 1. Mechanism of the furan–yne cyclization.

The overall regioselectivity of the reaction is determined by the regioselectivity of the ring opening of the intermediate arene oxide **3**.[5q] Thus selective reactions are obtained from furan substrates that contain substituents that are able to stabilize one of the two possible pentadienyl cations formed upon ring opening of the arene oxide.

Based on this principle, furans with donor substituents in the 3- or 5-position selectively deliver phenol derivatives in which the phenolic hydroxyl group is located *ortho* to the ring junction (Scheme 2). A loss in selectivity is observed with 4,5-disubstituted systems or furans without any additional substituent.[5a,p] Recently, phenols with the hydroxyl group *meta* to the ring junction also became accessible by means of a tandem reaction of diynes **5**.[8] In this case, the intermediate furans bear an electron-donating substituent in the 4-position, a substitution pattern that is not easily acces-

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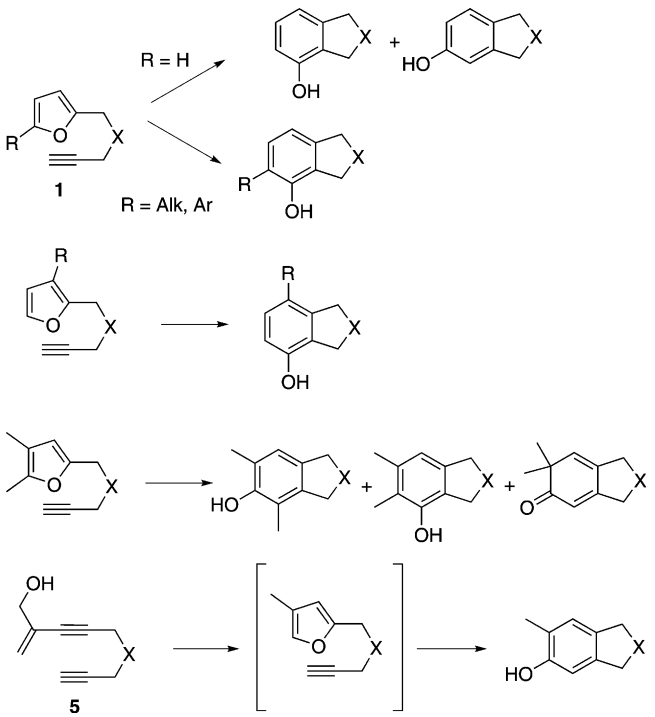


Scheme 2. Selectivity in the gold-catalyzed phenol synthesis.

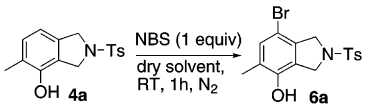
sible by means of classical synthetic chemistry but by the new route.

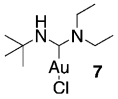
The furan–yne systems for a possible construction of pentasubstituted arene systems are challenging substrates themselves, and as shown in Scheme 2, no selective reaction can be expected for some of these starting materials. Inspired by the recent reports of Wang et al. on gold-catalyzed halogenation reactions with *N*-halosuccinimides,[9] we considered a one-pot reaction that includes gold-catalyzed phenol synthesis, gold-assisted halogenation, and subsequent palladium-catalyzed cross-coupling reaction as a promising strategy towards pentasubstituted arene systems. A possible one-pot procedure would be attractive, as purification of the intermediates could be circumvented, which not only saves time but also greatly reduces costs for energy and production of waste.[10] Our achievements are summarized in this contribution.

Results and Discussion

Our initial studies concentrated on the bromination reaction of the products of the phenol synthesis. These screenings were performed with test substrate **4a**, a substrate that can easily be obtained by means of gold catalysis (Table 1).[5a] To our delight, even the noncatalyzed reaction in 1,2-dichloroethene (DCE) showed a reaction at room temperature, and bromination was selectively observed *para* to the phenolic hydroxyl group (Table 1, entry 1). The constitution of the product could be unambiguously assigned by X-ray crystal structure analysis (Figure 1).[11] Unfortunately, the

Table 1. Screening different conditions for the bromination of phenol **4a**.



Entry	Solvent	Catalyst	Yield [%]
1	DCE	–	59
2	DCE	5 mol% $AuCl_3$	89
3	CH_2Cl_2	–	61
4	CH_2Cl_2	5 mol% $AuCl_3$	91
5	THF	5 mol% $AuCl_3$	87
6	CH_2Cl_2	5 mol%  7 5 mol% $AgSbF_6$	88

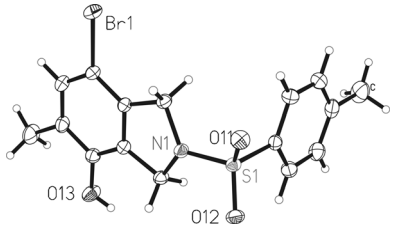
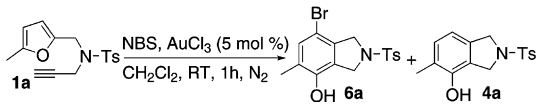


Figure 1. Solid-state molecular structure of **6a**.

yield of the reaction was not satisfactory (59% despite a complete conversion of the starting material), which might indicate competitive radical-type bromination reactions at the benzylic positions of the substrate[12] and subsequent reactions. If $AuCl_3$ was added as catalyst, the yield of the reaction could be significantly improved and 89% of the brominated product **6a** was isolated in DCE as solvent (Table 1, entry 2). The gold(III) probably acts as an oxophilic Lewis acid, coordinates to the carbonyl group of NBS, and thus enhances the Br^+ donor activity.[13] This accelerates the electrophilic bromination, which thus becomes much faster than the competing radical processes. The solvent dependency of the reaction turned out to be low and comparable results were also obtained in CH_2Cl_2 and THF (Table 1, entries 3–5). We also tested the gold(I)–nitrogen acyclic carbene (NAC) complex **7**,[14] which was activated by chloride abstraction by using silver hexafluoroantimonate (Table 1, entry 6; the control experiment with $AgSbF_6$ was negative). In CH_2Cl_2 this catalyst showed a comparable reactivity. This is of interest because some of the preceding reactions of potential tandem sequences might only work with gold(I) precatalysts.

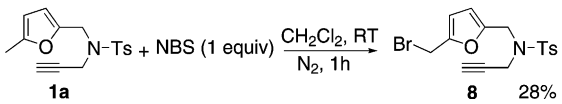
With these promising results in hand, we turned our focus on the evaluation of a one-pot reaction that started from the corresponding furan–yne system **1a** (Table 2). For this approach, the brominating reagent and the starting material were mixed in CH_2Cl_2, and the catalyst was added at room temperature. Unfortunately, the reaction turned out to be unselective and only a poor yield of the desired brominated

Table 2. Gold-catalyzed reaction of furane-yne **1a** and NBS.



Entry	NBS [equiv]	Yield of **6a** [%]	Yield of **4a** [%]
1	1	15	9
2	2	20	0

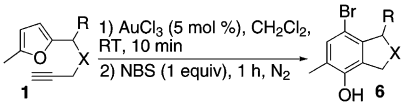
product **6a** besides minor amounts of intermediate phenol **4a** could be obtained with 1 equiv of NBS (Table 2, entry 1), although a complete conversion of the starting material was monitored. An excess amount of NBS suppressed the formation of the nonbrominated phenol **4a**, but the yield of the desired product **6a** did not significantly improve (Table 2, entry 2). The reason for the unselective course of the reaction is based on a fast and unselective reaction of NBS with starting material **1a**. A control experiment without the gold catalyst delivered only minor amounts of mono-bromination at the methyl substituent besides inseparable byproducts (Scheme 3). In this context, the formation of alkynyl bromide by NBS and a gold catalyst described by Corma et al.[15] might contribute to the formation of undesired side products.

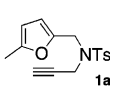
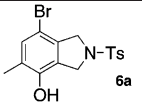
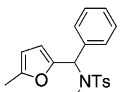
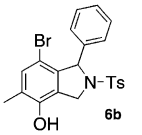
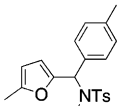
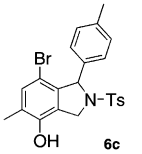
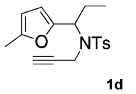
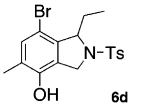
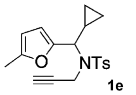
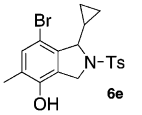
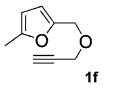
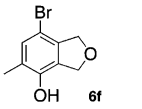


Scheme 3. The direct bromination of furan–yne **1a** is unselective; a yield of only 28% of **8** is obtained.

To circumvent decomposition of the starting material, we changed the protocol to a sequential one-pot procedure (Table 3). With the furan–yne substrate **1a**, a fast and clean formation of phenol **4a** took place within just a few minutes. After the complete conversion was detected by means of thin-layer chromatography, NBS was added. This led to a highly selective formation of 7-bromodihydroisoindole **6a** in an excellent overall yield of 87% (Table 3, entry 1). In THF as solvent, the reaction gave a slightly lower yield (73%). To evaluate the general applicability of this sequential one-pot protocol, a series of furan–yne derivates were converted under the same reaction conditions. Substrates **1b** and **1c**, with additional aromatic substitutents, showed no loss of selectivity (Table 3, entries 2 and 3). Despite the additional aromatic moieties, no trace of dibrominated product was observed even with 2 equiv of NBS. The bromination selectively occurred at the electron-rich phenol ring. Substrates **1d** and **1e** with ethyl (Table 3, entry 4) and cyclopropyl substituents (Table 3, entry 5) could also be converted in good overall efficiency. Changing the heteroatom in the tether from nitrogen to oxygen slightly reduced the yield (Table 3, entry 6), but the overall yield of this one-pot protocol was still satisfactory. Next we investigated furan–yne **1g**

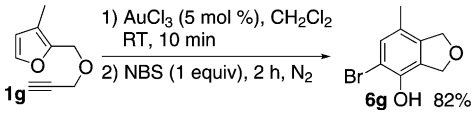
Table 3. Cyclization–bromination sequence for furan–ynes with substituent in 5-position.



Entry	Compound	Product	Yield [%]
1			87 (73)[a]
2			84
3			84
4			86
5			74
6			61

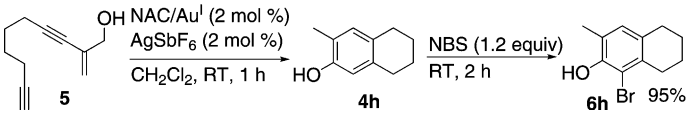
[a] Reaction in THF as solvent.

with a methyl substituent in the 3-position at the furan (Scheme 4). As mentioned earlier, this substrate is known to deliver the corresponding phenol with a methyl substituent in the *para* position. In this case, a comparable clean reaction was observed for the one-pot sequence and the bromination in the activated *ortho* position to the phenolic oxygen was highly selective. Synthetically, it is very useful that both the *ortho* and the *para* position of the product can be brominated by starting from different substitution patterns at the furan systems. It is noteworthy that, despite the oxygen tether, no reduction in yield was observed for this substrate.



Scheme 4. Cyclization–bromination sequence for furan–yne **1g** with substituent in the 3-position.

Finally, we tested en–diyne substrate **5** for a possible tandem sequence as well (Scheme 5). As we reported recently,[8] gold(I)–NAC complexes showed excellent performance for this domino reaction. Thus we did not change the

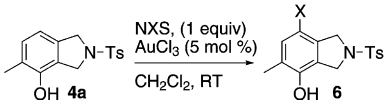


Scheme 5. Cycloisomerization/bromination of en–diyne **5**.

oxidation state of the catalyst and performed the bromination step with the gold(I) catalyst too. As mentioned earlier (see Table 1), for the bromination reaction the NAC complex showed similar performance as the gold(III) salt. Including the prior gold-catalyzed en-yne cyclization, product **6h** was obtained in an excellent overall yield (95% over the two reaction steps; Scheme 5). For this substrate, a selective bromination next to the phenolic oxygen took place. This is extremely valuable because only terminal alkynes are suitable substrates for the phenol synthesis and therefore the introduction of a substituent at this position prior to the phenol synthesis is impossible.

Next we investigated whether *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS) are also suitable for selective halogenation reactions of the phenol substrates. These reactions with standard test substrate **4a** are summarized in Table 4. In contrast to the NBS reaction, NCS turned out to

Table 4. Halogenation of **4a** with NCS and NIS.

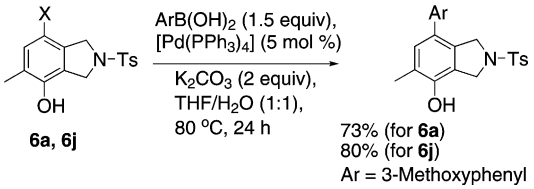


Entry	NXS	Catalyst	*t* [h]	Product	Yield [%]
1	NCS	–	24	**6i**	0
2	NCS	$AuCl_3$	24	**6i**	82
3	NIS	–	1	**6j**	63
4	NIS	$AuCl_3$	1	**6j**	91

be unreactive without the addition of the gold catalyst (Table 4, entry 1). The gold-catalyzed process was slower than with NBS, but yields were very good too (Table 4, entry 2). In the case of NIS, reactivity was observed without the catalyst, but due to the high reactivity of the NIS, the formation of several side products was detected and the isolated yield of the desired product was unsatisfactory (Table 4, entry 3). Like in the case of NBS, with NIS and the gold catalyst a highly selective reaction was observed (Table 4, entry 4), and we could isolate the product of the *para*-iodination reaction in excellent yield.

To evaluate the possibility of a further derivatization of the halogenated arenes, we tested the reaction of substrates **6a** and **6j** with 3-methoxyphenyl boronic acid under standard Suzuki coupling conditions. Both of the reactions delivered the pentasubstituted aromatic system in good yields within acceptable reaction times at elevated temperatures (Scheme 6).

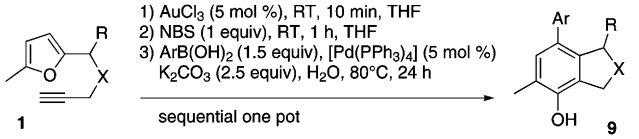
After the evaluation of all these single reaction steps, we finally investigated the possibility of a sequential one-pot reaction that consisted of a gold-catalyzed phenol synthesis,



Scheme 6. Suzuki coupling reaction of the brominated **6a** and **6j**.

a gold-catalyzed bromination reaction, and a palladium-catalyzed Suzuki coupling starting from furan–yne systems (Table 5).

Table 5. Sequential one-pot sequence consisting of furan–yne cyclization, bromination, and Suzuki coupling.



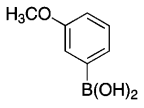
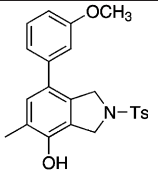
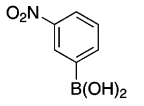
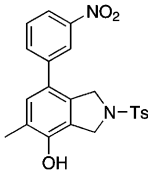
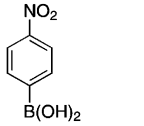
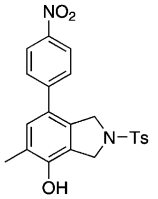
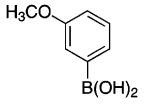
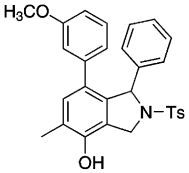
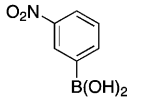
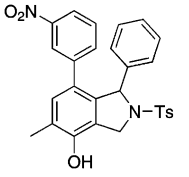
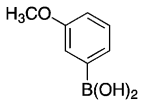
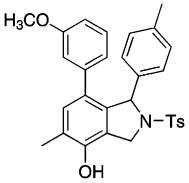
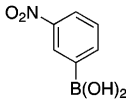
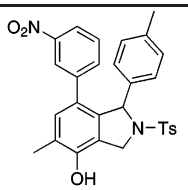
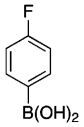
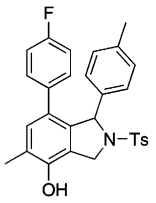
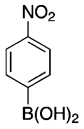
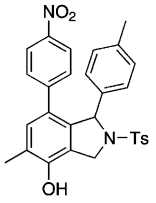
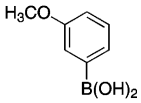
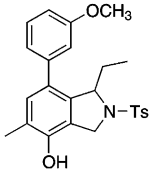
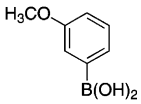
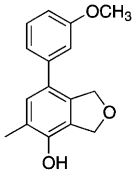
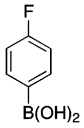
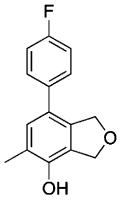
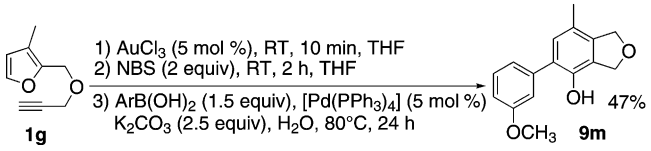
Entry	Starting material	$ArB(OH)_2$	Product	Yield [%]
1	**1a**		**9a** 	50
2	**1a**		**9b** 	40
3	**1a**		**9c** 	34
4	**1b**		**9d** 	71
5	**1b**		**9e** 	64
6	**1c**		**9f** 	60

Table 5. (Continued)

Entry	Starting material	$ArB(OH)_2$	Product	Yield [%]
7	**1c**		**9g** 	65
8	**1c**		**9h** 	70
9	**1c**		**9i** 	39
10	**1d**		**9j** 	75
11	**1f**		**9k** 	51
12	**1f**		**9l** 	52

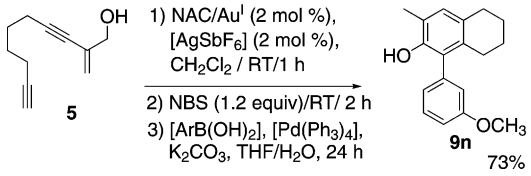
To avoid the necessity of changing the solvent after the first reaction step, the whole reaction cascade was performed in THF. The first two reaction steps were performed at room temperature. For the Suzuki coupling, besides the boronic acid, the base, $[Pd(PPh_3)_4]$, and water (equal volume to the THF) were added, and the temperature was increased to 80 °C. The results for the three-step protocol are shown in Table 4. With our standard test substrate **1a**, the three-step sequence delivered the final product **9a** in an overall yield of 50 % (Table 4, entry 1). The slight drop in yield relative to the isolated reaction steps is based on the first reaction step. A test reaction in THF revealed a yield of "only" 83 % for this single reaction step. The overall yield for a process that includes a change of solvent from CH_2Cl_2 to THF after the first two reactions increases the overall yield by about 10 %. If one considers the energy costs and the time saved, this drop in yield for the one-pot procedure should be acceptable for most of the substrates. Therefore, we also performed the other reactions without changing the solvent. Switching the substituent at the boronic acid to an electron-withdrawing nitro group led to a significant drop in yield (Table 4, entries 2 and 3), especially for the nitro group in *para* position, which has an additionally mesomeric effect (Table 4, entry 3). Interestingly, reactions with substrate **1b**, which contains an additional aryl moiety in the saturated tether, delivered significantly higher overall yields. Not only the electron-rich 3-methoxyphenyl boronic acid delivered a remarkable overall yield of 71 % (Table 4, entry 4), but also the nitro-substituted boronic acid, which still delivered 64 % of the pentasubstituted arene over three steps (Table 4, entry 5). Similar observations were made for tolyl substrate **1c**, which was converted to four different dihydroisoindoles (Table 4, entries 6–9). Yields were also up to 70 %, only the *para*-nitrophenyl boronic acid (Table 4, entry 9) led to a significant drop in yield (39 %). The increase in yield for these substrates is based on a higher yield for the phenol synthesis in the first reaction step. This was underlined by performing the phenol synthesis in THF for substrate **1c** (for the single reaction step, **4c** was isolated in 90 % yield). Furan–ynes with alkyl groups in the saturated tether are also suitable substrates. Compound **1d** with an ethyl substituent in the furyl position delivered an impressive yield of 75 % (over 90 % average yield for every single step!). Furan systems that bear an oxygen bridge also performed well, and good yields were obtained not only for the methoxyphenyl boronic acid (entry 11) but also for the electron-deficient *para*-fluorophenyl boronic acid (entry 12). The overall yields for the two steps are quite good, but one has to keep in mind that 75 % overall (entry 10) corresponds to 91 % on average for each of the three steps; the minimum overall yield from of 34 % Table 5 (entry 3), still represents 71 % on average for each step.

Last but not least, we explored the derivatization of other positions of the arene systems (Scheme 7). By changing the substitution pattern at the furan system (a methyl substituent in the 3-position instead of the 5-position), the one-pot procedure offers an attractive method for the introduction of a substituent in the *ortho* position to the phenolic oxygen by means of Suzuki coupling. For substrate **1g**, coupling with 3-methoxyphenyl boronic acid delivered pentasubstituted arene **9m** in good overall efficiency.



Scheme 7. Sequential one-pot transformation of furan–yne **1g**.

En–diyne substrate **5** was also applied to the Suzuki coupling protocol with 3-methoxyphenyl boronic acid



Scheme 8. Sequential one-pot transformation of endiyne-yne **5**.

(Scheme 8). For this substrate a change of solvent after the first two reaction steps was necessary, as the domino reaction in the first step does not proceed in THF as solvent.[8] Nevertheless, simple evaporation of the solvent, without purification, and subsequent redissolving of the residue in a THF/H_2O mixture, led to an excellent overall yield for the sequential one-pot procedure. This sequence allows the construction of pentasubstituted arene systems with the phenolic oxygen *meta* to the ring junction, thus a completely different substitution pattern at the resulting arene core is feasible by means of this starting material.

This type of conversion is highly useful for the synthesis of polyaromatic products,[16] and applications in the synthesis of natural/bioactive compounds or the synthesis of atropoisomeric compounds[17] are conceivable.

Conclusion

By using the same gold catalyst for two subsequent reaction steps, which consist of a furan–yne cyclization followed by a halogenation reaction, fivefold-substituted arenes are feasible under exceptionally mild reaction conditions and in a one-pot process. Controlled by the substituents at the starting furan core, two entirely different substitution patterns at the aromatic core can be synthesized. In addition, even en–diyne substrates can be used as starting materials, which enables the synthesis of another highly complex fivefold-substituted aromatic system that cannot be easily synthesized from furan precursors. The halogenation of the phenolic systems opens the possibility of further functionalization by means of palladium-catalyzed cross-coupling reactions. In three-step one-pot reactions highly complex fivefold aromatic systems can be constructed in an extremely short reaction sequence and in remarkable overall efficiency. This gold/palladium-catalyzed access to fivefold-substituted arenes with diverse substitution patterns should offer a powerful tool for organic chemists. Extensions of this concept to other gold-catalyzed conversions are under investigation.

It is interesting to compare these results with the concept of the C–C bond formation in gold catalyis induced by F^+ donors like Selectfluor.[18] In both cases, an organic substrate, a gold catalyst, and a boronic acid are used. In both cases, a halogen donor is needed and the halide does not appear in the final product. In the innovative gold-catalyzed reactions of olefins with Selectfluor, C–C bond formation is induced by the oxidation of gold. For the one-pot procedure presented here for alkynes, we also need a palladium catalyst for C–C bond formation and aryl bromides are intermediates. The use of the additional palladium catalyst is not inferior, because at the same time this method for the acetylenic substrate uses the cheaper NBS oxidant.

Acknowledgements

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