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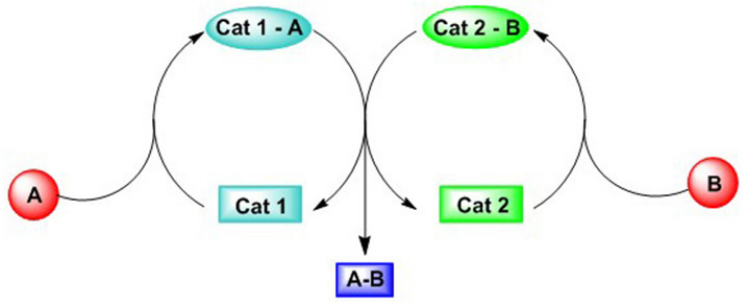
1,4-Reduction/allylation of α,β-unsaturated malonates and coumarins by copper/palladium dual catalysis

During the past decade, many catalytic strategies have been developed in organic chemistry. An important purpose of this field is the improvement of the already known methodologies. One of the ideas that have emerged consists in combining two or more catalysts in a unique sequence of reactions. The major advantage of this approach is the expansion of possible transformations, due to all the possible combinations of catalyzed reactions (For a review on cooperative multicatalyst systems for one-pot organic transformations, see [1]; for a review on current tandem catalysis, see [2]).

Within this concept of multi-catalytic reactions, several types of dual catalysis have been reported in the literature, such as organocatalysis/metallocatalysis [3, 4], biocatalysis/metallocatalysis [5, 6], or metallocatalysis/metallocatalysis systems [7]. This last category is often associated with the concept of restorative catalysis, where one metal performs one reaction whereas the other one is used to regenerate the catalytic species. However, another type of dual catalysis has been recently developed and described as cooperative dual catalysis [8-13]. In this case, both metals activate separately and selectively a substrate to generate intermediates which can then react with each other to yield the desired product (Scheme 1). This last category is now well established in the literature, and several examples have been recently reported [8-13].

Copper and palladium have already proved to be good candidates for this type of reaction. Indeed, their combination has led to two famous and highly reproducible examples: the Wacker-Tsuji process and the Sonogashira reaction.

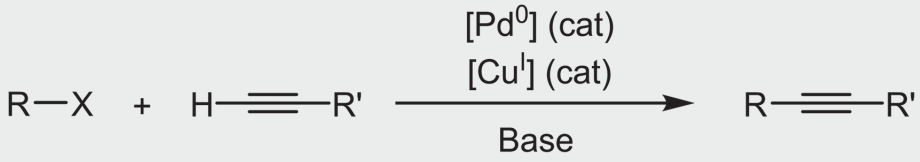


Scheme 1 : General mechanistic pathway of a cooperative catalysis system

Sonogashira reaction

The Sonogashira reaction consists in the cross-coupling between an aromatic halide and a terminal alkyne catalyzed by a palladium(0) complex and a copper(I) salt. This reaction has been published by Kenkichi Sonogashira in 1975.

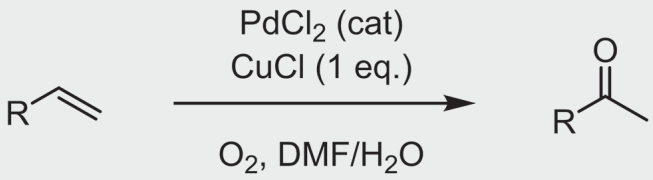
K. Sonogashira, Y. Tohda et al., « A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines », *Tetrahedron Lett.* **1975**, *16*, 4467.



Wacker process

The Wacker process or the Hoechst-Wacker process (named after the eponymous chemical companies of the same names) and the Wacker-Tsuji reaction (its laboratory transposition) consist in the oxidation of an alkene to an aldehyde or a ketone catalyzed by palladium(II) chloride and copper(I) chloride in the presence of air. It was the first reaction involving palladium-based organometallic compounds which was applied on an industrial scale. This method has been used in Germany since 1960 in the synthesis of acetaldehyde from ethylene.

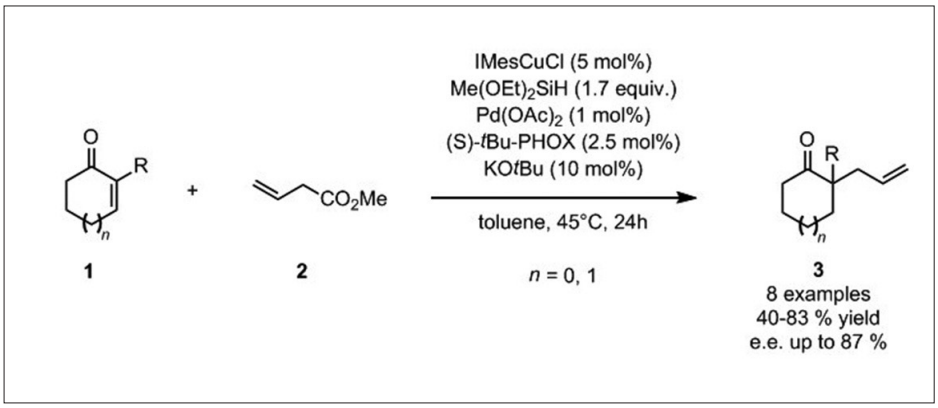
R. Jira, "Acetaldehyde from Ethylene—A Retrospective on the Discovery of the Wacker Process, *Angew. Chem. Int. Ed.* **2009**, *48*, 9034.



Furthermore, our group recently reported a Cu(I)/Pd(0) cooperative dual catalysis based on our experience in copper(I) catalysis [14-16] and on palladium(0)-catalyzed allylic alkylation [17, 18]. It allowed the asymmetric 1,4-reduction/allylation of enones in good yields and good enantioselectivities (Scheme 2) [19].

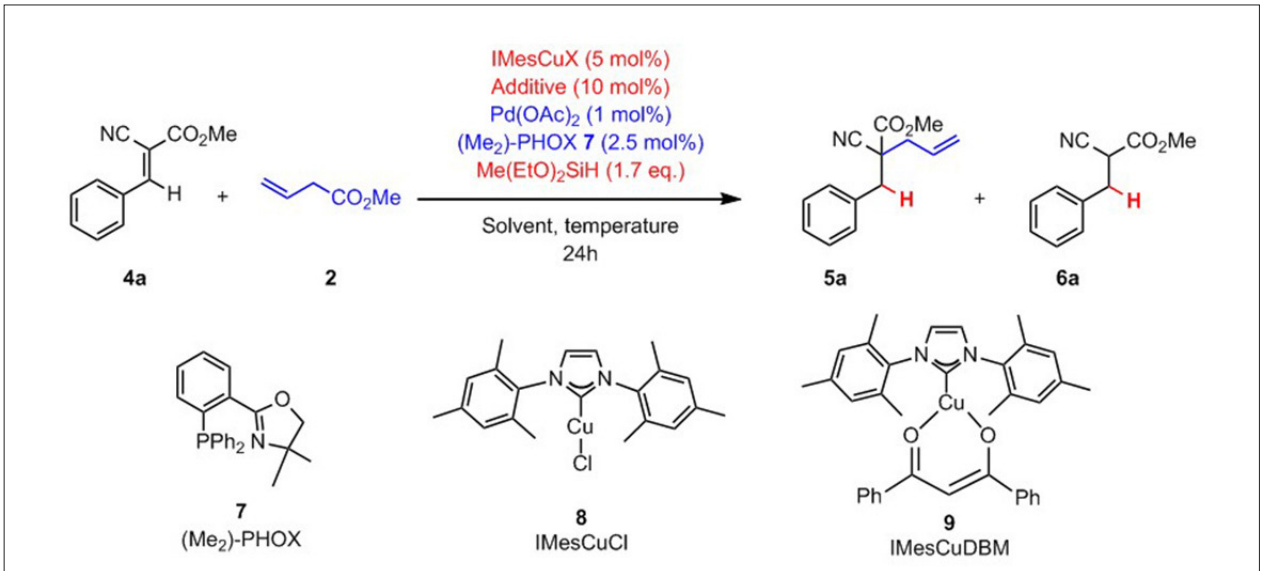
With this method, the 1,4-reduction/allylation of 5- and 6-membered rings were carried out. Our interest was to extend the scope of the reaction to other types of α,β-unsaturated carbonyls. The work described hereafter focused mainly on the use of α,β-unsaturated malonates and coumarins as substrates for this reaction.

We chose (*E*)-methyl 2-cyano-3-phenylacrylate **4a** as a model substrate to optimize the reaction on malonates (Table 1). Our interest in this moiety relies on its easy preparation and its application as a synthetic precursor of β-amino acids. As a starting point, we decided to test the best conditions obtained for the enones.



Scheme 2 : 1,4-reduction/allylation of enones catalyzed by a copper(I)/palladium(0) system

Table 1: Optimization of the dual catalysis on malonates



	IMesCuX	Additive	Solvent	Temperature	5a/6a ratio[a]
1	8	KO*t*Bu	THF	45°C	90/10
2	8	KO*t*Bu	Toluene	45°C	85/15
3	9	/	THF	r.t.	96/4

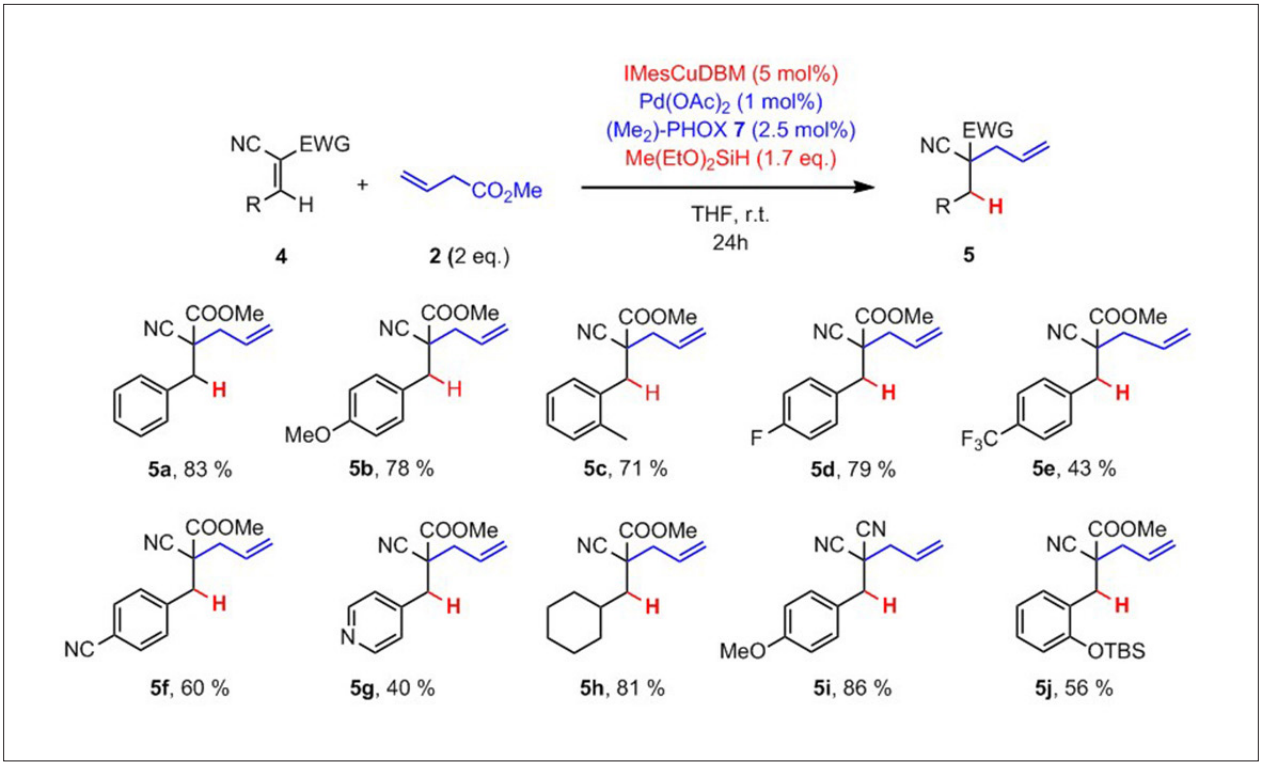
[a] Ratio determined by ^{1}H NMR spectroscopy ; complete conversion of **4a** was observed in all cases.

These tests confirmed the efficiency of the conditions previously employed. In all cases, complete conversion of the starting material **4a** was observed. The desired compound 5a was obtained as the major product, whereas the reduced product **6a** was always observed as the minor product. The conditions using IMesCuDBM (entry 3) were found to be the best without heating or using KO*t*Bu as an activating agent. Although the conditions with KO*t*Bu at 45°C (entries 1 and 2) were still efficient, their extension to other substrates revealed poor compatibility with several functional groups. The association of IMesCuDBM with THF at room temperature was found to be milder and more reproducible for the scope of the reaction.

The optimal conditions were applied to various other malonates (Scheme 3). The reaction showed a tolerance towards several functional groups, such as neutral or electron-donating substituents on the aryl moiety (**5a-5d**). Electron-withdrawing groups were also tolerated, but led to a lower yield (**5e-5g**). The activation of the electrophilic double bond by these substituents might make the reduction faster than the allylation and so explain the lower selectivity for the allylated product. Gratifyingly, aliphatic substitution at the β-position was also well tolerated (**5h**). Furthermore, replacing the ester moiety with another nitrile group easily afforded the desired product in a good yield (**5i**). Finally, a TBS-protected phenol also underwent the reaction conditions, affording the allylated product in a moderate yield (**5j**).

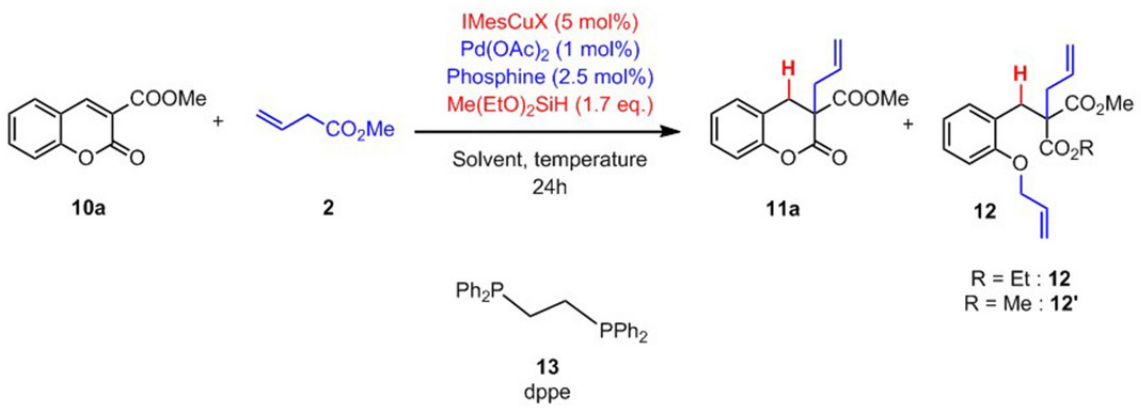
With those good results in hand, we focused on further extending this reaction to coumarins. The previously employed conditions were first applied to coumarin 10a for the optimization process (Table 2).

This optimization revealed the competition between two pathways; the first one lead to the desired product **11a**, whereas the other one gave two different diallylated products **12** and **12'**. Using IMesCuCl activated by KO*t*Bu at 45°C as copper source and the phosphine **13**, complete selectivity for the diallylated product was observed (Table 2, entry 1). We therefore decided to employ milder conditions, first switching the copper source to IMesCuDBM at room temperature (Table 2, entry 2) and then inverting the **10a/2** ratio (Table 2, entries 3-4). The dppe **13** was replaced by the phosphine **7** at this stage of the optimization. Progressively, the selectivity of the reaction was reversed to favor the desired product **11a**.



Scheme 3 : Scope of the 1,4-reduction/allylation of malonates

Table 2 : Optimization of the dual catalysis on coumarins

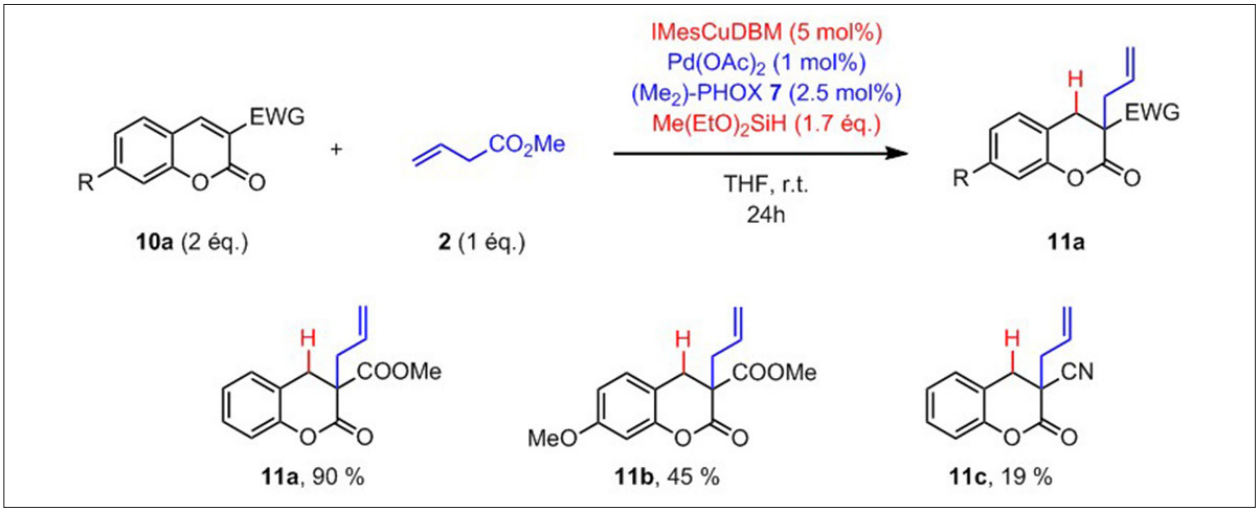


	IMesCuX	Phosphine	10a/2	Ratio 11a[f]	Ratio (12+12')[f]
1[a]	IMesCuCl[b]	13	1/2	0	100
2[d]	IMesCuDBM[c]	7	1/2	25	75
3[e]	IMesCuDBM[c]	7	1/1	40	60
4	IMesCuDBM[c]	7	2/1	90	10

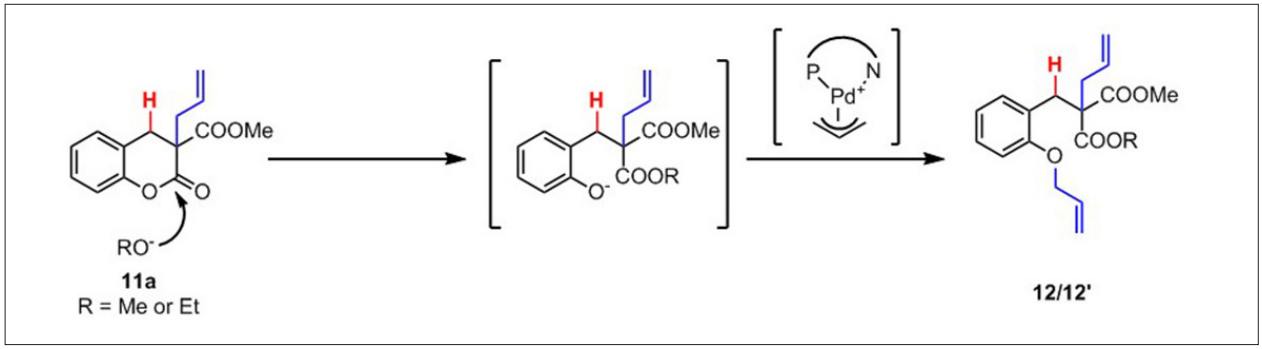
[a] Unless otherwise stated, conversion of the limitant material was complete ; [b] IMesCuCl (5 mol%), KO*t*Bu (5 mol%), toluene, 45°C ; [c] IMesCuDBM (5 mol%), THF, r.t. [d] Unidentified byproducts were observed in the crude mixture. [e] 96% conversion of the coumarin. [f] Conversion determined by ^{1}H NMR spectroscopy.

Three coumarins were tested in these optimized conditions (Scheme 4). The product **11a** was isolated in 90% yield. The 1,4-reduction/allylation was applied to two other substrates. Even though their low solubility allowed only a partial conversion, both desired products could be isolated (**11b-11c**).

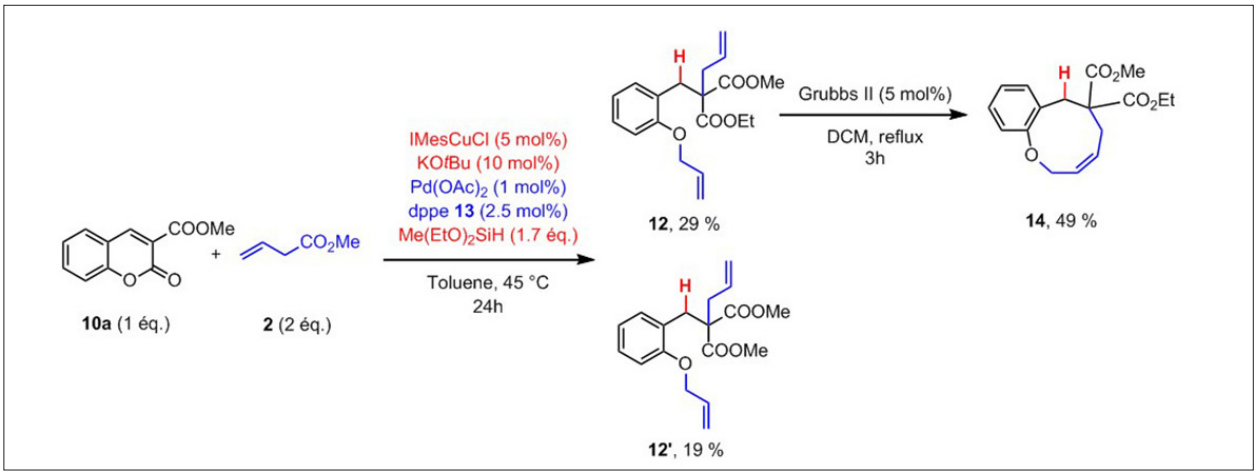
Finally, we focused on the diallylated products **12** and **12'**, which were formed through a combination of several transformations. In basic conditions, free alcoolates in the mixture can promote the ring-opening of the lactone (Scheme 5). Although they were at first observed as side products, their structure suggested that they could be interesting as precursor of valuable heterocycles.



Scheme 4 : Scope of the 1,4-reduction/allylation of coumarins



Scheme 5 : Proposed mechanism to the diallylated product



Scheme 6: Diallylation and ring-closing metathesis of the coumarin 10a

Products **12** and **12'** could be selectively formed using the first conditions tested (Table 2, entry 1). Afterwards, a ring-closing-metathesis reaction led to the formation of the oxonane 14 (Scheme 6). This heterocycle can be found in the structure of various natural products, such as marine toxins [20-23]. If extended to other lactones, this new methodology could allow the formation of this tedious moiety in only three steps starting from commercially available substrates.

In conclusion, we have successfully extended the copper(I)/palladium(0) cooperative dual catalysis system to α,β-unsaturated malonates and coumarins. Various substrates bearing different functional groups underwent our reaction conditions affording good yields and good selectivities. Furthermore, when applied to the coumarin substrates, this system allowed the isolation of a secondary product derived from five transformations which was further used to form an oxonene moiety.

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