

Allyl 4-Chlorophenyl Sulfone as a Versatile 1,1-Synthon for Sequential α -Alkylation/Cobalt-Catalyzed Allylic Substitution

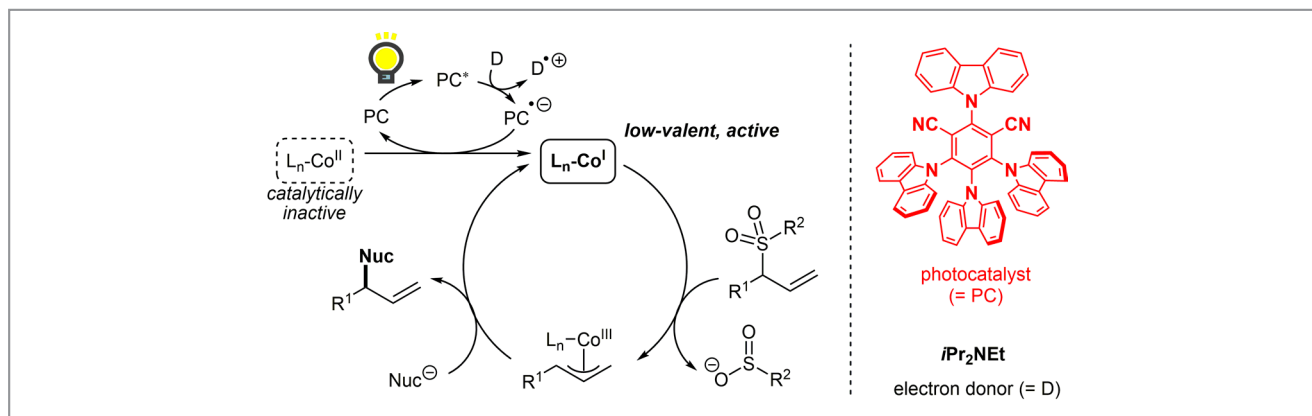
Synthesis **2020**, *52*, 1934–1946

Sulfones are well-known chemical chameleons, namely building blocks that can behave as either nucleophiles or electrophiles depending on how they are activated and reacted. For example, a sulfone can stabilize an adjacent carbanion or alternatively can be displaced by a carbon nucleophile, upon suitable activation. For this reason, some sulfones can be considered as 1,1-dipole synthons. This peculiar reactivity of sulfones continues to attract the interest of organic chemists and represents an invaluable source of new reactions. The story of this SYNTHESIS paper started with a discovery by Professor Kojima's and Professor Matsunaga's group at Hokkaido University (Japan) in 2018: at that time, they were studying the dual cobalt-photoredox catalysis for allylic alkylation. "The system can be considered as a new type of metallaphotoredox catalysis¹ and worked very well for branch-selective substitutions of allyl carbonates and allyl carboxylates," said Professor Kojima. He continued: "However, we were motivated to identify a unique feature of cobalt catalysis compared to the established rhodium or iridium catalysis." Gratifyingly, Professor Kojima discovered that the cobalt-photoredox system was uniquely effective for substitution of allyl sulfones, which proceeded via challenging C–S bond cleavage and was not feasible using the known noble-metal-based catalysis (Scheme 1).² Professor Kojima said: "Koji Takizawa and I also discovered that the 4-chlorophenylsulfonyl leaving group facilitated the allylic substitution, presumably due to greater

leaving-group ability of 4-chlorophenylsulfinate compared to phenyl sulfinate."

In 1990, Trost and Merlic proposed the potential of allyl sulfone as an ambiphilic 1,1-synthon.³ "Its application in multistep synthesis remained a challenge, however, partly because the regioselectivity in the molybdenum-catalyzed substitution of allyl sulfones remained modest," remarked Professor Kojima. He continued: "We envisioned that sequential base-mediated α -alkylation and cobalt-photoredox-catalyzed allylic substitution might provide a solution to this problem."

Graduate student Tomoyuki Sekino took over the study and explored the potential of allyl 4-chlorophenyl sulfone as a 1,1-synthon (Scheme 2). Professor Kojima said: "An unexpected problem came up in base-mediated α -alkylation. Initial trials using butyllithium and an alkyl iodide, followed by acidic workup using aqueous NH_4Cl , afforded an inseparable mixture of allyl sulfone and vinyl sulfone." This "isomerization problem" was solved by Professor Tatsuhiko Yoshino's and Professor Shigeki Matsunaga's suggestion that quenching the reaction under milder protonation conditions might circumvent the undesired isomerization. Professor Kojima said: "Following their advice, Tomoyuki identified the optimal workup method (addition of 1 M AcOH in THF at -78°C) which finally enabled the practical use of the allyl 4-chlorophenylsulfone as a 1,1-synthon."



Scheme 1 Design of photoredox-enabled cobalt catalysis for substitution of allyl sulfones

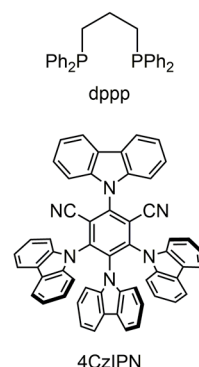
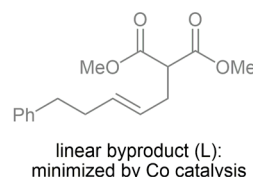
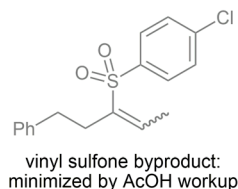
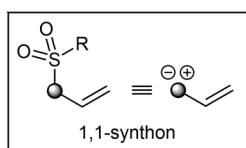
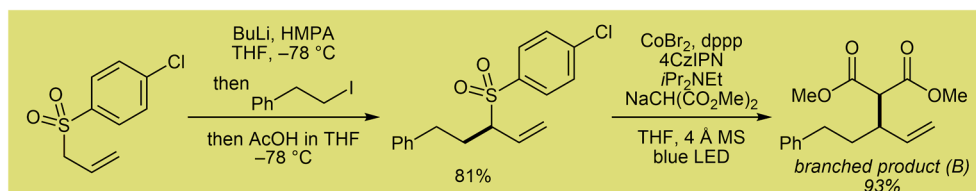
With support from undergraduate students Shunta Sato and Kazuki Kuwabara, Tomoyuki Sekino revealed the broad scope of the sequential α -alkylation/cobalt-catalyzed allylic substitution of allyl sulfones (Scheme 2). "In general, group 9 metal catalysis (rhodium⁴ or iridium⁵) affords branched products in high regioselectivity in allylic substitution," explained Professor Kojima. He continued: "Cobalt catalysis was no exception, and the photoredox-enabled cobalt catalysis allowed access to synthetically valuable branched products in >20:1 regioselectivity in most cases. Notably, functional groups including ester and Weinreb amide were tolerated under the two-step transformations. We anticipate that such functional group compatibility will be beneficial for future applications in the synthesis of complex molecules."

"Compared to rhodium- or iridium-catalyzed methods, the study of cobalt-catalyzed allylic substitution has just begun⁶," said Professor Kojima. He concluded: "Furthermore, the merger of photoredox and cobalt catalysis⁷ is also a new and untapped research area compared to nickel-photoredox⁸ or copper-photoredox⁹ systems. With these two promising directions in sight, we would like to unlock more potential and demonstrate the unique utility of photoredox-enabled cobalt catalysis for organic synthesis."

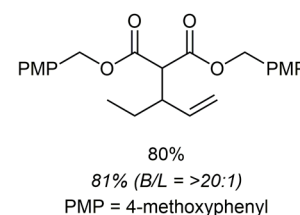
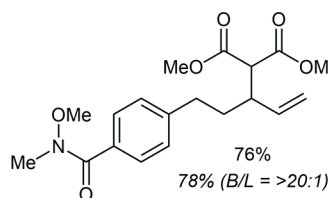
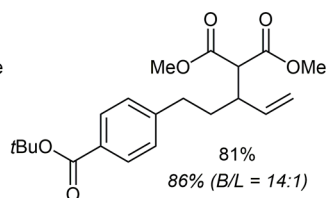
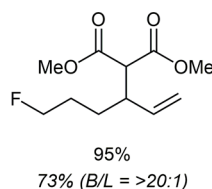
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Master's thesis

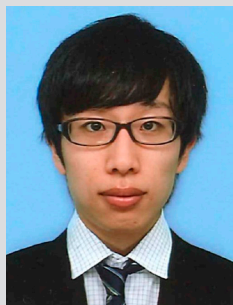


Selected examples: Yield of α -alkylation, Yield of allylic substitution



Scheme 2 Sequential transformations of allyl 4-chlorophenylsulfone as a 1,1-synthon

About the authors



T. Sekino

His research interest is the development of novel reactions employing cobalt metallaphotoredox catalysis.



S. Sato

Tomoyuki Sekino was born in Shizuoka (Japan) in 1993. He studied at the Department of Pharmaceutical Sciences, University of Shizuoka (Japan), where he received his B.Sc. in 2018 under the guidance of Prof. Kei Manabe. Since 2018 he has been carrying out his Ph.D. studies under the supervision of Prof. Shigeki Matsunaga in the Graduate School of Pharmaceutical Sciences, Hokkaido University (Japan). His research interest

Shunta Sato was born in Sapporo (Japan) in 1997. He studied at the Faculty of Pharmaceutical Sciences, Hokkaido University (Japan). In 2020, he received his B.Sc. degree and became a graduate student under the supervision of Prof. Shigeki Matsunaga. His main research interest is dual photoredox and transition-metal-catalyzed methodologies.



K. Kuwabara

Kazuki Kuwabara was born in Kanagawa (Japan) in 1997. Since 2017, he has been an undergraduate at Hokkaido University (Japan) and joined Prof. Shigeki Matsunaga's group in 2019. His research interests lie in visible-light photoredox catalysis.



K. Takizawa

Koji Takizawa studied chemistry at Hokkaido University (Japan) and obtained his B.Sc. in 2017 under the supervision of Prof. Shigeki Matsunaga. He earned his M.Sc. in the same group in 2019. Then he joined Sekisui Chemical Co., Ltd., Advanced Technology Institute Corporate R&D Center (Japan) in 2019. He is experienced in total synthesis, transition-metal catalysis and photoredox catalysis.



Prof. T. Yoshino

He received the 4th Thomson Reuters Research Front Award in 2016 for the studies on cobalt-catalyzed C–H functionalization reactions. His current research interests are focused on the metal-catalyzed C–H functionalization reactions, asymmetric catalysis, and the development of novel molecules and reactions for organic synthesis.



Prof. M. Kojima

transition with Prof. John F. Hartwig at UC Berkeley (USA), he joined Prof. Shigeki Matsunaga's group at Hokkaido University as an assistant professor in 2018. He is interested in photochemistry, transition-metal catalysis and novel methodologies for organic synthesis.

Tatsuhiko Yoshino received his Ph.D. in 2014 from the University of Tokyo (Japan) for his studies of homogeneous metal catalysis and organic synthesis under the guidance of Prof. Masakatsu Shibasaki and Prof. Motomu Kanai. He then joined the laboratory of Prof. Matthew W. Kanan at Stanford University (USA) as a post-doctoral fellow, where he worked on CO₂ utilization reactions. He was appointed as an assistant professor at Hokkaido University (Japan) in 2015, and promoted to a senior lecturer in 2018.

Masahiro Kojima studied chemistry at the University of Tokyo (Japan) and obtained his B.Sc. (2012) and Ph.D. (2017) for his studies of photoredox catalysis and related reactions under the guidance of Prof. Motomu Kanai. In 2014, he spent two months as a visiting student in Prof. Dirk Trauner's group at LMU Munich (Germany), working on total synthesis of natural products. After a postdoctoral study of metal-catalyzed C–H functionalization



Prof. S. Matsunaga

Shigeki Matsunaga earned his Bachelor's degree in 1998 from the University of Tokyo (Japan), where he continued his PhD work under the supervision of Professor Masakatsu Shibasaki and completed the work in 2003. He took up an assistant professor position in Prof. Shibasaki's group at the University of Tokyo in 2001 and was promoted there to a senior

lecturer in 2008. He joined Prof. Motomu Kanai's group at the University of Tokyo in 2010 and was promoted to an associate professor in 2011. In 2015, he moved to Hokkaido University (Japan) as a full professor. He is the recipient of the Chemical Society of Japan Award for Young Chemists (2006), Mitsui Chemicals Catalysis Science Award of Encouragement (2009), Merck-Banyu Lectureship Award 2010, Asian-Core-Program

Lectureship Awards 2015 and 2018 (Korea, Thailand, China, Singapore), 4th Thomson Reuters Research Front Award (2016), Negishi Award (2018), Mukaiyama Award (2020), and others. His research interests are in the development of cooperative asymmetric catalysts, C–H activation catalysts, and their application to the synthesis of biologically active compounds.