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From the gold-catalysed benzylation of arenes to the regio- and stereoselective synthesis of procyanidins dimers

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ABSTRACT

This work reports on a new intermolecular C–C coupling reaction between electron rich arenes and benzylic alcohols or ethers, catalysed by gold(III) salts, or other catalysts such as gold(I) and iron (III), and its application to the regio- and stereoselective synthesis of procyanidins dimers B1 and B3.

1. Introduction

Among the large family of tannins, procyanidins or condensed tannins are the most abundant species in grapes and wine, in which they are transferred during wine-making operations. They are oligomers of flavan-3-ols and are attracting attention for their key role in wine taste[1] as well as for their putative healing properties.[2] Their molecular diversity comes from the different monomeric constituents, the degree of oligomerization as well as the connectivity between the flavan units thus leading to an infinite library of these compounds. In order to reach the wine composition in oligomeric procyanidins, and their role in wine taste, a variety of pure and structurally determined synthetic standards is required. In addition to continuous efforts reported in the field,[3] new routes have to be developed to synthesize these compounds, in order to increase the degree of complexity of the standards available. Notably, the yield of the coupling reaction between the two flavan units has to be optimized by keeping the control of its regio and stereoselectivity, thus ensuring a stereoselective synthesis of procyanidins of higher degree of polymerization.

Gold was known for decades for its rich organometallic and coordination chemistry, but was considered as a poor catalyst until the early seventies and the pioneering work of Bond on the hydrogenation of alkenes catalysed by gold.[4] Consequently, the use of gold as catalyst has increased in an exponential manner over the past twenty years for various uses such as hydrogenations, oxidations, reactions with carbon monoxide, nucleophilic additions to C–C multiple bonds, as well as activation of alcohols and carbonyl groups.[5] Primarily this flourishing chemistry was mainly related to heterogeneous catalysis, especially due to the exceptional reactivity of gold nanoparticles.[6] Nevertheless, in the last decade the use of gold salts also increased, mainly due to the robustness of the catalysts and their high reactivity even at low temperature, so that the homogeneous gold catalysis cannot be ignored anymore both in organic chemistry[7] or in total synthesis developments.[8]

The functionalization of arenes via direct C–H replacement is one of the numerous reactions, in which gold catalysis recently showed its efficiency and represents an attractive way of forming C–C bonds under mild conditions. Although the first report of an aryl C–H activation with gold(III) salts goes back to the 30's,[9] this reaction received far less attention than those involving alkenes or alkynes. In this context the seminal work of Beller in 2006 reporting the first gold catalysed benzylation of arenes with benzyl alcohols and carboxylates[10] contrasted with the large amount of inter- or intramolecular Friedel–Crafts type reactions using gold(III) activated π systems as partners. In the course of finding new approaches to achieve C–C couplings with electron rich arenes and benzylic electrophiles, we became interested in the use of gold salts for such catalysis under mild conditions, which could be further applied to the synthesis of more complex molecules.

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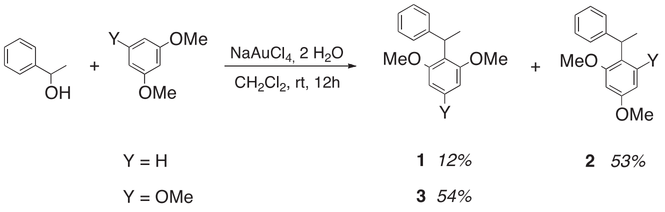
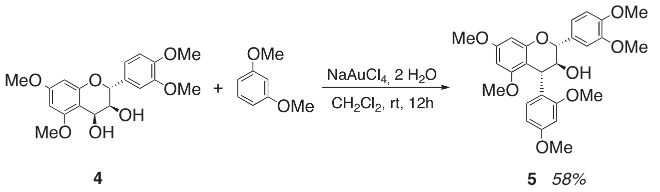
2. Results and discussion

We first studied the reaction between 1-phenylethanol and 1,3-dimethoxybenzene or 1,3,5-trimethoxybenzene, catalysed by gold(III) salts (Scheme 1) as model reaction. The choice of $NaAuCl_4$ as catalyst instead of $HAuCl_4$ was driven by observations in the nucleophilic substitution of propargylic alcohols showing its reactivity even at room temperature.[11]



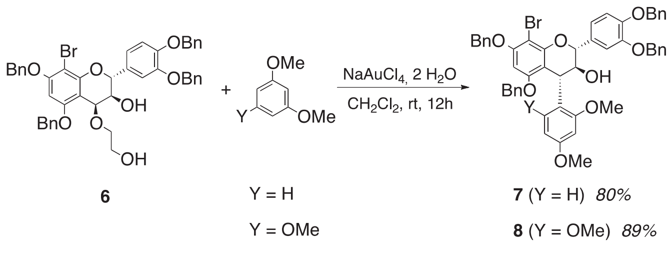
Scheme 1. Coupling of 1-phenylethanol with electron-rich benzenes.

The reaction was effective at room temperature, with only 5% of gold(III) catalyst, giving a 4.5:1 mixture of regioisomers **1** and **2** with a preferential *ortho*/*para* orientation. Interestingly, the use of 1,3,5-trimethoxybenzene as substrate led to the formation of the coupling product **3** in a fair yield of 54% indicating that an *ortho*/*ortho* disubstitution didn't have a negative effect on the outcome of the reaction. This result prompted us to apply the reaction to the tetra-*O*-methyl-4-hydroxycatechin **4**, prepared in two steps from the commercially available catechin, as the benzylic partner, with the 1,3-dimethoxybenzene as nucleophile (Scheme 2).



Scheme 2. Coupling of tetra-O-methyl-4-hydroxycatechin with 1,3-dimethoxybenzene.

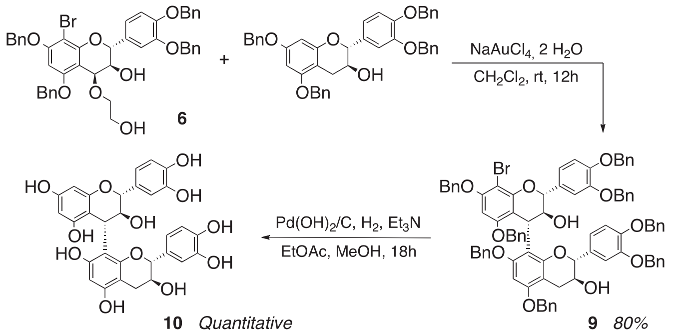
Under the same conditions, the coupling product **5** resulting from the *ortho*/*para* orientation was isolated in 58% yield, as the unique regioisomer. This change in reactivity can be explained by the increase of the steric hindrance of the benzylic alcohol, leading to a total discrimination between the two possible regioisomers. Nevertheless, the created stereogenic centre was only obtained with a poor 1.3:1 diastereoselectivity. This result led us to change the nature of the substrates, moving from benzylic alcohols to benzylic ethers. We then used the tetra-*O*-benzyl-4β-(2-hydroxyethyloxy)-8-bromocatechin **6** (Scheme 3), prepared in three steps from catechin.[3a,b] Indeed, this bidentate leaving group allowed us to get a total diastereocontrol, when using an excess of $TiCl_4$ as Lewis acid as shown in a previous work.[3f]



Scheme 3. Coupling reaction with tetra-O-benzyl-4ß-(2-hydroxyethyloxy)-8-bromocatechin.

As expected the use of the 2-hydroxyethyloxy moieties allowed to recover a total diastereocontrol in the formation of the new stereogenic carbon. Pleasingly, the use of a benzylic ether as substrate displayed an even better reactivity than the benzylic alcohol itself furnishing the coupling products **7** in 80% yield. Finally, the use of 1,3,5-trimethoxybenzene as nucleophile led to the formation of **8** in an excellent 89% yield, showing that the increase of the nucleophilic character of the aromatic could easily counterbalance the relative steric hindrance of the *ortho*/*ortho* disubstitution. Contrastingly to the use of the more oxophilic $TiCl_4$, which required 2 equiv of the Lewis acid for the reaction to proceed, this methodology proceeded under catalytic conditions in gold (5% of $NaAuCl_4$). Interestingly, there is to date no real example of gold catalysed arenes substitutions by using benzylic ethers as substrates as the main efforts were focused on more reactive benzylic alcohols[10,11] or epoxides.[12]

Encouraged by these promising results, we decided to apply our methodology to the stereocontrolled synthesis of procyanidin B3. An equimolar amount of tetra-*O*-benzylcatechin and C4-activated catechin derivative **6** were mixed in dichloromethane, at room temperature in the presence of 5% of $NaAuCl_4$ to give exclusively the octa-*O*-benzylated dimer **9** in an excellent 80% yield (Scheme 4). As observed with 1,3-dimethoxy- or 1,3,5-trimethoxybenzene as nucleophiles, the reaction proceeded with a total diastereocontrol of the created interflavan bond. Furthermore, it has to be noted the total regiocontrol of the reaction giving exclusively, as anticipated, the C4–C8 interflavan bond. Finally a one step debromination/debenzylation of **9**, catalysed by Pearlman's catalyst $Pd(OH)_2/C$ in the presence of triethylamine furnished quantitatively procyanidin B3 **10** with a total regio- and diastereocontrol in only four steps from tetra-*O*-benzylcatechin. It is worth noting that a similar approach for the one-step deprotection has also been recently used by Suzuki for the first regiocontrolled synthesis of a procyanidin dimer with a 4,6 interflavan bond.[13]



Scheme 4. Gold(III) catalysed synthesis of procyanidin B3.

The reaction was also extended to epicatechin derivatives to achieve the stereocontrolled synthesis of procyanidin B1, by using tetra-*O*-benzyl-4β-(2-hydroxyethyloxy)8-bromoepicatechin **11** under the conditions previously defined for procyanidin B3 synthesis. As expected, the reaction occurred with a double inversion of configuration, affording exclusively the octabenzylated dimer **12** with the natural configuration of the interflavane bond in a non-optimized 61% yield (Scheme 5).

These results contrast with the abovementioned strategies,[3a–g,13] which necessitated an equivalent or even excess amounts of Lewis acid to proceed. Indeed and contrarily to the more oxophilic Lewis acids such as $TiCl_4$ or $SnCl_4$, the relative weakness of the Au–O interaction allows the reaction to proceed