Gold Catalysis

A Gold(I)-Catalyzed Domino Coupling of Alcohols with Allenes Enables the Synthesis of Highly Substituted Indenes

Alexander Preinfalk, Antonio Misale, and Nuno Maulide*^[a]



Abstract: The reaction of aryl-substituted allenes with alcohols under gold catalysis led to highly substituted indenes in good yields, with low catalyst loading and under mild conditions. During this domino transformation, two C–C bonds are formed with water as the only byproduct.

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Polysubstituted indene derivatives are particularly important bicyclic scaffolds.^[1,2] Many of these form the core of biologically relevant substances, including antitumor, antiallergic, herbicidal, fungicidal, and antimicrobial compounds.^[3,4a–j] Besides that, indenes are also prevalent in materials science and as ligand precursors in homogeneous catalysis.^[1,5a–c]

Among the many methods reported for the synthesis of these compounds, one of the most important approaches is based on intramolecular Friedel–Crafts-type reactions.^[2,6,7a–n] In a recent example,^[7h] Toullec and co-workers reported the *N*-io-dosuccinimide(NIS)-induced cyclization of allenes leading to substituted 2-iodoindenes (Scheme 1 a), which can then be further functionalized.



Scheme 1. a) Electrophilic activation of arylallenes leading to 2-iodoindenes. b) α -allylation of enals and enones. c) Proposed pathway towards allyl- and benzhydryl-substituted indenes.

Inspired by a report by Bandini and co-workers^(Ba) on the gold-assisted α -allylation of enals and enones using an allenamide as precursor (Scheme 1 b), we envisioned a synthetic route in which an aryl-substituted allene reacts with an alcohol to undergo a domino C–C coupling sequence.^[Bb,9a–e] Such a reaction would form two C–C bonds in inter- and intramolecular fashion, and therefore lead to highly substituted indenes in a single step with water as the only reaction byproduct. Herein we present our results on the development of a domino goldcatalyzed C–C coupling process.

At the onset of our investigations, allene 1 and allylic alcohol 2 were selected as model substrates. Initial attempts to carry out the domino cyclization/C–C coupling focused on using 10 mol% of JohnPhosAu(MeCN)SbF₆ (A) and potassium carbonate as base. These conditions led to the desired product in only 4% NMR-yield (Table 1, entry 1). A subsequent screening



Is the curve of the out under anisythous conditions (1a) 2a) catalyst 1:2:0.1). [b] Determined by ¹H NMR analysis of the crude reaction mixture. [c] Determined by ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethylbenzene as internal standard. [d] Performed in absence of a gold catalyst. [e] Reaction was carried out using 1.1 equivalents of alcohol. [g] Reaction was carried out using 1.1 equivalents of alcohol. [g] Reaction was carried out using 1.1 equivalents of alcohol and 1 mol% catalyst. [h] Decomposition. [i] Isolated yield after purification. $A = John PhosAu(MeCN)SbF_{6}$

of various solvents revealed that dichloromethane allowed an increase in yield up to 65% (Table 1, entries 2–5). To investigate the potential role of silver salts in this transformation, $AgNTf_2$ was added to the reaction mixture. This always led to decomposition (Table 1, entries 6 and 7).^[10] Interestingly, in the absence of the base, the reaction displayed a faster and cleaner profile, affording the desired product quantitatively within five minutes at room temperature (Table 1, entry 8). Further attempts to lower the amount of allylic alcohol and catalyst loading had almost no effect on the reaction outcome (Table 1, entries 9 and 10).

Notably, the use of p-TsOH as catalyst led mainly to decomposition, while only 9% NMR-yield of desired product was observed (Table 1, entry 11).

With the optimized conditions in hand, we investigated the scope of this transformation. The reaction proceeded smoothly with a variety of different allenes. Notably, all reactions were run open to air and pre-drying of the solvent was not required. From Scheme 2 it can be seen how electron-neutral and -rich

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Supporting information for this article can be found under http://dx.doi.org/10.1002/chem.201603154.



aromatic systems afforded the desired products in good to excellent yields (3a-3f). Pleasingly, the reactions of 1e and 1f afforded selectively only one regioisomer, 3e and 3f, respectively. This coupling also tolerates allyl (3g), as well as linear (3a), branched (3h), and cyclic (3i) aliphatic substituents on the α -position of the allene. On the γ -position, mono- and disubstituted allenes afforded the corresponding products in excellent yields (3k and 3l). Terminal allene 1j also led to the desired product 3j in moderate yield and after a slightly longer reaction time.



Scheme 2. Substrate scope of the C–C domino coupling reaction.

Furthermore we found that allene **1** can also react with benzhydrol to deliver the corresponding benzylated products **5** (Scheme 3). The reaction proceeded smoothly with our model substrate, giving **5a** in excellent yield. However, this transformation appears less facile than the one involving the allylic alcohol **2a**, as reflected by the longer reaction times and slightly lower yields. The less activated substrates give products **5b** and **5f** in good yields. A longer aliphatic chain at the γ -position of the allene leads to a clean reaction and **5d** is obtained in 75% yield. Interestingly, more electron-rich allenes gave the desired products (**5c**, **5e**, and **5g**) in moderate yields.

Given the latter observation, we were naturally drawn to briefly examine the gold-catalyzed cyclization leading to simple indenes **6**. Interestingly, this transformation needed slightly different conditions and careful control of reaction time to avoid isomerization of the double bond towards the exocyclic isomer.^[11] To our delight (Scheme 4), subjecting model-allene **1 a** to the optimized conditions resulted in a very clean reaction and gave indene **6a** in 90% isolated yield.





Scheme 3. Substrate scope for the domino C–C coupling of differently substituted allenes with benzhydrol.

Changing the nature of the substituent at the α -carbon of the allene (R ' ' in Scheme 4) led to longer reaction times, but afforded products **6b** and **6c** in excellent yields. Disubstitution on the terminal position of the allene showed almost no effect on the reaction time and indene **6d** was obtained in 81% yield. Importantly, attempts at promoting this transformation employing Brønsted acid catalysis led to extensive decomposition of the allene substrate.



Scheme 4. Gold-catalyzed cyclization of allenes to indenes.

Further experiments to investigate the mechanism of the reaction were carried out employing the allenes in the presence of activated alcohols. Firstly, as also observed by the Bandini group,^[8a, b] we wanted to clarify the role of allylic ether **I**, which is a typical byproduct of the gold-catalyzed allylation reaction. Premixing of allylic alcohol **2a** and gold catalyst **A** in CD₂Cl₂ resulted in an equilibrium ratio of alcohol **2a** : ether **I** of 1:6.7. Adding allene **1a** to this mixture gave the corresponding product **3a** in the same yield as the original reaction (vide supra), but with a significantly longer reaction time (Scheme 5a). This strongly suggests that ether **I** is not an intermediate of the catalytic cycle, but rather a byproduct reversibly formed during the reaction.

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Scheme 5. Preliminary mechanistic investigations.

We then prepared allylic alcohols **2b** and **2c**. Upon reaction with allene **1 a** both led to the same product **3 m**, as confirmed by NMR analysis (see the Supporting Information, NOESY experiment) (Scheme 5 b). Since the C–C bond formation occurs selectively at the position where benzylic stabilization is highest, this result is suggestive of a cationic pathway via activation of the allylic alcohol by the gold catalyst.

We can rationalize these observations according to two possible pathways, both relying on the formation of an allylic carbocation. One possible pathway is the direct capture of the carbocation by the allene, which, in this case, would act as the nucleophile, forming another allylic carbocation. Friedel–Crafts cyclization then leads to the final product (Scheme 6, Pathway a). The second possibility would be a synergistic catalytic transformation with two cycles. Gold-catalyzed activation of the allylic alcohol to form the carbocation intermediate is accompanied by allene activation which, upon cyclization, forms an intermediate vinyl gold species. Combination of the latter species with the carbocationic intermediate then forms the product (Scheme 6, Pathway b).^[12,13] At this point it is not possible to rule out any of the two pathways. However, the failure of simple Brønsted acids to efficiently promote the reaction would appear to favor pathway b.

In summary, we have presented an atom-economical, goldcatalyzed domino C–C coupling of aryl-substituted allenes and activated alcohols. The corresponding substituted indenes were obtained in good yields, with low catalyst loadings and under mild conditions. Notably, these reactions proceed without a need for exclusion of air or pre-drying of the solvent. The cyclization of aryl-substituted allenes using gold catalysis was also achieved, and preliminary mechanistic evidence in favor of carbocationic intermediates was obtained.

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Scheme 6. Plausible mechanistic scenarios.

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Acknowledgements

We are grateful to the University of Vienna and the European Research Council (ERC StG 278872) for generous financial support. Ing. E. Macoratti and Dr. H. Kählig (University of Vienna) are gratefully acknowledged for expert assistance with chromatographic purification and NMR analysis.

Keywords: alcohols $\,\cdot\,$ allenes $\,\cdot\,$ domino $\,$ coupling $\,\cdot\,$ gold catalysis $\cdot\,$ indenes

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Received: July 1, 2016 Published online on

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Indenes

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A Gold(I)-Catalyzed Domino Coupling

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COMMUNICATION



Highly substituted indenes were obtained in good yields, with low catalyst loading and under mild conditions from the reaction of aryl-substituted allenes with alcohols under gold catalysis. During this domino transformation, two C–C bonds are formed with water as the only byproduct.



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The domino coupling of alcohols with allenes is reported by N. Maulide et al. in their Communication in page ■ ■. In this transformation, a gold catalyst orchestrates the sequential cyclisation and C–C coupling of aromatic allenes and benzylic alcohols to generate indene products in high yields. This reaction cascade proceeds with water as the only byproduct and does not need strict exclusion of moisture or oxygen."