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# Development of Multi-catalytic Strategies Based on the Combination between Iron-/Copper- and Organo-catalysis

Adrien Quintard\*<sup>[a]</sup>

*Dedicated to Professor Barry Trost on his 80<sup>th</sup> birthday*

**Abstract:** Despite the latest advances in catalysts efficiency, using one single catalytic activation mode can lead to considerable limitations. To overcome reactivity or selectivity issues, multi-catalytic combinations can represent interesting alternatives. This manuscript reviews the recent transformations developed in my group through the combination

between cheap iron or copper complexes and organo-catalysis. Combining these activation modes enables considerable synthetic economies inconceivable by using one single catalyst. The strategies developed to combine efficiently different catalysts as well as the resulting synthetic applications are discussed.

**Keywords:** Enantioselective synthesis · multi-catalysis · copper · iron · organocatalysis

## 1. Introduction

### 1.1 Why Multi-catalysis

During the last decades, catalysis has appeared as the method of choice to create valuable complex organic scaffolds while limiting steps and waste generation. Thanks to the tremendous efforts devoted to the optimization of appropriate metal complexes or organocatalysts, exquisite reactivity and selectivity can be attained in a broad range of useful transformations. This is especially true for enantioselective catalysis where the additional challenge of stereocontrol requires control of the reagents approach in 3 dimensions. However, despite the impressive efficiency of each field, use of a single catalyst is sometimes far from optimal. The activation of the desired substrates might not be sufficient or the geometry unsuitable to obtain decent levels of enantiocontrol.

At the beginning of the 21<sup>st</sup> century when organocatalysis saw a rapid blossom, an artificial mental barrier was created with the field of metal catalysis.<sup>[1]</sup> Researchers from each domain strongly argued in favor of their respective field of interest with advantages such as TON, TOF, air and moisture stability, price, selectivity. However, this analysis did not resist a close scrutiny of the reaction developed. For example, some metals complexes are cheap and stable in the presence of water or oxygen while some organocatalysts provide excellent TOF at low catalysts loadings.<sup>[2]</sup> The major differences between these two worlds lies in the way they activate organic molecules. This enables highly complementary activation modes, catalytic pathways and thus resulting transformations.

As a result, in order to bypass the inherent limitations of using a single catalyst, chemists started developing more elaborate multi-catalytic sequences.<sup>[3]</sup> Taking the best from the different worlds through the selective merging of metals and organocatalysts, exquisite reactivity and selectivity could be

obtained in a broad range of innovative transformations durably changing our vision of organic reactivity.<sup>[4]</sup>

Excellent and comprehensive reviews have been published on the successful combinations between metal- and organo-catalysis.<sup>[4]</sup> This review will highlight my group recent achievement in the successful combinations between cheap iron and copper complexes with various organocatalysts. These multi-catalytic transformations enable considerable synthetic shortcuts and synthetic economies as demonstrated in the rapid synthesis of complex molecules, natural products or new supramolecular hosts.

### 1.2 Reactions Types

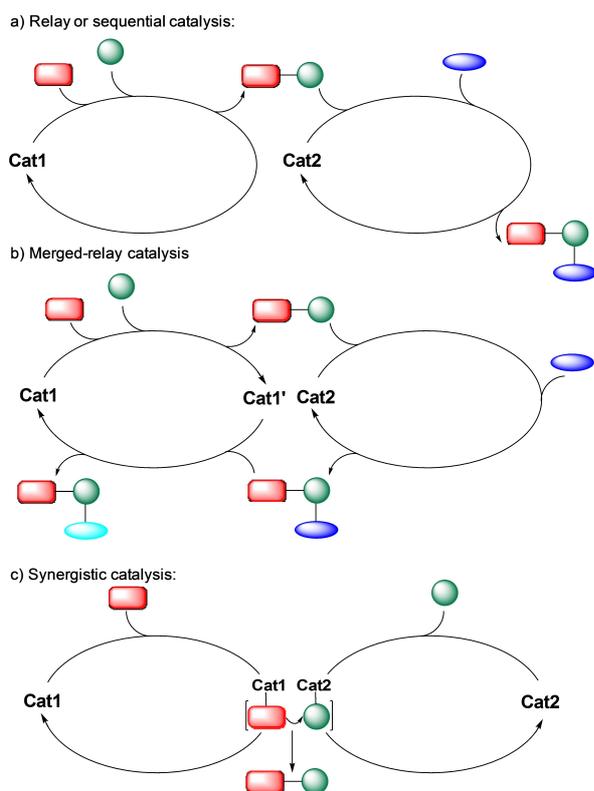
Different classifications have been proposed to define multi-catalytic transformations.<sup>[4]</sup> For a better clarity of the discussion, the multi-catalytic pathways involved in this review will be briefly defined in this section (Figure 1).

First of all, multi-catalytic reactions can be performed in a relay or sequential fashion (Figure 1.a). The first catalyst (**Cat1**) will trigger an initial catalytic cycle forming a first intermediate before the second catalyst (**Cat2**) ensures the formation of the final product through a distinct second catalytic cycle. This type of reactions can be performed mixing both catalysts at the onset through a cascade process or in one-pot adding catalysts and/or reagents sequentially. The interest of this approach is often attributed to minimization of operations notably associated with treatment and purifications resulting in limited waste generation. However, as will be

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**Figure 1.** Different categories of multi-catalytic reactions.

highlighted in this review, beside reducing the number of operations, the major advantage lies in the absence of isolation of the intermediates between the two catalytic cycles. As a result, if unstable compounds are generated after the first catalytic cycle, it can be in-situ trapped through the second cycle prior to its decomposition. Overall, this strategy can deal with the generation of otherwise unaccessible molecules ensuring the development of unique transformations.

In a second type, the two catalytic cycles can be interlocked in merged relay catalysis (Figure 1.b). In this case, **Cat1** generates an intermediate directly reacting through **Cat2** forming a new intermediate re-engaging with **Cat2'** to form the final product. It is really distinct from the first type thanks to this interconnection between both catalytic cycles so that

the overall process can be seen as occurring through a single global catalytic cycle. This implies huge mechanistic implications considerably impacting the reactivity. Most notably, one must take into account that in contrast to the first type, here the intermediate reacting with **Cat2** is only formed in low amounts corresponding at the maximum to the catalyst loading in **Cat1**. It will thus considerably impact the reactivity with **Cat2**, different from the same fundamental step taken alone.

The last type concerns synergistic catalysis where both catalysts activate different reactions partners in the same transition state (Figure 1.c). The cooperativity between **Cat1** and **Cat2** decreases the energy barrier for this transition state facilitating the desired bond formation leading to the final product. It should not be mistaken with bifunctional catalysis where both catalytic sites are present on the same catalyst.

### 1.3 Combining Inexpensive Copper or Iron Complexes with Organocatalysis

As for classical organometallic catalysis, during a long time organic chemists working on multi-catalysis have relied on the application of expensive complexes such as the ones based on Ir, Rh, Pd or Ru. However, thanks to the recent improvement in the catalytic activity of more eco-compatible copper or iron complexes, recent studies have highlighted their excellent properties when used in combination with organocatalysis.<sup>[5,6]</sup>

Beside their obvious reduced costs, a broad range of these metals complexes can be tolerant with a multitude of functions as well as with air or moisture. This can enable excellent compatibility with the organocatalytic cycles facilitating the development of innovative multi-catalytic transformations of broad applicability.

In this context, in 2013, I initiated a research program dedicated to the development of eco-compatible multi-catalyzed transformations. The goal was to decrease the number of steps as well as the waste generated in the construction of different key organic scaffolds. As will be highlighted in the next pages, selective combinations between iron or copper complexes and various organocatalysts were found to be excellent solutions towards this goal.



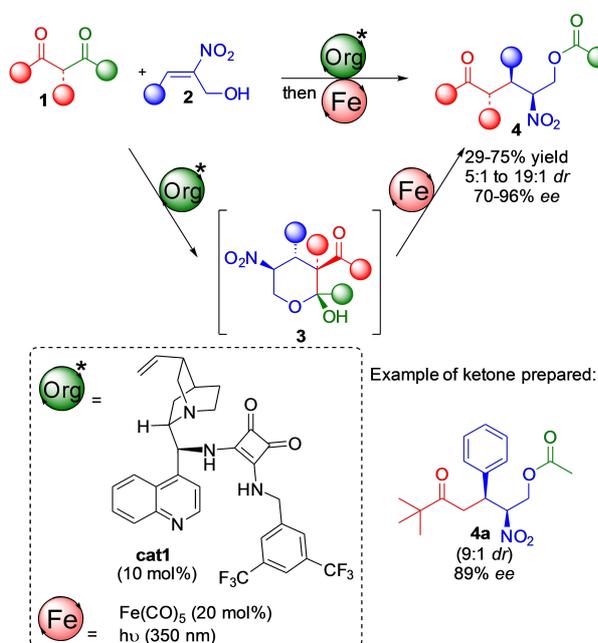
Adrien Quintard discovered chemistry at the technical institute of Castres from University Toulouse III before obtaining a Master degree in 2007 at Lyon (CPE Lyon/University Lyon I). He then moved to Geneva for a PhD obtained in 2011 for his work on metal- and organo-catalysis with Prof. Alexandre Alexakis. After a first Postdoc with Prof. Barry Trost at the university of Stanford, he joined Marseille in 2012 for a second Postdoc before obtaining in 2013 an ANR starting grant to initiate a new research program on multi-catalysis. He subsequently entered the CNRS as a senior researcher in 2014 with research interests encompassing a broad range of areas of organic chemistry (catalysis, synthesis, supramolecular chemistry). Recently, his contribution was recognized by the award of the young researcher 'Emergence' prize from the Organic Division of the French Chemical Society and he also obtained a Thieme Chemistry Journals award.

## 2. Iron- and Copper-combination with Organo-catalysis

### 2.1 Relay or Sequential Catalysis

Relay catalysis can be used to avoid the unnecessary isolation of the intermediate of a first catalytic cycle, thus reducing reaction costs. If this intermediate is unstable, such catalytic pathway provides genuine solutions to intercept it before its degradation. The addition of 1,3-diketones **1** to hydroxy-nitroolefins **2** followed by a Claisen fragmentation is an excellent example highlighting the interest of such sequential catalysis (Scheme 1).<sup>[7]</sup> Indeed, bifunctional organocatalyst **cat1** is able to promote this Michael addition of **1** to **2** with excellent levels of enantiocontrol. After the initial Michael addition, the alcohol present on **2**, cyclizes to form lactol **3**. However, as reported by the group of Enders, such hemiacetals are prone to a rapid dehydration providing the corresponding dihydropyrans.<sup>[8]</sup> Beside the synthesis of these dihydropyrans, such Michael addition of **1** to **2** would be valuable for the preparation of other type of scaffolds such as ketones **4** possessing additional nitro and protected alcohol functions.

The solution to divert lactols **3** to the expected linear ketones **4** was found by treating the reaction mixture with a catalytic amount of  $\text{Fe}(\text{CO})_5$  under UV irradiation. Under such conditions, a mild Lewis acid is generated able to activate **3** towards a clean fragmentation.<sup>[9]</sup> Through this sequential organo- iron-catalysis, a broad range of linear ketones **4** are



**Scheme 1.** Organocatalytic Michael-addition/iron-catalyzed fragmentation.

generated with excellent yields, diastereo- and enantio-control (Scheme 1).

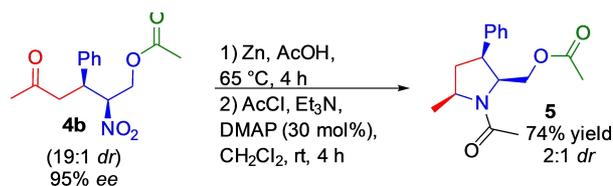
Of interest, through this cascade Michael-addition/fragmentation using diketones, the final adducts **4** are obtained in higher *ee* than through a classical addition of mono-ketones.<sup>[10]</sup> In addition, it also enables the synthesis of hindered ketones previously not accessible. For example, ketones such as **4a**, possessing a sterically demanding *tert*-butyl substituent are too hindered for their direct preparation from 3,3-dimethylbutan-2-one. Starting from the corresponding 1,3-diketones enhances the reactivity during the Michael addition while after fragmentation, the second ketone is transferred to act as a protecting group on the final product **4a**.

The synthetic utility of the transformation was demonstrated in the preparation of 2-(hydroxymethyl)pyrrolidine **5** after reduction of **4b** and protection of the free nitrogen to avoid decomposition of the rather unstable unprotected pyrrolidine (Scheme 2). Given the presence of pyrrolidine scaffolds in numerous bioactive molecules, catalysts or ligands, the rapid elaboration of these substituted heterocycles is of great interest.

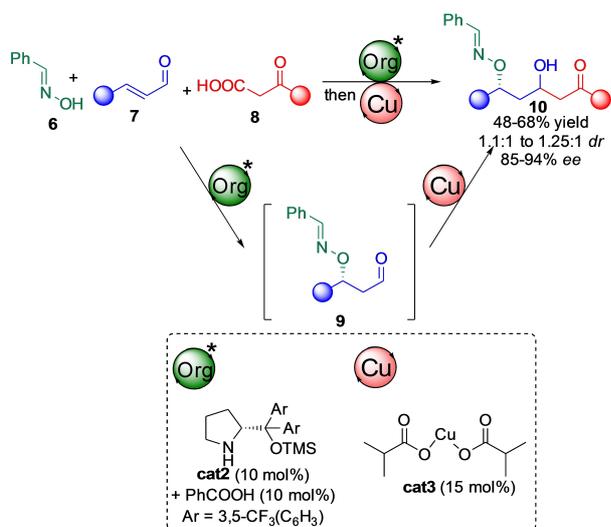
Aldehydes **9** arising from the organocatalytic oxa-Michael addition of oximes **6** to  $\alpha,\beta$ -unsaturated aldehydes **7** are another class of substrates lacking stability. They can undergo a rapid retro oxa-Michael reaction detrimental for the enantioselectivity.<sup>[11]</sup> As a result, they are often in-situ reduced to the corresponding alcohol to avoid any racemization and degradation. Therefore, directly intercepting these intermediates through another transformation can broaden the synthetic utility of this type of oxa-Michael addition. Most notably, aldolization of the adducts could provide shorter routes to 1,3,5-triols of great synthetic utility.

In order to efficiently intercept the initial Michael adducts **9** prior to their decomposition, it was necessary to implement a compatible aldolization method occurring under mild conditions. Keto-acids of increased reactivity are useful alternatives to classical ketones liberating only  $\text{CO}_2$  as side product.<sup>[12]</sup> Beside the improved kinetic profile towards addition to various electrophiles, they can be activated under mild conditions without the requirement for strong bases.

Using  $(\text{Cu}(i\text{-butyrate})_2)$  as simple copper catalyst,<sup>[13]</sup> the aldehydes **9** formed using **cat2** were efficiently transformed in the presence of keto-acids **8** to the aldolization products **10** (Scheme 3).<sup>[14]</sup> Secondary amine **Cat2** efficiently controlled the formation of the first stereogenic center through iminium activation. Use of the copper complex for the decarboxylative



**Scheme 2.** Derivatization of **4b** to substituted pyrrolidine **5**.

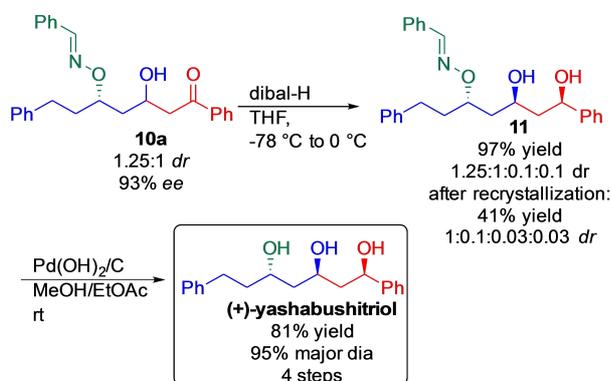


**Scheme 3.** Organocatalytic oxa-Michael addition/copper-catalyzed aldolization.

aldolization avoided any racemization and the final aldol products were isolated in 85 to 94% *ee* albeit with moderate diastereocontrol. This indicates that the oxime is poorly discriminating in the aldolization transition state.

Despite this modest diastereocontrol, the multi-catalytic sequence is of great synthetic interest in the context of polyketide synthesis.

It provides a platform to construct extended 1,3,5-triols rapidly from three widely available building blocks (Scheme 4). This was demonstrated in the short synthesis of natural (+)-yashabushitriol, previously requiring 9 to 11 steps for its preparation.<sup>[15]</sup> *Syn*-reduction of the ketone using dibal-H followed by diastereomers separation through selective recrystallisation formed diol **11**. Oxime hydrolysis revealed the triol network in a total of 4 steps for the preparation of this natural product.

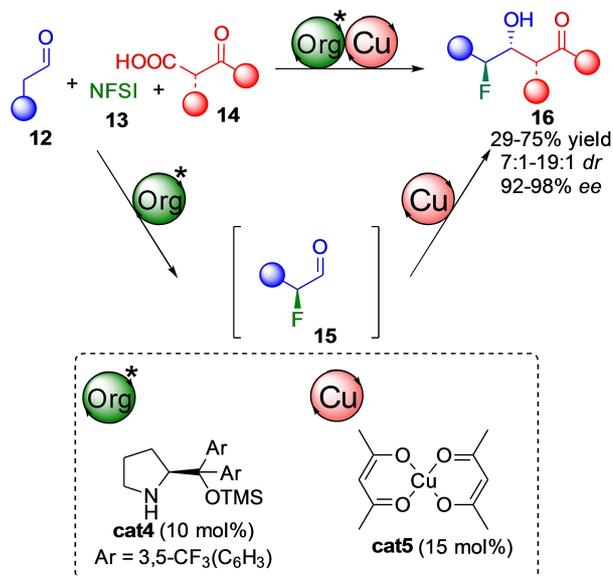


**Scheme 4.** Application in the synthesis of (+)-yashabushitriol.

Fluorine insertion in organic molecules has been widely used to modulate crucial properties such as lipophilicity, acidity of the adjacent functions, stability, conformation.<sup>[16]</sup> However, despite this interest, inserting chiral fluorohydrins in bioactive polyketide structure has been considerably neglected.<sup>[17]</sup> The most straightforward approach towards fluorinated complex polyols could involve aldolization of fluorinated aldehydes **15**. Enantioenriched fluorinated aldehydes **15** can be easily generated by enamine type **cat4** fluorination of aliphatic aldehydes using NFSI (Scheme 5).<sup>[18]</sup> However, once again, they are prone to rapid decomposition through a facilitated enol equilibrium and are usually reduced in-situ after the fluorination.

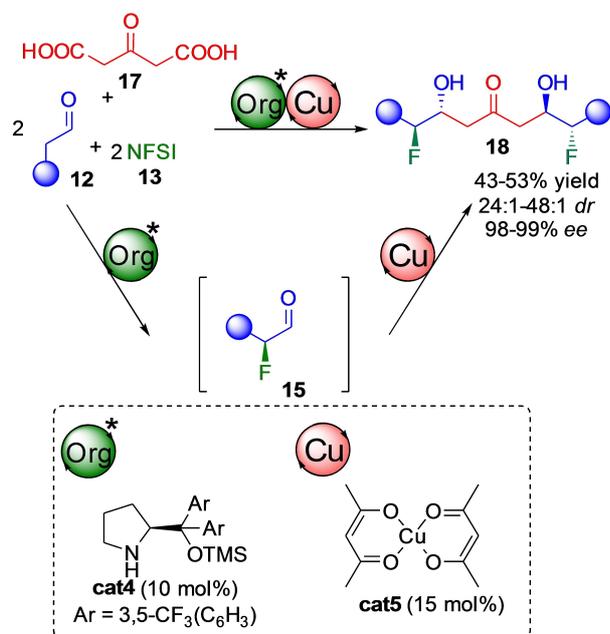
In order to intercept these sensitive intermediates, it was found that Cu(acac)<sub>2</sub> was efficient to promote a subsequent decarboxylative aldolization (Scheme 5).<sup>[19]</sup> In this case, fluorohydrins **16** possessing at least two contiguous stereocenters were isolated in excellent enantio- but also diastereocontrol ((92–98% *ee* and 7:1 to 19:1 *dr*). In this case, dipole-dipole interactions between the aldehydes and the fluorine atoms during the aldolization transition state lead to excellent *anti* selectivity on the final adducts. It must be pointed out that thanks to the excellent compatibility between the two catalytic cycles, the overall sequence can be performed in cascade, mixing all reagents and catalysts at the onset.

The multi-catalytic fluorination/aldolization method is useful to create simple fluorohydrins but given the complexity of most polyketides, methods directly assembling the core structure of extended 1,3-polyols are also highly desirable. The solution to this challenge was found by applying biosourced keto-diacid **17** in a bi-directional condensation

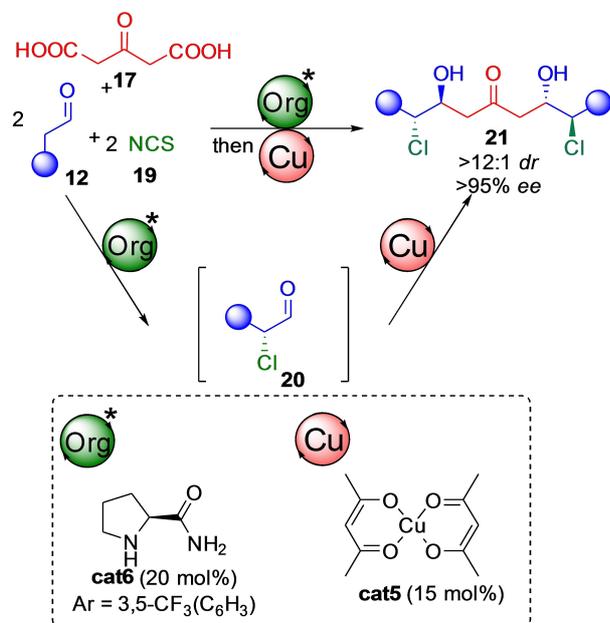


**Scheme 5.** Organocatalytic fluorination/copper-catalyzed aldolization.

(Scheme 6). This reactive acetone surrogate was famously used in 1917 by Robinson for his tropinone synthesis.<sup>[20]</sup> Applying this reagent to the multi-catalytic cascade, keto-diols



**Scheme 6.** Bi-directional organocatalytic fluorination/copper catalyzed aldolization.



**Scheme 7.** Bi-directional organocatalytic chlorination/copper-catalyzed aldolization.

**18** possessing 4 acyclic stereocenters were formed in excellent stereocontrol (>98% *ee* and >24:1 *dr*). In this cascade, two new carbon-carbon and two new carbon-fluorine bonds are selectively created.

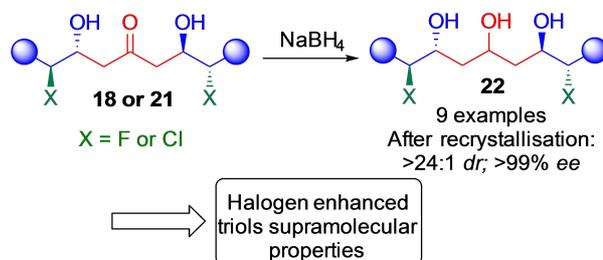
In addition to fluorinated keto-diols, it was recently discovered that the multi-catalytic sequence could be extended to chlorination (Scheme 7).<sup>[21]</sup> Using L-prolinamide **cat6** as enamine type organocatalyst, aldehydes **12** could be condensed with N-chlorosuccinimide (NCS) **19** forming chlorinated aldehydes **20**.<sup>[22]</sup> From **20**, bi-directional copper-catalyzed aldolization generated the chlorinated analogues of keto-diols **21** once again with excellent stereocontrol.

Keto-diols notably symmetric ones can be found in different natural products and are also known spiro-ketals precursors.<sup>[23]</sup> This strategy is highly efficient to prepare fluorinated analogues of these molecules with potentially improved properties.

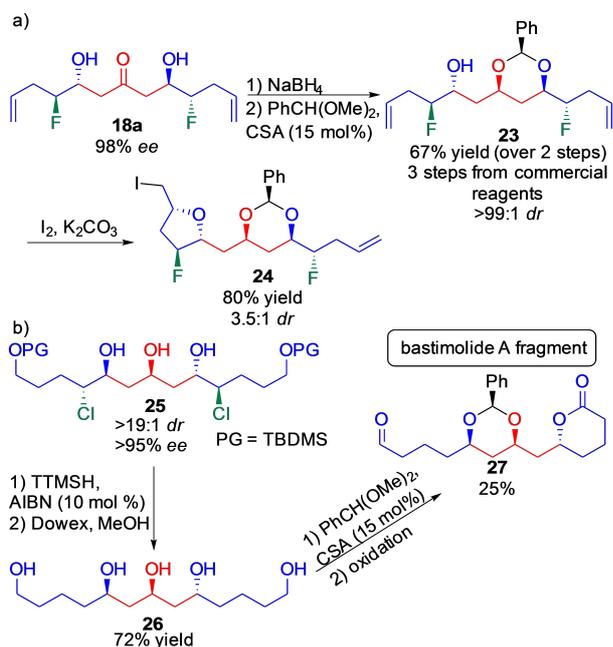
Beside the preparation of keto-diols, this strategy is mostly useful in the context of extended 1,3-polyols construction. Indeed, this motif is present in a variety of highly biologically active molecules.<sup>[24]</sup> Given the usually lengthy sequences required for their preparation, discovering alternative approaches potentially leading in a modular manner to polyol structures is of great interest.<sup>[25]</sup>

In this context treatment of the multi-catalytic halogenation/bi-directional aldolization products **18** or **21** with NaBH<sub>4</sub> gave access to a family of 1,3,5-triols possessing modular side chains (Scheme 8).<sup>[26]</sup> It was shown that the halogen atoms present in these triols (F or Cl) considerably improved their supramolecular properties in applications ranging from anion binding, catalysis to organogel formation.<sup>[26]</sup>

Beside these applications in supramolecular chemistry, the C<sub>2</sub>-symmetric triols can serve as useful building blocks to prepare biologically active scaffolds through strategic desymmetrizations. For example, from **18a** prepared in one single step from commercial products, it could potentially be used to insert rapidly fluorinated polyols into organic scaffolds (Scheme 9.a).<sup>[19]</sup> After ketone reduction, the stereochemistry on the central alcohol is revealed through the formation of the more stable *syn* acetal **23**. Iodoetherification differentiates the two side chains forming **24** possessing 7 controlled stereogenic centers and one terminal alkene available for future cross-metathesis reactions. From chlorhydrins **25**, radical promoted



**Scheme 8.** Halogenated 1,3,5-triols synthesis.



**Scheme 9.** Examples of desymmetrization of the multi-catalytic adducts.

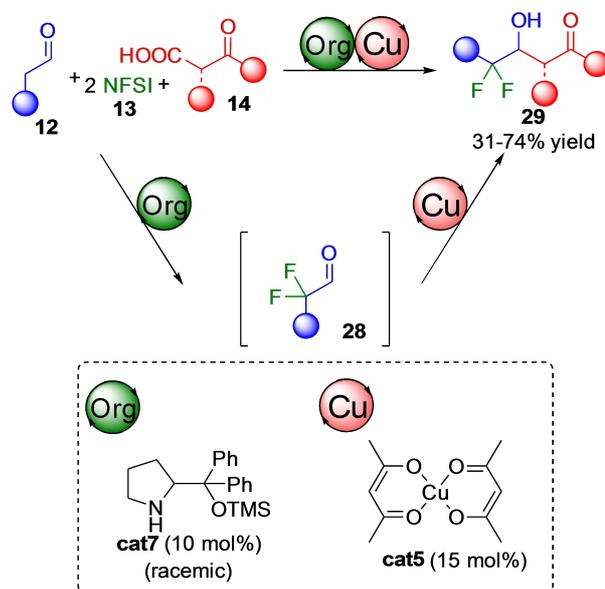
dechlorination followed by alcohol deprotection generated the core 1,5,7,9,13-pentahydroxy motif of Bastimolide A.<sup>[22]</sup> Final desymmetrization and alcohol oxidation created the advanced natural product fragment **27** (Scheme 9.b).

In addition to fluorohydrins, the organocatalytic fluorination/aldolization can also be extended to the preparation of original *gem*-fluorinated compounds **29** (Scheme 10).<sup>[27]</sup>

Using racemic **cat7** and a two-fold excess of NFSI, bis-fluorinated aldehydes **28** are generated and trapped through the copper-catalyzed aldolization. In the absence of chiral center on the intermediate aldehydes, the resulting gem-difluorinated final products are obtained in a racemic form albeit in moderate to good yields. Given the recent interest in the preparation of gem-fluorinated compounds,<sup>[28]</sup> this discovery of new type of fluorinated diols could find applications in the preparation of new drug analogues.

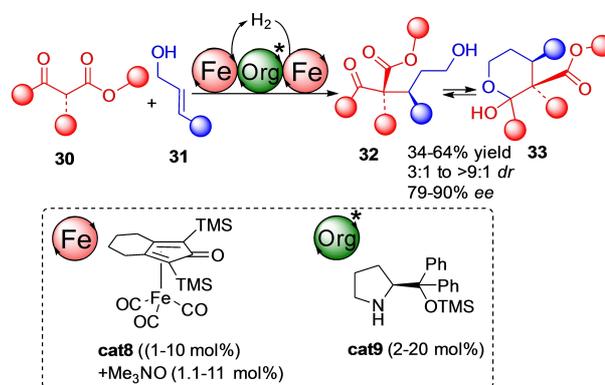
## 2.2 Merged Relay Catalysis

One of the main limitation of aminocatalysis lies in the necessary use of reactive aldehydes. These aldehydes are often accessed from alcohols before reducing them back again to the same oxidation state, resulting in undesired steps and waste generation. Merged relay catalysis is based on the interconnection between two catalytic cycles. The pathway created through these two interlinked systems can enable the discovery of innovative transformations considerably shortcutting existing routes.



**Scheme 10.** Multi-catalyzed bis-fluorination/aldolization.

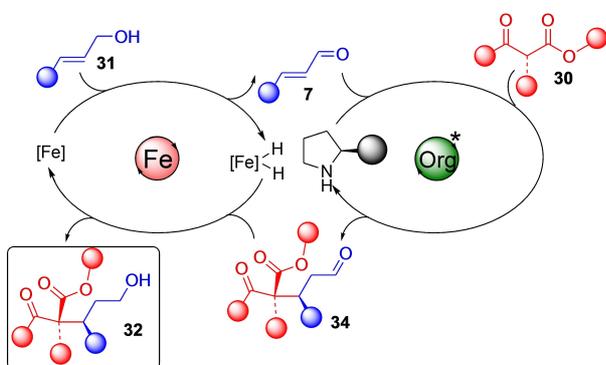
In 2013, my group reported that borrowing hydrogen where an organic molecule is activated through reversible hydrogen transfer,<sup>[29]</sup> and iminium organocatalytic cycles could be merged efficiently (Scheme 11).<sup>[30]</sup> This strategy enabled the enantioselective functionalization of allylic alcohols **30** with keto-esters **31**. The resulting products are enantioenriched alcohols **32** in equilibrium with the lactol forms **33**. The direct allylic alcohols functionalization process enabled the formation of these chiral alcohols in 79 to 90% *ee*. To develop this reactivity, the key finding was that iron-cyclopentadienone complex **cat8**<sup>[31]</sup> could promote the selective borrowing hydrogen under mild conditions and in the presence of the secondary amine catalyst **cat9**. In this system, the use of a small amount



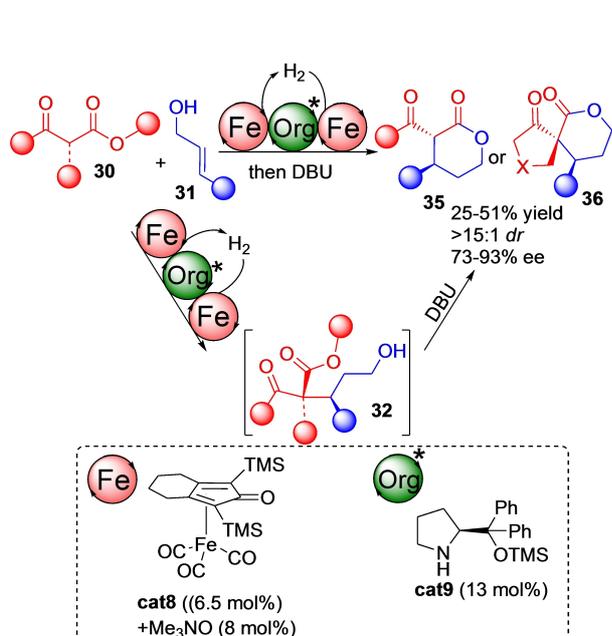
**Scheme 11.** Multi-catalyzed Iron- organo-catalyzed borrowing hydrogen.

of Me<sub>3</sub>NO ensures the formation of the active iron catalyst by removal of one CO from **cat8**.

The mechanism of the transformation is ongoing through an initial dehydrogenation of the allylic alcohol **31** by the activated complex [Fe] providing a catalytic amount of  $\alpha,\beta$ -unsaturated aldehyde **7** and of [Fe]H<sub>2</sub> (Scheme 12). This aldehyde **7** can then undergo nucleophilic addition of the keto-ester **30** through enantioselective iminium type activation forming the aliphatic aldehyde **34** where the chiral information has been controlled by the secondary amine catalyst. This aldehyde **34** is re-injected in the borrowing hydrogen for its reduction by [Fe]H<sub>2</sub> forming the final alcohol **32** and regenerating the initial dehydrogenation catalyst [Fe].



**Scheme 12.** Simplified mechanism of the allylic alcohol functionalization.



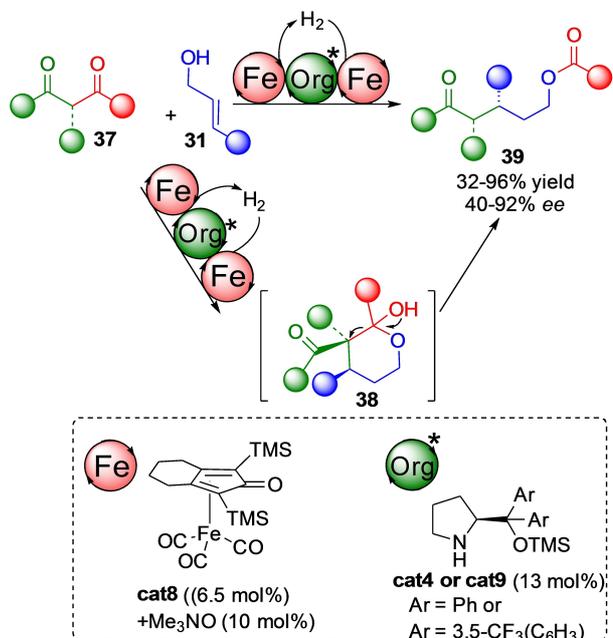
**Scheme 13.** Multi-catalyzed iron- organo-catalyzed borrowing hydrogen and one-pot lactonization.

In-situ treatment with DBU as organic base after the multi-catalytic borrowing hydrogen, further derivatized the alcohols **32** (Scheme 13).<sup>[32]</sup> This one-pot protocol creates rapidly interesting lactones **35** or more challenging spiro-lactones **36**. Once again, the stereochemistry is controlled by the organo-catalyst **cat9** providing the lactones in 73 to 93% *ee*. What is interesting to notice is that, from the intermediate alcohols **32**, the major diastereomers preferentially cyclize providing the lactones in usually excellent diastereocontrol.

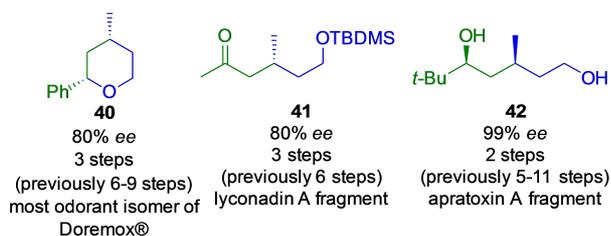
Beside the addition of keto-esters, it was discovered that di-ketones were also excellent pro-nucleophiles in the multi-catalytic borrowing hydrogen leading to an additional cascade (Scheme 14).<sup>[33]</sup>

From the multi-catalytic cascade lactol products **38**, the higher electron-withdrawing character of the ketones with respect to the esters, induced a Claisen type fragmentation directly forming the linear mono-ketones **39**. This strategy is interesting given the lack of reactivity of simple mono-ketones. Instead, starting from the corresponding di-ketones enables a strategic activation for the nucleophilic addition while at the end, the final mono-ketone is revealed and the terminal alcohol is directly protected as an ester.<sup>[34]</sup>

The considerable synthetic economies (redox, steps, protecting groups) provided by this strategy were demonstrated in the elaboration of different molecules of interest (Scheme 15). The most odorant isomer of the rose scent Doremox<sup>®</sup> or a fragment of lyconadin A were synthesized in only 3 steps vs. 6 to 9 steps previously. More impressively, the stereopure key fragment of apratoxin A could be prepared in



**Scheme 14.** Multi-catalyzed iron- organo-catalyzed borrowing hydrogen and acyl transfer cascade.



**Scheme 15.** Products prepared through the derivatization of the borrowing-hydrogen/Claisen fragmentation adducts.

only 2 steps while it previously required 5 to 11 steps for its synthesis.

### 2.3 Synergistic Catalysis

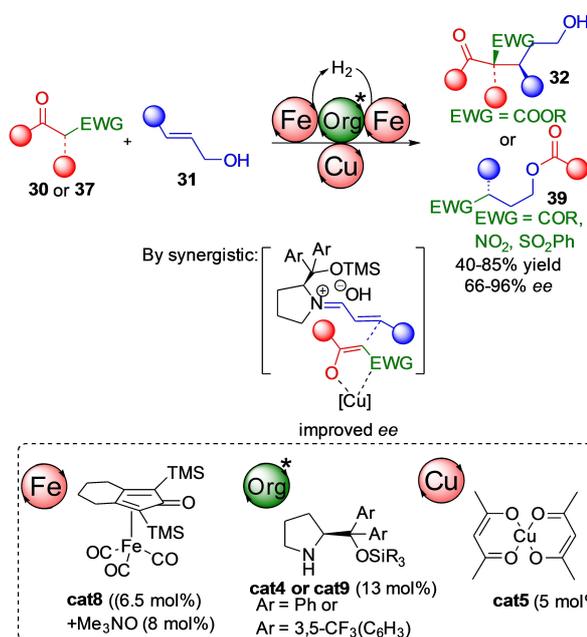
Synergistic catalysis enables the simultaneous activation of several reaction partners improving reactions kinetics and potentially selectivities. Given the interest and synthetic potential of the above-mentioned multi-catalytic borrowing-hydrogen, the mechanism was carefully investigated in order to try to further improve the results. Through this study, it was discovered that 1) the rate determining step of the process was the Michael addition of the 1,3-dicarbonyl compounds to the iminium ions; 2) a molecule of allylic alcohol was implicated in this Michael addition.<sup>[35]</sup>

In order to modulate this Michael addition transition state, our group found that adding a third catalyst improved both reactivity and selectivity (Scheme 16). The role of the copper complex added as third catalyst is to activate the pro-nucleophile during the Michael addition. This increases both reaction rate but also enantioselectivity. As a result, a broad range of pro-nucleophiles with electron-withdrawing substituents based on esters, ketones, sulfones or nitro groups underwent the addition to allylic alcohols in 66 to 96% *ee*.

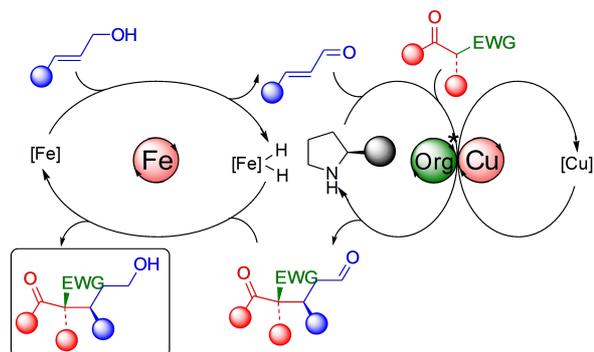
The overall mechanism is based on a relay-cascade combination with a synergistic copper- organo- catalysis depicted in Scheme 17. In this complex mechanism, each catalytic species is compatible with the others and performs the designed task with the appropriate kinetic and selectivity to furnish these expected enantioenriched alcohols.

In a last example, the power of synergistic catalysis has been applied to the development of a cascade di-decarboxylative Michael/aldol/dehydration (Scheme 18).<sup>[36]</sup>

Keto-diacid **17** could be condensed with  $\alpha,\beta$ -unsaturated aldehydes **7**, directly forming cyclohexenones **40**. In the presence of the single organocatalyst **cat4** activating the aldehyde through iminium ion formation, the expected cascade adduct was isolated in moderate 12% yield and 90% *ee*. However, synergistically activating the keto-diacid in the presence of Cu(*i*-butyrate) **cat3** considerably improved both reactivity and selectivity. In these multi-catalytic conditions, the synthetically relevant cyclohexenones<sup>[37]</sup> were isolated in



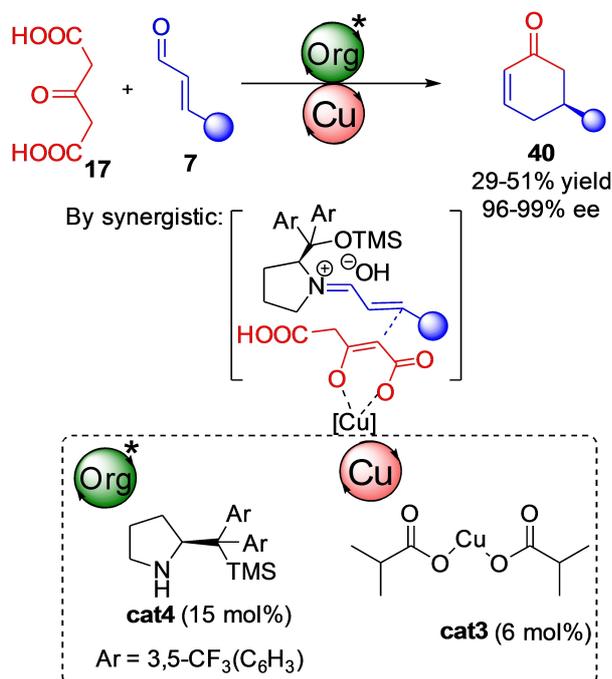
**Scheme 16.** Triple iron-, copper-, organo-catalysis borrowing hydrogen.



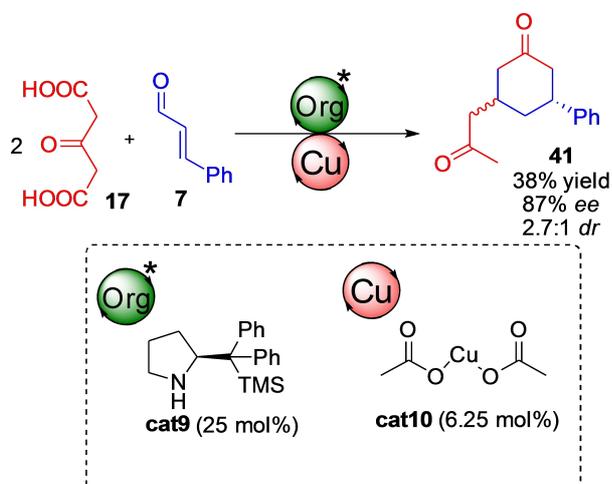
**Scheme 17.** Mechanism of the triple iron-, copper-, organo-catalysis.

29 to 51% yield and most interestingly, with enantiomeric excesses >96% *ee*.

Finally, by modulating the conditions notably adding an excess of keto-diacid **17**, the generated cyclohexenone **40** could be further derivatized through a cascade Michael addition (Scheme 19). Even though the yield remained modest, this product **41** is constructed through the formation of three new C–C bonds concomitant with the loss of 4 molecules of CO<sub>2</sub> and one molecule of water. Once again, the dual role of organocatalyst and copper complex is crucial both for the reactivity as well as for the stereoselectivity.



**Scheme 18.** Multi-catalytic cyclohexenone synthesis.



**Scheme 19.** Cascade cyclohexenone synthesis and additional acetone incorporation.

### 3. Summary

In conclusion, use of metal- or organo-catalytic activation alone can be limited in terms of reaction possibilities as well as selectivity. In contrast, taking the best from these two worlds in a multi-catalytic approach enables the development of highly selective transformations inconceivable through the

use of a single catalyst. Most notably, these multicatalytic reactions can be based on the use of inexpensive copper or iron complexes, improving their applicability. In this review, we have shown that the resulting transformations enable considerable synthetic economies. This was demonstrated in the rapid synthesis of different natural products or natural products fragments. Given all these advantages, I hope that the future will see more developments in this exciting field. Most notably, through the incorporation of additional catalysts in triple or quadruple catalytic sequences, generation of elaborated assembly lines should trigger the formation of scaffolds of enhanced complexity.<sup>[38]</sup> Given the potential selective activation of each reaction partners by the different catalysts, stereodivergent processes allowing the direct preparation of all possible stereoisomers should be developed. This type of sequences will require the identification and development of copper- and iron-based catalysts encompassing appropriate chiral ligands but the resulting multi-catalytic processes will bring chemists closer to Nature's complex machinery efficiency.

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