Practical and Regioselective Amination of Arenes Using Alkyl Amines

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Anilines are organic molecules made of an aromatic and an amine component linked through a carbon–nitrogen bond. The formation of these bonds is among the top five reactions carried out globally and it is used to prepare widely prescribed medicines, agrochemicals and materials. In general, these high-value molecules are assembled using multi-step sequences where the aromatic component is pre-functionalized to enable the formation of the C–N bond.

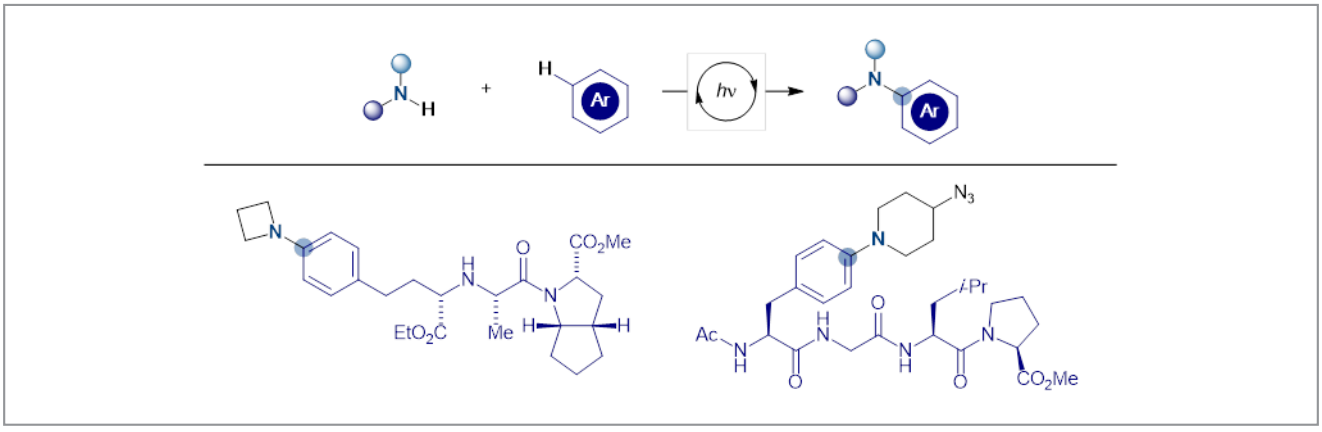
Photoredox catalysis can offer new and more environmentally sustainable solutions to the problem of synthesizing complex organic compounds – including N,N-disubstituted anilines – simply by harnessing the energy of light for promoting chemical reactions in the presence of a light-sensitive catalyst that can mediate electron transfers between readily available starting materials.

In this recent paper, the group of Dr. Daniele Leonori at the University of Manchester (UK) has developed a new chemical method that assembles anilines by direct reaction of aromatic and alkyl amines upon blue light irradiation (Scheme 1). Dr. Leonori said: "This streamlined process offers an improved and cost-effective strategy for the preparation and modification of complex and densely functionalized materials."

Through a collaboration with the pharmaceutical company AstraZeneca, the group has applied this new reaction to the modification of drugs, agrochemicals, peptides, chiral catalysts, polymers and organometallic complexes, and has demonstrated its scalability by flow technologies.

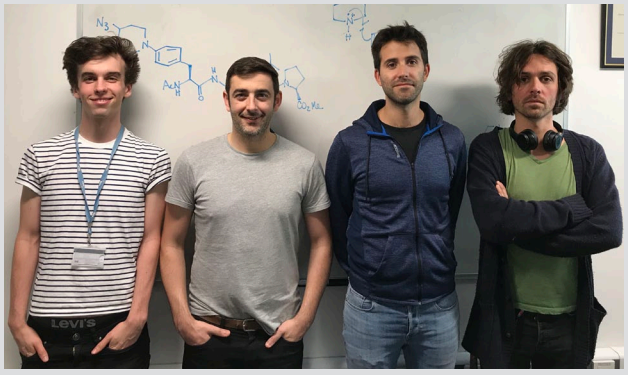
Dr. Leonori concluded: "We hope that this methodology will be perceived as a viable alternative to classical cross-coupling approaches and will be of use to researchers active in the area."

Professor David A. Nicewicz, an expert in photoredox catalysis from the University of North Carolina (Chapel Hill, USA) and an Editorial Board Member of SYNLETT, commented "This is a simple and elegant solution to the coupling of second amines and arenes and will likely find widespread use in pharmaceutical and agrochemical discovery programs."



Scheme 1 Photoredox catalysis enables the direct and selective coupling of unfunctionalized amines and aromatics. The methodology can be used for the late-stage modification of bio-active materials, small peptides and organometallic complexes.

About the authors



From left to right: A. J. McMillan, F. Juliá, D. Leonori and A. Ruffoni

Daniele Leonori (second from right) obtained his PhD in organic chemistry at the University of Sheffield (UK) under the supervision of Prof. Iain Coldham. After postdoctoral stays with Prof. Magnus Rueping and Prof. Peter Seeberger, he joined the group of Prof. Varinder Aggarwal FRS as research officer. Daniele started his independent career at the University of Manchester (UK) in 2014 and was promoted to Reader in 2018. He is the recipient of an EPSRC Early Career Fellowship, the ERC Starter Grant and the 2018 RSC Harrison-Meldola Memorial Prize.

Alessandro Ruffoni (right) studied medicinal chemistry at the Univerisita' di Milano Statale (Italy) and obtained his PhD at the same institution under the supervision of Prof. Francesca Clerici. Following a research stay in the group of Prof. Phil Baran (Scripps, USA), he moved to IRB Barcelona (Spain) under the supervision of Prof. Anthony Riera and Prof. Xavier Salvatella working on ID proteins. In 2016 he was awarded a Marie Curie Fellowship and joined Dr. Leonori's research group.

Fabio Juliá (second from left) obtained his MChem and PhD in inorganic chemistry at the University of Murcia (Spain) under the supervision of Prof. Gonzalez-Herreros for which he was awarded the prize for best PhD thesis in photochemistry by the Spanish Royal Society. Following a research stay in the group of Prof. Corey Stephenson (University of Michigan, USA), he joined Dr. Daniele Leonori's research group in 2017 as a postdoctoral research fellow.

Alastair J. McMillan (left) studied MChem with industrial experience at the University of Manchester (UK) with a year placement at AstraZeneca (Macclesfield, UK). In 2017 he started his PhD at the same institution under the supervision of Dr. Daniele Leonori.

James J. Douglas (not pictured) studied chemistry at the University of York (UK) and obtained his PhD from the University of St. Andrews (UK) under the supervision of Prof. Andy Smith. Following an Eli Lilly sponsored LIFA Industrial postdoctoral position under the supervision of Prof. Corey Stephenson (University of Michigan, USA), James joined AstraZeneca (Macclesfield, UK) where he is now Associate Principal Scientist. He is the recipient of the 2018 AstraZeneca IMED Scientist of the Year Award.

Thomas D. Svejstrup (not pictured) studied chemistry at the University of Bristol (UK) and then moved to Manchester (UK) to work under the supervision of Dr. Daniele Leonori for his PhD. Since 2018 he has been a postdoctoral research associate at AstraZeneca in Gothenburg (Germany).

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