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Complex molecule synthesis made easy

Nelli Elizarov, Pascal D. Giorgi,
Alexandra Yeromina, Sylvain Antoniotti

Abstract By the combination of suitable catalytic methodologies, the synthesis of complex molecules could be performed with limited footprints and energy consumption either in orthogonal mult catalysis, sequential one-pot reactions or sequential reactions in continuous flow. In this account, we present a selection of our recent results in this area of research where several catalysts such as supported metal nanoparticles, supported metal salts, or mineral and organic bases were combined. New and step-economical synthetic methods were thus developed either in standard batch reactors or in continuous flow using millifluidic technology.

1 Introduction

For most epistemologists and historians of science, organic synthesis was born serendipitously in 1828 when Friedrich Wöhler obtained urea from ammonium cyanide [1]. Since then, the art of synthesis has improved both in terms of the complexity of molecules synthesized and the efficiency of the synthetic methods used. In most instances, the chemical synthesis of a given molecule starts with commercially available building blocks, mostly from the petrochemical industry, but increasingly from bio-based resources [2]. The core structure of the building block is then modified following a series of sequential operations to increase the number of atoms, the number of covalent bonds and the degree of oxidation, like Nature does for example

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in the biosynthesis of complex terpenoids [3]. For larger molecules, two or more syntheses can be performed in parallel and their products merged at some point to converge towards the final structure [4]. In the light of the recent shift towards more sustainable processes in chemical synthesis, it has become desirable to discover and apply novel methodologies to fulfill the need for complex molecules to be used in health or well-being applications without compromising the quality of the environment and the level of resources left to future generations [5].

To contribute to this effort, we have recently developed complex catalytic systems simply hyphenated in the same reactor or synergistically assembled to perform multiple elementary steps of synthesis in one operation, thereby delivering complex molecules more easily. Catalysis is in itself a premium approach to discover chemical transformations with low impact in terms of waste generation and energy consumption by its intrinsic assets [6–8]. Specifically, our strategy is based on the design of complex reactions schemes triggered by a clean oxidation reaction of activated alcohols by gold nanoparticles (Au NPs) solely requiring O₂ as the terminal oxidant [9]. To achieve these one-pot/multi-step transformations, we needed an oxidizing system both specific of the allylic alcohol motif, and selective for the formation of aldehydes. In addition, this ideal oxidative catalytic system had to be compatible with the multicatalytic setting. These prerequisites were found with Au NPs operating under O₂ [10–14].

In this account, we present our recent results in this area of research where the Au NPs-catalyzed allylic alcohol oxidation has been combined with C-C bond forming tandem reactions such as Friedel-Crafts-type aldolisation/cyclisation and oxa-Michael addition/aldolisation to yield valuable bioactive molecules in one operation, making complex molecules synthesis easy.

2 Oxidation by supported gold nanoparticles

Gold nanoparticles (Au NPs) have been successfully used in various catalytic carbon-carbon and carbon-heteroatom bond-forming reactions and, thanks to their ability to activate molecular oxygen, in oxidation reactions of organic substrates [15–20].

Preliminary screening of catalysts and reaction conditions taught us that small supported Au NPs (2–3 nm of diameter) were suitable as a catalyst in toluene and THF for the oxidation of activated alcohols. Optimization studies and control experiments were thus performed with these catalysts in batch reactors on benzyl alcohol **1a**, a benchmark substrate for this type of

oxidation reaction [21]. To avoid both energy consumption and safety issues, a fixed pressure of O₂ of 1 atm was used.

These conditions were successfully applied to allylic alcohols such as cinnamyl alcohol **2a**, nerol **3a**, geraniol **4a**, and farnesol **5a** delivering the corresponding aldehydes in 66-99% yields and 66-99% conversion (Figure 1). With these results in hand, we started to study the reaction in continuous flow. Heterogeneous catalysis is well suited for being used in flow since catalytic reactors as simple as a column filled with the solid catalytic material could be used. In the case of reactions occurring in gas-liquid biphasic medium, the flow chemistry set up often outperforms batch reactors [22,23]. We therefore transposed our batch conditions with fixed-bed catalytic reactors containing Au NPs supported on Al₂O₃ and a tube-in-tube gas/liquid device for the O₂ supply. The optimized protocol in continuous flow was found to be more efficient for aliphatic substrates, the corresponding aldehydes **1-5b** being obtained in 84-87% yield (vs 66-68% in batch) at a flow rate of 0.444 mL.min⁻¹ for a residence time of 3.7 minutes. A better relative O₂ concentration could probably account for this improvement, as well as the limited residence time of the product in the reactor, thereby limiting the risk of degradation at 80°C [21].

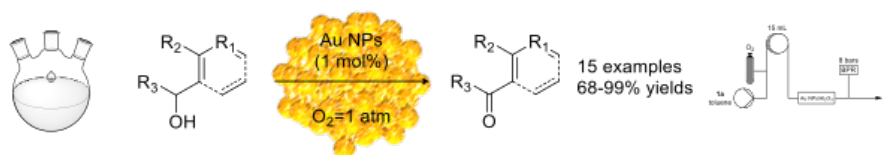


Fig. 1 Au NPs-catalyzed oxidation of activated alcohols.

3 Oxidation / Friedel-Crafts Aldolisation / Cyclisation

With this oxidation protocol tailored for our applications in hand, we next turned our attention to its combination with an aldol Friedel-Crafts-type reaction, requiring an aldehyde as the electrophilic partner and aryl nucleophiles.

Our study was initiated with benzyl alcohol derivatives and an electron-rich aryl nucleophile, such as veratrol **6**, in order to obtain unsymmetri-

cal benzophenones upon oxidation/aldol Friedel-Crafts-type/oxidation. To achieve this goal, we combined the Au NPs-catalyzed oxidation with a Bronsted acid-catalyzed reaction with the use of Amberlyst 15, a sulfonic organic resin. In spite of several attempts, we found that if the first and second steps occurred as expected with the oxidation of **1a** to **1b** and subsequent addition of **6**, the second oxidation to the corresponding benzophenone did not occur and the addition of a second veratrol unit yielded triarylmethanes such as **1a6** together with oxidation products benzoic acid **1c** and benzyl benzoate **1d** and other secondary products (Figure 2).

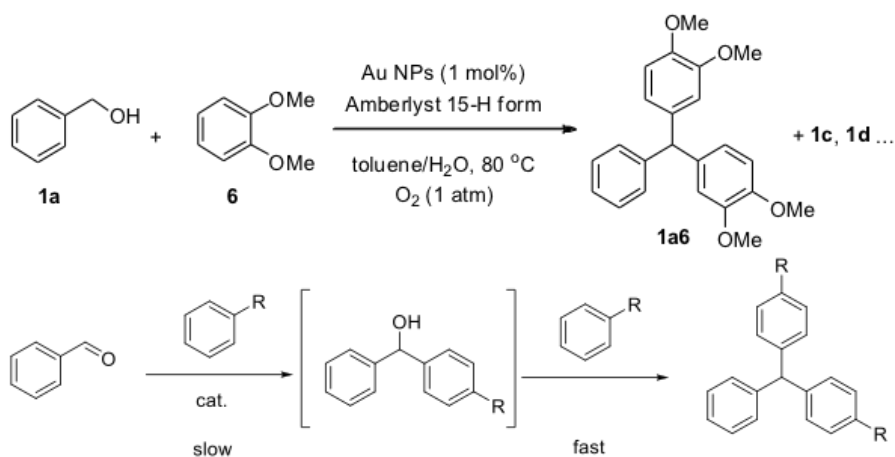


Fig. 2 Combined oxidation/aldol Friedel-Crafts type reaction.

Considering the reactivity of aldol Friedel-Crafts products, we decided to turn this reactivity to our favor using bifunctional substrates and aryl nucleophiles likely to react intramolecularly in a second time to yield complex cyclic structures. The aldehydic substrate would be generated in situ upon Au NPs-catalyzed oxidation of allylic alcohols under O₂.

We thus screened a series of Lewis and Bronsted acids in a test reaction with citral (mixture of **3b** and **4b**) and 5-methylresorcinol (orcinol) **7**, thereby focusing on the second step. If conventional Lewis acids delivered mixtures containing Δ 9- and Δ 8-tetrahydrocannabinol (THCC) **3aa**, the use of montmorillonite doped with metal cations (M-MMT) enabled the selective formation of *ortho*-THCC **3aa'**. Under optimized conditions using Ti-MMT as catalyst (10 mol%), a yield of up to 98% **3aa'** was obtained as a 83:17 mixture of Δ 9 and Δ 8 isomers (entry 13). The *cis/trans* ratio was found to be 8:2 in most cases. This result was rather unexpected since these compounds were

typically observed as side products in various syntheses of natural cannabinoids. In the same reaction conditions, but using olivetol **8** instead of **7**, *ortho*- Δ^9 -THC **3ab'** was obtained in 77% isolated yield (Figure 3) [24].

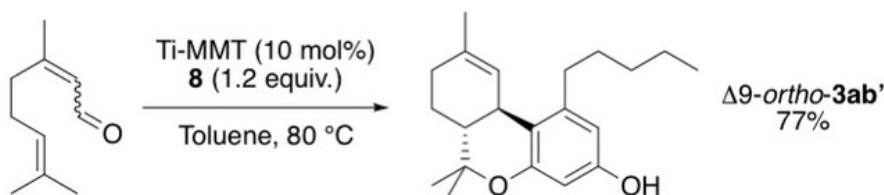


Fig. 3 Formation of the *ortho*- Δ^9 -THC **3ab'**.

A series of experiments was then undertaken to gain a better understanding of the regioselectivity of the reaction. First, the role of hydroxyl groups of **7** was evaluated. Citral was thus treated with modified alkyl resorcinols, in the presence of Ti-MMT (10 mol%) under our optimized conditions. Interestingly, the blockage of both hydroxyl groups by methylation or acetylation resulted in complete inhibition of the arylation reaction and the recovery of unchanged citral. Surprisingly, the blockage of a single hydroxyl group also completely inhibited the reaction. Based on these observations, and taking the regioselectivity in favor of *ortho*-isomers into consideration, we reasoned that Ti-MMT could influence the selectivity through a template effect where both hydroxyl groups would coordinate the interlamellar surface, combined with a Lewis-acid assisted Bronsted acid process (LBA process) allowed by Ti(IV) species. The nucleophilic attack of the arene would thus proceed via the most accessible position, in *ortho* relative to the alkyl substituent (Figure 4).

Considering our interest in the design of multicatalytic chemical processes, we performed a preliminary series of tests to combine an Au NP-catalyzed oxidation of allylic alcohols with the Ti-MMT-catalyzed cyclisation. Unfortunately, catalysts were not compatible in our conditions and the oxidation step was quenched in the presence of Ti-MMT. We thus moved towards continuous flow chemistry reactors.

The first stage of the batch/flow transposition was the optimization of the Ti-MMT-catalyzed step. At a 0.05 M concentration, a conversion of 100% of citral and 98% yield of cyclized products could be obtained with a column charged with 400 mg of Ti-MMT within 5 min residence time. With the implementation of a second catalytic column filled with Au NPs/ Al_2O_3 (1 g) and using the tube-in-tube technology for an efficient O_2 supply, the flow synthesis of *ortho*-THC and analogs was possible from **3a** (2.5 mmol scale) and enabled total conversion, and the formation of *ortho*-THCC **3aa'** (Δ^8/Δ^9

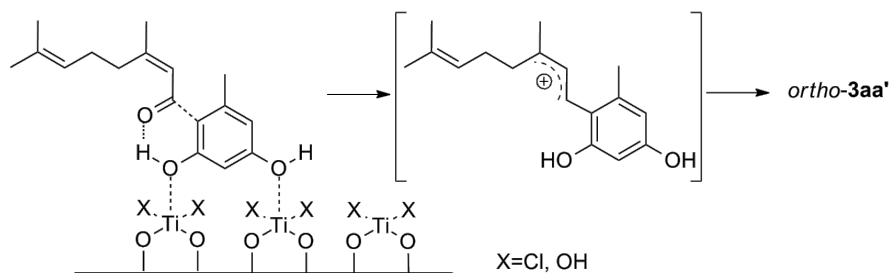


Fig. 4 LBA mode of activation at the Ti-MMT surface and subsequent regioselectivity of the reaction.

1:3.5) and *ortho*-THC **3ab'** ($\Delta 8/\Delta 9$ 1:6) with a 81 and 72% yield, respectively, from **7** and **8** (Figure 5). The first stage of the batch/flow transposition was the optimization of the Ti-MMT-catalyzed step. At a 0.05 M concentration, a conversion of 100% of citral and 98% yield of cyclized products could be obtained with a column charged with 400 mg of Ti-MMT within 5 min residence time. With the implementation of a second catalytic column filled with Au NPs/ Al_2O_3 (1 g) and using the tube-in-tube technology for an efficient O_2 supply, the flow synthesis of *ortho*-THC and analogs was possible from **3a** (2.5 mmol scale) and enabled total conversion, and the formation of *ortho*-THCC **3aa'** ($\Delta 8/\Delta 9$ 1:3.5) and *ortho*-THC **3ab'** ($\Delta 8/\Delta 9$ 1:6) with a 81 and 72% yield, respectively, from **7** and **8** (Figure 5).

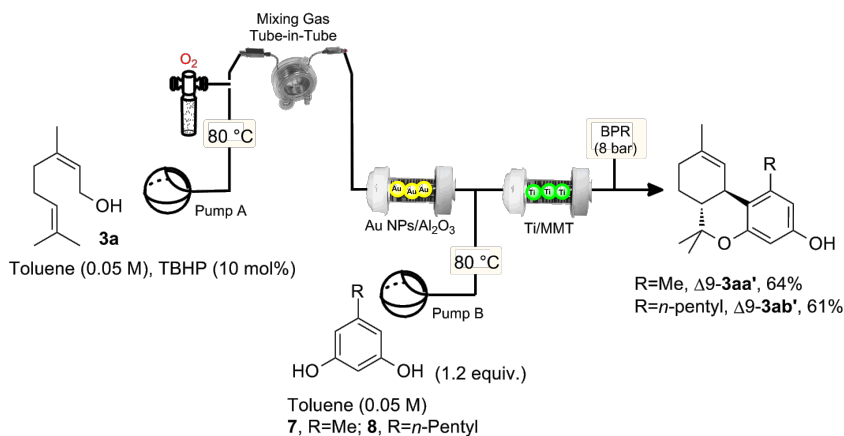


Fig. 5 Continuous flow set up for the synthesis of *ortho*-THCs **3aa'**-**3ab'**.

4 Oxidation / Hetero-Michael Addition / Addition / Crotonisation

Chromenes are motifs occurring in a large number of natural products exhibiting bioactivity and several synthetic methods to access these structures have been reported [25–33]. Our plan was to use the Au NPs/O₂ catalytic system to generate in situ α,β -unsaturated aldehydes further undergoing a base-catalyzed oxa-Michael addition of salicylaldehydes to yield chromenes substituted on positions 2, 3 and 5 in a bicatalytic one-pot/4-steps procedure thereby shortening the access to these chromene structures. Initial testing taught us that the two catalytic systems were not compatible, and a sequential one-pot process was thus developed.

Upon substrate-specific optimisation, we found that for aliphatic allylic alcohols, a mineral base such as K₂CO₃ (1.1 equiv., added as a methanolic solution) was efficient enough and chromenes were obtained in 59–67% yields. With cinnamyl alcohol derivatives, the use of an organic base such as pyrrolidine (30 mol%) in THF in the presence of molecular sieves (3 Å) was necessary for the reaction to proceed efficiently, and the expected chromenes were obtained in 86–93% yields. By replacing salicylaldehyde **9** (R₃=H, X=O) by *ortho*-aminobenzaldehyde **10** (R₃=H, X=NH), dihydroquinolines could be obtained similarly in 79–93% yields. Variation on the salicylaldehyde partner was also possible (Figure 6) [34].

In summary, we have developed a step- and atom-economical bicatalytic tandem process allowing a simplified access to biologically relevant chromene and 1,2-dihydroquinoline scaffolds with a large space of substitution possibilities. We have shown that up to five reactions could proceed in the same pot to convert simple starting materials into complex molecules by combining nanocatalysis and base-catalysis.

5 Conclusion

It is possible to perform intensive synthesis by adapting existing protocols or discovering new ones. To achieve these goals, the use of catalysis is the key to success for both basic and practical reasons. Combined with flow chemistry technology, complex molecule synthesis could be achieved easily and efficiently. These approaches could be further developed in the future toward an ideal goal of one-pot total synthesis.

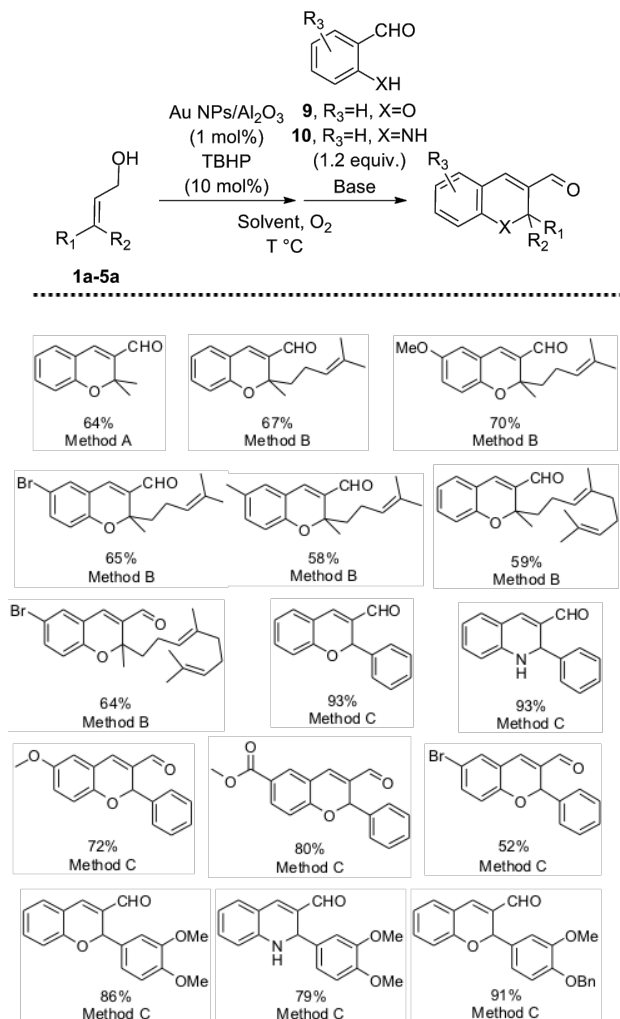


Fig. 6 Bicatalytic one-pot/4-steps synthesis of substituted chromenes/dihydroquinolines (Method A: triazabicyclodecene (TBD), Method B: K₂CO₃ Method C: pyrrolidine).

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