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# Catalytic C-C, C-N, and C-O Ullmann-Type Coupling Reactions: Copper Makes a Difference

Florian Monnier\*, and Marc Taillefer\*

## Keywords:

Ullmann - Copper – Ligand Effect – Arylation – Catalysis – Enantioselectivity - Chemoselectivity

## Introduction

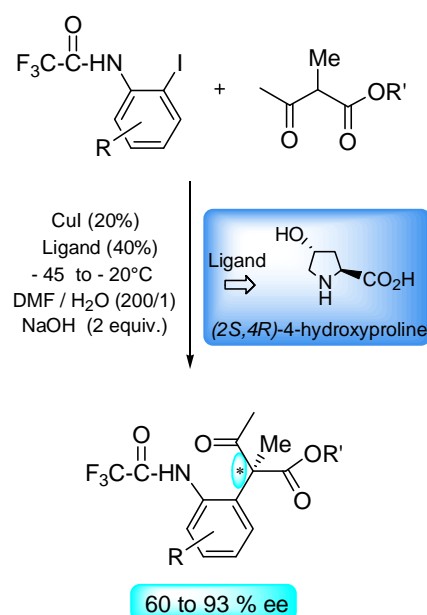
Copper-catalyzed arylations of nucleophiles (Ullmann, Ullmann-Goldberg and Ullmann-Hurtley condensations) have been well known for more than a century for being one of the most useful and practical methods in the formation of C(aryl)-N, C(aryl)-C and C(aryl)-O bonds.[1] These reactions are thus involved in numerous industrial applications such as the synthesis of intermediates as well as synthetic targets throughout the life science and polymer industries. However until 2000, Ullmann condensations have not been employed to their full potential. They indeed suffered from reduced synthetic scope as a result of the harsh reaction conditions often required, a limited substrate scope and the moderate yields obtained. Condensations were traditionally conducted at temperatures as high as 210 °C, often in the presence of stoichiometric amounts of copper reagents and preferentially with activated aryl halides.[1]. Early studies revealed rate enhancement when arylation were conducted in the presence of copper additive.[2] The additive compounds were thought to increase catalyst solubility and stability, but their exact role was not well

established. Finally in 2001, important breakthroughs [3] were achieved by two groups with the discoveries of versatile and very efficiency new copper/ligand systems (C-C, C-N or C-O coupling) allowing the use of catalytic amount of metal under very mild conditions (90-110°C). Since 2001, these works and the potentially attractiveness of copper has led to a spectacular resurgence of interest in catalyzed Ullmann-type reactions. Many groups have thus been developing so far new Cu/Ligand systems to improve the variety and efficiency of the coupling reactions. We present here recent major developments in Cu-catalyzed C-C, C-O and C-N bond formation. The two selected contributions are of highly impact for cross coupling reaction, and deal with enantioselective and chemoselective copper catalytic systems.

## Enantioselective copper catalytic systems

It is well established that nowadays enantiomerically pure compounds are more and more attractive for pharmaceutical and agrochemical chemistry in terms of activities and selectivities. Novel syntheses are thus a major challenge, which was recently achieved by Ma et al. [4a] The authors indeed reported an original Cu-catalyzed asymmetric coupling of various 2-iodotrifluoroacetanilides with 2-methyl acetoacetates assisted by (2*S*,4*R*)-4-hydroxy-proline as ligand and chiral source (scheme 1). Their methodology affords the corresponding coupling products, the 2,2-arylmethylacetoacetates, with the generation of  $\alpha$ -aryl enantiomerically pure carbon quaternary centers. These asymmetric

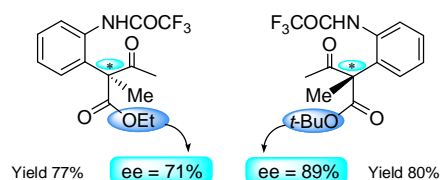
products were obtained in good yields (after 3 to 36 h in DMF with traces of water) in the presence of NaOH acting as a base at very low temperature (-45 to -20 °C) (Scheme 1). This innovative contribution is related by two important insights: The effective temperature reaction is the lowest ever reached for an Ullmann-type coupling. The last former records which concern C-O [4b] from aryl bromides, C-N [4c] and C-C (both from aryl iodides) [4e] couplings, were performed at room temperature. These exceptional smooth conditions are probably one of the key success for the second breakthrough presented in this article: the first example of a catalytic asymmetric Ullmann-type C-C coupling reaction.



**Scheme 1.** CuI-Catalyzed enantioselective coupling of 2-iodotrifluoroacetanilides with 2-alkyl acetoacetates

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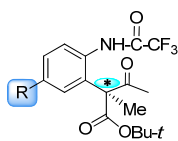
In a parametric study, authors showed that product ee's resulting from this novel chiral version of Ullmann coupling were depending on the nature of the ester of the 2-alkylacetoacetate (Scheme 2). Increasing size of ester moiety on the  $\beta$ -keto ester such with a  $\text{CO}_2t\text{-Bu}$  group indeed affords high ee's until 89 %, whereas the less hindered  $\text{CO}_2\text{Et}$  group gave lower ee's (until 71 %).



**Scheme 2.** Influence of the ester size moiety on ee

A second important parameter for the overall system efficiency is the electronic nature on the aromatic iodides (Scheme 3). Thus they tested different substituents on the aryl iodides, and they observed that electron donating groups on the aryl all lead to high conversion and ee's. On the other hand substrates bearing electron withdrawing groups either gave poor yields in the standard temperature conditions  $-45^\circ\text{C}$  (because of the formation of homocoupling byproducts) or require higher reaction temperature ( $-20$  to  $-30^\circ\text{C}$ ) to obtain satisfactory yield. By the way, this increasing of temperature affords an expected decrease of optical purity. Finally the authors also demonstrated the importance of the ligand, and the presence of the OH substituant on the proline appears to be a crucial parameter for the success of the reaction in terms of enantioselectivities and yields. However, ligand influence is not well understood.

R	yield	ee	T
Me	79	93	$-45^\circ\text{C}$
$\text{CH}_2\text{OH}$	77	91	$-45^\circ\text{C}$
OMe	78	87	$-45^\circ\text{C}$
F	81	83	$-30^\circ\text{C}$
I	79	81	$-20^\circ\text{C}$
$\text{CO}_2\text{Me}$	29	60	$-45^\circ\text{C}$



**Scheme 3.** Influence of substituent R on catalytic activity and ee

Work is now in progress to explore potential of this system, although authors already found a first interesting application example for the synthesis of an asymmetric intermediate of physostigmine which is a potential reversible inhibitor of acetyl- and butyrylcholinesterase and is employed clinically to treat glaucoma.

The efficiency of this novel catalytic system is presented as the result of a fine

tuning of different parameter discussed above. One of the key parameter proposed by the authors is the presence of ortho substituent that could participate via the chelation of the oxygen ( $\text{NH-C=O}$ ) with the copper centre to the stabilization of intermediates of the catalytic cycle. [4b,4d]

Worth noting that Ma's system is one of the first that described a metal-catalyzed asymmetric  $\alpha$ -arylation of  $\beta$ -keto ester. Few examples of asymmetric  $\alpha$ -arylation of enolates were already described, nevertheless they were catalyzed by system involving Pd [5a] or Ni [5b,c] precursors.

Although these results are of high impact in asymmetric catalysis, Ma's system presents however some limitations. First, their system is so far efficient only on aryl iodides whereas cheaper aryl bromides afford to the corresponding coupling product in poor yield and ee (43%, 37 % respectively). Secondly, as the authors reported in a previous publication concerning C-O bond formation with a related system [4b], the application field of the method is limited by the necessary presence of chelating substituent in ortho position. Despite those restrictions, Ma's results should potentially represent a benchmark in the field of catalyzed asymmetric Ullmann coupling.

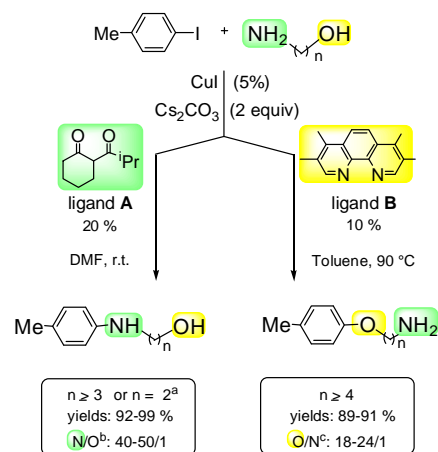
### Orthogonal Selectivity : N- vs O-Arylation

In the meantime, [6] Buchwald et al. reported important research results that deal with chemoselectivities in Ullmann-type coupling (scheme 4). In a first previous report in 2002 [7], authors presented several interesting pathways allowing the selective copper-catalyzed N- or O- arylation of  $\beta$ -aminoalcohols with aryl iodides in absence of any additional ligands. However this reaction failed to couple longer aminoalcohols, which seriously limited its applications field. Buchwald et al. have then proposed that this issue could be explained by the inability of the latter to play the role of ligand on copper salts though it was the case with  $\beta$ -aminoalcohols. The authors postulated that adding ligands could undergo this limitation and in 2007, they validate this hypothesis disclosing efficient Cu/Ligand systems chemoselective for the N- or O arylation from aryl iodides of longer aminoalcohols (scheme 4: study carried out with iodotoluene).

Thus the use of  $\beta$ -diketone **A** as ligand, could favour the N-arylation of aminoalcohols of various size ( $\beta$ -diketones

are efficient ligands [4c,8] for N-arylation of aliphatic amines).

On the other hand using a phenanthroline type ligand **B** afforded the corresponding O-arylation products (ligands **B** are effective for the O-arylation and O-vinylation of phenols or aliphatic alcohols [9]).



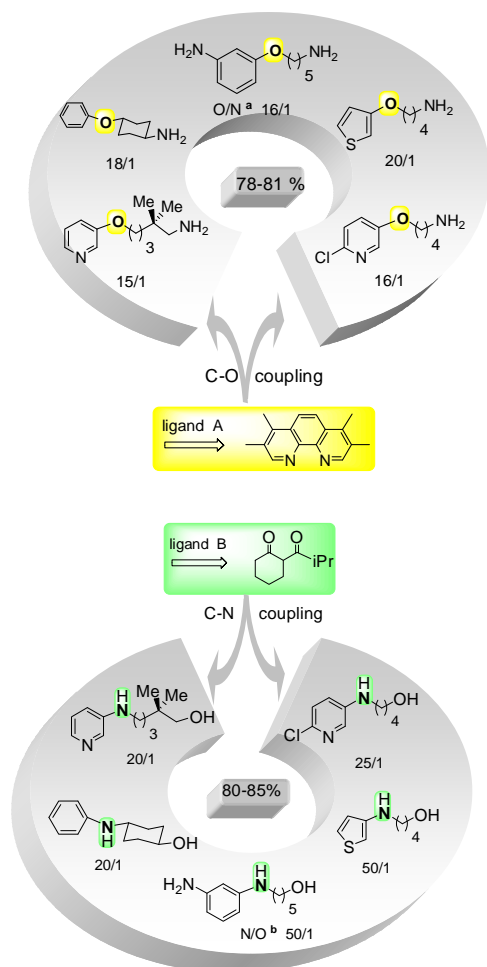
**Scheme 4.** N- vs O-Arylation of aminoalcohols. a) Without ligand. b) N/O selectivity. c) O/N selectivity.

Noteworthy that the selective N-arylation of amino alcohols was performed as expected [4c] at very low temperature ( $25^\circ\text{C}$ ). Starting from  $\text{C}_3$  to  $\text{C}_6$  spacer (Scheme 4,  $n \geq 3$ ), the corresponding N-C products were obtained in excellent 96-99% yield with chemoselectivities up to 45:1 (N/O coupling ratio). On the other hand weak performances were achieved for ethanolamine ( $\text{C}_2$  spacer) but as previously reported the efficient and selective N-arylation of the latter was obtained in ligand free conditions (92%; 40/1).[7]

For the corresponding O-arylation of amino alcohols good yields were obtained with a spacer of at least four methylene units (Scheme 4,  $n \geq 4$ ). However harder temperature conditions are needed ( $90^\circ\text{C}$  in toluene), and selectivities although good are low compares to the N-arylation process (18-24/1: O/N coupling ratio). With shorter amino alcohols ( $n \leq 3$ ), acceptable results were achieved for the 3-amino-1-propanol but only in absence of additional ligand.

An elegant illustration of this methodology was extended to various aryl or heteroaryl iodides and amino alcohols. (scheme 5). As in the model reaction obtained yields are very good and N-selectivities are higher than O-selectivities for a same substrate. With this set of orthogonal and complementary catalytic systems, a broad family of arylated amino

alcohols of various sizes is thus easily available.



**Scheme 5.** Chemoselective *N*- and *O*-arylation of various amino alcohols from aryl and heteroaryl iodides: orthogonal catalytic systems. <sup>a</sup>) O/N selectivity. <sup>b</sup>) N/O selectivity.

Concerning the mechanism, Buchwald et al. suggested that observed selectivities were closely based on the relative abilities of ligands to enrich Cu(I) electronically. *N*-arylation process would be favoured by the couple (A)Cu(I), whose lowered electrophilicity could disfavour the alcohol complexation. This proposition was supported by DFT calculations. The more acidic (B)Cu(I) would lead to the formation of a significant amount of copper-alcohol bound whose easy deprotonation could favour the *O*-arylation.

This very elegant system presents however the same limitation than those of Ma because it seems restricted to the use of aryl iodides. By the way, as mentioned by the authors in their conclusion, mechanism studies have to be deeply engaged to ensure

the key role of each ligand for this orthogonal selectivity.

## Outlook and Perspectives

The works described so far undoubtedly represent interesting major advances in terms of enantioselectivity [4a] and chemoselectivity.[6]

Other major achievements have been already reached for Cu-catalyzed Ullmann reactions since its renaissance in the early 2000's. Despite these significant advances, stimulating challenges which mainly belong to the field of sustainable development, have still to be performed (Scheme 6) : [1e]

- Find new ligands or catalytic systems to work at lower catalyst loading ( $\leq 1\%$  [Cu] mol.) to increase the turnovers and turnover frequencies (shorter reaction times). The goal is to reduce the amount of copper waste and to obtain more economically competitive systems.[10]

- The same goal could be also reached by the development of novel and efficient supported-copper/ligand systems that would permit regeneration and reuse of well-defined catalysts.[11] An other advantage of this concept is that it allows, by trapping the metal, to reach more easily low residual toxicity levels after work-up of reaction mixtures. This last point is an important parameter for drug synthesis.

- Find original and simple systems using environmentally friendly conditions. For instance green solvent, solvent-free reactions and/or catalytic system with non toxic metal for novel Ullmann-type reactions.[12]

- Discover efficient systems allowing the replacement of aryl iodides and bromides by less reactive aryl chlorides or sulfonates. The chlorides are indeed cheaper and the sulfonates could allow the introduction of chemistry of phenols in this Ullmann-type coupling.



**Scheme 6.** Stimulating challenges for Ullmann-type reactions.

From a general point of view, the low cost of copper and the use of readily accessible ligands provide indisputable advantage over the expensive Pd/ligand systems (often costly, unstable and complex ligands are used). However, the two types of catalysis are complementary. Indeed concerning the challenges indicated above, it is noteworthy that Pd-catalyzed chemistry has already successfully given highly efficient systems. Moreover mechanism involving Pd catalysis is better understood than those concerning the copper catalysis, for which comparatively few studies have been undertaken.[13]

Elucidating this mechanism could enable at least to partially reach the objectives indicated above. This point will probably constitute in the future the most exciting challenge to take up for the catalytic Ullmann reactions.

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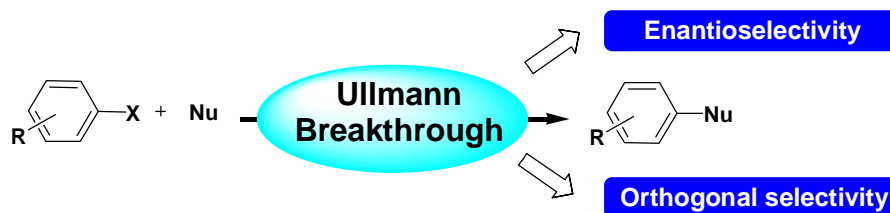
Layout 2:

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Florian Monnier\*, and Marc Taillefer\*  
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**Catalytic C-C, C-N, and C-O Ullmann-Type Coupling Reactions: Copper Makes a Difference**

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