

Discovery of Eco-compatible Synthetic Paths by a Multi-catalysis Approach

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Abstract: This article summarizes our recent developments in the discovery of multi-catalytic reactions. By efficiently taking the best from different worlds, the combination of several catalytic principles allows the invention of eco-compatible transformations rapidly assembling simple building blocks into elaborated enantioenriched molecules. This type of approach was successfully illustrated in the synthesis of cyclohexenones, keto-diols or in the direct functionalization of allylic alcohols by an enantioselective borrowing hydrogen. In addition, mechanistic understanding of the role of the different constituents enabled the fine-tuning of the catalytic systems considerably improving the efficiency notably in terms of enantiocontrol.

Keywords: Copper · Enantioselective synthesis · Eco-compatibility · Iron · Multi-catalysis · Organocatalysis



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1. Introduction

Organic chemistry has continuously evolved during the last decade allowing the generation of molecular frameworks of increasing complexity. Today, it appears that even the more complex natural products such as maitotoxin, a molecule possessing 98 stereogenic centers, should be accessible through organic chemists skills.^[1] This huge potential has been demonstrated at the industrial level with the preparation of eribulin. This last generation anti-cancer treatment, a highly complex molecule possessing 19 stereogenic centers, is currently prepared on the industrial scale through the use of organic chemistry transformations.^[2] However, when closely looking at the parameters associated with synthetic efficiency such as redox, atom, step or protecting group economies,^[3] the 62-step sequence required for the preparation of this drug is clearly not eco-compatible. As a result, chemists must continue to develop improved synthetic tools to be able to prepare all possible complex molecules rapidly, while minimizing waste generation.

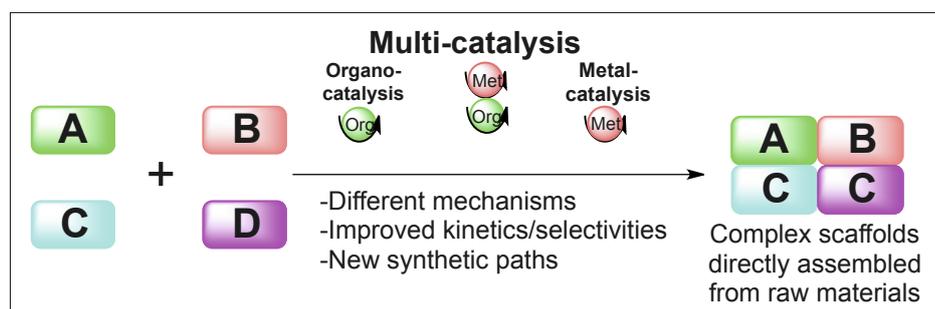
To find solutions to this problem, for years scientists have relied on the use of a single catalytic activation mode. However,

even though more efficient and selective catalysts are continuously being discovered, using only one catalyst might limit reaction potential. In answer to these apparent limitations, researchers have started looking at the selective combination between multiple catalysts. Taking the best from different worlds, notably from the fields of metal- and organo-catalysis, new mechanistic paths with improved efficiency were discovered facilitating the preparation of complex molecules (Scheme 1).^[4]

In the present article, we summarize our recent efforts at developing innovative multi-catalytic combinations. This work has allowed the discovery of various strategic paths enabling considerable synthetic economies.

2. Bio-resourced Keto-diacid in Multi-catalysis Cascades

In order to discover attractive synthetic routes, one must be able to assemble widely available materials into molecular frameworks of value. In this context, we recently took advantage of the peculiar reactivity of 1,3-acetonedicarboxylic acid (**1**), a bio-resourced molecule prepared in



Scheme 1. Multi-catalysis assembly line.

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kilogram scale from citric acid. This molecule is able to react in a bi-directional manner much faster than acetone while liberating two molecules of CO₂ as single waste.^[5] We initially attempted to condense **1** with cinnamaldehyde **2a** using an iminium activation promoted by secondary amine **cat1** (Scheme 2). After 1,4-addition of **1** to the α,β -unsaturated aldehyde, subsequent crotonization should provide chiral cyclohexenone **3a**.

Disappointingly, using a single catalytic activation mode, the cyclohexenone **3a** was obtained in moderate 12% yield and only 90% ee. However, turning to multi-catalysis considerably modified the reaction profile. Adding 6 mol% of Cu(*i*-BuCOO)₂, the final cascade product could be isolated in 50% yield.^[6] Moreover, the enantiocontrol was also improved to >98% ee highlighting the beneficial modification in the 1,4-addition transition state (enantio-determining step). This result indicates that a synergistic mechanistic pathway is occurring where the electrophile is activated through iminium ion formation and the nucleophile is activated by the copper catalyst. Coordination of keto-diacid **1** with Lewis acids such as Fe(acac)₃ could further be observed by UV titration, confirming the potential activation of the nucleophile by the copper salt.^[7] With this new synergistic copper-organo-catalytic tool in hand, different chiral enones of interest could be prepared directly in excellent enantiocontrol (>94% ee).^[8]

The discovery that Lewis acids such as simple copper salts could activate keto-diacid **1** prompted us to investigate the parent challenging bi-directional aldoliza-

tion (Scheme 3). Condensing in a cascade a ketone equivalent on two molecules of aldehydes **4** directly provides keto-diols **5**, direct precursors of 1,3,5-polyols, a motif of crucial importance present in numerous bio-active molecules (nystatin, peloruside, halichondrin, bryostatin, amphotericin B). However, despite the interest of this reaction, performing a catalytic bi-directional aldolization notably using the most interesting aliphatic aldehydes remained an unmet challenge when we started our investigations.^[9]

In this context, we discovered that under mild conditions, 15 mol% of Fe(acac)₃ or Cu(acac)₂ could selectively activate both keto-diacid **1** and aldehydes **4** to favor the formation of the desired keto-diols **5** (Scheme 3).^[7] However, even though challenging aliphatic aldehydes could be used in the transformation, the diastereoselectivities remained modest (1.2:1 dr for **5a**). In addition, the development of an efficient enantioselective version of this transformation was hampered by the competition between coordination of the keto-diacid and a chiral ligand to the metal center.

However, when a chiral center was placed in α -position of the starting aldehyde, a diastereoselective bi-directional aldolization was observed (Scheme 3). For example, the major diastereomer of **5b** could be formed in around 80% selectivity highlighting the strong facial selectivity control during the addition of **1** to the chiral aldehyde.

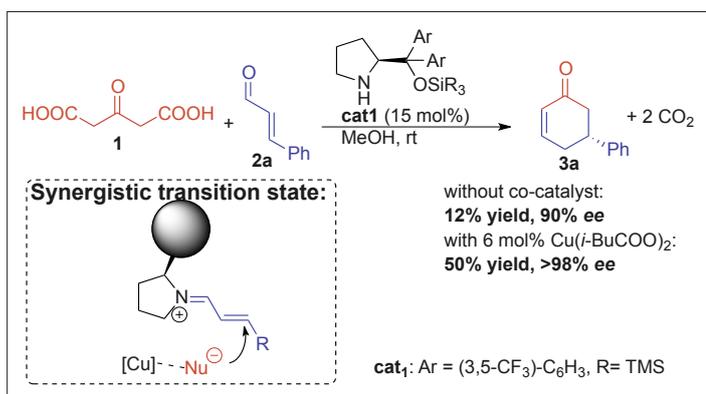
This result prompted us to further investigate other bi-directional reactions by attempting to tackle the construction of complex fluorinated polyols. Indeed, inserting fluorine atoms represents a method

of choice to modulate properties of organic molecules such as lipophilicity, conformation or acidity but remains a considerable challenge as soon as complex molecules are concerned.^[10] We recently questioned whether introducing fluorine in extended polyols would improve their bioactivity profile.^[11] However, the efficient construction of these fluorinated polyols required the development of innovative stereoselective cascades. In this context, the preparation of fluorinated keto-diols through a bi-directional aldolization would be of high interest to rapidly incorporate poly-fluorinated polyols into biologically active structures.

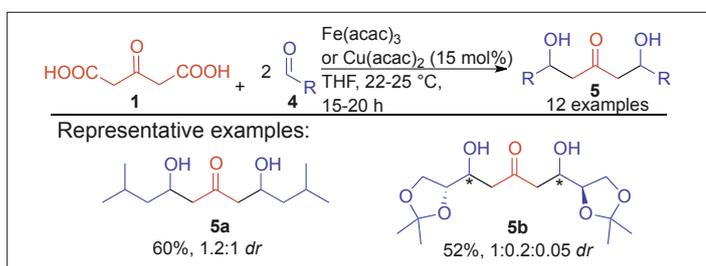
In order to successfully develop the projected transformation, sensitive enantioenriched fluorinated aldehydes **7** easily prone to racemization had to be generated and *in situ* selectively derivatized (Scheme 4). For this purpose, we hypothesized that a multi-catalytic combination between an amine-catalyzed aldehyde fluorination (enamine activation),^[12] and a selective aldolization would directly generate acyclic keto-diols **6** possessing four acyclic stereogenic centers and incorporating two fluorine atoms.

Gratifyingly, the mild conditions required for the copper-catalyzed bi-directional aldolization allowed the generation of the expected keto-diols in >98% ee. Moreover, equal efficiency was obtained when performing the reaction in one-pot consecutive manner or directly mixing all reactants at the onset (cascade). This highlights the perfect selectivity of the different catalysts notably to avoid side reactions such as the direct condensation of the keto-diacid with NFSI or with the starting aldehyde **4**.

Finally, when closely monitoring the reaction by mass spectrometry, we could observe the formation of the aldol adduct prior to CO₂ loss.^[13] This observation together with the formation of the major anti-isomer suggest a chair-like six-membered transition state for the aldolization with additional copper coordination to the aldehyde. Dipole-dipole repulsion between the fluorine and the aldehyde would explain the observed anti-diastereoselectivity (Scheme 4).^[14]



Scheme 2. Multi-catalytic cyclohexenones synthesis.

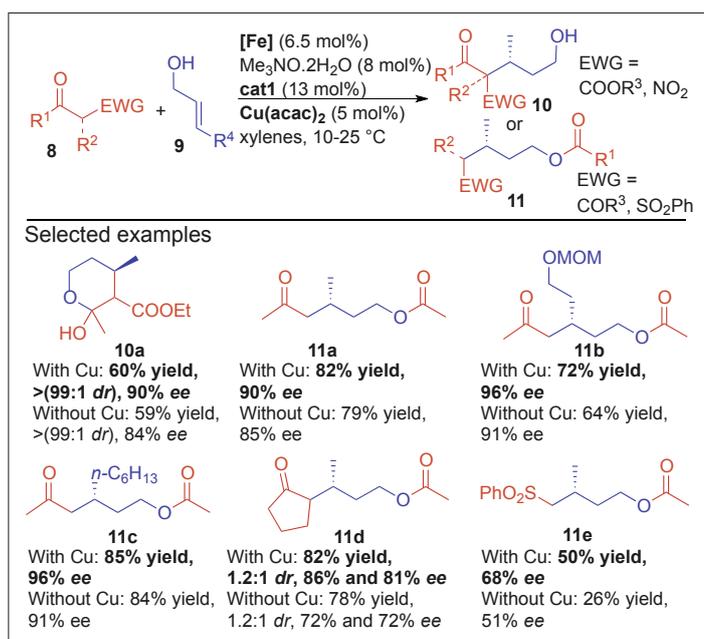


Scheme 3. Initial bi-directional aldolization.

3. Enantioselective Borrowing Hydrogen Cascades

In borrowing hydrogen transformations, a metal catalyst activates in a transient manner an organic molecule through reversible hydrogen transfer. The most famous representative example of this class of reactions is the direct alcohol amination.^[15] A wide range of different metal complexes are able to promote these

Scheme 6. Triple-catalytic borrowing hydrogen.



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