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Selective Double C–H Functionalization: A 4-Component Catellani Reaction.

Thomas Varlet, Luc Neuville, Géraldine Masson*

Institut de Chimie des Substances Naturelles, Université Paris Saclay, CNRS, UPR2301, 1 Avenue de la Terrasse, 91198 Gif-sur-Yvette cedex, France

*Correspondence : geraldine.masson@cnr.fr

Abstract: Achieving high selectivity through multiple C-H functionalization is a challenging topic. In this issue of *Chem*, Lumb, Luan and co-workers disclose a clever strategy taking advantage of steric remote effects for the synthesis of poly-substituted arenes through a 4-component Catellani reaction with remarkable regio- and chemoselectivity using readily available reagents.

Highly and contiguously substituted arenes are useful building blocks for numerous applications in the preparation of pharmaceuticals and in materials.¹ Hence, much attention has been focused toward their synthesis. Transition-metal-catalyzed direct C-H functionalization has become an extremely powerful tool for rapid construction of molecular complexity from simple precursors. Regioselectivity, is however an important issue in C–H activation approach, that has often been solved by using a directing group or a functional entry point into the arene.² In this context, the Catellani reaction, named after leader's group initial discover in 1997,^{3,4,5} allowed to perform a double 1,2-heterofunctionalization of aryl halides (Figure 1A). The 3-component cascade is catalyzed by palladium and mediated by norbornene (NBE), allowing assembling of aryl halide, alkyl halide and a third component (mostly alkene or alkyne). Mechanistically, the reaction proceeds through oxidative insertion of palladium into the aryl halide followed by insertion of NBE into this Pd(II) complex. Suitably positioned norbornane-Pd(II) subsequently undergoes a C-H palladation (*ortho* to the initial position of the halide), and the newly palladacycle can oxidatively add to the alkyl halide. Reductive elimination builds a first aryl-alkyl bond and simultaneously reforms the norbornane-Pd(II) unit. At this stage, a second *ortho'* C-H alkylation can proceed with the same alkyl halide followed by extrusion of NBE, and final arylpalladium species can react with the last component providing 1,2,3 substituted benzenoid rings. However, while highly valuable, such approach was limited to the synthesis of symmetric units. Indeed, the preparation of unsymmetrical trisubstituted arenes directly from simple aryl halides was unsuccessful due to a competitive C-H functionalization at two different *ortho*-sites with two different electrophilic reagents (alkyl halides) (Figure 1.B). In order to access non-symmetrical ones, transformations require to work from aryl halide already bearing the substituent on position 1 following a simple *ortho* C-H functionalization. To avoid the necessary blocking through *ortho*-substituents, Dong and co-workers designed bridgehead-substituted NBE (Figure 1.C).⁶ Introduction of this substituent blocks the second C–H functionalization furnishing an access to 1,2 substituted arenes. The synthesis of unsymmetrical 1,2,3-trisubstituted benzenoid cores was only recently achieved by Lautens and co-workers who developed elegant approaches that used a combination of intra and intermolecular event to distinguish between *ortho* and *ortho'* functionalities (Figure 1.D).^{7,8} Unbiased 1,2,3-trisubstituted arenes with two different electrophilic reagents remained to be solved. Indeed, such double C-H functionalization would generate structural complexity in a single step.

To address the aforementioned limitation, Lumb, Luan and co-workers describe in this issue of *Chem*, a novel strategy to expand the Catellani reaction to a 4-component synthesis of non-symmetrical trisubstituted arenes by carefully selecting electrophiles based on fine understanding of the mechanism.⁹ They hypothesized that individual *ortho* and *ortho'* C-H functionalization steps present useable differences in particular during the oxidation step of palladacycle to distinguish electrophiles. The authors reasoned that the first *ortho*-position is not sterically constrained and could react with a sterically demanding partner that would have high affinity for Lewis acid Pd(II) center. On the other side, second C-H functionalization, because of first step, is by far more constraint and could only react with small electrophiles with eventually lower affinity to Pd(II) complex. On the basis of this hypothesis, they selected anhydrides¹⁰ and benzyl bromides as two competing electrophilic reagents and acrylate for the catalytic cycle termination *ipso*-substitution (Figure 1.E). The authors expected to first perform the acylation and then the remaining *ortho'*-position would be functionalized by alkylation, assuring a high control of the regioselectivity (Figure 1.F). However, a number of competitive pathways which could erode the selectivity by leading to a mixture of di-alkylation and di-acylation resulting by-products could still occur (Figure 1.B). The authors managed to strongly prevent these side-reactions by selecting PdCl₂ as their source of Palladium and tris-2-furyl-phosphine ligand, with NBE and a carbonated base in THF or 1,4-dioxane, ensuring that this catalytic system only requires commercially available and easy to procure reactants.

Choice of solvents was dictated by the observation that *para*-substitution on aryl halides have a strong influence on reactivity on individual electrophiles leading in some case to bis-benylation or bis-acylation. In THF solvent, the highest selectivity for 4-component unsymmetrical coupling was achieved with moderately electron releasing and not inductively withdrawing substituents like alkyls, ethers or thioethers and amines functionalities. For more strongly withdrawing substituents, the selectivity favors di-benylation in THF. By changing to the less polar but more chelating 1,4-dioxane solvent, the authors managed to restore a high selectivity for 4-component coupling with aryl iodides bearing, among other groups, halogen substituents, trifluoromethyl, cyano and carbonyl functionalities in *para*-position. This observation is a reminder that remote substituent effects can have a strong influence over intermediate Pd-(II) complexes, though this influence is still difficult to rationalize.

With these two conditions (THF or dioxane), the authors achieved a broad scope with good to high regioselectivity and an impressive functionality tolerance (Figure 1.G). Various anhydrides containing aryloxy groups were investigated and successfully expanded to heteroaryl anhydrides and even to dicarbonates. The reaction tolerates a broad range of diversely substituted benzyl bromide. Methyl iodide was also successfully used for the selective introduction of methyl substituent. Terminal coupling event is not limited to acrylate moieties since a range of electron deficient olefins could be employed including ketone, ester, amide and even electron-deficient styrene. Interestingly, cyano group could be incorporated on the *ipso*-position using Cu-CN, giving access to highly functionalized aromatic nitriles with good selectivity. Substitution of aryl halide moiety has been fully investigated. Acylation occurs on the less hindered position allowing to access from 4,5-disubstituted and 3,4,5-trisubstituted iodides, highly congested tetra- and penta-substituted arenes. Impressively, hexa-substituted regio-defined diversified benzene nucleus was prepared in single step. Finally, a number of post-transformations were performed taking advantage of introduced side-chains to demonstrate the value of newly decorated arenes.

In summary, the methodology presented by Lumb, Luan and co-workers, is an excellent example of the importance of understanding a reaction mechanism. Thanks to their insights in the remote-steric interactions and subtle Lewis acid variation, the authors successfully exploited these properties to their advantages to develop a 4-component giving access to a broad range of unsymmetrical and highly substituted aromatic rings. This understanding has led to greatly expand the scope of the Catellani reaction, previously non-available in the 4-component approach. They also shed lights to subtle unsuspected remote-effects from the *meta* and *para* positions on the ring. Without any doubt, this work will help chemists to design new strategies in order to improve control in the aromatic C-H functionalization.

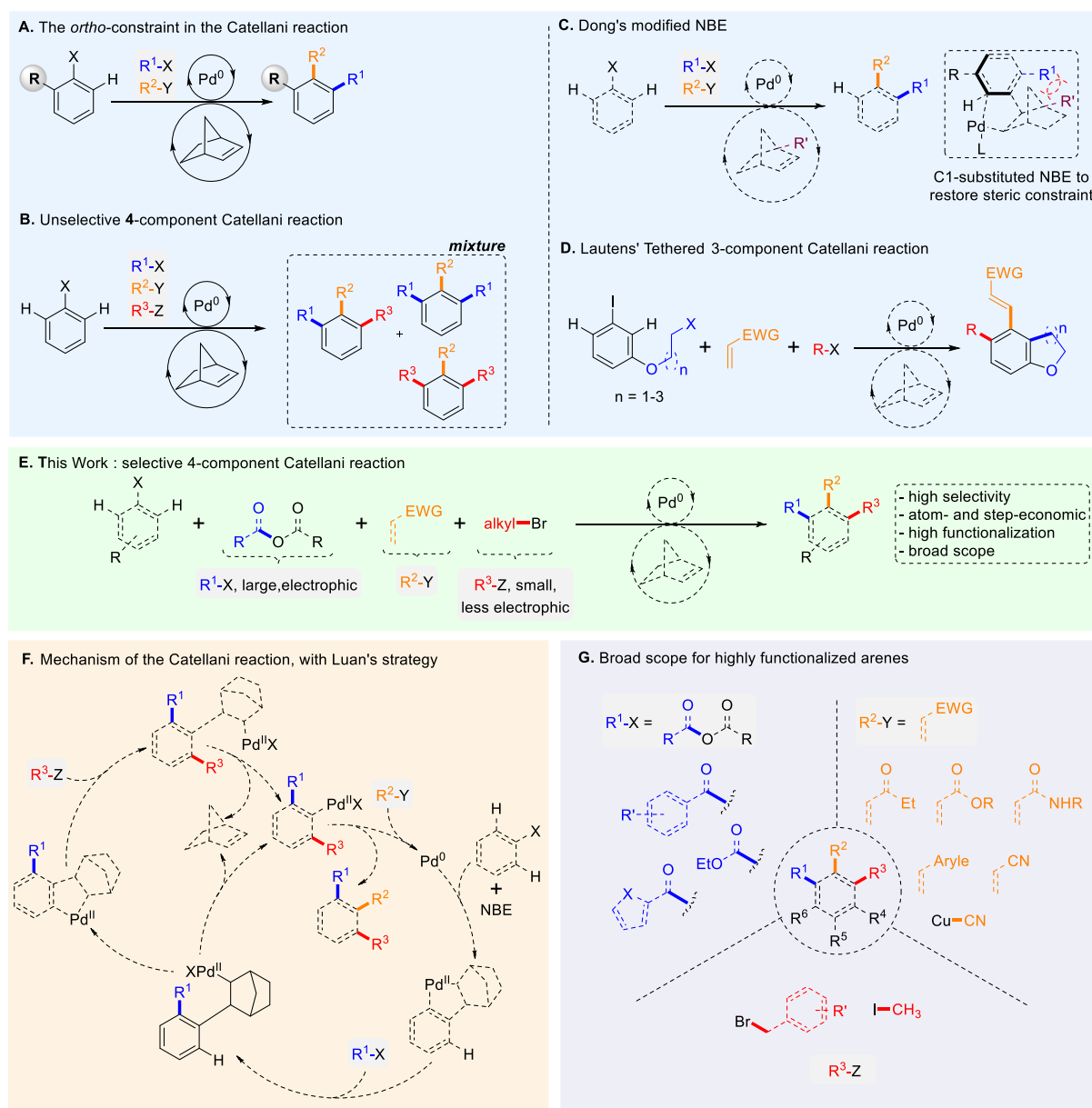


Figure 1. Overcoming the selectivity issues in the multicomponent Catellani reaction.

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