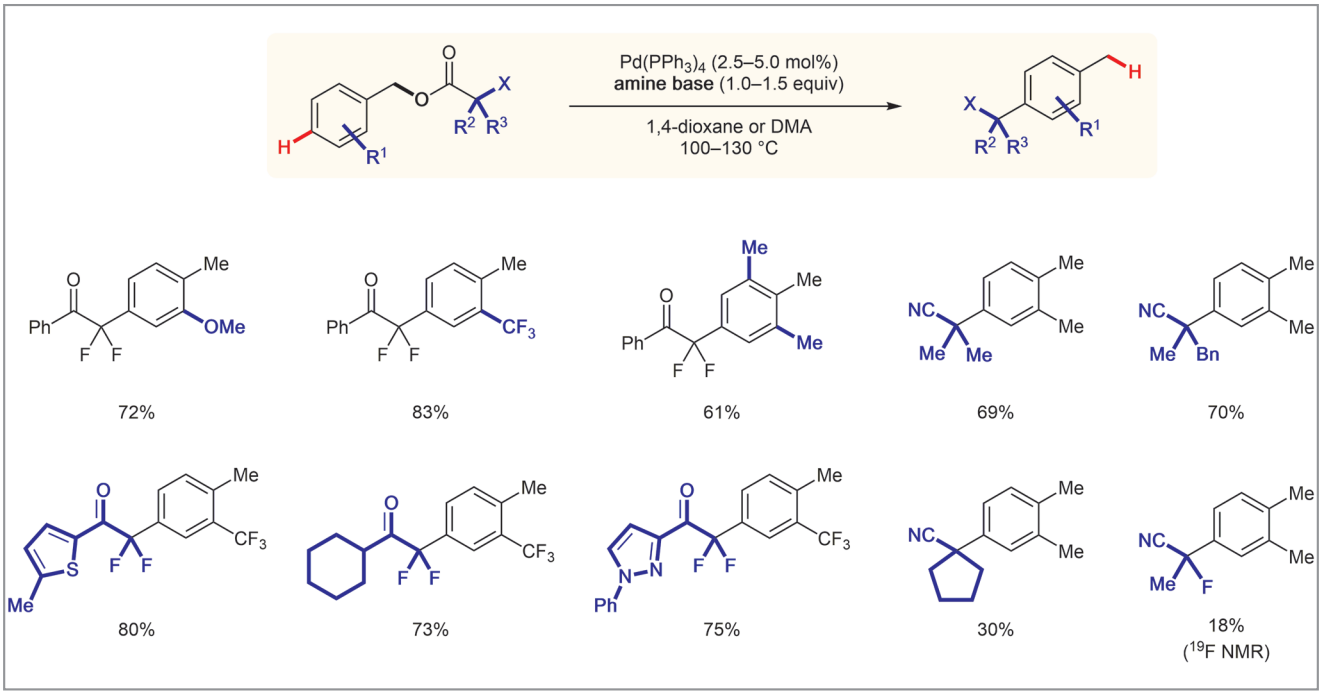
Connecting Remote C–H Bond Functionalization and Decarboxylative Coupling Using Simple Amines

Nat. Chem. **2020**, *12*, 489–496

Regiocontrolled rearrangements taking place in high yields using experimentally simple conditions are key assets in the organic chemistry toolbox, especially if such processes result in the selective functionalization of unactivated C–H bonds. Recently, the groups of Professor Ryan A. Altman at The University of Kansas (USA) and Professor Paul Ha-Yeon Cheong at Oregon State University (USA) joined forces to investigate a novel methodology for achieving the decarboxylative *para*-functionalization of benzyl ester derivatives promoted by palladium catalysts and simple amine bases.

"This was a fortuitous finding from the get-go," remarked Professor Altman. He continued: "At the outset of the project we were optimizing a decarboxylative benzylation reaction (*Angew. Chem. Int. Ed.* **2016**, *55*, 9080–9083), and one astute PhD student recognized an intriguing and unexpected minor side product that occasionally popped up in reactions. Her fortitude to first optimize and then characterize the minor side product revealed a *para*-selective functionalized arene, which was produced from a benzyl-substituted substrate. Though such products had been seen in analogous reactions, previous research teams could not control the chemoselectivity for benzylation vs. *para*-selective functionalization. However, we discovered that one could control the chemoselectivity using simple amine bases. Though there were initial concerns that the reaction would only work on fluorinated ketone-derived nucleophiles, later researchers expanded the scope of compatible substrates to include non-fluorinated and nitrile-based nucleophiles (Scheme 1)."

Professor Altman explained that rigorous mechanistic experiments and thorough computational studies by Professor Cheong's group supported a catalytic cycle involving an intriguing reversible dearomatization/irreversible base-

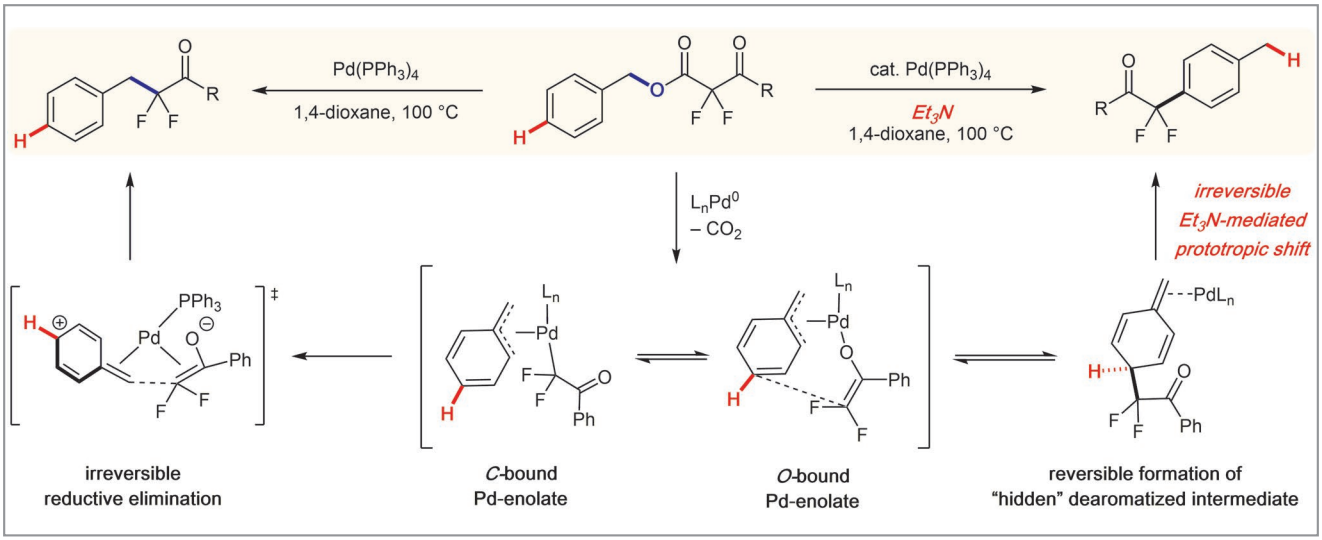


Scheme 1 A *para*-selective functionalization reaction converts benzylic electrophiles into *para*-functionalized toluene derivatives. Notably, the pK_a and size of the amine are essential for the reaction, with α,α-difluorinated ketone enolate-derived substrates requiring trialkylamine bases, and non-fluorinated nitrile-derived substrates requiring guanidine bases.

mediated rearomatization sequence that provided the *para*-substituted arene products (Scheme 2). Notably, the group's computational efforts revealed that the reaction proceeded through a "hidden" dearomatized intermediate that likely transiently exists in other catalytic processes and might be exploited in to-be-developed reactions. "This unusual finding will hopefully spark new insight and opportunities to access unique products as yet inaccessible by current means," said Professor Altman. He continued: "We hope to exploit this dearomatization/rearomatization sequence to expand the scope of the reaction to include a broad spectrum of alternate nucleophiles."

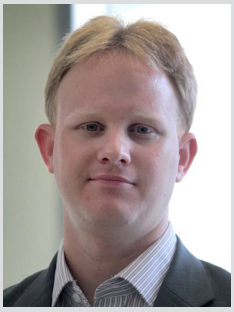
Also notably, the project connected two significant reaction paradigms in organic chemistry, namely decarboxylative coupling and C–H functionalization reactions. Professor Altman told us: "Although these two reaction paradigms typically require orthogonal substrates and proceed under complementary reaction conditions [e.g. Pd(0/II) vs. Pd(II/IV) cycles, basic vs. acidic additives, reductive vs. oxidative conditions], in our hands, simple amine bases linked the complementary mechanisms. Notably, this reaction did not require chelation or template assistance and functioned on a diverse array of electron-donating and electron-withdrawing arenes, which contrasts many C–H functionalization reactions of arenes."

"Overall, this was a complete team effort from start to finish with both the Kansas and Oregon State teams completely turning over personnel," said Professor Altman, who concluded: "Thus, the project really transcended two different generations of researchers in each laboratory, and is a testament to the scientific insight, grit, teamwork, and communication from both groups."



Scheme 2 The use of amine bases converted a decarboxylative benzylation reaction into a *para*-selective C–H functionalization. Both reactions proceed through L_nPd(benzyl)(enolate) complexes that exist as an equilibrium of O- and C-bound enolates. From the C-bound enolate, classical reductive elimination provides the benzylation product, while the O-bound enolate can undergo a reversible sigmatropic reductive elimination to generate a hidden dearomatized intermediate. This intermediate bears an acidic proton that, in the presence of an appropriate weak base, will undergo a 1,5-prototropic shift to deliver the product of *para*-selective functionalization.

About the authors



Dr. F. de Azambuja

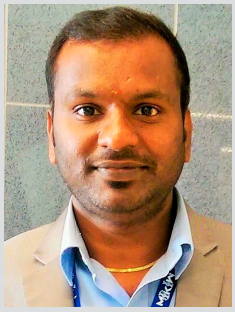
Francisco de Azambuja was born and raised in Brazil. He obtained his Ph.D. in chemistry from the State University of Campinas (Brazil) in 2015 and from there moved to WWU Münster (Germany) before joining Professor Altman's group at The University of Kansas (KU, USA) for an intense postdoctoral period, mostly dedicated to metal-catalyzed fluoroalkylation reactions. In 2018, he moved from KU Lawrence to KU Leuven (Belgium) to indulge his interest in catalytic materials. Since then, he has been developing novel reactions and metal-oxide based catalysts as alternatives to sensitive conventional transition-metal catalysts.

Dr. M. S. Yang

Ming-Hsiu Yang joined Professor Altman's group as a graduate student (2011–2017), focusing on the development of Pd-catalyzed fluoroalkylation reactions and metal-free transformations for accessing fluoroalkenes as peptidomimetics. She is currently a postdoctoral research associate in Professor Boger's lab at The Scripps Research Institute (USA). Her current research is focused on developing TLR agonists as immune modulators and their bioconjugates with immunogenic peptides.

T. Feoktistova

Taisiia Feoktistova obtained her B.S. (2017) at Whitworth University (USA) before starting her current studies under the supervision of Prof. Paul Ha-Yeon Cheong at Oregon State University (USA). Her current research interests are focused on utilizing DFT to elucidate reaction mechanisms.



Dr. M. Selvaraju

Manikandan Selvaraju received his B.Sc. (2004) and M.Sc. (2006) degrees from Bharathidasan University, Tiruchirappalli (India), and then worked as a Research Associate at GVK Biosciences, Hyderabad (India) from 2006–2009. He continued his education, earning his Ph.D. (2014) from National Chiao-Tung University (Taiwan), where he also worked as a postdoctoral research associate (2014–2017) under the supervision of Professor Chung-Ming Sun. Since 2017, he has worked as a postdoctoral research associate in Professor Altman's group at The University of Kansas (USA). Currently, his research interests include cross-coupling and C–H functionalization reactions.

Dr. A. Brueckner

Alex Brueckner obtained his B.A. in chemistry from Hanover College (USA) in 2015. He then joined the PHYC laboratory at Oregon State University (USA), where he completed his Ph.D. in 2019. In his Ph.D. work, he used cutting-edge computational chemistry techniques to study complex chemical systems. Since graduating, he has been a postdoctoral research fellow at Merck & Co., Inc., Kenilworth, NJ (USA). His current research efforts aim to understand the complex conformational landscape of macrocyclic peptides in the context of drug discovery.

M. Grove

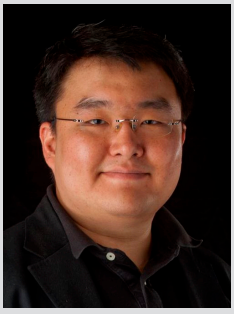
Markas Grove is a PhD candidate in the Cheong group at Oregon State University (OSU, USA). He received his B.S. in biochemistry from the University of Washington (USA) in 2012 and his M.Ed. from the University of Washington – Tacoma (USA) in 2014. After working at a public school from 2013–2016, he joined the Cheong group at OSU and received an M.S. in chemistry in 2019. Currently his research interests include group additivity methods for metal-oxo clusters, the application of metal-oxo clusters as thin-film precursors, and modeling kinetic effects in organic synthesis.

>>

© Georg Thieme Verlag Stuttgart • New York – Synform **2020/11**, A163–A166 • Published online: October 20, 2020 • DOI: 10.1055/s-0039-1691214

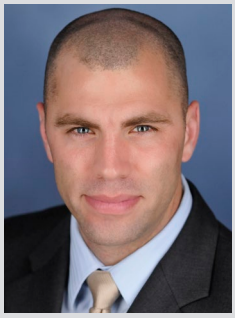
Dr. S. Koley

Suvajit Koley is a postdoctoral research associate in Professor Altman's group at The University of Kansas (USA). He received his B.Sc. degree from the University of Calcutta (India) in 2009. After obtaining his M.Sc. (2011) and Ph.D. (2017) degrees in organic chemistry with Prof. Maya Shankar Singh from Banaras Hindu University (India), he joined Prof. Ganesh Pandey's research group as a National Post-doctoral Fellow in the Center of Biomedical Research (India) from 2017–2018. His current research interests include cross-coupling reactions, C–H functionalization reactions, and reactions of fluorinated alkenes.



Prof. P. H. Y. Cheong

Paul Ha-Yeon Cheong is the Bert and Emelyn Christensen Associate Professor of Chemistry at the Department of Chemistry, Oregon State University (USA). Paul spent most of his youth in Indonesia and Thailand, before coming to the US for his post-secondary education. He was originally an English major in his undergraduate institution of Bowdoin College (Brunswick, ME, USA), before he switched to chemistry to receive his AB in 2001. He received his Ph.D. in organic chemistry from University of California Los Angeles (USA) in 2007 under the tutelage of Professor K. N. Houk. After a brief stint as postdoc in the same lab, he started his independent career at Oregon State in 2009. His research group's scientific passion is in exploring scientific mysteries by discovering and explaining hypotheses and principles that underlie chemistry and nature. Towards this goal, his group applies state-of-the-art computational chemistry techniques and tools to a wide array of scientific mysteries, ranging from synthetic organic chemistry to inorganic semiconductors.



Prof. R. A. Altman

Ryan A. Altman received a B.S. Chem. from Creighton University (USA) in 2003 and a PhD in organic chemistry from the Massachusetts Institute of Technology (USA) in 2008, studying as a Pfizer and National Institutes of Health predoctoral fellow in the laboratory of Professor Stephen L. Buchwald. He subsequently trained as an NIH postdoctoral fellow under the guidance of Professor Larry E. Overman at the University of California, Irvine (USA, 2008–2011), after which he joined the Department of Medicinal Chemistry at The University of Kansas (KU, USA) as an Assistant Professor. After his promotion to Associate Professor (2017), his group moved to Purdue University (USA) to join the Department of Medicinal Chemistry and Molecular Pharmacology and the Department of Chemistry (2020). The Altman group works at the interface of synthetic organic and medicinal chemistries, with synthetic emphases in the areas of organometallic and organofluorine transformations and unique chemical reactivities enabled by fluorinated substructures. The group's collaborative medicinal interests span a range of disease states, including pain, anxiety and mood disorders, and aging.