

S,O-Ligand Promoted *meta*-C–H Arylation of Anisole Derivatives via Palladium/Norbornene Catalysis

Angew. Chem. Int. Ed. **2022**, *61*, e202201750

Palladium-catalyzed C–H functionalization reactions have become powerful synthetic tools in organic chemistry. However, most of the reported examples rely on the use of directing groups to increase the reactivity and selectivity of these processes. Only a few examples of efficient Pd-catalyzed C–H functionalization on non-directed arenes have been reported, and the presence of an external ligand is generally required.

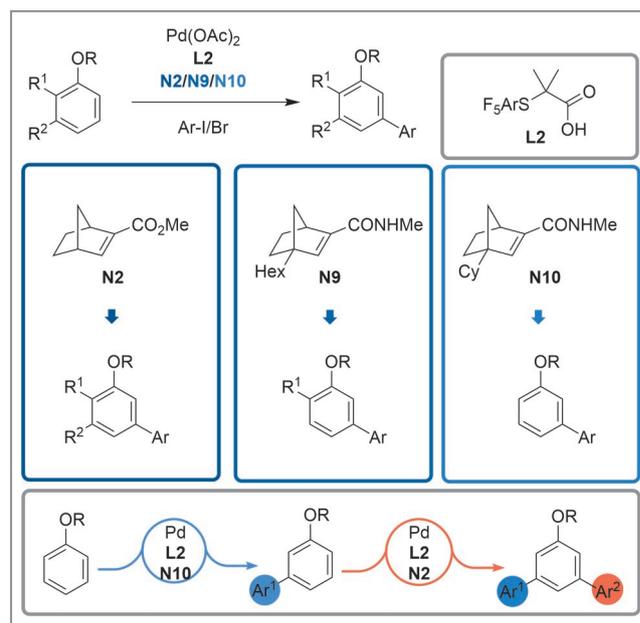
The research group of Professor M. Ángeles (Tati) Fernández-Ibáñez at the University of Amsterdam (The Netherlands) has discovered a new type of S,O-ligand, namely thioether carboxylic acid, that can promote a variety of C–H functionalization reactions on non-directed arenes. “A unique feature of the Pd/S,O-ligand catalytic system is its high catalytic activity, enabling the functionalization of substrates that are unreactive using other catalysts,” explained Professor Fernández-Ibáñez. She continued: “The site-selectivity of these processes is dictated by stereoelectronic effects, with the functionalization taking place at the most electron-rich position of the arene, similarly to electrophilic aromatic substitutions.”

The functionalization of electron-rich arenes at the *meta*-position is challenging. Recently, the *meta*-arylation of anisole derivatives using palladium/norbornene (Pd/NBE) cooperative catalysis was reported for the first time (*J. Am. Chem. Soc.* **2019**, *141*, 14870–14877). Professor Fernández-Ibáñez commented: “However, in this manuscript several limitations were found, as for example the catalytic system did not work for anilines or for anisoles bearing electron-withdrawing substituents. As we experienced in our lab, these types of substrates are reactive in C–H functionalization processes using our Pd/S,O-ligand catalytic system (*J. Am. Chem. Soc.* **2019**, *141*, 6719–6725; *Eur. J. Org. Chem.* **2021**, *2021*, 4132–4135). Thus, we decided to investigate if we could overcome the limitations of the previously reported catalytic system by combining the Pd/S,O-ligand with an appropriate NBE.”

Although the group’s initial efforts on anilines were unsuccessful in obtaining the desired product, they were happy to see that under the conditions previously reported, anisole could be functionalized at the *meta*-position in high yields, demonstrating the compatibility of the Pd/S,O-ligand catalyst with NBE. “The high activity of the new catalytic systems allowed us to reduce the amount of Pd catalyst, and the

NBE could be used in catalytic amounts, which is not very common in this type of transformation,” said Professor Fernández-Ibáñez. She continued: “In addition, anisoles bearing electron-withdrawing substituents, which were previously unreactive, were also *meta*-functionalized. Furthermore, we found out that by using the appropriate NBE, we could perform the unsymmetrical *meta*-diarylation of anisole, which is in my opinion highly relevant, as it is difficult to achieve with an alternative synthesis using the simple anisole as starting material.”

In addition to the methodology work, the group performed several experiments to obtain some insights about the mechanism of this transformation. “We were able to isolate the complex after the first C–H activation/NBE insertion, as well as the complex after the second C–H activation,” revealed Prof. Fernández-Ibáñez, continuing: “We were surprised to see that the first C–H activation was not the rate-limiting step, which is generally the case, especially for non-directed C–H



Scheme 1 Direct synthesis of *meta*-arylated anisoles by reversing the conventional site-selectivity using the Pd/S,O-ligand catalytic system in conjunction with norbornene

activation processes. We also observed that the presence of HFIP as solvent has a positive effect in the first C–H activation step. Although this behavior has been previously observed, the exact reason for this acceleration is still under debate and more research should be done in that direction.”

“The field of C–H functionalization still has, after more than 20 years of research, a large number of challenges that need to be overcome,” said Professor Fernández-Ibáñez. She concluded: “In the case of non-directed C–H functionalization reactions, the discovery of more active catalysts will be crucial for the development of new transformations such as those that involved electron-poor arenes. In addition, more active catalysts will also permit to reduce the catalyst loading, which is still too high in the majority of the reported methodologies for industrial applications. On the other hand, to achieve non-conventional selectivities, the use of NBEs as mediators is currently becoming a common approach. However, moving away from the NBE structure will open new possibilities for novel reactivities.”

Manuela van Borselen

About the authors



V. Sukowski

Verena Sukowski started her academic career after working as a trained laboratory worker at Beiersdorf Ag (Hamburg, Germany) in the prototyping development of skin care products. She received her BSc degree in pharmaceutical chemistry from the TH Köln – University of Applied Sciences (Germany) in 2017, including one year research traineeship in the group of Prof. José R. Pedro (University of Valencia, Spain). She obtained her MSc in 2019 from the Vrije Universiteit Amsterdam, spending a year in the group of Prof. Eelco Ruiters (VU Amsterdam, The Netherlands). Currently, she is pursuing a Ph.D. with Prof. Fernández-Ibáñez (UvA Amsterdam, The Netherlands), investigating synthetic methodologies in the field of non-directed C–H functionalization.



M. van Borselen

Manuela van Borselen graduated from Leiden University of Applied Science (The Netherlands) with her Bachelor of Applied Science in Organic Chemistry (2017). After completing a chemistry premaster programme at the University of Amsterdam (Netherlands, 2018) she went on to become a technician in the Synthetic Organic Chemistry group at the University of Amsterdam in the group of Prof. Fernández-Ibáñez (2020).



Dr. S. Mathew

Simon Mathew received his Ph.D. in supramolecular photochemistry from Flinders University (Australia) with Assoc. Prof. M. R. Johnston in 2008. He has worked in Australia, Japan (JSPS fellow, Prof. Hiroshi Imahori), Switzerland (Profs. Michael Grätzel & Md. Khaja Nazeeruddin), USA (Visiting Fellow, Assoc. Prof. Jared Delcamp) and The Netherlands (Solardam Fellow, Prof. Joost Reek) developing research on topics including biofuels, dye-sensitized solar, phototherapeutics, metal-organic frameworks, gas separa-

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tion membranes, supramolecular chemistry, and light-driven catalysis. Currently, he is a laboratory manager within the van 't Hoff Institute for Molecular Sciences, managing the single-crystal X-ray diffraction facility and developing projects addressing bioinspired photoelectrocatalytic devices for sustainable chemical transformations, fuel production and self-assembled systems.



Prof. M. A. Fernández-Ibáñez

M. Ángeles (Tati) Fernández-Ibáñez is an Associate Professor in Organic Chemistry at the University of Amsterdam (The Netherlands). She received in 2006 her Ph.D. cum laude from Universidad Autónoma de Madrid (UAM), Spain, under the supervision of Prof. José L. García Ruano. During that period, she carried out a predoctoral stay in Boston College (USA), with Prof. Scott J. Miller. Subsequently, she joined as a postdoctoral researcher

the group of Prof. Ben. L. Feringa at the University of Groningen (The Netherlands). After one year in the Medicinal Chemistry Institute at CSIC in Madrid (Spain), she moved to the UAM where she was appointed as Assistant Professor. In 2015 she took up a tenure-track position at the University of Amsterdam (The Netherlands) where she was promoted in 2017 to Associate Professor. Her research focuses on the development of new sustainable methodologies for the construction of complex organic molecules.