

Hydroxylamine-Mediated C–C Amination via an Aza-Hock Rearrangement

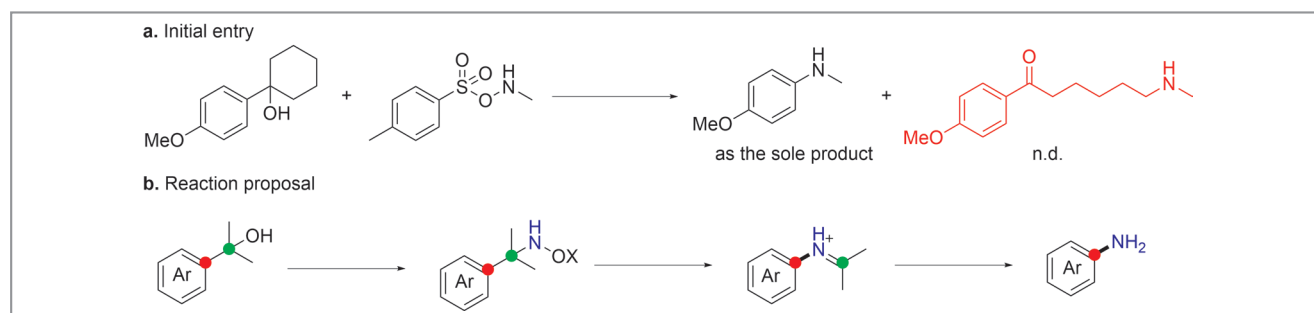
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Anilines are precursors to many industrial chemicals, including dyes, resins, perfumes, pigments, herbicides, fungicides, agrochemicals, pharmaceuticals, explosives, various polymers such as polyurethanes and rubber chemicals. “For this reason, aniline synthesis is a common task for many chemists, but is always accompanied by chemoselectivity issues using both traditional nitration–reduction or modern arene C–H amination,” said Professor A. Stephen K. Hashmi, from Heidelberg University (Germany), who added: “However, C–C amination is an alternative way to address such site-selectivity issues. A few methods have been reported for harnessing this strategy to afford the desired anilines, albeit with hazardous reagents or harsh conditions: decarboxylative amination,¹ Beckmann rearrangement,² and Schmidt-like rearrangement³ are among these methods. Therefore, new strategies for aniline synthesis via C–C amination in mild conditions are needed urgently.”

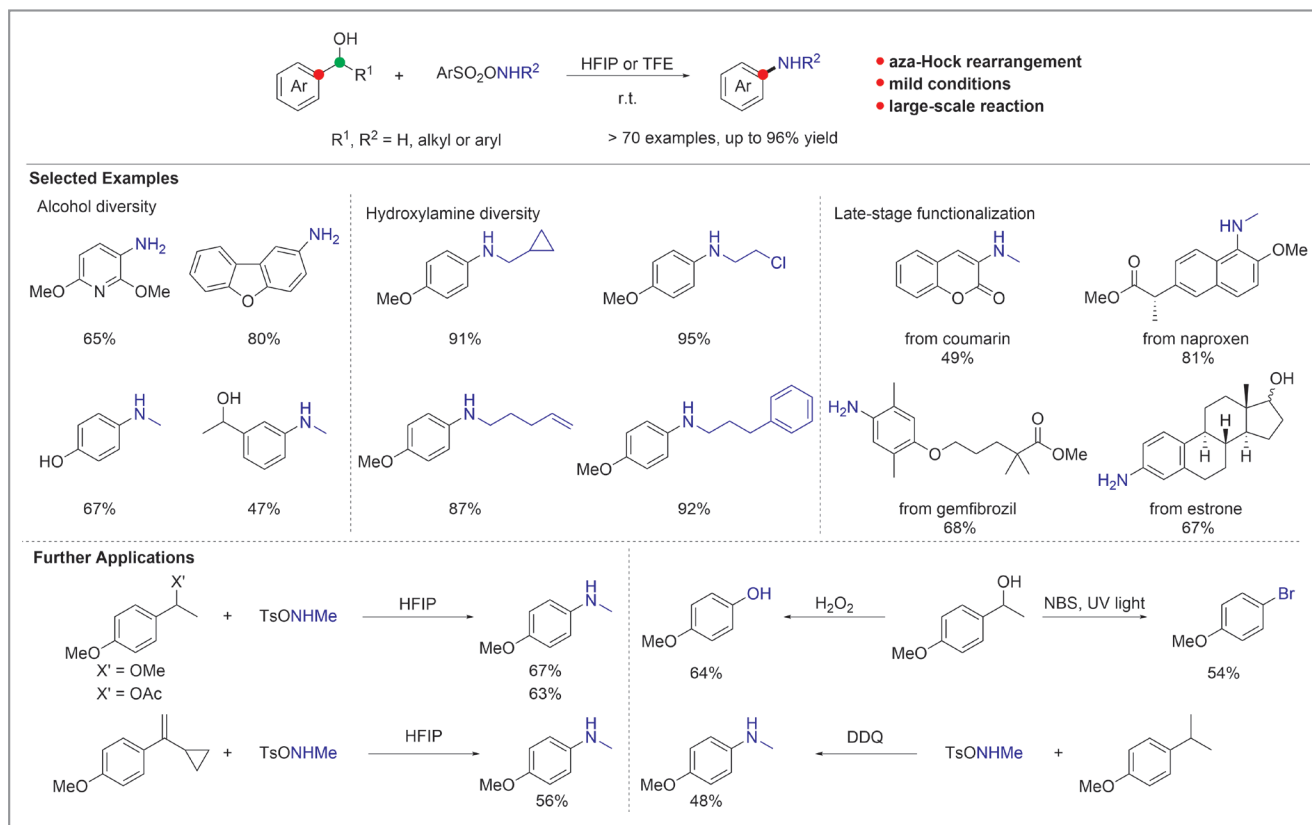
The group of Professor Hashmi is focused on gold chemistry and photochemistry research. “This aza-Hock amination – which plays a key role in our recent effort published in the title *Nat. Commun.* article – is based on our first work, ‘A metal-free direct arene C–H amination’,⁴ which was developed following a serendipitous discovery in 2019,” said Professor Hashmi, who revealed that following this research, first author Tao Wang wondered: “Can we afford the sole product of aniline isomers via the more challenging C–C amination pathway?” Professor Hashmi explained: “The initial entry point for such a conversion started from tertiary benzyl alcohol with the aminating reagent (TsONHMe) in HFIP, which presented an unexpected result: the aniline, rather than the aliphatic amine, was isolated as the sole product (Scheme 1a).” Subse-

quent experiments with different benzylic alcohols exhibited similar outcomes: anilines as the products. Then an aza-Hock rearrangement for the transformation was proposed by Tao Wang in the 2021 paper.⁴ “Cumene hydroxylamine derivatives, owing to the weak N–O bond (similar to the O–O bond in cumene hydroperoxide), are susceptible to a Hock-type rearrangement in an acidic solvent, yielding anilines as products,” explained Professor Hashmi (Scheme 1b).

“This aza-Hock amination shows quite a broad substrate scope (Scheme 2): a variety of anilines are accessible from normal benzylic alcohols/hydroxylamine derivatives,” said Professor Hashmi, who went on by explaining that late-stage functionalizations and large-scale reactions are also viable under the standard conditions; further application showed all benzylic cation precursors – like benzylic ether/ester, styrene and even alkylarenes – are accessible with the aza-Hock rearrangement, which serves as a valuable tool for aniline synthesis. “Besides, phenol and aryl bromide are also accessible with a similar strategy. For the substrate with two benzylic alcohol groups, only one alcohol group is cleaved,” said Prof. Hashmi, adding: “The hydrolysis of protonated imines in the reaction mixture, occurring only during the workup with sodium hydrogen carbonate (and not in situ with the one equivalent of neutral water formed in the reaction), explains the selective cleavage of one C–C bond instead of two C–C bonds in substrates with two reactive benzylic alcohol groups; the iminium group in the intermediate iminium tosylate electronically de-activates the arene ring, so the second benzylic alcohol does not react anymore.”



Scheme 1 Initial entry and reaction proposal



Scheme 2 Aza-Hock rearrangement: reaction scope and further applications

Prof. Hashmi concluded: “Despite some early evidence for such a reactivity pattern, its synthetic utility would be limited until it was confirmed for certain by our studies. Thus, our report might pave the way for further protocols based on this reactivity pattern in the future.”

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Philipp M. Stein received both his B.Sc. (2017) and M.Sc. (2019) degrees in chemistry from Heidelberg University (Germany). In recognition of his outstanding study achievements, he was awarded a scholarship from the Dr. Sophie-Bernthsen Fund. For his Ph.D. studies he joined the research group of Prof. A. Stephen K. Hashmi in 2019. He works in the field of homogeneous gold catalysis and the investigation of reaction kinetics. Since 2020 he is a full scholarship holder funded by the Hector Fellow Academy.



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Dr. C. Hu

Chao Hu was born in Jingzhou, P. R. of China. He received his Ph.D. in 2020 under the supervision of Prof. A. Stephen K. Hashmi at Heidelberg University (Germany), where his doctoral work investigated mainly gold-catalyzed cycloisomerization reactions. In 2021, he joined Prof. Tian Qin's group at the University of Texas Southwestern Medical Center (USA) for post-doctoral research on boron chemistry in drug discovery.



Dr. M. Rudolph

Matthias Rudolph studied chemistry at the University of Stuttgart (Germany). He received his diploma grade in 2004. After that he pursued Ph.D. studies in the field of gold catalysis under the supervision of A. Stephen K. Hashmi until 2008. Since 2008 he is permanently employed at the Ruprecht-Karls University, Heidelberg (Germany) as a scientific co-worker. His research interest is mainly focused on methodology development in the field of homogeneous gold catalysis.



Prof. A. S. K. Hashmi

A. Stephen K. Hashmi studied chemistry at Ludwig-Maximilians-Universität München (Germany). He obtained his diploma and PhD with Prof. G. Szeimies in the field of nickel- and iron-catalyzed cross coupling of highly strained organic compounds. As a postdoc with Prof. B. M. Trost at Stanford University (USA) he investigated palladium-catalyzed enyne metathesis. During his habilitation with Prof. J. Mulzer at Freie Universität Berlin (Germany), Frankfurt University (Germany) and the University of Vienna (Austria), he developed enantiomerically pure organopalladium compounds and new palladium-catalyzed conversions of allenes. In 1998, a Heisenberg fellowship of the Deutsche Forschungsgemeinschaft (German Research Foundation) for a proposal on gold-catalyzed reactions for organic synthesis – still a major focus of the group – was awarded to him. His next stations were the University of Tasmania (Australia) and Marburg University (Germany). He was appointed to associate professor for organic chemistry at Stuttgart University (Germany) in 2001 and since 2007 he is full professor for organic chemistry at Heidelberg University (Germany).