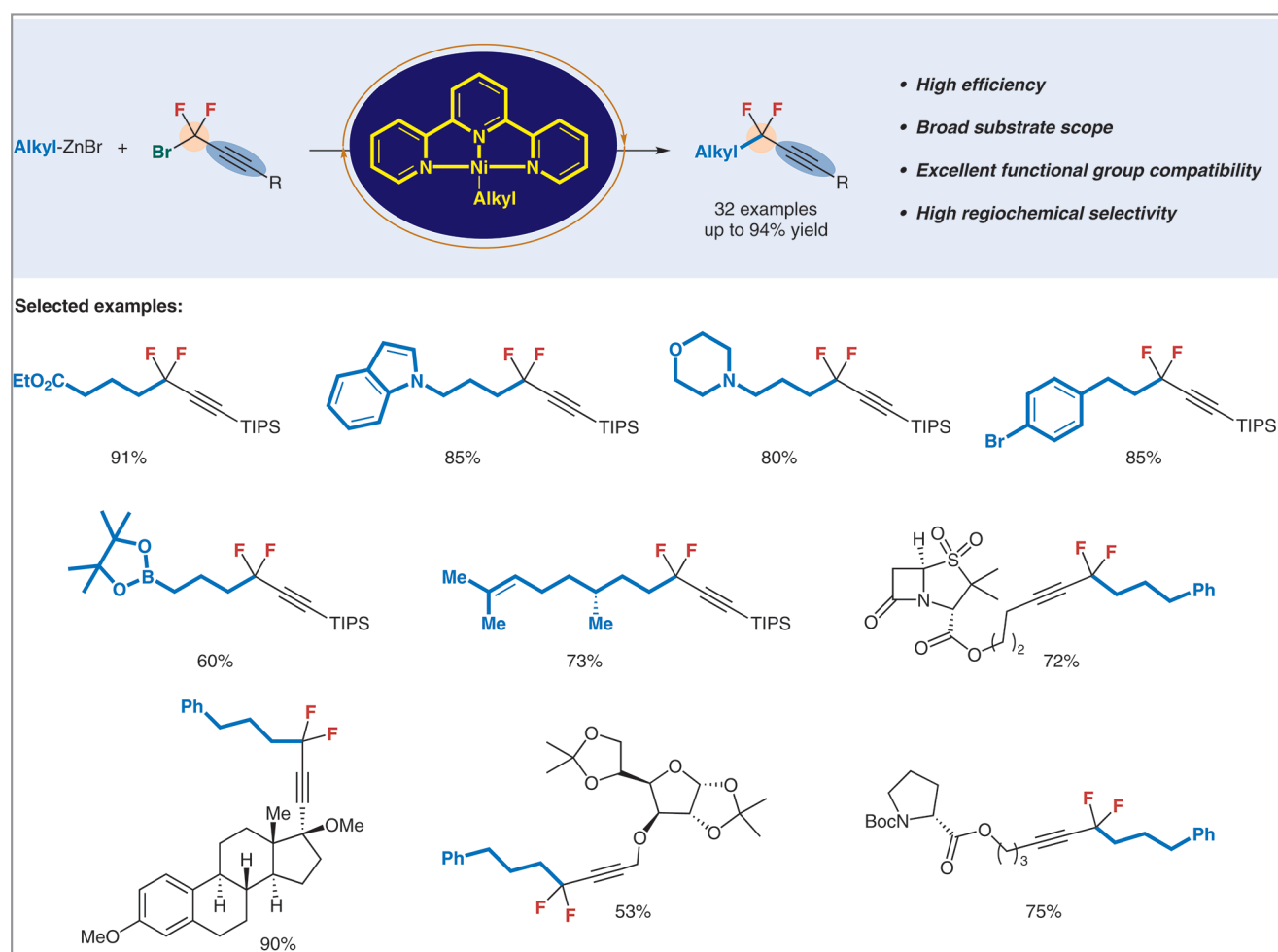


Highly Selective *gem*-Difluoropropargylation of Unactivated Alkylzinc Reagents Catalyzed by Nickel

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With increasing demands from both life and materials science sectors, the controllable introduction of fluorine atom(s) into organic molecules has become an attractive strategy to modulate physical and biological properties of functional molecules, owing to the unique characteristics of fluorine atom(s) and C–F bond.¹ Over the past decade, tremendous efforts have been made in developing new and general methods for site-selective fluorination and fluoroalkylations. Among the developed methods, transition-metal-catalyzed fluoroalkylations

have become a useful strategy for the construction of C–R_f (R_f = CF₃, CF₂R) bonds.² However, most of these methods rely on the construction of Ar–R_f bonds, whereas it remains a challenge to adapt the same strategy to form C_{sp3}–R_f bonds. Recently, the research group of Professor Xingang Zhang at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China) demonstrated the feasibility of forming C_{sp3}–CF₂R bonds by employing a transition-metal-catalyzed difluoroalkylation strategy (Scheme 1).



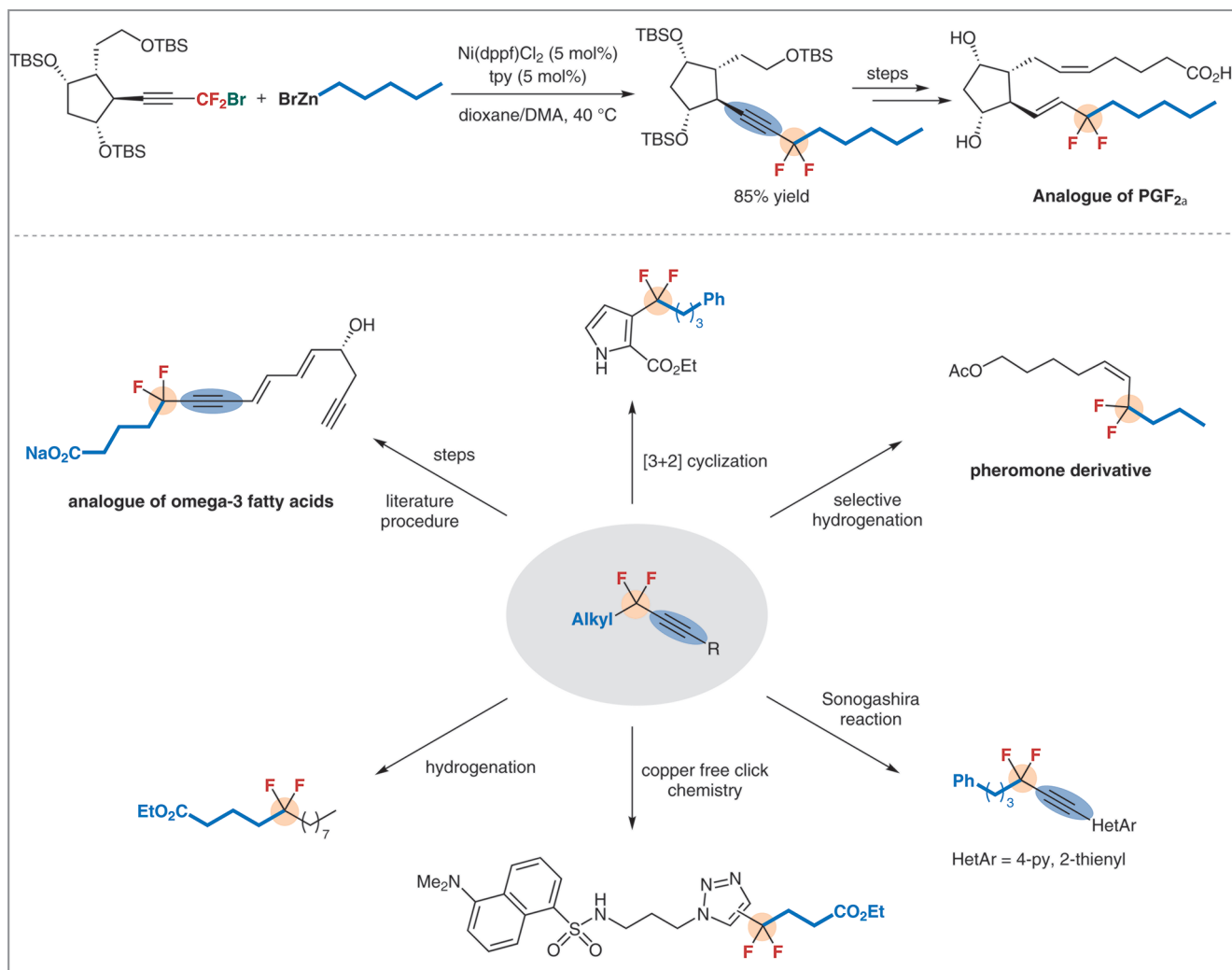
Scheme 1 Highly selective Nickel catalyzed *gem*-difluoropropargylation of unactivated alkylzinc reagents

“We had focused on transition-metal-catalyzed reactions for the direct introduction of fluorinated groups into organic molecules since we set up our group in 2008,³” explained Professor Zhang. He continued: “Although transition-metal-catalyzed cross-coupling reactions are one of the most powerful and efficient strategies to construct C–C bonds, some specific challenges remain unsolved in the construction of C–R_f bonds, such as the site-selective construction of C_{sp³}–R_f bonds. Our main contribution to the area in this work is the site-selective introduction of a CF₂ group into an aliphatic chain in a straightforward manner.” The new method designed by Professor Zhang led to *gem*-difluoropropargylated alkanes under mild reaction conditions with high efficiency, broad substrate scope and excellent functional group tolerance, even towards complex natural products (Scheme 1).

Transformations of the resulting difluoroalkylated products could produce a variety of analogues of biologically active molecules, including pheromones, omega-3 fatty acids and prostaglandin F_{2α} (PGF_{2α}), the active principle of eye drops used for sterilization treatment (Scheme 2).

“This reaction protocol thus serves as a general approach to accessing difluoroalkylated alkanes. Since the C–C triple bond is a versatile functional group, the resulting *gem*-difluoropropargylated alkanes provide good opportunities for applications in medicinal chemistry,” said Professor Zhang.

He also emphasized: “Although mechanistic investigations of nickel-catalyzed Negishi cross-couplings of alkyl electrophiles have been reported, the general catalytic pathway of these couplings remains uncertain and the outcome depends on the nickel catalysts and alkyl electrophiles used.⁴ To the



Scheme 2 Synthetic transformations of *gem*-difluoropropargylated alkanes

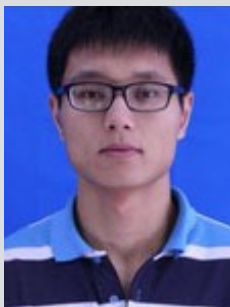
best of our knowledge, the mechanistic study of the Negishi cross-coupling of fluoroalkyl halides has not been documented so far.” Based on their preliminary mechanistic studies, Professor Zhang and coworkers revealed that a Ni(I/III)-catalytic cycle is involved in the reaction, which is initiated by the transmetalation of Ni(I) with alkylzinc to generate an alkyl nickel complex [alkylNi(tpy)].

Professor Zhang concluded: “An efficient method to site-selectively synthesize difluoroalkylated alkanes has been developed through a nickel-catalyzed cross-coupling reaction. In the near future, we are looking to use abundant and inexpensive industrial raw materials, such as small molecule fluoroalkanes,⁵ as fluorine sources to stereoselectively introduce fluorinated groups into organic molecules. We hope our long-

term efforts will provide cost-efficient and straightforward approaches for applications in the production of pharmaceuticals, agrochemicals and advanced functional materials.”

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About the authors



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Lun An was born in Shandong (P. R. of China) in 1990. He obtained his BSc degrees in chemistry and marine chemistry from Ocean University of China (P. R. of China) in 2013. With a strong interest in organic chemistry, he then moved to Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China) and began his graduate research under the supervision of Professor Xingang Zhang. His research interests are focused on site-selective

base-metal-catalyzed fluoroalkylation reactions and developing new and general methods to enantioselective fluoroalkylations.



C. Xu

Chang Xu was born in Kunming (P. R. of China) in 1992. He obtained his BSc degree in basic pharmacy from China Pharmaceutical University (P. R. of China) in 2015. With an interest in organic chemistry and medicinal chemistry, he then began his graduate studies at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China) under the supervision of Professor Xingang Zhang. His research interests are focused on the activation and transformations of small-molecule fluoroalkylanes and their applications in medicinal chemistry.



Prof. X. Zhang

Xingang Zhang was born in Xinjiang (P. R. of China) in 1975. He graduated in 1998 from Sichuan University (P. R. of China) and received a PhD in 2003 at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China). After his postdoctoral work at the University of Illinois at Urbana Champaign (USA) guided by Professor Wilfred A. van der Donk, he joined the faculty team of Shanghai Institute of Organic

Chemistry as a research associate professor in 2008, and became research professor in 2012. His current research interests are focused on organofluorine chemistry and chemical biology. He received the Thieme Chemistry Journals Award in 2014, the 2015 RSC Fluorine Chemistry Prize and 2015 Fifth Chinese Chemical Society (CCS)-Royal Society of Chemistry (RSC) Young Chemist Award.

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