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Cooperative Catalysis with Coupled Chiral Induction in 1,3-Dipolar Cycloadditions of Azomethine Ylides

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Dedicated to Prof. Miguel Yus on the occasion of his retirement.

Abstract: 1,3-Dipolar cycloadditions (1,3-DC) between imino esters (as precursors of *N*-metallated azomethine ylides) and π -deficient alkenes are promoted by cooperative asymmetric Lewis acid-Brønsted base catalysis. The components of these catalytic pairs are silver salts derived from enantiopure commercially available BINOL-based phosphoric acids and Cinchona alkaloids. Chiral phosphoric silver(I) salts promote HOMO raising of in situ formed 1,3-dipoles, whereas protonated cinchona alkaloids generate a LUMO lowering of the dipolarophiles resulting a global acceleration of the 1,3-DC. The best results were obtained with BINOL-derived silver phosphate and hydrocinchonine. Matching between both cooperative metallo- and organocatalyst results in an enhanced enantiomeric excess, superior to that reached by both separate components. NOESY experiments and DFT calculations are compatible with a non-covalent interaction (hydrogen bond) between both catalysts, which results in close contacts and mutually coupled chiral environments.

Scientists learn many key synthetic concepts from nature. The simple and sophisticated strategies employed in biocatalysis have been implemented in modern asymmetric synthesis, synergistic/cooperative catalysis^{1,2} being one of the most fascinating areas (Figure 1).³ Due to the opposite nature of chiral catalysts involved in these types of processes, they are free to interact to each other and give inactive species. To overcome this drawback it is necessary to select them in such a way that a reversible binding can occur allowing the corresponding substrate activation separately. Concerning the interaction of two chiral entities,⁴ successful metal catalyst-metal catalyst, metal catalyst-organocatalyst, and organocatalyst-organocatalyst have been reported.³

Within a wider context, Carreira *et al.*⁵ firstly introduced the concept of stereodivergent dual catalysis for the enantioselective α -allylation of aldehydes. In that case, related to the (a) strategy

of Figure 1, the selection of different combinations of catalysts provided access to all possible stereoisomers of a target compound in high enantiomeric excess. Therefore, this strategy is based on the independent chiral induction generated by both catalysts (Figure 1a). This model contrasts with the clear double chiral activation of a single substrate one (Figure 1b).

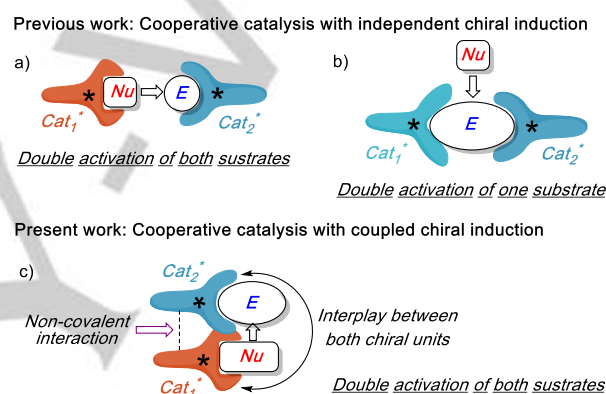


Figure 1. Possible cooperative catalytic models.

This necessary reversible binding, associated with the high stereocontrol exhibited, for example, by cycloadditions in their corresponding transition states allows to expand the scope and synthetic utility of them.^{6,7,8} Particularly, catalytic enantioselective 1,3-dipolar cycloaddition (1,3-DC)^{9,10} involving stabilized azomethine ylides and electrophilic alkenes have been promoted using different strategies: a) monofunctional chiral metal complexes;^{10a,c} b) bifunctional chiral complexes;^{10a,c,11} c) double chiral activation of metal catalysts;¹² d) monofunctional chiral organocatalysts;^{10a,c} and e) bi- or polyfunctional chiral organocatalysts.¹³ However, no cooperative catalysis generated by two chiral entities, bound by non-covalent interactions, activating both the dipole and the dipolarophile has been reported to date (Figure 1c).¹⁴

In this work, the effects of introducing chirality in the Lewis acid catalyst, together with the chirality of the Brønsted base, in the diastereo- and enantioselective 1,3-DCs between imino esters **1** and electrophilic alkenes **2** to give enantiomerically enriched prolines **3**, will be surveyed (Scheme 1). For this purpose, several *Cinchona* alkaloids **4-9** as chiral Brønsted bases and a series of chiral BINOL-derived silver phosphates,^{15,16} generated by mixing the corresponding chiral phosphoric acids **10-16** with silver carbonate for 1 h, at room temperature, will be evaluated.

Initially, the solution containing the chiral silver phosphate was allowed to react with imino ester **1a** and *N*-methylmaleimide (NMM, **2a**), in the presence (or absence) of the chiral base (reagents added in this order), in toluene as solvent, at rt avoiding

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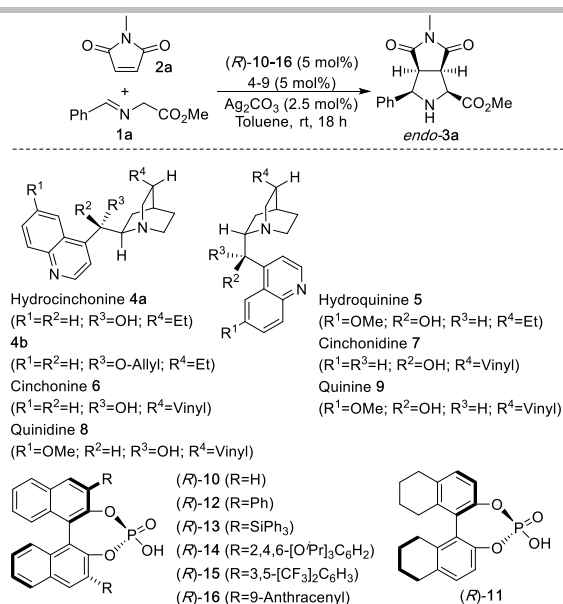
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Scheme 1. Cinchona alkaloids **4-9** and chiral BINOL-derived phosphoric acids **10-16** employed in 1,3-DC between imino ester **1a** and *N*-methylmaleimide **2a**.

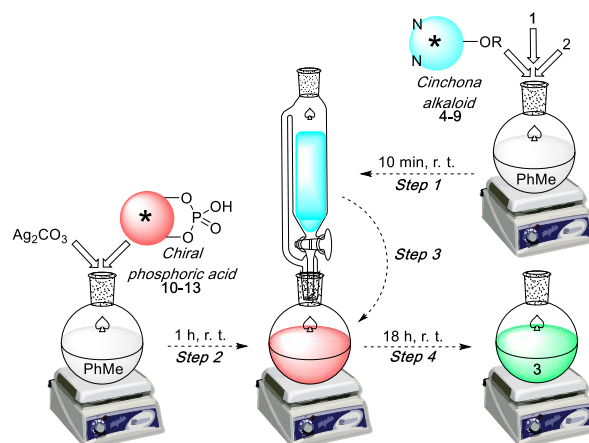
light exposure (Scheme 1 and Table 1).¹⁷ Preliminary results, obtained in the absence of a base, revealed that the best chiral silver phosphate was formed by silver carbonate and acid (*R*)-**10** giving *ent-endo-3a* in excellent both conversion and diastereoselectivity (>98:2 determined by ¹H NMR) although with moderate enantioselectivity (Table 1, entry 1). The mixture (*S*)-**10**/Ag₂CO₃ afforded the same results yielding cycloadduct *endo-3a* instead. The employment of phosphoric acids **11-13** gave lower enantioselectivity (Table 1, entries 2-4) whilst reactions performed with hindered silver phosphates, derived from acids **14-16**, furnished almost racemic *endo-3a* (data not included in Table 1). The bifunctional character of these chiral silver phosphates in this 1,3-DC was disrupted by the introduction of an external base, such as trimethylamine, lowering the enantioselectivity of the process (Table 1, entry 5). In the presence of Cinchona alkaloids as chiral bases (**4a**, **6-9**), the results were satisfactory, especially when cinchonine **6**, cinchonidine **7** (in this example *ent-endo-3a* was obtained), and hydrocinchonine **4a** were used (Table 1, entries 6-10). Hydrocinchonine **4a** was selected for the next experiments because a higher purity of the crude *endo-3a* product was observed by ¹H NMR. Under these conditions, other solvents such as THF, CH₂Cl₂, *tert*-butyl methyl ether, acetonitrile and methanol were tested and the *ee* was not improved (data not included in Table 1). The lowering of the temperature to 0 °C was not efficient in terms of conversion and enantioselectivity. The matched combination between phosphoric acid (*R*)-**10**/Ag₂CO₃/**4a** was demonstrated after analysis of the enantioselectivity obtained in the reaction mediated by the catalytic system formed by mismatched (*S*)-**10**/Ag₂CO₃/**4a** triad (Table 1, entry 11). According to this set of results, it was considered that the order of the addition of reagents (Cinchona alkaloid was added at the end) facilitated the reaction of the (*R*)-**10**/Ag₂CO₃ by itself with low enantioselectivity such as it was demonstrated in entry 1 of Table 1. So, a different addition order was attempted (Figure 2) where a better interaction chiral base-imino ester was ensured. This new procedure allowed to obtain cycloadduct *endo-3a* in 99% *ee*

(Table 1, entry 12). Identical result of **3a** was achieved employing the chiral phosphate (*R*)-**13**/Ag₂CO₃ and **4a** (Table 1, entry 14), but phosphoric acids **11**, **12**, and **14-16** furnished poor enantioselections of **3a** in low *ee*. The most important control in the enantioselection was provided by the chiral base (Table 1, entry 13) meanwhile the chiral silver phosphate cooperated to get the maximum level of chiral induction (Table 1, entry 12). The opposite configuration was easily generated using cinchonidine **7** together with (*R*)-**10**/Ag₂CO₃ giving *ent-endo-3a* in good conversion and 93% *ee* (data not included in Table 1). The absolute configuration of *endo-3a* was assigned by comparison of HPLC data and the specific optical rotations of purified samples with the reported ones in previous articles.¹⁸ So, the best conditions described in entry 12, employing commercially available chiral sources, were used for both mechanistic and scope studies.

Table 1. Optimization of the 1,3-DC between imino ester **1a** and NMM **2a**.

Entry	Chiral acid	Base	Conversion (%) ^[a]	<i>ee</i> (%) ^[b]
1	(<i>R</i>)- 10	—	100	60 <i>ent-endo-3a</i>
2	(<i>R</i>)- 11	—	96	34 <i>ent-endo-3a</i>
3	(<i>R</i>)- 12	—	100	20 <i>ent-endo-3a</i>
4	(<i>R</i>)- 13	—	100	26 <i>ent-endo-3a</i>
5	(<i>R</i>)- 10	Et ₃ N	100	52 <i>ent-endo-3a</i>
6	(<i>R</i>)- 10	4a	100	83
7	(<i>R</i>)- 10	6	91	83
8	(<i>R</i>)- 10	7	97	83 <i>ent-endo-3a</i>
9	(<i>R</i>)- 10	8	97	63 <i>ent-endo-3a</i>
10	(<i>R</i>)- 10	9	100	65
11	(<i>S</i>)- 10	4a	97	20
12 ^[c]	(<i>R</i>)- 10	4a	100	99
13 ^[c]	—	4a	100	83
14 ^[c]	(<i>R</i>)- 13	4a	100	99

[a] Determined by analysis of crude ¹H-NMR spectra. [b] Determined by standard or SCF HPLC using columns with chiral stationary phases. [c] Reaction performed using the addition protocol described in Figure 2.



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Figure 2. Optimized addition sequence of cooperative catalysts **1a**→**3**.

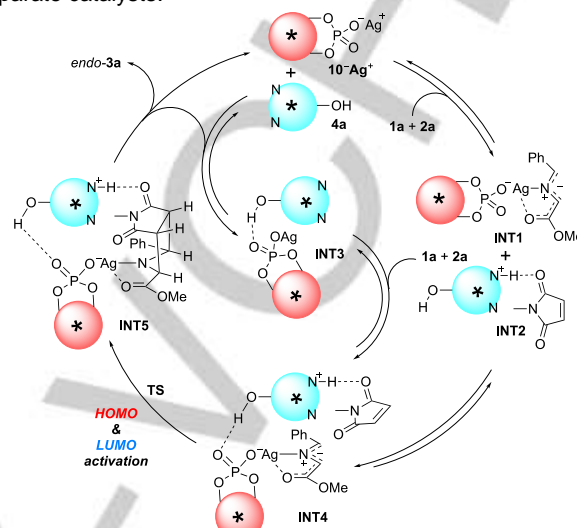
In order to better understand our experimental results, we analyzed in detail the parent 1,3-DC between imino ester **1a** and NMM **2a** in the presence of Ag_2CO_3 and catalysts (*R*)-**10** and hydrocinchonine **4a**. On the basis of previous studies¹⁹ on the mechanism of asymmetric catalyzed 1,3-DC between azomethine ylides and π -deficient alkenes, the catalytic cycle gathered in Figure 3 was considered. In addition, we optimized several stationary points associated with this mechanism by means of DFT calculations, which were carried out at the M06(PCM,solvent=PhMe)6-31G(d) & LANL2DZ//B3LYP/6-31G(d)&LANL2DZ level of theory.²⁰

According to this catalytic cycle, the protocol described in Figure 2 ensures that when the substrates **1a** and **2a** are added, the Ag^+ cation formed a chiral salt with the corresponding phosphoric acid. In the presence of both catalysts, imino ester **1a** generated an *N*-metalated azomethine ylide **INT1** that can react with dipolarophile **2a** or with its activated complex **INT2**. However, when the structure of **INT1** was optimized, and its reaction with **2a** was analyzed, we found that the chiral information of the phosphoric acid is not optimal to reach an effective blockage of one prochiral face of the dipole and low theoretical enantioselectivity towards *ent-endo-3a* was obtained ($ee_{\text{calc}} = -16$, see the SI for further details), in qualitative agreement with the experimental results (Table 1, entries 1-5). Similarly, DFT analysis of the reaction of **INT2** with the *N*-metallated azomethine ylide of **1a** in the absence of (*R*)-**10** resulted in a modest *ee* of 77%, also in qualitative agreement with the experimental results (see also the SI for additional details).

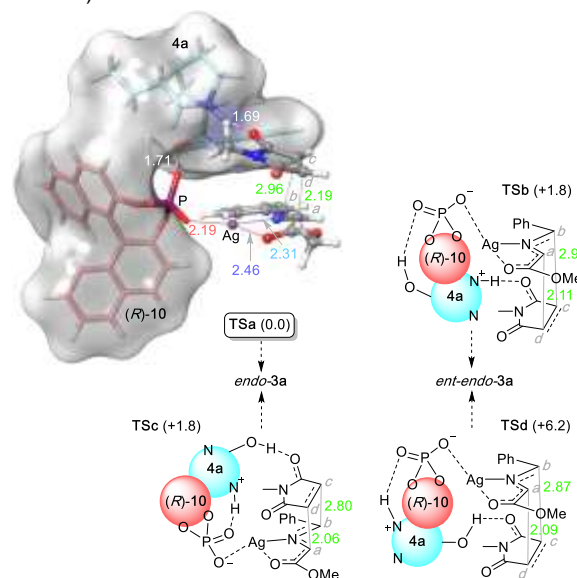
In parallel to activation of **1a**, phosphoric acid **10** or its silver salt **10-Ag⁺** (Figure 3) can interact with Brønsted base **4a** to form non-covalent complex **INT3** or, after forming the azomethine ylide moiety, **INT4**. In both intermediates, hydrogen bonding between the hydroxy group of **4a** and the phosphate group was shown by our DFT calculations. In addition, when the *O*-allyl derivative **4b**, was tested as chiral base in the 1,3-DC between **1a** and **2a** in the presence of Ag_2CO_3 and (*R*)-**10**, the formation of racemic *endo-3a* was observed. Besides, ¹H-NMR experiments with the **4a**/*R*-**10** pair showed that the quinuclidine moiety of **4a** was protonated and the surrounding proton resonances changed accordingly. Finally, NOESY correlations between **4a-H⁺** and the aromatic protons of (*R*)-**10** were observed, thus confirming the presence of complexes **INT3** and **INT4** gathered in Figure 3. In contrast, no NOESY contacts were observed in solution experiments with the **4b**/*R*-**10** pair. From intermediate **INT4**, cycloadducts **INT5** were formed via saddle points **TS**. This step of the catalytic cycle leads to *endo-3a* with concomitant release of the catalysts as the **10-Ag⁺/4a** pair or **INT3** intermediate.

We also calculated the possible transition structures leading to the **INT5** precursors connected with *endo-3a* and *ent-endo-3a*, denoted as **TSa-d** in Figure 4. We considered both $\text{OH}\cdots\text{O}=\text{P}$ and $\text{N}^+\text{H}\cdots\text{O}=\text{P}$ contacts between **10-Ag⁺** and **4a-H⁺**. Our calculations showed concerted although asynchronous [$\pi 4_s + \pi 2_s$] topologies, in which the C...C σ -bonds being formed are more advanced at the distal position with respect to the $\text{4a}^+\text{H}\cdots\text{O}=\text{C}(\text{NMM})$ interaction. These saddle points also show double FMO activation between both reactants. The phosphate moiety promotes a HOMO raising of the azomethine ylide and the protonated alkaloid unit generates a LUMO lowering via the above-mentioned hydrogen bond between **4a-H⁺** and **2a**. Among the four saddle

points shown in Figure 4, **TSa** is the one of the lowest energy because of optimal interaction between the phosphoric and alkaloid units. The solvent accessible surface (SAS) shows close contacts between both chirality sources, in agreement with the NOESY experiments. Consequently, a quite rigid structure is formed, which generates and enhances chiral induction with respect to the separate catalysts.

**Figure 3.** Proposed catalytic cycle for the successful cooperative non-covalent catalysis involving catalysts **10** and **4a** via double FMO activation.

This induction results in a preferential [*a*(Si)...*d*(Si)/*b*(Re)...*c*(Re)] *supra-supra* interaction (Figure 4) that ultimately leads to cycloadduct *endo-3a*, in nice agreement with the experimental results. The other transition structures **TSb-d** exhibit less than optimal interactions. In particular, the $\text{N}^+\text{H}\cdots\text{O}=\text{P}$ hydrogen bonding between both catalytic units were calculated to be less efficient than the $\text{OH}\cdots\text{O}=\text{P}$ interactions, a result compatible with the lack of enantioselectivity observed in the presence of *O*-allyl derivative **4b** (vide supra). All these calculations result in a computed enantiomeric excess of $ee_{\text{calc}} = 92\%$, in good agreement with our experimental result of 99% (see the SI for further information).

**Figure 4.** Transition structures **TSa-d** associated with 1,3-DCs between **1a** and **2a** to give *endo-3a* and *ent-endo-3a* in the presence of catalysts Ag_2CO_3 , **4a** and (*R*)-**10**. All structures were fully optimized at the M06(PCM,solvent=Ph Me)

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/6-31G(d)&LANL2DZ//B3LYP/8-31G(d)&LANL2DZ. Bond distances are given in Å. Numbers in brackets are the relative free energies at 298 K, in kcal/mol.

With this information, the survey of the versatility of this cooperative enantioselective 1,3-DC was carried out using BINOL-derived silver phosphate and hydrocinchonine (Figure 5). NMM dipolarophile **2a** was a suitable dipolarophile for these transformations and reacted satisfactorily with methyl, isopropyl and *tert*-butyl benzylideneglycinates in good yields and very high to excellent diastereo (>98:2 *dr*) and enantioselectivities of *endo*-**3a-c**, methyl ester being the most appropriate starter. Alanine derivative **1** was also allowed to react with the catalytic system and **2a** affording *endo*-**3d** in 93% *ee*. Proline derivative **1** was also allowed to react with the catalytic system and **2a** affording *endo*-**3e** in 61% yield and 96% *ee* (Figure 5). More hindered substrates and different dipolarophiles as *ortho*-substituted arenes in the imino group of **1** and *tert*-butyl acrylate were tested together in the same reaction affording *endo*-**3f** in good yield (78%) and excellent *ee* (>99%).

β -Nitrostyrene is an excellent dipolarophile that, generally, promotes an *exo*-approach towards the dipole, but in this reaction, unexpected *endo*-cycloadduct **3g** was the major diastereoisomer isolated with a 95% *ee*. This result also supports the proposed interaction dipolarophile (nitro group)-protonated quinuclidine described in **INT4** (Figure 3). Chalcone and 4-methoxychalcone were also essayed with methyl iminoglycinate **1a** giving excellent enantioselectivity and high yields of *endo*-**3h-j**.

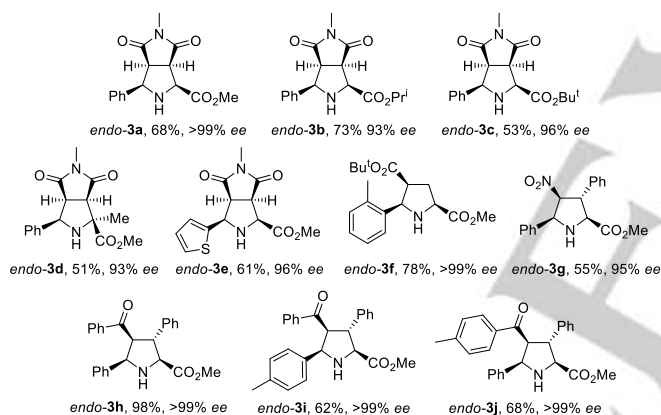


Figure 5. Scope of the cooperative non-covalent 1,3-DC catalysis in the presence of catalysts **4a** and (*R*)-**10**.

In conclusion, in this work an efficient *endo*-diastereo and enantioselective 1,3-DC of azomethine ylides based on a cooperative asymmetric Lewis acid-Brønsted base catalysis has been presented. Silver(I) salts of chiral phosphoric acids are poor asymmetric catalysts for this reaction. *Cinchona* alkaloids, in turn, are efficient in terms of chiral induction. In contrast, matched non-covalent coupling between both cooperative catalysts results in a significant improvement of the observed *ee*'s. We think that the concepts presented in this communication can be applied to other reactions involving doubly FMO-activated nucleophilic and electrophilic substrates.

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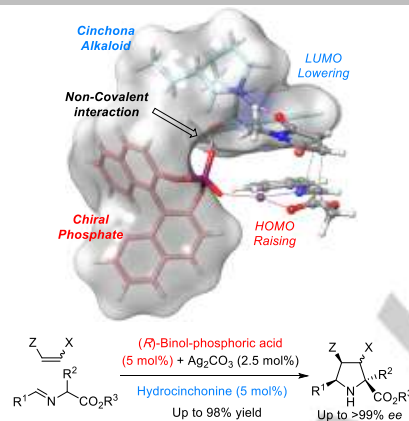
Keywords: asymmetric catalysis • cooperative catalysis • cycloadditions • DFT calculations • enantioselective synthesis

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Entry for the Table of Contents

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Better together. Enhanced non-additive enantiocontrol is observed in asymmetric 1,3-DC between imino esters and alkenes in the presence of commercially available Lewis acid-Brønsted base catalytic pairs. This cooperative catalysis is based on FMO-mediated activation of both reactants. The reinforced combined chiral induction relies on contacts between both catalysts mediated by a non-covalent interaction under mild conditions.



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Cooperative Catalysis with Coupled Chiral Induction in [3+2] Cycloadditions

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- [1] When two or more substances that produces an effect greater than the sum of their individual effects can be considered as synergism. In addition, two or more entities working or acting together willingly for a common purpose or benefit involving mutual assistance in working towards a common goal is considered cooperativity. According to these similar definitions we establish that a synergy can be produced by two catalysts in a double activation catalysis or in a single activation catalysis. It is convenient to point that a dual or bifunctional catalysis: a) S. Matsunaga, M. Shibasaki, *Chem. Commun.* **2014**, 50, 1044-1057; (or even a cascade catalysis) are not considered as cooperative or synergistic processes: b) A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, 3, 633-658.
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