Tunable Gold-catalyzed Reactions of Propargyl Alcohols and Aryl Nucleophiles

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Gold-catalyzed transformations of 1,3-diarylpropargyl alcohols and various aryl nucleophiles were studied. Selective tunable synthetic methods were developed for 1,1,3-triarylallenes, diaryl-indenes and tetraaryl-allyl target products by C3 nucleophilic substitution and subsequent intra- or intermolecular hydroarylation, respectively. The reactions were scoped with regards to gold(I)/(III) catalysts, solvent, temperature, and electronic and steric effects of both the diarylpropargyl alcohol and the aryl nucleophiles. High yields of triaryl-allenes and diaryl-indenes by gold(III) catalysis were observed. Depending on the choice of aryl nucleophile and control of reaction temperature, different product ratios have been obtained. Alternatively, tetraaryl-allyl target products were formed by a sequential one-pot tandem process from appropriate propargyl substrates and two different aryl nucleophiles. Corresponding halo-arylation products (I and Br; up to 95% 2-halo-diaryl-indenes) were obtained in a one-pot manner in the presence of the respective N-halosuccinimides (NIS, NBS).

Introduction

Propargyl substrates represent a versatile group of substrates for a great variety of gold-catalyzed transformations. Propargylic esters may undergo a series of inter- and intramolecular transformations, initiated by a gold-catalyzed 1,2- or 1,3-acyl shift (Scheme 1a), to give the respective gold carbenoid or allene species, which both may be prone for further transformations.[1–7] The Fiksdahl group has contributed to the progress of gold catalysis in organic synthesis by the development of a number of cycloaddition reactions based on the highly reactive terminal propargyl acetal substrates and a series of reactants through initial gold-catalyzed 1,2-alkoxy shifts.[8–26]

Our studies demonstrate the particular potential and versatility of propargyl acetals in gold(I)-catalyzed cycloaddition reactions.

The combination of a C-1 alcohol leaving group in non-terminal propargyl alcohols 1 (Scheme 1b) and an external protic aromatic nucleophile ArH allows for a similar allene reaction pathway as the 1,3-acyl shift of propargyl esters (Scheme 1a–ii). Thus diaromatic (PhII, PhI) propargyl alcohols 1 and aryl nucleophiles are reported to give triaryl-allenes 3 and indenes 4 by gold catalysis (Scheme 1b).[17] The initial allenes 3, formed by i) S$_N$Ar' nucleophilic aryl attack at C3, undergo subsequent ii) intramolecular hydroarylation by a Nazarov cyclisation-like step[27,28] by heating, to give indene product 4 (Scheme 1c). Whether heating assisted the Au-allene interaction or the Nazarov cyclisation was not discussed. In general, the indene formation by ii) cyclisation (Scheme 1c) of the vinyl-gold intermediate could potentially take place by incorporation of either of the two phenyl groups (PhI or PhII in Scheme 1) of allene 3. Reaction with PhI would proceed via a doubly stabilized benzylic carbocation but would give a potential geminal di-aryl-substituted indene product. However, as proved by the obtained indene products 4, steric effects and incorporation of PhI via the planar gold cationic mono-benzylic intermediate, seemed to be dominant for successful reactions. An alternative iii) intermolecular hydroarylation pathway of allenes 3 with a second aromatic nucleophile ArH, affording 1,1,3,3-tetraaryl-allylic product 5, could be envisioned, but has not previously been studied.[29] Additionally, the competing direct iv) ary C1 nucleophilic substitution on propargyl alcohols 1 would yield 1,1,3-triarylpropargyl products (2) by gold catalysis[30–32] also known with other transition metals or Lewis acids.[33–36]

Allenes are important subunits in a variety of natural products and pharmaceutical related compounds,[37,38] as well as versatile synths in synthetic organic chemistry because of their ability to undergo a diversity of transformations in inter- or intramolecular fashion. Gold interacts with allenes, and may form stable, isolable complexes.[38] Gold-catalyzed transformations of allenes mainly involve cycloadditions or inter-/intramolecular nucleophilic addition reactions,[39] including hydroarylations.[40] Thus, a variety of carbon- or heterocycles can be produced by allene cyclizations.[41] The gold catalyst can coordinate to either allenic double bond, and the regioselectivity of the subsequent nucleophilic attack depends on the structure of both the allene substrate and the reactant, and different products may be formed. Hence, efficient and simple approaches for allene synthesis are important. In addition to the presently studied synthesis of allenes by gold-catalyzed
intermolecular reaction of benzylic propargylic alcohols and aryl nucleophiles, \[ \text{allenes} \] are normally synthesized by prototropic rearrangement of the corresponding propyne, \[ \text{by sigma-tropic rearrangements, as well as Cu}^{\text{II}}-\text{catalyzed coupling, additions to enynes, 1,2-eliminations and Wittig-type reactions.} \[ \text{The indene (1}H\text{-indene) structure moiety (4) is an attractive scaffold due to its biological activities. Indene is a stable structure, resisting oxidation of the cyclopentene ring even by harsh conditions. Several metal-catalyzed reactions are used for synthesis of substituted indenes. The Au-catalyzed indene cyclisation of propargyl acetates proceeds through the allene precursor and gives different indene regioisomers by 1,2- and 1,3-acyl shift, followed by hydroarylation. This reaction is further developed with propargyl alcohols.} \[ \text{The Fiksdahl research group is currently working on the development of novel Au}^{\text{I}}\text{ and Au}^{\text{III}}\text{ complexes. We have established a set of standardized Au-catalyzed test-reactions for screening and evaluation of the catalytic ability of new Au}^{\text{I}}\text{ and Au}^{\text{III}}\text{ complexes. The results demonstrate how the catalyst properties and stability are dependent on ligand structure, and the importance of ligand design. High catalytic activity has been proved in selected test reactions, such as propargyl based transformations. As gold-catalyzed transformations of nonterminal propargyl alcohols are not commonly reported, we wanted to investigate the potential of the reaction of propargyl alcohols 1 with aromatic nucleophile ArH (Scheme 1) in order to be included in our list of gold-catalyzed model reactions. Based on the previous studies of the reaction, which applied a limited choice of Au catalysts and mainly focused on formation of the indene product 4, we have carried out a more comprehensive study to look closer at reaction conditions and additional products. With the aim of understanding factors favoring selective synthesis of allenes 2, indenes 4 and possible tetraaryl-allylic 5 products, the reactions were scoped with regards to solvent, Au catalyst, electronic and steric effects of propargyl alcohol 1 and aryl nucleophiles.} \[ \text{Results and Discussion} \[ \text{Synthesis of Propargyl Alcohols} \[ \text{A range of propargyl alcohols 1a–i with varied electronic and steric properties were prepared from electron-rich and electron-deficient aldehydes 6a–e and arylalkynes 7a–d (Scheme 2). LDA deprotonation of arylalkynes 7 and nucleophilic attack of the corresponding lithium acetylide on added aldehyde 6,} \[ Scheme 1. Gold-catalyzed transformations of propargyl substrates. a) Reactivity patterns of propargyl esters. b) Reaction of propargyl alcohols 1 with aryl nucleophiles, ArH. c) Suggested mechanism for Au-catalyzed formation of i) 1,1,3-triarylsubstituted allenes 3, ii) diaryl-indenes 4, iii) 1,1,3,3-tetraaryl-allyl products 5 and iv) propynes 2, from propargyl alcohol 1 and aryl nucleophiles ArH/Ar'H.
gave the desired propargyl alcohol products 1 (41–67%). The electron-rich alkyne 1f was isolated in low yields (18%), due to challenging purification.

**Au-Catalyzed Reactions of Propargyl Alcohols with Aryl Nucleophiles**

It soon became clear that the reactions of propargyl alcohols 1 with aryl nucleophiles ArH (Scheme 1b,c) were more complex than previously reported. In addition to variable ratios of allene 3 and indene 4 products, also the competing C1 substitution products 2 and 2solv could be formed, depending on the nucleophilic ability of ArH and solvent. Our hypothesis was that the reaction of propargyl alcohols 1 and aryl nucleophiles could be tuned to give either the initially formed allene 3 by C3 substitution or to further proceed to the 1,3-diaryl-indene product 4 by intramolecular hydroarylation. Consequently, the scope of the reaction and the allene 3/indene 4 product selectivity was investigated by varying time, temperature, gold catalyst, solvent (Table 1), propargyl alcohol (Table 2) and aryl nucleophile (Table 3a). Also, the formation of tetraaryl-allyl products 5 was studied by intermolecular hydroarylation of allene 3 with a second nucleophilic aryl compound (Table 4).

Effect of Time, Temperature, Solvent and Gold Catalyst

Initial studies verified that proper choice of reaction time and temperature could favor formation of either allene 3 or indene 4 (Scheme 2).

**Table 1.** Effects of gold catalyst, reaction time, temperature and solvent on reaction outcome.\[a\]

| Entry | [Au] (equiv. AgSbF6) | Solvent | Product ratio [%]\[b\] | R.t., 15 min | 80°C, 90 min |
|-------|---------------------|---------|------------------------|-------------|-------------|
| 1     | 1 JohnPhosAu[1](ACN)SbF6 | F2–EtOH | 74 (3) 3a 19 0 0 8 (2) | 0 90 |
| 2     | Me2SAuCl            | F2–EtOH | 74 (3) 3a 19 0 0 5 0 95 |
| 3     | AuCl3              | F2–EtOH | 0 10 86 4 5 7 93 |
| 4     | AuBr3              | F2–EtOH | 0 10 85 5 0 7 93 |
| 5     | KAuCl2             | F2–EtOH | 0 9 91 0 8 2 90 |
| 6     | AuBr3              | EtOH       | – – – – – – (20°) 76 | 0 0 |
| 7     | AuBr3              | ACN       | – – – – – – 75 0 25 |
| 8     | AuBr3              | MeNO2     | – – – – – – 0 10 5 85 |
| 9     | AuBr3              | DCM       | – – – – – – 35 3 5 7 |
| 10    | AuBr3 (2)          | DCM       | 0 6 90 4 6 0 94 (5 h) |
| 11    | AuCl–IPr (1)       | F2–EtOH   | 0 10 (15) 55 20 0 0 93 (24 h) |
| 12    | AuCl–IPr (1)       | F2–EtOH   | 0 16 (8) 56 20 – – 2 – |
| 13    | AuCl–IPr (1)       | DCM       | 34 5 61 – – – – |
| 14    | AuCl–IPr (2)       | DCM       | 0 8 92 0 0 2 98 (24 h) |

[a] Standard procedure: A mixture of Au catalyst (5 mol%), propargyl alcohol 1a (1 equiv.) and MesH (6 equiv.) in solvent (1 mL) was stirred at given temperature and time before addition of water, a few drops of NEt3 and extraction into diethyl ether, followed by removal of solvent in vacuo. [b] Compounds ratios (1a, 2a, 2solv, 3a, 4a) are based on 1H NMR integration of the resulting reaction mixtures. 1H NMR shift values of characteristic signals, used for compound identification and quantification in product mixtures, are shown in green numbers above and are given in ppm. [c] DCM reflux at approx. 40 °C.
4 target products. Hence, the reactions of substrate 1a with mesitylene nucleophile (MesH, 6 equiv.) in trifluoroethanol (F3-
EtOH) were tuned both for selective formation of allene 3a (r.t., 15 min) and the diaryl-indene 4a, (80 °C, 1.5 h). A selection of commercially available AuI and AuII catalysts (5 mol%) were tested (Table 1).

It appeared that the choice of gold salts strongly affected the outcome of the reactions. The two tested AuI salts JohnPhosAu(ACN)SbF6 and Me3SAuCl (entries 1,2), were weak catalysts for the initial allene 3a formation (19% at r.t., 15 min), and large amount of substrate 1a (74%) remained unreacted. In contrast, AuII salts (AuCl3, AuBr3, KAuCl4) generated the initial allene 3a product in high yields (85–91% ; entries 3–5) by similar mild conditions. However, both AuI and AuII salts afforded high conversion into indene product 4a by heating (90–95%; 80–85 °C, 1.5 h; entries 1–5). KAuCl4 generated the initial allene 3a most selectively (91%); while Me3SAuCl afforded the final indene product 4a most efficiently (95%) by heating. But only gold(III) salts were unique to allow appropriate temperature tuning of the reactivity to give high yields of both allene 3a or indene 4a target products in F3-
EtOH.

Previously reported studies concluded that the AuBr3-catalyzed formation of indene 4 was strongly dependent on the solvent, as the reaction was unsuccessful in refluxing toluene and THF, while moderate to high yields were obtained in DCE and CF3-
EtOH at reflux."15 To avoid fluorinated solvents, other more conventional solvents for gold catalysis were attempted for indene formation (Table 1, entries 6–10). Competing nucleophile C1 substitution by the aryl nucleophile MesH or the solvent (F3-
EtOH) was expected to take place to give varying amounts of unwanted by-products 2a and 2aBr. In ethanol, the propargyl ether 2aOE was mainly formed (76%, entry 6), while in acetonitrile (entry 7), the C1 aryl substitution product 2a dominated (2a: 4a; 3:1 ratio). As not all gold complexes may be compatible with F3-
EtOH, nitromethane could serve as an alternative non-fluorinated solvent for the reaction. High reactivity and selectivity were obtained in MeNO2 (85% indene 4, entry 8), but somewhat lower than in F3-
EtOH (93%, entry 4). Reduced reactivity would be expected in DCM, a common solvent for Au catalysis, due to lower reflux temperature. In fact, only modest conversion of substrate 1a into allene 3a (57%) and indene 4a (5%) took place in DCM (entry 9).

Standard activation of AuI-Cl pre-catalysts by anion exchange with an appropriate weakly coordinating anion is performed by addition of 1 equiv. of the respective silver salt. However, increased yields in gold(III)-catalyzed reactions, including AuCl3 and AuII-NHC, have been obtained by increasing the number of equivalents of AgSbF6 (from 1 to 2), presumably due to generation of a more electrophilic gold(III) species."17-19 In fact, a dramatic effect of the AuBr3-catalyzed reaction in DCM was observed by addition of AgSbF6 (2 equiv.), and full conversion of substrate 1a gave highly selective formation of allene 3a (90%, r.t., 15 min) and indene 4a (94%, reflux (40 °C), 5 h), respectively (entry 10).

Studies on the catalytic potential of NHC-AuI and AuII salts (I–III) (entries 11–14) showed modest catalytic ability and moderate yields of allene 3a (55–61%, r.t. 15 min, entries 11–13) in DCM by standard procedure (1 equiv. AgSbF6). However, addition of 2 equiv. of silver salt, increased the NHC-AuI (III) catalytic activity to give full conversion and superior amounts of allene 3a (92%, DCM, r.t. 15 min, entry 14). Excellent yields of indene 4a were formed by heating with both AuI-NHC (I) in F3-
EtOH and NHC-AuCl3 (III) in DCM (93–98%, 40–80 °C, 24 h, entries 11 and 14).

Thus, highly selective formation of either allene 3a or indene 4a from propargyl alcohol 1a may take place at low and high temperature, respectively. By varying reaction time and temperature, as well as gold catalysts and solvents, the most promising tunable catalytic conditions were obtained by the AuII halide salts (AuCl3, AuBr3, KAuCl4) in F3-
EtOH, or with gold(III) catalysts AuBr3-\{(AgSbF6)2\} and AuCl3-SiPr{(AgSbF6)2} in DCM. The scope of the reaction was therefore further studied.

Effect of Diarylpropargyl Alcohol Properties

In order to study how the electronic and steric characteristics of propargyl substrate 1 may impact the Au-catalyzed reaction, a series of modified propargyl alcohols 1-Ar1-Ar2 were reacted with mesitylene in the presence of AuBr3 at mild and more harsh reaction conditions (20–80 °C in F3-
EtOH; Table 2). Due to steric effects by aryl-incorporation for formation of indene products 4 (Scheme 1c) the cyclization reaction only took place with non-substituted phenyl Ar2 group (Ar2 = Ph). Thus, a prerequisite for successful, tunable, and selective allene and indene synthesis was the use of 3-phenyl-propargyl alcohol substrates (1-Ar2-
Ph), such as 1-Ph-
Ph, 1-(2,6-diMe)Ph-
Ph and 1-Mes-
Ph (1a,1b,1c) with electron-rich and/or bulky Ar1 groups. These substrates had great ability to allow temperature fine-tuning to afford selective and nearly quantitative formation of either alkenes (3a-c, 85–100%, r.t.) or subsequent intramolecular hydroarylation indene products (4a-c, 93–100%) at low or high temperature, respectively (entries 1, 2, 3).

The electron-rich propargyl alcohols 1-(4-
OME)Ph-
Ph, 1-
Ph-(4-
OME)Ph and 1-
Ph-Mes (1e, 1f, 1h; entries 5, 6, 8) were not appropriate substrates for aryl nucleophilic C3 substitution, and the anisole and mesitylene substrates gave no conversion or complex mixture of products at r.t. or by heating. On the other hand, the electron deficient substrates 1-(4-
CF3)Ph-
Ph and 1-
Ph-(4-
CF3)Ph (1d, 1g; entries 4, 7) mainly activated for unwanted C1 substitution byproducts 2d and 2g (53/65%), along with allenes 3d and 3g (43/26%). Allene 3d did undergo cyclization into indene 4d by heating. Unexpectedly, C1-substitution product 2d also gave indene 4d by slow rearrangement. Hence, by 5 h reaction time and 10 mol% AuBr3, indene 4d (64%) and an additional inseparable indene product (X, 31%) was formed (entry 5). Treatment of the (4d + X) mixture with meta-chloroperoxybenzoic acid (MCPBA) enabled separation of unreacted unknown indene X from a mixture of unidentified products. The unknown X was shown (NMR, HRMS) to be the 2-Br-indene derivative 4d-
Br, which probably is formed by electrophilic bromination, due to AuBr3 decomposition into nanogold/Au0. A pure sample of 2-Br-indene 4d-
Br (entry 5) was prepared for characterization, by NBS in situ.

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treatment of allene 3d, and the 2-bromo-structure was confirmed.

Attempts to slow down the C1-aryl substitution at 0 °C resulted in no substrate conversion at all. However, by modifying substrate 1-Ph-(4-CF₃)Ph (1g) by blocking unwanted C1 substitution with introduction of ortho/para methyl groups (Ar¹ = mesitylene), full conversion of the electron-deficient substrate 1-Mes-(4-CF₃)Ph (1i) took place into the corresponding allene 3i (95%, entry 9). The electron-deficient allene 3i was, however, unstable and did not undergo further indene cyclization, in contrast to the successful cyclization of allene 3b, formed from the other ortho-2,6-dimethyl-blocked electron-rich substrates 1b, 1c (entries 2, 3).

The results showed that gold(III)-catalyzed reactions of modified diaryl-propargyl alcohols 1-Ar¹-Ar² with mesitylene to give selective allene 3 or indene 4 products are highly sensitive to electronic and steric factors in both aryl groups. However, 1-aryl-3-phenyl-propargyl alcohols (1-Ar¹-Ph), with electron-rich and/or bulky Ar¹ groups were excellent substrates for selective allene 3 and indene 4 synthesis (up to 99%). The pure allenes 3a-d and indene 4a-d products were prepared for characterization (NMR, HRMS).

Effect of Aromatic Nucleophiles, Ar¹H and Ar²H

Allene 3 and Indene 4 Target Products: A study of allene/indene formation was performed with substrate 1a and different aromatic nucleophiles Ar¹H with varied electron density and steric properties (Table 3a, Scheme 3a). Only the reaction of pentamethylbenzene (entry 2) followed the original selective AuBr₃-catalyzed pathways (C3 substitution/intramolecular hydroarylation), but even higher yields were obtained than with mesitylene (entry 1; from Table 2), as the allene 3j and indene 4j products were quantitatively formed at room temperature and by reflux conditions, respectively. The reaction with the 1,3,5-trisopropylbenzene nucleophile gave an unexpected outcome (entry 3), as no allene intermediate was seen, while the C1 solvent substitution product 2a³⁻⁴⁻Br (>80% at r.t.) was readily formed and directly generated the final indene product 4k (<99%) under reflux conditions. A separate control experiment with a pure sample of the propargyl ether product 2a³⁻⁴⁻EtO and mesitylene confirmed that quantitative formation of indene 4a directly took place without any observation of the expected allene intermediate 3a. The electron-rich and strong Ar¹H aromatic nucleophiles anisole and the bulky 1,3,5-trimethoxybenzene favored unwanted C1 substitution products 2l and 2m (entries 4, 5, 80–99%). A series of other aryl compounds (ethylbenzene, p-xylene, toluene, styrene, tert-butylbenzene, phenyl acetate, acetanilide, N-Ts-anilide, nitrobenzene, 1,3-di- CF₃ benzene, N-methylpyrrole, thianaphthene) failed to give allene 3 or indene 4 products.

Thus, successful tunable formation of target allene 3 or indene 4 products seems to require moderately activated Ar¹H alkylbenzene nucleophiles, while strong alkoxyaryl nucleophiles react by undesired C1 substitution. The pure allene 3j (99%)

Table 2. Studies on diarylpropargyl alcohol 1 properties^[a] (a)

| Entry | 1-Ar¹-Ar² | Product ratio [%]^[b] (% iso. yield) | Product ratio [%]^[c] (% iso. yield) |
|-------|------------|-------------------------------------|-------------------------------------|
| 1     | Ar¹ = Ph;  | 1a 0 10 3a: 85 (40) 5 0 7 0 4a: 93 (92) |
| 2     | Ar¹ = 1-(2,6-diMe)Ph | 1b 0 0 3b: 98 (81) 2 0 0 0 4b: >99 (78) |
| 3     | Ar¹ = 1-Mes | 1c 0 0 3c: >99 (37) 0 0 0 0 4c: >99 (50) |
| 4     | Ar¹ = 1-(4-CF₃)Ph | 1d 4 2d: 53 3d: 43 (19) 0 0 2d: 5 0 4d: 69 (29) |
| 5     | Ar¹ = 1-(4-OMe)Ph | 1e - - - - - - - - - |
| 6     | Ar¹ = Ph;  | 1f <10 0 0 0 - - - - |
| 7     | Ar¹ = 1-(4-CF₃)Ph | 1g 0 2g: 65 3g: 26 0 - - - - |
| 8     | Ar¹ = 1-Mes | 1h 0 0 0 0 0 - - - - |
| 9     | Ar¹ = 1-Mes, Ar² = (4-CF₃)Ph | 1i 5 0 3i: 95 (40) 0 - - - - |

[a] Standard procedure: AuBr₃ (5 mol%) with propargyl alcohol 1 (1 equiv.) and MesH (6 equiv.) in F3-EtOH (1 mL). The mixture was stirred at r.t. for t min before addition of water, a few drops of NEt₃ and extraction into diethyl ether followed by removal of solvent in vacuo. [b] Compound ratios (1, 2, 3, 4) are based on ¹H NMR integration of the resulting reaction mixtures. [c] Complex product mixture; including the 2e⁻Br⁻ product, which was prepared in 28% yield for identification. [d] Additional 5 mol % AuBr₃ added to reaction mixture; 80 °C for 5 h. Products 4d and 4d-Br could not be separated. [e] Unidentified product mixture.
and indenes 4j and 4k (unstable; 56% and 15%) were prepared for characterization (NMR, HRMS).

The developed halocarbonylation strategy to synthesize functionalized 2-haloindenyl from propargylic alcohol substrates represents a gold-catalyzed tandem reaction with aryl carbon nucleophiles, in contrast to other similar iodination reactions, which include heteroatom nucleophiles. The 2-halo-sp²-carbon moiety represents a versatile reactive position for subsequent transformations, such as a series of efficient Pd-catalyzed C–C coupling reactions, which may give rise to a great variety of indene based target products.

**2-Haloindenes**: As aryllallenes are known to provide 2-iodoindenes by iodocarbocyclization in the presence of NIS, a one-pot iodoarylation strategy from propargylic alcohol 1a was tested for iodo-incorporation in products 4 (Table 3b, Scheme 3b). Actually, iodo-modified hydroarylation reaction conditions successfully allowed for electrophilic iodonation through intramolecular iodoarylation of triarylallene 3a and 3j inter-

### Table 3. Properties of aromatic nucleophiles Ar³H in formation of indene products 4, 4j, 4k

| Entry | Reactants: a) 1a + Ar³H | Product ratio [%] (% isol. yield) r.t., 15 min | Product ratio [%] (% isol. yield) 80 °C, 90 min |
|-------|------------------------|-----------------------------------------------|-----------------------------------------------|
| 1     | Mesitylene (Table 2)   | 2a 10                                         | 3a 85 (40)                                    |
| 2     | PentaMe-Ph              | 2a 10                                         | 3a 85 (40)                                    |
| 3     | Anisole                 | 2m: > 80%                                      | 2m: > 80%                                     |
| 4     | 1,3,5-tri-iPr-Ph        |                                               |                                               |
| 5     | 1,3,5-triOMe-Ph         |                                               |                                               |

![Scheme 3. Studies of aromatic nucleophiles Ar³H and Ar⁴H in on-pot tandem formation of a) indenes 4 by intramolecular hydroarylation; b) halo-indenes 4-X by intermolecular haloarylation and c) tetraaryl-allyl products 5 by intermolecular hydroarylation.](image-url)
mediates by in situ addition of NIS (N-iodo-succinimide) to the respective allene (3a,j) reaction mixtures (r.t., 15 min.). Thus, the corresponding 2-iodo-diaryl-indene products 4a-I and 4j-I (90–95 %, entry 6) were formed in one-pot gold(III)-catalyzed transformations of propargyl alcohol 1a. No competing aromatic halogenation took place at the phenyl groups by this chemoselective reaction. As expected, the corresponding NBS reactions were somewhat less efficient than the NIS halogenations, and 78 % of the corresponding bromo-arylation product 4a-Br was formed (entry 7) from substrate 1a. As discussed above (Table 2, entry 5), lower amounts of the 2-Br-derivative and 78 % of the corresponding bromo-arylation product formations were somewhat less efficient than the NIS haloarylations, selectivity reaction. As expected, the corresponding NBS reactions (Table 4, Scheme 3c). By a one-pot procedure, addition of the allyl product was attempted with allene 1a (5 mol %) with propargyl alcohol at a temperature, time, product ratio [%] (isol. yield)

| Entry | Reactants: 3a+Ar3H (equiv.) | Temperature, Time | Product ratio [%] (isol. yield) | regio-isomer (E,Z ratio) |
|-------|-----------------------------|-------------------|-------------------------------|------------------------|
| 1     | Indole (1)                  | 80 °C, 1.5 h      | 13 55 5                       | 5a 27                  | 3-pos. (6:1) |
| 2     | Indole (1)                  | 80 °C, 6 h        | 14 0 5                        | 5a 81 (37)             | 3-pos. (6:1) |
| 3     | Thiophene (1)               | 80 °C, 1.5 h      | 4 0 51                        | 5b 20 (16)             | 2-pos.     |
| 4     | Thiophene (5)               | 80 °C, 1.5 h or r.t., 24 h | 10 0 30                  | 5b 32 (27)             | 2-pos. (5:1) |
| 5     | Thiophene (0.5)             | r.t., 24 h        | 15 0 38                       | 5b 28 (24)             | 2.5-pos.   |
| 6     | Furan (1)                   | 80 °C, 1.5 h      | 17 0 38                       | 5b 43 (37)             | 2.5-pos.   |
| 7     | Benzofuran (1)              | r.t., 24 h        | 10 0 21                       | 5c 45 (20)             | 2.5-pos.   |
| 8     | Benzothiophene (1)          | r.t., 24 h        | 8 0 44                        | 5d 69 (53)             | 2-pos.     |
| 9     | Anisole (1)                 | r.t., 24 h        | 10 45                         | 5e 43 (42)             | 4-pos.     |
| 10    | 1,3,5-(OMe),-Ph (1)         | r.t., 24 h        | 9 0 18                        | 5f 73 (58)             |            |
| 11    | Benzofuran, benzothiophene, anisole, 1,3,5-(OMe),-Ph | 80 °C, 1.5 h | 5–10 0 90–95 | 0 | |
| 12    | (N-Me-jpyrrole)             | r.t., 48 h        | 10 85 5                       | 0                      |           |
| 13    | Furan (5 equiv.), (Me-jpyrrole) | 80 °C, 1.5 h | Complex product mixtures | | |

[a] Standard procedure: AuBr3 (5 mol %) with propargyl alcohol 1 (1 equiv.) and aryl nucleophile Ar3H (6 equiv.) in F2-EOH (1 mL). The mixture was stirred at T °C for 10 min before addition of water, a few drops of NEt3, and extraction into diethyl ether followed by removal of solvent in vacuo. [b] Compound ratios are based on 1H NMR integration of the resulting reaction mixtures. [c] One-pot reaction; after full conversion into allene 3a (r.t., 15 min), the second nucleophile, Ar3H (1–5 equiv.) was added to the reaction mixture and stirred at T °C for t hours. [d] ratio double-bond stereoisomers (E/Z). [e] Ratio of regioisomers.

**Tetraaeryl-allyl Products 5**: Attempts with allene 3a to follow an alternative competing gold(III)-catalyzed intermolecular hydroarylation pathway with a second external aryl nucleophile (Ar3H) to afford 1,1,3,3-tetraaryl-allyl products were promising (Table 4, Scheme 3c). By a one-pot procedure, addition of the heterocyclic indole to the initially formed allene 3a reaction mixture, efficient incorporation of 3-indole took place by intermolecular hydroarylation. The amount of target tetraaryl-allyl product 5a increased by heating from 1.5 h to 6 h (27–81%; 80 °C, entries 1,2). The preferred site for electrophilic substitution on indole is C3 rather than C2, as expected from the greater electron density at C3 of the enamine structure moiety and higher stabilization of the iminium cation formed by C3 attack. In contrast to most aryl nucleophiles Ar3H below (entries 6–10), the indole reactions afforded target 3-indol-substituted product 5a as E/Z-double-bond stereoisomers (6:1). The facts that no conversion took place at r.t., and that the competing indene by-product 4a was only formed in minor amounts (5 %), may indicate that the gold(III)-catalyzed indole hydroarylation follows a different reaction mechanism than the other aryl nucleophiles.

Our results for intermolecular hydroarylation with five-membered heterocycles were in accordance with expected reactivity and positional selectivity. The order of reactivity in electrophilic substitution of these heterocycles has been shown to be thiophene < furan < pyrrole. In contrast, it is known that the C3/C2-positional selectivity (β:α ratio) of five-membered heterocycles increases with increasing ability of the heteroatoms to stabilize the correspondingonium states of the elements (O < S < N < P). The less reactive thiophene did undergo a more efficient hydroarylation with a large excess of thiophene (5 equiv., entries 3–4), also without heating. The thiophene nucleophile gave regioselective 2(α)-substitution products 5b (obtained as a 5:1 mixture of E/Z isomers) as sulfur...
products 5a—triOMe-benzene nucleophiles afforded highest yields of target phile properties. The indole, benzofuran, thiophene and 1,3,5-
with aryl nucleophiles were studied in order to identify the
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provides insufficient stabilization relative to the indole cation giving 3-substitution. Thiophene did additionally undergo double hydroarylation to give mixtures of 2-mono- and 2,5-bis-products 5b and 5b-bis (32%; 28%; entry 4). However, almost selective formation of the bis-product 5b-bis (43%) was observed with a limited amount of thiophene (0.5 equiv., entry 5), demonstrating the higher nucleophilic ability of the mono-product 5b to undergo a second hydroarylation. We attempted to identify the double-bond stereoselectivity of the indole and thiophene product 5a and 5b product mixtures by NOESY NMR but no conclusive data were obtained. However, based on steric factors of the bulky tetraaryl-allyl structure, the E-double bond would be expected in all products 5, as shown in Scheme 3.

The furan nucleophile also demonstrated the expected preference for α-substitution. Being more electron-rich and reactive, furan favored complete bis-hydroarylation and gave the 2,5-bisfuran product 5c-bis (45%, 80 °C, 1.5 h, entry 6) from equimolar reactions, while benzofuran afforded mono-hydro-
arylation product 5d by C2 attack (69%, r.t., 24 h, entry 7). Electrophilic substitution of benzothiophene usually give both α and β isomers. Thus, the benzothiophene reactions gave 1:1 mixtures of C2-/C3-regioisomers 5eα and 5eβ (48% in total, entry 8). Benzothiophene was less reactive towards the electrophile than thiophene (60%, entry 4). Both the slightly and the highly activated phenyl derivatives, anisole and 1,3,5-triOMe-benzene, successfully afforded the respective tetraaryl-allyl products 5fg in variable degrees by similar conditions (45–73%, r.t., 24 h, entries 9, 10). Selective para attack afforded anisole-product 5f.

At higher temperature, benzofuran, benzothiophene, anisole and 1,3,5-triOMe-benzene were not incorporated by intermolecular hydroarylation, as the competing indene 4α (90–95%) formation took place by selective intramolecular hydro-
arylation (entry 11). By similar harsh conditions, the reactive furan, pyrrole and N-Me-pyrrole Ar’H nucleophiles only gave undefined product mixtures via allene 3a (entries 12, 13). By addition of aniline or hydrazine-Boc nucleophiles to the allene 3a reaction mixture at r.t., no further reaction took place and allene 3a was recovered, probably due to amine N-coordination and deactivation of the gold catalyst, demonstrating that gold catalysis is required for subsequent indene 4α formation.

Thus, the one-pot intermolecular hydroarylation tandem process was successful with several aryl nucleophiles Ar’H, which provided tetraaryl-allyl products 5 as mixtures of stereo-, regio-isomers or mono/bis-adducts, depending on Ar’H nucleo-
phile properties. The indole, benzo(furan, thiophene and 1,3,5-
triOMe-benzene nucleophiles afforded highest yields of target products 5a—g (60-81% yield). The pure tetraaryl-allylic 5a—g as well as the 5b-bis and 5c-bis products were prepared for characterization (NMR, HRMS).

Conclusion

Gold-catalyzed transformations of diarylpropargyl alcohols 1 with aryl nucleophiles were studied in order to identify the most promising i) catalytic conditions, ii) propargyl alcohol substrates 1 and iii) aryl nucleophiles for tunable and selective preparation of 1,1,3-triallylalenes 3, diaryl-indenes 4 or 1,1,3,3-tetraaryl-allyl 5 products.

i) Optimized conditions for highly selective formation of allene 3a or indene 4a from dipheny1propargyl alcohol 1a and mesitylene nucleophile were developed by varying reaction time and temperature, as well as gold catalysts and solvents. The most promising and tunable catalytic condi-
tions (up to 92% 3a/98% 4a) were obtained with AuX3 halide salts in F3EtOH, or with gold(III) catalysts Au3Br5-
(AgSbF6)2 and Au3Cl3·SiPr-AgSbF6 in DCM.

ii) Further studies showed that selective gold(III)-catalyzed reactions of modified diarylpropargyl alcohols 1-Ar’-Ar” with mesitylene are sensitive to electronic and steric factors in both aryl groups. The 3-phenyl-propargyl alcohols 1-Ar’-
Ph with electron-rich and/or bulky Ar” groups (1-Ph-Ph, 1-
Mes-Ph, 1-(2,6-dime)Ph-Ph) allowed successful temperature fine-tuning of reactivity to afford selective and quantitative formation of allene 3a–d or indenes 4a–d.

iii) Generally, successful tunable and selective formation of initial allenes 3 (by C3 substitution at r.t.) or subsequent indene 4 products (by intramolecular hydroarylation by heating) required moderately activated Ar’H arylbenzene nucleophiles. Stronger alkoxyaryl nucleophiles reacted by undesired C1 substitution and failed to react by the tunable dual pathways. The present allene-indene synthetic strategy is useful for further indene functionalization, such as halogenation, as shown by the chemoselective formation of corresponding 2-iodo and 2-bromo indenes (4-I, 4-Br; 78–95%) by one-pot intramolecular allene 3 haloarylation in the presence of NXS. The 2-haloindenes are appropriate substrates for further Pd-catalyzed reactions. An alternative intermolecular hydroarylation of allene 3a with a second external aryl nucleophile Ar”H provided tetraaryl-
allyl products 5 (up to 81% yield). Several strong nucleophiles (indole, thiophene, furan, benzo(furan, benzothiophene, anisole and 1,3,5-triOMe-Ph) successfully followed this reaction path-
way by a sequential one-pot tandem process. Specific stereo-, regio-isomers or mono/bis versions of tetraaryl-allyl products 5 were identified for each group of heteroaromatic nucleophiles.

Experimental Section

General

All reactions, except the synthesis of gold complexes, were performed under inert N2 atmosphere. Commercial grade reagents were used without any additional purification. Dry solvents were collected from a MB SPS-800 solvent purification system. All reactions were monitored by NMR and/or thin-layer chromatogra-
phy (TLC) using silica gel 60 F254 (0.25 mm thickness). TLC plates were developed using UV-light, p-anisaldehyde stain, or I2 stain. Flash chromatography was performed with Merck silica gel 60 (0.040–0.063 mm). 1H and 13C NMR spectra were recorded by a Bruker Avance DPX 400 MHz or a Bruker Avance III 600 MHz spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (TMS) as an internal standard. Coupling
constants (J) are given in Hz. Specific NMR assignments (1H, 13C) of synthesized and purified products 2–4 below, based on 2D NMR studies (COSY, HSQC, HMBC, NOESY), are available in Supporting Information. Accurate mass determination (HRMS) was performed on a "Synapt G2-S" Q-TOF instrument from Water TS. Samples were ionized with an ASAP probe (APCI) or ESI probe with no chromatographic separation performed prior to mass analysis. Calculated exact mass and spectra processing was done by Waters TM Software Masslynx V4.1 SCN871.

Preparation of Diarylpropargyl Alcohols (1)

**General Procedure A**: A solution of arylacetylene 7a–d (1–1.1 equiv.) in dry THF was cooled to 0 °C and LDA (1.5 equiv., 2 mL in THF) was added slowly under a N2-atmosphere. The solution was stirred for 30 min before addition of aldehyde 6a–e (1 equiv.). The solution was stirred for 2 h and was allowed to warm to r.t. before being quenched with aqueous NH4Cl (sat., 10 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over Na2SO4, and the solvent was removed in vacuo. Purification by flash column chromatography (EtOAc:pentane) yielded pure propargyl alcohols 1a–d.

Preparation of C1 Substitution Products (2)

See Supporting Information for preparation of products 2a,d,g,j,m; 2a\textsuperscript{o}, 2b\textsuperscript{o}, 2c\textsuperscript{o}, 2d\textsuperscript{o}, 2e\textsuperscript{o}, 2f\textsuperscript{o}, 2g\textsuperscript{o}, 2h\textsuperscript{o}.

Preparation of 1,1,3-Triarylallenes (3)

**General procedure B**: Propargyl alcohol 1 (1 equiv.) and an aromatic nucleophile (1–6 equiv.) were dissolved in either F2\textsubscript{2}EtOH or MeNO\textsubscript{2} (1 mL). A solution of AuBr3 (0.05 equiv.) in the same solvent (1 mL) was added, and the solution was stirred at r.t. for 15 min. H2O (5 mL), a few drops of NEt\textsubscript{3}, and diethyl ether (5 mL) were added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL), and the combined organic layers were dried over Na2SO4, followed by removal of the solvent in vacuo. Purification by flash column chromatography (EtOAc:pentane) yielded allenes 3.

Preparation of Diarylindenes (4)

**General Procedure C**: Propargyl alcohol 1 (1 equiv.) and an aromatic nucleophile (1–6 equiv.) were dissolved in either F2\textsubscript{2}EtOH or MeNO\textsubscript{2} (1 mL). A solution of AuBr3 (0.05 equiv.) in the same solvent (1 mL) was added, and the solution stirred at 80 °C for 1.5 h. H2O (5 mL), a few drops of NEt\textsubscript{3}, and diethyl ether (5 mL) were added, and the layers separated. The aqueous layer was extracted with diethyl ether (3 × 5 mL), and the combined organic layers were dried over Na2SO4, followed by removal of the solvent in vacuo. Purification by flash column chromatography (1:200 EtOAc:pentane) yielded indenes 4.

Preparation of 2-Halo-indenes (4–X)

**General Procedure D**: Propargyl alcohol 1a (1 equiv.) and aromatic nucleophile (1–6 equiv.) were dissolved in 1 mL F2\textsubscript{2}EtOH and AuBr3 (0.05 equiv.) was added. The resulting mixture was stirred for 15 min at room temperature. After conversion to the allene 3a/j was complete, NXS (1.1 equiv.) was added, and the reaction was stirred for 15–120 min. After completion of the reaction, diethyl ether was added and the organic phase was washed with sat. NaHCO\textsubscript{3}, followed by washing with brine, drying over anhydrous Na2SO4, and evaporation of the solvent in vacuo. The crude products were then purified by column chromatography.

Preparation of Tetraaryl-allyl Compounds (5)

**General Procedure E**: Propargyl alcohol 1a (1 equiv.) and mesitylene (6 equiv.) were dissolved in 1 mL F2\textsubscript{2}EtOH and AuBr3 (0.05 equiv.) was added. The resulting mixture was stirred for 15 min at room temperature. After conversion to the allene 3a was complete, the aryl nucleophile (1–10 equiv.) was added, and the reaction mixture was stirred at an appropriate temperature and time. After completion of the reaction, diethyl ether was added and the organic phase washed with water, followed by washing with brine, drying over anhydrous Na2SO4, and evaporation of the solvent in vacuo. The crude products were then purified by column chromatography.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: allene · aryl nucleophiles · gold catalysis · propargyl alcohol · tunable conditions

[1] N. Marion, S. Diez-González, P. De Frémont, A. R. Noble, S. P. Nolan, Angew. Chem. Int. Ed. 2006, 45, 3647–3650; Angew. Chem. 2006, 118, 3729–3732.
[2] B. G. Pujanaskui, B. A. Bhanu Prasad, R. Sarpong, J. Am. Chem. Soc. 2006, 128, 6786–6787.
[3] D. J. Gorin, I. D. G. Watson, F. D. Toste, J. Am. Chem. Soc. 2008, 130, 3756–3777.
[4] K. Miki, K. Ohe, S. Uemura, J. Org. Chem. 2003, 68, 8505–8513.
[5] K. Miki, K. Ohe, S. Uemura, Tetrabhedron Lett. 2003, 44, 2019–2022.
[6] J. Marco-Contelles, E. Soriano, Chem. Eur. J. 2007, 13, 1350–1357.
[7] N. Marion, S. P. Nolan, Angew. Chem. Int. Ed. 2007, 46, 2750–2752; Angew. Chem. 2007, 119, 2806–2809.
[8] J. E. Aaseng, N. Iqbal, J. E. Tungen, C. A. Spenger, A. Fiksdahl, Synth. Commun. 2014, 44, 2458–2467.
[9] J. E. Aaseng, N. Iqbal, C. A. Spenger, A. Fiksdahl, J. Fluorine Chem. 2014, 161, 142–148.
[10] A. C. Reiersølmoen, E. Østrem, A. Fiksdahl, Eur. J. Org. Chem. 2018, 2018, 3317–3325.
[11] H. F. Jónsson, S. Evjen, A. Fiksdahl, Org. Lett. 2017, 19, 2202–2205.
[12] H. S. M. Siah, M. C. Hogsnes, N. Iqbal, A. Fiksdahl, Tetrahedron 2016, 72, 1058–1068.
[13] S. Evjen, A. Fiksdahl, Eur. J. Org. Chem. 2016, 2016, 2858–2863.
[14] S. Evjen, A. Fiksdahl, Tetrahedron 2016, 72, 3270–3276.
