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

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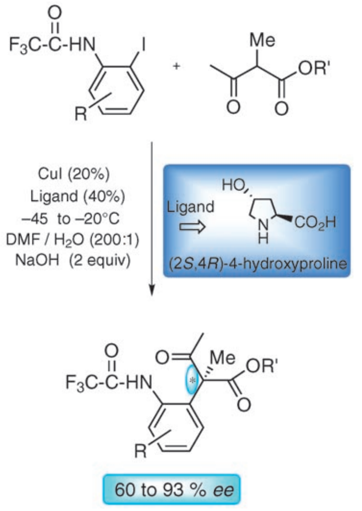
arylation · copper · cross-coupling · enantioselectivity · homogeneous catalysis

The copper-catalyzed arylation of nucleophiles (Ullmann, Ullmann–Goldberg, and Ullmann–Hurtley condensations) has been known for more than a century as one the most useful and practical methods for the formation of C(aryl)–N, C(aryl)–C, and C(aryl)–O bonds.[1] These reactions are involved in numerous industrial applications, such as the synthesis of intermediates and synthetic targets in the life science and polymer industries. However, up until 2000, Ullmann condensations had not been used to their full potential: They 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 usually with activated aryl halides.[1] However, some studies revealed an enhancement of the reaction rate when the arylations were conducted in the presence of an organic additive.[2] The additives were thought to increase the solubility and stability of the copper catalyst, but their exact role was not well established. Finally in 2001, important breakthroughs[3] were achieved by two research groups with the discoveries of versatile and very efficient new copper/ligand systems (for C–C, C–N, or C–O coupling) which allowed the use of a catalytic amount of metal under mild conditions (90–110 °C). Since 2001, these studies and the potential attractiveness of copper has led to a spectacular resurgence of interest in catalyzed Ullmann-type reactions. Many research groups have thus developed new copper/ligand systems to improve the variety and efficiency of the coupling reactions. We present here recent major developments in this field—published in the last few months—concerning enantioselective and chemoselective reactions that use copper catalysts.

It is well established that enantiomerically pure compounds are becoming more and more attractive for the pharmaceutical and agrochemical industries in regard to their activities and selectivities. Novel syntheses are thus a major challenge, and one such example was recently reported by Ma and co-workers.[4a] The authors described a Cu^{I}-catalyzed asymmetric coupling reaction of various 2-iodotrifluoroacetanilides with 2-methyl acetoacetates in the presence of (2*S*,4*R*)-4-hydroxyproline, which acts as both a ligand and a chiral source (Scheme 1). Their methodology affords the corresponding coupling products, the 2,2-arylmethyl acetoacetates, with the generation of enantiomerically pure α-aryl 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 as a base at very low temperature (−45 to −20 °C; Scheme 1). This innovative contribution is noteworthy for two important reasons: The effective temperature reaction is the lowest used for a successful Ullmann-type coupling reaction. The lowest temperature reported for previous C–O,[4b,g] C–N,[4c,f,g] and C–C[4e] coupling reactions was room temperature. The smooth conditions employed probably contribute to the second significant feature of this study: it is the first example of a catalytic asymmetric Ullmann-type C–C coupling reaction. The authors showed that the *ee* values of the products were



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

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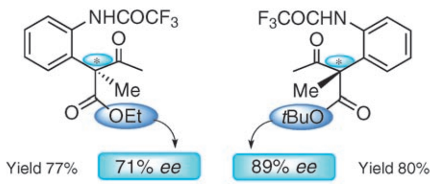
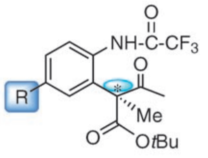
dependent on the nature of the ester group in the 2-alkyl acetoacetate (Scheme 2). Increasing the size of the β-keto ester, such as through the use of a CO_2tBu group, affords high *ee* values (up to 89 %), whereas the less hindered CO_2Et group gave lower *ee* values (up to 71 %).



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

A second important parameter for the overall efficiency of the system is the electronic nature of the aromatic iodides. The authors tested different substituents on the aryl iodides, and they observed that electron-donating groups on the aryl group lead to high conversion and *ee* values (Scheme 3). However, susbstrates bearing electron-withdrawing groups either gave poor yields at the standard temperature (−45 °C, formation of homocoupling by-products) or required higher temperatures (−20 to −30 °C) to obtain satisfactory yields. This increase in temperature apparently results in a decrease in the optical purity, as expected. Finally the authors also demonstrated the importance of the ligand in the reaction, with the OH substituent on the proline ring appearing to be crucial for the success of the reaction in terms of enantioselectivity and yield. However, the influence of the ligand is not well understood.

R	Yield/%	*ee*/%	*T*/°C
Me	79	93	−45
CH_2OH	77	91	−45
OMe	78	87	−45
F	81	83	−30
I	79	81	−20
CO_2Me	29	60	−45



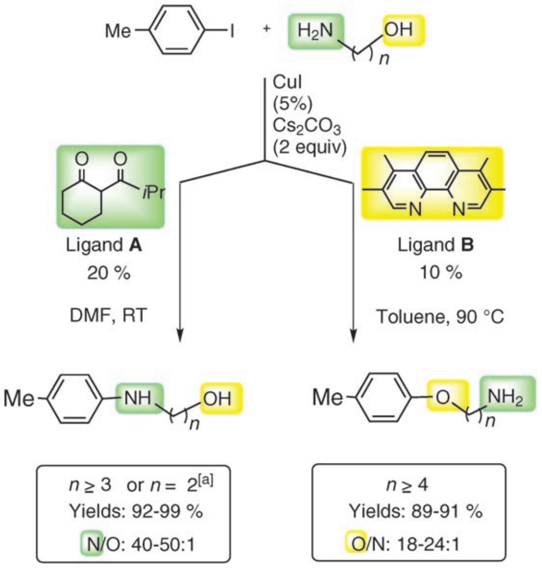
Scheme 3. Influence of substituent R on the catalytic activity and *ee* value.

The efficiency of this novel catalytic system was attributed to a fine tuning of the different parameters discussed above. One of the key parameters proposed by the authors is the presence of an *ortho* substituent that could participate, through chelation of the oxygen atom (NH−C=O) with the copper center, in the stabilization of intermediates in the catalytic cycle.[4b,d]

It is worth noting that the reaction developed by Ma and co-workers is one of the first metal-catalyzed asymmetric α arylations of a β-keto ester. A few examples of the asymmetric α arylation of enolates have already been described, but they were catalyzed by a system involving Pd[5a] or Ni[5b,c] precursors.

Although these results are of high importance in asymmetric catalysis, the system developed by Ma and co-workers has some limitations. First, their system is so far only efficient with aryl iodides; cheaper aryl bromides afford the corresponding coupling products in poor yield (43 %) and *ee* values (37 % *ee*). Secondly, as the authors reported in a previous publication concerning the formation of a C−O bond by using a related system,[4b] the scope of the method is limited by the necessary presence of a chelating substituent at the *ortho* position. Despite those limitions, the study should represent a potential benchmark in the field of catalyzed asymmetric Ullmann coupling.

Buchwald and co-workers[6] reported important results in regard to the chemoselectivity of Ullmann-type coupling reactions (Scheme 4). In a previous report in 2002,[7] Job and Buchwald presented several interesting pathways that allow the selective copper-catalyzed N or O arylation of β-amino alcohols with aryl iodides in the absence of any additional ligands. However, this reaction failed to couple longer amino alcohols, which seriously limited its field of application. Buchwald and co-workers then proposed that this issue could be explained by the inability of the latter to play the role of the ligand for the copper salts, whereas the β-amino alcohols could. The authors postulated that adding ligands could solve this limitation, and in 2007 they validated this hypothesis by disclosing efficient copper/ligand systems that were chemoselective for the N or O arylation of longer amino alcohols by aryl iodides (Scheme 4: study carried out with iodotoluene).



Scheme 4. N versus O arylation of amino alcohols. [a] Without ligand.

Thus, the use of β-diketone **A** as a ligand favored the N arylation of amino alcohols of various size (β-diketones are efficient ligands[4c,8] for the N arylation of aliphatic amines). On the other hand, using the phenanthroline-type ligand **B** afforded the corresponding O-arylation products (ligands of type **B** are effective for the O arylation and O vinylation of phenols or aliphatic alcohols[9]).

It is noteworthy that the selective N arylation of amino alcohols could be performed, as expected,[4c] at room temperature (25 °C). When amino alcohols containing C_3–C_6 spacers

(Scheme 4, $n = 3$–6) were used, the corresponding products were obtained in excellent yield (96–99%) with chemoselectivities of up to 45:1 (N/O coupling ratio). On the other hand, poor chemoselectivity was achieved with ethanolamine (C_2 spacer), but as previously reported, ethanolamine can be efficiently and selectively N arylated under ligand-free conditions (92%; 40:1).[7]

Good yields in the corresponding O arylation of amino alcohols were obtained with a spacer of at least four methylene units (Scheme 4, $n \geq 4$). However, higher temperatures are needed (90 °C in toluene), and selectivities, although good, are low compared to the N-arylation process (18:1–24:1 O/N coupling ratio). Acceptable results were achieved for the shorter 3-amino-1-propanol, but only in the absence of an additional ligand.

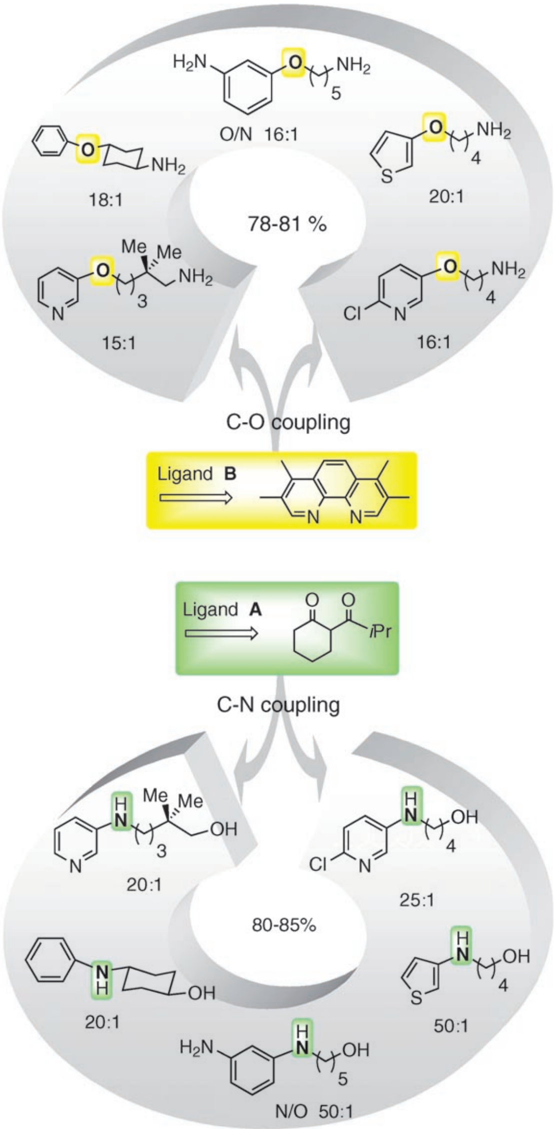
This methodology was applied to various aryl or heteroaryl iodides and amino alcohols (Scheme 5). As in the model reaction, the obtained yields are very good and the N selectivity is higher than the O selectivity for any one substrate. This set of orthogonal and complementary catalytic systems thus provides easy access to a broad family of arylated amino alcohols of various sizes.

Concerning the mechanism, Buchwald and co-workers suggested that the observed selectivities were closely based on the relative abilities of ligands to donate electrons to the Cu^I center. An N-arylation process would be favored by the couple $\{(\mathbf{A}^-)Cu^I\}$, whose lowered electrophilicity could disfavor complexation of the alcohol. This proposition was supported by DFT calculations. The more acidic $\{(\mathbf{B})Cu^I\}$ species would lead to the formation of a significant amount of the copper-bound alcohol, whose easy deprotonation could favor the O arylation.

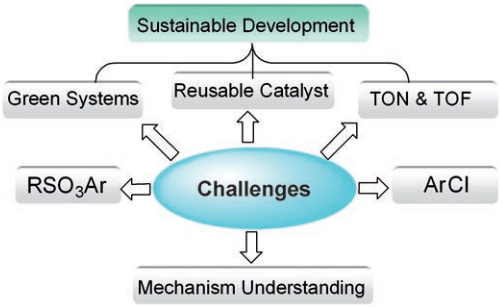
This very elegant system, however, seems restricted to the use of aryl iodides, and thus possesses the same limitations as the system developed by Ma and co-workers. As mentioned by the authors in their conclusion, extensive mechanistic studies have to be involved to ensure the key role of each ligand for this orthogonal selectivity.

The studies described so far undoubtedly represent interesting advances in terms of enantioselectivty[4a] and chemoselectivity.[6] Other major achievements have already been obtained for copper-catalyzed Ullmann reactions since its renaissance in the early 2000s. Despite these significant advances, stimulating challenges which often belong to the field of sustainable development, have still to be met (Scheme 6), such as:[1e]

- Find new ligands or systems that work at lower catalyst loading (≤1 mol% [Cu]) 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 development of novel and efficient supported copper/ligand systems that would permit regeneration and reuse of well-defined catalysts.[11] Another advantage of this concept is that it allows, by trapping the metal, to more easily reach low residual toxicity levels after work-up of reaction mixtures. This last point is an important parameter for drug synthesis.



Scheme 5. Chemoselective N and O arylation of various amino alcohols with aryl and heteroaryl iodides: orthogonal catalysts.



Scheme 6. Stimulating challenges for Ullmann-type reactions.

- Find original and simple systems that operate if possible under environmentally friendly conditions: for example, use a green solvent[12a] or use ligand-free[12b,c,d] or solvent-free reactions.

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

From a general viewpoint, the low cost of copper and the use of readily accessible ligands provide an indisputable advantage over the expensive palladium/ligand systems (often costly ligands are used).[1e] However, the two types of catalysis are complementary. Indeed, concerning the challenges indicated above, it is noteworthy that Pd catalysts have already led to highly efficient systems. Moreover, the mechanism of palladium catalysis is better understood than that of copper catalysis, for which comparatively few studies have been undertaken.[13]

Elucidating this mechanism could enable the objectives indicated above to be at least partially met. This point will probably constitute one of the most exciting challenges in the future for the development of catalytic Ullmann reactions.

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