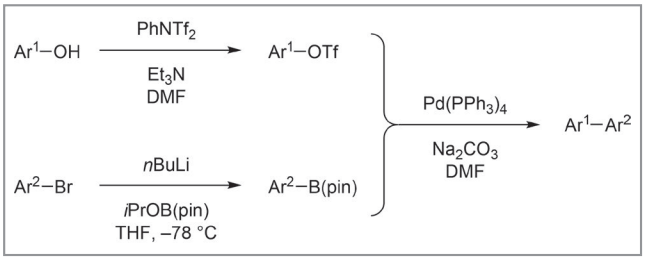
Suzuki–Miyaura Coupling of Aryl Nosylates with Diethanolamine Boronates

Synthesis **2023**, *55*, 3159–3171

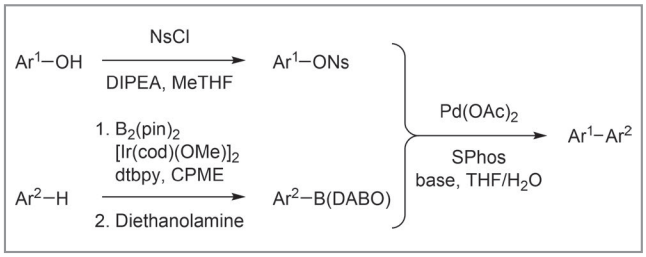
This SYNTHESIS paper was authored by a research team led by Dr Philipp Kohler, from the Chemistry Process R&D group, Idorsia Pharmaceuticals Ltd. (Allschwil, Switzerland). Dr Kohler told SYNFORM: "Our work was inspired by a recent development project, in which we had to implement a Suzuki coupling of two heterocyclic entities: one with a phenolic functionality, the other featuring a boronate. In the discovery route, the building blocks were activated in the standard fashion: the phenol (Ar^1) as the triflate, the other building block (Ar^2) as the pinacol boronate, which was prepared through lithiation of the corresponding bromide and quenching with a suitable borylation reagent."



Scheme 1 Discovery route

Dr Kohler explained that both Ar^1–OTf and Ar^2–B(pin) were oils and used as crude material or purified by chromatography. Additionally, the conditions for their preparation were not considered favorable due to cryogenic conditions. "We accepted the challenging goal to find derivatives that were prepared under 'process-like' conditions and purified by crystallization," he said, continuing: "This led us to the identification of the nosylate and the diethanolamine (DABO) boronate as suitable, crystalline substrates. The ensuing Suzuki coupling required some screening of conditions because of the lowered reactivity compared to the triflate/pinacol boronate combination."

Eventually, the authors ended up preparing the nosylate using NsCl and DIPEA in 2-methyltetrahydrofuran (MeTHF) – a green reaction solvent. "The boronate was prepared by C–H borylation using an iridium catalyst and $B_2(pin)_2$," said Dr Kohler. He went on: "The intermediate, non-crystalline, pinacol boronate was converted into the DABO boronate by reaction with diethanolamine, resulting in crystallization from the reaction mixture. For the Suzuki coupling, reaction optimization resulted in a system of $Pd(OAc)_2$ and SPhos. These conditions were successfully scaled up to 600 g scale."



Scheme 2 Scale-up route

Based on this success story, the authors were motivated to generalize the Suzuki coupling conditions to make them available for a wide range of relevant substrates. At this point, they were less interested in optimizing the formation of the substrates themselves, since the synthesis of nosylates as well as DABO boronates is well described in the literature. Hence, they recommenced their work by identifying more general reaction conditions for the coupling on model substrates, which were identified using the authors' $Pd(OAc)_2$/XPhos/K_2CO_3 system. Dr Kohler explained: "Water was required for conversion; therefore, one can assume the free boronic acid to be the reactive species. We went on to prepare a variety of nosylates and DABO boronates to investigate the substrate scope. To our delight, all of the prepared starting materials turned out to be highly crystalline, thereby validating our rationale. Most of the substrates were successfully tested in the Suzuki coupling, although certain heterocyclic DABO boronates and sterically hindered nosylates were not tolerated. In a competition experiment, a reactivity order of Cl > ONs > OTs was determined."

Dr Kohler ended by saying: "We believe that this piece of work has relevance for process chemists, as it offers the benefit of crystalline substrates in combination with a common catalytic system. Furthermore, we hope that it raises awareness in discovery chemistry for the various possibilities of modern cross-coupling reactions, which are not necessarily limited

  • Published online: October 17, 2023 • DOI: 10.1055/s-0040-1720612

to optimization of the catalytic system itself." He concluded: "A potential extension of the work might be the generalization of the previously mentioned sequence of C–H borylation and conversion into the DABO boronate, followed by Suzuki coupling."

About the authors

Dr. P. Kohler

Philipp Kohler received his Ph.D. in 2010 from ETH Zürich (Switzerland) with Prof. F. Diederich. He then moved to the University of California, Irvine (USA), for postdoctoral studies with Prof. L. E. Overman. In 2012, he accepted a position as R&D chemist at Dottikon ES (Switzerland), before moving on to Idorsia (then Actelion), Switzerland, in 2014. He has been active as a process chemist at Idorsia since then, working on >10 small-molecule APIs spanning preclinical to late-stage development.

T. Perrin

Timothé Perrin obtained his Master's degree in molecular and macromolecular chemistry from the National College of Chemical Engineering in Mulhouse (France) in collaboration with Idorsia (Switzerland), where he worked in the medicinal chemistry department with Dr. S. Diethelm, in 2023. He then worked for 4 months as a research associate in process chemistry under the supervision of P. Kohler, Idorsia. He is currently employed as a process development chemist at PolyPeptide (Belgium).

Dr. G. Schäfer

Gabriel Schäfer obtained his PhD in 2014 from ETH Zürich (Switzerland) under the supervision of Prof. J. Bode. After completing a postdoctoral research stay with Prof. F. D. Toste in Berkeley (USA), he started his industrial career in 2015 as a Process Chemist at Actelion Pharmaceuticals (Switzerland). After the acquisition of Actelion by J&J and the subsequent demerger of Idorsia Pharmaceuticals in 2017, he worked as a Senior Scientist in Idorsia's Chemistry Process R&D group (Switzerland). In this function, he developed robust and scalable chemical routes for Idorsia's preclinical candidates and clinical assets. In 2020, he was promoted to Group Leader of the Chemistry Process R&D group, leading a fantastic team of 20 highly motivated people. His work has been published in over 20 publications and patents. He also serves as a member of the 'Early Career International Advisory Board' of Helvetica Chimica Acta.

  • Published online: October 17, 2023 • DOI: 10.1055/s-0040-1720612