



HAL
open science

Complex molecule synthesis made easy

Nelli Elizarov, Pascal Giorgi, Alexandra Yeromina, Sylvain Antoniotti

► **To cite this version:**

Nelli Elizarov, Pascal Giorgi, Alexandra Yeromina, Sylvain Antoniotti. Complex molecule synthesis made easy. Université Côte d'Azur Complex Days, M. Argentina; S. Barland; P. Reynaud-Bouret; F. Cauneau; K. Guillouzouic; U. Kuhl; T. Passot; F. Planchon, Jan 2018, Nice, France. pp.77-86. hal-02014226

HAL Id: hal-02014226

<https://hal.science/hal-02014226>

Submitted on 15 Feb 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Copyright

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

Sylvain Antoniotti
Université Côte d'Azur, CNRS, Institut de Chimie de Nice. e-mail: [sylvain.
antoniotti@unice.fr](mailto:sylvain.antoniotti@unice.fr)

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).

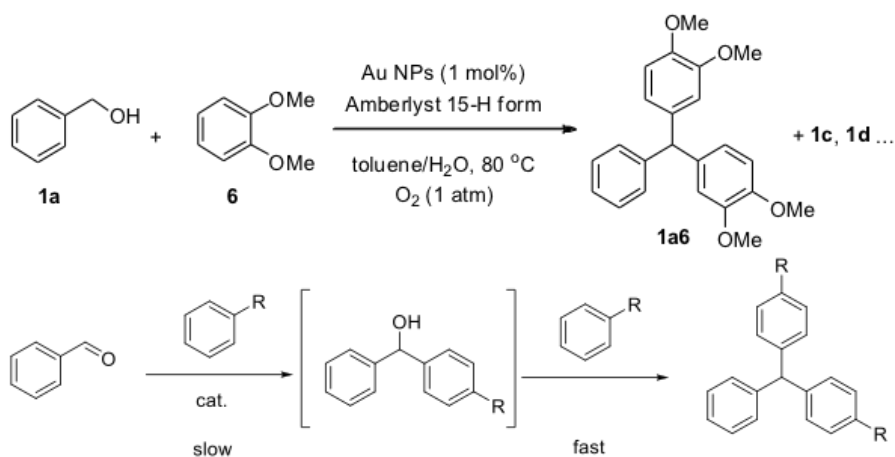


Fig. 2 Combined oxidation/aldol Friedel-Crafts type reaction.

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 O_2 .

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 $\Delta 9$ - and $\Delta 8$ -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 $\Delta 9$ and $\Delta 8$ 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].

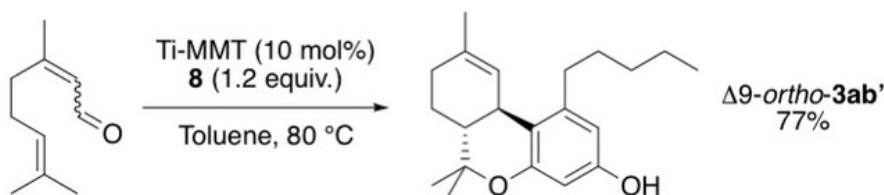


Fig. 3 Formation of the *ortho*- Δ^9 -THC **3ab'**.

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

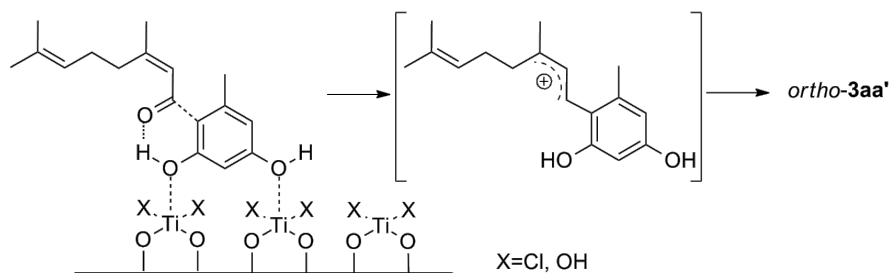


Fig. 4 LBA mode of activation at the Ti-MMT surface and subsequent regioselectivity of the reaction.

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).

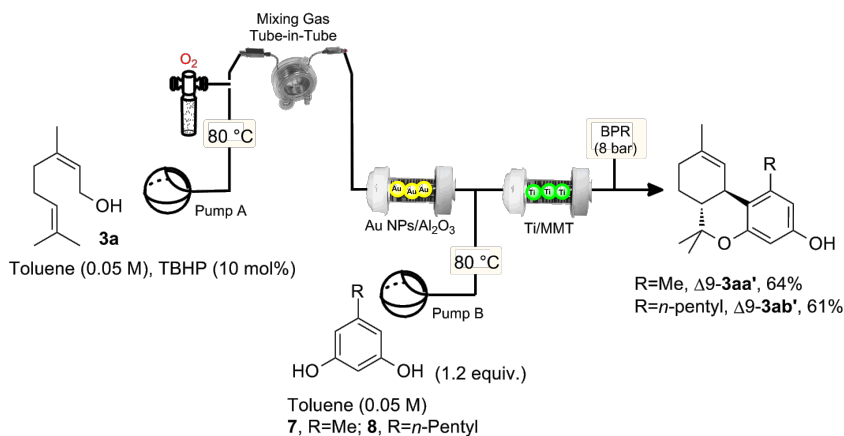


Fig. 5 Continuous flow set up for the synthesis of *ortho*-THCs **3aa'**-**3ab'**.

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.

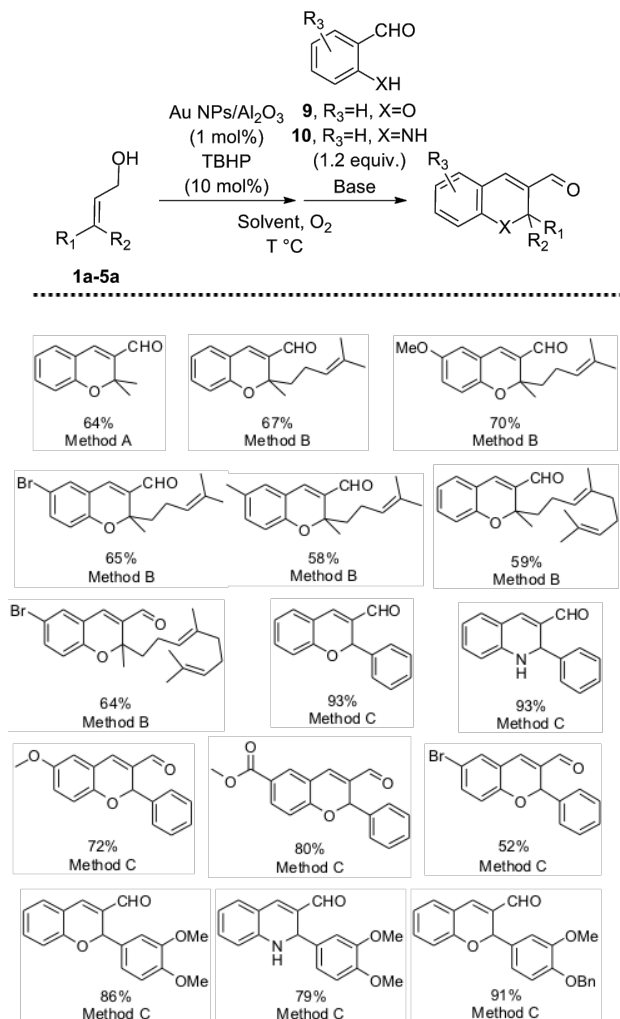


Fig. 6 Bicatalytic one-pot/4-steps synthesis of substituted chromenes/dihydroquinolines (Method A: triazabicyclodecene (TBD), Method B: K_2CO_3 Method C: pyrrolidine).

References

1. Friedrich Wöhler. Ueber künstliche bildung des harnstoffs. *Annalen der Physik*, 88(2):253–256, 1828.
2. Sylvain Antoniotti. *Chimie verte - Chimie durable*, page 192. Ellipses, Paris, 2013.
3. Thomas J Maimone and Phil S Baran. Modern synthetic efforts toward biologically active terpenes. *Nature chemical biology*, 3(7):396–407, 2007.

4. Kyriacos Costa Nicolaou and Tamsyn Montagnon. *Molecules that changed the world.*, page 385. Wiley-VCH Verlag GmbH, Weinheim, 2008.
5. Chao-Jun Li and Paul T Anastas. Green chemistry: present and future. *Chemical Society Reviews*, 41(4):1413–1414, 2012.
6. Avelino Corma and Hermenegildo Garcia. Lewis acids: from conventional homogeneous to green homogeneous and heterogeneous catalysis. *Chemical Reviews*, 103(11):4307–4366, 2003.
7. Roger A Sheldon. E factors, green chemistry and catalysis: an odyssey. *Chemical Communications*, (29):3352–3365, 2008.
8. Meenakshisundaram Sankar, Nikolaos Dimitratos, Peter J Miedziak, Peter P Wells, Christopher J Kiely, and Graham J Hutchings. Designing bimetallic catalysts for a green and sustainable future. *Chemical Society Reviews*, 41(24):8099–8139, 2012.
9. Pascal Giorgi and Sylvain Antoniotti. Catalytic tandem reactions triggered by the introduction of a carbonyl function. In Atta ur Rahman, editor, *Advances in Organic Synthesis*, pages 1–31. Bentham Science Publishers, 2017.
10. Sudhir E Dapurkar, Zameer Shervani, Toshiro Yokoyama, Yutaka Ikushima, and Hajime Kawanami. Supported gold nanoparticles catalysts for solvent-free selective oxidation of benzylic compounds into ketones at 1 atm o₂. *Catalysis letters*, 130(1-2):42–47, 2009.
11. Antonio Buonerba, Cinzia Cuomo, Sheila Ortega Sánchez, Patrizia Canton, and Alfonso Grassi. Gold nanoparticles incarcerated in nanoporous syndiotactic polystyrene matrices as new and efficient catalysts for alcohol oxidations. *Chemistry-A European Journal*, 18(2):709–715, 2012.
12. Takashi Takei, Tomoki Akita, Isao Nakamura, Tadahiro Fujitani, Mitsutaka Okumura, Kazuyuki Okazaki, Jiahui Huang, Tamao Ishida, and Masatake Haruta. *Advances in Catalysis*, pages 1–126. Elsevier Academic Press Inc, San Diego, 2012.
13. Emmanuel Skupien, Rob J Berger, Vera P Santos, Jorge Gascon, Michiel Makkee, Michiel T Kreutzer, Patricia J Kooyman, Jacob A Moulijn, and Freek Kapteijn. Inhibition of a gold-based catalyst in benzyl alcohol oxidation: Understanding and remediation. *Catalysts*, 4(2):89–115, 2014.
14. Hiroyuki Miyamura, Ryosuke Matsubara, Yoji Miyazaki, and Shū Kobayashi. Aerobic oxidation of alcohols at room temperature and atmospheric conditions catalyzed by reusable gold nanoclusters stabilized by the benzene rings of polystyrene derivatives. *Angewandte Chemie*, 119(22):4229–4232, 2007.
15. Didier Astruc. *Nanoparticles and catalysis*. John Wiley & Sons, 2008.
16. Younan Xia, Hong Yang, and Charles T. Campbell. Nanoparticles for catalysis. *Accounts of Chemical Research*, 46(8):1671–1672, 2013.
17. Manolis Stratakis and Hermenegildo Garcia. Catalysis by supported gold nanoparticles: beyond aerobic oxidative processes. *Chemical Reviews*, 112(8):4469–4506, 2012.
18. Philippe Serp and Karine Philippot, editors. *Nanomaterials in Catalysis*. Wiley-VCH: Weinheim, Germany, 2013.
19. Serena Biella and Michele Rossi. Gas phase oxidation of alcohols to aldehydes or ketones catalysed by supported gold. *Chemical communications*, (3):378–379, 2003.
20. Cristina Della Pina, Ermelinda Falletta, Laura Prati, and Michele Rossi. Selective oxidation using gold. *Chemical Society Reviews*, 37(9):2077–2095, 2008.
21. Pascal D Giorgi, Nelli Elizarov, and Sylvain Antoniotti. Selective oxidation of activated alcohols by supported gold nanoparticles under an atmospheric pressure of o₂: Batch and continuous-flow studies. *ChemCatChem*, 9(10):1830–1836, 2017.
22. Naiwei Wang, Tsutomu Matsumoto, Masaharu Ueno, Hiroyuki Miyamura, and Shū Kobayashi. A gold-immobilized microchannel flow reactor for oxidation of alcohols with molecular oxygen. *Angewandte Chemie*, 121(26):4838–4840, 2009.

23. Sangeeta Roy Chaudhuri, Jan Hartwig, Lukas Kupracz, Torben Kodanek, Jens Wegner, and Andreas Kirschning. Oxidations of allylic and benzylic alcohols under inductively-heated flow conditions with gold-doped superparamagnetic nanostructured particles as catalyst and oxygen as oxidant. *Advanced Synthesis & Catalysis*, 356(17):3530–3538, 2014.
24. Pascal Giorgi, Virginie Liautard, Mathieu Pucheault, and Sylvain Antoniotti. *Eur. J. Org. Chem.*, 11:1307–1311, 2018.
25. Naoki Iwata, Naili Wang, Xinsheng Yao, and Susumu Kitanaka. Structures and histamine release inhibitory effects of prenylated orcinol derivatives from rhododendron dauricum. *Journal of natural products*, 67(7):1106–1109, 2004.
26. Marialuisa Menna, Anna Aiello, Filomena D’Aniello, Concetta Imperatore, Paolo Luciano, Rocco Vitalone, Carlo Irace, and Rita Santamaria. Conithiaquinones a and b, tetracyclic cytotoxic meroterpenes from the mediterranean ascidian aplidium conicum. *European Journal of Organic Chemistry*, 2013(16):3241–3246, 2013.
27. Yoshihiro Noda and Misato Yasuda. Enantioselective synthesis of (-)-(r)-cordiachromene and (-)-(r)-dictyochromenol utilizing intramolecular snar reaction. *Helvetica Chimica Acta*, 95(10):1946–1952, 2012.
28. Dipak Harel, Sami A Khalid, Marcel Kaiser, Reto Brun, Bernhard Wünsch, and Thomas J Schmidt. Enecalol angelate, an unstable chromene from *ageratum conyzoides* L.: total synthesis and investigation of its antiprotozoal activity. *Journal of ethnopharmacology*, 137(1):620–625, 2011.
29. Maryla Szczepanik, Robert Obara, Antoni Szumny, Beata Gabryś, Aleksandra Halarewicz-Pacan, Jan Nawrot, and Czesław Wawrzęczyk. Synthesis and insect antifeedant activity of precocene derivatives with lactone moiety. *Journal of agricultural and food chemistry*, 53(15):5905–5910, 2005.
30. Manuel C Broehmer, Nicole Volz, and Stefan Braese. Thieme chemistry journal awardees—where are they now? microwave-assisted rhodium-catalyzed decarbonylation of functionalized 3-formyl-2h-chromenes: A sequence for functionalized chromenes like deoxycordiachromene. *Synlett*, 2009(09):1383–1386, 2009.
31. Kegang Liu and Xiaohua Jiang. Regioselective and enantioselective domino aldol-oxa-michael reactions to construct quaternary (chroman) stereocenters. *European Journal of Organic Chemistry*, 2015(29):6423–6428, 2015.
32. Henrik Sunden, Ismail Ibrahim, Gui-Ling Zhao, Lars Eriksson, and Armando Cordova. Catalytic enantioselective domino oxa-michael/aldol condensations: Asymmetric synthesis of benzopyran derivatives. *Chemistry—A European Journal*, 13(2):574–581, 2007.
33. Xiang-Wei Du and Levi M Stanley. Tandem alkyne hydroacylation and oxo-michael addition: Diastereoselective synthesis of 2, 3-disubstituted chroman-4-ones and fluorinated derivatives. *Organic letters*, 17(13):3276–3279, 2015.
34. Pascal D Giorgi, Peter J Miedziak, Jennifer K Edwards, Graham J Hutchings, and Sylvain Antoniotti. Bicataltic multistep reactions en route to the one-pot total synthesis of complex molecules: Easy access to chromene and 1, 2-dihydroquinoline derivatives from simple substrates. *ChemCatChem*, 9(1):70–75, 2017.