

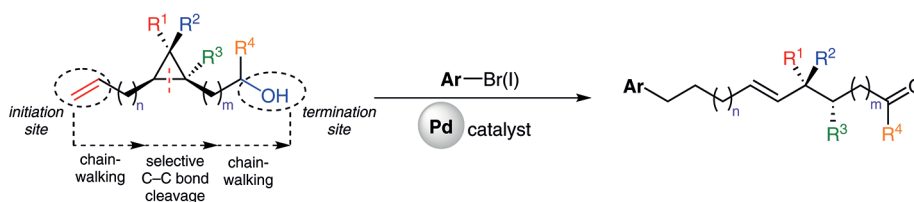
A Unique Palladium-Catalyzed Heck Arylation as a Remote Trigger for Cyclopropane-Selective Ring Opening

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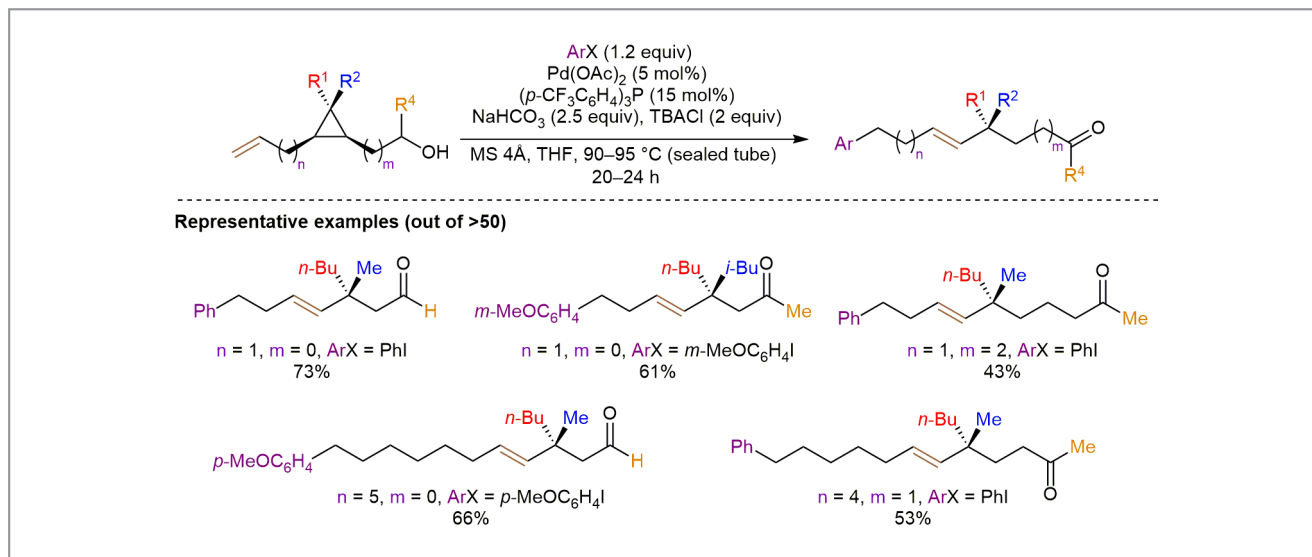
The concept of remote functionalization, originally coined by Breslow in 1972,¹ relates to the selective functionalization at a site away from the site of a functional group. Following this pioneering work, an impressive body of work has been reported for the remote functionalization of non-reactive molecules in the gas phase.² However, after these reports, the field became rather dormant, most probably due to the synthetic difficulties encountered, until the last few years when there has been a resurgence of interest in this approach. It is now considered as one of the hottest topics in synthetic organic chemistry thanks to the contributions of worldwide leading research groups.³ Initially, the research group of Professor Ilan Marek (Technion – Israel Institute of Technology, Haifa, Israel) had developed the remote functionalization of hydrocarbon chains by merging two cutting-edge methods, namely the allylic C–H bond activation and C–C bond cleavage of ω -ene cyclopropanes.⁴ “Although particularly straightforward if one wants to distantly control positioned acyclic quaternary and tertiary stereocenters, this approach required stoichiometric amounts of zirconocene derivatives,⁵” explained Professor Marek, who continued: “We wanted to design a new system where the remote functionalization could be performed catalytically, but all our attempts to develop the zirconium-catalyzed remote functionalization of hydrocarbons failed.” Although very disappointing, these repetitive failures led Jeffrey Bruffaerts, Alexandre Vasseur and Sukhdev Singh, all co-workers in Professor Marek’s research group, to envisage alternative catalytic processes that would allow these highly regarded but complex remote functionalization transformations to occur. “Since secondary sp^3 organo-palladium species readily undergo β -H elimination and re-addition, as proved

by the synthetically relevant work of Baudoin,⁶ Mazet,⁷ and Kochi,⁸ my co-workers were expecting that the Heck arylation reaction could potentially trigger a chain-walking mechanism and selective ring-opening reaction,” recalled Professor Marek. Indeed, early work dating back to the mid-1970s mentioned that the arylation of homoallylic alcohols led to the migration of palladium converting alcohols into ketones.⁹ “The power of this approach was beautifully illustrated when enantiomerically enriched stereocenters were created on ω -alkenol by the research groups of Sigman¹⁰ and Correia and Pflatz,¹¹” said Professor Marek. So, would the palladium-catalyzed Heck reaction triggering a Pd walk and selective ring opening of substituted cyclopropyl carbinols potentially be a powerful approach? “If such a transformation was possible, the clear advantage of this strategy would reside in the rather easy diastereo- and enantioselective preparation of polysubstituted cyclopropanes that would be translated into acyclic stereocenters after unfolding of the three-membered ring (Scheme 1),” was Professor Marek’s answer.

“Using the simplest diastereomerically pure model substrates, the modified Larock’s experimental conditions proved to be the most efficient protocol to provide the acyclic products in good yields and selectivities as unique (*E*)-isomers (Scheme 2),” said Professor Marek. The scope of the reaction is very broad, as could be seen in the original paper, and summarized by the few representative examples described below. “Aryl iodide (as well as aryl bromide) as a coupling partner possessing a functional group, such as an electron-donating or electron-withdrawing group – including an interesting methyl ketone moiety – react similarly with the starting substrates. Various substitution patterns on the quaternary stereocenter



Scheme 1



Scheme 2

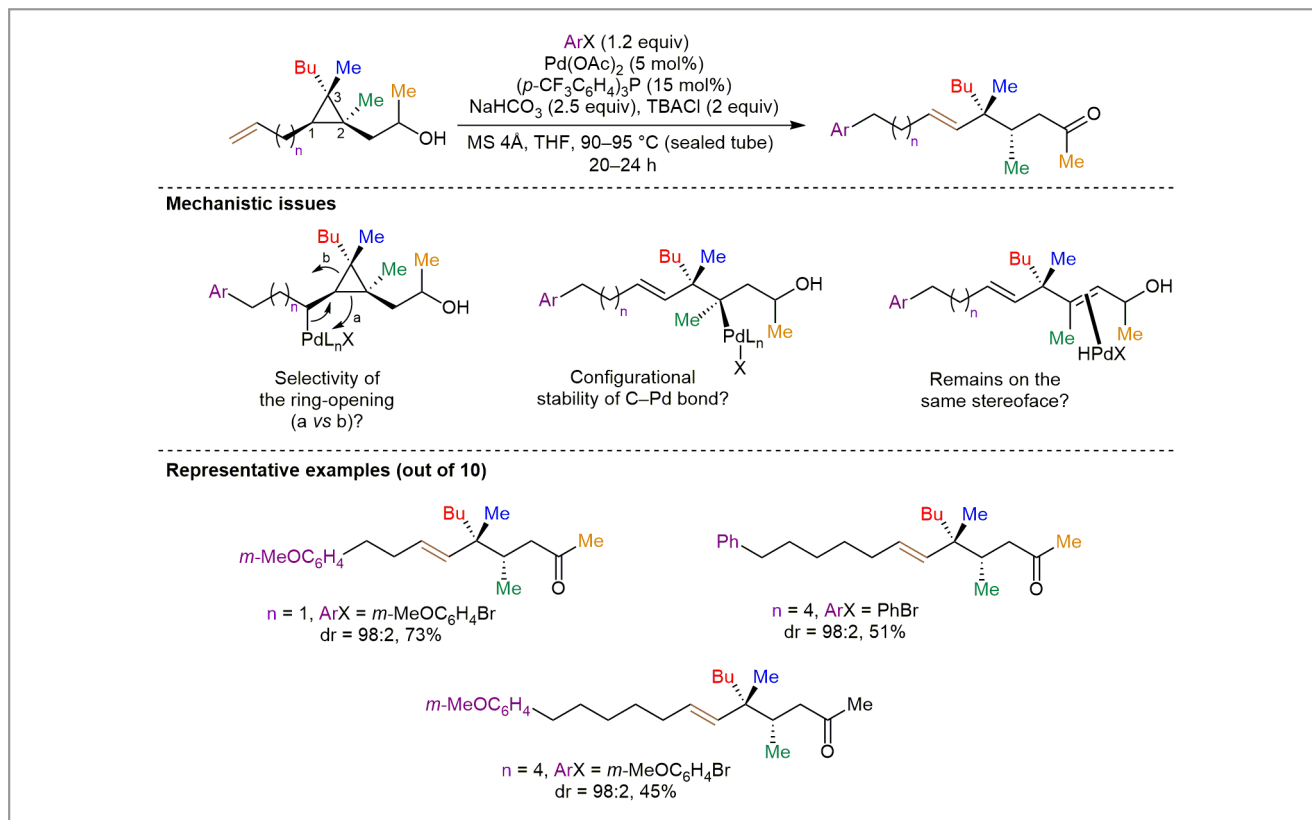
(R^1 and R^2) and secondary alcohol derivatives also underwent similar transformations to provide the corresponding ketones. Even more interesting is that the chain-length variation does not actually alter the efficiency of this combined transformation ($n = 4, m = 2$, Scheme 2),” explained Professor Marek.

The next level of complexity that was investigated by Professor Marek’s research group concerned the unfolding of 1,2,2,3,3-pentasubstituted cyclopropanes as illustrated in Scheme 3. “In this case, not only might the selectivity of the C–C bond cleavage be difficult to control (both C1–C2 and C1–C3 bonds have the same substitution level), but also the ring opening would lead to a species containing a stereogenic C-center palladium species and the issue of its configurational stability needed to be considered (Scheme 3),” he explained. “Moreover, when the Pd walk proceeds further through the *syn*- β -H elimination, a planar olefin is formed and the chirality can only be preserved if the Pd species does not disengage from the olefin and re-adds on the same stereoface. Gratifyingly, my outstanding team was able to show that the products resulting from the remote arylation of ω -alkenyl cyclopropyl alcohols were obtained in satisfactory yields as a single set of diastereoisomers (dr = 98:02), suggesting that the Pd does not disengage during the process and migrates on the same stereoface,¹²” said Professor Marek. He continued: “These results open vast perspectives for the metal walk all over carbon skeletons possessing stereogenic centers.”

“It is now clear that the remote functionalization by metal walk opens new perspectives in organic synthesis and many more organic chemists will embrace this concept and benefit

from all the advantages and opportunities it has to offer. In conclusion,” Professor Marek said, “it has been a real privilege to be associated with such talented co-workers and without their inspiration, dedicated work and input, none of this would have seen the light of day.”

Antonia Fank



Scheme 3

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About the authors



J. Bruffaerts

the development of novel remote functionalization based synthetic methodologies, mostly applied to hydrocarbons.



Dr. A. Vasseur

worked on transition-metal-assisted remote functionalization of alkenes. In 2015, he moved to the Ecole Centrale de Marseille (France) where he is currently working on the synthesis of secondary phosphine oxide–palladium complexes and their applications in organic synthesis as a Teaching and Research Temporary Attaché (ATER) in the research group of Professor Alexandre Martinez, Dr. Laurent Giordano and Dr. Didier Nuel.



Dr. S. Singh

Jeffrey Bruffaerts was born in Brussels (Belgium) in 1990. He graduated from the Université Catholique de Louvain (Belgium) where he was awarded a BSc (2011) and an MSc (2013), during which he worked under the supervision of Professor Olivier Riant. Since then, he has joined the laboratory of Professor Ilan Marek at the Technion – Israel Institute of Technology (Israel) for his doctoral studies. His PhD thesis is focusing on

Alexandre Vasseur was born in Revin (France) in 1982. He studied chemistry at the University of Reims Champagne-Ardenne (France). He completed his PhD studies in 2012 on Pd-catalyzed dehydrogenative Heck reactions of heteroarenes with electron-rich and/or hindered alkenes under the supervision of Dr. Jean Le Bras. He then joined the group of Professor Ilan Marek at Technion – Israel Institute of Technology (Israel) and

Sukhdev Singh was born in Sirsa, Haryana (India) in 1980. After completing his MSc in chemistry from Delhi University (India), he spent six months in Jubilant Chemsys Limited (India), a leading CRO industry situated in Noida (Uttar Pradesh). Meanwhile, he qualified in the national eligibility examination and was awarded a Junior Research Fellowship from UGC India. He then joined the research group of Professor Ashok K.

Prasad at Delhi University (India) for his PhD thesis and worked in the area of heterocyclic chemistry. Part of his PhD thesis work was completed at Paris Descartes University (France) under the supervision of Professor Hamid in the area of synthesis of fluorinated amino acids. He was awarded his PhD in 2012. He joined the group of Professor Ilan Marek at the Technion – Israel Institute of Technology (Israel) in 2013 as a postdoctoral fellow and his research work is mainly focused on remote functionalization and transition-metal-mediated selective cyclopropane ring opening.



Prof. I. Marek

Ilan Marek was born in Haifa (Israel), educated in France, and received his PhD in 1988 from the University Pierre et Marie Curie, Paris (France) under the guidance of Professor J. F. Normant. In 1989, he was a postdoctoral fellow in Louvain-la-Neuve (Belgium) with Professor L. Ghosez and obtained a research position at the CNRS in France in 1990. After obtaining his Habilitation in Organic Chemistry, he moved to the Technion – Israel Institute of Technology (Israel) at the end of 1997 where he currently holds a Full Professor position. Since 2005, he holds the *Sir Michael and Lady Sobell Academic Chair*. He has received many awards for academic excellence and for teaching. He is a member of the advisory board of several journals and serves as Senior Editor of the Patai series. He is concerned with the design and development of new and efficient stereo- and enantioselective strategies for the synthesis of important complex molecular structures. He is particularly interested in developing carbon–carbon bond-forming as well as carbon–carbon bond-activation processes that create multiple stereocenters efficiently in a single-pot operation. Understanding of reaction mechanisms gives insight into the origins of chemo- and stereo-selectivity, and governs optimization towards the most efficient and general protocols for his methodologies. His vision is that we should provide an answer to challenging synthetic problems but it has to be coupled with unique efficiency and elegance.